OPIOIDS FOR BREATHLESSNESS IN HEART FAILURE

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Thesis Abstract

Breathlessness is a common and problematic symptom in heart failure. Opioids have traditionally been considered as analgesics, but a potential role for their use in breathlessness is beginning to emerge. This thesis commences with a review of the existing literature in support of a possible role for opioids in the management of breathless in heart failure. A systematic review of existing human symptom control studies in this thesis suggests that opioid administration may have a small but significant benefit in chronic heart failure. However, only six studies were included in the review and most were either small or of poor methodological quality. This presents a relative gap in the knowledge on this topic.

A randomised controlled trial was therefore performed to assess the effect of opioids on breathlessness in chronic heart failure. This crossover trial involved the comparison of two oral opioids with placebo. Thirty-five participants completed the trial, making it the largest trial of its type in this area. Opioid administration was shown to be safe in this patient cohort. No statistically significant differences were demonstrated for breathlessness severity between treatments.

Participants were subsequently invited to participate in a three month open label extension. Thirty three participants in total were followed up with thirteen remaining on active therapy. This is the first trial of its type in breathlessness in heart failure and represents the longest participant follow-up in this area. Whilst not as robust as the initial trial, this extension period revealed that opioid continuers rated a statistically significant improvement in breathlessness severity from baseline compared to non-continuers.

Finally, a semi-structured interview study in ten participants with heart failure revealed for the first time that opioids are acceptable in this population and they describe troublesome symptoms that might respond to opioid treatment.

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Finally, I thank my wife Emma, my daughter Jessica and my father George, who have encouraged and supported me throughout this entire process.

Author's Declaration

The research presented in this thesis was initiated and conducted by the author. Dr Miriam Johnson and Professors David Torgerson and Martin Bland had input into the randomised controlled trial study protocol. In addition, Dr Johnson and Dr Lesley Jones assisted with the qualitative research protocol. The author was involved in study participant screening, approach, consent, trial drug administration, data collection, database formation, trial management and data interpretation. Mandy Walters, research nurse, assisted with some of the screening and telephone follow-up for the randomised controlled trial. All subsequent statistical analysis, interpretation and hypothesis generation for both quantitative and qualitative elements are the author's own work. The author is therefore completely responsible for the research presented in this thesis.

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Chapter 1:

Opioids for breathlessness in heart failure: How might drugs traditionally regarded as analgesics improve other symptoms?

"Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."

Thomas Sydenham

Section 1) Introduction

Thomas Sydenham (1624-1689), the great English physician and apothecary, was one of the pioneers of opioid therapy in Western medicine, creating a solution of opium, sherry and spices to manage a variety of ills in his patients (Hamilton and Baskett, 2000). Opioids or "morphine-like medicines" have an historical association with healing, suffering (through addiction and misuse) and even war. Today, opioids are used widely in the management of pain in many patients worldwide. Increasingly there is evidence that opioids may help to relieve another troublesome symptom, namely breathlessness.

Traditionally, opioids have been left "in reserve" for patients as they approach death and so are most familiar to physicians in palliative medicine. With growing recognition of alternative uses of opioids however, they are increasingly incorporated in a patients' overall management as their symptoms worsen. Those chronic diagnoses that are most associated with breathlessness include cancer, chronic obstructive airways disease and heart (or cardiac) failure. Physicians are more comfortable with the administration of opioids in cancer patients and there is a small but growing evidence base for the use of opioids in Chronic Obstructive Pulmonary Disease (COPD) to manage breathlessness (Jennings *et al.*, 2001, Abernethy *et al.*, 2003). However, similar research into the relief of breathlessness with opioids in CHF has been slow to materialise. This is despite the number of patients living with chronic heart failure (CHF) increasing at this time (Department of Health, 2000, Thomas and Rich, 2007) and therefore more patients are likely to require symptom relief. Opioids are already recommended for breathlessness in chronic heart failure in clinical guidelines (SIGN, 2007) once other therapies have been administered. This use however is recommended without a defined evidence base and uptake of this guideline has been slow due to this and perceived problems with opioid therapy in general.

This chapter aims to provide some of the background information as to the importance of research in this area. The research topic incorporates a number of subjects including heart failure, breathlessness as a symptom and knowledge of opioids. A brief overview of heart failure in Section 3 will detail the background in relation to the research topic with consideration for the need for research in this area, but is not designed as a comprehensive review of heart failure. It simply describes some of the background to CHF and discusses some of the investigations and interventions referred to in the RCT

(Chapter 4). The sensation of breathlessness in particular is difficult to quantify and the mechanisms as to why CHF patients may be breathless will be discussed in Section 4. Existing therapies for the management of breathlessness in general will also be discussed.

Opioids are proteins produced naturally by the body and exert their effects by activating opioid receptors. These naturally occurring "endogenous" opioids and the receptors that they activate will be discussed in Section 2. In addition, the site of action of exogenous opioids (i.e. external / pharmaceutical) will be detailed.
This will be followed by a review in Chapter 2 of the potential role of opioids in the mechanisms involved in the pathophysiology of heart failure including studies in animal models and the potential problems in interpretation that the use of such models may have. This chapter of the thesis will conclude with a summary of the key findings and with an assessment of the need for research in this area.

Section 2) Opioids: Morpheus awakes in the mammalian world

2.1 Historical Perspective

Opioids have been manipulated by physicians for centuries, although knowledge of endogenous opioids (those naturally occurring in the body) has only become apparent within recent years. In circa 3400 BC the Sumarians first documented the cultivation of the opium poppy (*papaver somniferum*) in lower Mesopotamia (Hamilton and Baskett, 2000). Hippocrates detailed the use of the extract of the poppy in medicine in the fourth century BC. Later Galen, a Greek physician in the second century AD, administered opium extracted from the opium poppy to patients to relieve pain and, of relevance to this thesis, to improve the clinical status of patients with symptoms suggestive of heart failure amongst other diagnoses (Waldhoer *et al.*, 2004). In essence therefore, one could say that this thesis builds on evidence collected about two millennia ago! Since that time, the active compounds from the opium poppy have been isolated and subsequent synthetic analogues have been produced. Morphine (named after Morpheus, the God of sleep and dreams) was first isolated over 200 years ago by Friedrich Serturner, a German chemist (Huxtable and Schwarz, 2001, Hamilton and Baskett, 2000). Many synthetic and non-synthetic preparations have since been developed. "Opioid" is the all-encompassing term for all substances with a pharmacological action similar to morphine and all other "morphine-like" medicines. "Opiate" is a narrower term used for only the alkaloid derivatives of the opium poppy, rather than all products with morphine-like properties. Hence "opioid" is the correct term to use in our context and will be referred to throughout this thesis.

2.2 Endogenous opioids

The human body produces its own natural (endogenous) opioid proteins and these have been implicated in a number of processes. Opioid receptors are stimulated by the binding of these endogenous opioid proteins that are released as a natural response to injury, infection, trauma, stress and surgery amongst other causes (Molina, 2006). It is considered that these naturally occurring opioids may mediate the metabolic and haemodynamic responses required to restore homeostasis (Molina, 2006).

Three main types of endogenous opioid peptides exist; enkephalins, dynorphins and endorphins. Interestingly, all of these three main types of endogenous opioid share the same amino-terminal amino acid sequence (Tyr-Gly-Gly-Phe-Met or Tyr-Gly-Gly-Phe-Leu) suggesting a similar method of activation at the receptor level (Roques *et al.*, 1999). These proteins are derived from larger protein precursors that are encoded by three different genes; pro-enkephalin, pro-dynorphin and pro-opiomelanocortin (Simon and Gioannini, 1993) {please refer to Cesselin 1995 for a review on this topic}. In general terms, the genetic information stored in the DNA code is transcribed in the nucleus of the cell forming a copy of the DNA in the form of messenger ribonucleic acid (mRNA). This mRNA is translated into a sequence of amino acids by ribosomes in the cytoplasm. These collections of linked amino acids become proteins when they are complete and able to adopt their natural shape (Thibodean and Patton, 1997). Hence measurement of mRNA can be a surrogate for measurement of the particular production of certain proteins (such as endogenous opioids or opioid receptors).

Table 1.2.1 below demonstrates some of the endogenous peptide products from these precursors, noting the similarity of amino acid structure of the different endogenous opioid peptides. These genes and their genetic protein products are expressed in different locations in the human body. The locations with reference to the cardiovascular and respiratory systems will be discussed later. Differential splicing of the precursor proteins may result in other opioid or non opioid products. This is particularly apparent for pro-opiomelanocortin.

Table 1.2.1: Endogenous opioid products of the three opioid precursors (Adapted from Roques *et al.* (1999)

Precursor	Peptide	Amino acid sequence	Other non-opioid products from precursor
Pro-enkephalin	Met-enkephalin	Tyr-Gly-Gly-Phe-Met	
	Leu-enkephalin	Tyr-Gly-Gly-Phe-Leu	
	Met-enkephalin-8	Tyr-Gly-Gly-Phe-Met-Arg-Gly-Leu	
	Met-enkephalin-Arg-Phe (MEAP)	Tyr-Gly-Gly-Phe-Met-Arg-Phe	
Pro-dynorphin	Dynorphin A	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Trp-Asp-Asn-Gln	(Also neo-endorphins)
	Dynorphin B	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr	
Pro-opiomelanocortin (POMC)	B-endorphin	Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ala-Ile-Val-Lys-Asn-Ala-His-Lys-Lys-Gly-Gln	Melanotropic (Melanocyte Stimulating hormone – MSH); Corticotropic peptides (e.g. ACTH)

Given that common amino-acid sequences are shared between endogenous opioids, all opioid receptors can be activated by each opioid protein if sufficient concentrations of peptide are reached (Simon and Gioannini, 1993). However, given the differences in size and sequence between these compounds, the three main types of endogenous opioids

have preferences for the three types of opioid receptor. These receptor : peptide associations are detailed in the next section.

The production of endogenous compounds should not be seen in isolation as in general a variety of feedback mechanisms can adjust the production of many other compounds and this is also true for opioids. For example, Pro-opiomelanocortin (POMC) undergoes enzymatic cleavage in the pituitary into Adreno-Cortical Thyrotropic Hormone (ACTH) and Beta-Lipotrophin, which is the immediate precursor of beta-endorphin. In normal human subjects, beta-endorphin levels rise in the circulation in conjunction with ACTH following stimulation of corticotrophin releasing factors from the hypothalamus (McLoughlin *et al.*, 1993). Beta-endorphin may be shortened by enzymatic cleavage outside the pituitary (its main site of production) into alpha-, gamma- or delta- endorphin dependent upon the site of cleavage (McLoughlin *et al.*, 1993). No clear physiological role for beta-endorphin has yet been identified (Guillemin *et al.*, 1977).

Similarly, the potential roles for other circulating endogenous opioids is unclear. Met-enkephalin has been isolated in human plasma (Boarder *et al.*, 1982, Clement-Jones *et al.*, 1980), with no obvious defined role. The presence or absence of dynorphins in plasma is difficult to assess by current techniques (McLoughlin *et al.*, 1993) and hence their role in circulation is similarly difficult to elucidate.

Understanding of the endogenous opioid agonists has suffered from unclear nomenclature based on initial discoveries. Examples of this include the nociceptin or orphanin protein, similar in structure to dynorphin, which does not have the amino-acid sequence necessary to activate the three recognised opioid receptors. This protein has been termed "opioid" without the necessary ability to activate traditional opioid receptors (Reinscheid *et al.*, 1995) and therefore caution should be used when interpreting data from papers involving nociceptin as an agonist. 'Endomorphins' are another similar example (Venkatesan *et al.*, 2003). Hence the nomenclature of peptides similar in structure to the traditional opioid proteins has further complicated the research in this area. Studies involving such peptides have been excluded from this thesis given the unknown and probably unrelated site and action of these proteins.

Caution is also advised when interpreting some of the data involving enkephalins in particular. Some studies have detected enkephalin-like proteins (such as MEAP {Met5 Enkephalin-Arg6-Phe7} or met-enk-arg-gly-leu) which can occur due to differential

splicing of the precursor protein and may or may not be involved in endogenous opioid activity in a similar way to met- or leu-enkephalin peptides. Measurement or administration of such proteins might be relevant in such studies as they are formed from the same common preproenkephalin precursor as met- or leu-enkephalin (Pepe *et al.*, 2004), but at best these are surrogates for the enkephalins of interest. For example, MEAP has been located in basic science studies involving rat and guinea pig in both lung (in high concentrations) and heart (Tang *et al.*, 1982), but at different selective ratios to met-enkephalin in those tissues. Studying MEAP may not be relevant, as it appears to undergo differential splicing from pre-pro-enkephalin than met-enkephalin (van den Brink *et al.*, 2003). Barron (2000) describes MEAP as the "promiscuous peptide" due to its stimulation at low doses of both delta and kappa receptors, with mu receptor stimulation also occurring at higher concentrations of ligand, indicating uncertainty of its method of activity. It is difficult to know whether these surrogates for enkephalin compounds are truly involved in opioid activity. To the best of my knowledge, the potential differences in detection of these different enkephalin-like proteins are not discussed in detail in the wider literature and this further adds to the complexity and confusion surrounding endogenous opioids.

2.3 Opioid receptors

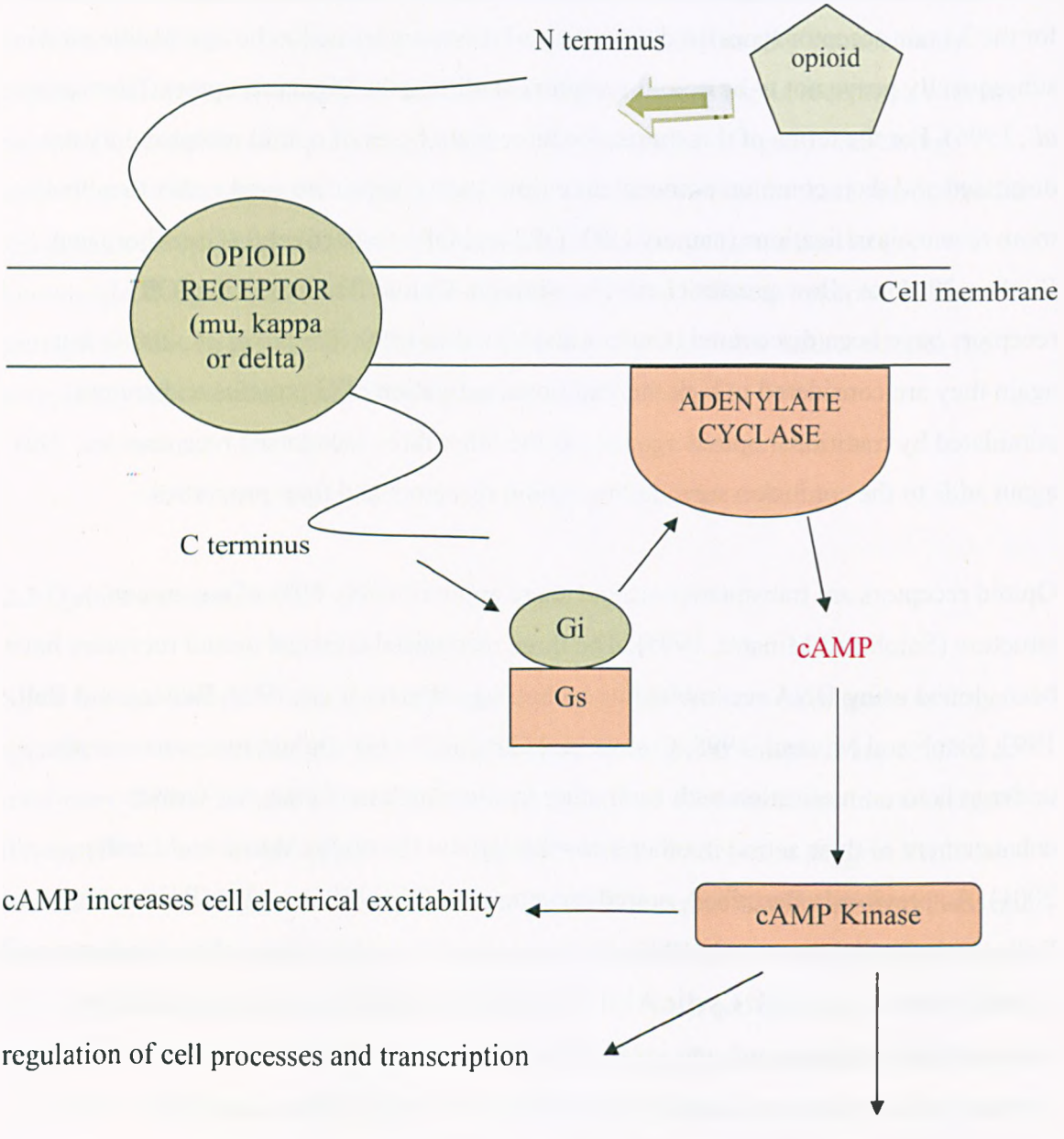
Since the elucidation of opioid receptors in the body, efforts have been made to target specific opioid receptors with new opioid drugs. These opioid receptors are coupled to inhibitory G proteins and exist in different locations and concentrations in a variety of tissues (Davis and Pasternak, 2005), which adds further evidence to suggest a role in maintaining homeostasis. Three main types of opioid receptor have been described: mu, kappa and delta (Kosterlitz, 1985). These three types have been recently cloned using DNA technology (Gaveriaux-Ruff and Kieffer, 1999, Satoh and Minami, 1995). Other receptors have previously been described, but remain poorly characterised (Waldhoer *et al.*, 2004). Further subtypes of these three known receptor classes are believed to exist (Davis and Pasternak, 2005). Depending on their type and location, activation of these receptors have differing effects which has lead to the possibility of more targeted drug therapy using synthetic opioid drugs that have different receptor profiles.

Research into receptor:opioid interactions is difficult due to both the relative affinities of opioids for each receptor and the comparative distributions of opioids and receptors in the body. Distribution of opioid receptor subtype and endogenous opioids can be varied both in different species and within the same species. Many investigators have noted very similar distribution of opioid receptors between mammalian species, but that the relative concentration of receptors and type of receptor differs widely at these sites between species (Khatchaturian *et al.*, 1993).

Definitions of opioid receptors are also not assisted by reclassification (to OP receptors for the 3 main receptor types) and discovery of receptors termed to be opioid-like which subsequently prove not to be opioid receptors at all (e.g the Sigma receptor) (Dhawan *et al.*, 1996). For the terms of this thesis, the three main types of opioid receptor only are discussed and their common nomenclature (mu, kappa, delta) are used rather than their more recent classifications (namely OP3, OP2 and OP1 respectively) (Groneberg and Fischer, 2001) to allow greater clarity. In addition, Opioid Receptor-Like (ORL) receptors have been discovered (Connor and Christie, 1999, Trescot *et al.*, 2008), but again they are considered to lack the traditional activation of G proteins and are not stimulated by traditional opioid agonists as the other three recognised receptors are. This again adds to the confusion surrounding opioid receptors and their properties.

Opioid receptors are transmembrane and share approximately 60% of a common structure (Satoh and Minami, 1995). The three recognised classical opioid receptors have been cloned using DNA recombination technology (Evans *et al.*, 1992, Reisine and Bell, 1993, Satoh and Minami, 1995, Connor and Christie, 1999). Opioid receptors can also undergo heterodimerisation with each other in situ which may lead to a further enhancement of their action in other areas throughout the body (Martin and Prather, 2001). As previously described, opioid receptors are G-protein coupled (Reisine and Bell, 1993, Zimlichman *et al.*, 1996) and have an inhibitory action on the manufacture of cAMP (Pepe *et al.*, 2004). Cyclic AMP is responsible for maintaining intracellular calcium concentrations and subsequent myocardial contractility (Figure 1.2.1). This is in contrast to a hormone involved in the perpetuation of heart failure, namely norepinephrine (norepinephrine) which has a stimulatory action on adenylate cyclase, thus increasing intracellular calcium concentrations and contractility (Mann *et al.*, 1992). The location of opioid receptors in relation to the cardiorespiratory system and the interaction of opioids with neurohormones like norepinephrine and its importance is discussed in Chapter 2.

Figure 1.2.1: Diagram to show the relationship between transmembrane opioid receptors, G proteins and the manufacture of cyclic AMP through adenylate cyclase. Opioid receptor stimulation through endogenous opioids causes a stimulation of the inhibitory G protein system (Gi). This in turn reduces the production of cAMP by adenylate cyclase. cAMP has multiple downstream effects, which are therefore inhibited by opioid receptor stimulation. Conversely, norepinephrine stimulates Gs (stimulatory G proteins), causing an increase in cAMP production and enhancement of its downstream effects. Adapted from Trescot *et al.* (2008).



2.4 Exogenous opioids and opioid antagonists

All pharmaceutical (exogenous) opioids essentially have a similar class effect with respect to analgesia and side effect profile, despite efforts to target certain classes of receptors. However, they do differ by route of administration, bioavailability, duration of action, route of excretion and potency (Oxberry and Simpson, 2005). The side effect profile can vary between individual patients and opioid used, with different opioids having a greater frequency of certain opioid-related side effects and lower frequency of others. Hence, a growing number of pharmaceutical opioids have been developed and they are widely used throughout healthcare. Clinically, opioids are prescribed on an empirical basis until an agent is found that is effective without intolerable side effects (Davis and Pasternak, 2005). Common side effects may include nausea, vomiting, drowsiness, itch, constipation and dry mouth (Oxberry and Simpson, 2005). More serious potential effects such as tolerance, dependence, significant respiratory depression and addiction are considered rare when opioids are prescribed by appropriately trained healthcare professionals (Hanks *et al.*, 2004). Despite this, widely held beliefs concerning "morphine" and associated strong analgesics are held by lay, patient and healthcare populations (Lambert *et al.*, 2007). This "opiophobia" may prevent use of opioids despite a clinical indication and this phenomenon is described further in the qualitative chapter of the thesis (Chapter 6).

Despite these effects, opioids have a number of advantages that have been utilised in anaesthesia. In particular, there is minimal direct depression of cardiac function, preservation of autoregulation of blood flow to vital organs including the heart, and absence of interactions with cardiac drugs. In addition, the control of mechanical ventilation and toleration of endotracheal tubes is also improved with opioid drugs (Hug, 1999). These cardio-respiratory factors have allowed intra-operative use of exogenous opioids and demonstrates that use of opioids is compatible with cardiac medications. Unfortunately the safety of opioid use in some patient groups is still questioned (Auret and Schug, 2005, Cattermole and Graham, 2009, Hoffman and Reynolds, 1987) despite palliative care and anaesthetic experience. The RCT and three month follow-up chapters will seek to address the fears of some that even low doses of opioids cause significant clinical cardiorespiratory interference and adverse events.

Many opioid antagonists have been developed to counteract the effect of opioids at the cellular level. Some antagonists are designed to target a single receptor class, others (like

naloxone) have multiple opioid receptor affinities at sufficient concentrations (Davis and Pasternak, 2005). Opioid antagonists have been used by researchers to explain the pharmacological mechanisms of action of opioids, or clinically by observing the effects of the antagonist then extrapolating the findings to propose a hypothesis of the actions of opioids (Davis and Pasternak, 2005). This is a complex area, however, as sufficient doses of antagonist are required to block the effect of opioids, antagonists tend to have a shorter duration of action and many opioids can stimulate more than one class of receptor.

2.5 Endogenous and exogenous opioid:receptor affinities and interactions

It remains unclear whether endogenous opioids can exert an effect by systemic release into the circulation, or whether their release must be localised within the same tissue as the location of opioid receptors (i.e. an autocrine or paracrine effect) (Khatchaturian *et al.*, 1993). Most experimentation with exogenous opioids in mammalian species models has involved systemic administration, which is typically the means by which morphine-like medicines are administered in humans. As with other compounds, various disease states may cause up- or down-regulation of receptors, as potentially will the chronic administration of agonists or antagonists. These potential limitations and complexities must be taken into account when evaluating the literature.

Table 1.2.2 reveals the common endogenous and exogenous opioid agonists and antagonists. It should be noted that these compounds predominantly exert their effects through the receptors stated, though there is variable activation of other opioid receptors dependent on dose and location. For example, met- and leu- enkephalins have high affinity for delta receptors, low affinity for mu receptors and negligible affinity for kappa receptors (Corbett *et al.*, 1993b). Dynorphins A and B have highest affinity for kappa, but also affinity for mu receptors with less (though still present) affinity for delta (Corbett *et al.*, 1993b). Lastly, Beta endorphin has almost comparable affinity for both mu and delta receptors, with low affinity for kappa sites (Corbett *et al.*, 1993b). Hence opioids can activate all receptors at sufficient concentrations, but have varying specificity for receptor types. The non-selective nature of these endogenous opioid peptides has limited their use in clinical experimentation.

Table 1.2.2: Endogenous and exogenous opioids and their receptor stimulation:

Endogenous agonists	**Receptor preference**
Dynorphins	Kappa
Endorphins	Mu
Enkephalins	Delta
Common Exogenous agonists	
Morphine	Mu
Diamorphine	Mu
Oxycodone	Mu / Kappa
Fentanyl	Mu
Codeine	Mu
Exogenous antagonists	
Naloxone	Mu*
Naloxicine	Mu
Naltrexone	Mu*
Norbinaltorphimine	Kappa

* Antagonises all opioid receptors at comparatively low concentrations (for naloxone mu>kappa>delta)

Most of the exogenous opioid agonists are selective primarily for mu receptors, with variable amounts of selectivity for kappa and delta receptors. In addition, the relative potencies of administered opioids are different dependent upon the actual compound and route of administration. For example, oral morphine is considered to be approximately ten times more potent than oral codeine, with doses adjusted accordingly (Twycross *et al.*, 2002). This adds to the complexity of research in this area. For a comprehensive review see Herz (1993).

For reference for the RCT study detailed later in the thesis, the relative affinities of the synthetic opioids used and endogenous opioids classes are displayed in Table 1.2.3. These affinities are relative to each group (exogenous and endogenous) and should not be considered as directly comparable. Relative affinities have been used as there remains conjecture over the actual potencies of these compounds at receptor sites in different species. Neither of the two synthetic compounds mentioned bear direct relation to any of

the endogenous opioid proteins, but morphine could be considered as similar to the endorphins as the mu receptor is predominantly stimulated, whereas oxycodone could represent both endorphins and dynorphins as the mu and kappa receptors are predominantly activated.

The oxycodone affinities in particular have been difficult to elucidate, since different studies involving oxycodone have varying affinities expressed at the kappa receptor. Oxycodone is broken down into oxymorphone (and subsequently to oxymorphols and nor-oxymorphone) and noroxycodone (subsequently reduced to noxycodols and nor-oxymorphone). All these metabolites have differing affinities for the opioid receptors and it remains unclear as to the metabolites that cause the analgesic effects observed with oxycodone. For example, in an in vitro study, Lalovic *et al.* (2006) demonstrated a low affinity for oxycodone at the kappa receptor, but also a low affinity for the mu receptor compared to morphine, despite their similar analgesic properties in vivo. In contrast, Ross & Smith (1997) and Nielsen *et al.* (2007) demonstrate that kappa-receptor binding antagonists prevent the analgesic response of oxycodone but not morphine in rat studies, implying that the method of action of oxycodone is via a kappa receptor mediated mechanism. In essence, this area is complex and conclusive results from these receptor-binding studies do not appear to be present as a consensus in the literature to date. Hence, overall effects of oxycodone are a combination of effects on both kappa and mu receptors predominantly.

Table 1.2.3: Relative affinities of endogenous and exogenous opioids on opioid receptors from *in vitro* studies {adapted from: (Fowler and Fraser, 1994, Pugsley, 2002, van den Brink *et al.*, 2003, Corbett *et al.*, 1993a) }

Opioid	**Mu**	**Kappa**	**Delta**
Endorphin	+++ (>50%)	-	++ (>40%)
Enkephalin	+ (<10%)	-	++++ (>90%)
Dynorphin	+ (20%)	+++ (>60%)	+ (<10%)
Morphine	++++ (>95%)	- (<1%)	+ (<5%)
Oxycodone	+++	++	+

As with all medication, some individuals respond differently to the administration of opioids than others. Variation in response occurs for both a class effect of opioids themselves and for individual opioids in a given patient. This is important to consider prior to any interventional trial involving medications as individual responses will alter patient-related outcomes. Individual variation exists for the pharmacokinetics and pharmacodynamics of these drugs (Rollason *et al.*, 2008). Pharmacokinetic factors such as the transport and metabolism of exogenous opioids, and pharmacodynamic factors such as the type and frequency of opioid receptors and the signalling pathways associated with the effects of opioids can all have the potential for individual variation (Smith, 2008). Hence there are a number of points in the process from absorption to excretion that can vary between different patients. Genetic factors may be important in response, but studies in this area are difficult to perform and as yet genetic markers are unable to be used to predict either the efficacy of opioid treatment or the development of adverse effects with treatment (Skorpen *et al.*, 2008).

2.6 Conclusion

The isolation of opioid receptors and endogenous opioid ligands has given a greater scientific interest for the manipulation of opioids as a potential means of regulating certain diseases or body processes. Traditionally opioids were viewed as analgesics, but recent research at the cellular level has implicated a potential role for opioids in a variety of homeostatic processes. The clinical evidence for a role for opioids in heart failure in described in the literature review.

The endogenous opioid system and proposed role in homeostasis is difficult to interpret in relation to both human physiology and cardiorespiratory disorders as a specific entity in isolation. As Khachaturian *et al.* (1993) correctly discuss, the agonists and antagonists used can activate numerous receptor types given sufficient concentrations. Opioid precursors may be differentially processed in different locations (see table 1.2.1 for potential products of POMC for example). In addition, care must be taken when extrapolating animal or basic science work into the proposed effect in humans in vivo. These uncertainties further complicate the pharmacological research of endogenous opioid function (Khatchaturian *et al.*, 1993).

2.7 Key points

- Opioids are proteins produced naturally by the body and appear to have a role in homeostasis as they are widely distributed in many tissues
- Opioid receptors can be manipulated using external (or exogenous) opioids in pharmaceutical form
- Some exogenous opioids have different receptor profiles to others, but tend to share class effects. Commonly used opioid antagonists are generally non-specific for opioid receptors at high doses
- Pharmaceutical opioids are considered to have their intended method of action through the mu opioid receptor, but relative affinities for other receptor types vary between compounds (compare morphine and oxycodone)
- Pharmaceutical opioids have traditionally been involved in pain management and anaesthesia, the latter owing to their lack of interference with common cardiac drugs compared with other anaesthetic agents
- The area of research into opioids is complex due to the lack of specificity of opioids for the three main types of opioid receptors and the measurement of precursor proteins that act as surrogates for the opioid compound of interest
- Discoveries of proteins with similar characteristics to endogenous opioids or opioid receptors, that lack their traditional opioid-like effect, has further complicated interpretation
- Individual human variation in the pharmacokinetics and pharmacodynamics of opioids also complicates the area of clinical research in humans
- Symptom based opioid research is under-researched possibly reflecting the reluctance of the prescription of opioids

3.1 Historical perspective

The syndrome of heart failure was probably first described in texts from the fourth century BC following observations from Hippocrates of excess fluid in bodily tissues coupled with increasing shortness of breath (Katz, 2004). For a number of centuries thereafter it was considered that this was a result of the development of a "cold humour" until Harvey described the concept of a circulation of fluid around the body in 1628. Following this, the signs and symptoms of heart failure could be related to haemodynamic causes. From the 18th century onwards, further advances in understanding were made following observations of the structural changes that occur in the heart in cardiac failure, namely hypertrophy of the cardiac muscle or dilatation of the atrial and ventricular cavities, both of which result in cardiac enlargement (Katz, 2004).

Since the development of Starling's law and subsequent identification of structural changes and neurohumoral factors, our understanding of heart failure has changed further. Starling's law states that, up to a point, progressive dilatation of the heart can be advantageous in that further dilatation increases the ability of the heart to perform work, and therefore maintain the circulation (Opie, 2001). It would therefore appear that the body institutes structural changes to the circulation (i.e. cardiac hypertrophy or dilatation) and produces chemical factors into the circulation (neurohumoral factors) that seek to maintain the output of the heart in cardiac failure. Ultimately, if the cause of the cardiac failure is not removed, many of these factors are over-produced or have increasing effects that are deleterious to the cardiovascular system in an attempt to maintain circulation (Packer, 1988). This is part of the difficulty in the management of heart failure, progressive clinical deterioration in cardiovascular function in the long term caused in part by mechanisms instituted to maintain circulation in the short term. As knowledge of these proposed mechanisms advances, it is clear that the syndrome of heart failure is extremely complex involving multiple interactions of anatomical, functional and biological alterations (Mann, 2004a).

Only in the past century have drug therapies been available that target the proposed haemodynamic and neurohumoral changes that occur in heart failure. These will be discussed in more detail later in this chapter.

3.2 Definition of heart failure

Heart failure is a clinical syndrome that can be divided by time to onset (into acute and chronic) or by causative mechanism depending on the timing of the greatest limitation of function in the cardiac cycle (into systolic or diastolic). It can be further subdivided according to aetiology; the most common aetiologies in the Western world comprising of ischaemic heart disease, hypertension and cardiomyopathy (Weatherall *et al.*, 1996). The acute management of heart failure can differ from chronic management, hence the distinction between acute and chronic types. Acute heart failure can present as either pulmonary oedema or as fluid overload and is initially treated with diuretic therapy to diminish volume overload. Chronic heart failure (CHF) can decompensate to produce symptoms of pulmonary oedema or fluid overload, typically requiring higher doses of diuretics in the short term, but is otherwise managed with drugs that prevent further deterioration in cardiac function.

In addition, systolic heart failure (with impairment of cardiac function occurring during ventricular contraction) differs from diastolic heart failure (which occurs due to impaired filling of the heart) (Chatterjee and Massie, 2007). The latter condition is less recognised and although can demonstrate similar clinical findings on examination has been neglected in the research literature. Therapies to treat systolic heart failure are well researched, but the optimum management of diastolic heart failure is much less well known (Chatterjee and Massie, 2007). Most research trials for heart failure in general incorporate measures of severity for systolic failure, resulting in exclusion of diastolic patients. For the purposes of accuracy in this thesis therefore, and given these differences, the term "heart failure" will relate to chronic heart failure (CHF) occurring due to systolic dysfunction.

3.3 Incidence and prevalence of heart failure

The incidence and prevalence of heart failure is increasing with the average age of the population and greater survival after acute coronary events (Department of Health, 2000, Kannel, 2000, Thomas and Rich, 2007). It represents a significant cause of morbidity and mortality. In 2002, it was considered that up to 900,000 people had a diagnosis of HF in the UK (Petersen *et al.*, 2002). It is the most common cause of death in hospitalised patients and was found to be the most common cause of all hospital re-admissions in a

small Scottish study (McMurray *et al.*, 1993). Given this significant burden, in recent years there has been great interest in the management of heart failure. The emergence of specific drug treatments such as ACE inhibitors and Angiotensin receptor antagonists and the re-emergence of Beta-blocker therapy in the management of this condition have lead to an improvement in the underlying disease process by slowing the rate of development of more severe symptoms (Satwani *et al.*, 2004, Davies, 2006). However, this will inevitably result in higher numbers of patients living through heart failure, often with significant symptoms causing detriment to their quality of life. Indeed, the predicted burden of heart failure demonstrates notable suggested increases in the prevalence of heart failure, in hospital admissions and GP consultations from extrapolation from previous epidemiological data (Stewart *et al.*, 2003). These patients will still experience troublesome symptoms due to their disease, but it is feasible that they will have a longer period with these symptoms than prior to the introduction of the standard therapy we use today. Hence it is likely that there is an increasing prevalence of patients with CHF and in turn an increased number of symptomatic patients living through their disease. This makes the focus on symptom control for these patients more important.

3.4 Pathophysiology

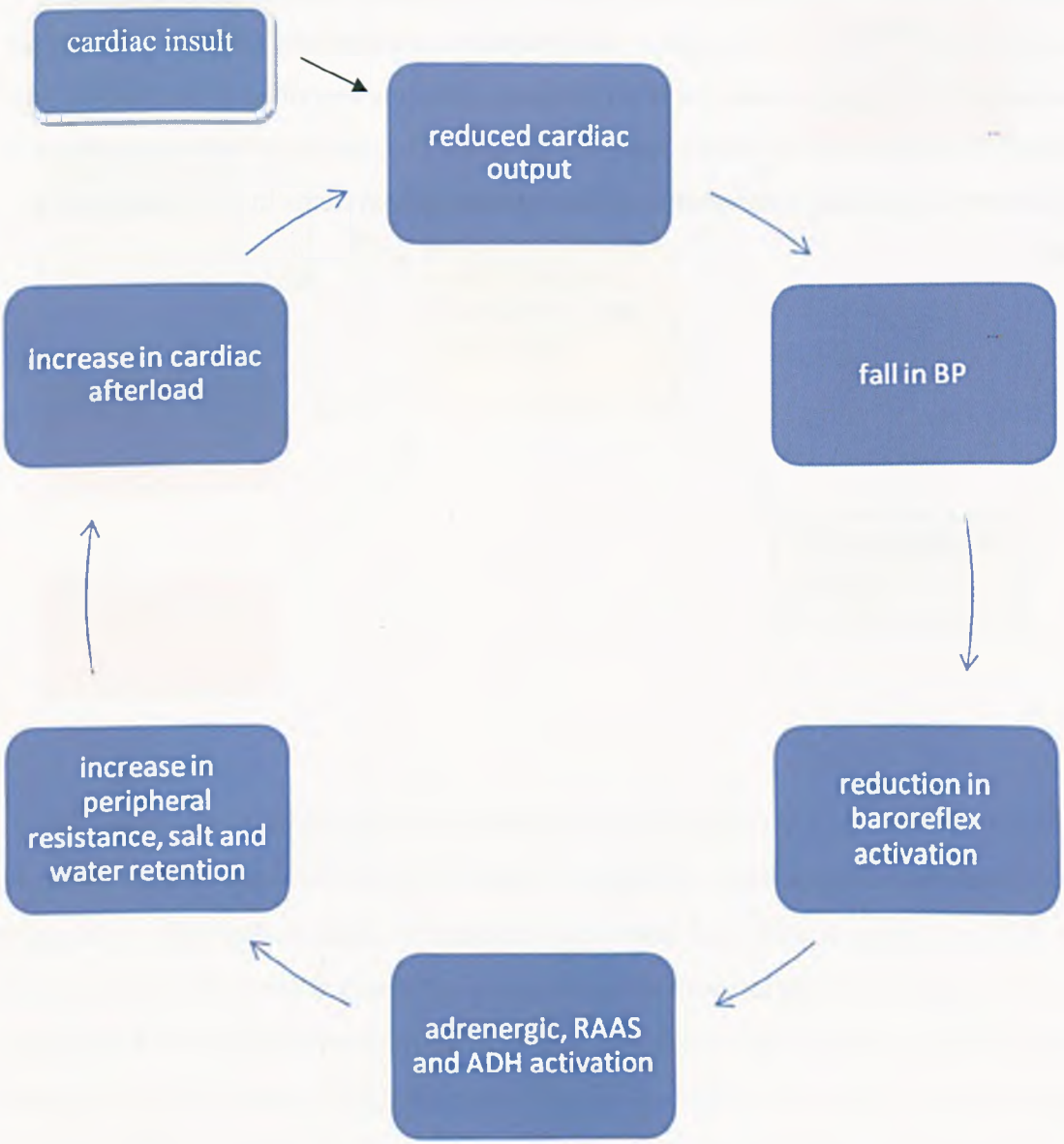
The pathophysiology of heart failure is well researched elsewhere in the literature (See Section 2, Heart failure: a companion to Braunwald's heart disease, Ed. Mann D.L. 2004 for a review). Various systemic changes occur in heart failure following an initial cardiac insult, resulting in cardiac dysfunction. Cardiac dysfunction leads to a reduced cardiac output, with further cardiac insults resulting in greater cardiac dysfunction. Reductions in cardiac output result in the activation of compensatory mechanisms that exist to preserve oxygen delivery to vital organs through haemodynamic changes (Roig, 2006). These changes in CHF include the chronic activation of the neuroendocrine system, producing a number of circulating factors that include opioids (Fontana *et al.*, 1993, Francis *et al.*, 1985, Francis, 1990) and results in activation of the sympathetic nervous system, peripheral vasoconstriction and salt and water retention (Roig, 2006, Francis *et al.*, 1985). This neurohumoral or neurohormonal activation is one important theory and mechanism to explain the events that occur in CHF (Katz, 2004, Watson *et al.*, 2006, Roig, 2006, Packer, 1988). Some of these neurohormones and their effect in CHF are much better researched than others. The effect of these naturally occurring (endogenous) opioids in CHF is under-researched compared to some of these other circulating factors.

It is important to note that most of the neurohormones accepted to play a role in the progression of heart failure are required for the normal homeostasis of the human body. For example, norepinephine (noradrenaline) is required to increase adrenergic drive in response to exercise, traumatic injury or a variety of other stresses that require an increase in cardiac output (Port *et al.*, 2004). However, this release is relatively transient in normal circumstances but becomes detrimental if its activation is prolonged.

In normal circumstances, baroreceptors in the heart and great vessels regulate blood flow to the vital organs by inhibiting both the sympathetic nervous system and Anti-diuretic hormone (ADH) via impulses sent to the cardiovascular centres in the brain. Whenever blood flow is compromised however, as following a cardiac insult, these baroreceptors monitor the subsequent fall in cardiac output and reduce the number of inhibitory signals sent to the brainstem. This results in activation of the sympathetic nervous system leading to increased blood flow and retention of fluid via stimulation of RAAS and ADH to maintain blood volume (Packer, 1988).

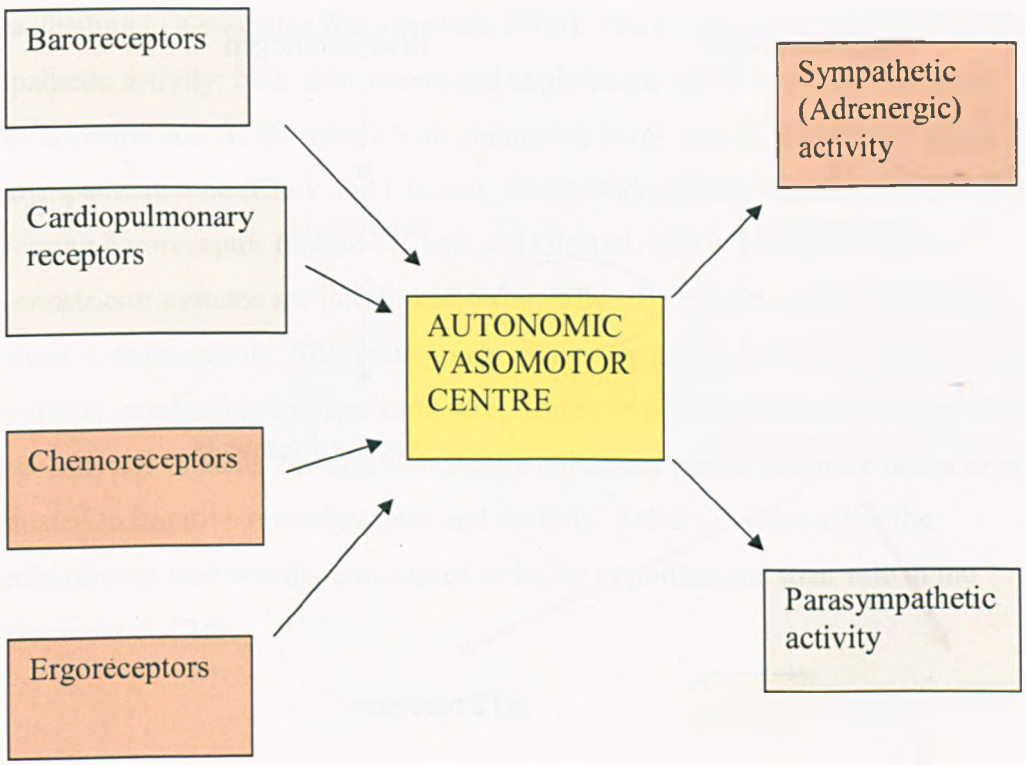
Patients with CHF have markedly reduced baroreceptor activity (Hirsch *et al.*, 1987), resulting in a reduced number of inhibitory signals and ultimately an overactivity of these vasoconstrictor systems (Clark and Cleland, 2000, Watson *et al.*, 2006, Ferguson *et al.*, 1984). Various chemical factors - "neurohormones" - are implicated in the correct functioning of these vasoconstrictor systems, with norepinephrine and adrenaline involved in the functioning of the sympathetic nervous system and ADH, Angiotensin, Aldosterone and Renin involved in the Renin-Angiotensin-Aldosterone (RAAS) vasoconstrictor system. In general, these factors are released to maintain the systemic circulation in response to cardiac dysfunction. This is considered beneficial in the short term, but is increasingly seen as detrimental in the longer term (Benedict *et al.*, 1993, Mann *et al.*, 1992, Roig, 2006, Clark and Cleland, 2000). In CHF the chronic activation of the sympathetic nervous system increases vascular resistance and has a positively inotropic effect, ultimately increasing workload and afterload for the struggling heart in chronic heart failure. This in turn reduces cardiac output, leading to further sympathetic activation and so on (van den Brink *et al.*, 2003) as demonstrated in Figure 1.3.1 below.

Figure 1.3.1: Cycle of involved mechanisms following a cardiac insult that reduces cardiac output. Reduced cardiac output leads to a subsequent fall in blood pressure, resulting in a lowering of the basal output from arterial baroreceptors. This in turn results in an attenuation of the inhibition of the sympathetic nervous system, causing amongst other effects an activation of RAAS, an increase in peripheral resistance and subsequent increase in blood pressure. This therefore seeks to increase the afterload to the heart. Ongoing cardiac insults, as in CHF, results in a continuation of this cycle, which is ultimately results in the ongoing activation of the sympathetic NS and further cardiac insults. (Adapted from Cleland and Clark 2000 and Francis *et al* 1985).



In addition to arterial baroreceptors, mechanical receptors (ergoreceptors in skeletal muscle) and chemoreceptors are all considered responsible for maintaining sympathetic activity in heart failure (Watson *et al.*, 2006). Chemoreceptors monitor levels of blood gases in the circulation and are thought to influence respiratory function by altering respiration according to serum levels of oxygen and carbon dioxide (Duffin and McAvoy, 1988). Hypoxia leads to an activation of these receptors and subsequent relay of this information to the NTS in the brain, which in turn can activate the sympathetic nervous system (Madden and Morrison, 2005). Baroreflex stimulation normally reduces the effect of chemoreceptor (chemoreflex) activation and vice versa (Somers *et al.*, 1991), so in human CHF where baroreflex activity is reduced, chemoreceptor activity is enhanced (Heistad *et al.*, 1974). In addition, peripheral chemoreceptors in the lung adjacent to alveolar capillaries have an input into the central autonomic centres in the brain (Holaday, 1983). These reflexes and receptors are potentially important as they are also implicated in mechanisms for breathlessness, which is described in more detail later. Figure 1.3.2 illustrates the relative inputs to the autonomic centre in the brainstem and outputs to the opposing sympathetic and parasympathetic systems in both health and in CHF.

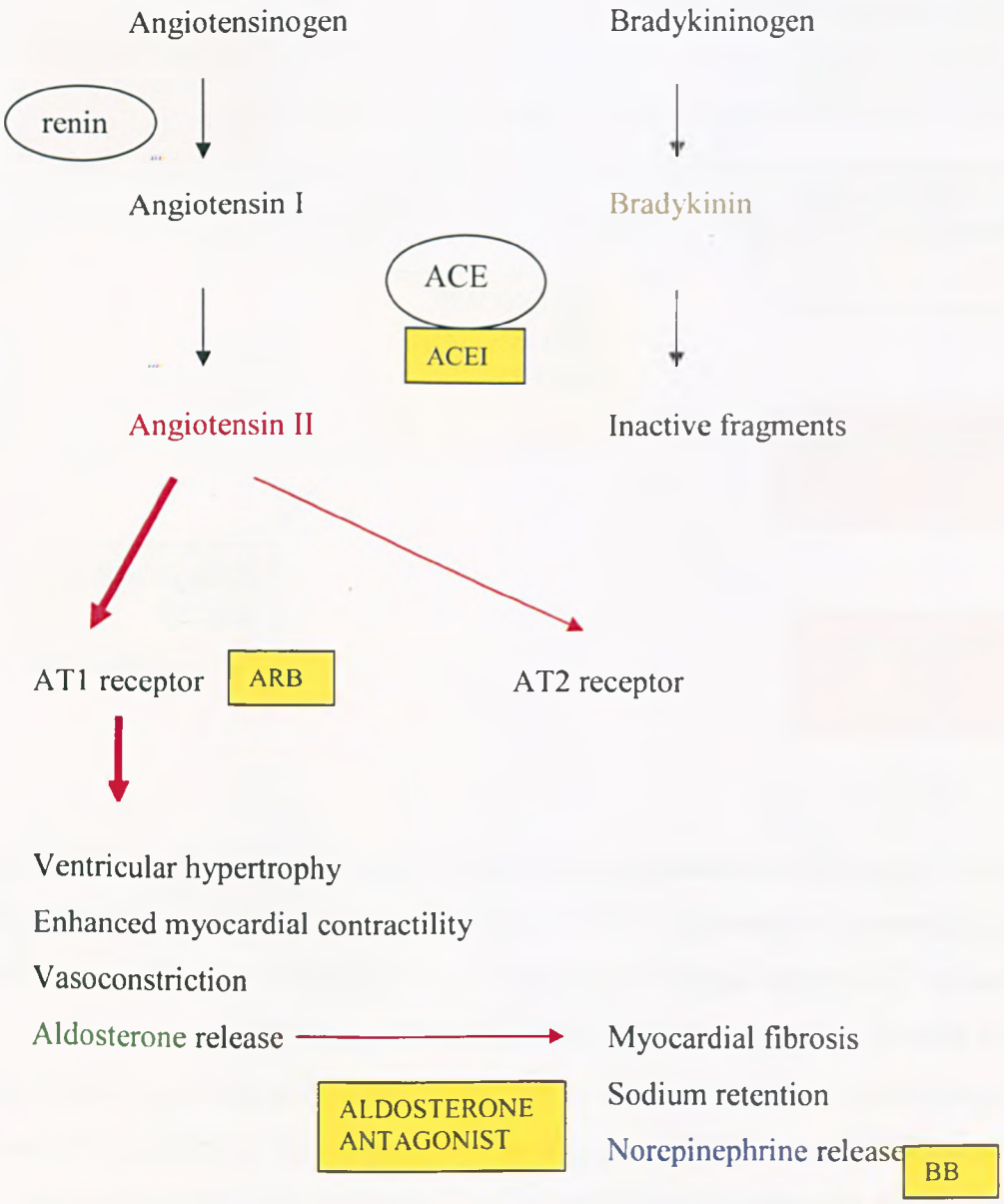
Figure 1.3.2: The relative balance of inputs to the vasomotor centre in the brainstem and subsequent outputs through the sympathetic and parasympathetic systems to regulate cardiovascular function. In health, there is a relative balance of baroreceptor and cardiopulmonary receptor input greater than chemoreceptors and ergoreceptors to the vasomotor centre, leading to a relative output from the centre favouring the parasympathetic system over the sympathetic. In CHF, the opposite is true, with a greater emphasis on the inputs from chemo- and ergo-receptors leading to enhanced sympathetic activity (i.e. a relative change in balance to favour sympathetic activation over parasympathetic) – adapted from Clark & Cleland 2000



The Renin-Angiotensin-Aldosterone-System (RAAS) has also been implicated as one of the major systems contributing to CHF and has been the target of much pharmaceutical intervention. This system again is important for normal homeostatic regulation of blood pressure and salt and water retention, but becomes detrimental if its activation is prolonged following the development of decreased cardiac output after an initial cardiac insult as in CHF (Camm, 1998). Angiotensin II is a potent vasocontrictor and its presence activates further cascades of downstream effects including remodelling of the heart musculature and production of other peptides important in CHF such as Aldosterone.

Figure 1.3.3 demonstrates the importance of the RAAS system and also the site of action of some drugs used in CHF described in section 2.7.

Figure 1.3.3: To illustrate the major neurohormones involved in the progression of CHF. Renin in the kidney converts angiotensinogen to angiotensin I; ACE converts Angiotensin I to ATII and de-activates bradykinin in the lung. ACEI act at the level of ACE, ARBs act on the AT1 receptor, Spironolactone inhibits Aldosterone effects, betablockers (BB) antagonise the actions of norepinephrine. Key neurohormones and their relationship to each other are shown in colours. Aldosterone production has a negative feedback effect on renin activity.



As previously stated, sustained over-activation of the sympathetic nervous system and RAAS is detrimental. For example the SOLVD and CONSENSUS multicentre RCT studies in CHF revealed that patients with more severe CHF exhibited higher levels of norepinephrine and angiotensin II. Subsequently patients with CHF were more likely to die during follow-up if they had higher circulating levels of norepinephrine, angiotensin II and aldosterone, adding weight to the argument that neurohormonal control in CHF was important for prognosis (Francis *et al.*, 1990, Eriksson *et al.*, 1994). In addition, data from the Val-HeFT trial also demonstrated that CHF patients with lower norepinephrine concentrations and lower levels of RAAS activation had a lower mortality (Latini *et al.*, 2004). It is suggested that both the sympathetic nervous system and RAAS are chronically activated in CHF and that RAAS can increase sympathetic activity and vice versa, leading to a cascade (Watson *et al.*, 2006). The RAAS system has direct effects on sympathetic activity; both aldosterone and angiotensin II potentiate the effects of norepinephrine and ACEI reduce both circulating levels of norepinephrine and increases parasympathetic tone (Clark and Cleland, 2000). Aldosterone also has a direct effect on depressing baroreceptor function (Clark and Cleland, 2000). Hence these two vasoconstrictor systems are interlinked through the effects of the neurohormones involved in their activity. This is demonstrated in Figure 1.3.4 which attempts to show the cyclical interlinking of these important factors in CHF. Chronic activation of these vasoconstrictor systems through neurohormonal de-activation therefore needs to be attenuated to improve mortality rates and severity. Table 1.3.1 describes the neurohormones traditionally considered as being important and their role in the development of CHF.

Figure 1.3.4: Diagram of the chronic activation of the sympathetic nervous system through potentiation of norepinephrine from the key events and systems involved in CHF. The red line demonstrates the interlinking of RAAS and the sympathetic nervous systems. Otherwise the colour scheme is designed to link to the other figures in section 3.

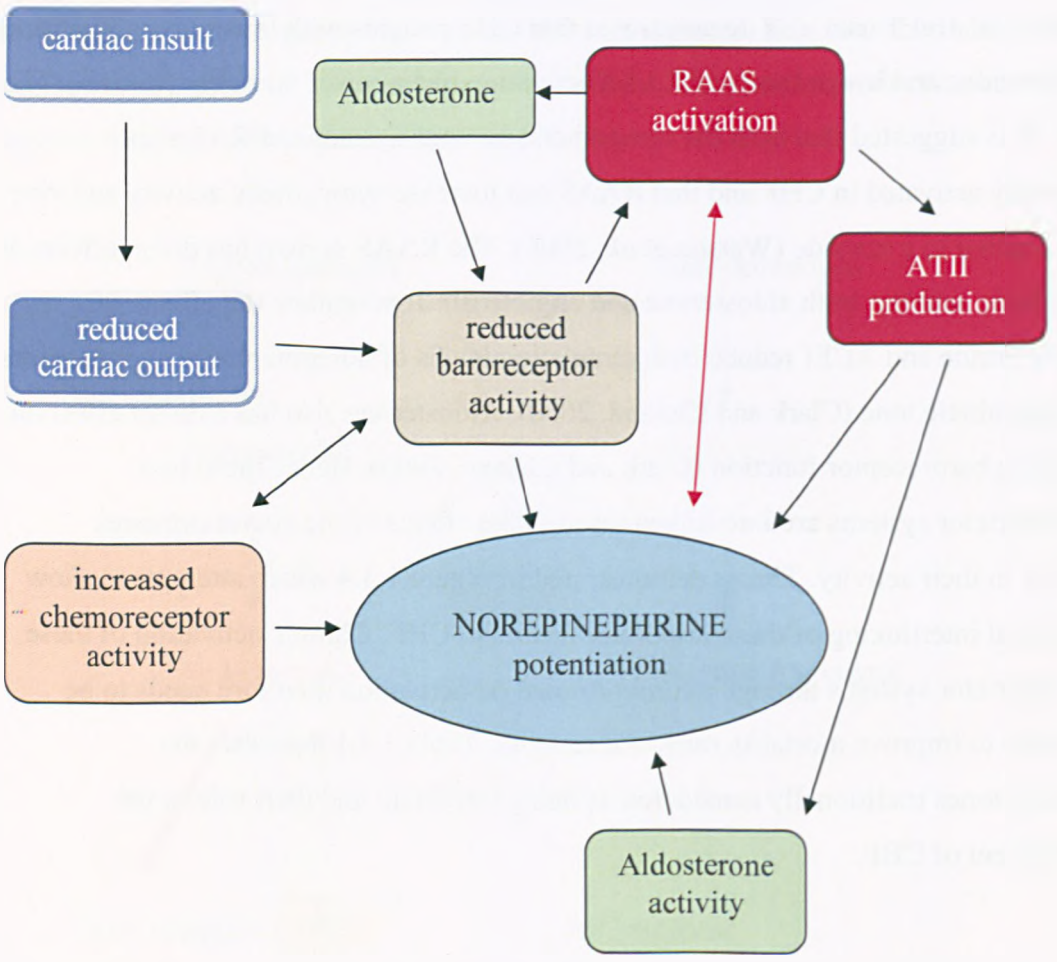


Table 1.3.1: Summary of Neurohormones traditionally considered in heart failure {Adapted from (Swanton, 2003, Watson *et al.*, 2006, Benedict *et al.*, 1993, Mann, 2004b)}

Neurohormone	Level in CHF	Role / Potential effect
Norepinephrine	Elevated in relation to severity of CHF	Implicated in enhanced sympathetic overdrive to maintain cardiac output but cardiotoxic if exposure prolonged (mediated via cAMP increases in intracellular calcium) leading to further cardiac muscle dysfunction. Vasoconstriction, activation of RAAS, sodium reabsorption increased
Natriuretic factors (ANP, BNP)	Elevated in relation to severity of CHF	Natriuretic and diuretic (reducing salt and water retention), reduces rate of cardiac remodelling, inhibits Renin Angiotensin Aldosterone system, Aldosterone and Vasopressin (ADH) release
Endothelin	Increased in plasma in relation to severity of CHF	Upregulated receptors may have role in cardiac fibrosis and circulating endothelin causes vasoconstriction
Angiotensin II	Released in response to failing cardiac output	Involved in remodelling of myocardium through fibrosis and hypertrophy; salt and water retention; peripheral vasoconstriction; activation of norepinephrine and aldosterone release
Aldosterone	Cardiac release increased	Promotes sodium retention, leading to fluid retention. Also implicated in remodelling of cardiac muscle, scar formation & enhancing norepinephrine

Not all neurohormones released in heart failure are considered detrimental and it is considered that some are released (e.g. natriuretic peptides, bradykinin) in order to balance or counter over-stimulation of the more detrimental types (e.g. norepinephrine) (Roig, 2006, Packer, 1988). Natriuretic peptides released in CHF, for example,

antagonise the actions of RAAS as shown in Table 1.3.1. Hence certain neurohormones may actually be cardioprotective rather than detrimental to the failing myocardium, and circulating levels of these hormones are not necessarily indicative of causing myocardial damage per se themselves. Alternatively, some of these neurohormones may simply reflect the process of CHF and the level of neurohormonal activation; higher levels of natriuretic peptides for example having a worse prognosis than those without (Latini *et al.*, 2004, Balion *et al.*, 2006). Unfortunately in CHF, the balance of these neurohormones tends to favour those ultimately resulting in a maladaptive process and further progression of CHF. It is therefore not so simple to suggest that all neurohormones have a detrimental effect in CHF and it is possible or feasible that opioids released in CHF may have a potentially cardioprotective effect. This possibility is explored further in Chapter 2.

Other changes can also occur in heart failure, such as cardiac muscle remodelling, arrhythmias, metabolic disturbances and impaired end-organ function (Cleland, 2004) but discussion of these complex events is beyond the scope of this thesis. Suffice to say that neurohormonal activation is one unifying theory that results in many of these changes in heart failure and is therefore considered extremely important to regulate. Current treatments for CHF are generally targeted towards reversing the processes that are seen to occur in CHF, particularly neurohormonal changes. Further limitation of any detrimental neurohormonal activation is considered to be beneficial, particularly as many current drug interventions indirectly attempt to further reduce sympathetic overdrive (Davila *et al.*, 2005) or vasoconstrictor activation and remain the target for future heart failure therapies (Massie and Shah, 1995). Although opioids have been identified as part of this overall neurohormonal activation, therapy has been limited to acute heart failure and end-stage chronic heart failure without a good clinical evidence base.

3.5 Clinical syndrome of heart failure

Heart failure can be classified using the New York Heart Association (NYHA) grading system which assesses the functional status of the patient. This is a measure of how limited the patient is by typically the most predominant symptom, namely breathlessness. Other symptoms of heart failure can include oedema, fatigue, cough, anorexia, cachexia and other systemic symptoms (Johnson and Gibbs, 2006). This observation of a systemic disease impacting on the overall physiology of the patient has led researchers to further

investigate the variety of neurohumoral substances that are produced during heart failure, as described above. For a review of the clinical signs and symptoms, please refer to Mann (2004b).

Recently the Heart Failure Association of the European Society of Cardiology produced a position statement for the involvement of palliative care in heart failure (Jaarsma *et al.*, 2009). They detail key areas for improvement or integration, including delivery of care, education, health policy and notably the need for research. A relative gap exists in the evidence base for the clinical use of interventions that control disease progression and those that actually target the symptoms produced rather than the pathological processes. The management of breathlessness in particular and the current hypotheses as to the mechanisms involving in the development of breathlessness are detailed in Chapter 3.

3.6 Diagnosis and prognosis

The diagnosis of CHF is based on a history of the spectrum of symptoms described above, clinical signs and investigations to confirm the diagnosis. The investigations included in the standard diagnosis for CHF are described below. Again, this is not a comprehensive review but designed to provide a brief background for reference later for the RCT (Chapter 4). Ongoing review of signs and symptoms are required to determine disease progression and to review any potentially reversible factors. The New York Heart Association classification (Table 1.3.2) is a commonly used measure involving categories of functional status. These categories are important as they not only describe the patient's status but are also a useful prognostic tool. The major problem with the classification is that it is subjective, but when used correctly as part as a generalised assessment it can be useful to monitor general improvement or deterioration (Francis and Tang, 2004a).

Table 1.3.2: The NYHA classification of CHF

Functional Class	Functional capacity
I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or angina pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or angina pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure may be present at rest. If any physical activity is undertaken, discomfort is increased.

In accordance with Department of Health Guidelines (DoH 2000), required investigations for CHF include:

- 12 Lead ECG
- Echocardiogram
- Other investigations to add weight to the clinical symptoms and signs or to exclude other causes of breathlessness (for example; Chest x-ray, B-type natriuretic peptide (BNP), Haemoglobin concentration, renal function, weight)

The ECG is a useful tool to assess the underlying rate and rhythm of the heart. Arrhythmias may be indicative of the cause of heart failure, or may represent one of the consequences of heart failure. The presence of arrhythmias can represent another marker of disease severity and may be a potential source of additional treatment that may benefit the patient other than standard anti-heart failure therapy alone. Heart rate variability and analysis of the ventricular complexes may provide further clues towards the aetiology of heart failure or can act as prognostic markers (Stevenson, 2004). A more detailed review of the potential changes in heart failure can be found in Mann (2004b).

Echocardiography is used to confirm the diagnosis of heart failure from the clinical findings elicited from the history and examination of the patient. It allows the structure and function of the heart to be assessed. It is useful to determine the nature of heart failure (e.g. systolic or diastolic) and aetiology of the disease (e.g valvular abnormalities, cardiomyopathy or ischaemic heart disease). Part of the examination includes an assessment of the left ventricular ejection fraction (EF). This is an estimate of the ratio of stroke volume to end-diastolic volume, which can vary from day to day in the same patient and has a degree of inter-operator variability (Francis and Tang, 2004a). Absolute numerical values of the ejection fraction are therefore not wholly reliable due to this variation in assessment. However, it does provide as estimate of the degree of systolic dysfunction (LVSD) which has an inverse relationship with ejection fraction (i.e. the lower the ejection fraction the greater the degree of systolic dysfunction) (Francis and Tang, 2004a). Magnetic resonance imaging is considered to provide a more reliable estimate of ejection fraction, though echocardiography will remain in routine practice due to its ease of use and ease of availability.

In addition, diagnostic tests to allow more rapid identification of heart failure in patients attending with breathlessness have been devised. Given the aetiology of heart failure, many patients will have co-existing diagnoses contributing to breathlessness. For example, a heavy smoker may have heart failure, ischaemic heart disease, chronic obstructive pulmonary disease or even lung cancer that may result in breathlessness. One such diagnostic test involves measurement of plasma b-type natriuretic peptide (BNP) levels. BNP is a protein released by the cardiac ventricles as a result of myocardial stress (Ambrosino and Serradori, 2006). It is stored as a larger peptide (pro-BNP) and is released following enzymatic cleavage to N-terminal pro-BNP (NT-proBNP), which is inactive, and BNP (the active product) (Francis and Tang, 2004b). Measurement of BNP typically involves the evaluation of NT-proBNP as a surrogate measure for BNP (Clerico *et al.*, 2007) and in this respect the terms NT-proBNP and BNP are used interchangeably. BNP measurement is useful in two ways. Firstly, it has a negative predictive value whereby normal levels are predictive of the absence of heart disease (Maisel *et al.*, 2008). A level above 50pg/ml is considered indicative of CHF (Swanton, 2003) which can aid diagnosis. Secondly, patients with more severe heart failure tend to have higher concentrations of circulating BNP (Ambrosino and Serradori, 2006). BNP and NT-proBNP are also independent predictors of mortality in CHF (Balion *et al.*, 2006). Monitoring of BNP levels is not yet routine in the UK, but this may change in

forthcoming years and it is recommended in Royal College of Physicians Guidelines for CHF (NICE guideline number 5 2003).

3.7 Current pharmacological management of CHF

The Department of Health (2000) developed guidelines for the management of CHF as part of their National Service Framework for care. These guidelines were produced in the light of large multicentre randomised controlled trials, often in thousands of patients. As documented previously, targets for drug therapy have been those detrimental neurohormones chronically released following a cardiac insult. Recommendations for the treatment of CHF included use of Angiotensin Converting Enzyme Inhibitors (ACEIs) as the first line treatment. Clinical trials and experience demonstrate that these drugs prolong life, delay progression of CHF and can improve symptoms. These drugs are often titrated in dose in combination with Beta blockers, which have been shown to reduce mortality in combination with ACEIs. Previously beta blockers had been considered potentially detrimental (Cleland *et al.*, 1998) and are still normally prescribed in patients with stable heart failure symptoms only. With co-prescription of diuretics, this combination of three drug classes forms the mainstay of therapy for most CHF patients. As their condition becomes more advanced, aldosterone antagonists have been shown to reduce mortality in patients on existing standard therapy (RALES study investigators, 1996, Pitt *et al.*, 2003) and digoxin withdrawal in CHF is recognised to increase hospital admissions and worsen symptoms, suggesting a symptom benefit with digoxin in CHF (Packer *et al.*, 1993). These drugs are therefore added in to the pharmaceutical regimen in selected patients. Other drugs involved in the prolongation of natriuretic peptide activity (Packer *et al.*, 2002) and reduction of other potentially detrimental neurohormones such as endothelin are undergoing clinical trials (Packer *et al.*, 2005).

Since the Department of Health guidelines in 2000, Angiotensin receptor blockers (ARBs) have emerged as an alternative to ACEI in intolerant patients and Aldosterone antagonists have been evaluated for symptomatic CHF in European and American guidelines for CHF management (Swedberg *et al.*, 2005, McMurray and Swedberg, 2006). Table 1.3.3 summarises the common drugs used in CHF. The site of action of these drugs can be seen in Figure 1.3.3 shown earlier.

It can be seen that effective drug management has targeted the relative reduction in effect of the neurohormones secreted in CHF. As opioids are part of the neurohormonal picture, enhancing the effect of these substances may be seen to contradict the conventional wisdom of reducing the effect of the neurohormones secreted (for example ACEI reduce the formation of ATII, Beta-blockers reduce the effect of norepinephrine etc.). However, manipulation to enhance the effect of opioids does not set a precedent in terms of neurohormones. For example, prolongation of the effect of natriuretic factors is considered beneficial (Packer *et al.*, 2002) and therefore it is feasible to suggest that some neurohormones are best inhibited, and some (possibly opioids) are best stimulated.

Table 1.3.3: Pharmaceutical intervention strategies in CHF

Drug	Action	Benefit in CHF	RCT examples
ACEI	Inhibit Angiotensin Converting Enzyme (thus preventing formation of the potent vasoconstrictor ATII)	Mortality reduction Delay progression Symptom improvement	SOLVD 1991 CONSENSUS 1987
Beta blockers	Inhibit Sympathetic Overdrive associated with CHF	Mortality reduction in combination with ACEI	COPERNICUS 2001 CIBIS I 1994 CIBIS II 1999 MERIT-HF 1999
ARB	Inhibit effect of Angiotensin II by blocking the AT1 receptor	Comparable mortality and hospital admissions to ACEI	ELITE II 2000
Aldosterone antagonists	Prevents development of myocardial fibrosis, intravascular depletion and catecholamine and endothelin release (Mann chap 9) through aldosterone inhibition	Mortality reduction in combination with ACEI	RALES 1999 Pitt *et al* (2003)
Diuretics	Reduction of oedema & excess fluid	Improvement of acute symptoms with mortality reduction	Latta et al (1990), Allman and Norris (1990) – comparative studies only
Digoxin	Increases availability of calcium in cardiac muscle resulting in inotropic effect	Reduced hospital admissions with digoxin	DIG mortality trial 1997 RADIANCE 1993

Hence management of chronic heart failure is directed mainly towards prevention of further myocardial injury rather than treatment of specific symptoms. This is important for research as therapies targeted at slowing the rate of progression of CHF have dominated the literature in this area for the past few decades. Multi-centre randomised controlled trials involving thousands of patients advocate the use of the current standard treatment regimens. However, primary endpoints for these trials have concentrated on either rates of death or rates of hospitalisation. Quality of life and the patient experience whilst living through chronic heart failure has generally not been considered as part of these studies, except as secondary endpoints. The focus of these large trials was to demonstrate treatment efficacy and rates of hospitalisation and death due to chronic heart failure have fallen since the introduction of these therapies (Department of Health, 2000). More importantly, as a result of these trials, patients with CHF are living longer with their disease, leading to an expanding cohort of patients who are kept alive by their standard therapy (Thomas and Rich, 2007, Kannel, 2000, Stewart *et al.*, 2003).

Symptom control research therefore has been relatively neglected but given that many patients are living through the disease with symptoms that adversely affect their daily lives, research into improving symptoms provides a potential avenue for improving the quality of life of a great number of patients. Instead of looking from the perspective of the disease by trying to modify or slow progression of symptoms, relatively little is known about the management of problems like breathlessness once a patient has CHF sufficient to cause symptoms despite the use of preventative approaches. Hence a relative gap in our knowledge exists in the area of symptom palliation in CHF.

Non-pharmacological interventions for advancing heart failure are also available but are beyond the scope of this review. Please see McMurray and Swedberg (2006) for a review of the evidence for the above treatments. Various other drugs are being evaluated for symptomatic heart failure, including cardiac inotropes, but again discussion of this is beyond the scope of this thesis (see Oxberry & Johnson (2008) for review).

Although ACEIs may not only slow the progression of disease but also improve symptoms, relatively few of the drugs listed above are considered to directly improve symptoms in CHF. Most have been designed to prolong life or maintain the functional class of the patient, as mortality, NYHA class and rate of hospital admissions are most frequently the primary outcomes of the large multicentre cardiology RCTs in this area.

As noted previously, symptom management and quality of life are either secondary outcomes or not considered at all in the analysis (especially in the earlier RCTs). Evaluating treatments from the patient perspective of quality of life and symptom control has thus far often been a secondary priority. Hence, a potential knowledge gap exists for therapies that have the primary goal of symptom control. The general management of breathlessness in CHF from a symptom based perspective is discussed in the next section.

3.8 Key points

- Heart failure is a complex systemic disease process that can be subdivided into many types according to aetiology, timing or type of physical dysfunction
- Stable symptomatic CHF should be considered as a different disease to acute heart failure or acute-on-chronic heart failure due to different reasons for the development of symptoms including breathlessness
- The incidence and prevalence of chronic heart failure is increasing due to the ageing population, better survival after acute cardiac events and improved drug therapies
- Various systemic changes including the release of neurohormones occur in heart failure, most of which are considered detrimental and that may be potentially manipulated by drug therapy
- Neurohormonal activation has been targeted by effective drug therapies, most of which focus on reducing the impact of the neurohormone (such as for norepinephrine, angiotensin, aldosterone), but not exclusively (consider natriuretic hormones)
- Much of the current recent pharmaceutical research has focussed on the reduction of the speed of progression of the disease rather than symptom control
- Diagnosis and disease progression typically involves the measurement of ejection fraction on echocardiography alongside a suitable clinical history with BNP emerging as an adjunct to this process
- There is growing recognition that heart failure patients should have better palliation of their symptoms

- More patients are living through chronic heart failure with symptoms that at present are poorly palliated due in part to a lack of available evidence of the efficacy of symptomatic measures
- It could be said that the initial reluctance by medical practitioners to use opioid medications without information from an evidence base mirrors the initial counter-intuitive thoughts surrounding the use of beta-blockers in chronic heart failure. Despite previous misgivings, beta blocker therapy has now become accepted practice in chronic stable heart failure

Section 4) Breathlessness – a problematic symptom

4.1 Introduction

Breathlessness is a common symptom in many disease states and can become more problematic as the condition becomes more advanced. Daily episodes of breathlessness are reported in over half of chronic heart failure (CHF) patients taken from a representative community sample in the UK and this understandably impacts on their quality of life (Barnes *et al.*, 2006). Hence breathlessness represents a troublesome symptom for many patients with CHF, with the prevalence of this symptom likely to rise given the rising prevalence of this chronic disease.

The terms "dyspnoea" or "dyspnea" and breathlessness have been used interchangeably in the literature to date. The American Thoracic Society (ATS) has defined breathlessness as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioural responses" (American Thoracic Society, 1999). For the purpose of this thesis, breathlessness, shortness of breath and dyspnoea will be used interchangeably.

4.2 Measurement of breathlessness

Many physical indicators are utilised in clinical practice as surrogates for dyspnoea, but none are necessarily specific for the actual *sensation* of feeling short of breath. Measuring oxygen saturation, for example, simply informs the clinician of the level of oxygenation in the blood, and respiratory rate per minute can be influenced by a number of factors (hyperventilation due to anxiety, for example). Hence various subjective measurement tools have been developed in order to measure and monitor the sensation of breathlessness from the perspective of the patient.

These tools include Numerical Rating Scales (NRS), Visual Analogue Scales (VAS), Verbal Rating Scales (VRS) and the modified Borg scale for breathlessness. Recently the value of these scales has been evaluated from a clinical perspective. It is considered that a change of 10% in a VAS scale, or 1 point on the modified Borg score as being

clinically significant (Booth, 2006). It is also recommended, given the complexity and multi-factorial nature of breathlessness, that these scales should be used in combination with each other and with physical physiological measurements (Booth, 2006). Descriptors for breathlessness have also been formulated which reveal that patients with different diagnoses resulting in breathlessness describe different qualitative experiences for the feeling of dyspnoea. Wilcock *et al.* (2002) is one study that compares responses of the feeling or sensation of breathlessness between patients with differing primary diagnoses and suggests that patients with different aetiologies for their symptoms describe a different experience. For example, patients with a lung cancer mass describe the inability to get enough air, feeling out of breath and breathing that requires more effort as the most common responses. In contrast, CHF patients most commonly describe feeling out of breath, chest tightness and inability to get enough air. This suggests that the description of breathlessness differs from one disease to another, further complicating the method of evaluating the patient experience.

Given these observations, the development of dyspnoea is likely to be multi-factorial potentially involving the peripheral and central respiratory systems, cardiovascular system and other inputs from the periphery and higher cortical centres. In heart failure, a number of potential mechanisms have been proposed. Of course, given the more elderly nature of the heart failure population, patients often have co-existing respiratory disease, notably chronic obstructive airways disease, which can further complicate the nature and mode of breathlessness.

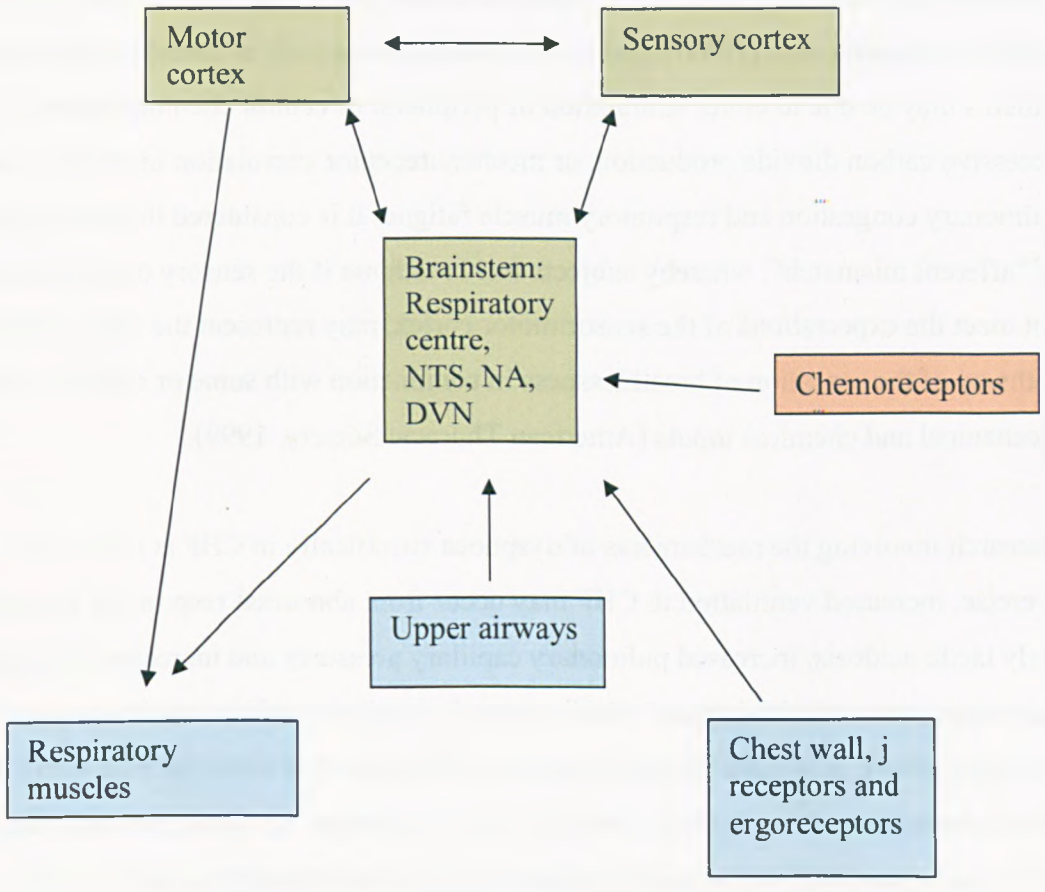
4.3 Respiratory homeostasis – control of breathing

In order to understand the potential mechanisms of breathlessness and possible management strategies to employ, one must first consider the mechanisms involved in normal function. Respiratory activity is co-ordinated by the respiratory centre in the brain. This centre receives inputs from both the periphery and centrally and modulates the control of breathing based on these inputs. It also exhibits an intrinsic rhythm to breathing, generated from within the brainstem, and exerts the necessary effects via neurons that innervate the respiratory muscles including the diaphragm (Florez and Hurle, 1993).

Regulation of respiratory function is derived primarily by the autonomic nervous system involving sympathetic and parasympathetic components (Mazzone and Canning, 2002). Peripheral and central chemoreceptors located in blood vessel walls deliver information regarding changes in circulating arterial gas concentrations and pH. Information is transmitted by the carotid (IX nerve) and aortic (X – vagus – nerve) nerves whose nerve afferents terminate in the nucleus tractus solitarius (NTS). This is the same autonomic centre responsible for cardiovascular homeostatic maintenance (Holaday, 1983) as discussed previously.

Autonomic effects are regulated by opposing pathways, the sympathetic and parasympathetic {the parasympathetic being the predominant regulator of function (Mazzone & Canning 2002)}. The major parasympathetic components in the brainstem linked to the NTS are the NA (nucleus ambiguous) and DVN (dorsal vagus nucleus). Sympathetic outflow is regulated through the NTS to the hypothalamus (Holaday, 1983). Information is also obtained by the respiratory centre from stretch receptors in the respiratory muscles and pulmonary mechanoreceptors located within the airways themselves. These mechanoreceptors include a subtype termed juxta-capillary ("j" receptors) which monitor chemical irritation in the airway mucosa. Again, information is carried from these sites by the vagus nerve to the NTS (Florez and Hurle, 1993). Figure 1.4.1 illustrates these points. Interestingly, many of these structures are important sites for location of opioid receptors as discussed in Chapter 2. In addition, an analogy of breathlessness with pain has been suggested, given that the areas involved in the sensory cortex are similar for pain and breathlessness in imaging studies in humans and that the neurophysiology for pain and breathlessness may therefore be similar (Lansing *et al.*, 2009). Opioids are powerful analgesics and it is interesting to hypothesise that they may also be involved in breathlessness management. A review of respiratory homeostasis can be found in Mazzone & Canning (2002) but it is interesting to speculate the potential role both centrally and peripherally of opioids in the regulation of breathing function. What is not known is whether opioid expression at these sites alters in breathless patients compared to normal controls.

Figure 1.4.1.: Respiratory function mediated by the autonomic nervous system {adapted from Manning & Schwarzstein (1995)}: Afferent information from peripheral structures (chest wall, j receptors, chemoreceptors and ergoreceptors) input into the respiratory centre in the brainstem using the sensory vagus nerve. Inputs from the sensory cortex also occur at this point. The respiratory centre instructs a respiratory response to this information via the motor cortex to the respiratory muscles. Arrows indicate the direction of flow of information. Areas shaded in green are located in the CNS, blue areas are located in the peripheral respiratory system.



4.4 Mechanisms of breathlessness in CHF

Many potential mechanisms of dyspnoea or the sensation of breathlessness at rest or on movement have been proposed. In general, due to the small scale nature of the studies performed thus far, conclusions as to the potential mechanisms of breathlessness have been extrapolated across basic science and animal models of dyspnoea as well

breathlessness induced in healthy human models. Studies involving breathlessness in chronic heart failure patients are rare.

A number of potential mechanisms for the formation of dyspnoea in general have been proposed but the pathophysiology of intractable breathlessness in disease remains poorly understood. These suggested mechanisms include the effect of hypoxia and hypercapnea via central and peripheral chemoreceptors; alterations in localised feedback from receptors in the lung to irritation, stretch and interstitial congestion in pulmonary capillaries; changes in vagal inputs supplying afferent information to the central nervous system; altered feedback from muscular chest wall and juxta-capillary mechanoreceptors (Manning and Schwartzstein, 1995, Chua and Coats, 1995, Thomas and von Gunten, 2002). Yokoyama *et al* (1994) hypothesise that dyspnoea seen in chronic heart failure patients may be due to either stimulation of peripheral or central chemoreceptors by excessive carbon dioxide production, or mechanoreceptor stimulation in the lung due to pulmonary congestion and respiratory muscle fatigue. It is considered that the hypothesis of "afferent mismatch", whereby subjects feel breathless if the sensory experience does not meet the expectations of the sensorimotor cortex, may represent the final common pathway of the sensation of breathlessness in conjunction with some or all of the other mechanical and chemical inputs (American Thoracic Society, 1999).

Research involving the mechanisms of dyspnoea specifically in CHF is scarce. On exercise, increased ventilation in CHF may occur from abnormal respiratory patterns, early lactic acidosis, increased pulmonary capillary pressures and increased physiological pulmonary areas of "dead space" (Sullivan *et al.*, 1988). In addition to those mechanisms described above, abnormal breathing patterns are observed in some patients with CHF. These abnormal patterns include Cheyne-Stokes respiration (cyclical rises and falls in ventilation associated with episodes of apnoea and concomitant hypoxaemia) and periodic breathing (rises and falls in ventilation without true periods of apnoea). Sometimes these patterns are present at rest or during sleep; some patients require exercise to demonstrate the phenomenon (Ribeiro, 2006). These abnormal breathing patterns are associated with poorer prognosis in CHF and increased sympathetic activity (Leung *et al.*, 2006, Leung *et al.*, 2003, Corrà *et al.*, 2006). Ponikowski and colleagues (Ponikowski *et al.*, 1999) studied 74 chronic stable heart failure patients to identify such patterns. They discovered over half of the patients had either Cheyne-Stokes or Periodic breathing episodes. These patients had more advanced symptoms, reduced baroreceptor

activity and increased chemosensitivity when compared to heart failure patients with normal breathing patterns, in keeping with sympathetic overactivation.

Sleep disordered breathing or sleep apnoea is also prevalent in patients with heart failure, through chronic enhanced activation of the sympathetic nervous system and is similarly associated with a worse prognosis (Ferreira *et al.*, 2006). Hence, sympathetic overdrive is considered to be a mechanism in the sensation of breathlessness in CHF in a number of different breathing patterns. The proposed mechanisms of breathlessness specific for CHF are detailed in Table 1.4.1.

Table 1.4.1: Potential mechanisms for breathlessness in CHF {from Chua and Coats (1995), Manning & Schwarzstein (1995), Ferreira et al (2006)}

Mechanism	**Proposed theory in CHF**
Ventilation abnormalities	Restrictive lung pattern secondary to loss of lung volume due to cardiomegaly and stiffening of lung parenchyma due to fluid retention. Reduced effective diffusion due to ventilation : perfusion mismatch.
Pulmonary function abnormalities	Reduced transfer factor in CHF resulting in reduced lung compliance, alveolar oedema resulting in reduced gas exchange and bronchial hyper-responsiveness due to interstitial oedema leading to airway narrowing.
Pulmonary haemodynamics	Elevation of pulmonary vessel pressures leading to fluid accumulation and eventual fibrosis of small vessels, resulting in reduced microvascular permeability.
Chemoreceptors	Increased sensitivity of arterial peripheral and central chemoreceptors to hypoxia and CO_2 in CHF.
Mechanoreceptors	Heightened response of j-receptors in the lung to stretch and irritants secondary to pulmonary oedema resulting in an increased stimulus for ventilation in CHF. Upper airway and facial mechanoreceptors may be responsible for the improvement seen with moving air across the face.
Ergoreceptors in skeletal muscle	Enhanced sensitivity of these mechano/metabo-receptors allowing increased ventilation at lower levels of muscular exercise, perceived as dyspnoea.
Muscle function	Decreased diaphragmatic and accessory muscle function due to histochemical and metabolic changes as a result of CHF with subsequent muscular weakness and reduced endurance.
Periodic / Sleep disordered breathing patterns	Heightened respiratory drive during exercise probably related to the sympathetic overdrive seen in CHF and resulting in the sensation of feeling out of breath.
Cortex-afferent "mismatch"	Neuromechanical dissociation between mechanical effort and the mechanical response of the respiratory system, leading to sensations of unsatisfied respiratory effort. Considered to be the final common pathway of breathlessness.

Given the nature of these proposed mechanisms, it is clear that the sensation of breathlessness is a complex and multi-factorial symptom. Interventions should not therefore be attempted in isolation and should form part of a multi-faceted approach. It is unlikely therefore that significant breathlessness will be totally abolished by one therapy alone.

4.5 Management of breathlessness

In the absence of any potentially reversible cause, acute episodes of breathlessness in heart failure are treated with a combination of both pharmacological and non-pharmacological treatments (Johnson, 2007, Millane *et al.*, 2000). The majority of these interventions are provided without any substantial evidence base to recommend their use (Oxberry and Lawrie, 2009). In addition, there are few other drugs that are used or in the process of development to help alleviate this distressing symptom. Hence, palliative care guidelines for management of intractable breathlessness tend to generalise for all disease aetiologies, as so little evidence exists for symptom management in specific disease categories. The experiences of treatments for breathlessness in one disease tend therefore to be extrapolated to all diseases involving breathlessness. In general, these guidelines are also employed for breathlessness secondary to other diseases such as COPD or lung cancer.

The relief of intractable breathlessness requires a multi-modal approach, given that the mechanisms for breathlessness are multi-factorial. Correct positioning of the patient, explanation of the proposed management strategy to reduce anxiety, breathing retraining techniques and the use of a hand-held fan to deliver air across the face have been suggested for all patients (please see Bausewein *et al* (2008) for review). Pharmaceutical strategies are employed in addition to these simple measures, dependent on the nature of the breathlessness, aims of treatment and stage of advancement of the disease.

The first pharmaceutical management strategy to mention is the use of oxygen. A trial of oxygen therapy is suggested if the patient is hypoxic or if it is considered by the clinician to be beneficial (particularly if the patient is anxious) (Abernethy *et al.*, 2005). Correction of hypoxia alone however may not result in relief of dyspnoea, and non-hypoxic patients may still find a symptom benefit from oxygen therapy (Thomas and von Gunten, 2003). Only very small, poor quality trials of oxygen therapy for dyspnoea exis

in CHF (Booth *et al.*, 2004) and there is a suggestion that use of oxygen is no different to the use of air via a face mask (Davis, 1999). It is now considered that the continuous movement of cool air over the sensory distribution of the 2nd and 3rd branches of the trigeminal nerve of the face is beneficial due to the stimulation of mechanoreceptors (Booth *et al.*, 2008) and that some of the improvement seen due to oxygen therapy is secondary to this mechanism. Hence, simple therapy with a hand-held fan may provide relief in some patients. In addition, most patients with CHF are not hypoxic yet remain breathless (Munger *et al.*, 1994).

Opioids are used for breathless patients with advanced disease and the evidence for this use in CHF is detailed in Chapter 3. Traditionally, opioids have been thought to reduce respiratory drive to hypercapnea and hypoxia and hence are considered to be useful in the management of dyspnoea through the reduction of respiratory effort (Poole *et al.*, 1998). They provide the mainstay of pharmaceutical therapy for breathlessness in terminal illness (Oxberry and Lawrie, 2009). A Cochrane review by Jennings *et al* (2001) demonstrated a small but statistically significant symptom improvement with opioids given by either the oral or parenteral route in a total of nine trials in patients with dyspnoea from various aetiologies. No differences were noted between oral and parenteral routes in the meta-analysis and the studies were too small to recommend one opioid over another. Since that review, Abernethy *et al* (2003) performed an adequately powered placebo controlled RCT of sustained release oral morphine (MST) in patients with intractable breathlessness. The majority of the 48 patients involved had a diagnosis of COPD. Thirty eight patients completed the study, again with a small but statistically significant improvement of breathlessness with MST 20mg daily. This dose is equivalent to 5mg Oramorph liquid taken 4 times a day (Twycross *et al.*, 2002). Further analysis of this data suggested that the four patients with a diagnosis of coronary disease, including CHF, had a better response than those without coronary disease (Currow *et al.*, 2007). This secondary paper is discussed in further detail in Chapter 3. Opioids have also been shown to increase exercise capacity in patients with COPD in a small pilot study (Light *et al.*, 1989). In addition to a potential role in breathlessness, patients with a chronic cough have also shown a symptom benefit with morphine in a small pilot study (Morice *et al.*, 2007). The Scottish SIGN guidelines already recommend opioids for the treatment of breathlessness in CHF without an evidence base in support of this (SIGN, 2007).

Benzodiazepines are the other major pharmacological group used for intractable breathlessness. Again, only a small evidence base exists for their use and results are

extrapolated across all breathless aetiologies due to the paucity of research. It appears that they should be used as an adjunct to other therapies for breathlessness in patients where anxiety may be a component (Thomas and von Gunten, 2003). There are no studies for the relief of breathlessness specifically in CHF involving benzodiazepines. Other interventions include heliox (Ahmedzai *et al.*, 2004) and nebulised furosemide (Stone *et al.*, 1994, Shimoyama and Shimoyama, 2002, Kohara *et al.*, 2003) but these therapies are significantly under-researched and are used on the basis of clinical recommendation rather than from a substantial evidence base.

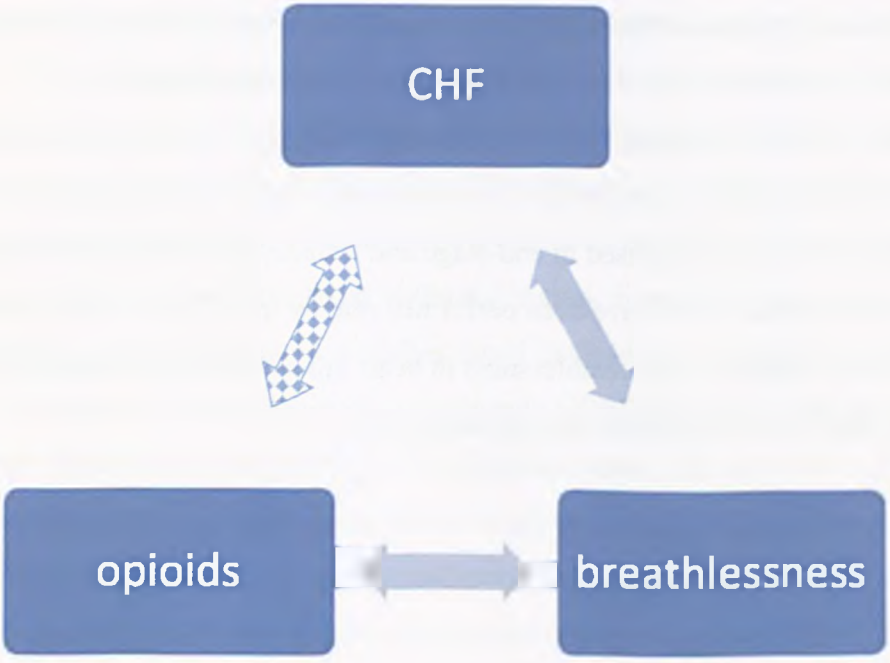
4.6 Key points

- Breathlessness is a common symptom in heart failure patients
- Surrogate markers are often used to describe breathlessness which is a sensation that is difficult to measure with standard physical methods
- The description of breathlessness in heart failure is under-reported
- The generation of breathlessness is likely to be multifactorial, with an alteration in the sensation of the expected level of respiration required compared to the actual feedback from respiration (cortex-afferent mismatch) possibly representing the final common pathway
- The autonomic centre in the brainstem is responsible for receiving inputs from the respiratory system and modulating the respiratory response. The autonomic centre is also involved in cardiovascular regulation as described earlier
- Few treatments currently exist for managing intractable breathlessness and results from small efficacy trials tend to be extrapolated across all disease groups
- Opioids are already utilised in end-stage and intractable breathlessness. The few small RCTs that exist have been performed mainly in COPD or lung cancer
- Current treatments for breathlessness in heart failure are under-researched and are provided from a historical clinical perspective

Section 5) Chapter summary

This first chapter incorporates three topics that at first glance only appear to be partially related. However, closer inspection reveals a relative gap in our knowledge. The relationship between these three topics is illustrated in Figure 1.5.1 below. It is clear that CHF patients become breathless as a part of worsening disease. Some of the mechanisms considered to be important in the formation of breathlessness in general also apply to breathlessness in CHF, though there are some mechanisms of breathlessness that are specific for CHF. Opioids form a key part in the pharmaceutical management of intractable breathlessness in advanced disease, albeit without a large evidence base to support its use. Several authors have noted both the lack of symptom control / palliative care research in heart failure and the potential clinical benefits of opioids used in the endstage management of breathlessness (Fischer, 1998, Cushen, 1994, Higginson, 1993). To date, there is little research evidence in this area, despite the ongoing clinical use of opioids. What is as yet unclear is what role opioids might play in CHF and more specifically what effect they might have for breathlessness in CHF.

Figure 1.5.1: Relationship between opioids, breathlessness and CHF. Whilst there is relatively clarity regarding the link with CHF and breathlessness, and breathlessness and opioid treatment, there is less of a well known link between opioids and CHF



A central theory for the formation of CHF following an initial cardiac insult involves the activation of the neurohormonal system. These neurohormones are involved in the normal regulation of homeostasis, but are upregulated following an initial cardiac insult which is considered beneficial in the short term. However, prolonged activation of some neurohormones are considered detrimental. For example, activation of the sympathetic nervous system, resulting in elevated norepinephrine and epinephrine, is detrimental and is targeted by drug therapy with beta-blockers. Opioids are also considered to be one of these classes of neurohormones, but it is unclear in the general cardiology literature as to their considered role. Evidence for their proposed action is discussed in Chapter 2. However, it is interesting to note that beta-blockers were once considered detrimental for CHF, yet now form a main part of standard therapy due to an improvement in the research evidence to support their use. Perhaps further research into opioid manipulation may alter the perceived view of opioids in a similar manner.

A number of general mechanisms have been hypothesised for the formation of breathlessness for all disease states. Specific mechanisms are also proposed for specific disease states, including CHF, which can be incorporated into the scheme for generalised breathlessness. Opioids are considered to be beneficial for generalised intractable breathlessness in advanced disease from all aetiologies, but evidence for this is often extrapolated from lung cancer or COPD disease states. Clinical evidence for the use of opioids for breathlessness in CHF is detailed further in Chapter 3. However, given that specific mechanisms that are considered to contribute to breathlessness in CHF are part of the general neurohormonal activation (particularly sympathetic activation), it is interesting to hypothesise that manipulation of another neurohormone group, opioids, may have a greater role in breathlessness management in CHF compared to generalised breathlessness in other groups where this does not occur. In addition, sites of autonomic (sympathetic) processing in the brain are also considered to be implicated in the formation of generalised breathlessness. These are also the sites for high concentrations of opioid receptors as discussed in the next chapter. Can we expand on the clinical knowledge of opioids for breathlessness in heart failure first demonstrated over two thousand years ago?

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Chapter 2:

Evidence for opioid activity in the cardiorespiratory system

Section 1: Basic science and animals (non-heart failure models)

This chapter will provide some of the background to the proposed mechanism for opioids in human heart failure. The chapter will be divided into four sections. The first of these will document the evidence for opioid involvement in the cardiorespiratory system from basic science experimentation and localisation in animals. The second part will detail those experiments in whole animals with models of heart failure. The third section will demonstrate the measurement and proposed actions of endogenous and exogenous opioids in normal human subjects. The last section will discuss the presence of circulating endogenous opioids in humans with heart failure and will act as a link to the third chapter involving studies using exogenous opioids in human heart failure.

1.1 Opioid receptor distribution in the mammalian cardiorespiratory system

As mentioned in Chapter 1 Section 2, opioid peptides differentially activate three types of opioid receptor in the human body (mu, kappa and delta). Of the endogenous opioids, endorphins preferentially activate mu receptors, enkephalins preferentially activate delta receptors and dynorphins have a preference for kappa receptors.

Opioid receptors have been discovered in various locations using tissue hybridization studies and Polymerase Chain Reaction (PCR) methods in animals (Pugsley, 2002). Most studies have focussed on localisation of receptors within the rat. Opioid receptors have been located at various sites in the brain that are implicated in either the perceived cardiorespiratory centres, responsible for controlling and regulating cardiac and respiratory function, or in sites implicated in the autonomic control of cardiorespiratory activity. Mu, kappa and delta receptor populations have been isolated in rat brain samples in the nucleus tractus solitarius (NTS) and nucleus ambiguous (NA), in addition to the vagus nerve and cerebral cortex (Goodman *et al.*, 1980, Mansour *et al.*, 1988, Nomura *et al.*, 1996). Opioid receptors have also been located in various other central elements of the autonomic nervous system in the rat brain (area postrema in medulla, locus coeruleus and caudate nucleus) (Atweh and Kuhar, 1977a, Atweh *et al.*, 1978). Opioid receptors are present in particularly high concentrations at the NTS in rat brain, the site of the primary baroreceptor synapses (Atweh and Kuhar, 1977b, Atweh *et al.*, 1978, Mansour *et al.*, 1988) and chemoreceptor inputs (Mazzone and Canning, 2002). As discussed in

the previous chapter, these autonomic, baroreceptor and chemoreceptor inputs have a proposed role both in cardiovascular regulation and the development of breathlessness.

In summary, opioid receptors are found in high numbers in the brainstem close to the site of the perceived cardiovascular and respiratory centres with possible influence on the autonomic nervous system. To further emphasise this point, the area around the area postrema (AP) in the brain near the blood brain barrier has high concentrations of opioid receptors. This is important as all afferent baroreceptor fibres pass through this area and it is a potentially important for interneuronal influence (Holaday, 1983). As previously described in Chapter 1, the autonomic nervous system has an important regulatory role in both cardiovascular and respiratory homeostasis and it appears feasible that opioids may be involved in regulatory mechanisms in both cardiovascular and respiratory activity.

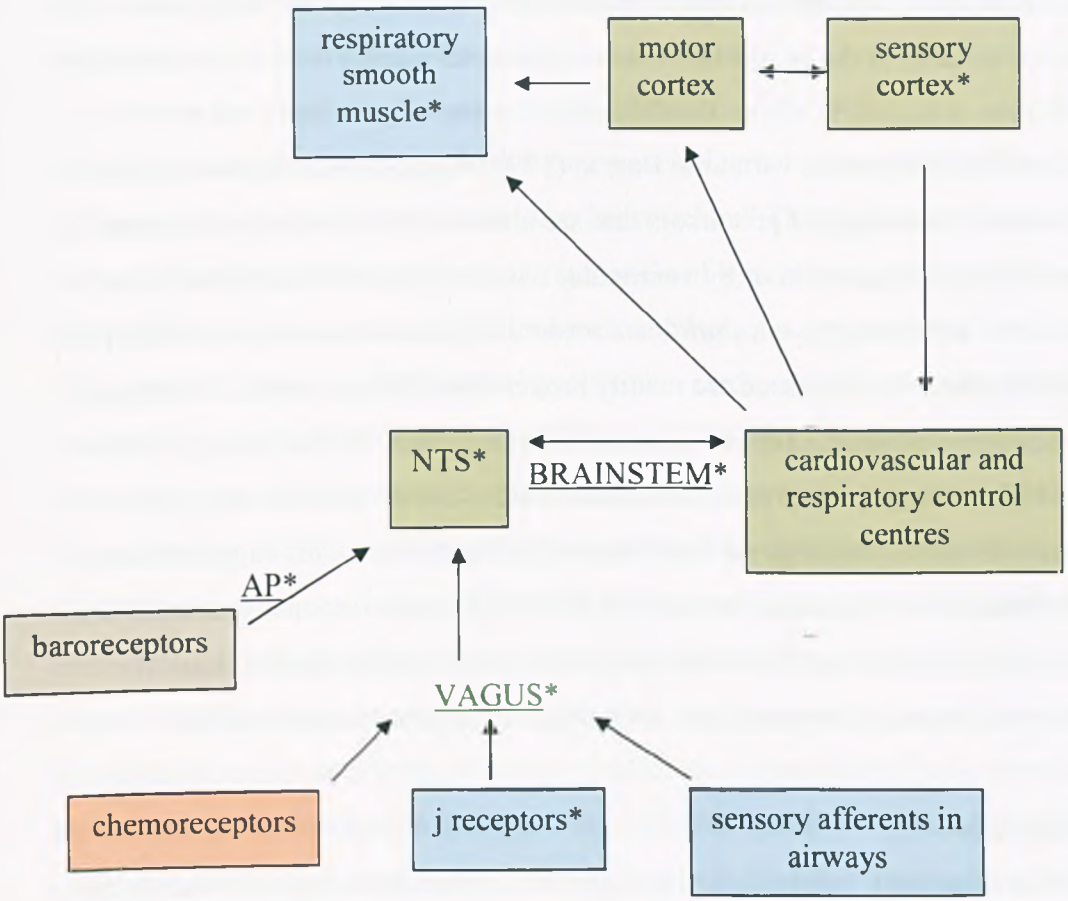
In addition to sites in the brain and neuronal tissue, opioid receptors are also peripherally in organs and tissues. However, not all opioid receptors are distributed in the body in equal proportions or in different times of development. For example, mu opioid receptors are located peripherally in the lungs, adrenals and kidneys but are not expressed in adult cardiac myocytes in the rat (Wittert *et al.*, 1996). This is in contrast to kappa receptor mRNA which is expressed in the mouse heart and CNS (Pugsley, 2002) and delta receptor mRNA which has been isolated in lung, adrenal, kidney and with abundance in cardiac tissue in the rat (Wittert *et al.*, 1996). Interestingly, in contrast to adults, neonatal rat hearts contain kappa and mu opioid receptors, but very low levels of delta receptors, suggesting that opioid receptor expression changes at different stages of development (Ela *et al.*, 1997, Zimlichman *et al.*, 1996). There is some evidence that opioid receptor expression and level of opioid peptides increase with age in rat models (Boluyt *et al.*, 1993, Caffrey *et al.*, 1994). Hypertensive rats express a greater density of kappa receptors in the heart than normotensive rats (Zimlichman *et al.*, 1996). It is unclear whether opioid expression is a cause or an effect of these pathological or ageing processes.

Animal experimentation with opioid agonists and antagonists have provided evidence to suggest that mu receptors predominantly and delta receptors (to a lesser degree) are involved in the regulation of respiratory activity (Florez and Hurle, 1993). Kappa receptors are not expressed in the same numbers in the respiratory nuclei in the brainstem in animals (May *et al.*, 1989) and it is interesting that kappa agonists do not cause respiratory depression, unlike mu or delta agonists (Florez and Hurle, 1993). In the respiratory system, all three opioid receptors are present in the nerve fibres innervating

rat and guinea pig airways (Groneberg and Fischer, 2001, Bhargava *et al.*, 1997). In addition, mu and particularly delta receptors are distributed in lung parenchyma (Bhargava *et al.*, 1997) and they have also been demonstrated in lung homogenates and vagal fibres in the lungs (Ayesta and Florez, 1989). Florez and Hurle (1993) postulate that j receptors may be involved in some of the clinical effects seen following rapid injection of mu opioids, suggesting that opioid receptors are highly concentrated at the site of these pulmonary juxtacapillary mechanoreceptors (j receptors). These receptors relay information via the vagus nerve to the autonomic centre in the brain, again suggesting involvement of opioids in respiratory regulation. Systemic injection of enkephalin analogues cause a triad of signs attributable to the action of j receptors in the lung, mediated through the vagus nerve (Sapru *et al.*, 1981). These factors suggest that opioids may be involved in the relay of peripheral information from the lungs to the autonomic centres in the brain, and hence may be influential in the perception of breathlessness.

It is considered that stimulation of mu receptors in particular is involved in the inhibition of airway smooth muscle constriction through inhibiting neurogenic cholinergic stimulation (Groneberg and Fischer, 2001). Therefore it would appear that opioids are involved in the regulation of bronchoconstriction through their effect in the autonomic nervous system on inhibition of acetylcholine release in the lung, rather than through direct effects on lung tissue (borne out by the lack of efficacy of nebulised opioids in human clinical studies – see Chapter 1 Section 4). Figure 2.1.1 describes the location of opioid receptor sites in relation to important mechanisms for cardiorespiratory control and builds on the information shown in Figure 1.4.1.

Figure 2.1.1.: Opioid receptor location at sites important to the regulation of the cardiorespiratory system (* denotes potential sites of action from knowledge of receptor locations from basic science and animal studies). Areas shaded in green are located in the CNS, blue areas are located in the peripheral respiratory system.



More recently, PET (Positron Emission Tomography) scanning in five healthy human subjects using highly selective inert agonists for delta and mu receptors revealed the presence of both mu and delta receptor populations in the myocardium of the human heart (Villemagne *et al.*, 2002). An inert agonist selective for kappa receptors was not used and therefore the presence or absence of this subtype could not be elucidated. To the best of my knowledge this is the first and only study to demonstrate the presence of these 2 receptor types in humans in vivo. These findings give further argument to the wide species variation observed in the type and location of opioid receptors which makes translation of in vitro animal data into in vivo human models difficult.

1.2 Endogenous Opioid distribution in the mammalian cardiorespiratory system

In addition to the variability of opioid receptor distribution in the heart and lungs, opioid peptide precursors are also distributed in a variety of ways. Various opioid peptides can be synthesised, stored and released by myocytes (Barron, 1999). Millington *et al.* (1999) have demonstrated that cardiac myocytes in the rat heart are able to differentially synthesise endogenous opioids from their precursors. Precursors of the endogenous opioids are distributed in the sympathetic nerves that innervate the heart in a variety of animals (Barron *et al.*, 1995). Given the differential nature of precursors and peptide concentrations and the species variation, Barron (1999) suggests that the atria may be more responsible for storage of precursors that are ultimately released as endogenous opioid peptides for utilisation in or by ventricular tissues. Van den Brink (2003) also suggests that the heart may have a significant reserve of precursor proteins (notably pre-pro-enkephalin) that when released are readily broken down by enzymatic cleavage to the active endogenous opioids (eg enkephalin) which are much shorter lasting prior to their degradation. The inference from these observations is that the heart may utilise opioids in an autocrine, paracrine and possibly endocrine manner. This suggests that there is the potential for opioids to be released from the heart in response to stimuli that either act locally or are released into the wider circulation. The three main types of endogenous opioids and their precursors are detailed in separate sections below.

1.2.1 Enkephalins

Enkephalins are the most widely quoted endogenous ligands in the literature due to the discovery of significant levels of enkephalin, and notably its precursors, in cardiac samples. Enkephalins have been discovered in isolated dog heart tissue (Barron *et al.*, 1992) and mRNA Proenkephalin, the precursor of Met- and Leu-enkephalin is highly expressed in the adult rat heart, particularly the left ventricle myocytes (Weil *et al.*, 1998). Enkephalin concentrations are much lower than pro-enkephalin levels, suggesting that these proteins are stored as precursors and released as required in small amounts (Barron *et al.*, 1995, Pepe *et al.*, 2004). Interestingly pro-enkephalin expression in the adult rat heart is 4 times greater in the left ventricle than the right, suggesting greater enkephalin release into the systemic and coronary circulations (Weil *et al.*, 1998).

In isolated sections of guinea pig heart, Steele *et al.* (1996) discovered small amounts of Leu-enkephalin in both sympathetic and sensory axons innervating the heart whereas Met-enkephalin was not expressed. Enkephalins are also widely distributed in

sympathetic neurones and the adrenal medulla in bovine tissue (Livett *et al.*, 1982) and the lung in rats and guinea pigs (Tang *et al.*, 1982). Enkephalins have been located at the sites of the cardiovascular control centres in the rat brain including the NTS (Mansour *et al.*, 1988, Rutherford and Gundlach, 1993). These results suggest that enkephalins may have a role in cardiovascular regulation at the peripheral level in heart tissue, in release into the systemic circulation, at the neuronal level in the transmission of information in the autonomic nervous system and at a central level with involvement at the cardiorespiratory centre in the brain.

Are enkephalin concentrations altered during pathological processes related to cardiorespiratory insufficiency other than heart failure? There is a possible correlation of increased cardiac enkephalin levels in rat models of hypertension versus normotensive rats, without an increase in enkephalin levels at other sites (e.g. lung) in these animals (Dumont and Lemaire, 1988) and in hypertrophic cardiomyopathy in some animal studies (Ouellette and Brakier, 1988, Ouellette *et al.*, 1991). Hamsters with hypertrophic cardiomyopathy had 3-4 times the concentration of ventricular preproenkephalin than those hamsters without cardiomyopathy, suggesting involvement of opioid synthesis in the development of cardiomyopathy and notably heart failure (this is routinely used as an animal model of heart failure) (Ouellette and Brakier, 1988). It is unclear whether increased synthesis is a result of, or response to, cardiomyopathy and whether this effect is deleterious or advantageous. Similarly, ventricular expression of pre-pro-enkephalin and enkephalin concentration is raised 3-4 fold in rat models of myocardial infarction compared with normal controls (Paradis *et al.*, 1992). Elevated levels of cardiac enkephalins or enkephalin activity are also seen in rat models of ageing (Caffrey *et al.*, 1994). Isolated cardiac ventricular myocytes in the rat have been shown to store enkephalin precursors and produce enkephalins following stimulation (Springhorn and Claycomb, 1992). As discussed previously, the measurements for enkephalin activity and stimulation vary, with leu- or met-enkephalin measured in some samples and MEAP and other larger potential precursors measured in others. To illustrate the problem, Springhorn and Claycomb (1992) comment that MEAP is isolated from neonatal rat hearts, but met-enkephalin and not MEAP is isolated from adult rat myocardial tissue, suggesting differential splicing at different stages of development. Accurate interpretation of these studies taken together is therefore not without difficulty.

1.2.2. Dynorphins

Spampinato *et al.* (1991) describe the presence of dynorphins in cardiac tissue from a variety of species including human samples. Dynorphins are located within sympathetic nerve fibres that innervate coronary blood vessels and cardiac myocytes in the guinea pig heart (Wegener and Kummer, 1994). Steele *et al.* (1996) determined the presence of high concentrations of dynorphin in sympathetic axons innervating the heart, and to a lesser extent sensory axons in this model. This study suggests that endogenous opioid peptides (notably dynorphins) are present in both sensory and autonomic pathways in the heart in this animal model (Steele *et al.*, 1996). There is some evidence to suggest that precursors of dynorphin are synthesised by myocardial tissue (Ventura *et al.*, 1998), although overall there is much less evidence to suggest a role in heart tissue when compared to enkephalins.

Dynorphins and other highly selective agonists for kappa receptors do not cause significant respiratory depression in analgesic doses in many species, though this picture has been complicated by the previous lack of selective agonists (most have some mu receptor activation causing small amounts of respiratory depression medicated by mu activation in the brainstem)(Florez and Hurle, 1993). This is evidence supporting the low numbers of kappa receptors in the respiratory centre in the brainstem.

It is difficult to know if dynorphins have circulatory or respiratory activities in animal or human subjects. However, a potential role may be apparent owing to the location of ACE in lung tissue. Interestingly, ACE not only degrades ATI to ATII, it also cleaves dynorphin-13 into its much less potent compound dynorphin-12 (with a 50-230 times weaker binding affinity for the kappa receptor) in *in vitro* studies (Vickers *et al.*, 2002). This suggests that the enzyme responsible for the production of a potent vasoconstrictor may also be responsible for the degradation of another neurohormone. Clearly further work is required to elucidate the nature of this effect in vivo, but it would not be surprising that ACE degrades a potentially protective neurohormone in addition to stimulating a deleterious one.

1.2.3 Endorphins

Endogenous endorphins have the least evidence for a potential role in cardio-respiratory function. Of note, beta-endorphin and endorphin precursors (POMC) were located in adult rat atrial tissue in similar distribution to ANP, but were virtually absent in ventricular myocytes using immunohistochemical and mRNA techniques. Steele's study

in the guinea pig heart failed to isolate the presence of endorphins (Steele *et al.*, 1996). However, in addition to enkephalins, endorphins also cause respiratory depression when administered systemically (Florez and Hurle, 1993), suggesting that they can act at sites involved in respiratory regulation but studies have yet to identify them at relevant locations.

1.3 Summary for the location of endogenous opioids and opioid receptors in the cardiorespiratory system

Given the different locations of opioid receptors and opioid synthesis in the heart it is considered that opioids may exert localised autocrine or paracrine effects (van den Brink *et al.*, 2003, Pepe *et al.*, 2004, Wittert *et al.*, 1996) in addition to possible endocrine effects via the circulation (Molina, 2006). The relatively high expression of delta receptors, and to a lesser extent kappa receptors, suggests that the secretion of enkephalins and dynorphins by myocardial tissue are involved in a paracrine role. Table 2.1.1 demonstrates the locations of opioid receptors in relation to the identification of endogenous opioid agonists. Note that most of the studies have involved rat tissue and may not be directly comparable to human subjects. Some endogenous ligands are present in the absence of their corresponding receptor and vice-versa, which make assessment of their function at those sites problematic. In addition, a multitude of techniques have been used to isolate receptors and their endogenous opioid ligands, some of which may be more accurate than others. Although endogenous opioid peptides have been located in the cardio-respiratory system it is unclear how they are implicated in normal cardiorespiratory activity and how they might influence or be influenced by pathological processes such as heart failure. In terms of local function in the myocardium, one can observe that enkephalins may play a localised role in regulation as the main receptors that they activate are also present. Dynorphins on the other hand are only expressed as precursors but their preferred receptors are present in myocardium. Mu receptors are not present in myocardium in animal studies, despite the presence of endorphins, though these receptors have been isolated in humans in myocardial tissue. This illustrates the potential for inter-species variation, which makes interpretation of these findings difficult.

Research involving opioid receptor and endogenous opioid locations in the respiratory system is less prominent than that in the cardiovascular system. Mu and delta receptor

populations are found in lung tissue. Activation of mu receptors inhibit smooth muscle bronchoconstriction through autonomic regulation of respiratory smooth muscle. Opioids may have a role in transmission of information from j receptors into the autonomic nervous system, suggesting a role in respiratory control, though the evidence for this is weak.

Care must also be taken in the review of these effects and location of receptors and ligands in isolation. As Mulder & Schoffelmeer (1993) correctly draw attention to, given that opioid receptors exist in pre- and post-synaptic locations both centrally and peripherally, in addition to location within non-neuronal tissue (e.g. heart, lungs), the direct effect of systemic application of opioids may be inhibitory in some locations and potentially excitatory in others. The result of which depends on the net magnitude of effect. This is one of the problems with the interpretation of basic science studies in isolation.

Table 2.1.1: Location of receptors in the cardiorespiratory system in relation to the sites of known endogenous opioid concentrations (Symp NS = sympathetic nervous system, Parasymp = parasympathetic nervous system, resp nuclei = respiratory control centre in the brain). Squares with Y indicates evidence for the presence of that receptor or ligand, N indicates not detected and a blank square represents no good evidence confirming presence or disproving absence.

Receptors or ligands	Myocardium	Myocardial neurones	Lung	Symp NS	Parasymp NS	Autonomic brain	Resp nuclei
Mu	*		Y		Y	Y	
Endorphin	Y					Y	N
Kappa	Y		Y			Y	
Dynorphin	Y	Y (symp & sensory)		Y		Y	
Delta	Y		Y			Y	
Enkephalin	Y	Y (symp & sensory)	Y	Y	Y	Y	Y

*Presence located using PET in in vivo human studies – not demonstrated in adult animal studies (seen in neonatal only)

1.4 Responses to the application of endogenous opioids in basic science and animal studies

1.4.1 Effect on vascular tone

No direct effect on vascular tone was observed in in vitro studies of morphine sulphate administered to canine vascular smooth muscle (Flaim *et al.*, 1977). In normal rats, systemically administered beta-endorphin resulted in hypotension and that this effect was reduced by 5HT (serotonin) antagonists (Lemaire *et al.*, 1978). Interestingly, no

consistent effect has been demonstrated in altering blood flow specifically through pulmonary vessels with direct application of opioids in in vitro studies (Groneberg and Fischer, 2001) suggesting there is no local effect of opioids in the lung vasculature. A more extensive and representative action of opioids on vascular tone is detailed in human subjects in Chapter 2 Section 3.

1.4.2 Effect on sympathetic and parasympathetic stimulation

Given the location of opioid receptors and endogenous opioids within the autonomic nervous system, a number of studies have detailed the effects of administration of opioids in basic science and animal models on these sympathetic and parasympathetic nervous systems. Kappa and delta receptor agonists reduce cardiac output, heart rate and stroke volume in isolated heart preparations, in contrast to mu receptor agonists which have little effect on isolated heart preparations (Vargish and Beamer, 1989). These actions may be mediated in part by inhibition of the sympathetic nervous system. This corroborates the findings of higher concentrations of kappa and delta receptors, but not mu receptors, in myocardial tissue in animals.

As detailed previously, norepinephrine is a principle transmitter for the actions of the sympathetic nervous system. Interestingly, Klein *et al.* (1981) noted an inhibition of norepinephrine release from sympathetic nerve endings in bovine tissue with increasing concentrations of Beta endorphin i.e. an inhibitory feedback mechanism. Similar findings are demonstrated with met-enkephalin in feline models (Gaddis and Dixon, 1982). Stimulation of presynaptic Mu receptors in the rat brain inhibits release of presynaptic norepinephrine in in vitro studies (Mulder and Schoffelmeer, 1993, Carr, 1997). Feldberg and Wei (1986) demonstrated a reduction in sympathetic tone to the heart and blood vessels in anaesthetised normal cats when morphine was administered subcutaneously or in the cisterna magna in the brain (a site considered to have autonomic influence), though isolated experiments such as this may not relate well to normal physiological processes. In a separate study, intravenous morphine has been shown to depress sympathetic reflexes at the spinal level in rats (Uchida *et al.*, 1999). Chemical sympathectomy leads to an increase in enkephalins and enkephalin precursors in isolated rat hearts (Younes *et al.*, 2000), suggesting that sympathetic stimulation and opioid production are interlinked. However, not all authors have been able to establish this link (Caffrey *et al.*, 1994).

Interestingly, in the heart beta-adrenergic receptors and opioid receptors are co-expressed and are coupled to functionally opposite G protein families (beta-adrenergic receptors to

stimulatory G proteins and opioid receptors to inhibitory ones as discussed earlier in Chapter 1 section 2) (Pepe *et al.*, 2004). It is not inconceivable therefore that stimulation of opioid receptors has the opposite effect to stimulation of beta-adrenergic receptors. Indeed, enkephalin administration markedly reduces the effect of beta-adrenergic stimulation by norepinephrine in the isolated rat heart (Pepe *et al.*, 1997) and also attenuates the norepinephrine induced rise in intracellular calcium and hence contractility in isolated rat ventricular myocytes (Xiao *et al.*, 1997). This is important particularly in CHF as sympathetic overstimulation results in a worsening of the disease process and is implicated in some of the proposed mechanisms of breathlessness such as periodic breathing or cheyne-stokes respiration. Anything that opposes this overstimulation may therefore have beneficial effects in CHF.

In support of the hypothesis that opioids may have an inhibitory action on the effects of norepinephrine activity, stimulation of cardiac kappa opioid receptors reduces the activity of beta-adrenoreceptors, particularly in myocardial ischaemia (Wong and Shan, 2001). It is considered that stimulation of Gs protein activation of cAMP by B-adrenergic stimulation may be attenuated by stimulation of Gi (inhibitory) proteins by opioid receptors that reduce cAMP production (Wong and Shan, 2001, Pepe *et al.*, 2004). Enkephalin administration inhibits pre-synaptic transmission in the sympathetic nervous system in guinea pigs and this action is reversed by naloxone (Konishi *et al.*, 1981). Endogenous dynorphin administration reduces the response of guinea pig atrial tissue to adrenergic stimulation (Ledda *et al.*, 1984), though there was considerable variation seen in the responses between different atrial preparations which calls the results of this study into question. Similar experiments by the same team in isolated guinea pig atria revealed that dynorphin produced a dose-dependent reduction in the cardiac response to adrenergic stimulation (through exogenous norepinephrine application) and this effect was inhibited by naloxone (Ledda *et al.*, 1985). They hypothesise that kappa receptor stimulation was involved, though this assumption was based on previous data and not formally tested. Administration of dynorphin as an intravenous infusion into the coronary circulation of anaesthetised dogs revealed a significant reduction in norepinephrine activity following stimulation in the left cardiac nerve which in turn resulted in a reduction in both ventricular pressure and myocardial oxygen consumption (Gu *et al.*, 1992). Administration of naloxone prevented these effects. The authors hypothesise that endogenous opioids may regulate cardiac function by regulating overactivity of norepinephrine. Taken together, these studies give weight to the hypothesis that endogenous opioids inhibit sympathetic overdrive in heart failure.

Interestingly, withdrawal of morphine following chronic high dose administration in rats results in enhanced cardiac norepinephrine activity, associated with both enhanced cAMP production and an influx of calcium in the heart (Martínez *et al.*, 2003). Opposing this sympathetic overdrive may help with both reducing the rate of disease progression and help with coexistent breathlessness in symptomatic patients.

It is interesting to hypothesise that opioids naturally may exert a cardioprotective effect in response to overstimulation of the sympathetic nervous system in acute and chronic heart failure. Since the 1970s it has been suggested that morphine inhibits the release of norepinephrine at various sites in the rat brain (Mulder and Schoffelmeer, 1993). Similar findings have been noted in other animal species, though the pre-synaptic opioid receptors activated to elicit this response appear to be different dependent on the species involved (Mulder and Schoffelmeer, 1993). It is conceivable that norepinephrine release could be antagonised by opioids at other sites. However, whilst it is an attractive unifying hypothesis that the inhibition of detrimental persistent sympathetic over-stimulation in heart failure is achieved in part by activation of endogenous opioid systems, it should be remembered from these studies that not all opioid receptor types or endogenous opioids have been located in vivo in humans at sites that may influence this process.

Less is known about the role of endogenous opioids and the parasympathetic nervous system. Experiments with isolated segments of inferior mesenteric ganglia of guinea pigs revealed that enkephalin containing pre-synaptic neurons may be involved in the release of acetylcholine from post-synaptic neurons. Addition of a synthetic enkephalin analogue resulted in inhibition of acetylcholine release and this effect was reversed with naloxone (Konishi *et al.*, 1981). Mu-selective opioids are considered to have an action at the cardiac vagal neurons located in the nucleus ambiguous in the rat. Administration of mu selective opioid at this level reduces the action of glycinergic inputs, which in turn increases the parasympathetic activity to the rat heart (Venkatesan *et al.*, 2003). These mammalian experiments add further interest to the potential role of opioids in autonomic control.

Cholinergic neurotransmission in the lung is considered to mediate constriction of the airways (compare the effect in blood vessels where the sympathetic nervous system is involved in constriction). An in vitro study involving normal human airway tissue revealed a reduction in airway acetylcholine neurotransmission in the autonomic nervous system by administration of mu receptor agonists, which potentially would reduce airway

constriction (Belvisi *et al.*, 1992). This suggests that opioids may be involved in the regulation of airway control, although human clinical studies in asthma in particular (where constriction of the airways leads to breathlessness and wheeze) have not determined a therapeutic use for inhaled mu opioids (Groneberg and Fischer, 2001). Not all opioids are implicated in the peripheral regulation of respiratory function. In particular, stimulation of kappa receptors produces no direct effects on the airways (Groneberg and Fischer, 2001).

Table 2.1.2 below details the various cardiovascular effects of opioid agonists when delivered either centrally or peripherally in the rat. Some of these effects are likely to be mediated via the autonomic nervous system. In particular, norepinephrine release is inhibited by kappa or delta receptor stimulation when agonists are administered peripherally. Application directly at the NTS, a key site of autonomic control of cardiorespiratory activity, yields different effects for different opioids. However, it should be noted that the artificial insertion of opioid agents to targeted central structures in animals may yield very different results to the systemic administration of opioid compounds in humans, particularly when one considers that central injection of opioid may yield much higher concentrations within central structures than could ever be achieved by systemic administration. Therefore, although the central administration is of interest, the activity of opioids administered systemically is of more relevance to the clinical situation in humans.

Table 2.1.2: Cardiovascular effects of opioid receptor stimulation following central or systemic administration of opioid agonists in the normal adult rat (adapted from (Ventura *et al.*, 1992, van den Brink *et al.*, 2003):

Opioid receptor	**Agonist action when administered centrally**	**Agonist action when administered systemically**
Mu (Endorphin)	Hypotension Bradycardia	Peripheral vasodilation Bradycardia
Delta (Enkephalin)	Medulla / brainstem application: Hypotension & Bradycardia NTS or intracisternal application: Hypertension and tachycardia	Inhibition of norepinephrine release & sympathetic vascular constriction Hypotension Bradycardia
Kappa (Dynorphin)	NTS: Biphasic effect on blood pressure (increase initially then progressive reduction)	Inhibition of norepinephrine release & sympathetic vascular constriction Hypotension Bradycardia Inhibition of catecholamine release from adrenal medulla

1.4.3 Effect on cardiac muscle contractility

Separate to the effects on the autonomic nervous system by opioids as described above, opioid agonists have been shown to directly inhibit cardiac muscle contractility (interestingly delta and kappa agonists inhibit atrial contraction and mu agonists inhibit ventricular contraction in guinea pig tissue) (Mantelli *et al.*, 1987, Barron, 1999). In isolated rat and guinea myocardial tissue, opioids reduce muscular excitability by both reducing action potential amplitude and increasing the threshold for myocardial stimulation (Rashid and Waterfall, 1979). Exogenous opioids may affect sodium, calcium and potassium channel currents in neurons and cardiac tissue (Pugsley, 2002). Activation of delta and kappa receptors suppresses cardiac contractility by reducing calcium influx into the myocardium in *in vitro* experiments involving adult rat left ventricular myocytes (Ventura *et al.*, 1992). Delta receptor activation in particular by enkephalins results in a negatively inotropic action on cardiac contractility. Mu agonists

had no effect in this study. Caffrey *et al.* (1986) demonstrated that blocking opioid receptors with the opioid antagonist naloxone administered via the coronary arteries increased contractility of the dog heart and that propranolol (a beta blocker) negated that response. They hypothesise that inhibition of cardiac opioid receptors facilitates adrenergic activity. In a similar study, Kindman *et al.* (1991) concluded that opioid inhibitors may enhance the contractility of rabbit myocardium to beta-adrenergic agonists, but on review of the results both opioid agonists and antagonists had the same effect on the myocardium and hence the action of opioids with beta agonists is unclear if one took this study in isolation. However, these studies demonstrating reduced cardiac contractility with opioids are contradicted by other studies showing the opposite effect (Laurent *et al.*, 1986, Tai *et al.*, 1992).

1.4.4. Effect in cardiac ischaemia

It has already been demonstrated that opioids have a cardioprotective effect in the phenomenon of ischaemic preconditioning (Pepe *et al.*, 2004, Schultz and Gross, 2001). This preconditioning of the heart using brief episodes of hypoxic ischaemia protects the myocardium during a prolonged ischaemic event later, i.e. the damage caused by prolonged ischaemia is less than if no preconditioning had occurred previously. Opioids are considered to have a role in this mechanism. Ventricular cardiac myocytes taken from chick embryos were subjected to ischaemic conditions resulted in significant myocyte injury over a prolonged period. A brief episode of ischaemia (5 minutes) followed by a more prolonged period, resulted in myocyte protection against ischaemia due to hypoxic conditions (Liang and Gross, 1999). A similar response was observed when myocytes were pre-treated with morphine sulphate, suggesting that this preconditioning response involved in cardioprotection may be mediated by opioid mechanisms. Low concentrations of naloxone added to the medium negated this response, suggesting a role for opioid receptors in the protective mechanism (Liang and Gross, 1999). Isolated human atrial tissue, taken from patients undergoing coronary bypass grafting has been shown to express delta-receptor mRNA and that stimulation of these receptors prior to ischaemia results in a similar process as ischaemic pre-conditioning, inferring that stimulation of delta receptors may be involved in this protective process (Bell *et al.*, 2000).

Similarly, Lishmanov & Maslov (2004) describe that stimulation of mu and kappa receptors inhibit the arrhythmogenic action of norepinephrine in ischaemic conditions, again conferring protection to the isolated myocardium. Additionally, hypoxic states

reduce the threshold of morphine activity considerably in vitro (Johnson *et al.*, 1985). Hence the activity of circulating opioids may be increased during ischaemia. This phenomenon may represent a role for opioids as a protective mechanism against the potentially damaging effects of hypoxia. Similarly, the endogenous opioid system may be involved in circulatory shock {for review refer to Molina (2006)}.

1.4.5 Effect on Angiotensin II

Very few studies detail the effect of opioids on circulating neurohormones that are considered to be involved in chronic heart failure. The effect on norepinephrine activity is detailed above. Perhaps this lack of information reflects a need for basic opioid research to gain pace with the research enjoyed by the study of other neurohormones in heart failure. The effect of opioids on the renin-angiotensin system is really the only other neurohormonal mechanism detailed in the literature to date.

Angiotensin II is considered to exert its vasoconstrictive response in part at the level of the area postrema (Xue *et al.*, 2003), the site of high opioid receptor concentrations (Atweh & Kuhar 1977a). Szilagyi and Ferrario (1981) demonstrate that opioid antagonists reduce the vasoconstrictive response of angiotensin II at the area postrema in normal dogs, antagonising the action of the RAAS. On further review of this paper however, the dogs used in this study were all anaesthetised using morphine in this study which is an obvious confounder and therefore the results of this study should be treated with caution. Administration of enkephalins, B-endorphin or morphine centrally inhibit angiotensin II mediated vasopressin (ADH) release in rat models (Summy-Long *et al.*, 1981b, Summy-Long *et al.*, 1981a) also suggesting that opioids antagonise the central actions of angiotensin.

1.4.6 Effect on chemoreceptor activity

As previously discussed, chemoreceptors, the monitors of blood gas concentrations, have an increased sensitivity in CHF and are implicated in the proposed mechanisms of dyspnoea. Interestingly, administration of opioids in normal humans and animals may alter their activity. The chemoreceptor response to hypoxia is diminished by systemic opioid administration, with a subsequent reduction in hypoxic drive (in addition to hypercapnoeic drive) at the respiratory centre (Florez and Hurle, 1993, Chua *et al.*, 1997). Administration of met-enkephalin to carotid arteries in anaesthetised normal cats resulted in a rapid inhibition of spontaneous chemoreceptor discharge at the carotid sinus (McQueen and Ribeiro, 1980). Morphine was a less potent inhibitor of chemoreceptor

activity. Pre-treatment with naloxone negated the effect of morphine and substantially reduced the effectiveness of enkephalin (McQueen and Ribeiro, 1980). A human study of this effect in CHF (Chua *et al,* 1997) can be found in Chapter 3. This may be an important mechanism as to the known action of opioids on respiration, and provides a link between proposed mechanisms of breathlessness, CHF and the effect of opioids.

1.5 Conclusion

It is clear from these basic science and animal studies that both opioid receptors and endogenous opioids are distributed at sites where they could influence cardio-respiratory mechanisms. However, extrapolation of these results to human subjects has to be made with caution. It is unclear whether, for example, these receptors are up- or down-regulated in human heart failure. There is simply not the evidence currently to know definitively if opioid receptors are involved in cardiorespiratory mechanisms in humans. However, there is increasing recognition that given the distribution of opioid receptors in these studies, it is possible that they do play a potential role in humans and hence the importance of opioids in the possible regulation of various body processes. It is clear that opioids and opioid receptors are distributed widely throughout the body. However, it is still not known specifically how opioids regulate their effects on cardiovascular and respiratory function. The presence of opioid receptors in the regions of the brain that are concerned with control of respiratory and cardiac function may be responsible for some of these actions. Location within sympathetic and parasympathetic neurons that innervate the heart and cardiovascular system may have also play a role, particularly for the cardiovascular effects seen following opioid administration. Local activity following release into cardiac myocytes and vasculature could explain some of the local effects seen, particularly vasodilation.

Results from a number of animal studies suggest opioid receptor antagonists at reasonable doses appear to have few cardiovascular effects in normal non-anaesthetised animals not under stress, which might suggest that the endogenous opioid system is only activated under stressful or pathophysiological conditions (Faden and Holaday, 1979, Faden, 1993).

Stimulation of the endogenous opioid system appears to attenuate the actions of two potent mechanisms responsible for the formation and perpetuation of CHF, namely

norepinephrine and angiotensin, in *in vitro* animal studies. Given the research and clinical application of medications (beta blockers and ACEI) that also reduce the overstimulation of these detrimental vasoconstrictor systems in humans, it is interesting to hypothesise that stimulation of the opioid system may have an additional effect in reducing the effects of these detrimental systems in human heart failure.

Section 2) Animal models of heart failure and effects of opioids

In the section above, the importance of location of endogenous opioids and opioid receptors in non-CHF animals or basic science examples was discussed. This section will review the research involving animal models with induced CHF. Dog models of cardiac failure are the most prevalent in the literature generated so far in support of the basic science research detailed previously. Given the historical wariness of opioid compounds in the medical community, "opiophobia", the majority of studies have involved the use of opioid antagonists in the hope that these agents will have a beneficial effect, if the assumption that opioid agonists are detrimental is correct. As can be seen in this thesis, my primary argument is that the current evidence suggests that opioids may be beneficial in CHF and not detrimental. This should be considered on review of the studies below that involve opioid antagonism.

The first of such studies to be discussed here involves dogs with right-sided congestive cardiac failure (Sakamoto and Liang, 1989). The authors hypothesised that patients with heart failure have diminished baroreceptor reflexes secondary to the centrally-mediated action of endogenous opioids. Restoration of these reflexes could theoretically be performed through opioid inhibition. Right heart failure was induced in 16 dogs by tricuspid valve avulsion and pulmonary artery constriction. Four weeks after the initial procedure the dogs were included in the trial if they exhibited signs of right heart failure. These right heart failure dogs demonstrated significantly reduced baroreceptor sensitivity and elevated plasma B-endorphin concentrations compared to the sham controls. Significant results included increased baroreflex sensitivity by the opioid antagonists naloxone and naloxozine (a relatively selective mu receptor antagonist) in the right heart failure dogs compared to the sham operated controls. Similar results did not occur with selective delta receptor antagonists or antagonists that did not cross the blood brain barrier, leading to the theory that opioid inhibition in these dogs was mediated through central mu opioid receptors. In contrast to the authors' analysis of some of their results, there was little overall change in haemodynamics in the heart failure dogs following opioid reversal.

Interestingly, the right heart failure dogs demonstrated circulating B-endorphin levels significantly higher than the sham-operated dogs. It is considered that B-endorphin levels may be raised in human heart failure (Kawashima *et al.*, 1991), as will be discussed in

Section 4. However, the animal preparation differed from clinical left ventricular failure as left atrial pressures were unchanged, unlike in human heart failure with left ventricular dysfunction. It has therefore been called into question whether this dog model is an accurate reflection of the role of opioids in human chronic cardiac failure.

Another study involving the induction of symptoms of left heart failure in dogs by initiation of ventricular pacing concluded that the secretion of B-endorphin does not exacerbate circulatory dysfunction in chronic left ventricular heart failure (Mellow *et al.*, 1992). Plasma B-endorphin levels in these animals were the same as control subjects. Unfortunately the dogs were anaesthetised using morphine during pacemaker insertion, which is an obvious potential confounding factor. In addition to this, as the authors discuss, the assay used to measure B-endorphin levels was not necessarily specific for B-endorphin alone and may have also detected a similar compound, B-lipotrophin.

In response to this, Himura *et al.* (1994) performed a similar trial involving dogs who were cardiac paced and developed pacing-induced congestive heart failure. In this study, basal plasma B-endorphin levels were elevated in the heart failure dog models. However, on this occasion administration of naloxone had no effect on the depressed baroreflex activity in the paced animals, unlike the study in right heart failure models. However, naloxone administration did increase heart rate, blood pressure and cardiac output in these dogs with increases in plasma B-endorphin and norepinephrine in response. Use of a longer acting opioid antagonist, naltrexone, prevented the reduction of baroreceptor activity seen in dogs with surgically induced right heart failure (Yatani *et al.*, 1997).

Another study employed the right heart failure model to attempt to determine the cardiovascular mode of action of naloxone in cardiac failure (Imai *et al.*, 1994). Despite reproduction of the findings in the study by Sakamoto and Liang (1989) in that administration of an opioid receptor antagonist increased mean cardiac output and aortic pressure, it was a selective delta receptor antagonist that produced these findings. A selective mu antagonist did not reproduce these effects. Hence the authors postulated that naloxone exerts its effects via delta receptor antagonism, in contrast to the conclusions of Sakamoto and Liang (1989).

It is difficult to know how to interpret some of these conflicting results and right heart failure models for the management of cardiac failure involving chronic left ventricular dysfunction in humans. These dog models of heart failure tended to have diminished

baroreceptor activity when compared to sham-operated dogs and plasma B-endorphin and norepinephrine levels tended to be higher in the affected animals. These elevated hormonal levels are consistent with human heart failure. It is clear that influencing baroreflex activity and haemodynamic changes with opioid antagonists have been inconsistent with these different animal models of heart failure. Certainly, the method of induction of heart failure in these models is more likely to reflect acute processes, rather than the chronic neurohumoral activation seen in human chronic heart failure.

Extrapolation of results from animal experiments does not necessarily reflect the experience observed in human subjects. This does not mean that all animal studies are irrelevant, but results must be taken in the context of the experiment and principles of good research practice. Frequently the aim of research in animals is different to that in humans, often requiring analysis of potential methods of action rather than clinical effectiveness of treatment and hence protocols and experimental designs may differ (Musch, 2007). The animals used are often young, without co-morbidities and without polypharmacy, unlike the usual human clinical situation (Hackman, 2007). However it could be argued that many human clinical studies of safety or efficacy are conducted in young subjects (typically males) not in receipt of other competing medications.

Of more concern is that animal trials are often of poor quality with methodological problems and there is a lack of systematic review of the available literature (Hackman, 2007, Sandercock and Roberts, 2002). The aptly named "RATS" group (Reviewing Animal Trials Systematically) have suggested the more widespread use of systematic reviews of animal studies and detail only six available reviews in total that assess how the animal research had informed the allied clinical research in human studies (Pound *et al.*, 2004). On a similar note, Perel *et al.* (2006) conducted systematic reviews for six interventions performed in both animals and humans. They determined that three interventions had similar outcomes in both animals and humans, but three did not, indicating a relatively low level of concordance between animal and human studies. Both Pound *et al.* (2004) and Perel *et al.* (2006) rightly call into question how animal studies directly relate to human trials and comment on the need for greater methodological quality and consistency and need for systematic reviews to help inform human trials with greater accuracy. Hence, although animal experiments can help to inform a pathological process or help to predict the safety or efficacy of a drug, results from such studies should not be viewed in isolation.

Section 3) Effect of opioids in normal human subjects

Surprisingly little is documented regarding the action and effect of administered opioids in normal human subjects since the isolation of morphine by Serturner in the 19th century. Some of the clinical effects (both intended and adverse effects) have been documented earlier in Chapter 1. The following effects are taken from the perspective of the cardiorespiratory system in isolation.

Demonstration of the action of opioids on vascular tone in animal and human studies is mixed and the mechanism of any response seen is unclear. In a very early study, the administration of 10-30mg morphine intramuscularly did not result in a significant change in blood pressure whilst supine, but caused both bradycardia and hypotension, occasionally manifested as syncope, in normal human individuals when subjected to a sudden head-up tilt thirty minutes post administration (Drew *et al.*, 1946). This finding of postural hypotension was corroborated in a subsequent study in normal man by Weil *et al,* (1975). Rubin and colleagues (Rubin *et al.*, 1983) attempted to demonstrate an effect in normal volunteers with an enkephalin analogue, but the variability of their baseline and subsequent measurements detract from their results. In 47 normal human subjects, intravenous morphine was shown to produce a significant dilation of venous and arteriolar vessels (Zelis *et al.*, 1974). These authors hypothesised that this response was due to a reduction in the effect of sympathetic discharge as arteriolar dilation with morphine was blocked by co-administration of phentolamine. Certainly this would fit with the hypotheses for the role of the sympathetic nervous system in the propogation of CHF demonstrated in Chapter 1 Section 3 (Figure 1.3.1). If opioids do reduce cardiac preload and afterload their production would oppose the haemodynamic activities of norepinephrine and the sympathetic nervous system as a whole.

Similarly, administration of intravenous morphine to the forearms of 37 normal medical students revealed a notable reduction in hand (and not forearm) vascular resistance. The authors suggest that this reduction in cutaneous vascular resistance probably occurs through a central mechanism (not local effects) and in turn this could reduce cardiac afterload and hence reduce overall cardiac work (Cohen and Coffman, 1981). An early double blind parallel group RCT in a total of 17 patients with coronary artery disease identified a small reduction in cardiac work following administration of 8mg morphine sulphate administered intravenously (Alderman *et al.*, 1972). A reduction in left

ventricular work and end-diastolic pressure may not be advantageous in the acute setting (Peacock *et al.*, 2008) but in the chronic stable setting of CHF, reduction in ventricular work may be advantageous (as demonstrated by the beneficial effect of beta-blockers). In conclusion, the effect of exogenous opioids in normal subjects has potentially advantageous effects in terms of heart failure management and the mechanism of action may be delivered through antagonism of the sympathetic nervous system.

It has been considered for a number of years that opioid administration results in peripheral histamine release in blood vessels which may contribute to the vasodilation seen with opioids in humans (Feldberg and Paton, 1950). Local concentrations of histamine following opioid administration may be sufficient to account for local vasodilation, but are thought unlikely to cause a systemic reduction in blood pressure alone (Feldberg and Paton, 1950, Johnson *et al.*, 1985). Interestingly there appears to be an inconsistent species dependent response to pre-treatment with anti-histamines with the response to opioids (Fennessy and Rattray, 1971, Evans *et al.*, 1952). Mansour and colleagues observed the effect of morphine (IV 15mg) in reducing forearm vascular resistance and increased forearm blood flow in humans but could not demonstrate any effect of anti-histaminic compounds on this arteriolar dilation (Mansour *et al.*, 1970). This is in contrast the findings of Grossmann *et al.* (1996) in 15 healthy volunteers who noted that intravenous morphine administration resulted in significant venodilation in dorsal hand veins which was abolished by co-infusion of anti-histamines. Of course, it is feasible that the constituents of the injection (other than the morphine) result in venous irritation and subsequent histamine release (interestingly injections of fentanyl, another mu opioid agonist, caused no vasodilation). Certainly, histamine release alone would not correlate with the improvement in breathlessness seen with opioids when administered in acute heart failure. Indeed, histamine itself can produce bronchoconstriction and wheeze (Weatherall *et al.*, 1996), thus resulting in deterioration of respiratory symptoms, in contrast to the effects seen from opioid administration clinically. However, it is not clear as to the level of contribution on vasodilation that this mechanism has, rather than the autonomic response to opioids resulting in the effects observed.

Aside from the haemodynamic consequences of morphine administration, in human subjects increasing doses of systemic opioid firstly cause a dose-dependent reduction in minute volume and ventilation, leading in turn to a rise in arterial carbon dioxide (CO_2) concentration (Keats, 1985). In addition to reducing the frequency of ventilation, opioids also reduce the chemoreceptor responsiveness to this rise in arterial CO_2, thus leading to

an overall reduction in ventilation for a given arterial CO2 concentration (Florez and Hurle, 1993). With increasing doses, the frequency of respiration reduces more than further reduction in tidal volume (Keats, 1985), due mostly to an increase in the time used for expiration. Weil and colleagues (1975) measured the ventilatory responses of six normal men to 7.5mg subcutaneous morphine sulphate. The researchers noted both a very mild reduction in resting frequency of ventilation and a significant reduction in hypoxic ventilatory drive following morphine administration. They also postulate that this decreased responsiveness to chemical stimuli is enacted through peripheral chemoreceptors (Weil *et al.*, 1975). This is important, as exaggerated chemoreceptor activity occurs in CHF, and it is possible that this is attenuated by morphine administration. The effect of opioids in normal humans appears to positively influence some of the detrimental systems considered to be responsible for breathlessness in CHF, notably reduction in chemoreceptor response and influence centrally at the respiratory centre in the brainstem.

Section 4) Endogenous opioid release in human heart failure

4.1 Presence of endogenous opioids in human heart failure

To identify whether systemic opioids are involved in CHF it is important to assess whether opioid concentrations in circulation are higher or lower than normal subjects. For example, circulating levels of Beta endorphin appear to be raised in stable chronic heart failure. Oldroyd *et al.* (1995) could not consistently demonstrate a chronically elevated plasma level above the normal range of their assay in 34 chronic stable heart failure patients who had stopped taking their usual cardiac medications. This result conflicts with the data presented by other authors. Plasma B-endorphin levels were raised in 37 patients with congestive cardiac failure compared to age and sex-matched controls in a study by Kawashima *et al.* (1991). These authors also revealed that patients with more severe disease tended to have higher concentrations of circulating plasma B-endorphin with a negative correlation with cardiac output. Similar results were shown by radio-immunoassay of B-endorphin in a Chinese study of 131 participants with a negative correlation of B-endorphin with left ventricular ejection fraction (Zheng *et al.*, 1991). Perna *et al.* (1997) demonstrated a consistently raised B-endorphin level in more severely affected patients with chronic heart failure compared to normal subjects. This was mirrored by resting norepinephrine levels which were also higher in more severely affected heart failure patients. With exercise, B-endorphin levels rose in all subjects to a similar peak value (i.e. greater proportional rise in normal subjects with exercise) in this small study of 37 participants. They postulate that the activation of the endogenous opioid system may balance the effect of increased adrenergic drive with exercise. Fontana and colleagues also demonstrated significantly higher levels of endogenous opioids in acute heart failure patients compared to similar healthy controls in conjunction with elevated levels of norepinephrine and natriuretic factors (Fontana *et al.*, 1993). Plasma Beta endorphin levels did not correlate with severity of disease, whereas enkephalin and dynorphin concentrations were higher in more severely affected patients. Of course, this is not necessarily applicable to CHF. Hence, it is unclear whether Beta endorphin levels in particular remain consistently elevated in chronic heart failure, or whether it is the presence of acute stressors or decompensations in this population that result in transient rises of beta endorphin secretion (Fontana *et al.*, 1993).

In addition to the effects of local release of opioids in peripheral autonomic neurones, the central nervous system and locally in cardiovascular structures, Holaday (1983) hypothesises a role for circulating levels of opioids. He suggests that circulating levels of opioids are unlikely to be able to cross the blood brain barrier due to their size and polarity, but may be able to influence the autonomic nervous system centre at the area postrema in the brain (as discussed previously, an area with high opioid receptor concentration). Certainly, this theory is plausible, given that this particular area is known from the literature relating to the mechanisms of vomiting to be accessible by circulating levels of hormones despite them being unable to penetrate the blood brain barrier in rat models (Koga *et al.*, 2003, Carpenter *et al.*, 1984). In summary, although the amount of evidence is small, it would appear that circulating opioids of all three endogenous types are elevated in HF. Whether this is part of a beneficial or detrimental neurohormonal process, or whether it simply reflects the actions of stressors on the body, is unknown.

4.2 Effect of opioids on venous tone in human heart failure

In heart failure patients, Vismara *et al.* (1976) demonstrated in a small study (n=13 heart failure patients) that the effect of morphine on venous tone was small compared to the overall beneficial clinical effects seen following administration in pulmonary oedema. Morphine does appear to cause venodilation, but it does so both in normal individuals and in heart failure and therefore cannot be used to fully explain its effect on dyspnoea. In acute heart failure, central mechanisms of ventilatory control are perhaps as important as circulatory changes, by allowing the patient to breathe more regularly and with more control, resulting in reduced anxiety and further improvement in subjective breathlessness. In a small study of 10 patients with acute heart failure complicating myocardial infarction, Morphine (0.2mg/kg body weight) reduced blood pressure and heart rate (Timmis *et al.*, 1980). Similar results were found in an earlier study comparing these patients with normal controls (Thomas *et al.*, 1965). Again the effects of opioids in acute heart failure are similar to those discussed previously in normal individuals, but this does not mean that the effect would be the same necessarily for CHF. No such evidence on venous tone or peripheral resistance with opioids in CHF yet exists.

4.3 Effect of opioids on neurohumoral changes in human heart failure

4.3.1 Norepinephrine and the sympathetic nervous system

Sympathetic overdrive from increased chronic norepinephrine activity is considered detrimental in CHF (Clark and Cleland, 2000, Roig, 2006). Norepinephrine levels are increased in CHF (Eriksson *et al.*, 1994) and therefore reducing or blocking this chronic activation should therefore be encouraged. In acute severe congestive heart failure high circulatory levels of beta-endorphin, enkephalins and dynorphins correlate with elevated plasma norepinephrine concentrations (Fontana *et al.*, 1993, Fontana *et al.*, 1998). It is unclear as to whether increased levels of some of these endogenous opioids are maintained into stable chronic disease rather than during acute exacerbations. For example, the same authors later determined elevated levels of Atrial Natriuretic Peptide and Endothelin in association with elevated Beta endorphin and Norepinephrine in acute congestive heart failure without elevated enkephalin or dynorphin concentrations at baseline (Fontana *et al.*, 1998). Interestingly, further acute mental stress in these patients increased the levels of all of the above hormones and the infusion of naloxone in these patients during mental stress significantly increased blood pressure, heart rate and norepinephrine concentrations versus placebo. In a small randomised double blind crossover study of ten CHF patients, infusion of beta-endorphin resulted in a significant reduction in norepinephrine concentrations (Cozzolino *et al.*, 2004), similarly suggesting an antagonistic effect of opioids on sympathetic activity. What is not known is whether endogenous opioids are released because of, or in response to, norepinephrine stimulation? This is important as opioids may be released as a balance to the effects of norephinephrine, which potentially could be beneficial in the long-term. What is also unknown is whether administration of exogenous opioid in addition to beta-blocker therapy has an additional therapeutic benefit on the effects of norepinephrine. It is interesting to speculate that opioids could be utilised as either an adjunct to therapy in addition to beta-blockers, or as an alternative to beta blockers in those heart failure patients who were unable to tolerate them due to relative contraindications to their use or excessive side effects.

4.3.2 Angiotensin II

It is interesting to consider that opioids may antagonise some of the actions of angiotensin II. This is obviously a beneficial effect as use of angiotensin II inhibitors have been shown to confer survival advantage and a reduction in heart failure related hospital admissions in the multicentre SOLVD and CONSENSUS trials (CONSENSUS

Trial Study Group, 1987, The SOLVD Investigators, 1991). Norepinephrine levels were significantly reduced following treatment with an ACE inhibitor (Eriksson *et al.*, 1994) and as discussed in Chapter 1 Section 3, the RAAS and sympathetic systems are interlinked. However, there is no evidence for an association or interaction of Angiotensin II / RAAS and opioids in human CHF.

4.3.3 Opioids and Endothelin

The role of Endothelin in the manifestation of heart failure is gaining interest, given its potent vasoconstrictor role (Teerlink, 2005). Elevated levels of Beta endorphin are correlated with high concentrations of endothelin in human cardiac failure (Fontana *et al.*, 1998) suffering from acute exacerbations, although strictly speaking this is considered to be a different population to stable CHF. Interestingly, Wang & Hung (2003) have shown a reduction in endothelin concentrations in symptomatic congestive heart failure following administration of IV morphine (3mg) in a small study comparing heart failure and breathless non-heart failure patients. In addition, a significant reduction in plasma concentrations of endothelin following infusion of B-endorphin in a double blind placebo controlled crossover study involving ten patients with CHF has been demonstrated (Cozzolino *et al.*, 2004). Opioids may therefore also have a role in reducing the potentially deleterious effects of endothelin, possibly via the activation of mu or delta receptors.

4.3.4 Opioids and Natriuretic Peptide

Natriuretic peptides are considered to be beneficial in human CHF (Brandt *et al.*, 1993). ANP for example inhibits angiotensin II and promotes diuresis, which is important for those patients with CHF in fluid overload. In an observational study of the effects of morphine in normal humans, Ogutman *et al.* (1990) noted the increase in plasma ANP following administration of IV morphine at either 0.15mg/kg or 0.3mg/kg. Unfortunately there was no control group so direct comparisons could not be made against placebo and no other effects (respiratory rate, urine output, blood pressure etc) were documented, limiting the study findings. Interestingly, activation of kappa-opioid receptors also induces a diuretic response (Leander *et al.*, 1982, Rimoy *et al.*, 1991) which may potentially be of benefit in patients with pulmonary oedema in the chronic and acute heart failure setting.

Endogenous opioids are degraded by a variety of proteases or enzymes. One such protease, Neutral endopeptidase (also known as enkephalinase or NEP) is an enzyme that

degrades certain opioid peptides more readily than others. As the name suggests, met- and leu- enkephalins are preferentially broken down by this enzyme, whereas the endorphins and dynorphins are much less susceptible to degradation by this particular enzyme (Hersh, 1984). NEP is widely distributed in the body, particularly in the lung and CNS (Erdos and Skidgel, 1989). Of note is that NEP is also responsible for the degradation and inactivation of ANP in vivo (Erdos and Skidgel, 1989, Roques and Beaumont, 1990). NEP inhibitors have been commercially devised by the pharmaceutical industry, primarily to reduce NEP degradation of ANP and BNP, and are considered to be beneficial in heart failure as the effects of these natriuretic peptides are preserved (Maki *et al.*, 2001). As discussed in Chapter 1 Section 3, this involves a reduction in vasoconstriction & sodium retention and slowing the rate of cardiac remodelling. The OVERTURE trial in CHF noted similar effects of the NEP inhibitor (Omapatrilat) versus Enalapril (ACEI) in 5770 patients with CHF. Outcomes such as risk of death or hospitalisation were not significantly different between the two different treatment groups (Packer *et al.*, 2002). Unfortunately there was no assessment of symptom response between treatment groups in these patients. The drug used (Omapatrilat) is considered to have efficacy versus ACE and hence the lack of noticeable superiority over common ACE inhibitors has meant that further research into its use has been inhibited, mostly on the basis of cost. Is the beneficial effect of inhibiting NEP purely mediated though the prolongation of activity of ANP alone, or can we also surmise that the prolongation of opioid activity (particularly enkephalin activity) also has a beneficial effect by inhibiting NEP? This evidence adds further weight to our hypothesis than opioids may be beneficial for CHF patients.

4.4 Non-symptom control studies in human CHF

As quoted previously, Cozzolino *et al.* (2004) detailed the effect of Beta endorphin infusion in a small RCT involving CHF patients (NYHA 2-3). In addition to the statistically significant reduction in norepinephrine and endothelin concentrations with beta-endorphin compared to placebo, there was no change in circulating BNP or renin concentrations one hour following infusion, though this time period may not have been sufficient enough to observe any "downstream" effects in these peptides. However, it is unclear as to the clinical value of this infusion, which increased beta-endorphin by 100 times the basal circulating level. Certainly one could not extrapolate a potential role for beta-endorphin from this study alone given the magnitude of the increase, which is

unlikely to be discovered naturally in CHF. However, if infusion of pharmaceutical opioids that activate the mu receptor such as morphine demonstrate a similar response this may be useful in determining a potential cardioprotective role. The authors conclude that high doses of beta-endorphin could preserve cardiovascular function, but they hypothesise that this is through increasing the inotropic function of the heart, which would appear contradictory to a cardioprotective role versus overstimulation through norepinephrine.

Section 5) Chapter summary

As can be seen in the sections above, there is some evidence to support a possible role for opioids in CHF. Unfortunately there has been no consistent approach to research in this area. Studies in animals and humans have attempted to link severity of heart failure with elevated levels of endogenous opioids as part of an overall neurohormonal response, which was viewed as detrimental in CHF. This has subsequently led to early trials involving the use of opioid antagonists in the management of heart failure symptoms, without notable success. It has now emerged that some neurohormones, like natriuretic peptides, might be beneficial in CHF and hence the prolongation of their response should be encouraged. Tantalisingly, natriuretic peptides are degraded by the enzyme neutral endopeptidase (enkephalinase), which also degrades opioid peptides (notably enkephalins). Should we now take a second look at opioids?

Information concerning the possible role of opioids in cardiorespiratory regulation comes mostly from basic science or animal studies, both of which need to be looked at with caution when interpreted in terms of human CHF. Again, a previous lack of distinction for stable chronic heart failure and acute types of heart failure does not allow easy interpretation of studies that are apparently relevant. In particular, dog models of right sided heart failure may not represent the patient experience in CHF. Of interest is that mu and delta opioid receptors have been located at sites in the brain implicated in autonomic cardiorespiratory control and in the proposed formation of intractable breathlessness in humans. Opioid receptors are also located peripherally in the heart and lungs, notably kappa receptors in the heart (plus recently mu in human studies) and mu receptors in the respiratory system. This may be important in the light of the respiratory effects of opioids for intractable breathlessness as most pharmaceutical opioids have a preferential affinity for mu receptors, with oxycodone also having a notable affinity for kappa receptors in

addition to mu. Stimulation of kappa receptors results in a diuretic response in humans, potentially useful for acute heart failure where fluid overload causes symptoms such as breathlessness, but perhaps not so important for stable chronic heart failure where other mechanisms causing breathlessness may be more prominent. In this case, different types of opioid may have differing effects in both cardiovascular and respiratory parameters, particularly important for breathlessness control in CHF.

It remains unclear from the literature as to whether endogenous opioids rise in response to, or because of, worsening heart failure. This distinction is important, as opioids may actually have a beneficial role in cardiovascular regulation. Endogenous opioids and receptor expression increase in various cardiovascular models of cardiovascular disease, including hypertension and the ageing process. Opioid release has been noted as deferring a degree of cardioprotection in the phenomenon of ischaemic preconditioning. Probably the most important point in this chapter is that opioids may antagonise the release and effects of norepinephrine, the neurohormone thought most responsible for the development and prolongation of CHF and also has a role in specific mechanisms of breathlessness in CHF. Administration of opioid in normal humans results in a reduction in blood pressure and heart rate on tilting and reduces the response to carbon dioxide through blunting the chemoreceptor response. In CHF, chemoreceptor activity is enhanced, hence this activation may be antagonised by opioids. It is unclear whether these effects are manifested through antagonism of the sympathetic nervous system, but at the cellular level norepinephrine causes an increase in cAMP through activation of stimulatory G proteins, whereas opioids tend to reduce cAMP through activation of inhibitory G proteins.

There is therefore enough evidence to suggest a role for opioids in the cardiorespiratory system, that detrimental sympathetic activation in CHF may be attenuated by endogenous opioids and that opioid concentrations rise in CHF. This circulating rise mirrors both detrimental neurohormones such as norepinephrine and beneficial neurohormones such as natriuretic factors. The effect of this rise in endogenous opioids is therefore a subject for conjecture. The effect of opioid administration in normal humans is actually poorly researched given its long history of use and abuse, but exogenous opioids do reduce tidal volume at small doses and cause respiratory depression in much larger doses. One might extrapolate that the mechanisms involved in this phenomenon might also be those same mechanisms implicated in the relief of dyspnoea with opioids. The clinical use of opioids for breathlessness control in CHF will be discussed in the following Chapter.

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Chapter 3:

Systematic Literature review:

Human symptom control studies in CHF

Section 1) Introduction: What clinical evidence exists to suggest opioids may help breathlessness?

Opioids have been used for many years in the management of acute heart failure and in the patient who is actively dying on the basis of clinical experience and consensus rather than a robust evidence base. However their use in the patient with chronic heart failure (CHF) has been discouraged. This is partly due to historical and often unsubstantiated concerns about cardio-respiratory depression (Johnson and Gibbs, 2006).

Opioids are accepted in the management of breathlessness in patients with malignant lung disease who remain breathless despite optimum management, and who are not necessarily imminently dying. A Cochrane review regarding the use of opioids in patients in the management of breathlessness in incurable disease (cancer and non-malignant disease) concluded that there was clinical evidence to suggest a small but significant symptom improvement with oral or parenteral opioids in this patient population (Jennings *et al.*, 2001). However, the review only included one trial that specifically involved CHF patients as a distinct group.

Although there is limited evidence for the use of opioids in the management of breathlessness in many life-limiting diseases (Jennings *et al.*, 2001) there has been little research in heart failure patients specifically. This is somewhat surprising as morphine has been used for many years in the management of acute cardiac failure (Millane *et al.*, 2000). For example, Beltrame *et al,* (1998) remains the only RCT of morphine use in acute HF and this was a study of treatment comparisons involving other widely used therapies in the management of acute symptoms rather than evaluating the effect of morphine alone. Intravenous nitrates (Nitroglycerin 2.5 microgram/min / N-Acetylcysteine 6.6 microgram/min over 24 hours infusion) were compared with an intravenous diuretic (Frusemide 40mg stat dose / Morphine 1-2mg IV over 5 minutes) combination in a prospective open label randomised study of 69 consecutive patients presenting with clinical and radiological findings of acute pulmonary oedema. Treatments were repeated at 60 minutes and throughout the next 24 hours if there was inadequate clinical response. Additional medication could also be introduced if there was an inadequate response to treatment. Clinical outcomes were the primary and secondary outcomes and similar improvements were observed between both groups using intention-to-treat analyses.

Unfortunately the method of randomisation and level of blinding in this study is unclear, particularly as the treatment regimens vary so widely. It is feasible that a patient may improve simply by having a continuous infusion with the knowledge that treatment is ongoing. Additionally, given the acute nature of clinical symptoms observed and the necessary provision for alternative treatments, the effect of individual therapies on outcome may be blurred. If there is no standardised procedure for initiation of additional therapies and decisions are based on clinical parameters alone, the study may be left susceptible to bias by the treating team. Variable doses of treatment medications (such as morphine 1-2mg) also make outcomes less clear per treatment dose. There were only physician-rated assessments of dyspnoea, with no assessment by the patient, which could again lead to bias. Of note also is that morphine did not cause respiratory depression which is often quoted as a reason not to use opioids in cardiorespiratory disease.

More recently, the ADHERE study (Peacock *et al.*, 2008) provided a retrospective analysis of 147362 episodes of hospitalisation in patients with acute decompensated heart failure. The analysis focuses on those patients who received morphine with those who did not and commented that use of morphine was an independent predictor of mortality in acute heart failure. Patients in receipt of morphine required more admissions to intensive care, had a longer hospital stay on average and were more likely to be in receipt of additional interventions. In summary, it would appear that the use of morphine in acute heart failure was disadvantageous. However, retrospective studies are only as good as the information that has been documented and there is no clear indication whether use of morphine was part of the cause of the decline of these patients, or part of the effect of the decline. For example, patients with more severe heart failure, or end-stage heart failure, may have received morphine for symptomatic relief of breathlessness, but of course these patients are more likely to die than those with less severe symptoms. In addition, as Schuler *et al.* (2008) correctly discuss in their letter following the publication of the trial, the timing or reason for morphine use is not known as it may have been used as part of anaesthesia on or prior to intensive care. Whilst this study highlights that the issue of use of morphine should be investigated, this can only adequately be achieved by the use of properly constructed RCTs.

The above trials involve opioids in patients with acute heart failure symptoms. The following systematic literature review will involve the breathlessness symptom control trials in chronic heart failure with opioids that currently exists.

Section 2) Literature review process

2.1 Selection criteria

The purpose of this literature review is to clarify the current evidence base relating to the management of breathlessness with opioids in human chronic heart failure (CHF).
A scoping search prior to the systematic search suggested that there was little published evidence regarding the use of opioids in the symptom management of human adults with CHF.

The primary research question was:

> Do opioids improve the sensation of breathlessness (dyspnoea, dyspnea) in heart (cardiac) failure in a human adult population?

2.1.1 Study designs

All randomised controlled trials (crossover and parallel design) investigating the use of exogenous opioids in the management of breathlessness in heart failure in adults were included. Observational studies involving exogenous opioids were also included. Well conducted randomised controlled trials can be viewed as the gold standard of research, whereas observational or epidemiological studies are prone to a number of potential selection biases (Gordis, 2004). However, given the paucity of research in this area, non-randomised trials of poorer quality had to be included to provide background to the topic.

2.1.2 Participants

Studies involving children were excluded as childhood cardiac diseases are often very different in aetiology to adult cardiac diseases. This was to allow comparison between similar subjects and similar aetiologies. Adults were defined in this review as participants aged 18 years and older. Trials involving acute and not chronic heart failure were excluded; as previously discussed the mechanisms for breathlessness in acute heart failure are different to those causing dyspnoea in chronic heart failure. Non-human studies were not included in this specific search, but have been discussed in chapter 2.

2.1.3 Intervention

Any type, preparation and route of administration of opioid medication were included (Step 2 analgesics: codeine, tramadol; and Step 3: morphine, fentanyl, oxycodone, hydromorphone or methadone). To generate the maximum number of studies to be included there was no restriction on the duration of treatment.

2.1.4 Outcome measures

The primary outcome measure for trials in human subjects with heart failure was patient reported breathlessness using validated scales (Borg breathlessness scale, Numerical rating scale, Verbal rating scale, Visual Analogue scale). These are recognised scales for the measurement of breathlessness as described in Chapter 1 Section 4. Secondary outcome measures in these trials included quality of life, sleep, patient satisfaction, activities of daily living, mood, secondary care admissions and adverse events (major and minor). These outcome measures will be particularly valuable from a patient perspective and for clinicians who manage heart failure as they describe the physical and emotional impact of any changes in breathlessness severity.

Section 3) Search strategy

The Cochrane library, Medline (1950 - 01/03/2009), Embase (1980 - 01/03/2009) and Cinahl (1982 – 01/03/2009) databases were searched using the National Electronic Library for Health (NELH) advanced search engine. At the time of writing, this has now become the NHS Evidence Health Information Resources Portal. An example of the search strategy used on Medline is outlined below. There was no limitation with regards to dates or language in order to minimise bias. It is unlikely that a search of other key databases (e.g.AMED, PsychINFO) would produce results of relevance given this clinical topic.

Search strategy (Medline 1950-present) using NELH advanced search platform:

1. SEARCH: OPIOID
2. SEARCH: ANALGESICS-OPIOID#.DE. OR RECEPTORS-OPIOID#.DE.
3. SEARCH: OPIATE
4. SEARCH: ENDORPHIN
5. SEARCH: ENDORPHINS#.W..DE. OR BETA-ENDORPHIN#.DE.
6. SEARCH: ENKEPHALIN
7. SEARCH: ENKEPHALINS#.W..DE.
8. SEARCH: DYNORPHIN
9. SEARCH: DYNORPHINS#.W..DE.
10. SEARCH: 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
11. SEARCH: MORPHINE
12. SEARCH: MORPHINE#.W..DE.
13. SEARCH: DIAMORPHINE
14. SEARCH: TRAMADOL
15. SEARCH: TRAMADOL#.W..DE.
16. SEARCH: CODEINE
17. SEARCH: CODEINE#.W..DE.
18. SEARCH: METHADONE
19. SEARCH: METHADONE#.W..DE.
20. SEARCH: OXYCODONE
21. SEARCH: OXYCODONE#.W..DE.
22. SEARCH: HYDROMORPHONE
23. SEARCH: HYDROMORPHONE#.W..DE.
24. SEARCH: FENTANYL
25. SEARCH: FENTANYL#.W..DE.
26. SEARCH: ALFENTANIL
27. SEARCH: ALFENTANIL#.W..DE.
28. SEARCH: BUPRENORPHINE
29. SEARCH: BUPRENORPHINE#.W..DE.

30. SEARCH: 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29
31. SEARCH: BREATHLESSNESS
32. SEARCH: BREATHLESS$
33. SEARCH: DYSPNEA
34. SEARCH: DYSPNEA#.W..DE.
35. SEARCH: DYSPNOEA
36. SEARCH: 31 OR 32 OR 33 OR 34 OR 35
37. SEARCH: CARDIAC ADJ FAILURE
38. SEARCH: HEART-FAILURE-CONGESTIVE#.DE. OR CARDIAC-OUTPUT-LOW#.DE.
39. SEARCH: LEFT ADJ VENTRICULAR ADJ SYSTOLIC ADJ DYSFUNCTION
40. SEARCH: VENTRICULAR-DYSFUNCTION-LEFT#.DE.
41. SEARCH: HEART ADJ FAILURE
42. SEARCH: 37 OR 38 OR 39 OR 40 OR 41
43. SEARCH: 1 OR 2 OR 3 OR 30
44. SEARCH: 36 AND 43
45. SEARCH: 44 AND 42
46. SEARCH: 42 AND 43
47. SEARCH: (10 OR 30) AND 36
48. SEARCH: (10 OR 30) AND 42
49. SEARCH: 47 AND 48
50. SEARCH: 49 AND (CLINICAL-TRIALS# OR PT=CLINICAL-TRIAL#)

Reference lists from eligible studies were reviewed to identify further studies of relevance. The National Research Register and MRC Research Register were searched to identify any funded research in progress. Searching the grey literature was not possible as part of this student project.

Section 4) Literature review search results (01/03/2009):

The results for three database searches (Medline, Cinahl and Embase) are shown in the figures below. Search results are given for the three main search categories, with subsequent results of all three categories combined in an amalgamated category. A description of those articles that appear potentially relevant based on title and abstract of the article are also given. In addition to this, the search of the Cochrane library (01/03/2009) revealed 22 results from Cochrane central register of controlled clinical trials involving the search terms: opioid (all text) and heart or cardiac failure (all text). One article was found of relevance (Johnson *et al*, 2002).

Figure 3.4.1: Results from the Medline database search (1950 - 01/03/2009):

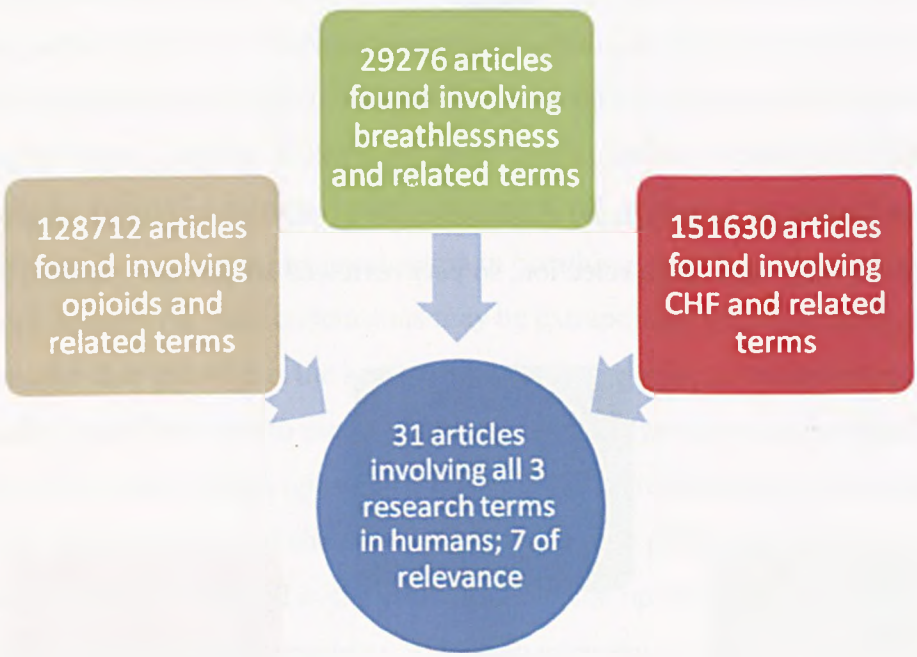


Figure 3.4.2: Results from the Embase database search (1980 - 01/03/2009):

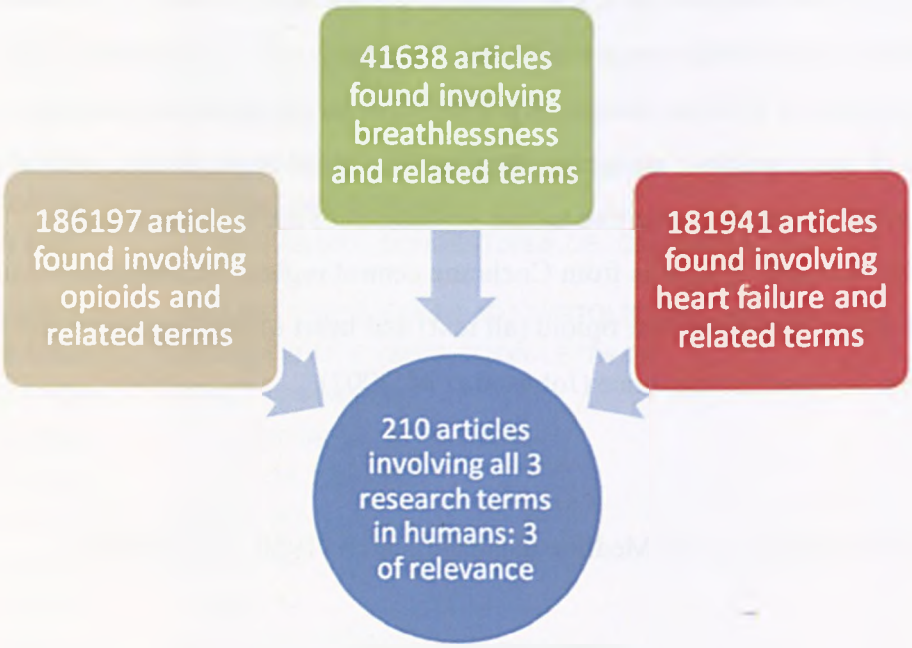
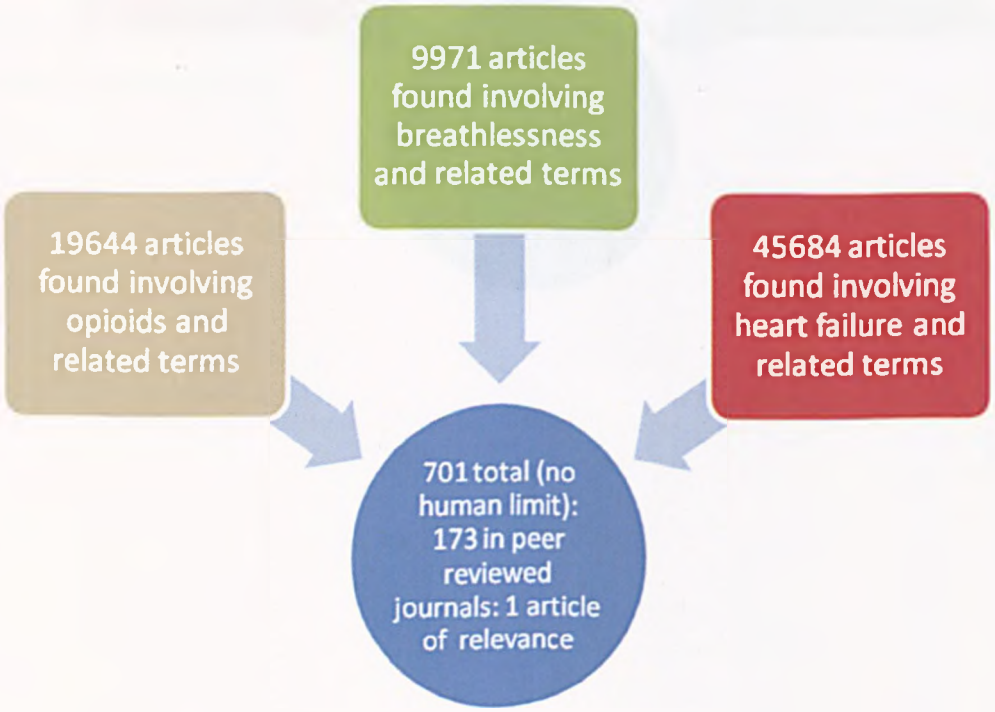


Figure 3.4.3: Results from the Cinahl database search (1982 – 01/03/2009). This database does not have a limit for human selection, so peer reviewed articles are included as an extra step:



In total, eight articles of relevance were discovered using the above measures once duplicates from the databases were removed. Three articles were discarded from this list. The rejected articles are documented in Table 3.4.1. The article by Westphal & Campbell (2002) involving nebulised morphine for dyspnoea in patients with a terminal illness, including CHF, did not contain any primary data and was thus discarded. The article by Gauna *et al.* (2008), involving the use of opioids in four terminally ill patients with breathlessness did not recruit any patients with CHF. The authors had CHF in their selection criteria and so the article was selected by the search engine, but the four patients involved in the trial had diagnoses of COPD, lung cancer or pulmonary fibrosis and hence the trial was rejected on the basis that it did not involve CHF.

As described in Chapter 1 Section 4, abnormal breathing patterns are associated with poorer prognosis in CHF (Leung *et al.*, 2006, Leung *et al.*, 2003, Corrà *et al.*, 2006). Ponikowski and colleagues (Ponikowski *et al.*, 1999) noted an association of abnormal breathing patterns with more advanced symptoms, reduced baroreceptor activity and increased chemosensitivity when compared to heart failure patients with normal breathing patterns. The role of chemoreceptors is of potential interest given that they are also implicated in sympathetic overstimulation in CHF. A recent review by Buchanan *et al.* (2009) details the role of chemoreceptors in breathing control and breathlessness in respiratory disease, but their conclusions may be extrapolated to breathlessness in CHF. They consider that the NTS is the key location for the relaying of chemoreceptor information to the forebrain to mediate the sensation of dyspnoea. As previously noted, the NTS is also a site of high opioid activity. Opioids therefore may have an important role at this site in the relay of chemoreceptor information processing in higher centres in dyspnoea in CHF. As detailed in the previous chapters, opioids may play a role in attenuating the sympathetic overdrive, reduced baroreceptor activity and increased chemosensitivity associated with advancing CHF. Hence those patients with abnormal breathing patterns may benefit the most from administration of exogenous opioids for breathlessness.

Administration of dihydrocodeine, a weak opioid, to eight of these patients in a randomised double blind placebo controlled manner led to an improvement in breathing pattern and associated significant reduction in chemosensitivity (Ponikowski *et al.*, 1999). Four of these patients with periodic breathing had a return to entirely normal breathing patterns following addition of dihydrocodeine. These results add to their earlier

findings discussed later in this review (see Chua *et al.* (1997)). This study is not included in the formal literature review as there was no subjective measurement of dyspnoea in the participants.

Table 3.4.1: Table of excluded studies following literature search

Author	Trial description	Reason for rejection
Westphal & Campbell 2002	Observations of use of nebulised morphine of terminal dyspnoea in general	No primary data; review only of use of nebulised morphine and reviewers experience without documented data
Gauna et al 2008	Observational study of use of morphine in 4 patients with dyspnoea	No patients with CHF selected, though this was part of the inclusion criteria for the study as a potential cause for breathlessness allowing inclusion
Ponikowski 1999	RCT of dihydrocodeine versus placebo in 8 CHF patients	Documented change in breathing pattern but no subjective patient rating of change in breathlessness

Section 5) Human symptom control studies in CHF: Included studies

Five articles that matched the selection criteria were therefore included. All of these studies were limited by small sample size. Methodological quality, assessed using scales such as the Jadad score (Jadad *et al.*, 1996) was not attempted as so few identified trials were blinded RCTs. Level of evidence grading using a NICE guideline approach (Gysels and Higginson, 2004) was performed and is detailed in Table 3.5.1.

The first of these studies to describe involves the use of the weak opioid, dihydrocodeine. It has already been noted that codeine administration allows greater toleration of hypercapnea in normal subjects (Stark *et al.*, 1983), potentially via chemoreceptor manipulation. Chemoreceptors monitor levels of blood gases in the circulation and are thought to influence respiratory function by altering respiration according to serum levels of oxygen and carbon dioxide (Duffin & McAvoy 1988). It is considered that these chemoreceptors become upregulated in chronic heart failure, resulting in an exaggerated sensitivity to reduction in circulating oxygen or increased carbon dioxide, leading in turn to an augmented ventilatory response and hence the sensation of breathlessness (Chua *et al.*, 1996). As described in previous chapters, opioids may be involved in reducing the sympathetic activation that is involved in the upregulation of these chemoreceptors. As can be seen in Figure 1.3.4, reduction in chemoreceptor activation may alter the activation of the major detrimental neurohormonal systems in CHF (namely the sympathetic system and RAAS). Chua *et al.* describe the effect of dihydrocodeine on breathlessness and exercise tolerance in 12 male heart failure patients in a randomised double blind placebo controlled trial (Chua *et al.*, 1997). Participants received placebo or dihydrocodeine (1mg/kg body weight) on separate days, one hour prior to exercise and chemosensitivity assessment. Taking an average male to weigh 70kg, this represents a conventional treatment dose of dihydrocodeine (British National Formulary, 2006). Participant blinding was attempted by dissolving interventions in identical lemon drinks prepared by pharmacy. Details as to the randomisation of the sequence of study medication are not given. This is important as if the majority of participants received the active intervention second they may be more used to the subjective testing procedures, leading to bias in the results, particularly in a small study. However, the sequence should not alter the characteristics of the physical (non-subjective) chemosensitivity tests. Also, for chronic disease states, the effect of repeated dosing rather than single dosing is likely to have greater clinical impact.

Given this, the authors noted a significant fall in hypoxic chemosensitivity in these patients with dihydrocodeine compared to placebo (mean reduction of 40% from placebo value; p value = 0.005). Similar but less impressive results were discovered for hypercapnic chemosensitivity (a mean difference of 16% from placebo values p=0.01). These reductions in chemosensitivity were coupled with a corresponding increase in exercise tolerance (mean exercise duration 455 seconds {SE +/- 27 seconds} versus 512 seconds {SE +/- 27 seconds} on dihydrocodeine; p = 0.001) and peak oxygen consumption (mean 18.0 ml/kg/min +/- 0.6 ml/kg/min versus 19.7 ml/kg/min +/- 0.6 ml/kg/min; p = 0.002) on the active treatment. The Borg score, a subjective measure of breathlessness, was also lower in the active treatment group, indicating a symptomatic improvement. However, it was only significantly lower after 6 minutes of exercise and was not significantly different at peak exercise. Even at 6 minutes, the mean difference in the 11 point Borg score between placebo and dihydrocodeine was only 0.69. It is questionable as to whether this truly relates to a notable symptomatic improvement, as a difference of greater than one point on the Borg scale is considered to be clinically significant (Booth, 2006). In addition, these last three measures may be influenced by treatment sequence. The article concludes that manipulation of chemosensitivity with opioids may benefit patients with chronic heart failure by reducing the elevated sensitivity of chemoreceptors, reducing the sensation of breathlessness and thus improving exercise tolerance.

In a similar study, sixteen consecutive stable chronic heart failure patients were recruited to a prospective randomised placebo controlled trial involving low dose diamorphine (Williams *et al.*, 2003). Patients completed a modified Bruce treadmill exercise protocol immediately following either placebo or diamorphine 1-2mg IV. The study is defined as randomised double blind but there are no details to the blinding or randomisation process. It is unclear as to why different doses of diamorphine were used for different participants.

Again, the authors noted a significant improvement in aerobic exercise capacity with diamorphine through a significant reduction in ventilatory response. Interestingly, the greatest improvement occurred at sub-optimal exercise levels, which might suggest that opioids would assist those most with breathlessness on moderate exertion. Mean oxygen consumption at 6 minutes was 15.7 ml/kg/min (SEM: 1.0 ml/kg/min) for diamorphine versus 14.7 ml/kg/min (SEM: 0.9 ml/kg/min) for placebo (p = 0.01). At maximal

exercise mean oxygen consumption was 21.1 ml/kg/min (SEM 1.6 ml/kg/min) and 20.2 ml/kg/min (SEM: 1.5 ml/kg/min) respectively in favour of diamorphine. However, these results might be counter-intuitive, as for a given workload a lower oxygen consumption would be preferable. There was also no significant difference with treatment on exercise duration. Unfortunately there was no patient related assessment of an improvement in breathlessness performed to correlate with the physical aerobic improvement. It is unclear therefore how this study relates to breathlessness in CHF. As for the study by Chua *et al.* (1997) there were no participant withdrawals and low opioid doses were considered to have a good safety and side effect profile.

A randomised double blind placebo controlled crossover pilot study evaluated the effect of oral morphine on breathlessness in 10 NYHA grade III/IV heart failure patients (Johnson *et al.*, 2002). Patients were randomised to oramorph 5mg four times a day or placebo for four days followed by a two day washout. The crossover design allowed patients to act as their own controls. Randomisation was performed by an external source and participants and investigators remained blind to intervention. Breathlessness scores on a 100mm visual analogue scale improved significantly from baseline to day one on active treatment (median improvement of 23mm: $p = 0.022$). It could be argued that mean values could have been used to describe values for visual analogue scores. Interquartile ranges were given alongside median values as a measure of variability. The improvement was maintained throughout the active treatment course. A placebo response was also observed which returned to baseline values at day four of treatment. Six of the ten participants correctly identified the active treatment arm, but the majority of these participants received morphine as the first intervention in the crossover. It should be noted that this is the only repeat dose study of opioids solely in CHF patients. The authors conclude that oral morphine has a role in relieving breathlessness in heart failure patients.

The use of nebulised morphine has been discussed in a two patient case reports based on the manipulation of peripheral opioid receptors in the lung (Farncombe and Chater, 1993). Nebulised therapy was added to an optimal heart failure treatment regimen, with an initial subjective benefit. However, therapy had little effect on blood gases or vital signs in the two patients and ultimately one patient had to be converted to subcutaneous morphine as she did not tolerate the nebulised treatment. Most of the study observations came from physician or nurse rated improvements rather than patient rated changes and no formal methods of subjective assessment of breathlessness were used. Co-morbidities

such as pre-existing lung disease and multiple concurrent therapies administered during the intervention may be confounding factors. In general, the use of nebulised morphine has fallen out of favour in the clinical management of breathlessness for all diseases due to its lack of consistent objective benefit (Jennings *et al.*, 2001) and the presence of alternative routes that are easier to administer to patients.

Currow *et al.* (2007) produced a further analysis of the study by Abernethy *et al.* (2003) involving patients with intractable dyspnoea from various aetiologies. Originally, participants were given 20mg of sustained release oral morphine or placebo per day for four days in a randomised controlled crossover fashion. In the original study, 38 patients were recruited, of which four were described as having a cardiovascular co-morbidity. Compared to those patients who did not have any documented cardiovascular disease, those with an abnormality responded better to morphine versus placebo (mean response 39% change in breathlessness score with morphine versus placebo on a 100mm VAS compared to 10% mean change if no cardiovascular disease was present). This outcome is potentially of interest, given that patients with cardiovascular disease (including CHF) may benefit more from opioids for breathlessness than those without. However, this secondary analysis has a number of potential flaws. Firstly, the sample number (four affected patients out of 38) is too low to derive meaningful outcomes. Secondly, other factors such as a better performance status and lack of availability of home oxygen are also associated with a better response to morphine. Of course, we do not know whether the patients with cardiovascular disease have better performance status in this trial, or availability to home oxygen, and it is possible that these patients respond better due to the presence or absence of these factors and not due to their underlying disease. Presumably the authors cannot factor these potential differences into the statistical analysis due to the small sample size. Thirdly, the original crossover study had no washout period between interventions which may have allowed a carryover of treatment effect from first to second interventions, although comparison of end of treatment, rather than change from baseline was performed. In essence, the single assessment at day 4 of treatment meant that a four day washout period occurred between interventions. It is open to question whether this four day period was sufficient to be confident that an adequate period was observed between assessments. The Summary of medicinal Product Characteristics (Napp Pharmaceuticals) for sustained release morphine preparations quotes a systemic morphine half life of four hours, but the sustained nature of release advocates a constant release of drug for 12-24 hours dependent on preparation. Hence in effect only three days of washout occurred, which arguably still should have been

sufficient. Lastly, the original study regards all patients to have breathlessness primarily due to respiratory pathologies (mostly COPD) and not due to cardiovascular disease, which have been documented as a co-morbidity only (or non-dominant aetiology for dyspnoea). These "cardiovascular" co-morbidities are not discussed further, and may not actually involve true CHF. However, it should be appreciated that the authors do not state that patients with cardiovascular disease have better outcomes with morphine, only that further research in the area is warranted given their secondary analysis. The RCT described in Chapter 4 will provide evidence to support or disprove this notion specifically for CHF.

One further article was discovered following general reading of the research literature that did not appear in the literature searches. This illustrates the limitations of such literature reviews, however as the study was an observational pilot trial the literature search did not appear to neglect trials of great relevance. The study, by Davies *et al.* (1990) determined the response of administration of dihydrocodeine 1mg/kg in ten subjects with NYHA grade III CHF. Addition of dihydrocodeine was shown to reduce dyspnoea during exercise at a "standard" workload. Dyspnoea assessment was made using a visual analogue scale. Administration of naloxone increased dyspnoea at a standard workload in these patients. The study has only been reported as an abstract in the Cardiac Society Newsletter in 1990 and hence the outcome data and quoted statistical significance cannot be scrutinised in a proper manner. Hence, no further comment can be made regarding their quoted figures. The participants and researchers appear not to have been blinded to treatment and the interventions appear not to have been given in a random fashion. Lack of clarity concerning the methodology limits the usefulness of the study, but it has been quoted for completeness.

Table 3.5.1: Summary of human symptom control studies involving opioids:

Authors	Trial description & evidence grade	Intervention	Participant number	Results	Limitations
Chua et al 1997	Double blind crossover RCT (IB)	Oral Dihydrocodeine (1mg/kg) versus placebo	n=12 male NYHA grade II or III	Increased exercise tolerance and oxygen consumption coupled to reduced chemosensitivity. Improved subjective Borg breathlessness score	Participant number; Intervention sequence
Johnson et al 2002	Double blind crossover RCT (IA)	Oral morphine (5mg) four times a day versus placebo	n=10 male NYHA grade III or IV	Improvement in subjective breathlessness VAS score	Participant number
Williams et al 2003	Double blind crossover RCT (IC)	Intravenous Diamorphine (1-2mg) versus placebo	n=16 (n=15 male)	Improved aerobic capacity primarily by improved oxygen consumption	Unclear active intervention; Participant number; No details of blinding or randomisation
Farncombe & Chater 1993	2 patient case series (IIIC)	Nebulised morphine (2.5mg)	n=2 (1 male)	Reporter assessment of improved breathlessness and clinical status alongside other therapies	Case series; subjective observational outcomes; co-existing respiratory diseases

Table 3.5.1: Summary of human symptom control studies involving opioids (continued)

Authors	Trial description & evidence grade	Intervention	Participant number	Results	Limitations
Currow et al 2007	Post hoc analysis of cardiac patients following RCT of dyspnoea by Abernethy et al 2003 (IIIC)	Oral sustained release morphine (20mg)	n=4	Improvement in patient rated 100mm VAS score for breathlessness	Post hoc analysis of primary data only; cardiac abnormalities not detailed; Participant number; Respiratory disease defined as the cause for dyspnoea
Davis et al 1990	Observational pilot study (IIIC)	Dihydrocodeine 1mg/kg	n=10 NYHA III	Improvement in subjective VAS score on exercise	Observational study only; no blinding; abstract published only

In addition to these symptom control studies, Kindman and Fowler (1989) investigated the action of naloxone on 6 patients with stable congestive heart failure (NYHA II and III). They hypothesised that, despite clinical improvements seen in acute heart failure with opioids, that release of opioids during cardiovascular shock was a deleterious effect. Hence use of opioid antagonists may be justified. Various bolus concentrations of naloxone were administered, but there were no significant effects on cardiovascular parameters (including left ventricular pressures, cardiac output and peripheral resistance) although of course this interventional study is limited by very small participant numbers in a stable population without evidence of cardiovascular shock. No evidence of effect is not the same as no effect, but if nothing else this study demonstrates the previously perceived detrimental effects of opioid use in CHF literature.

Section 6) Chapter summary including review limitations

The criteria for inclusion of studies in CHF was broad to maximise the number of included studies in this area that has been under-researched. For example, all pharmaceutical opioids were included as therapeutic measures. Had there been sufficient trials, subgroup analyses could have been attempted for immediate and controlled release preparations, method of administration (oral, subcutaneous, IV, nebulised) and class of opioid (step 2 analgesics versus step 3). Given the heterogeneous nature of the studies selected; the type of participant; nature of intervention; difference in measurements, at rest or on exercise; no meaningful meta-analysis of the data could be performed. Only with greater clarity and standardisation of outcome measurements, greater use of randomised controlled trials and studies involving greater numbers of participants will this lack of good quality evidence be addressed.

A number of potential biases may occur from the selection of English articles only. For example, Gregoire *et al.* (1995) demonstrated a change in the outcome of one meta-analysis had non-English language articles been incorporated into the analysis. All settings, any duration of follow-up and all ethnic groups in trials were included in order to maximise the likelihood of finding eligible research. This approach conversely may reduce study validity. Level of evidence grading was performed solely by the author, but for publication in peer reviewed journals the process should be repeated by a second reviewer independent of the first, with consensus reached for selection and grading of included studies.

Only small symptom control studies in both heart failure and non-heart failure patients exist but they suggest that opioids could be beneficial in the management of breathlessness. However, the current research evidence eludes to a greater potential for the use of morphine to regulate the cardiovascular changes seen in heart failure in addition to the management of clinical symptoms such as breathlessness. Despite the vast number of studies that involve the three individual components of interest, only six studies from the systematic literature search have been identified that involve an assessment of breathlessness severity with opioid agonists in CHF. These are a heterogeneous collection of studies involving small numbers of participants (54 in total) and multiple types and doses of opioid. Clearly there is the potential for publication bias for these studies. Only three involved the collection of primary data with RCT

methodology, the gold standard of quantitative research (Tilling *et al.*, 2005), in CHF. Therefore, there is a distinct lack of good quality, adequately powered RCTs in this area of symptom control of breathlessness in CHF.

On a wider point, greater distinction must be made between those patients with stable CHF, acute heart failure and those CHF patients who have acute exacerbations as these represent three different patient groups with different likely aetiologies for breathlessness. The early literature in particular does not make this distinction clear, allowing subsequent comparison difficult. One further point is the relation of the current breathlessness trials with the actual clinical situation of living through CHF. Only one trial involving primary data collection (Johnson *et al.*, 2002) monitored the effects of multiple dosing with opioids, rather than a single dose as for the other studies quoted. Assessment of multiple dosing should take preference to single dosing if the overall clinical effect on CHF is to be determined, particularly if secondary components involved with breathlessness such as change in quality of life or physical function are to be measured in addition to alteration in breathlessness severity.
Taken together, these studies show that there is a small but expanding evidence base recommending the use of opioids in chronic heart failure patients for the management of breathlessness. So far it is unclear which cohort of patients will derive most symptom control benefit; those patients with low grade symptoms who are able to achieve greater exercise potential or those more advanced (NYHA III-IV) who have a greater symptomatic burden.

Finally, several gaps in the knowledge therefore exist in the management of breathlessness in CHF with opioids. These include the requirements for:

- A larger sample study of CHF patients with breathlessness to corroborate the findings of the ten patient pilot study by Johnson *et al.* 2002.
- An assessment of different opioids in breathlessness management in CHF, given that all the opioids quoted in the literature have a high affinity for mu receptors only, rather than the use of oxycodone that has reasonable affinity for the kappa receptor as well as the mu receptor, which may have a different response in CHF as detailed in Chapter 2.
- An expansion in data from repeated dose studies and randomised controlled trials to improve the quality of the existing literature, including safety of opioids in CHF.

- An assessment of the factors that may predispose a patient to responding to opioid therapy for breathlessness.
- A longer term follow-up of participants in receipt of opioids greater than the four days of repeat dosing by Johnson *et al.* 2002, the longest follow-up of all subjective breathlessness studies in CHF.

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Chapter 4:

Randomised controlled trial of opioids for breathlessness in heart failure

Section 1) Introduction

1.1 Why is symptom control with opioids for breathlessness in CHF important?

Breathlessness is a defining symptom of heart failure and forms the basis of the New York Heart Association (NYHA) grading. It is a cause of patient distress and has a significant impact on quality of life, which is thought to be poorer than some patients with incurable cancer (Murray *et al.*, 2002). The prevalence of chronic heart failure (CHF) is increasing with the increasing age of the population and with better survival following acute coronary events (Thomas and Rich, 2007), suggesting that symptom control will become a greater issue in a growing number of patients.

Patients with advanced heart failure can still be limited by breathlessness, despite the development of therapies currently used in standard clinical practice. These treatments have typically involved the prevention of disease progression through manipulation of neurohormones released in CHF and have been evaluated using endpoints such as rates of hospitalisation and mortality. As discussed in Chapter 3, very few studies have been performed that evaluate response to symptom control therapies, particularly in breathlessness in CHF. From this evidence there is clearly a need to further explore the role of opioids for breathlessness in CHF.

Breathlessness is a complex symptom with multifactorial aetiologies as described in Chapter 1 Section 4. Measurement of breathlessness severity is only one component of the evaluation of a breathless patient. Other modalities such as assessment of quality of life, physical function and distress caused by breathlessness are also important (Lehman, 2006a). For breathlessness in CHF in particular, sympathetic overactivation through production of norepinephrine is considered to contribute to dyspnoea through changes in respiratory patterns (Corrà *et al.*, 2006, Leung *et al.*, 2006).

1.2 Opioid therapy for breathlessness

Opioid therapy forms the mainstay of treatment for intractable breathlessness in disease states including CHF without an extensive evidence base or clarity regarding its method of action in dyspnoea (Oxberry and Lawrie, 2009). Endogenous opioids are released in

CHF as part of a global neurohormonal response. As described in Chapter 2, there is a suggestion from basic science and animal studies that endogenous opioids may counteract some of the effects of norepinephrine, one of the principle detrimental neurohormones in CHF. Small studies have shown a potential for breathlessness relief in general with opioids (Jennings *et al.*, 2001), given that opioids may counteract the effects of norepinephrine it may have an additional impact in breathlessness due to CHF.

Opioids such as morphine and oxycodone bind to the three types of opioid receptor distributed throughout the body, but it is considered that morphine preferentially binds to mu-opioid receptors, whereas oxycodone has an affinity for kappa as well as mu receptors (Davis and Pasternak, 2005). Oxycodone has a higher oral bioavailability than oral morphine and is considered to have a lower level of inter-individual variation in plasma concentrations (Kalso, 2005). Both morphine and oxycodone produce opioid-related side effects, but their relative frequencies can be different. For example, oxycodone is considered to have a lower incidence of opioid-induced itching (Kalso, 2005). Kappa receptor agonists also induce a diuretic response in humans (Rimoy *et al.*, 1991). Given that they have slightly different receptor activation profiles, have different relative frequencies of side effects and may have different effects on diuretic response, it is important to assess their relative roles in breathlessness management in CHF.

The mechanism of action of opioids in breathlessness is currently unclear. Symptom improvement may be a class effect for all opioids, but individual types of opioid may have a different magnitude of effect. The evidence for the distribution of mu and kappa receptor populations and their endogenous agonists, described in Chapter 2, suggests that exogenous agonists of these receptors may have different effects on cardiorespiratory function. The evidence for opioids in breathlessness in general involves mu agonists selectively. The additional effect of a partial kappa agonist on diuresis would make oxycodone an attractive opioid in CHF. Hence morphine, a preferential mu agonist, should be involved in breathlessness studies to allow comparison with previous studies predominantly involving mu agonists. Oxycodone is potentially an attractive alternative with its dual mu and kappa agonism. The two treatments are therefore compared with each other and with placebo to assess response.

Unlike breathlessness in cancer where there have been a number of studies evaluating the effects of opioids (see Jennings et al for Cochrane review), there has only been one small pilot study of repeat dosing in heart failure patients by Johnson *et al.* (2002). The paucity

of research into opioids and heart failure has been noted (Cushen, 1994, Fischer, 1998). Current clinical practice either involves the prescription of morphine for breathlessness or a reluctance to use morphine without efficacy studies. This double blinded cross-over study compared the effects of two opioids against placebo for the relief of breathlessness in advanced CHF.

Primary research question:

Do morphine and oxycodone relieve breathlessness in patients with NYHA grade III/IV heart failure receiving optimal medical therapy?

1.3 Aims and objectives

Primary objective:

- To assess the relative benefits of oral morphine and oral oxycodone in the management of breathlessness in advanced heart failure.

Secondary objectives:

- To monitor any subsequent changes in distress caused by breathlessness, physical function, coping with breathlessness and satisfaction with treatment.
- To assess the impact of morphine or oxycodone on quality of life in heart failure.
- To confirm tolerability of therapy in this patient population and to assess relative merits of morphine versus oxycodone.
- To explore the characteristics of breathlessness in heart failure patients.

Section 2) Trial Method

2.1 Participant profile

This study was a three-arm prospective, double-blind, randomised, placebo controlled, cross-over single centre study involving patients with NYHA Grade III/IV heart failure receiving optimal medical therapy. This patient group was selected because the impact of breathlessness is high and therefore may have the most to gain from improved breathlessness management. A cross-over design was chosen to reduce the number of study participants required as it is recognised that it is difficult to recruit to palliative care studies. Optimal medical therapy was defined as use of Angiotensin II antagonists or Angiotensin receptor blockers (ARBs) and diuretics at stable doses for at least one month. Presence of heart failure was defined by systolic impairment on echocardiography with an ejection fraction of less than 45%. A BNP blood test was also performed prior to study entry to document the severity of CHF. Patients were excluded if they had co-existing malignant disease or respiratory disease sufficient to potentially confound the results given that a clinical benefit with opioids has already been demonstrated in these patient groups. This exclusion was based on clinical history, hospital records and Peak Expiratory Flow Rate (PEFR) parameters (PEFR < 150ml/min excluded).

Patients were also excluded if they had true allergies to opioids, or if they were in receipt of any medications that have a potential interaction with opioids, which may confound the results. In addition, patients who had used any opioid medication (including weak or step 2 opioids such as codeine and tramadol) in the past month were excluded for the same reasons. Patients with a Glomerular Filtration Rate of <=30 ml/min (as calculated by the Cockcroft and Gault formula) were also excluded given that both active interventions are renally excreted.

2.2 Interventions

The two intervention arms consisted of oral morphine sulphate (5mg) and oral oxycodone (2.5mg) administered four times a day for a total of four days. All three interventions were administered in liquid form and all three were clear, colourless

liquids. The oral liquid placebo was manufactured in accordance with MHRA guidelines by Calderdale and Huddersfield NHS Trust pharmacy manufacturing unit. The placebo was designed to have very similar characteristics to the active medications (a clear, colourless liquid with the same viscosity and similar taste). Oxycodone liquid (concentration 5mg in 5ml) and Morphine liquid (concentration 10mg in 5ml) allowed equivalent opioid doses for the same volume of liquid (2.5ml for all three interventions) in order to maintain blinding.

The oral liquid placebo had to be manufactured to a pre-determined formula and method, according to guidelines set out by the MHRA. The formula of the placebo mixture was designed by Huddersfield pharmacy as was manufactured as shown in Table 4.2.1:

Table 4.2.1: Ingredients involved in the manufacture of the placebo and method of production

Ingredients	Method of production
Syrup BP 15% v/v Methyl Hydroxybenzoate 0.1% w/v Propyl Hydroxybenzoate 0.01% w/v Citric Acid 5% soln q.s Distilled water to 100% v/v	1. Make up the citric acid 5% solution 2. Dissolve the Methyl and Propyl hydroxybenzoate in 200ml of boiling distilled water 3. When dissolved add to the syrup in a 1 litre measure 4. Make up to volume with distilled water. 5. Mix well and check the pH (needs to be between 4-5). 6. Reduce the pH using the Citric Acid solution above. 7. Pack, cap and label in a 500ml amber glass bottle with Click-Lock tamper evident cap.

Trial participants were also given a supply of anti-emetic medications (Domperidone 10mg-20mg PRN TDS) and laxatives (Senna II PRN ON) for use in the event of the most common side effects related to opioid use, namely nausea, vomiting and constipation. These were referred to as concomitant medications in the trial.

2.3 Randomisation

Once eligible patients had been identified, approached and agreed to give informed consent, participants were randomly allocated to one of six possible permutations for the order of the three interventions (oral morphine, oral oxycodone or placebo). A schematic representation is detailed below in Table 4.2.2. The codes for randomisation were generated using a computer program and were kept by pharmacy who were independent of the study process. The pharmacy subsequently dispensed all three medications for use in the required sequence with identical labels except for the treatment order. Hence the investigators and participants remained blinded to the treatment sequence to prevent any methodological bias. Click-locked bottle adapters and tamper evident seals were employed to prevent incorrect utilisation of the study medications.

Table 4.2.2: The six possible combinations of the order of interventions (each participant assigned to one combination):

Combination	Week 1 treatment	Week 2 treatment	Week 3 treatment
One	Placebo	Morphine	Oxycodone
Two	Placebo	Oxycodone	Morphine
Three	Morphine	Placebo	Oxycodone
Four	Morphine	Oxycodone	Placebo
Five	Oxycodone	Placebo	Morphine
Six	Oxycodone	Morphine	Placebo

2.4 Participant Assessments

Participants were monitored on all four days whilst on treatment. Assessment of breathlessness severity, distress due to breathlessness, satisfaction with treatment, presence of side effects and use of concomitant medications occurred on all four days. A face-to-face baseline and one hour post dose assessment was conducted on day 1 and a similar assessment occurred on day 4 for each of the three treatments. In addition on these days participants undertook physical assessments and were asked to rate their quality of life, physical function, impression of change in breathlessness and description of the nature of the breathlessness. On days 2 and 3 of the four day treatment participants

were contacted by telephone. Assessments were taken at rest with the same equipment to allow standardisation. A summary of these assessments is detailed below in Table 4.2.3. Appendix 5 documents an example of the assessment booklet created for the day 1 treatment 1 assessment.

4.2.3 Schedule of assessments for each participant (repeated for each intervention)

	Day 1 Baseline	Day 1 1 hour	Day 2	Day 3	Day 4
Data collection	*Visit*	*Visit*	*Phone*	*Phone*	*Visit*
Pulse Blood pressure Respiratory rate Oxygen saturation	X	X			X
NRS* breathlessness, distress, satisfaction, drowsiness, nausea	X	X	X	X	X
Constipation	X		X	X	X
Borg score**	X	X	X	X	X
SF-12***	X				X
Breathlessness descriptors****	X				X
Karnofsky performance status†	X				X
Global rating of change in breathlessness††					X
Concomitant medication	X		X	X	X
Adverse events	X	X	X	X	X

Key:

*11-point Numerical rating scale (NRS) of average breathlessness over the past 24 hours (anchored with "not breathless" and "worst breathlessness imaginable"):

0 1 2 3 4 5 6 7 8 9 10

Not breathless — Worst Breathlessness Imaginable

NRS breathlessness scores correlate very closely with VAS breathlessness scores (Powers & Bennett 1999) whereby mean breathlessness scores are considered equivalent (eg mean 5 on NRS equates to 50 mm on VAS). Hence, the clinically important change in VAS quoted as 10% by Booth *et al* (2006) would equate to one point on an eleven point NRS.

** The Borg score, a self-assessment instrument validated for use in breathlessness (Borg, 1982) was completed. The modified Borg score was used, but will be referred to simply as the Borg score in the thesis.

*** The SF-12 validated Quality of Life (QoL) score acute version 2 (Ware *et al.*, 1996) was assessed at baseline (pre-treatment) and day 4 for each of the three study arms.

****Breathlessness descriptors (Wilcock *et al.*, 2002) used to describe the quality of a participants' breathlessness from a fifteen item questionnaire. These 15 items were presented in a random order to prevent any preference due to the order or sequence of the items.

† The validated Karnofsky performance status scale (Mor *et al.*, 1984). This scale incorporates the components of physical activity, work and self care of patients.

†† The Global rating of change score is a measurement of response to treatment (Guyatt *et al.*, 1993). Participants were asked if their breathlessness has changed and if so by how much on a verbal rating scale.

2.5 Study Endpoints

Primary: Severity of breathlessness as measured by the validated Borg score and Numerical Rating Scale (NRS) for breathlessness (average and worse over past 24 hours and current level).

Secondary: 1) Distress from breathlessness as measured by the NRS score for distress.

2) Satisfaction with treatment of breathlessness and coping with breathlessness as measured by the NRS scores for satisfaction and coping with breathlessness.

3) Assessment of the overall change in breathlessness severity as measured by the Global rating of change in breathlessness score.

4) Assessment of the characteristics of breathlessness in heart failure patients by using the descriptors for breathlessness.

5) Adverse effects as measured by NRS scores for nausea and drowsiness, constipation assessment, use of concomitant medications and identification through self report of other events that may or may not be attributable to study drug.

6) Toleration of therapy through compliance monitoring and safety profile of each intervention through measurement of physical observational parameters.

7) Quality of life scores as measured by the validated SF-12 Quality of Life Questionnaire.

8) Change in validated Karnofsky performance scale of physical activity.

2.6 Statistical considerations

Initial assessment by a statistician of sample size using modelling techniques from the morphine pilot study by Johnson *et al* (2002) suggested that a sample size of 33 evaluable patients would be required to determine a one point change in breathlessness score ($\alpha = 0.05$; $\beta = 0.8$). Further discussions with Professor Martin Bland, Professor of Statistics in Healthcare at York University led to a feasible aim for recruitment of 48 participants in order to achieve enough data for analysis allowing for a generous withdrawal rate of over 30%. This is important to allow for in studies with patients with advanced disease where withdrawal rates may be quite significant.

Study data were entered and analysed using the SPSS statistical package version 14. All data were analysed according to intent-to-treat criteria. Statistical comparisons compared the measurements of primary and secondary outcomes between individuals for each treatment. As the results from a crossover trial are not independent, this involved the use of paired methods of comparison of outcomes between treatments, for example the

Wilcoxon Signed Rank test for continuous non-parametric data. Paired t-tests were used if the data was normally distributed. McNemars test was used for any paired dichotomous data. These statistical tests do not allow for period effects, so the likelihood of such effects were also measured. Senn (2002) recommends the calculation of a change in a parameter between individual active treatments and placebo, allowing the difference between individual treatments to be observed and this approach was adopted in the analysis.

Missing data is a well recognised problem in longitudinal studies, particularly with patients with advanced disease. Missing data was managed by using extreme values. By making the assumption that the missing value is the worst it could be for the intervention and the best it could be for the placebo, if there remains a statistically significant difference between active treatment and placebo then one can be sure that the results are robust. Other techniques that were considered involved building a regression equation to predict the value of the missing data from the baseline characteristics from patients with no missing values or the use of other imputation techniques.

At the end of the study, the participants were asked which of the three arms they prefer most and were given the opportunity to continue that treatment on an open-label basis if an active drug was identified. As a continuation to the study, participants were invited to return three months after cessation of the study for a repeat BNP blood sample and repeated assessment measures to assess the effect of therapy over a longer time period. The results from this open-label follow-up are discussed in Chapter 6.

2.7 Regulatory approvals

This clinical trial for investigational medicinal products was conducted in accordance with the UK regulations for clinical trials 2004. The study was given authorisation by the Leeds East Ethics Committee, Hull and East Yorkshire Research and Development Department and Medicines and Healthcare Regulatory Authority (MHRA). Yearly updates were required for Ethics and the MHRA to highlight study progress and presence of adverse events. The local NHS Research and Development department audited the study every three to six months to ensure adherence to Good Clinical Practice guidelines. These guidelines were strictly adhered to, particularly in respect of adverse event, serious adverse event and serious unexpected adverse event reporting in accordance with

standard operating procedures for clinical trials. Details of trial reference numbers are given in Appendix 3.

2.8 Ethical considerations

Given the nature of the patient population, an attempt was made from the outset to incorporate the minimum number of assessments and measurements necessary so not to inconvenience the participant unduly but to monitor the effects of treatment closely. The length of the trial overall (three weeks), the nature of assessments (face to face on days 1 and 4 and via telephone on days 2 and 3) and the flexibility of the researcher in the place of assessment (clinic, hospital ward or home) reflected the consideration for trial participants. The study adhered to the Good Clinical Practice guidelines for the reporting of adverse events as set out by the Hull and East Yorkshire NHS Trust R&D department standard operating procedures.

Section 3) Results: Screening information, demographic data and period-sequence interaction assessment

The Academic Cardiology heart failure database was utilised to screen potential trial participants. Patients attending heart failure clinics were screened in a period from 15th November 2007 to 30th April 2009 (18.5 months in total). The screening results are described in Figure 4.3.1. From the 2135 patients identified on the database as complaining of dyspnoea, only 239 of these were identified as being potentially eligible for study inclusion. These patients were all reviewed in clinic to assess eligibility. Of these patients, only 84 patients fulfilled the inclusion criteria of the study. Reasons for non-inclusion of the remainder are described in Table 4.3.1.

Figure 4.3.1: Consort diagram for patient screening and inclusion to RCT:

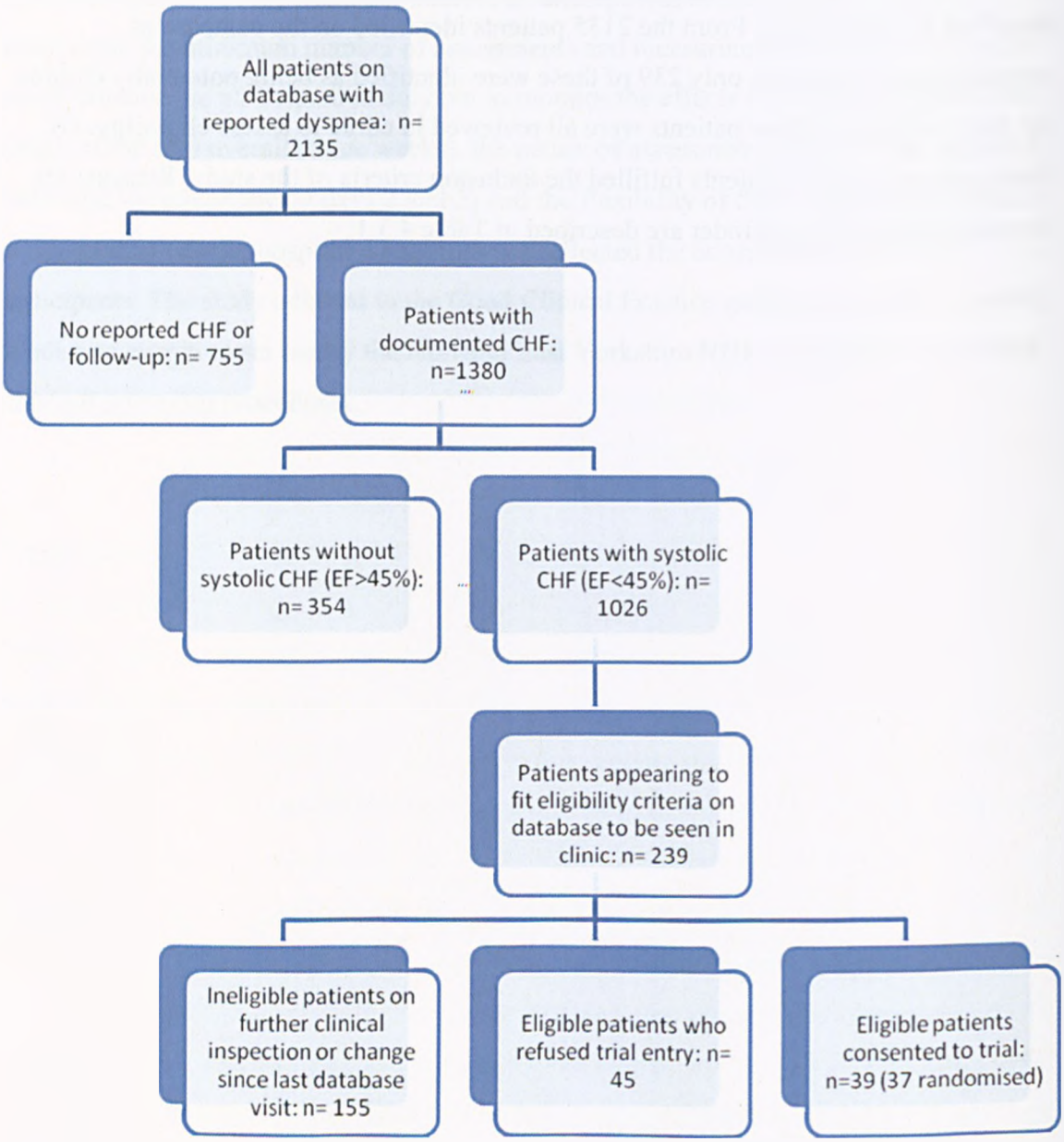


Table 4.3.1: Reasons of ineligibility for patients identified through the heart failure database (n=237 of which 84 eligible)

Reason	Patient number
NYHA II at clinic	47
No breathlessness described at clinic	9
COPD / Asthma / Lung pathologies coexistent	18
Renal failure (GFR <30)	5
Not in receipt of ACEI, ARB or Diuretic	4
Drug change at clinic visit	9
Receiving opioids already	9
In other medical trials involving trial medications	9
Improved EF at clinic visit (EF too high)	11
Ineligible according to investigator – including too poorly for entry, multiple co-morbidities, previous compliance issues, main carer to ill spouse, due CRT or PPM in near future, drugs with known opioid interaction, opioid allergy	34

3.1 Participant sample data

Table 4.3.2 below describes the baseline demographic data for all randomised participants. Thirty-five participants completed all three treatment periods in the RCT and are included in the overall analysis. Two participants withdrew due to adverse events and their details are described below. The sample is predominantly an elderly male one, with ischaemic heart disease as the predominant aetiology. Most patients were receiving both beta-blocker and ACEI/ARB therapy in accordance to the current clinical guidance. It should be noted that all participants were in receipt of either and ACEI or an ARB in concordance with the inclusion criteria, with some participants on both treatments. There were no obvious differences in baseline characteristics between completed patients and those that withdrew from the study.

Table 4.3.2: Demographic data for included patients (n=35)

Age (Mean +/- SD) Range	70.2 years (+/- 11.1 years) 41 – 89 years
Gender	Male 30 ; Female 5
Documented Aetiology	DCM 3 IHD alone 25 IHD / Hypertension 7
NYHA Grade	Grade 3: 31 Grade 4: 4
Ejection fraction: Mean +/- SD	33.5% +/- 6.5%; range 15% to 44%
GFR Calculated: (Mean +/- SD)	70.4 ml/min +/- 36.2 ml/min
eGFR: (Mean +/- SD)	55.6 ml/min +/- 19.4 ml/min
Beta blocker present	30
ACEI present	28
ARB present	26
Aldosterone antagonist present	21
Digoxin present	4
BNP : mean and median	Mean 210.3 pmol/l; Median 91.1 pmol/l
PEFR: mean and median	Mean 262.1 l/min; Median 246 l/min

The two participants that withdrew were males aged 65 and 74 years, both NYHA 3 with aetiology of DCM and IHD respectively. Ejection fraction for these two patients lay just above the mean for completed patients (36% and 40%) with calculated GFR either side of the mean value for completers at 72 and 48 ml/min respectively. Both of these patients were in receipt of ACEI and Aldosterone antagonists with one patient also receiving beta-blocker and digoxin therapies. BNP levels were 103 and 91.4 pmol/l for both patients, a little below the mean value for the 35 included patients but still within the overall range of BNP values and close to the median value for the sample. Peak flow results were 190 and 232 l/min, just lower than the median value for the sample, but not at the extremes of measurements. In this regard, these patients had no obvious demographical baseline differences to the patients who completed the study. Thirty-five participants were included in the subsequent data analysis.

Baseline values for NRS and Borg scores for breathlessness and Karnofsky status are detailed in Table 4.3.3. This table demonstrates this population has average levels of breathlessness of over 5 on an 11-point NRS, with episodes of breathlessness at their worst measuring an average of over 7/10 on an 11-point NRS. Overall this indicates a moderate to high level of breathlessness in this sample population. A Mean Karnofsky score of 70 represents a level at which the participant cares for self, but is unable to carry on normal activity or to do active work.

Table 4.3.3: Mean, median and sample variability as measured by the standard deviation for breathlessness severity (average and worst) and performance status at baseline for the 35 included participants.

	NRS Average breathlessness	NRS Worst breathlessness	Borg Worst breathlessness	Borg Average breathlessness	Karnofsky score
Mean	5.1	7.2	4.3	2.9	70
Median	5	7	4	3	70
Standard deviation	1.80	1.53	2.03	1.40	5.90

3.2 Sequence and Period Analysis

A period effect occurs when the response to treatment changes over time (from one period to another), for example due to a change in the underlying disease. A sequence or treatment-period effect occurs when there is a difference in response from one treatment period to the next, most often in crossover trials due to the "carrying over" of a treatment effect due to an inadequate drug washout phase. Both of these two potential effects are important as the results due to a treatment may not be valid if either of these two properties exist. There are a number of different ways in which possible period and sequence effects can be determined. This section will review and test some of these approaches.

The results from the NRS of average response to breathlessness were taken for comparison, as this scale was defined as the primary outcome measure for the study. First, the Day 4 responses in NRS Average breathlessness were subtracted from the Day 1 (baseline) responses for each of the three treatment interventions. These were then

divided into two groups of two interventions: the first with oramorph followed by placebo, and vice versa; secondly those participants who received oxynorm before placebo and vice versa. The data was treated as for two separate crossover trials involving oramorph and placebo, and oxynorm and placebo. The treatment / period response between oramorph and oxynorm (both active interventions) was not considered relevant.

In accordance with the management plan set out by Altman (1991), tables were produced as shown below for oramorph and placebo, then oxynorm and placebo:

D1-D4 Placebo response on NRS (1)	D1-D4 Oramorph response on NRS (2)	(1)-(2) difference	(1)+(2)/2 average

In total four tables were produced, reflecting the four different sequences (oramorph before placebo; placebo before oramorph: oxynorm before placebo; placebo before oxynorm).

To test for a period effect, given that the data was not normally distributed, Mann-Whitney U tests were employed to assess the potential impact of time on the outcome between active and placebo treatments. Non-significant results indicate no evidence of a period effect.

These results are as follows:

Placebo before Oramorph versus Placebo after Oramorph: $p = 0.208$

Placebo before Oxynorm versus Placebo after Oxynorm: $p = 0.243$

In the absence of a sequence effect, the patients average response to interventions should be the same regardless of the order in which the interventions are administered. Firstly, one can compare the baseline results for each week of therapy, to ensure that the three day washout was adequate. If it was not, one could expect to see lower mean NRS Average breathlessness scores following active treatment the preceding week. Tale 4.3.4 illustrates the NRS breathlessness scores for each intervention for each of the six possible treatment sequences.

Table 4.3.4: Mean baseline average NRS and average Borg breathlessness scores prior to each of the three interventions by treatment sequence

Sequence	Oramorph		Oxynorm		Placebo	
	Mean NRS	Mean Borg	Mean NRS	Mean Borg	Mean NRS	Mean Borg
Oramorph-Oxynorm-Placebo (n=4)	4.50	2.75	4.00	2.25	3.25	1.75
Oramorph-Placebo-Oxynorm (n=5)	4.00	2.60	4.40	1.80	5.40	3.20
Oxynorm-Oramorph-Placebo (n=6)	2.67	1.67	5.33	2.75	4.67	2.75
Oxynorm-Placebo-Oramorph (n=6)	4.83	2.83	5.50	2.83	5.67	2.33
Placebo-Oramorph-Oxynorm (n=6)	4.50	2.50	3.83	2.17	5.17	2.50
Placebo-Oxynorm-Oramorph (n=8)	4.25	3.13	5.13	3.48	5.50	3.56

Note that the numbers for each sequence are not identical (not the same numbers in each group) due to the sampling procedure – sequences were determined at random, rather than using block design which would attempt to equalise the numbers in each sequence group.

If the active drugs were not having adequate washout, one would expect the placebo baseline values to be low compared to when placebo was administered first, before the active interventions. Also, if the second active intervention also had a low value following the first active intervention, this could be interpreted as being a negative washout period or residual drug still being present. If placebo values were low after both active interventions this may imply a synergistic response if washout has not been effective. In the case of the table above, it can be seen that when placebo is given first, the NRS average values are little different to when placebo is second following either oramorph or oxynorm, suggesting that there is no effect from week 1 active drug and the following weeks' placebo.

A more formal analysis of sequence effect is determined by using the Mann Whitney U test for non-normal data, as shown below for comparison of the mean average NRS scores for the two periods for oramorph/placebo and oxynorm/placebo:
Average of the 2 periods (Placebo before Oramorph and Oramorph before placebo): Mann Whitney U test – $p = 0.512$
Average of the 2 periods (Placebo before Oxynorm and Oxynorm before placebo): Mann Whitney test –$p = 0.853$
Both of these values are non-significant indicating no evidence of any treatment-period interaction.

Finally, two scatterplots of the difference between the periods against the average of the periods were performed for oramorph versus placebo and oxynorm versus placebo. Vertical separation of the groups is indicative of a difference between the treatments. If there is no treatment-period interaction there should be no horizontal difference between the groups, and the data should lie symmetrically either side of the line y=0. These have been performed but are not shown.

An alternative method to assess for period and sequence effect is to use analysis of variance {ANOVA}(Bland and Altman, 2007). One way analysis of variance for treatment-period and period demonstrate no statistically significant results, indicating no evidence of a treatment-period or period effect with day 4 outcomes (F value 1.96 and $p= 0.15$ when period is a factor and $F= 0.12$ and $p= 0.89$ when treatment is a factor). In summary, the above calculations reveal that there were no notable treatment-period or period interactions, allowing further analysis of the data to occur.

4.1 Treatment differences in primary outcome: breathlessness severity

Table 4.3.5 below demonstrates the differences between baseline (day 1) and completion of the intervention (day 4) for each of the three interventions. Positive values represent a reduction in rating score and hence symptom improvement. Negative values represent symptom deterioration. Differences were calculated as described in the RCT protocol.

Table 4.4.1: Shortness of breath outcomes for all three interventions (mean difference with standard deviation: n=35)

	Oramorph	Oxynorm	Placebo
NRS Average breathlessness: Mean difference (SD) and median difference	Mean 0.41 SD 2.51 Median 1	Mean 1.29 SD 2.19 Median 1	Mean 1.37 SD 1.86 Median 1
NRS Worst breathlessness: Mean difference (SD) and median difference	Mean 0.80 SD 2.55 Median 1	Mean 1.43 SD 2.70 Median 1	Mean 1.91 SD 2.50 Median 2
Borg Worst breathlessness: Mean difference (SD) and median difference	Mean 0.16 SD 2.06 Median 0.5	Mean 0.87 SD 2.31 Median 1	Mean 0.80 SD 1.93 Median 1
Borg Average breathlessness: Mean difference (SD) and median difference	Mean -0.01 SD 1.96 Median 0	Mean 0.33 SD 1.67 Median 0	Mean 0.27 SD 1.66 Median 0

As can be seen from these results, there is a notable placebo response in all measurements of breathlessness, whether rated on average in the day or at its worst in the day. Of the two active interventions, oxynorm had the higher mean difference in scoring compared with oramorph, which had the only increase in score (a very slight worsening of breathlessness from day 1 to day 4 of treatment). Overall the changes in NRS scoring are small, but are consistent with a one point improvement regarded as a clinically

important difference. Mean differences for Borg are lower than those for NRS and this factor will be explored later.

The data was generally normally distributed, sometimes it had a positive skew (Q-Q plots for normality performed but not shown). In order to allow comparison between ratings for NRS and Borg for average and worst breathlessness severity, paired non-parametric tests were the most suitable. Wilcoxon signed ranks tests were used to test for associations between interventions (day 1 to day 4 differences compared) for both NRS and Borg scoring systems. The results from these tests are shown in Table 4.4.2:

Table 4.4.2: Wilcoxon signed ranks test results for breathlessness severity change (day 1 minus day 4 scores) between the three interventions

Rating scale	Wilcoxon comparison between interventions
NRS Average breathlessness	Placebo change in score versus Oramorph change: Z = -1.52; p= 0.129 Placebo change in score versus Oxynorm change: Z=-0.13; p=0.893 Oxynorm change in score versus Oramorph change: Z=-1.70; p=0.089
NRS Worst breathlessness	Placebo change in score versus Oramorph change: Z = -1.69; p= 0.092 Placebo change in score versus Oxynorm change: Z= 0.68; p= 0.50 Oxynorm change in score versus Oramorph change: Z=-0.81; p=0.42
Borg Worst breathlessness	Placebo change in score versus Oramorph change: Z=-1.41; p= 0.16 Placebo change in score versus Oxynorm change: Z=-0.087; p=0.93 Oxynorm change in score versus Oramorph change: Z=-1.05; p=0.29
Borg Average breathlessness	Placebo change in score versus Oramorph change: Z = -0.30; p= 0.76 Placebo change in score versus Oxynorm change: Z=-0.34; p= 0.73 Oxynorm change in score versus Oramorph change: Z=-0.65; p=0.52

There are no significant differences between treatments for any breathlessness rating scale. This is unsurprising given the placebo response seen in Table 4.4.1. One might argue that there is a trend favouring oxynorm over oramorph in change of breathlessness, particularly on the Average NRS breathlessness measure (p = 0.09), but this is not supported by the other measurement tool outcomes.

How do the responses compare for each individual case? Table 4.4.3 below documents the mean change in breathlessness score from day 1 to day 4 (with standard deviation)

for participants between oramorph and placebo and oxynorm and placebo. Negative values represent a greater mean improvement for placebo than active treatment. The overall differences in mean responses to active treatment versus placebo are small.

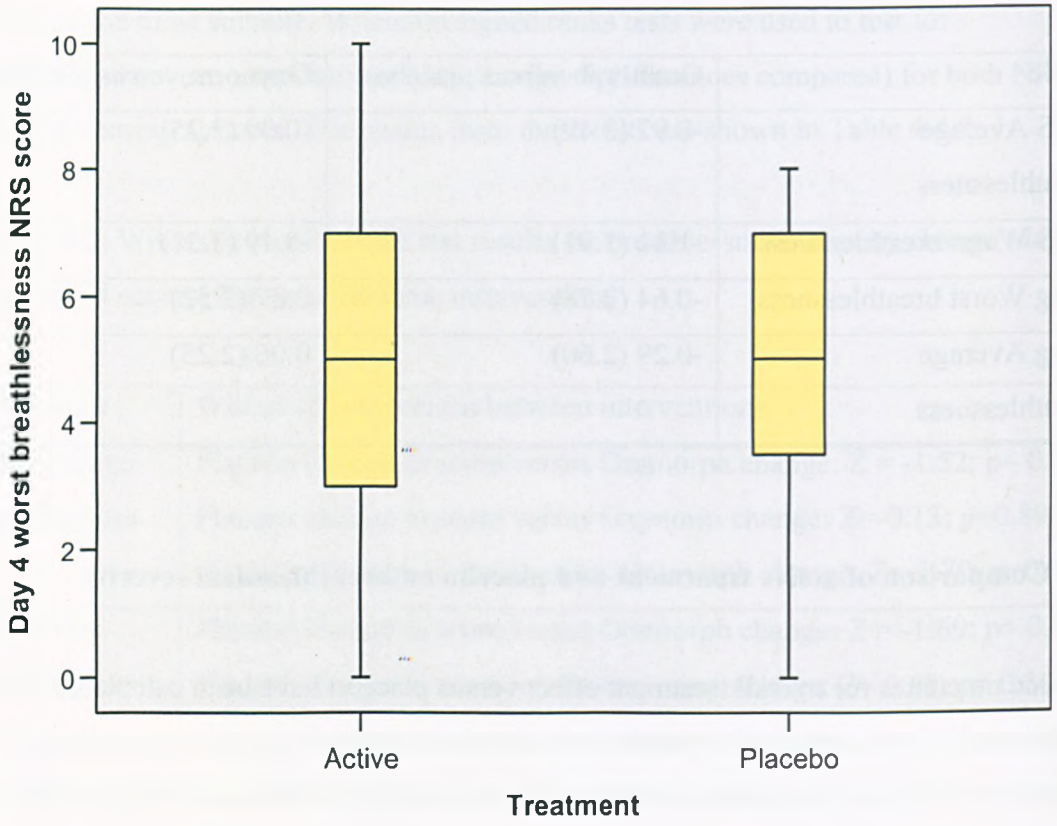
Table 4.4.3: Mean change in breathlessness score (day 1 to day 4) comparison between active interventions and placebo for breathlessness severity scales.

Scale	Oramorph versus placebo	Oxynorm versus placebo
NRS Average breathlessness	-0.97 (3.49)	-0.09 (2.25)
NRS Worst breathlessness	-1.11 (3.91)	-0.49 (3.31)
Borg Worst breathlessness	-0.64 (2.78)	0.07 (2.52)
Borg Average breathlessness	-0.29 (2.60)	0.06 (2.25)

4.2 Comparison of active treatment and placebo on breathlessness severity

Pooled outcomes for overall treatment effect versus placebo have been calculated. Responses to oramorph and oxynorm were included together in an "active treatment" group and compared to placebo. A boxplot demonstrating median and interquartile ranges for active treatment versus placebo (Figure 4.4.1) is shown below for day 4 worst breathlessness and is representative for all other boxplots for NRS or Borg ratings. There is a difficulty in further analysis of this due to the nature of the pairing of placebo values to active values. There does not appear to be any difference between response to placebo and response to pooled active treatment for breathlessness over the four day intervention period.

Figure 4.4.1: Boxplot to show the median and interquartile range for NRS worst breathlessness scoring at day 4 for pooled opioid treatments (oramorph and oxynorm) and placebo for the 35 completed datasets. Higher values represent more severe breathlessness.



4.3 Change of NRS or Borg breathlessness scores over time on treatment

Differences between scores at the start and end of treatment may not fully reflect the complete participant experience. Measurements of breathlessness were taken at baseline (day 1), day 2, day 3 and day 4 for NRS and Borg measures of breathlessness. Below are two examples of line graphs for NRS Average and Worst scores (also representative for Borg Average and Worst score graphs (not shown)):

Figure 4.4.2: Line graph to demonstrate change of mean NRS average breathlessness scores over time for each intervention. Higher values represent worse breathlessness.

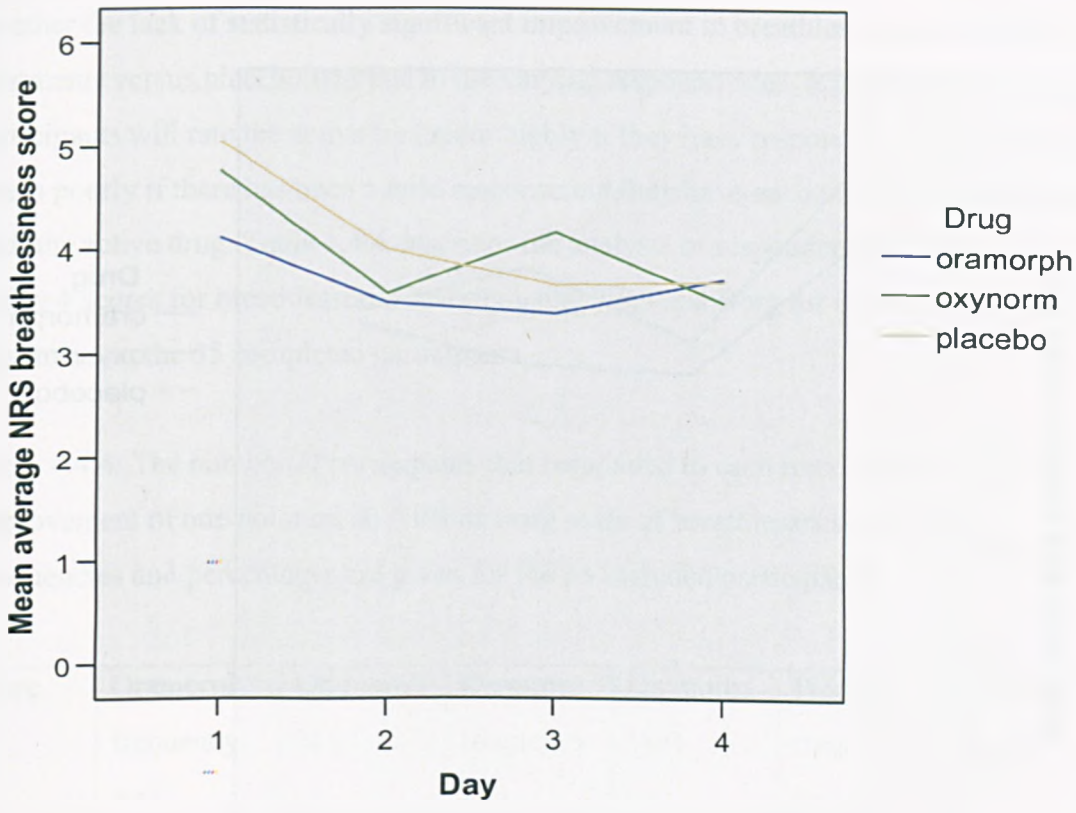
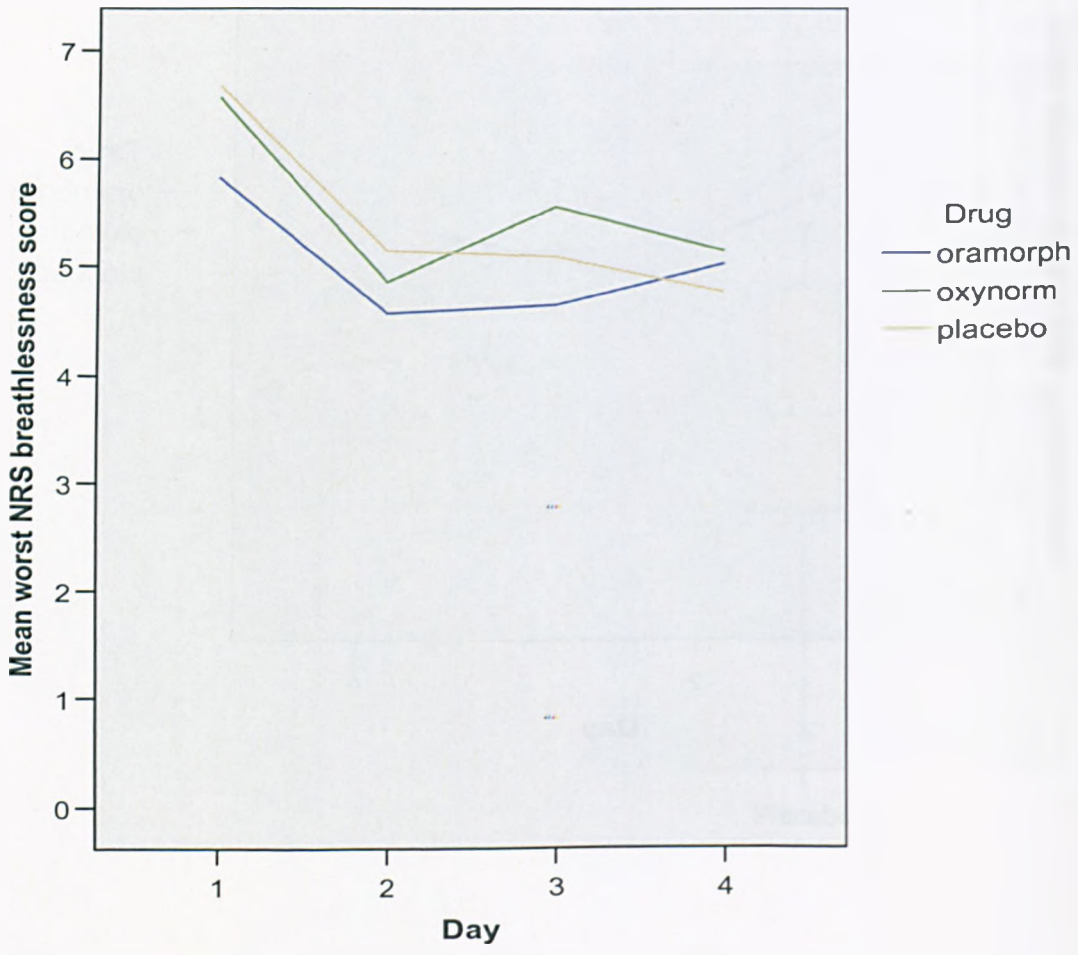


Figure 4.4.3 Line graph to demonstrate the change in mean worst NRS breathlessness score over time for each intervention. Higher scores represent worse breathlessness severity.



These two graphs illustrate that an initial reduction in breathlessness scores occurs after the first day and is maintained throughout the remainder of the treatment course. The mean placebo score for breathlessness on day 1 (baseline) is higher than for the active treatments, with the overall day 4 mean scores at the end of treatment being approximately the same for all three interventions.

4.4 Percentage data for NRS/Borg responders for the three interventions

A clinically significant cut-off has been identified for improvement in NRS or Borg-rated breathlessness severity, as discussed previously. This analysis sought to determine whether the lack of statistically significant improvement in breathlessness for active treatments versus placebo was due to the varying response rates. It is feasible that some participants will rate the active treatment highly if they have responded, but others may rate it poorly if there has been a mild response but they have encountered adverse effects with the active drug. Table 4.4.4 describes the analysis of responders of change in day 1 to day 4 scores for breathlessness severity using NRS and Borg for the three different treatments in the 35 completed participants.

Table 4.4.4: The number of participants that responded to each intervention with an improvement of one point on an NRS or Borg scale of breathlessness severity. Frequencies and percentages are given for the 35 included participants.

Score	Oramorph frequency >=1	Oramorph % >1	Oxynorm frequency >=1	Oxynorm %>1	Placebo frequency >=1	Placebo %>1
NRS Average	19	54.3%	22	62.9%	22	62.9%
NRS Worst	23	65.7%	21	60.0%	24	68.6%
Borg Worst	17	48.6%	17	48.6%	14	40.0%
Borg Average	16	45.7%	11	31.4%	10	28.6%

There appears to be little difference between the three treatments using the NRS scale for breathlessness, demonstrating the large placebo response in the trial, with almost two-thirds of participants on NRS Average breathlessness rating an improvement of one or above. However, the average score for the Borg scale for breathlessness does demonstrate a favouring for oramorph over the other two treatments. This may simply represent an anomaly in the data, particularly as the median score for breathlessness on this scale is not significantly different to the other two interventions.

4.5 Comparison output in the style of Abernethy *et al* (2003)

The crossover study of 38 patients with refractory dyspnoea (mostly COPD) by Abernethy et al (2003) described their output in terms of absolute values on the last day of treatment for both oral morphine and placebo, rather than measuring the difference between baseline and last day of treatment for each intervention. Table 4.4.5 below provides data in the form as provided by Abernethy to allow direct comparison of results.

Table 4.4.5: Day 4 values (end of treatment) for NRS Average breathlessness for each of the three interventions:

	Oramorph (n=35)	Oxynorm (n=35)	Placebo (n=35)
Mean	3.71	3.49	3.69
Standard deviation	2.40	2.03	1.98

As can be observed in this table, day 4 scores for each of the three interventions are similar, with oxynorm having the lowest mean value indicating the least breathlessness on average breathlessness NRS scores. These means and standard deviations are similar to those found by Abernethy *et al.* (2003), which will be explored further in the discussion. Similar results are seen for worst breathlessness score on NRS and average and worst Borg scores (results not shown).

The difference between treatments for each participant was calculated for oramorph versus placebo and oxynorm versus placebo. The mean of these differences between interventions was 0.03 (95% CI for the difference was 0.88 to 0.94) for oramorph versus placebo. A positive result favours placebo as it represents the oramorph average score minus placebo score (lower scores indicate less breathlessness). A mean of -0.20 (95% CI for the difference: -0.85 to 0.45) was observed for oxynorm versus placebo. This result favours oxynorm as negative values here represent lower breathlessness scores for oxynorm and hence better breathlessness. Unlike in the Abernethy study, it is debatable that these distributions of differences between active and placebo interventions are normally distributed with Q-Q plots and histograms, however if one assumes normality, paired t test can be performed (although non-parametric tests would be more accurate to use in this study analysis).

Paired statistical tests (for normal distributions) of the differences in the same patient between active and placebo interventions are shown in Table 4.4.6 below with t statistics. Similarly, Wilcoxon paired signed ranks test statistics are also calculated as these are more appropriate for our non-parametric sample (given by the Z statistic).

Table 4.4.6: Analysis of the difference of day 4 Average NRS breathlessness scores between active treatments and placebo using parametric and non-parametric paired tests

Treatments	Test	Test statistic	p value
Oramorph versus placebo	Paired t-test	t statistic: 0.064	0.95
Oramorph versus placebo	Wilcoxon	Z statistic: -0.022	0.98
Oxynorm versus placebo	Paired t-test	t statistic: -0.626	0.54
Oxynorm versus placebo	Wilcoxon	Z statistic: - 0.756	0.45

It is unsurprising that both analyses are non-significant given that the 95% confidence intervals for the differences both cross zero. Taken together, these results indicate that for the primary outcome measure of breathlessness severity there are no statistically significant differences between active treatments and placebo whether baseline (day 1) to day 4 differences are used as described in the protocol, or whether other methods such as analysis of day 4 scores alone are utilised.

4.6 Global impression of change in breathlessness

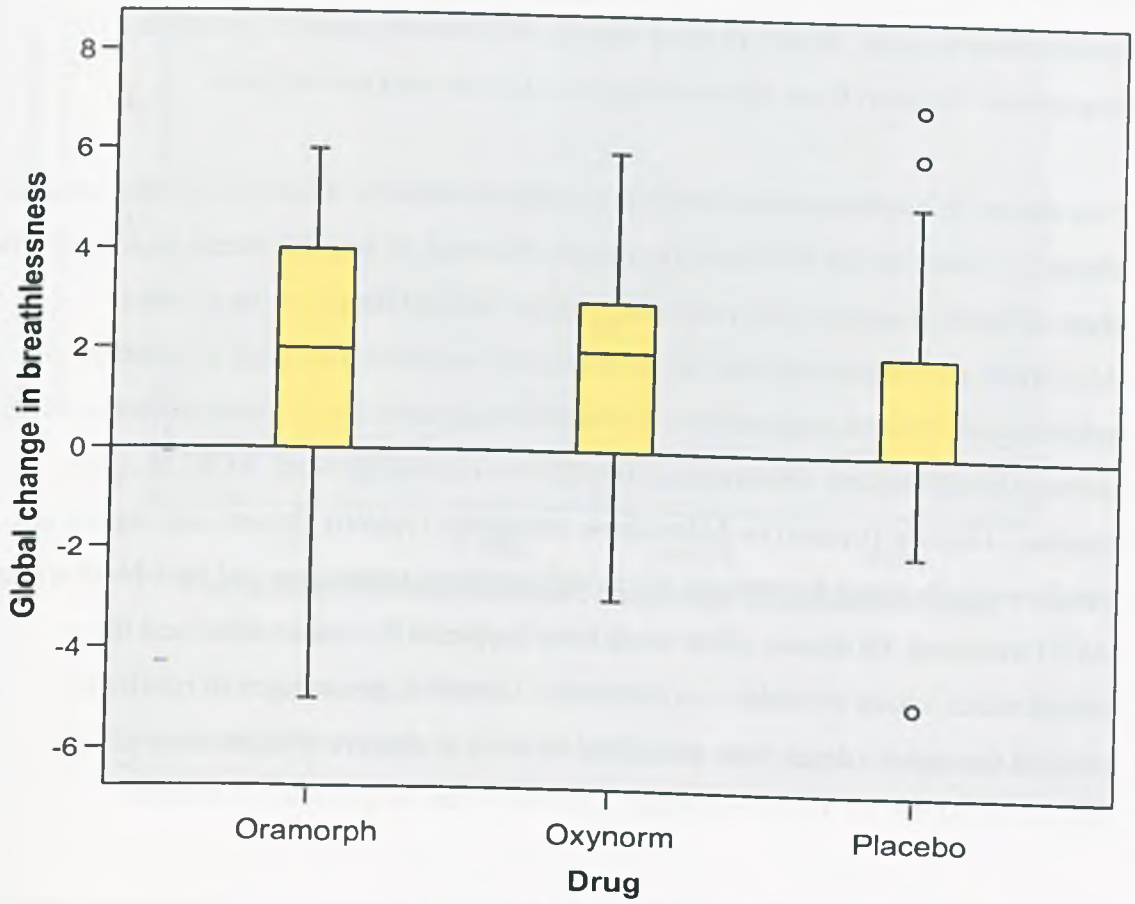
At the end of each intervention, participants were ask to rate whether their breathlessness had improved, worsened or remained the same on a 15 point global impression of change scale. Table 4.4.7 demonstrates the mean and median result at the end of each intervention.

Table 4.4.7: Global impression of change of breathlessness over the full course of treatment for each intervention measured by mean change in score, standard deviations and median change for the three groups

Intervention	Mean change	Standard deviation	Median change
Oramorph	1.40	2.96	2
Oxynorm	1.51	2.36	2
Placebo	1.14	2.52	0

Wilcoxon comparisons between treatments show no statistically significant differences ($Z = -0.32$; $p = 0.75$ and $Z = -0.70$; $p = 0.48$ for placebo versus oramorph and placebo versus oxynorm respectively). These results show a median difference of 2 for both active interventions corresponding to an improvement in global breathlessness, with no change for placebo. An improvement of 2 relates to a "little better" rating of breathlessness over that intervention period. However, mean differences do not demonstrate such a notable difference between interventions and non-parametric testing for active versus placebo interventions show no statistically significant improvement for either oramorph or oxynorm versus placebo. Figure 4.4.4 illustrates the range, interquartile range and median value for each intervention.

Figure 4.4.4: Boxplot demonstrating global impression of change rating of breathlessness severity at the end of each treatment period. Higher positive scores represent a greater improvement from baseline, negative scores indicate worsening breathlessness severity from treatment baseline.



The interquartile ranges for each intervention lie at zero and above, indicating a perceived improvement in breathlessness for each week. The mean global change score for oramorph in particular is affected by a long negative whisker, suggesting a few participants alone rated oramorph caused a worsening of their breathlessness on global change measures, resulting in a lower mean value compared to the median. The placebo boxplot has three outliers above or below the range whiskers. The two patient samples that noted a large placebo response on global impression of change had the individual interventions investigated by Hull Pharmacy to check the sequences. The independent laboratory in Southport confirmed the correct randomisation sequences.

4.7 Comparison of baseline medication characteristics with breathlessness outcomes

Given that there is no statistically significant difference overall in change of breathlessness severity between the three interventions, are there characteristics of participants that did respond to active therapy that might lead to tailored therapy to specific groups of individuals. Do demographic features, such as severity of disease, concomitant medical therapy or other factors influence response to opioids in a CHF population? Some of these factors are explored in the next two sections.

The change in breathlessness severity on treatment might be related to existing medical therapies. However, no consistent results are observed for breathlessness response to the three different treatment interventions for either NRS or Borg scoring systems. McNemars non-parametric tests for dichotomous variables were used to identify relationships between responders to oramorph or oxynorm (>= 1 improvement on NRS average breathlessness versus placebo) with beta-blocker (yes/no), ACEI or ARB (yes/no), Digoxin (yes/no) or Aldosterone antagonist (yes/no). Statistically significant results were observed for both oxynorm and oramorph responders and beta-blockers and ACEI treatment. Of course, these could have happened by chance alone and these dichotomous values are rather too simplistic. Therefore, percentages of maximum advised therapeutic doses were calculated in order to observe whether dose of beta blocker or ACEI/ARB was important, rather than just its presence or absence.

The line charts below (figures 4.4.5 and 4.4.6) show a comparison of the mean scores for NRS Average breathlessness for both oramorph and oxynorm in the participant sample dependent on beta-blocker dose. It is interesting to note an improved response to oramorph for patients on maximal beta-blocker therapy, whereas the opposite is true for oxynorm. I suspect this may have happened by chance as one would expect if opioids were to have a class effect on breathlessness that a consistent response would be seen for increasing beta-blocker dose if this was relevant for response to opioids. Similar calculations for ACEI or ARB doses show no such pattern with dose of ACEI/ARB and response to opioid (data not shown).

Figure 4.4.5: Line graph to show the mean change in NRS Average breathlessness severity for oramorph (baseline to day 4) dependent on percentage recommended maximum beta-blocker dose. Positive values represent breathlessness improvement

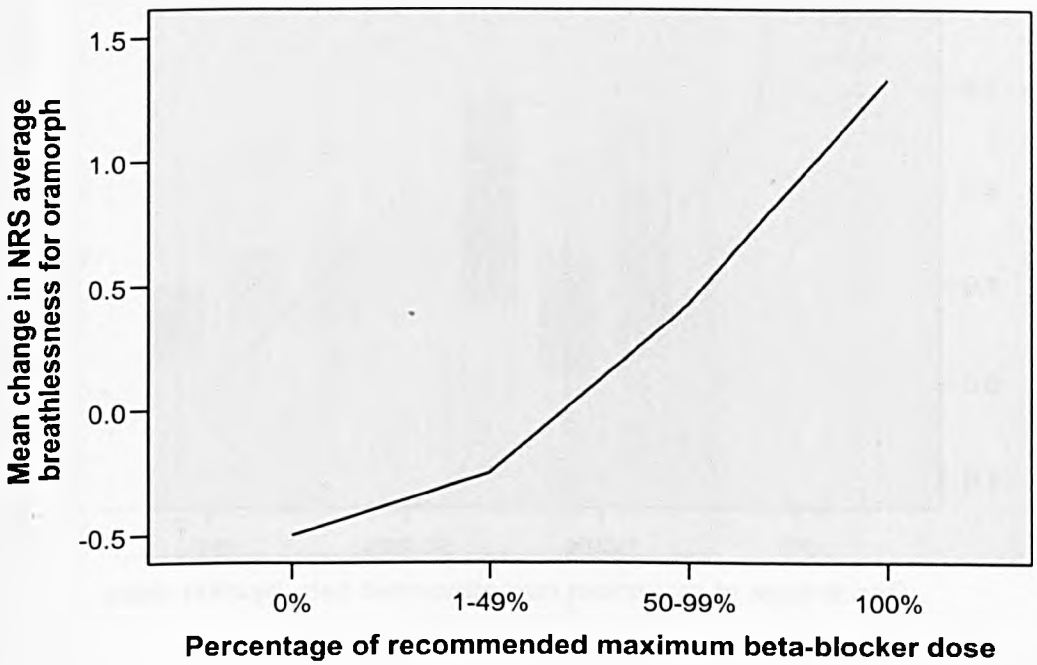
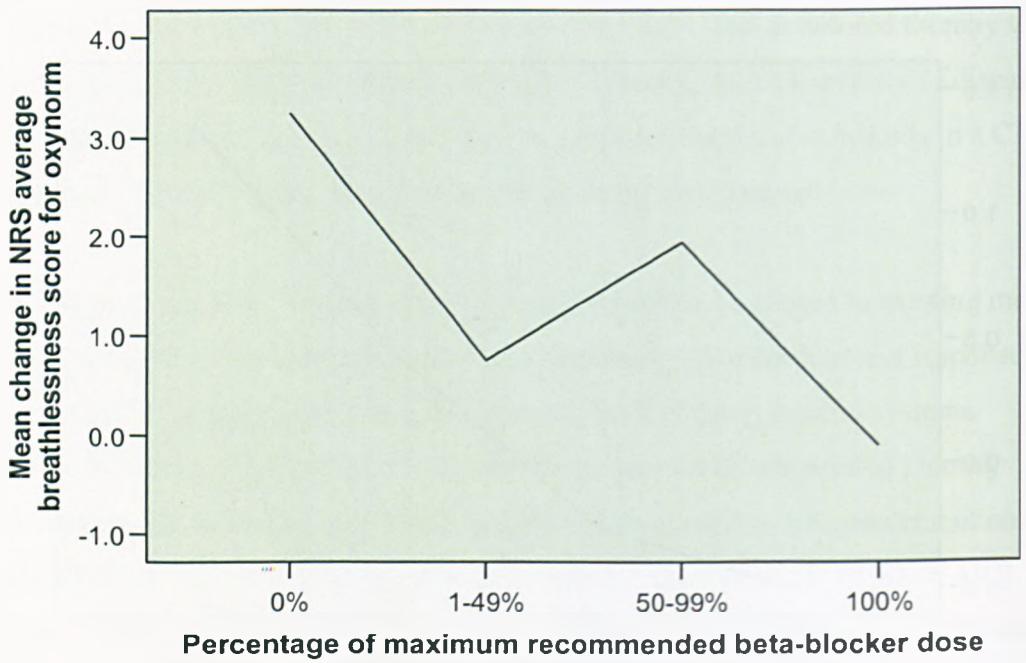


Figure 4.4.6: Line graph to show the mean change in NRS Average breathlessness severity (baseline to day 4) for oxynorm dependent on percentage recommended maximum beta-blocker dose. Positive values represent breathlessness improvement



4.8 Comparison of demographic characteristics with breathlessness outcomes

The following boxplots (figures 4.4.7, 4.4.8 and 4.4.9) show the response of certain aetiological groups to change in breathlessness score with each intervention. Response by NYHA status, gender and aetiology are demonstrated. It can be seen that there is little trend for any one particular factor in most cases. However, participants with dilated cardiomyopathy appear to respond better to opioids than other CHF diagnostic groups.

Figure 4.4.7: Boxplot to show the change in NRS Average breathlessness scores for each intervention dependent on NYHA functional status (NYHA III n = 31, NYHA IV n = 4). Positive values represent an improvement in breathlessness score.

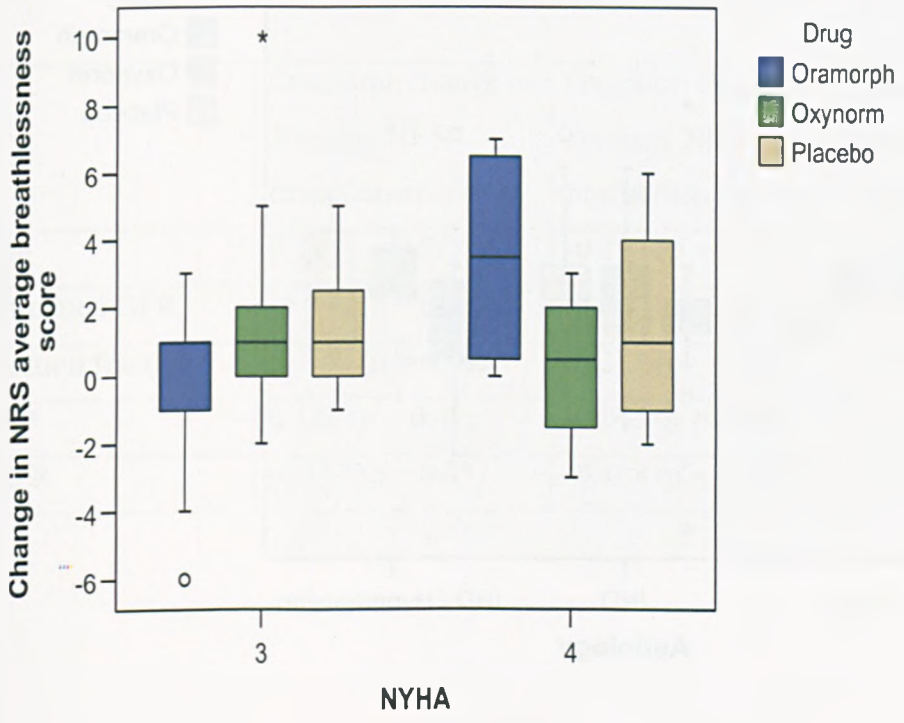


Figure 4.4.8: Boxplot to show the change in NRS Average breathlessness scores for each intervention dependent on gender (female n = 5, male n = 30). Positive values represent an improvement in breathlessness score.

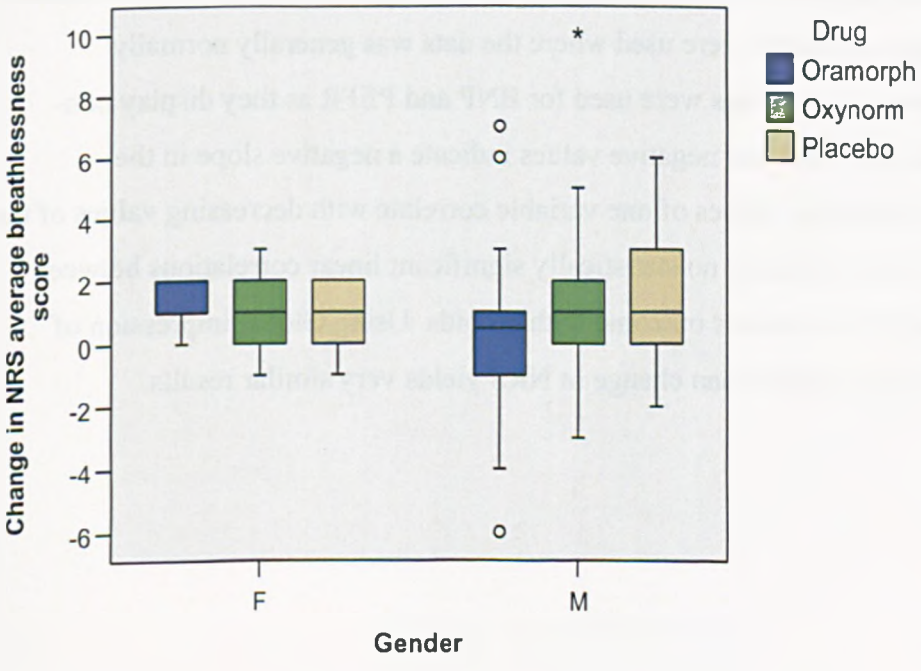


Figure 4.4.9: Boxplot to show the change in NRS Average breathlessness scores for each intervention dependent on aetiology of CHF (DCM n = 3, IHD alone n = 25, IHD and hypertension n = 7). Positive values represent an improvement in breathlessness score.

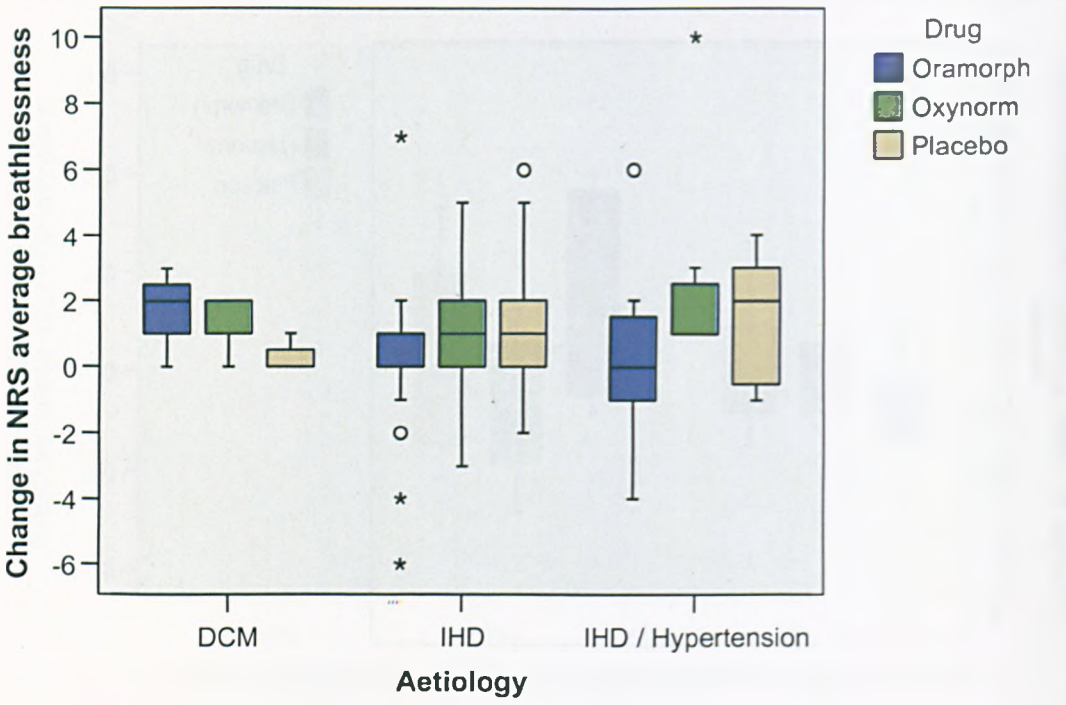


Table 4.4.8 below details the association between change in average NRS breathlessness severity score for each intervention against age, renal function (GFR), ejection fraction and BNP. Pearson correlates were used where the data was generally normally distributed, spearman correlates were used for BNP and PEFR as they display non-normal distributions. Note that negative values indicate a negative slope in the correlation, i.e. increasing values of one variable correlate with decreasing values of the other. As can be seen there are no statistically significant linear correlations between these factors and breathlessness outcome with opioids. Using Global impression of change as an outcome rather than change in NRS yields very similar results.

Table: 4.4.8 Pearson correlation coefficients of linear association for baseline factors for change in Average NRS breathlessness (day 1 to day 4 change) for each intervention versus demographic baseline factors (spearman correlations given for BNP and PEFR as detailed above):

	Oramorph change in Average NRS breathlessness n=35	Oxynorm change in Average NRS breathlessness n=35	Placebo change in Average NRS breathlessness n=35
Age	0.11 (p = 0.52)	-0.193 (p = 0.27)	0.053 (p = 0.76)
Estimated GFR	-0.048 (p = 0.79)	0.081 (p = 0.65)	-0.187 (p = 0.28)
Ejection fraction	-0.040 (p = 0.82)	-0.172 (p = 0.32)	-0.035 (p = 0.84)
BNP	0.128 (p = 0.47)	-0.013 (p = 0.94)	0.293 (p = 0.09)
PEFR	-0.137 (p = 0.43)	-0.108 (p = 0.54)	-0.159 (p = 0.36)

Section 5) Results: Comparison of breathlessness rating scales

5.1 Comparison of worst, average and current breathlessness measures

During the progress of the trial, the impression was that current shortness of breath was not as discerning or not as descriptive as average or worst. How does current breathlessness rating compare with these other two measures? Table 4.5.1 demonstrates the comparison of the cumulative range of values, mode and median scores for Average, Worst and Current breathlessness on NRS for all 35 participants involving all three interventions.

Table 4.5.1: Cumulative values for range, mode and median scores for Average, Worst and Current NRS breathlessness rating

	Average breathlessness on NRS (n = 420 responses)	Worst breathlessness on NRS (n = 420 responses)	Current breathlessness on NRS (n = 525 responses)
Range of values	0-10	0-10	0-10
Mode	5	5	0
Median	4	5	2
SD	2.15	2.55	2.26

As can be seen, the mode for current SOB was zero, with a range of values the same as for average and worst SOB on NRS. This is also displayed in graphical form below, with current SOB detailed first followed by worst SOB NRS for comparison.

Figure 4.5.1: Bar chart demonstrating the frequency of all responses at a given score of Current NRS breathlessness, irrespective of intervention (n= 525 responses)

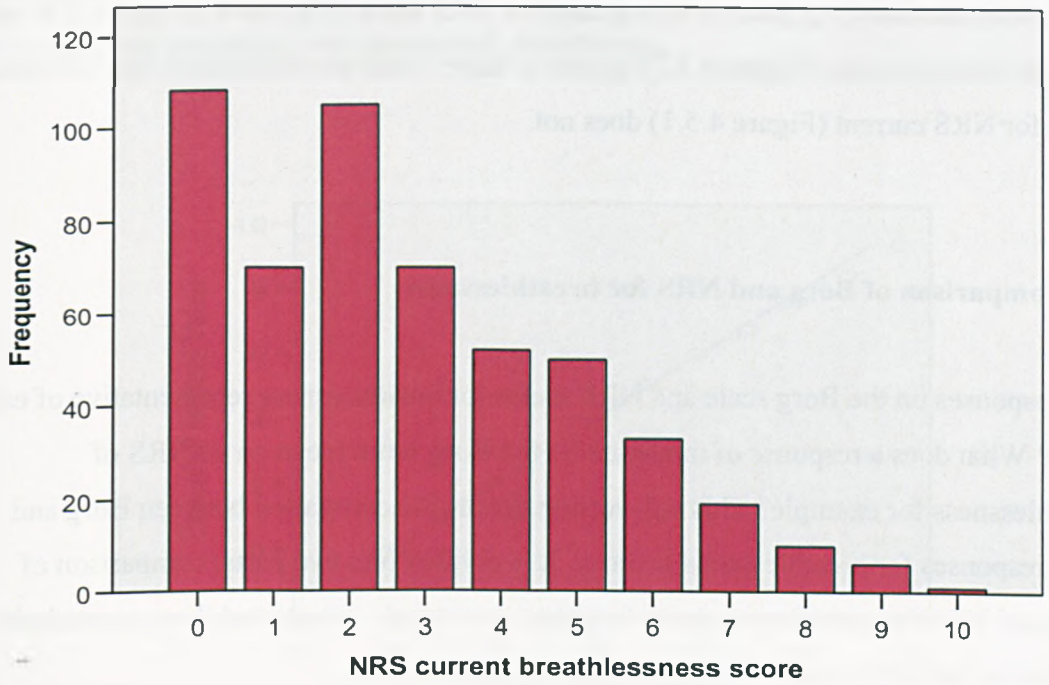
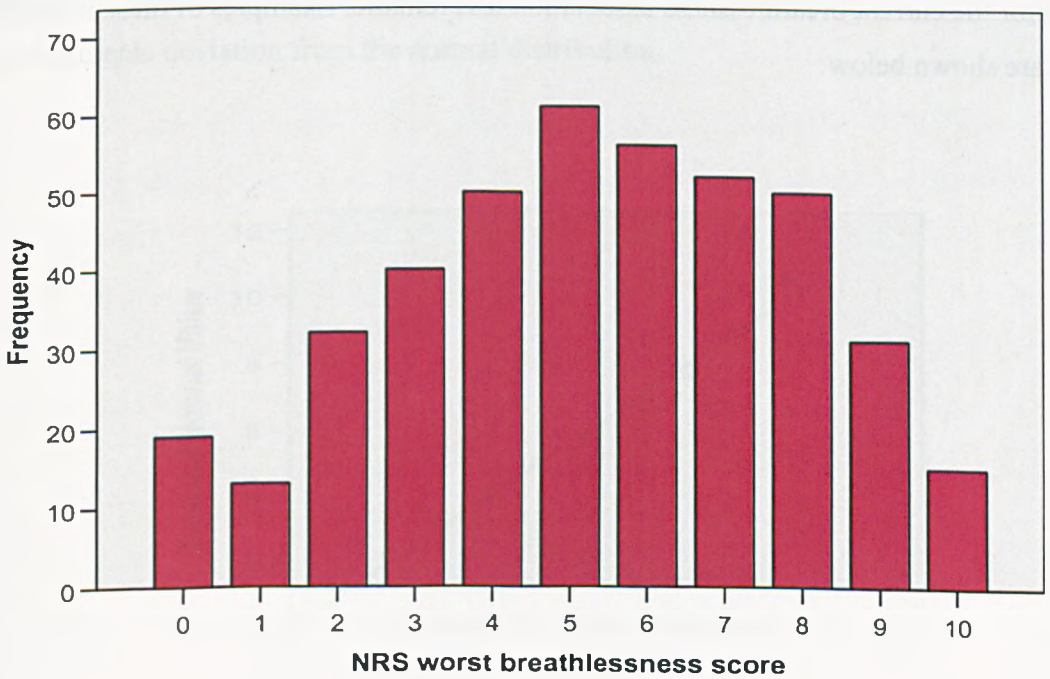


Figure 4.5.2: Bar chart of the frequency of responses for a given score on the Worst NRS rating scale for breathlessness, irrespective of intervention (n = 420 responses)



It can be observed therefore that current breathlessness measurement may not be as discerning for measurement of treatment effect as the majority of results tend towards zero. Note also that Q-Q plots or histograms for NRS worst (Figures 4.5.2 and 4.5.4) and average breathlessness (Figure 4.5.3) appear to have a near normal distribution, whereas those for NRS current (Figure 4.5.1) does not.

5.2 Comparison of Borg and NRS for breathlessness

Are responses on the Borg scale and NRS scales for breathlessness representative of each other? What does a response of moderate on the Borg score mean on an NRS of breathlessness for example? This sub-section details the correlation between Borg and NRS responses for breathlessness severity. It is divided into two parts; comparison of Borg and NRS for specific situations (average, worst and current) and then a cumulative analysis of all NRS versus all Borg results for breathlessness.

Pearson correlation coefficients were used to calculate the linear relationship between worse, average and current scores of Borg and NRS for breathlessness. Q-Q plots for normality revealed a near normal distribution for NRS for average and worst breathlessness, with positive skew for current breathlessness, which might make the p value for the current breathlessness association less reliable. Examples of these normality plots are shown below:

Figure 4.5.3: Normal Q-Q plot for NRS Average breathlessness (n = 420 responses). Deviation from the line between the expected normal value and the actual value at either end represents deviation from the normal distribution.

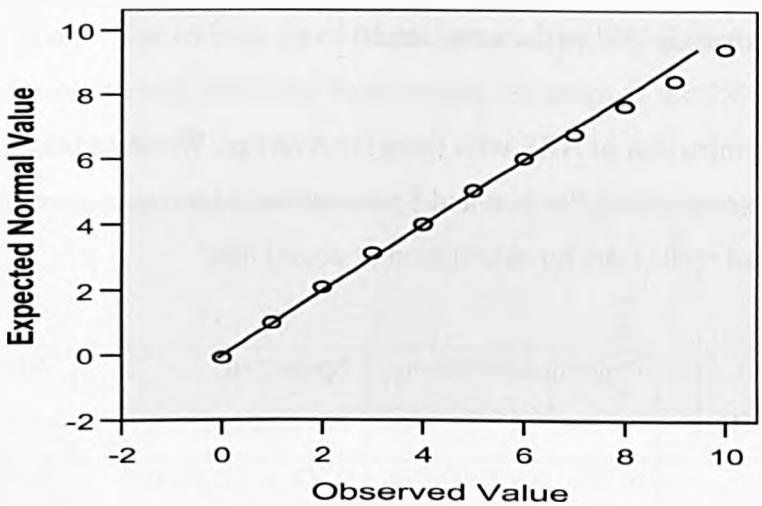
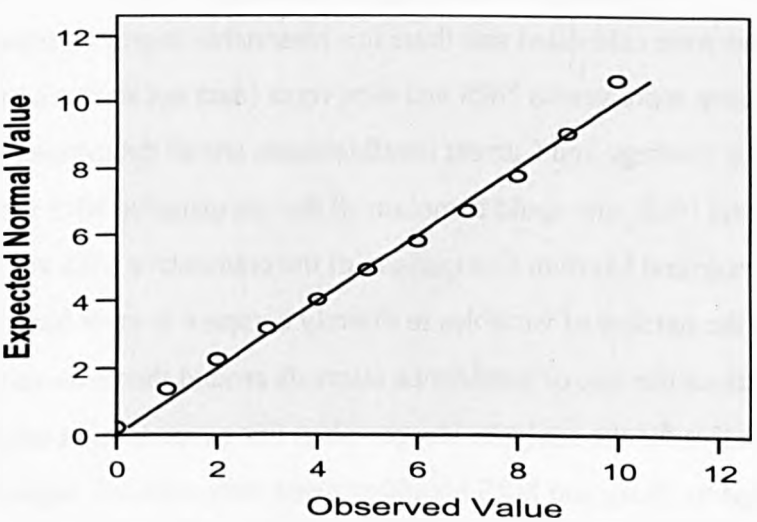


Figure 4.5.4: Normal Q-Q plot for NRS Worst breathlessness (n = 420 responses). Deviation from the line between the expected normal value and the actual value at either end represents deviation from the normal distribution.



Pearson correlation coefficients for NRS score against corresponding Borg for Average, Worst and Current responses were all significant and are described in Table 4.5.2 below. Not assuming normality, especially relevant for current breathlessness, Spearman correlation coefficients for Borg and NRS were also significant. Non parametric tests of association of this paired data for Average, Worst and Current breathlessness given by the Wilcoxon signed ranks test also noted significant results, indicating that alternative approaches to analysis lead to the same result.

Table 4.5.2: Comparison of NRS with Borg for Average, Worst and Current breathlessness scores using Pearson and Spearman tests for linear correlation and Wilcoxon signed ranks tests for association of paired data

NRS versus corresponding Borg	Pearson correlation	Spearman correlation	Wilcoxon signed ranks test
Average breathlessness	0.70 $p < 0.0005$	0.72 $p < 0.0005$	Z statistic = -14.54 $p < 0.0005$
Worst breathlessness	0.79 $p < 0.0005$	0.83 $p < 0.0005$	Z statistic = -16.25 $p < 0.0005$
Current breathlessness	0.81 $p < 0.0005$	0.81 $p < 0.0005$	Z statistic = -13.66 $p < 0.0005$

These tests demonstrate significant association between Borg and NRS scores for average, worst and current breathlessness. Error bars and boxplots for all three categories of breathlessness were calculated and there is a reasonable degree of separation for a given level of Borg score versus NRS and vice versa (data not shown here). However, given that Worst, Average and Current breathlessness are all determined on the same scale for Borg and NRS, one could cumulate all the comparative NRS results with Borg for Worst, Average and Current. Comparison of the cumulative NRS and Borg scores would increase the number of variables to directly compare in error bars, and subsequently reduce the size of confidence intervals around the mean values. This could be more informative for the analysis. Hence, when this accumulation occurs, 1365 responses (paired for Borg and NRS breathlessness) were collated. Again, NRS cumulative breathlessness scores were near normally distributed (data not shown). However, the cumulative Borg score deviated from the normal distribution at higher

values. Unsurprisingly, Wilcoxon signed ranks test for cumulative NRS versus cumulative Borg was again highly significant (Z value: -25.99; $p<0.0005$). Error plots with 95% confidence intervals around the mean were subsequently generated for NRS at a given level of Borg score and vice-versa (Figures 4.5.5 and 4.5.6).

Figure 4.5.5: Error plot showing the mean and 95% confidence interval for the mean NRS score for a given value of Borg-rated breathlessness (n=1365 paired responses). Circles represent mean values, with bars representing the range of the 95% confidence interval for the mean.

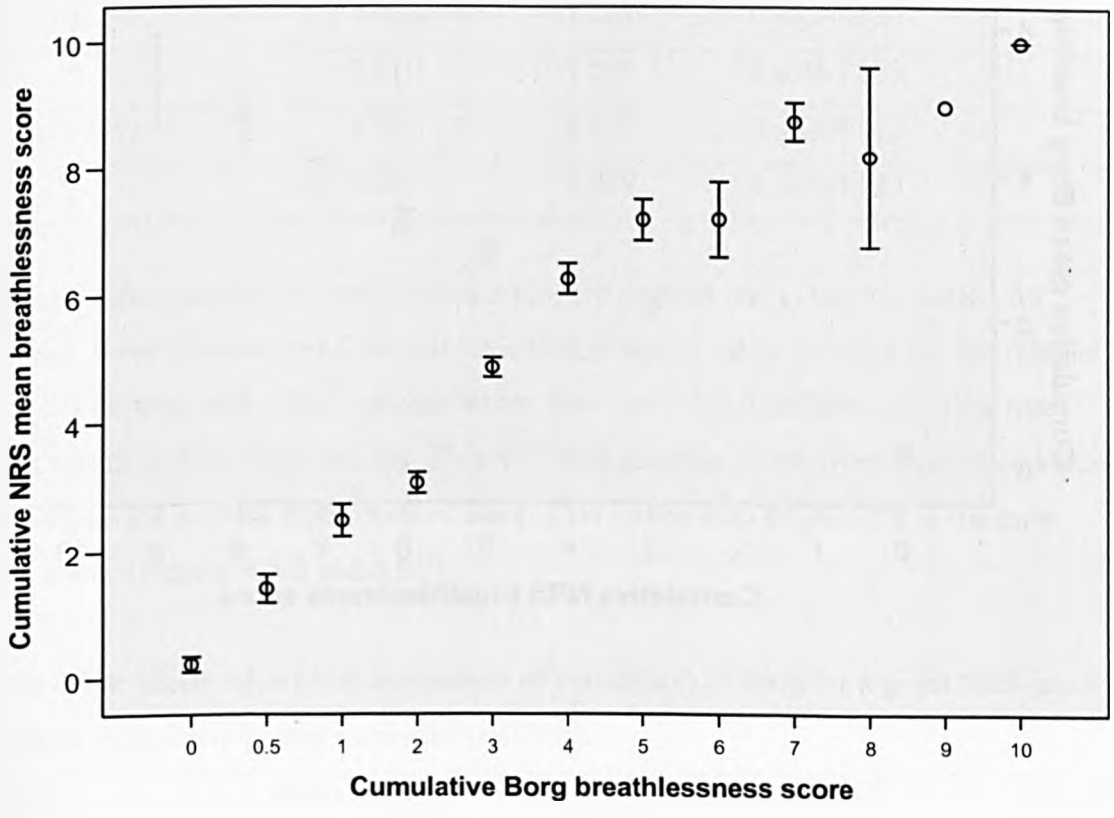
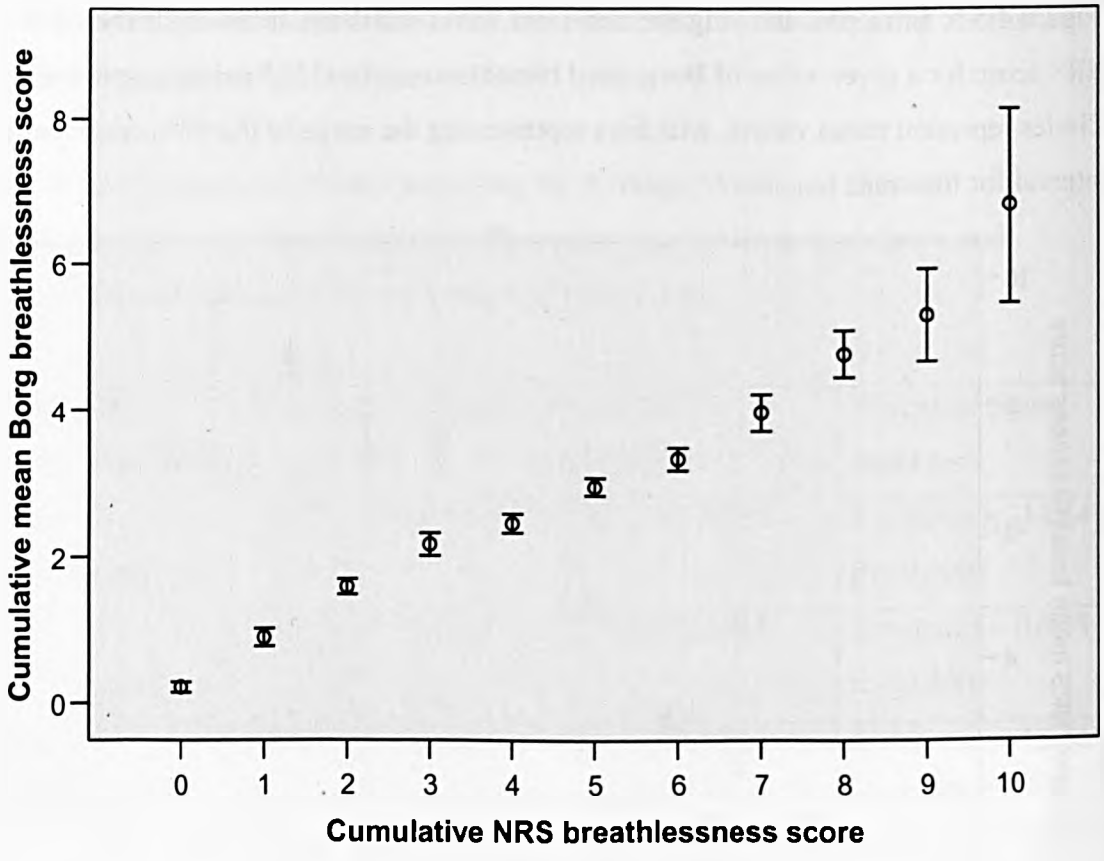


Figure 4.5.6: Error plot showing the mean and 95% confidence interval for the mean Borg score for a given value of NRS breathlessness (1365 paired responses). Circles represent mean values, with bars representing the range of the 95% confidence interval for the mean.



As can be seen there appears to be a straightforward near linear relationship for Borg versus NRS mean values of Borg for a given NRS score (Figure 4.5.6). Again there is a good degree of separation for NRS scores for a given Borg score (Figure 4.5.5) up until and including a Borg score of five, representing "severe" breathlessness. Before this point is reached there appears to be a near linear relationship with discrete mean values of NRS without overlap of the 95% confidence intervals. This is re-iterated in Tables 4.5.3 and 4.5.4.

Table 4.5.3: Mean value (with assessment of variability) of NRS for a given Borg score based on cumulative paired responses (n=1365 paired responses)

Borg	Mean NRS	SD	95% CI
0 – none	0.221	0.660	0.107-0.335
0.5 – very very slight	1.406	1.193	1.176-1.635
1 – very slight	2.491	1.717	2.234-2.749
2 – slight	3.070	1.405	2.906-3.233
3 – moderate	4.862	1.591	4.705-5.019
4 – somewhat severe	6.268	1.453	6.024-6.513
5 – severe	7.203	1.287	6.882-7.525
6	7.210	1.228	6.619-7.803
7 – very severe	8.767	0.817	8.462-9.072
8	8.200	1.989	6.777-9.623

Values for Borg scores of 9 and 10 (maximal) are omitted due to too few results for analysis. It can be observed from this table that at higher values of Borg, the confidence intervals for the mean values become wider, thus one is less confident about the true mean values at these higher levels. This will be in part due to the lower number of values for comparison at these high levels of Borg. This can be seen graphically in the error plots above (Figures 4.5.6 and 4.5.7).

Table 4.5.4: Mean value (with assessment of variability) of Borg for a given NRS score based on cumulative paired responses (n=1365).

NRS	Mean Borg	SD	95% CI
0	0.212	0.443	0.142 – 0.283
1	0.891	0.616	0.771-1.010
2	1.583	0.759	1.478-1.687
3	2.162	1.013	2.011-2.313
4	2.446	0.850	2.317-2.576
5	2.952	0.868	2.830-3.074
6	3.336	0.847	3.183-3.490
7	3.960	1.256	3.712-4.208
8	4.767	1.390	4.443-5.091
9	5.302	2.840	5.471-8.129

Note that there is a greater degree of separation for a given Borg number than for a given NRS number for SOB. This is also confirmation that one cannot comment on Borg severity greater than 5, as the mean Borg for an NRS of 9 is only just above 5, and that 9 is close to the very maximum of the NRS score. The comparison between NRS and Borg breathlessness mean scores appears to have a linear relationship. Linear regression analysis was therefore performed using SPSS in order to create an equation where an NRS can be estimated from a given Borg score and vice versa. In order for this analysis to be valid, the residual values (the difference between those observed and expected values) have to follow a normal distribution and have uniform variance and histograms of these unstandardised residuals demonstrate this (graphs not shown). Two sets of models for comparison of NRS to Borg and vice versa were produced. The first incorporated the comparison of the total cumulative Borg and NRS results. The second only included those results leading up to and including a Borg score of 5, given that the number of values above this point are few and may distort the model. Hence, two sets of equation for conversion between the two breathlessness measures are as follows:

For a given Borg score converting to NRS: NRS score = 0.945 + (1.202 x (Borg score))

For a given NRS score converting to Borg: Borg score = 0.336 + (0.543 x (NRS score))

For a given Borg score (up to and including 5) converting to NRS:

NRS score = 0.595 + (1.389 x (Borg score))

For a given NRS score converting to Borg (up to and including 5):

Borg score = 0.56 + (0.45 x (NRS score))

Significance tests and confidence intervals for the intercepts and gradients of these linear models are described in Table 4.5.5 below.

Table 4.5.5: Assessment of the linear models for Borg and NRS conversion. Significance levels represent the degree of confidence around the values for intercept and gradient of the individual model

		t statistic	Significance	95% CI
Borg conversion to NRS (cumulative)	Intercept: 0.945	13.3	<0.0005	0.805 – 1.084
	Gradient: 1.202	50.6	<0.0005	1.156 – 1.249
NRS conversion to Borg (cumulative)	Intercept: 0.336	6.7	<0.0005	0.238 – 0.434
	Gradient: 0.543	50.6	<0.0005	0.522 – 0.564
Borg conversion to NRS (Borg <6)	Intercept: 0.595	7.7	<0.0005	0.443 – 0.747
	Gradient: 1.389	46.5	<0.0005	1.330 – 1.447
NRS conversion to Borg (Borg <6)	Intercept: 0.56	13.2	<0.0005	0.477 – 0.643
	Gradient: 0.45	46.5	<0.0005	0.431 – 0.469

Which of the two sets of models are best to use? The table below allows comparison of these models to see the difference between the model and actual values observed in the participant sample.

Table 4.5.6: Comparison of the mean Borg scores for a given NRS and vice versa from the actual data collected, the cumulative model and the limited linear regression model (for Borg scores up to 5)

NRS Actual	Mean Borg	Cumulative model	Limited model (Borg <6)	Borg Actual	Mean NRS	Cumulative Model	Limited model (Borg <6)
0	0.21	0.34	0.56	0 – none	0.22	0.95	0.60
1	0.89	0.88	1.01	0.5 – very very slight	1.41	1.55	1.29
2	1.58	1.42	1.46	1 – very slight	2.49	2.15	1.98
3	2.16	1.97	1.91	2 – slight	3.07	3.35	3.37
4	2.45	2.51	2.36	3 – moderate	4.86	4.55	4.76
5	2.95	3.05	2.81	4 – somewhat severe	6.27	5.75	6.15
6	3.34	3.59	3.26	5 – severe	7.20	6.96	7.54
7	3.96	4.14	3.71				
8	4.77	4.68	4.16				

It can be seen that for a given NRS score, the cumulative model for Borg score is closer to the actual mean score in the sample. Hence the formula 0.336 + (0.543 x NRS) should be used to calculate the corresponding Borg score. For a given Borg score, the cumulative and Borg <6 models are similar. For ease of use therefore, both unrestricted cumulative score models should be used.

5.3 Analysis of preferred week intervention with breathlessness scores

Some patients appear to have a clinical response to both active and placebo treatments. This is reflected both in the breathlessness scores and by studying the week of treatment that participants preferred the most when questioned at the end of the three-week study having had all three treatments. Whilst still blinded, of the 35 completed participants, 14 preferred the week corresponding to oramorph and 9 preferred the week corresponding to oxynorm. However, 11 patients selected placebo as their preferred week of treatment for

breathlessness, with one participant having no preference for any week of treatment. The intervention selected had no bearing on the week it was received, with 14, 9 and 11 participants selecting their first, second and third week on treatment respectively. This demonstrates again that treatment sequence had no relationship on outcome, as noted previously in the sequence effect analysis in Section 3.2.

How did the choice of their preferred week of therapy for breathlessness compare with their breathlessness severity scores? The histogram below shows the comparison between those participants that chose each intervention compared to their scores for average breathlessness change on NRS. One would expect to see the greatest response in breathlessness improvement on NRS for the intervention that was chosen in the preferred week (i.e. those that chose oramorph as their preferred week should demonstrate higher NRS values for oramorph than for the other two interventions). One might also expect to see an opioid treatment effect, whereby the choice of one active intervention in the preferred week gave the highest mean breathlessness response, but that the other active treatment yielded a smaller but still greater response compared to placebo. Interestingly, those participants that chose oramorph at the end of therapy (n=14) had very little difference in NRS Average breathlessness outcomes, whereas the participants who selected placebo had a marked placebo response. In addition, those that preferred oxynorm had a notable improvement in breathlessness score, but showed no such improvement on the other active intervention, in fact their scores deteriorated on oramorph. A similar pattern is seen for all other NRS and Borg change in breathlessness outcomes (data not shown).

Figure 4.5.7: Mean change in NRS Average breathlessness scores for each intervention for the three groups of treatment preference at the end of the trial. Positive values represent an improvement in breathlessness severity between day 1 and day 4 of treatment.

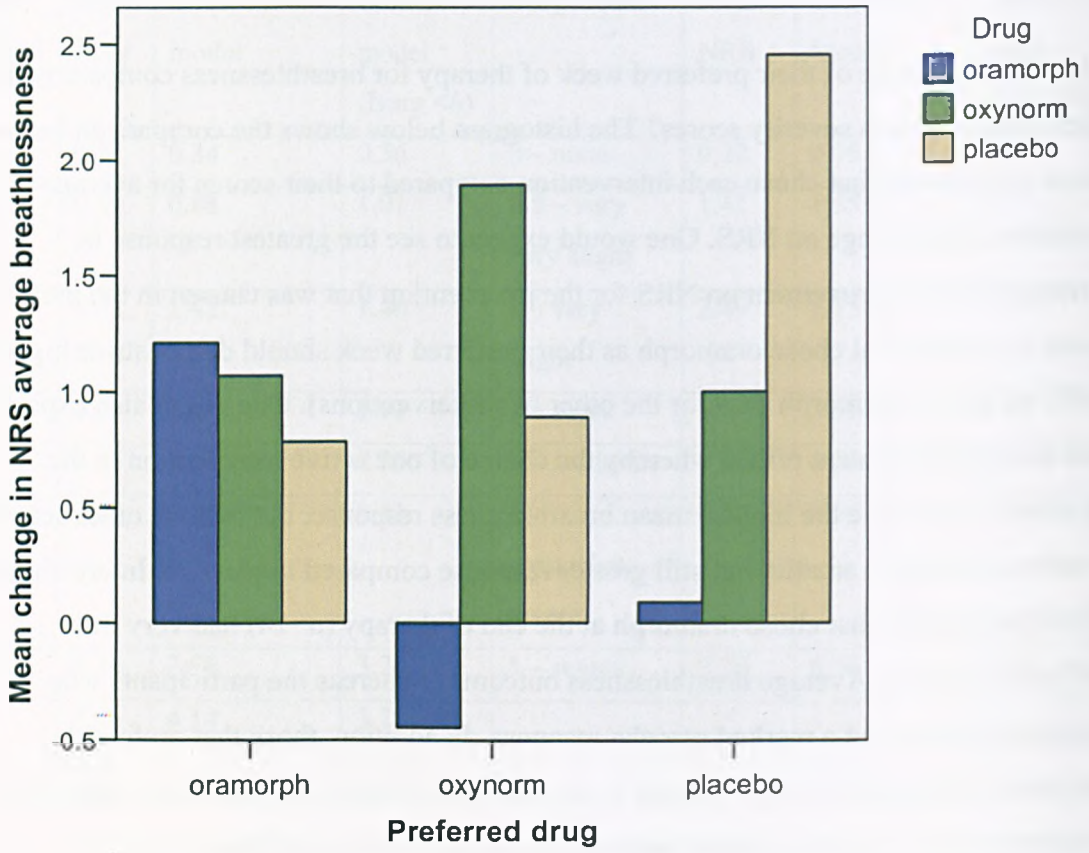
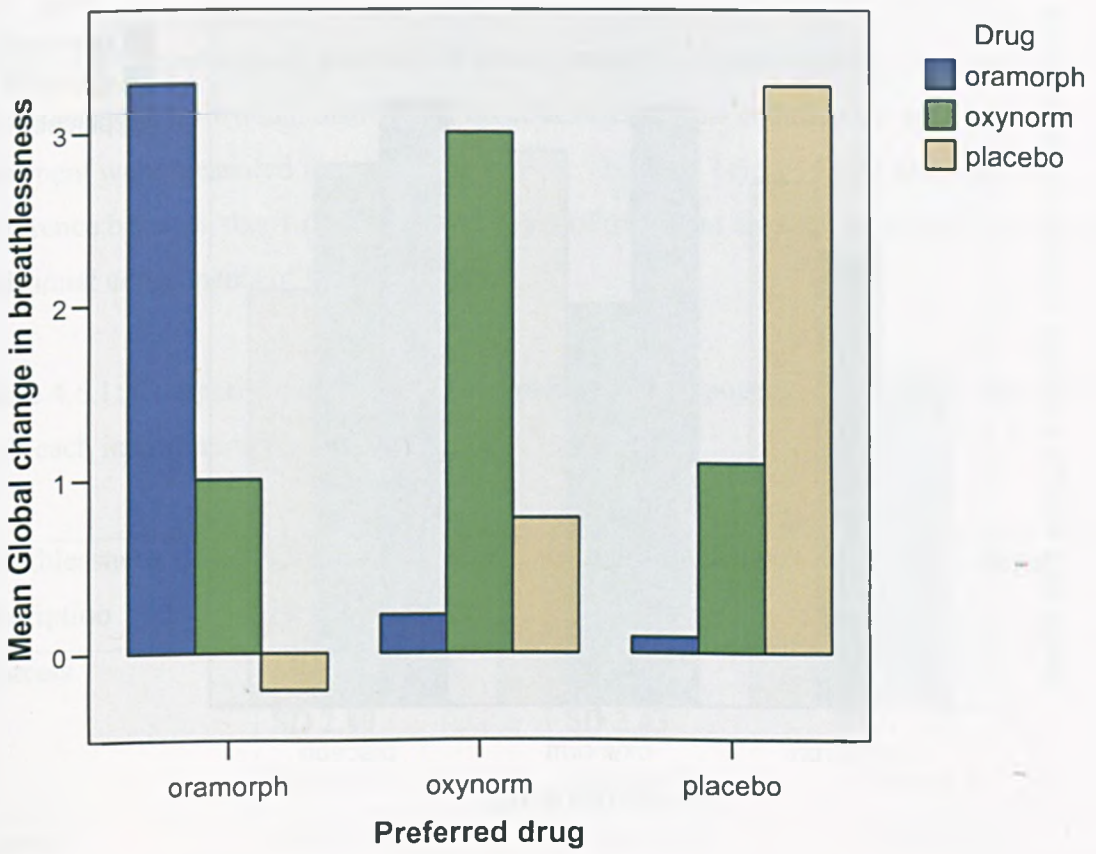
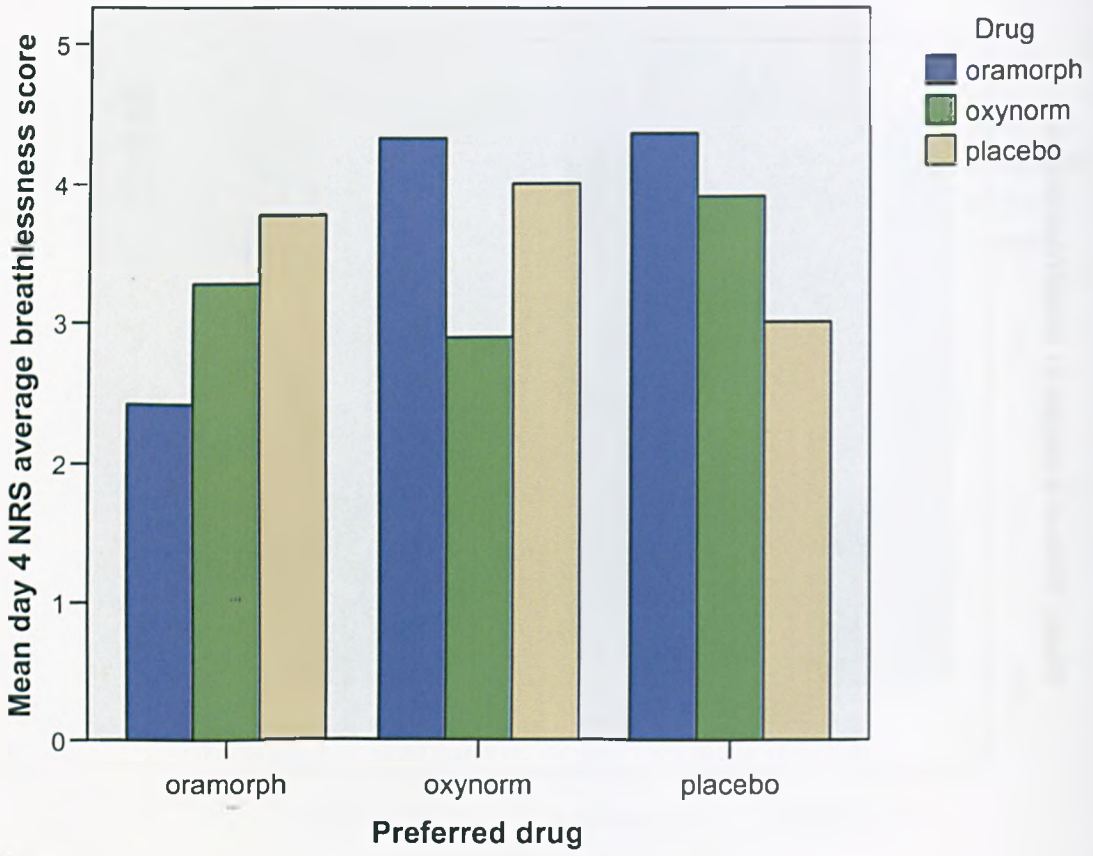


Figure 4.5.8: Global impression of change scores for breathlessness severity for each of the three interventions for the three groups of treatment preference at the end of the trial. Positive scores represent an improvement in breathlessness.



In contrast, Global impression of change scores, when compared to preferred week, do correspond to what one might expect (week preferred for breathlessness corresponds to the greatest mean improvement seen in global rating for that week compared to the other interventions). In addition, simply using day 4 values for NRS Average breathlessness, rather than change in breathlessness from baseline to day 4, also correspond to preferred week.

Figure 4.5.9: Histogram to show day 4 Average NRS breathlessness values for each intervention for each week preferred at the end of the trial. Lower values indicate the best breathlessness scores in this case, in contrast to change in breathlessness scores.



Section 6) Results: Secondary outcome measures

6.1 Comparison of additional components of shortness of breath

Additional components of shortness of breath, namely how participants coped with breathlessness, how much distress did breathlessness cause and their satisfaction with treatment were measured for each intervention. The table below (4.6.1) describes the difference between day 1 (baseline) and day 4 of treatment for each intervention for these additional components of breathlessness.

Table 4.6.1: Comparison of the change of additional components of shortness of breath with each intervention period

Breathlessness description	Oramorph change (n=35)	Oxynorm change (n=35)	Placebo change (n=35)
Distress	Mean 0.57 SD 2.49 Median 0	Mean 1.40 SD 2.43 Median 0	Mean 1.77 SD 2.65 Median 1
Coping	Mean 0.03 SD 1.85 Median 0	Mean -0.60 SD 2.16 Median 0	Mean -0.43 SD 2.17 Median 0
Satisfaction	Mean -0.83 SD 3.14 Median 0	Mean -0.34 SD 2.94 Median 0	Mean -1.37 SD 2.80 Median -1

Comparison of day 1 and day 4 was made whereby a positive value indicates a reduction in value from day 1 to day 4. In this case, negative values for distress indicate a worsening of that factor, whereby negative values for coping or satisfaction indicates an improvement in those factors. As can be seen in the table, the placebo week yielded an improvement in patient reported distress and satisfaction, with comparable values for coping with breathlessness with the active treatments. Overall the changes in these parameters are small. No significant statistical associations were noted between treatments using Wilcoxon signed rank tests.

6.2 Quality of life as measured by the SF-12 survey

Quality of life scores were calculated for all 35 participants at baseline and at day 4 for each intervention. Individual scores were re-coded and divided into eight separate domains. These domains are then individually weighted to calculate a score out of one hundred for physical and mental function affecting quality of life.

Mean baseline score for physical components of quality of life was calculated as 28.15, whereas the mental component mean was 47.24. No significant differences were determined between day 4 scores for each intervention using Wilcoxon signed ranks tests for paired variables.

6.3 Adverse events: Changes in clinical observation data with each treatment

The safety of opioid treatment with reference to cardiorespiratory parameters was monitored at the start and end of each intervention. Table 4.6.2 illustrates the change in clinical cardiovascular observations from baseline (pre-intervention) to day 4 of the intervention for all 35 participants. Positive values represent an increase in the value of that observation, negative values represent an decrease in value over time.

Table 4.6.2: Changes in cardiorespiratory observations with each intervention between baseline and day 4 of treatment

	Oramorph	Oxynorm	Placebo
Resting pulse difference (beats per minute)	Mean 0.03 SE 1.76	Mean -5.83 SE 1.19	Mean 2.34 SE 1.14
Resting systolic BP difference (mmHg)	Mean -5.34 SE 2.34	Mean -1.31 SE 2.51	Mean -0.34 SE 2.72
Resting diastolic BP difference (mmHg)	Mean -5.74 SE 2.08	Mean -2.80 SE 2.69	Mean -1.09 SE 1.85
Resting respiratory rate change (breaths per minute)	Mean -0.46 SE 0.46	Mean -1.60 SE 0.42	Mean -0.86 SE 0.46
Resting O_2 saturations difference (%)	Mean -0.71 SE 0.33	Mean -0.49 SE 0.34	Mean -0.31 SE 0.28

Standard error of the mean is quoted as a function of how good the estimate of the mean is, rather than quoting the standard deviation which is more important if one was interested in the overall distribution of the samples. Of course, standard deviation can be calculated from the standard error.

Treatment with either oxynorm or oramorph did not result in large reductions in either blood pressure, respiratory rate or oxygen saturations compared to placebo. There was a mean fall in systolic and diastolic blood pressure of approximately 5 mmHg for oramorph, with a lower corresponding fall of about 2.5 mmHg for oxynorm. A drop of less than 1% in oxygen saturations was observed for all three interventions. None of the changes in these observational parameters were statistically significant using paired t-tests.

Similarly, clinical observations were also taken one hour after the first administration of each intervention in all 35 participants. Table 4.6.3 below reveals the mean changes with standard errors of the standard observations taken between baseline and one hour. Positive values represent an increase in the value of that observation, negative values represent an decrease in value over time.

Table 4.6.3: Change in cardiorespiratory observations following the first dose of each intervention at one hour post-dose compared to baseline

	Oramorph	Oxynorm	Placebo
Resting pulse change (beats per minute)	Mean -0.80 SE 1.19	Mean -4.29 SE 1.10	Mean -2.65 SE 0.95
Resting systolic BP change (mmHg)	Mean -0.86 SE 1.77	Mean -1.26 SE 2.17	Mean 0.82 SE 2.78
Resting diastolic BP change (mmHg)	Mean -1.40 SE 1.78	Mean -0.26 SE 1.60	Mean 0.53 SE 2.07
Resting respiratory rate change (breaths per minute)	Mean -1.14 SE 0.29	Mean -1.60 SE 0.27	Mean -1.11 SE 0.33
Resting O_2 saturations change (%)	Mean -0.46 SE 0.29	Mean -0.20 SE 0.26	Mean -0.59 SE 0.27

As with the follow-up data at day 4, neither active treatment causes a large drop in blood pressure or reduction in respiratory rate or oxygen saturations compared to placebo.

6.4 Adverse events: Physical side effect incidence

The incidence of adverse events was documented on each study day for each of the three interventions in all 35 participants who completed the three-week trial. The most common side effects with opioids were determined a priori in the protocol, with NRS scales developed for nausea and drowsiness and a specific question asked about constipation (present or absent). All other adverse events were volunteered by the participants themselves when adverse events in general were under enquiry. This data is shown in Table 4.6.4. For the NRS scales, negative values indicate a worsening of the symptom, positive values indicate an improvement in the severity of the adverse event.

Table 4.6.4: Adverse events documented for each intervention

Adverse event	Oramorph	Oxynorm	Placebo
Nausea NRS (day 1 day 4 difference)	Mean -1.57 SD 2.90 Median 0	Mean -0.43 SD 1.63 Median 0	Mean 0.20 SD 2.18 Median 0
Drowsiness NRS (day 1 day 4 difference)	Mean -0.40 SD 2.67 Median 0	Mean 0.37 SD 2.64 Median 0	Mean 0.69 SD 2.55 Median 0
Constipation on day 4	12	10	4
Vomiting	3	2	0
Itch	3	0	0
Lightheadedness / Drunkenness /Dizziness	7	4	1
Headache	2	0	1
Abdominal pain	1	0	0
Sweating	1	1	0
Dry mouth	2	0	0

For NRS rated events between day 1 and day 4, nausea and drowsiness both worsened slightly from baseline with oramorph. Nausea scoring with oxynorm also worsened slightly, but less than for oramorph. This suggests that out of the two active interventions, oxynorm was better tolerated. Wilcoxon signed rank test statistics showed a statistically significant difference between oramorph and oxynorm and oramorph and placebo for nausea ($p = 0.04$ and $p = 0.01$ respectively). No other statistically significant differences were noted between oxynorm and placebo or for any drowsiness scoring between groups.

Of the patient volunteered adverse events, of the two active treatments oxynorm appeared to be the better tolerated. The numbers represent the number of participants affected, not the number of episodes, but most participants only experienced a single episode of the adverse event. One serious adverse event (SAE) occurred during the RCT. This single SAE that occurred at the end of the three-week study occurred on the last day of the placebo therapy and was attributed to a transient ischaemic attack, of which the patient had suffered on numerous previous occasions.

6.5 Karnofsky performance status

Table 4.6.5 below describes the mean (with standard deviation) Karnofsky performance status scores for day 4 and the difference between baseline and day 4 for each treatment. As can be observed there are little differences in performance status over this time period for each intervention. Negative values for change in score represent improvement in performance status. The data is not normally distributed and unsurprisingly Wilcoxon signed ranks tests show no statistical differences between treatments (data not shown).

Table 4.6.5: Comparison of Karnofsky scores for each intervention

	Karnofsky score on oramorph (n=35)	Karnofsky score on oxynorm (n=35)	Karnofsky score on placebo (n=35)
Mean day 4 score (SD)	70.6 (5.91)	69.7 (7.07)	69.4 (5.91)
Mean change in score from day 1 to day 4 (SD)	-1.4 (4.94)	-0.3 (4.13)	0 (2.43)

6.6 Compliance

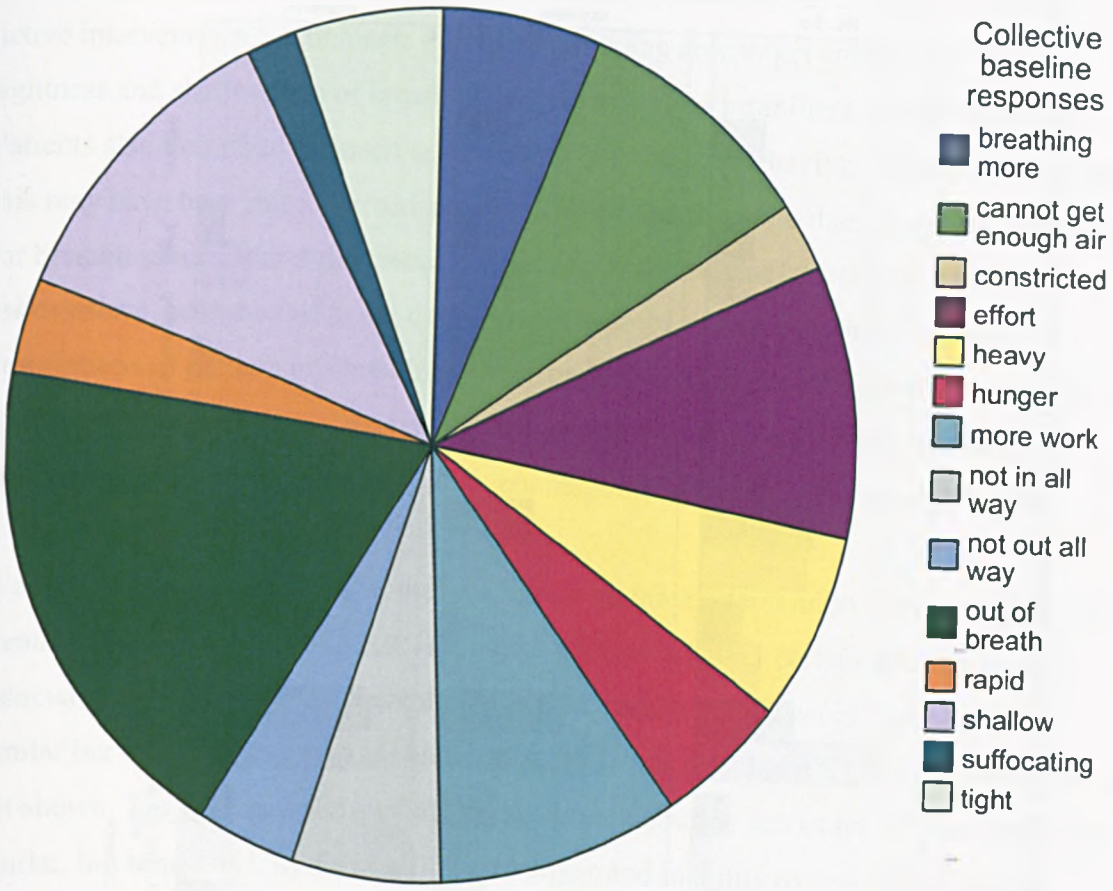
Measurement of compliance with treatment occurred in two ways. The first was participant reported number of missed doses of treatment. Of the total length of follow-up for three weeks on the 35 completed patients, the number of missed doses reported was 47 episodes, which relates to an average per person of 0.11 missed doses per day. Missed doses reported on oramorph were 18, missed doses on oxynorm were 22 and missed doses on placebo totalled 7 episodes respectively.

Secondly, volumes of the residual medication were measured at the end of the trial to assess compliance by this method. One participant discarded his week one treatment bottle by accident, which corresponded to the oramorph week. Hence mean values were calculated for the other 34 completed participant datasets. Each treatment bottle contained 50ml of either active drug or placebo and participants were advised to take 2.5ml four times a day for four days, which totals 40ml. Hence, a residual of 10ml should be present in each bottle for each treatment if compliance with treatment was 100%. In fact, mean residual volumes were 16ml for oramorph, 15ml for oxynorm, and 16ml mean residual for placebo. In total, this relates to 0.57 missed doses per day, slightly higher than the participant reported level.

6.7 Breathlessness descriptors

Participants were asked to rate the quality of their breathlessness by completing an assessment of breathlessness descriptors (3 descriptors chosen from a list of 15) at baseline (day 1) and day 4 for each of the three treatments. The pie chart below (Figure 4.6.1) reveals the proportion of descriptors chosen in total from a pooled collection of all baseline responses (3 responses x 3 baseline visits x 35 participants = 315 responses in total):

Figure 4.6.1: Pie chart to illustrate collective baseline responses of the 35 completed participants:



All 15 potential responses are elicited in the analysis. The most common responses are:

Feeling out of breath

Breathing requires effort

Breathing requires more work

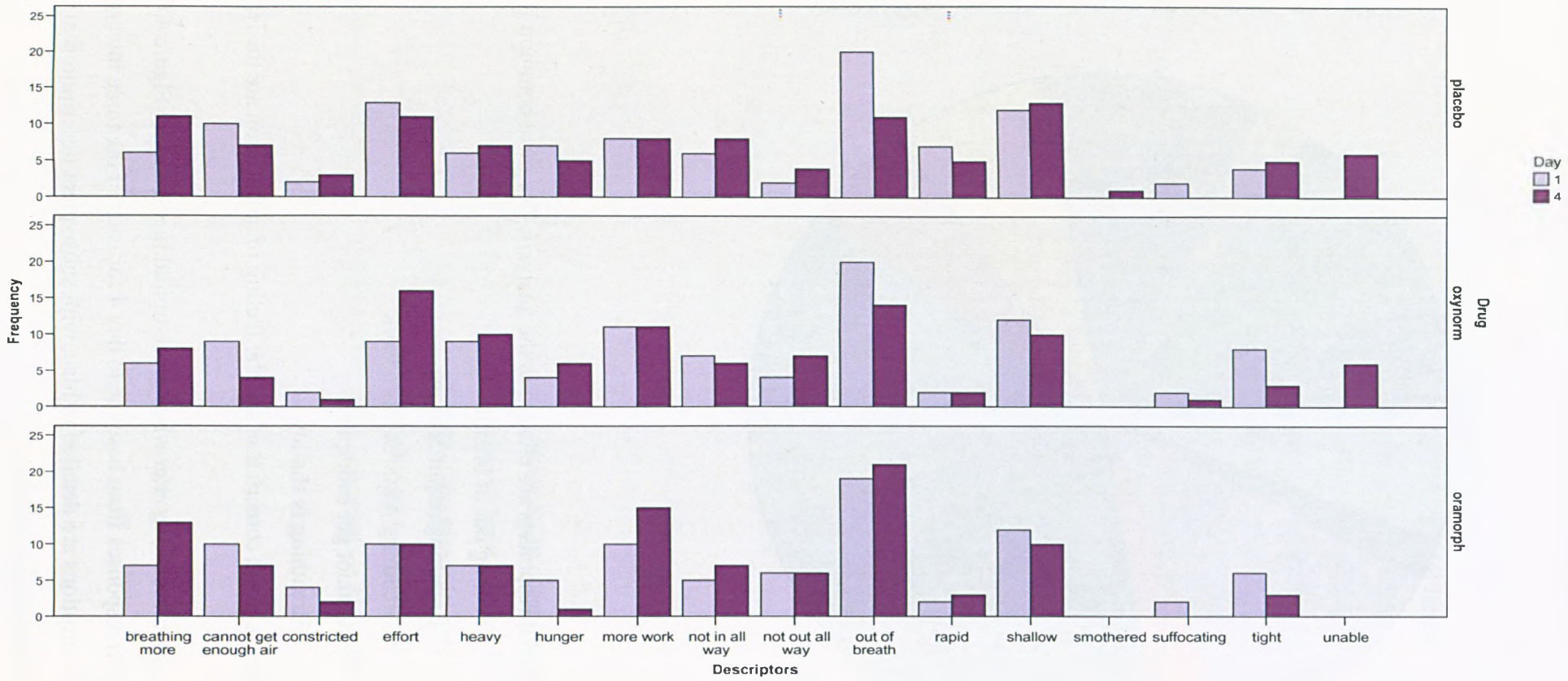
Cannot get enough air

Breathing is shallow

Chest tightness, chest constriction and the feeling of suffocation are the least frequently reported.

Do responses to breathing alter when given opioid medications? Figure 4.6.2 describes the change in responses from baseline to day 4 for each of the three interventions. Baseline descriptions are detailed in lilac, with subsequent descriptions at day 4 of therapy documented in purple.

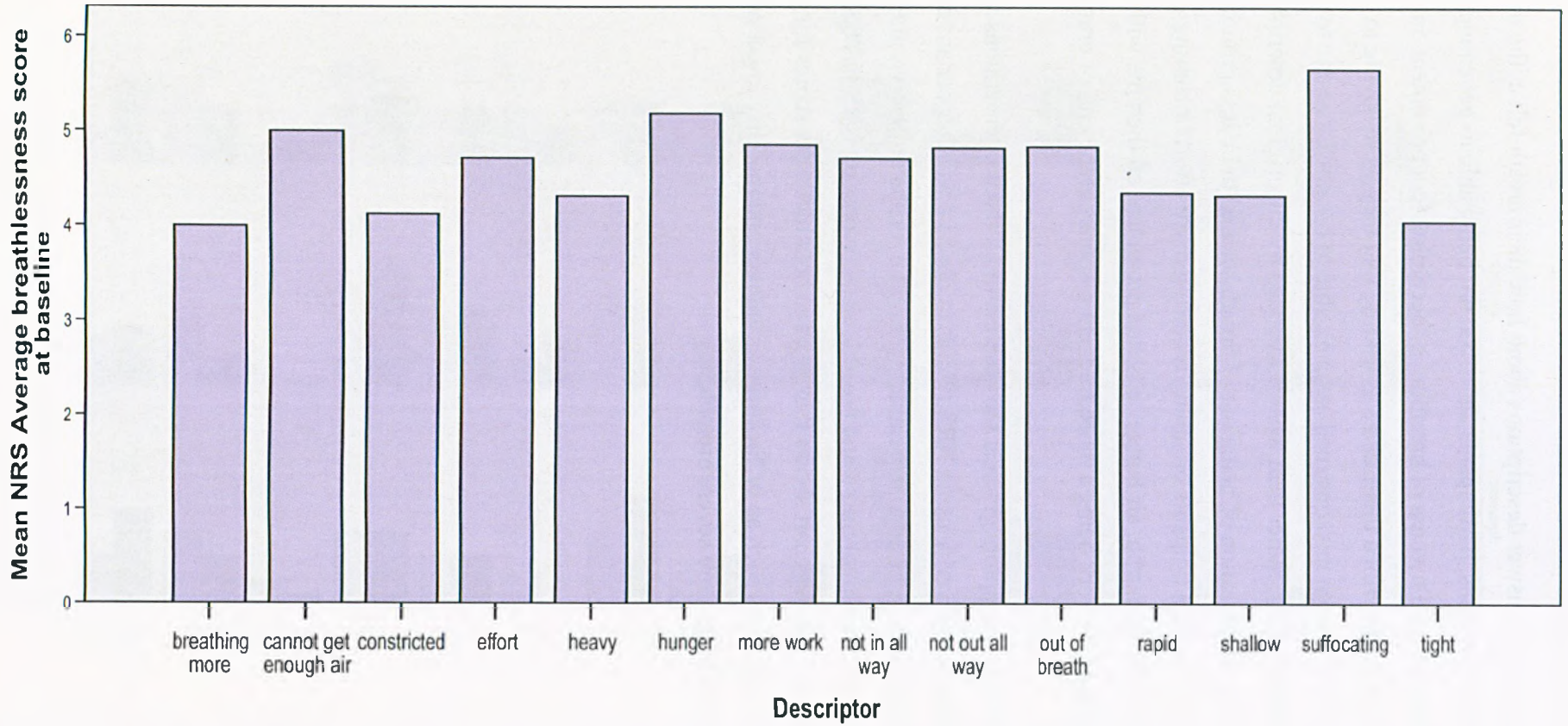
Figure 4.6.2: Change in breathlessness descriptor responses between baseline (day 1) and end of treatment (day 4) for each intervention (n=35 for each intervention)



In general, responses for all three interventions were similar. Some participants were unable to give a response as their perceived improvement in breathlessness rendered them unable to answer descriptions about how their breath felt at the time. For both active interventions, participants described not being able to get enough air, chest tightness and shallowness of breathing as becoming less prominent on opioid therapy. Patients also described themselves as finding that they were having to breathe more, but this may have been misconstrued as being able to breathe more due to success in therapy for breathlessness, rather than what is intended by the original description. Specifically for oxynorm, sensation of being out of breath seemed to be less prominent, with descriptions of participants breathing requiring more effort becoming more prominent. In addition, for oramorph, air hunger was less prominent on therapy, with breathing requiring more work being a more frequent response at the end of oramorph therapy.

In addition, descriptors given at the baseline of all three interventions were compared to breathlessness severity using NRS ratings to observe whether certain descriptors are associated with more severe breathlessness. The results are shown in Figure 4.6.3. A similar bar chart involving worst breathlessness scores on NRS has been performed but is not shown. The bar chart shows that average breathlessness scores for all descriptors are similar, but terms such as suffocating, air hunger and inability to get enough air are associated with more severe breathlessness.

Figure 4.6.3: Bar chart illustrating the Mean NRS Average breathlessness scores for each descriptor expressed at every baseline measurement taken (n = 315 baseline descriptor responses)



Section 7) Discussion: sampling, study conduct, methodological review and points to note in the analysis

7.1 Participant sample

The CONSORT diagram (Figure 4.3.1) illustrates some of the issues involved in trial recruitment using an existing database. One of the benefits of using such a utility is to identify potential patients that may fit the inclusion criteria prior to their clinic appearance, thus allowing the provision of targeted resources towards patients that may both fit the criteria and may be interested in participation in clinical trials. Patients who had expressed a preference not to be involved in clinical trials were documented on the database and therefore should not be approached. This approach meant that potentially eligible patients could be better targeted in cardiology clinics. In addition to using the database, clinic doctors and nurses were given the inclusion and exclusion criteria in case they reviewed any patients who may fulfil eligibility that did not appear to on the database. In this circumstance, patients were given the participant information sheet and were told they would be contacted by the research team within one week.

Despite these measures and persistence by both myself and the research nurse, only 39 participants were consented for the trial over a period of just over 18 months. Approximately the same number of patients were eligible and approached but refused entry. Over two hundred patients appeared to fit the criteria from the database, but the majority of these did not fulfil eligibility on inspection in clinic. This highlights one of the major problems with the use of an existing database in the fact that it is historical. CHF patients describe variable symptoms and medications over time and this is particularly noticeable when patients are only reviewed every year as tends to be the policy in the Hull and East Yorkshire NHS Trust. Hence, the majority of patients who appeared to fit eligibility from the database who were subsequently reviewed were in fact ineligible at the time of review.

This highlights a number of points. Altman (1991) correctly states that there is frequently an optimistic number of proposed recruits and this is demonstrated here as less than 5% of breathless patients were eligible and agreed to enter the study. Future studies of a similar nature could be multi-centred to allow greater exposure to eligible patients. Alternatively, care of the elderly clinics or GP surgeries could be involved to approach eligible patients, as many patients with CHF in the district may not have been referred to

the heart failure service due to ongoing review by these other specialities. The main problem with this approach would be accessing echocardiography services to allow accurate up-to-date imaging by the cardiology service. At the start of the trial I considered that the inclusion criteria for the study was quite wide and had that not been the case, many fewer patients would have been included. This is the balance to be struck between making the criteria too wide, not allowing accurate review of the study population of interest and making the criteria too narrow and not finding sufficient numbers to reach preset statistical power. On reflection, I consider that this balance was probably correct in this study given the limits on time, resources and nature of single-centre research, particularly as the number of participants detailed in the power calculation was surpassed. Future studies of a similar nature need to take this important point into account when protocols are being devised.

Although half of the patients approached refused entry into the trial, this figure is probably representative for trials of this type. I did note however that some potential participants declined trial entry on the basis that they were advised not to drive for the duration of the study. If the trial were to be repeated, I would probably rephrase that advice to suggest that, as with all new medications, one should not drive if they feel that the effects of the medication meant they felt they were unable to perform this activity safely.

Details of the patient sample selected are noted in Chapter 4 Section 1 of the results. There were no differences between the 35 participants that completed the study and the two that withdrew due to adverse events. Is the sample representative of advanced heart failure patients with NYHA class 3 or 4 symptoms? Certainly, the baseline values for breathlessness severity on NRS indicate that the study population has a moderate to high level of breathlessness. The aetiology of heart failure, taken from the database and therefore open to interpretation, predominantly involved patients with ischaemic heart disease, in keeping with available statistics of the aetiology of CHF (Davis *et al.*, 2005). Hypertensive heart disease and dilated cardiomyopathy were also included, but no patients with documented valvular disease as the sole cause of heart failure were included. The sample taken was predominantly male, which is in keeping with most other trials where there is a preponderance of male participants. The age of the sample is in keeping with other similar studies of breathlessness (Jennings *et al.*, 2001, Johnson *et al.*, 2002, Abernethy *et al.*, 2003).

One could argue that participants with symptomatic disease (NYHA 3 or 4) might be expected to have a lower mean ejection fraction, or higher mean BNP result, than that observed in the results. This might reflect the nature of our sample and the problems associated with research in advanced disease. Patients with advanced disease and the most troublesome symptoms may be unable to attend regular clinic follow-ups due to ill health and therefore may not attend for echocardiogram or blood testing. A decision may have been made not to subject advanced patients to unnecessary interventions. Hence, the sample might reflect those patients who are symptomatic with abnormal ejection fraction and BNP, but not those so advanced that might have a short life expectancy and worse heart failure parameters. The frequency of the medication for heart failure is probably representative for symptomatic disease, with beta-blockers, ACE inhibitors / adrenoreceptor blockers and aldosterone antagonists all represented in high frequencies, in accordance with current treatment guidelines for symptomatic CHF.

7.2 Study conduct

The process of research recruitment and follow-up from a practical aspect can be found in Appendix 4. This details more of the day-to-day activities involved in non-commercial trials based in the NHS.

It is noticeable from the study that of the 39 patients consented, 35 participants completed the three-week crossover with full sets of data. This represents a very low drop-out rate for any clinical trial, but particularly for a trial involving symptomatic patients with relatively advanced disease (Dorman *et al.*, 2009). Withdrawals from crossover studies are particularly important to keep to a minimum due to the nature of the analysis of the subsequent data. Two patients no longer fitted eligibility between consent and trial commencement. This was due in part to the medication delays experienced in the study, which in turn was compounded by the relatively short expiry of the treatments (90 days). This meant that participants had to start the trial prior to three weeks before the medication expiry date and that medications had to be ordered with a great deal of advanced notice. Delays in the set-up of the trial in Huddersfield that were beyond my control led to the two patients consented being unable to be included as their disease process changed over time. This was very unfortunate and disappointing.

A number of factors were involved in the collection of so much fully completed data. Firstly, the initial trial was short and hence did not involve long detailed follow-up with the potential for lost participant follow-up. Secondly, participants were contacted on every day that study data was required, which acted as a reminder for the participants to complete their assessments. Although this could be considered as being quite intensive for the participants, I believe they were quite reassured to have daily contact, it allowed a rapport to be established and tended to only last about 5 minutes for the telephone and 20 minutes for the day 4 visit. Thirdly, only two researchers were involved in contact (either myself or the research nurse) so participants were familiar with the point of contact on each occasion, rather than being contacted by multiple researchers. The handling of missing values was documented *a priori*, however this did not have to be enacted due to the vigilance of the assessment process.

Fourthly, there was flexibility concerning the place and timings of assessments. The option of reviewing participants in their own homes was invaluable for both consenting purposes and for detailed follow-up, as symptomatic patients may not have wanted to attend twice a week for review. Of the 37 randomised participants, the vast majority were seen in their own home environment. The study did not require hospital attendance for monitoring so could be performed almost anywhere with portable equipment. I believe this was a major factor in participant recruitment and subsequent follow-up. The crossover nature of the design of the trial allowed participants to receive both potentially active and placebo medications, rather than a parallel group design that would not allow some to receive the active medication, which may have been important in their decision to continue within the study. Lastly, participants felt they had few other options for symptom improvement and had often had to manage their symptoms for a long period of time. The opportunity to try something for a short period to potentially help both themselves and others meant they were more likely in my opinion to continue in the trial.

7.3 Review of methodology

Randomised controlled trials are considered the gold standard approach to quantitative research owing to the reduction in potential biases with the randomised double-blind approach (Tilling *et al.*, 2005). A cross-over design was chosen to reduce the number of study participants required; it is recognised that it is difficult to recruit to palliative care studies (Dorman *et al.*, 2009). For a given level of precision in estimation fewer observations have to be obtained for a cross-over trial compared to a parallel-group design (Senn, 2002). A disadvantage of crossover studies in palliative care in particular is that it is necessary for the patients to be stable for the duration of the study to avoid a period effect and this can be a problem with malignant disease. However, the patient sample in this study was taken from a stable population of chronic heart failure sufferers and analysis for period did not reveal any such effects.

Crossover trials have the advantage of eliminating between-patient variation between treatments and it is very suitable for observing treatment effects in stable chronic diseases such as asthma that cannot be cured but involve symptom control (Senn, 2002). Although CHF patients may deteriorate over time, the period at which they remain stable can be measured in years (Lehman, 2006b) and thus could be referred to as a chronic disease with periods of stability. Participant withdrawals can also be difficult, particularly in crossovers where a participant may withdraw during the first treatment period. If the same occurs in a parallel trial, at least this incomplete data may be used, but in a crossover study use of this data is difficult as no direct information of comparison of treatments can be made (Senn, 2002).

Participants were allocated to their treatment sequence using a simple form of randomisation. If the effect of time was important (e.g. for a long period of time, rather than just a few weeks), in order to bring balance into the study a Latin square approach could be used if there is a suspicion that trends may occur over time that might affect the experiment (Senn, 2002). This approach negates any effect of period. This is not the case for the current trial, but this method should be considered for trials of a longer duration.

Bausewein *et al.* (2007) in their systematic review of tools used to measure breathlessness in multiple aetiologies recommend the use of uni-dimensional scales (such as modified Borg scale) alongside an assessment of the impact on quality of life or physical function and additional components such as assessment of anxiety related to

breathlessness. The approach has been followed in this RCT, however, debate still exists as to the gold standard measurement tools to use for specific situations, dependent on setting, length of follow-up and disease aetiology. The authors recommend VAS or Borg as uni-dimensional measures, but actually acknowledge earlier in the article that NRS may be superior to VAS due to its ease of use and repeatability. The NRS and Borg scales for breathlessness were understandable and repeatable, could be used over the telephone (unlike VAS) and could be analysed using comparison of mean values (unlike verbal rating scales). Average, Current and Worst ratings of breathlessness are recommended by Wilcock et al. (1999). A recent consensus statement also recommends the use of NRS or modified Borg scores for measurement of breathlessness severity involving these timepoints for breathlessness in palliative care (Dorman *et al.*, 2009). It also recommends the assessment of mastery over breathlessness and related anxiety with breathlessness, both of which have been incorporated in the RCT assessment by additional components of breathlessness such as coping and distress rating.

The SF-12 questionnaire of quality of life was incorporated in the RCT as an easy to use validated measure. Its use has benefits and limitations. It is not specific to CHF, making the results generalisable to other studies of advanced disease causing breathlessness, but is not disease specific for comparison with other studies in CHF. Since there is no defined gold standard measure in CHF, the choice of measure is difficult. However, the limitations on physical function (climbing stairs, playing golf, moving a table) do not reflect the patient experience with CHF. Items such as inability to shower without symptoms, tying shoelaces or bending over would appear to better quantify the experience in CHF.

Immediate release preparations of the above drugs were used rather than sustained release preparations. This reflects current clinical practice in many centres in the UK and follows the recommendations in the BNF and SIGN guidelines. In addition, it was considered to be easier for the patients to distinguish the trial medication (in immediate release liquid form) from their usual multiple medication therapy in tablet form. Sustained release tablets may have affected compliance rates given that patients have so many other tablets to remember.

Oral morphine (oramorph) and oral oxycodone (oxynorm) were chosen as they do not have ceiling doses, unlike weaker opioids (step 2 analgesics such as codeine or tramadol) and are used the most widely in clinical practice. The doses considered for oral morphine

and oral oxycodone were considered to be clinically equivalent (British National Formulary, 2006). Oral morphine was chosen because of the previous pilot study and because oramorph is specified as an unlicensed indication for the management of breathlessness in both the British National Formulary (BNF) and Scottish NHS Clinical Guidelines (SIGN, 2007). Oxycodone was chosen for a number of reasons. It is used as a common alternative to morphine in palliative medicine. As discussed previously, it has a different morphine receptor profile in humans and may have less side-effects in a patient group who may not have consistent optimal renal function (Davis and Pasternak, 2005). In addition, there is some evidence to suggest that kappa agonists like oxycodone may promote diuresis (Leander *et al.*, 1986, Rimoy *et al.*, 1991) which may have an additional benefit in those breathless CHF patients who also have excess fluid.

The doses of oramorph and oxynorm were derived from equivalent doses used in the literature (Johnson *et al* 2002, Abernethy *et al* 2003 to quote 2 examples) and from existing clinical practice (Oxberry and Lawrie, 2009). A non-significant statistical difference in this RCT for the primary outcome measure (change in average breathlessness) was observed between active and placebo treatments. It could be argued that higher doses of medication might have resulted in a statistically significant result. Was the dosing schedule correct?

On reflection, the doses used were appropriate given the existing evidence in breathlessness in other aetiologies. Given the nature of the participant population and the design of the study it was probably the correct dose. Had the dose been too high, the number of withdrawals would have potentially been much greater, leading to loss of data and statistical problems in the analysis. Drop-outs in crossover trials present a particular problem and it is the case that more completed datasets are preferable to less. Future trials should reflect the fact that the optimum dose of opioid in CHF is as yet unknown and a study with a factorial design might be the best way to determine the optimum dose in opioid naive CHF patients. This factorial design could include a placebo arm, with oramorph given at doses of 5mg QDS and 10mg QDS orally for example. A parallel group design would not have quite the same problems with loss of data from treatment withdrawals as would a cross-over design, although a greater participant number would be required. Alternatively, a sequential design could include the increase of dose of opioid in participants who show no or little response to the initial dose (e.g. 2.5mg QDS), though this may be difficult to analyse in an appropriate way. Certainly there is scope to examine this area more closely in future studies.

The four day intervention period was chosen to allow drug to reach steady state given that the half life of oral morphine (oramorph) and oral oxycodone (oxynorm) is between 1.5 and 4 hours according to their summary of medicinal product characteristic literature. In addition, the pilot study by Johnson *et al.* (2002) revealed a return to baseline values for treatment effect over 4 days of placebo administration. A possible sequence effect was avoided by incorporating a three day washout period between interventions. It is considered that a period of five half lives is required for elimination of a drug from the body and therefore at least 20 hours (5x4 hours) was necessary (British National Formulary, 2006). This presumes a normal renal function, and given that many patients with heart failure also have co-existent renal impairment (Lehman, 2006b) and that these opioids are renally excreted (Twycross *et al.*, 2002), a longer washout period was indicated. An assumption for analysis was made in that this passive washout period was sufficient to allow return to the patients' natural baseline state. An alternative approach to this methodology was taken by the Abernethy (2003) study as discussed in Chapter 3. In this study, participants were switched to the alternative treatment without washout, but day 4 values were taken without baselines. This would allow washout to occur during the second treatment phase, although the criticism of this is that the treatment period needs to be sufficient enough to both allow treatment effect and washout from the previous intervention to occur. Four days in total was allowed for this process to occur, as opposed to a more generous seven days in this study.

Measurements for physical observations were taken using the same electronic equipment (blood pressure cuff, pulse oximeter) so as to reduce the bias that may have been introduced by using different machines with slightly different calibration. All physical observations were measured at rest to allow comparison at a steady state. Similarly, participants were reviewed by myself with or without the research nurse on every day 1 and day 4 of therapy, with standardised telephone follow-up by myself or the research nurse on days 2 and 3 of treatment. Hence, data collection only occurred with two individuals, blind to intervention, so as not to introduce any further bias. Logistically, data collection by only one researcher alone would not have been possible given the other daily constraints on work and time.

7.4 Points to note in the analysis

Frequently there is more than one method to analyse the data collected and I have attempted to describe different methods according to statistical convention, type of outcome most appropriate to the data described and what has been published already in the literature to allow direct comparison. Sometimes data has been analysed in different ways in order to demonstrate that the outcome is approximately the same despite the statistical method chosen, as long as it is appropriate according to the statistical requirements tests observe.

Should arithmetic means be used in the interpretation of numerical rating scales? The NRS could be described as a discrete quantitative measure. Altman (1991) and Campell & Machin (1999) state that it is reasonable to treat discrete data as continuous in statistical analysis. Medians and means are quoted in some parts of the analysis, as medians can be useful as a descriptive statistic.

Non-parametric tests were used when distributional assumptions were not met, continued for consistency for both oxynorm and oramorph. These tests are not as powerful as parametric tests (Campbell and Machin, 1999), but given the small sample size unless the data appeared to be clearly normally distributed using histograms or Q-Q plots it was probably more appropriate to use non-parametric methods. In this regard, any positive statistical associations that were found did not depend on a dubious assessment of data normality. In the data analysis though, there was little difference between the outcome of parametric and non-parametric tests on the sample collected, so in practice this distinction made little difference on study outcomes.

Paired data forms a large part of the three week analysis as a result of the cross-over design. Using this method one attempts to remove between subject variability to consider within-subject differences with intervention.

Throughout this analysis the null hypothesis is that there are no differences between interventions. Bland recommends in crossover trials that differences between individual treatment outcomes and baselines ideally should not be used, as this will increase the measurement error (personal communication). In this study, the three baseline measurements can be included in an analysis of variance equation which could improve power and therefore the measurement of the estimate. Senn (2002) suggests that

difference from baseline measures are frequently used in clinical trials for analysis as long as the variances between baseline and outcome are assumed to be the same. The use of the baselines has the benefit of reducing the variation in the participant sample by using analysis of covariance techniques. However, in practice the purpose of the crossover trial is to allow the reduction of variability between interventions by using the same subjects for each intervention, hence reducing the variability by this fact alone. Having the baseline data can be of benefit in complex statistical analysis and in time series analysis, but is not necessary for adequate comparison of interventions in a crossover trial (in contrast to a parallel group design).

Altman also recommends analysis of variance techniques as long as values follow a normal distribution. He discusses that these methods are conservative in that they err on the side of caution (i.e. tend not to disprove the null hypothesis) and suggests that for multiple comparisons modified paired t tests are recommended if the method of analysis is not detailed in advance. This shows that there are a number of ways to analyse the data, which I have attempted to demonstrate in the results and discussion. The protocol made reference to differences between baseline (day 1) and day 4 of therapy as the outcome measures used and therefore I have followed this structure in the analysis. However, comparison of day 4 results for each intervention would appear to be acceptable and if the trial were repeated less emphasis need be made with regard to baseline values on each intervention. From the results, using differences between time points appears to lead to estimates that appear to fit better to the normal distribution, allowing use of paired t tests, compared to using day 4 data alone. Alternatively, this day 4 data could be transformed using log transformations for example, which could be used instead to allow parametric tests to be used.

Whilst there is some interest in the outcomes of the three individual treatments in the trial, often the outcome of most interest is not the individual outcome to intervention, but how the interventions compare. To that effect, as described by Senn (2002), the difference between treatments is the analysis of interest and response versus placebo is noted as the most important analysis in the results. However, some information about the individual intervention outcomes are recorded to allow the reader to appreciate the overall effect for each intervention.

The intention to treat statement is important and all participants will have had their data analysed regardless of the latter review of their eligibility suitability. Senn (2002) would

also not discard the data of participants that were unable to fully complete the trial as long as there was complete data from at least one full period of intervention. This was not the case in this study as both participants who withdrew did so in the first week of treatment. Senn (2002) describes that in practice the information derived from these participants can only really contribute indirect information to the overall trial process, but that this data should not be discarded fully if at least one period of intervention has been completed. Some crossover trials may have participant data that is incomplete for each timepoint of measurement for each intervention, but all interventions have been completed. There is some discussion around the best method of dealing with this problem. In the protocol, I had considered the use of clearly marked imputation values that would reflect the worst value that could be achieved. This would allow a great deal of confidence in any subsequent statistically significant results. However, in the event of large amounts of missing data, I would consider the approach by Senn (2002) who recommends carrying the last available measurement forward to impute, or by making an estimate of the missing value dependent on the other results given. In practice, this might allow the continuation of any trend seen between interventions in a large patient sample with large amounts of missing data over time, but adequate explanation of the frequency of missing values and the potential effects on the statistical outcomes should be made clear in the discussion, as this method may lead to misleading overestimates of effect.

7.5 Sequence and period analysis

There remains much debate as to the method of analysis and importance of period and treatment-period interactions. For example, Senn (2002) states that he never tests for carry-over of treatments. He recommends that trial design should involve the use of adequate washout periods based on the best available estimation that drug clearance will have occurred and that there will always have to be the acceptance that carry-over will not have seriously affected the results one of many assumptions in a clinical trial (Senn 2002).

Senn (2002) also states that if sequences are assigned in a purely random basis, as in this study, any period effect could be ignored in the subsequent analysis, as random allocation is consistent with the belief that the period effect is negligible. This is converse to the argument for block randomisation which would require the analysis of any period effects. However, for the sake of completeness, analysis for possible period and sequence

effects has been performed and the subsequent data analysis takes no allowance for the effect of period, given that no period effects have been demonstrated.

Section 8) Discussion: Primary outcome measure: change in breathlessness score

8.1 Baseline and end of treatment comparisons for breathlessness on NRS and Borg scales

No statistically significant differences were shown to occur for NRS- or Borg-rated breathlessness severity between oramorph, oxynorm or placebo for the 35 completed patients (Table 4.4.2). Baseline (day 1) and end of treatment (day 4) differences in NRS and Borg scores were calculated for each intervention. In this fashion, negative results indicated a higher day 4 score, and hence a worsening of breathlessness. Similar results were observed for both worst and average scores. All calculations (except for oramorph treatment difference in average breathlessness on a Borg scale) resulted in positive values, indicating a symptom improvement between baseline and end of treatment for all three interventions. In particular, mean differences on NRS scoring (worst and average scores) were the greatest for placebo (Table 4.4.1), indicating a noticeable placebo effect. Smaller mean differences were observed for Borg rating compared to NRS. Non-parametric statistical tests for paired data were used for comparison due to the non-normal nature of the outcome measures.

A change of 1 point on an 11 point NRS score (or 10% on a 100mm VAS) for breathlessness is considered as clinically important (Booth, 2006, Powers and Bennett, 1999) and hence a mean change in score with oxynorm (1.29 for average NRS and 1.43 for worst breathlessness NRS change) in particular might be considered, on its own, as being clinically important. However, given that these changes are comparable to the effect by placebo on breathlessness scores, this demonstrates important points. Firstly, it illustrates the importance of an adequate placebo comparison in clinical trials. Secondly it demonstrates the importance of good randomisation and double blind techniques, so not to influence the responses to the active treatments over placebo and thus not potentially subvert the trial results. Thirdly, the placebo results may be affected by the regression to the mean phenomenon. This phenomenon can occur in all trials, but particularly for subjective concepts with a degree of measurement error (Morton and Torgerson, 2005). Measurement of extreme values at baseline are likely by chance alone to regress to the mean on retesting, simply because extreme values are more affected by error than those near the average value. Lastly, it would appear that any differences in breathlessness with the interventions are small on either NRS or Borg scales.

8.2 Comparison of pooled active results and placebo on breathlessness severity

Pooled responses for active treatment, incorporating results for both oxynorm and oramorph versus placebo were calculated. As expected from the results seen earlier, there does not appear to be any difference between the effect of active treatment and placebo on breathlessness severity at day 4.

This combination of active therapy approach to analysis is a reasonable way to assess a difference, but it has a number of technical issues. Firstly, it involves the combination of paired estimates in the same individual, rather than in a typical two to one randomisation versus placebo where there are twice as many participants receiving active treatment, but all estimates are independent and not paired. Secondly, and more importantly, if one treats the active interventions as having equal weighting in this pooled analysis, one could argue against the reasons why the analysis of two active interventions was performed in the first place. Taking these points into consideration, whilst this combination of active treatments is of interest, it should form the basis of another properly constructed trial of one active treatment versus placebo, or an RCT comparing responses in breathlessness severity between both active interventions rather than involving a placebo arm. Hence no further analysis has been performed involving a combined active intervention group.

8.3 Change in NRS and Borg scores for breathlessness over time

It is possible that results on day 4 at the end of treatment fail to capture or reflect the overall changes in scoring over the course of therapy (Pang *et al.*, 2008). Line graphs illustrating the mean change in NRS scores (average and worst breathlessness) are shown in the results. Similar graphs exist for the mean change in Borg score over time (not shown). Collectively these graphs demonstrate an initial reduction in breathlessness scoring (hence symptom improvement) from day 2 of treatment which is sustained over subsequent days for all three interventions. Here it can be seen that responses start to occur by one day of treatment (four doses of intervention) and continue throughout the course of treatment, and that baseline placebo scores are higher than for the active interventions, hence the relatively large mean score differences between baseline and end of therapy for placebo versus active interventions seen above. This difficulty in

extrapolation of treatment effects due to this large decrease between baseline and end of treatment for placebo led to the consideration of analysis in another form, to match a similar trial in the literature for breathlessness in mostly COPD patients. Hence a comparison with results with the Abernethy *et al.* (2003) study is made in section 8.5.

Area under the curve (AUC) methods could have been used to describe the cumulative response to each intervention in comparison (Pang *et al.*, 2008). Figure 4.4.2 describes the response over time for the three interventions, but a formal analysis of the response over time could have been attempted if there was a notable difference between interventions. However, AUC measures are difficult to calculate and for evenly spaced observations over time, Altman (1991) describes that the mean of all the measurements could be used as an approximation. Given that Figure 4.4.2 shows no discernable difference over time for active treatments and placebo, this further analysis is not necessary to improve the understanding of the difference between interventions and has therefore not been performed.

8.4 Potential factors that might influence response to opioids for breathlessness in CHF

Non-statistically significant results were shown in the response to active treatment versus placebo for breathlessness rating. Could it be the case that certain individuals respond better to treatment and hence it might be targeted to those individuals who might derive a benefit? Previously, it has been considered that excessive neurohormonal activation is detrimental and the release of endogenous opioids may be part of a protective mechanism possibly similar to the release of natriuretic peptides. Endogenous opioids released at the time of sympathetic activation in CHF might be involved in attempting to regulate over-activation. Excessive sympathetic activation might also be involved in the development of abnormal breathing patterns in CHF. Hence, if opioids reduce this sympathetic response, and this is the mechanism by which breathlessness is improved, one could surmise that patients with only partially controlled neurohormonal activation might show a greater improvement in breathlessness than those with better control. One might expect therefore that patients on sub-maximal beta-blocker or ACEI/ARB therapy, or those not receiving aldosterone antagonists, might have a better response to opioids for breathlessness. This theory however is not borne out by the analysis in Section 4.8.

Beta-blockers are responsible for reducing the sympathetic overdrive in CHF. Sympathetic overdrive might be responsible for the altered breathing patterns in CHF. If opioids operate by a similar mechanism to beta-blockers, one might expect those patients on lower doses of beta-blockers might respond better to opioids than those on maximal doses, where sympathetic stimulation may be better treated. Figures 4.4.5 and 4.4.6 correspond to the change in average NRS scores on oramorph and oxynorm respectively with beta-blocker dose. For oxynorm, the premise that participants receiving lower doses of beta-blocker have a higher mean response in breathlessness to treatment compared to those on higher doses appears to be true. The improvement in breathlessness severity with treatment is marked for those not receiving any beta-blockers. The opposite appears to be true for oramorph, though the values are smaller, calling this hypothesis into question. A longer period on treatment is probably necessary to influence sympathetic overdrive in CHF, as most trials with beta-blocker therapy had a much longer follow-up period (Whorlow and Krum, 2000). In addition, maximum treatment with ACEI or ARB did not alter response to opioids on breathlessness in this sample. What is apparent here is that any overall effect of opioids as a group is unclear, but further studies involving this area appear warranted.

Are there any other recognisable differences between those that have an improvement in breathlessness with opioids than those who do not? Given the relatively small participant sample, the analyses in Section 4.4 and 4.9 were calculated to act as a guide for future research ideas rather than definitive evidence for effect in specific groups, though it would be helpful if one could identify characteristics to aid physicians to target patients who might respond better to opioids than others. Responders to opioids involved those participants that had an improvement of one point or more on average NRS breathlessness score with either or both opioid treatments, non-responders were those that did not. A one point change was selected as this has been identified as the minimally important clinical change in breathlessness (Powers and Bennett, 1999, Booth, 2006).

Overall there is little difference between demographic groups; in particular there is not a consistent opioid response dependent on NYHA status (one might expect those with more severe symptoms should respond better to opioids for breathlessness). From a diagnostic perspective, those participants with dilated cardiomyopathy respond well to opioids, but this participant group is small (n=3) and this may just represent a statistical anomaly. One might expect that those more severely affected by their disease might respond better to opioids. As can be seen from the correlation data, there appears to be no

association between age or severity of disease as measured by BNP and ejection fraction. There would appear to be no association between severity of CHF as measured by NT-BNP and response to opioid medications for breathlessness. In particular, those most severely affected on the BNP scale (ie highest BNP) did not have a consistently greater response to opioids. Those participants with a worse renal function also do not appear to have a greater response to opioids, suggesting that they are adequately cleared from the body in these participants with a GFR of 30ml/min or greater.

Participant data was also divided into those that did not respond to either treatment versus placebo, those that responded to one and those that responded to both active therapies against placebo. Response was again determined as a difference of NRS average breathlessness severity change of one or greater for active treatment versus placebo (those with no difference or placebo favoured were grouped as no response). This again is a post-hoc analysis and therefore the analysis has not been included in the results section. However, there were no obvious major differences between those who responded to treatment and those that did not in relation to ejection fraction, BNP or PEFR. This is also true for values just taken from day 4 rather than a change in value with intervention (data not shown). Overall, no consistent aetiological factors such as disease severity or baseline demographic factors could be identified that could help clinicians target individuals for therapy with opioids for breathlessness using these methods.

8.5 Comparison with the analysis performed by Abernethy *et al.* (2003)

Analysis was performed on the data in the same fashion as set out in the Abernethy *et al* (2003) study to allow direct comparison of the data and outcomes between the two studies. As seen in Figure 4.5.7, change in breathlessness scores from baseline to day 4 for each intervention may not accurately measure the participant experience, particularly observed in those participants that favoured oramorph treatment at the end of the three week period, yet their change in NRS or Borg scores did not reflect this. As discussed by Pang *et al.* (2008), changes in subjective assessments such as breathlessness scores have the problem that trial participants may not accurately recollect their previous rating. This might mean that improvement or worsening of breathlessness may not be accurately assessed if recollection of previous scores is not correct, though this is a potential problem for much longer duration trials than this RCT. Hence, an alternative analysis

was considered in the thesis write-up based on a similar study in a different patient group.

Average shortness of breath scores might be considered as comparable if one took the premise that one point on an NRS is comparable to 10mm on a VAS score (Powers and Bennett, 1999). Hence the quoted means for scores in the Abernethy study (40.1 for morphine and 47.7 for placebo) are comparable to the average NRS breathlessness scores in this sample (mean 3.7 for oral morphine and 3.69 for placebo). Standard deviation for VAS in the Abernethy study was 24 for morphine and 26 for placebo; again this is comparable to the variability in this study (SD 2.4 for oramorph and 1.98 for placebo). The main differences appear to be that the mean difference between treatments for each participant was very low in this study compared to the Abernethy result. In addition the variability around the mean for the difference between active and placebo interventions is lower for the Abernethy study and does not cross zero, giving rise to a statistically significant result between morphine and placebo. This does not occur either for oramorph or oxynorm versus placebo in this study and hence the results are non-significant. Reducing the variability by increasing the sample size may lead to a statistically significant difference. Hence this RCT may be experiencing a Type II error effect (i.e. the sample size is too low to demonstrate a difference between interventions if such a difference exists), although such small mean differences are observed that a vastly greater number of participants would be required, if this is a true representation of the population, in order to achieve a significant positive result. It is encouraging to discover similar mean values for breathlessness severity between intractable breathlessness of two different aetiologies, however the magnitude of the placebo effect in this RCT resulted in no statistically significant difference between active treatments and placebo, whereas a smaller placebo induced effect on breathlessness severity was observed by Abernethy.

Performing this type of analysis in the manner of a published article in the British Medical Journal was not designed to detract from the analysis method set out in this protocol, but to allow discussion around analysis methodology in a similar study design. The Abernethy study (2003) has already been discussed in Chapter 3.

8.6 Global impression of change in breathlessness and preferred week

When participants were asked whether they considered their breathlessness had changed over the course of that particular treatment at the end of the treatment period (their "global impression" of change in breathlessness), the mean and median response to active interventions was greater than that for placebo. The median scores in particular were greater with a median change of two for oramorph and oxynorm compared to no median change for placebo. A difference of two points corresponds to a "little better" response to the change of breathlessness over the course of that intervention. This difference in median scores demonstrates both a skew in the data, particularly for placebo given the mean value of 1.14, and an appearance that the study had a number of individuals that rated placebo treatment as having a particularly good effect and a few individuals that rated active treatment as having a particularly detrimental effect on breathing. One can observe this in the boxplot of global change comparisons (Figure 4.4.4). Oramorph in particular has a long whisker in negative territory for global change indicating that a few individuals rated the response to oramorph as being poor for their breathlessness, lowering the mean value.

The response to placebo on the other hand, where there are a couple of outlying points that show a large placebo response, causes an increase in the mean value for these individuals. This is an important point in the analysis of a treatment for breathlessness that has a small potential improvement for patients with CHF. It is clear that some individuals considered that their breathing either got worse on active therapy or did not change enough for them to notice. It would be unusual for any treatment to have a dramatic effect on symptoms in all individuals. Does the lack of a significant mean difference in rating scores between oramorph and oxynorm and placebo mean that these interventions have no role in the management of breathlessness in CHF? Use of the median values in this instance may represent the true effect for the majority of the sample and demonstrates the possibility of an improvement in breathlessness in opioids measured by the global change scale.

Comparison of global impression of breathlessness change scores with interventions and the preferred week analysis yielded some interesting results. Figure 4.5.8 demonstrates that global impression of change scores appear to accurately reflect the patient experience on the preferred week analysis in that participants that chose an individual intervention independently rated that intervention as having the greatest improvement on

global change score. It also demonstrates that some participants favour one opioid for breathlessness, but the other opioid was little different to placebo. This suggests that the practice of switching opioids may be useful in patients who do not appear to respond to one opioid, but may respond to another with a slightly different receptor profile. It would therefore seem to be important to try another opioid if the first opioid prescribed does not have an effect on a patient's breathlessness.

Section 9) Discussion: Comparison of breathlessness rating

What is the best way to capture the patient experience in a short trial of pharmaceutical intervention for breathlessness? During the study it became apparent that the rating of current breathlessness was not as discerning as either worst or average breathlessness ratings. This is demonstrated in the results, where the mode or most frequent response in participants for the current rating of breathlessness was zero and median value was only two (contrast average and worst ratings). The variability around the results as indicated by the standard deviation was similar for current as the other two parameters. The bar charts (Figures 4.5.1 and 4.5.2) further emphasise the point that current breathlessness does not follow the same distribution as average or worst breathlessness. This problem is particularly true for ambulant patients, who consider that they only feel breathlessness during or directly after movement and do not describe breathlessness at rest. The ratings were taken when participants were sitting at rest, hence this cohort of participants who do not consider themselves breathlessness at rest would score zero on current rating. This therefore would not change if their breathing improved on treatment and hence current rating would not be a useful measure in this circumstance. It would appear that current measures should be considered for movement-related trials of breathlessness (such as use of treadmills or exercise bicycles) and not interventional trials at rest in my experience.

Average and worst ratings of breathlessness did appear to be measuring different qualities of breathlessness and although some participants would occasionally score average breathlessness higher than worst (which is counter-intuitive), most understood that different modalities were under enquiry. Virtually all participants considered their worst breathlessness was during or after movement with showering, climbing stairs and, for the more severely affected, tying shoelaces and bending down being the most frequently reported activities to induce breathlessness. Future studies could make a more detailed enquiry, using patient narrative, as to the induction of breathlessness on movement and consideration sought to improving the patient experience at home by adaptations or aids appropriate to CHF patients with breathlessness. Consideration could be made for occupational therapist interventions such as hand-held "pick-me-ups", Velcro shoes or stairlifts as examples.

Which of the two rating scales, numerical (NRS) or Borg scale for breathlessness should be considered for use in clinical trials of breathlessness in CHF? There appears to be

little consensus in the existing literature as to which is the best scale to use in what situation and whether both are measuring the same quality of the breathless experience. The most commonly used scales for breathlessness in advanced disease are NRS, VAS and modified Borg (Bausewein *et al.*, 2007). NRS scores have been shown to correlate highly with VAS scores (Gift and Narsavage, 1998, Powers and Bennett, 1999), but both NRS and Borg are considered to be as repeatable and as reproducible measures as VAS (Wilson and Jones, 1989, Wilcock *et al.*, 1999, Grant *et al.*, 1999). There is a gap in the knowledge here. Firstly, NRS and Borg scales have not been compared in breathlessness outcomes thus far. Secondly, comparison of breathlessness scales has not occurred in CHF, as the above examples have concerned cancer-related breathlessness or breathlessness in normal individuals. It is considered that NRS scales are easier to use than VAS and are preferred by patients (Powers and Bennett, 1999), so comparison of NRS and Borg scores in CHF is important if these are the easiest scales to use and have the ability to be used over the telephone (unlike the VAS score).

The NRS scale is designed as an eleven point discrete quantitative scale of gradually ascending severity. The Borg scale has been designed as a similar discrete scale with a verbal description of the severity of breathlessness next to the numerical rating and has a graduated incremental quality whereby a rating of 4 is twice as severe as a rating of 2, or a rating of 2 is twice as severe as a rating of 1 (Bausewein *et al.*, 2007). This is not the case for the numerical scale. This allows a comparison of scales. For example if a study quoted breathlessness severity on a Borg scale, what would that severity be on an NRS scale and vice-versa? It would be useful if one was familiar with one scale and not the other to be able to have a calculation of comparison of scales to allow one to understand the potential impact of the findings and whether those findings were representative of previous trials that have reported an outcome using the other rating strategy. To the best of my knowledge, no study has been published in CHF that addresses this important quality.

Correlations for Borg and NRS for each parameter of breathlessness rating (Average, Worst and Current) showed a high degree of statistical significance between scores. Cumulating the scores from these three parameters allows a greater sample number to be compared between Borg and NRS, which similarly shows a very high degree of statistical significance between Borg and NRS rating for this cumulative scoring. A linear relationship between NRS and Borg is observed up to and including a Borg score of 5 (severe) with a reasonable degree of separation between mean values. For a given

Borg score up to 5 (severe), none of the 95% confidence intervals for mean values of NRS overlap, indicating statistically significant associations. Hence one can observe that a Borg score of 2 (slight) for breathlessness approximately equates to a score of 3 on NRS, a score of 3 on Borg (moderate breathlessness) translates to 5 on NRS and a score of 5 on Borg (severe) equates to a score of 7 on NRS for breathlessness. As higher values are reached of Borg, the decreasing number of samples result in higher variability and less confidence of the true mean value.

Similarly, for a given value of NRS, mean Borg scores follow a similar near linear distribution with very little overlap of 95% confidence intervals for the mean values of Borg for a given NRS score. Hence, a score of 3 on NRS can be translated as a score of 2 (slight breathlessness) on Borg, 5 on NRS equates to 3 (moderate) on Borg and 7 on NRS translates to a score of 4 (somewhat severe) on Borg. What is interesting here is that a high score on NRS (9 out of a maximum of 10) only translates to a score of 5 on Borg (severe). The NRS scale is at its maximum at 10 and therefore cannot exceed this level. This suggests that NRS scoring should be used for studies with a lower expectation for the severity of breathlessness and that Borg scores should be used for studies with a higher degree of symptom severity. Conversely, NRS may be better for lower scores for breathlessness, as it can determine more subtle changes at lower levels than for Borg. The high degree of separation of points on both scales allows a reasonable comparison between rating scales, so that studies that involve one scoring system could be interpreted and compared with studies that involve the other method of scoring.

Linear model equations were generated for a given Borg or given NRS for breathlessness. These models are shown below and appear to produce a close approximation to the actual mean values described in the sample.

For a given Borg score converting to NRS: NRS score = 0.945 + (1.202 x (Borg score))
For a given NRS score converting to Borg: Borg score = 0.336 + (0.543 x (NRS score))

Of course, if there were a greater amount of data, the variability would be reduced around the true mean values and a better set of linear regression equations could be calculated (though calculations incorporate 1365 responses in total). Rather than producing an exact value for Borg or NRS therefore, they should be used to determine approximate values on each scale when compared to each other. This then allows comparison between quoted NRS or Borg results in the literature. not so exact to the mean values described

and although modelling equations are useful, tables of the mean values seen may be more accurate.

Do average NRS or Borg breathlessness scores measure change in breathlessness accurately? This is impossible to tell, but comparison of scores compared to the participant-rated preferred week gives one an interesting insight. Participants were asked to rate which week they preferred the most for their breathlessness at the end of the study and were invited to continue on open label therapy on that basis. Participants who stated they preferred the week corresponding to oramorph did not rate that week very highly over and above the other two interventions, unlike those that preferred the oxynorm or placebo week for their breathlessness. Although this outcome may have occurred simply by chance, it shows that the differences in outcome between the three interventions are small even in those who stated a preference for a particular intervention.

It also demonstrates two other points. Firstly, those participants who favoured oramorph for breathlessness did not rate oxynorm highly and vice versa, particularly on global impression of change (Figure 4.5.8). In clinical terms, this might allow the opioid switching of therapy as occurs in pain management. For some individuals, oramorph might be poorly effective for their pain, or cause side effects at specific doses. Switching to an alternative opioid such as oxynorm may allow better symptom control (Quigley, 2004). This is also true in reverse for oxynorm to oramorph and may be due to individual variation to opioid medications. What is clear from Figure 4.5.8 is that participants might not respond to one type of opioid, but may to another. Hence any trial of therapy in clinical practice may benefit from consideration of an opioid switch should initial treatment prove ineffective for that individual for breathlessness.

Secondly, global impression of change more accurately predicts a participants' preferred week of treatment than change in NRS average breathlessness scores (Figures 4.5.7 and 4.5.8). This might support the theory that NRS average breathlessness measures are not correctly recording the actual change in breathlessness process on treatment. In addition to the large placebo response in a few individuals and negative response in a few individuals to active treatment, this may have a role in the neutral outcome in breathlessness severity in the trial. If participants knew their previous NRS or Borg scores, would this outcome change? One might expect that knowledge of previous scores might result in a better association between preferred week for breathlessness and NRS or Borg rating. Certainly, the change in NRS scores contrasts to those seen with global

impression of change scores, which do associate with the patient rated preferred week. Using day 4 values only rather than change in NRS scores should perhaps be used to provide a more accurate representation of response, as these values in breathlessness do correspond to the week preferred for breathlessness by participants at the end of the study in a similar fashion to global impression of change in breathlessness. As Bland & Altman (2007) correctly describe, measurement errors involved in calculating differences from baseline have the potential to influence outcome. This may be the factor behind the anomaly of the oramorph change in breathlessness score with preferred week using this method compared to global change or day 4 NRS values alone (Figures 4.5.7 to 4.5.9)..

Section 10) Discussion: Secondary outcome measures

10.1 Secondary outcome measures: Additional components of shortness of breath

Additional components of shortness of breath, namely satisfaction with treatment, coping with breathlessness and distress caused by breathlessness were analysed as surrogates for breathlessness improvement in addition to direct questioning about breathlessness change. No significant differences were noted with change in these parameters between the three interventions. Improvements in distress rating and coping with breathlessness were most notable for oxynorm and placebo, whereas satisfaction with treatment was best for oramorph and placebo.

Participants found responses to these parameters with varying degrees of certainty. Frequently, participants would state that they were not "distressed" by their breathing, but nonetheless did find the condition problematic. Most participants stated that they coped "pretty well" with their breathlessness at baseline and therefore any change in this parameter was not particularly discriminatory. The satisfaction scoring question had interference from how the participant felt with the conduct of the trial, rather than satisfaction with the intervention. Participants also found satisfaction with existing therapy at the start of each intervention difficult to quantify, as many did not consider that they were on existing therapy to manage breathlessness. One could infer that their existing treatment for CHF managed breathlessness by preventing a worsening of the disease process, but participants did not make this inference themselves and did not find this question easy to answer at baseline. Hence the value of these questions in their current form, in language or statements that CHF patients may find difficult to comprehend in the manner intended, should be put under scrutiny as useful adjuncts to breathlessness scoring.

10.2 Secondary outcome measures: Quality of Life (QOL) change

The SF-12 measure (acute version) was utilised to assess quality of life in this sample of CHF patients. The individual scores given are recalculated into separate domains and this was performed using the SF-12 Users manual (Ware *et al.*, 2002). Further calculation allows the determination of physical and mental components of quality of life. The

authors of the SF-12 have based their calculations on the general US population and a mean value of 50 out of 100 represents the mean value for the average population. Hence, lower values than 50 are lower than the average for this US population sample, higher values representing a better than average score.

The mean values for this sample of 35 patients with CHF were 28.15 for the physical components and 47.34 for the mental components of quality of life. Both mean values are given out of a maximum score of 100. According to Ware *et al* (2002), the physical component value is lower than two standard deviations away from the standard population mean (50/100). This suggests that CHF patients in our sample are compromised in their quality of life predominantly due to physical restrictions, rather than adverse psychological effects of disease. The mental or psychological component mean scores are little different to the typical average for the US population upon which the scoring system is based.

The SF-12 manual also quotes mean physical and mental component quality of life scores for heart disease in general based on 678 patients. Physical mean component scores for heart disease are quoted as 39.16 out of 100, whereas mental component scores are quoted as 47.00 (Ware *et al.*, 2002). This suggests that our sample of CHF patients specifically rate their overall quality of life lower than the standard for heart disease, predominantly through physical rather than psychological limitations.

None of the three interventions caused a significant change in any of the domains of participant reported quality of life. However, this is unsurprising for the three week component of the study and change over time with treatment will be more revealing rather than very short term changes.

10.3 Secondary outcome measures: Observation data

It could be argued that part of the reluctance to use opioids in CHF patients derives from historical evidence of either adverse cardiovascular changes or respiratory depression. Both of these properties would be considered as potentially detrimental in this patient group. It was therefore important to note changes with treatment at doses considered clinically relevant for breathlessness management. Historically, data on the effects of opioids on a population have involved the use of large doses of drug administered

intravenously in normal participants free from disease. This data is then extrapolated to different patient groups as a justification for use of the drug or to prevent its use (see Chapter 2). The data presented here provides evidence that suggests that there is little effect of oral opioids in the short term on pulse, blood pressure, respiratory rate or oxygen saturations at these doses in CHF patients. The analysis incorporates both immediate effects within one hour and over the four day treatment period. Results for the three month follow-up on opioids are detailed in Chapter 5.

Treatment with oramorph derived the largest mean fall in blood pressure (5mmHg) at the end of the intervention period compared with oxynorm and placebo. This effect appears to manifest itself over time as one hour follow-up data does not support the magnitude of this fall as an initial response. Is a fall of this magnitude clinically significant? As detailed in the side effect profile, oramorph did have more episodes of associated dizziness on treatment and this may be manifested by a fall in blood pressure. One could argue therefore from this sample that oxynorm may be the better opioid to use in patients with low blood pressures as the fall in blood pressure is smaller than that for oramorph in this patient sample, even though the differences are small. Changes in all respiratory parameters (respiratory rate and oxygen saturations on air) are minimal for both opioids versus placebo and do not support the notion that opioids are detrimental on respiratory function in these oral doses.

These findings are supported by the study by Allen *et al.* (2005) in 11 patients with pulmonary fibrosis. A clinically equivalent dose of 2.5mg diamorphine given intravenously to elderly opioid naive patients did not cause significant reductions in heart rate, respiratory rate, systolic blood pressure or oxygen saturations at 30 minutes post dose compared to baseline, although the magnitude of the reductions seen in blood pressure and heart rate surpass those seen in this RCT. Similarly, Mazzocato *et al.* (1999) revealed no significant differences in cardiorespiratory observations with a higher dose of subcutaneous morphine (5mg) in seven opioid naive patients with cancer. From the data in the present study, opioids are safe to use clinically in CHF and do not appear to interact with concurrent anti-CHF medications at the doses described.

10.4 Secondary outcome measures: Side effect profile

Table 4.6.4 displays the adverse effect profile for each intervention. The differences in NRS between baseline (day 1) and day 4 for both nausea and drowsiness demonstrate a worsening of those symptoms for oramorph. This effect is not seen for either oxynorm or placebo. The differences are not statistically significant between treatments except for nausea, but if oxynorm and oramorph had similar effects on breathlessness, one might choose oxynorm as the drug of first choice if it produced less in the way of adverse events. Similarly the number of other patient volunteered adverse events possibly, probably or definitely associated with treatment were higher for oramorph than for oxynorm or placebo. Typically these involved the kinds of adverse events normally associated with opioid therapy, such as itch, vomiting, sweating, dry mouth and lightheadedness. It has been noted that oxynorm has a different side effect profile to oramorph, particularly for the incidence of opioid-induced itch (Kalso, 2005). Given that the frequency of these adverse events was notably higher for oramorph than oxynorm, for similar levels of breathlessness improvement a clinician may choose to prescribe oxynorm first line if for no other reason than toleration of therapy at these doses.

Constipation was difficult to measure in the study and day 4 comparisons have been given between treatments, rather than a change in bowel habit between days 1 and 4 of treatment. This approach has been taken in part to simplify the overall outcome to allow easy comparison between interventions. In addition, constipation is a symptom that may not be fully resolved as part of a short washout period between interventions. Although the active drugs themselves will have been cleared from the body, their effects on a symptom like constipation in a population whose bowel habits may be sluggish in the first place may carry-over into the next week of treatment and may therefore affect the overall results if days 1 and 4 of the next therapy are compared. The three month follow-up data may reveal a trend to constipation on those continuing active treatment and may be a better indicator as to whether constipation becomes a problematic symptom on active therapy (Chapter 5). The only serious adverse event documented in the study occurred during placebo and was not considered to be related to the trial interventions.

10.5 Secondary outcome measures: Physical function

The Karnosfky tool was utilised to assess change in performance status in the trial participants. As the results show in Section 6.5, there are little differences over the short course of intervention using this method of assessment. As with change in QOL, the main outcome measure envisaged for this assessment was change over 3 months of intervention to allow change to occur over time. So, as expected, little immediate change is observed on intervention. A slight trend towards benefit is seen with oramorph in particular compared to placebo, but this improvement is very small and not likely to be clinically significant. The assessment is also physician rated, and although blinded, remains a proxy assessment of physical function based on what the physician is told by the participant.

10.6 Compliance

Compliance, or concordance with medications, is difficult to measure. Two attempts were made to estimate the degree of non-compliance in the trial. Firstly, participants were asked daily whether they had missed any doses of trial medication. Reasons for any missed doses were not sought. Similar numbers of missed doses were noted for both active treatments with less for placebo. Some participants may have simply forgotten to take their medicine which allows for a certain degree of non-compliance, but the greater number of episodes on active treatment suggests that side effects were also partly responsible. Overall, compliance with intervention as measured by this method was high.

Participants may be unwilling or unable to volunteer whether they had missed doses of medication, which suggest that simply enquiring whether they had missed doses may lead to an exaggerated assessment of overall compliance. The residual volumes from each week were also measured when the trial bottles were collected. Accurate monitoring of residual volumes relies on factors such as collection of the residual amounts without tampering to the contents (such as washing the bottle out by accident) or by accidental spillage. Using the measurement of residual volumes did not show any differences between the active interventions or the placebo. One might expect that non-toleration of active therapy may lead to reduced compliance. However, this might be counterbalanced by the possible effectiveness of active treatment, whereby participants may be tempted to take more of a medication they find helpful for breathlessness during the washout phase.

In any case, compliance overall was high and the study results were not influenced by non-compliance by a few individuals.

10.7 Secondary outcome measures: Breathlessness descriptors

Breathlessness descriptors provide useful additional information regarding the language of dyspnoea, which is a complex symptom to quantify and describe. Most trials, including this one, have a primary focus on breathless severity, but there is growing recognition that the patient experience also involves the quality of the sensation and that common physiological mechanisms may operate in generating the patient experience of breathlessness in respiratory disease (Smith *et al.*, 2009). Descriptors can be grouped into clusters, which have been modified by different authors since their inception. The 15 item descriptions most commonly used in CHF by Mahler *et al.* (1996) and Simon *et al.* (1990) are the same, but their entry into different clusters are different (Garrard and Williams, 2008). Given this discrepancy, I have not used clustering in the primary analysis but simply quoted the individual descriptions expressed. Comparison of the data with some of these clusters will be performed later.

A total of four previous studies have detailed the nature of breathlessness descriptors in CHF, involving a total of 82 patients. Hence, this current RCT represents the largest study of breathlessness descriptions in stable CHF thus far (n=35). The most common descriptions from these trials are described in the Table 4.10.1 below. An X has to be provided in the columns for Simon *et al.* (1990) as no numerical detail is available from their paper.

Table 4.10.1: Frequency of breathlessness descriptor responses or the four trials that involve CHF patients

Descriptor	Simon 1990 (n=5)	Mahler 1996 (n=17)	Wilcock 2002 (n=30)	Caroci 2004 (n=30)	Most common described
Rapid	X			3	
Not out all way		5		4	
More work				10	
Constricted				3	
Shallow				9	
Effort	X	8		16	X
Hunger	X			10	
Smothered	X			11	
Heavy	X			7	
Out of breath	X	6	17	17	X
Not in all way		5		7	
Tight		5	10	9	X
Unable to get enough air	X		10	19	X
Breathing more				6	
Suffocating	X			11	

Simon and colleagues (1990) describe five patients with CHF in their study, though at the time of data collection two of those had acute symptoms and probably do not have the same experience as those with stable CHF. Their paper does not define actual values for the descriptors proposed by the patients and a list of 19 was originally used, revised down to 15 in the final outcome. However, the "best three" responses were selected out by the study authors. Eight descriptors were selected out by the study authors and it is difficult to draw conclusions from this, as only 15 responses in total would be expected from 5 participants.

Mahler *et al.* (1996) move forward from this initial study and involve a total of 17 participants with CHF asked to rate their best 3 of 15 descriptors. Most frequent responses involve the work and effort of breathing, corresponding well to the data in Section 6.7. They attempt to devise clusters of descriptions, whereby responses that are commonly volunteered together, or that appear to reflect a similar participant experience are grouped into defined clusters. This appears to work well for smothering and suffocating (the "suffocating" cluster), breathing requiring effort, more work, inability to get enough air and feeling out of breath (the "work/effort" cluster) and my chest is tight or constricted (the "tight" cluster). The "work/effort" cluster contains four of the top six responses in Section 6.7, hence it would appear that this cluster represents a good fit to the patient experience in CHF. Clustering becomes less significant for other responses in the analysis by Mahler, which makes their overall use difficult as it appears that some responses have a better association in a cluster than others. Hence certain clusters can be open to some debate as to which descriptors are incorporated and this occurs with all four of the studies quoted here.

The study by Wilcock *et al.* (2002) was designed to compare descriptors between different patient groups. Participants with CHF (n=30) described feeling out of breath (57% of respondents), chest tightness (33%) and inability to get enough air (33%) as being the three most frequently selected responses. Unfortunately, there is no other data quoted as to the frequencies of the other descriptors for CHF. Again, participants described all descriptors that applied to them, but these responses were reduced to a "best three" per participant for the purpose of analysis. The descriptor "I cannot get enough air" was common to patient groups of all aetiologies in their study. Similarly, inability to get enough air was prominent in this RCT, but "feeling out of breath" was the most prominent descriptor for our CHF patients. This concurs with Wilcock, whose most prominent descriptor in CHF was also feeling "out of breath".

The article by Caroci & Lareau (2004), designed as a comparison between patients with COPD and CHF, does not appear to have used descriptions in the same way as this current RCT or the other trials quoted, as the total number of descriptions should total 90 (3 given by each of the 30 CHF patients) instead of the total number described in their table (142 responses). I suspect that patients were asked to volunteer which of the 15 descriptors applied to them, without a necessity to select three descriptors only. Hence this study can be used as a reference point, but cannot be directly compared to studies

that have kept to the total of three rule as a greater number of references have been selected by a number of different individuals. Of course, we do not know whether some individuals selected fewer than 3 descriptions and whether some selected almost all of the descriptions. This approach may give a sense of the patient experience, but having three descriptors for each patient allows equal weighting of responses for each patient, rather than in their analysis whereby one patient who only scores one descriptor has a tenth of the weighting in the results to one that describes 10 descriptors. Inability to get enough air, feeling out of breath and breathing requiring effort are the most frequent responses, which concurs with the most popular choices in the RCT.

Although it is difficult to draw accurate conclusions from the four studies above the most frequently volunteered descriptions in CHF are; my breathing requires effort, my chest feels tight, inability to get enough air and feeling out of breath. This compares to the four most common descriptions in the RCT, all greater than 10% of all responses, and two of which that correspond to the literature overall, namely; effort, more work, out of breath and breathing is shallow. Inability to get enough air is relatively common in our sample (7.5% of responses), chest tightness is lower than 5% but the more commonly associated descriptions in the early literature with breathlessness in CHF, smothering and suffocating, only represented a total of less than 2% in our sample. Clustering responses appears to make a prominence of the breathing work and effort cluster in our sample of CHF patients.

Requesting breathless descriptors had a number of practical problems in the trial. One potential problem would be that of using exactly the same list in the same order of response, whereby participants may always choose descriptors at the top of the list as they read through if they feel they apply. This is not the same as which descriptors best reflect the participant experience. By ensuring that the sequence is delivered in a purely random order (using randomisation.com for the random sequences) this ensures that the order of descriptors has no bearing on the overall selection of descriptors.

If participants considered their breathing had improved markedly, they were unable or unwilling to give descriptions, and it is unclear as to how this should be managed in the analysis. Also, as described previously, participants at rest might not consider themselves breathless, so descriptions of current breathlessness caused some consternation with some participants. One way round this to provide greater clarity may be to ask for their three descriptions as they are today, rather than the prompt "right now". The analysis of

descriptions have involved all baseline descriptions or all changes in descriptors with treatment. It should be considered that in this analysis the same 35 participants have responded and given the apparent consistency of response care must be taken in the interpretation of the results, since the same patient may have responded in the same way on multiple occasions, leading potentially to a source of bias. However, allowing all responses to be analysed allows a greater number of responses to be compared, allowing the potential for greater clarity and inclusion of greater amounts of useful data.

What is interesting in this RCT is that there is a consistency in response to breathlessness descriptors over time and with different interventions, as evidenced by the bar charts for each intervention. Some descriptions changed with active therapy, notably inability to get enough air, chest tightness and shallowness of breathing for both active interventions and being out of breath and air hunger becoming less prominent for oxynorm and oramorph respectively. This is an interesting outcome as chest tightness, inability to get enough air and feeling out of breath are prominent descriptions for CHF in the literature and in addition shallowness of breathing is also prominent in our sample. This might suggest that, from use of descriptors alone, opioids may be influencing the underlying mechanisms behind shortness of breath in CHF.

Breathing requiring more work or effort however appeared not to be changed by opioid therapy at day 4. Lansing *et al.* (2009) suggest than descriptions of work and effort of breathing are more associated with peripheral respiratory factors such as muscle fatigue and respiratory nerve afferents rather than increased chemoreceptor drive, which, it is suggested, is more compatible with the sensation of air hunger. Although these descriptions are prominent in our sample, they are little changed by opioid therapy, which might suggest that opioids have the potential to alter perception of breathlessness at the peripheral respiratory level given their receptor locations as described in Chapter 2, but in practice do not affect this area of the cardiorespiratory pathway.

The differences here are small and overall one can see that there is a good degree of consistency of response for each of the interventions (Figure 4.6.2). Hence the impact of opioids at these doses on the sensation of breathlessness as measured by breathlessness descriptors would appear to be small. One has to be careful in interpreting in change of breathless descriptions as their presence or absence does not indicate improvement or worsening, simply that the participant related emphasis is different, rather than the complete absence of the previous description. Also, three descriptors are volunteered at

each assessment, but there is no emphasis on the rating of those descriptions. It would be interesting to ask participants to grade the importance of each description in order to observe whether the relative emphasis changes with intervention in future studies.

For the first time, baseline values of NRS average breathlessness scores were compared to the descriptors given at baseline in CHF patients. In general, mean breathlessness severity was the same for all descriptors, however the description of suffocating in particular was associated with more severe breathlessness. This description was not frequently reported in this sample, so the score may be a chance finding. Descriptions such as breathing more, chest tightness and chest constriction were associated with less severe mean average breathlessness. Sadly, these are not amongst the most frequent responses in CHF in this sample. It would have been interesting to monitor response with treatment had the most common descriptions of breathlessness in this CHF sample (namely breathing requiring more work and effort, feeling out of breath and my breathing is shallow) had also been associated with more severe breathlessness scores. However, analysis of breathlessness severity and descriptors of breathlessness nevertheless gives an interesting insight into the potential relationship of breathing severity with patient experience and further studies should seek to address this in other populations.

Section 11) Conclusion

This study is the largest RCT of opioid therapy for breathlessness in CHF, reaching the required number for statistical power, involving thirty five completed participants. Opioids appear to be safe to use in the doses quoted in CHF and are generally well tolerated as only two participants withdrew due to adverse effects from the thirty seven randomised. Breathlessness remains a problematic symptom in CHF, with respondents quoting a mean average breathlessness severity score of over five on an eleven point NRS in this representative sample.

No statistically significant differences were apparent for either opioid treatment versus placebo on NRS or modified Borg breathlessness severity scores. A large placebo effect was observed which may represent temporal changes or regression to the mean effects. A small improvement in breathlessness severity is apparent on global impression of change scores for opioid therapy over placebo, but again this improvement is not statistically significant. This indicates that there is little short-term benefit for opioid therapy for breathlessness over placebo. No specific characteristics of those participants who did respond to opioid therapy have been identified from assessment of disease severity, aetiological or demographic factors. However, responders to one opioid frequently did not respond to the other and vice versa. Hence, opioid switching may be useful in CHF patients who initially do not respond to one particular opioid. Oxycodone in particular was better tolerated than oramorph, with a lower incidence of reported adverse events and might be considered as the first line opioid to use.

For the first time, modified Borg scores and NRS scores have been compared for breathlessness severity in CHF. The modified Borg appears to be more useful to assess extreme values of breathlessness severity in very symptomatic disease, whereas NRS is more sensitive for smaller changes at lower values of breathlessness severity. Similarly, measurement of current breathlessness is less descriptive than average or worst breathlessness ratings due to its skewed distribution towards zero, which coincides with its modal value. Assessment of breathlessness descriptions were in keeping with other studies in CHF, with work and effort of breathing being prominent in responses in this sample. These descriptions did not dramatically change with opioid therapy.

Although not formally assessed, it became clear during the trial that many participants had to adapt their lifestyle in accordance with their limiting symptoms. This adaptation to circumstance had a number of effects on activity, role, mood and self esteem. Some of these concepts were taken forward into the qualitative trial, involving different patients with CHF, as will be discussed in Chapter 6. All participants who completed the RCT were asked their preferred week of treatment for breathlessness. If this corresponded to an opioid medication, and the participant wanted to continue therapy, they were invited for further review at three months on treatment. Those that did not want opioid treatment or did not select their best week for breathlessness as an opioid week were invited back at three months as a control group. This open label treatment period forms the basis of the analysis in Chapter 5.

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Chapter 5:

Randomised controlled trial: Three month open label follow-up

Section 1) Introduction

Initial changes in breathlessness and related quality of life are important to measure with the introduction of a new therapy. The three-week RCT, involving a crossover of three interventions for four days each, monitored the initial changes in these parameters and proved the initial safety of opioids at small doses in CHF. However, in a clinical situation, it is likely that a patient may be exposed to a longer treatment course, especially when provided on an outpatient basis. Away from the research environment, patients may receive therapy on a trial period for a number of days or weeks to ascertain the efficacy of the treatment. This allows the patient to have a greater perception of symptom changes and whether continuation of therapy would be of benefit in their individual circumstance.

Continuation of open-label therapy in this way following a research trial bears a more similar relationship to the clinical environment. Clinically, patients are given a treatment, then assessed whether they perceive that treatment has been effective for them. Therapeutic efficacy may occur even if the patient is experiencing a kind of placebo effect. Does this mean that treatments that have not been proved to be fully effective using RCTs be withdrawn from individuals even though they perceive a symptom or quality of life benefit? From the myriad of medications used in clinical practice, very few have been proven in their efficacy in well constructed RCTs, yet use of these medications persists on an individual basis for all manner of conditions.

This three month open label extension to the RCT allows a greater comparison with the potential use for opioids in the clinical environment. The aims were to assess the longer-term effects of opioids on breathlessness, quality of life, physical function and safety in CHF. In addition, a longer follow-up period allows any changes to occur with therapy that might not be observed over a four day treatment period, such as neurohormonal changes. The open label follow-up may provide preliminary data that could be used to inform clinical trials in the future. No such trial has yet been performed over this time period for opioids for breathlessness in CHF. No requirement was made of participants to continue treatment in the active group. This was to allow greater comparison with the clinical situation observed in the case of a therapy not having a perceived beneficial effect when used on a trial basis in the management of symptoms.

Section 2) Three month follow-up trial methods

Participants who completed the RCT were invited to proceed with therapy based on the description of their preferred week of treatment for breathlessness. This did not involve a review of the breathlessness scores made for each week or comparison of the global impression of change values. It simply relied on the participants' recollection of their best week of breathlessness control. Participants could continue on the therapy selected if they wished to do so as long as it coincided with an active treatment. Those not wishing to continue or those that selected placebo on the de-blinding of their preferred week did not receive active treatment but were placed into a control group. Un-blinding needed to occur to allow the administration of a hospital prescription for opioid treatment (subjected to the scrutiny of any prescription for controlled drugs). Hence participants were not randomised into active and control groups but instead were self-selected.

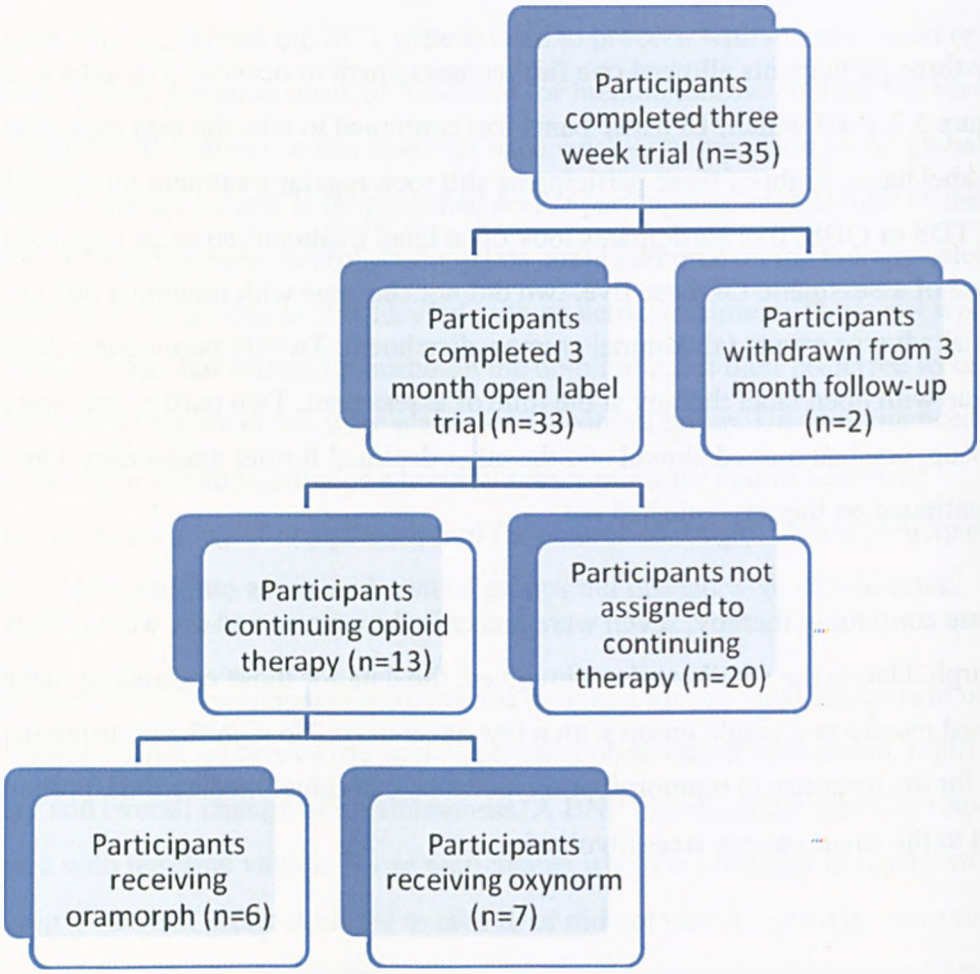
After three months all participants were invited to attend for one final assessment of breathlessness scores, quality of life scores, physical observation assessment, impression of therapy and overall change in breathlessness. A BNP blood sample was also requested to compare with baseline values. Those participants who were initially in receipt of open label therapy, but then either declined to take it, or did not take it regularly, were still classed as being in the treatment group. This allowed the principle of intention to treat to be observed. Those that did not receive open label treatment remained in the control group. The active and control group assessments were compared using t-tests for independent samples (compare the RCT analysis) where the data was normally distributed, or Mann-Whitney U tests for non-normal continuous data.

Section 3) Three month follow-up results: Descriptive data of those that continued therapy and those that did not

Thirty-three participants allowed one further assessment to occur at 3 months as shown in Figure 5.3.1. Of which, 13 participants had continued to take the trial medication on an open label basis. Eight of these participants still took regular treatment for breathlessness either TDS or QDS; five participants took open label treatment on an as required basis at the time of assessment. Of these five, two did not continue with treatment due to potential adverse events (abdominal cramps, diarrhoea). Twenty participants did not continue with open label therapy at the time of assessment. Two participants were lost to follow-up, one had moved abroad and the other declined further assessment. One of these had continued on therapy, one had not.

Of those continuing therapy, seven were prescribed oxynorm and six were prescribed oramorph. Due to the small numbers involved, the data for those continuing therapy was analysed mostly as a single group with a few exceptions. No significant differences were noted for the response to oramorph or oxynorm as individual medications, probably due in part to the small sample sizes involved.

Figure 5.3.1: Participants in the three month follow-up open label trial



The demographic properties of participants that continued with opioid therapy and those that did not are shown in Table 5.3.1. In particular, there was no difference with age or gender, but participants with a higher ejection fraction, higher BNP concentration and those with poorer renal function were more likely to continue. Mann Whitney U tests revealed a statistically significant difference with estimated renal function (eGFR) for continuers and non-continuers ($Z = -2.08$, $p = 0.04$), though a non-significant result was observed for ejection fraction and baseline BNP concentrations between these two participant groups ($Z = -1.68$, $p = 0.09$ for ejection fraction and $Z = -1.00$, $p = 0.32$ for BNP). Non-parametric tests did not reveal any difference between beta-blocker dose or

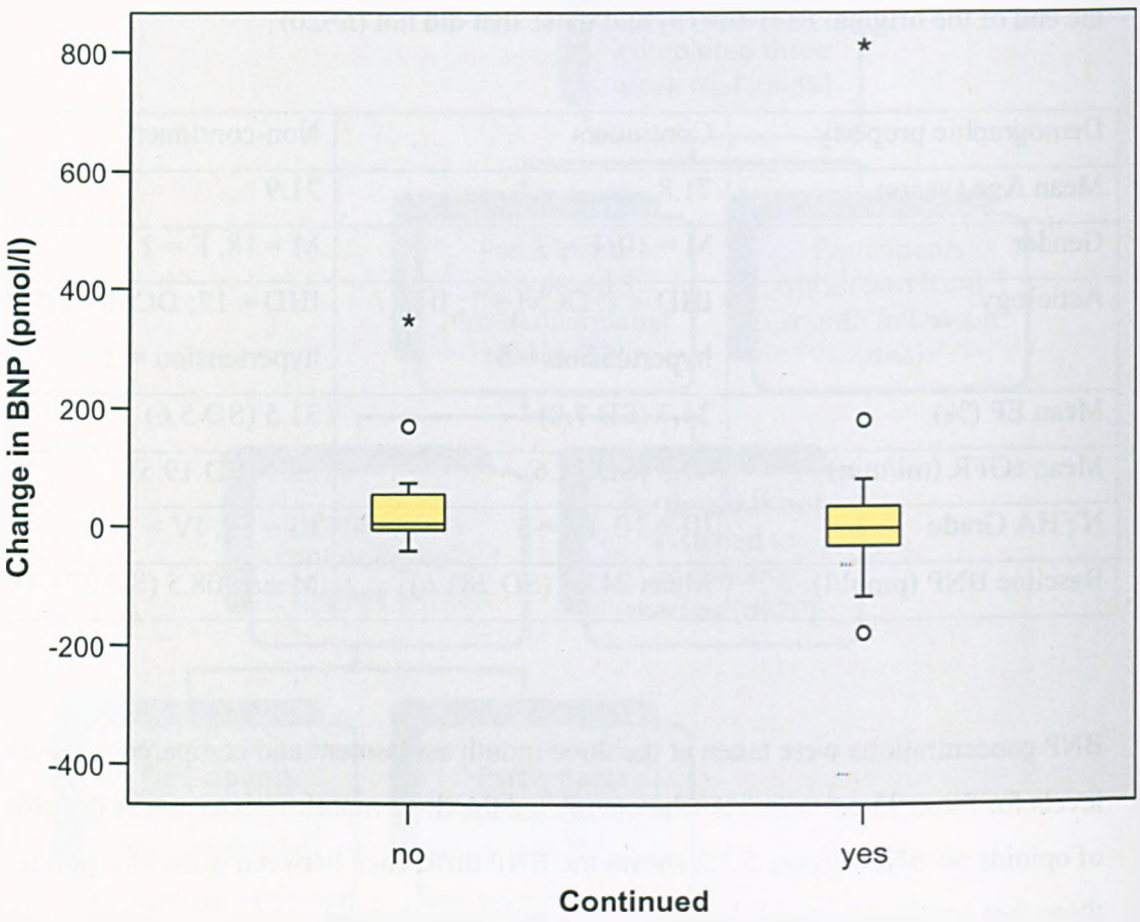
ACEI/ARB dose and whether participants continued or not (Mann-Whitney U test: Z = -0.55, p = 0.59 for beta blockers; Z = -0.39, p = 0.73 for ACEI/ARB).

Table 5.3.1: Demographic properties of participants that continued with opioid therapy at the end of the original RCT (n=13) and those that did not (n=20)

Demographic property	Continuers	Non-continuers
Mean Age (years)	71.8	71.9
Gender	M = 10, F = 3	M = 18, F = 2
Aetiology	IHD = 7; DCM = 1; IHD / hypertension = 5	IHD = 17; DCM = ; IHD / hypertension = 2
Mean EF (%)	34.7 (SD 7.0)	31.5 (SD 5.6)
Mean eGFR (ml/min)	47.3 (SD 17.6)	59.1 (SD 19.5)
NYHA Grade	III = 10, IV = 3	III = 19, IV = 1
Baseline BNP (pmol/l)	Mean 243.3 (SD 281.6)	Mean 208.5 (SD 273.7)

BNP concentrations were taken at the three month assessment and compared to baseline levels for those 33 participants who completed the three month visit to assess the effect of opioids on BNP. Figure 5.3.2 shows the BNP difference between these two points for those that continued opioid therapy (n=13) and those that did not (n=20). Positive values represent a worsening of BNP concentration. Mean values were 60.6 pmol/l (SD 242.0 pmol/l) and 36.2 pmol/l (SD 86.7pmol/l) for opioid continuers and non-continuers respectively. However, given the extreme outlier in the active treatment group, median values may be more representative. The median change for the opioid continuers was -2.2 pmol/l, whereas non-continuers had a median change in BNP of 4 pmol/l.

Figure 5.3.2: Boxplot to illustrate the change in BNP concentrations (pmol/l) between baseline and three month follow-up for those that continued opioid therapy (n=13) and those that did not (n=20)



Section 4) Three month results: Primary outcome measure: change of breathlessness severity

4.1 Change in NRS and Borg breathlessness measures

Comparisons were made for worst and average ratings of breathlessness between the first participant baseline visit and those taken at the end of the three month follow-up period. Mean values for change in breathlessness measures over this period are shown in Table 5.4.1 for those continuing on treatment and those not. Negative values indicate a worsening of the symptom over time. In addition independent samples t test results and Mann-Whitney U test results are also shown for comparison of continuers with non-continuers. Normality is not assumed and although NRS and Borg measures for average and worst tend to show a near-normal distribution, this might not be assumed given the small sample size and hence the less powerful non-parametric measures have also been given for completeness.

Table 5.4.1: Change in mean breathlessness severity scores from day 1 baseline of the RCT to the end of the three month open label extension for those that continued opioid treatment and those that did not

Change in score (day 1 baseline to 3 month follow-up)	Continuers (n=13)	Non-continuers (n=20)
NRS Average breathlessness: Mean difference (SD)	2.00 (3.37)	0.00 (2.13)
NRS Worst breathlessness: Mean difference (SD)	2.54 (3.04)	0.15 (2.54)
Borg Worst breathlessness: Mean difference (SD)	1.81 (3.26)	0.50 (1.81)
Borg Average breathlessness: Mean difference (SD)	1.31 (2.18)	-0.08 (1.31)

Greater variance as detailed by the standard deviation is noted for the group continuing treatment due in part to the smaller sample size in that group. Mean differences for Borg are lower than for NRS, which can be explained with the comparative work involving NRS and Borg shown earlier in Chapter 4 Section 5. Although there is a trend to

improvement in these breathlessness measures, for all continuers the outcomes are not statistically significant except for worst NRS breathlessness, shown in Table 5.4.2. This may be due to the comparatively small sample size. Non-parametric tests to assess difference between treatment outcomes at three months did not show any statistically significant differences between oramorph and oxynorm for NRS and Borg outcomes, though it should be noted that the numbers involved are small.

Table 5.4.2: Statistical tests for the comparison of the change in breathlessness severity scores from baseline to the end of three month follow-up for those that continued opioid therapy (n=13) and those that did not (n=20)

	t statistic	p value	Mann Whitney U p value
NRS Average breathlessness	-1.91	0.07	Z = -1.72 (p = 0.09)
NRS Worst breathlessness	-2.51	0.02	Z= -2.42 (p = 0.02)
Borg Worst breathlessness	-1.33	0.20	Z= -1.07 (p = 0.29)
Borg Average breathlessness	-1.84	0.08	Z= -1.30 (p = 0.19)

4.2 Change in breathlessness scores on active therapy

Does the effect on breathlessness severity become greater or does it reduce over time on active treatment? In order to investigate this, comparison has been made with day 4 scores and three month scores on those continuing active treatments. Seven participants continued with oxynorm and six with oramorph therapy.

Table 5.4.3 below describes the change in breathlessness over time for those continuing on treatment between the day 4 values for that particular drug at the end of the RCT phase and the three month follow-up results (n=13). Negative values represent a deterioration in breathlessness score over this period. Greater differences are observed with the NRS scores compared to Borg, in keeping with the previous comments.

Table 5.4.3: Comparison of breathlessness severity scores from the end of the treatment phase in the RCT for that drug (day 4) and the end of the three month open label follow-up phase for those receiving active treatment (n=13)

	NRS average breathlessness change	NRS worst breathlessness change	Borg worst breathlessness change	Borg average breathlessness change
Mean	-1.15	-1.08	-0.42	0.00
Median	-1.0	-1.0	0	0
SD	1.28	1.55	1.00	1.19

There are no differences between treatments (oramorph and oxynorm) over this period. The data is not shown as the numbers are small (n=7 for oxynorm and n=6 or oramorph) but there would appear to be little difference between the treatments in terms of breathlessness measure improvements between day 4 and three months of treatment.

Though there is a reduction in the effect of treatment over the three month treatment period, if one compares the non-continuers scores at three months with their placebo day 4 scores, the worsening of breathlessness scores over time is more marked with the non-continuers compared with those that continued with active treatment. This point is illustrated in Table 5.4.4. In particular, scores for worst breathlessness for non-continuers are much worse over the three month time period.

Table 5.4.4: Comparison of breathlessness severity scores from the end of the treatment phase in the RCT for placebo (day 4) and the end of the three month open label follow-up phase for those not continuing with active treatment (n=20)

	NRS average breathlessness change	NRS worst breathlessness change	Borg worst breathlessness change	Borg average breathlessness change
Mean	-1.60	-2.70	-1.33	-0.80
Median	-1.0	-2.0	-1	-0.5
SD	2.23	2.81	2.61	1.87

4.3 Global impression of change

Comparison for the global impression of change rating was made at three months from baseline for those continuing of treatment and those not, shown in Table 5.4.5.

Table 5.4.5: Mean and median global impression of change in breathing scores over 3 months for those continuing opioid therapy and those not continuing treatment

	Continuers (n=13)	Non-continuers (n=20)
Mean (SD)	2.62 (3.36)	-0.65 (1.76)
Median	3	0

Continuers rated an improvement in overall breathlessness equating to a "moderate" improvement in global rating, whereas those not continuing noted a slight worsening of mean rating. Global impression of change is near normally distributed using a Q-Q normality plot (data not shown), and independent samples two tailed t-test between those continuing and those not reveals a statistically significant association (t -3.2, p = 0.005). Similarly, non-parametric Mann Whitney U tests show a p value of 0.005 if normality is not assumed. Hence the null hypothesis that there is no difference between continuers and non-continuers is rejected for global impression of change measures and it appears that those continuing have a statistically significant improvement in breathlessness at three months.

A comparison for those that continued with oramorph and those that continued with oxynorm was analysed for global change in breathlessness to assess the relative effects of both drugs on the improvement observed versus non-continuers. The mean score for oramorph (n=6) was higher than the mean score for oxynorm (n=7): 3.67 compared to 1.71, but due to the sample size involved this difference was not statistically significant using non-parametric tests (Mann Whitney U: Z statistic: -1.16 p = 0.25).

Section 5) Three month follow-up results: Secondary outcome measures

5.1 Change in additional components of breathlessness

Distress, coping with breathlessness and satisfaction with treatment were compared between baseline (day 1 treatment 1) and three-month follow-up for both continuing and non-continuing groups. Negative values indicate a worsening of distress at three months and an improvement in coping and satisfaction scores at three months. Mann Whitney U tests were used as the data were not normally distributed.

Table 5.5.1 Mean change in additional components of breathlessness scores from baseline to the end of the three month follow-up for those on opioid treatment and those not continuing with treatment. Mann Whitney U test results are given to show the comparison between these two groups.

	Non-continuers (n=20) mean score (SD)	Continuers (n=13) mean score (SD)	Mann Whitney U Z statistic	Statistical significance
Distress	0.80 (3.75)	1.31 (3.07)	-0.30	0.77
Coping	0.30 (2.00)	-0.85 (3.18)	-0.82	0.41
Satisfaction	-0.45 (3.46)	-2.85 (3.63)	-2.06	0.04

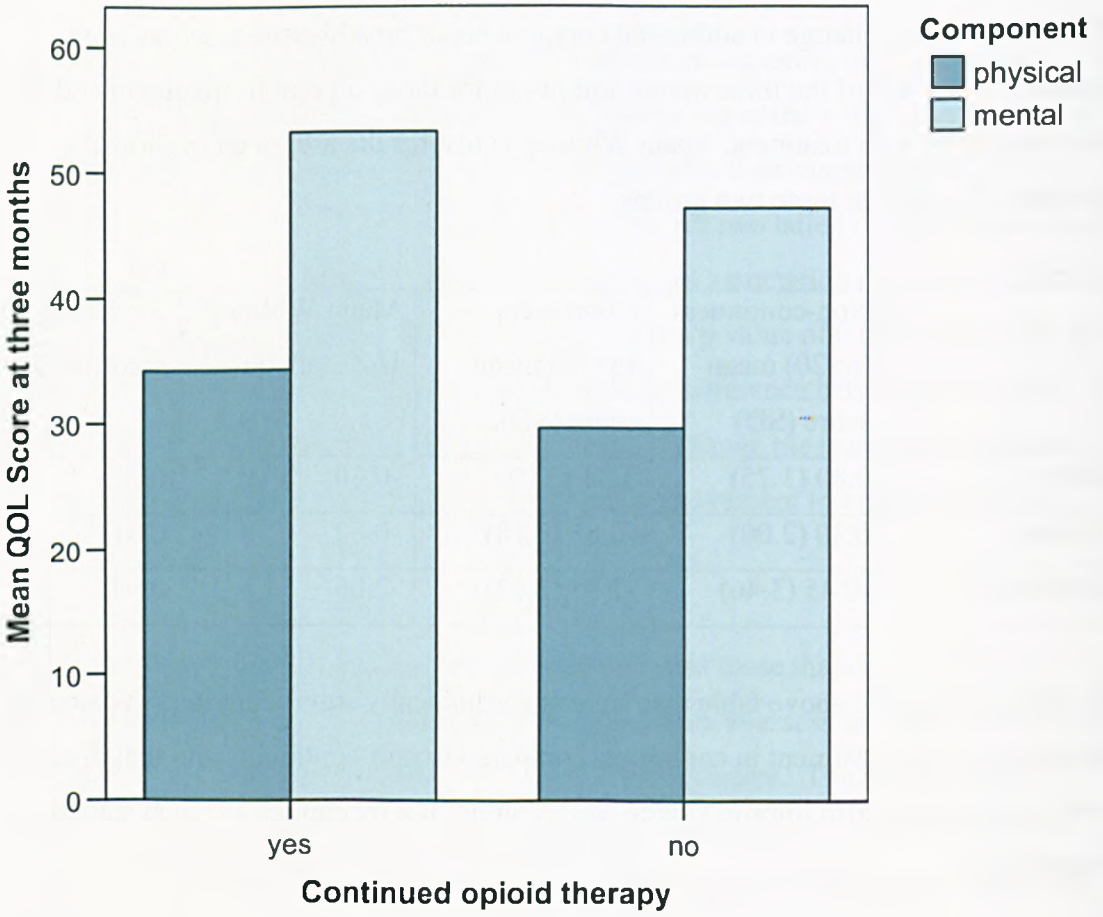
It can be seen in the above table that there is a statistically significant improvement in satisfaction with treatment in continuers compared to non-continuers and that distress and coping scores also improved with treatment but not by enough to reach statistical significance.

5.2 Change in quality of life parameters at three months

The physical and mental component scores for quality of life were calculated at three months for all 33 participants. The mean physical component score for all participants was 31.41 with the mean mental component score of 49.49 (both scores calculated out of 100). Scores were also compared for those that continued with opioid therapy (n=13) and those that did not (n=20). Treatment with opioids resulted in an improvement in both

mean physical and mental component quality of life scores. For physical components of QOL, opioid continuers scored a mean value of 34.13 for physical components of QOL, compared to a mean of 29.65 for non-continuers. Similarly, mental component scores for opioid continuers were also higher with a mean of 53.18 for continuers and 47.10 for non-continuers. However, no statistically significant differences were noted between those that continued with opioids and those that did not ($p = 0.097$ and $p = 0.105$ for physical and mental component scores respectively).

Figure 5.5.1: Comparison of physical and mental component scores for those that continued opioid therapy and those that did not continue.



To assess whether an improvement with physical components of QOL correlated with an improvement in worst breathlessness scores (often associated with movement), QOL scores were compared with NRS and Borg worst breathlessness severity. Spearmans correlation coefficients revealed no significant correlation between three month worst

breathlessness scores on either scale with QOL physical function (data not shown; p= 0.11 for physical components and p=0.15 for mental components).

5.3 Change in observation data from baseline to three months

Results were compared for the three month continuers and non-continuers with therapy with the initial baseline (day 1 week 1 treatment) scores. The change in score was calculated for each participant (n=33) with means and standard deviations for each clinical observation under study documented in Table 5.5.2 below. Negative values represent an decrease in value over time. The standard errors and standard deviations for pulse and blood pressure in particular are large, indicating the variability of this small sample. These changes in observations are near-normally distributed (data not shown), so independent t test results were calculated between those that continued on treatment and those that did not. There is little difference in observation data between those on treatment and those not on treatment at three months and any small differences are not statistically significant at the 5% level.

Table 5.5.2: Change in clinical observations from initial baseline to the end of the three month follow-up period for those continuing with opioid therapy and those not continuing. T test statistics for independent samples are given for comparison of these two groups for each cardio-respiratory parameter

	Non-continuers (n=20) mean change (SE	Continuers (n=13) mean change (SE)	t statistic	Statistical significance
Pulse	-0.30 (1.12)	-0.31 (1.49)	-0.004	0.97
Systolic BP (mmHg)	3.55 (3.29)	-2.46 (5.53)	-0.93	0.36
Diastolic BP (mmHg)	4.40 (3.08)	-4.23 (6.57)	-1.19	0.25
Respiratory Rate	-1.40 (0.73)	-0.62 (1.23)	0.55	0.59
O2 saturations (%)	0.80 (0.36)	-0.46 (0.56)	-1.89	0.07

Although the numbers involved are small, the data was analysed to compare baseline and three month values for those participants who continued on oxynorm with those on oramorph. The table below displays this change in observation data and again negative values represent an decrease in the value of that observation over time.

Table 5.5.3: Change in clinical observations from initial baseline to the end of the three month follow-up period for those continuing with opioid therapy with oramorph and oxynorm. T test statistics for independent samples are given for comparison of these two groups for each cardio-respiratory parameter where appropriate. Standard errors of the mean are given in brackets

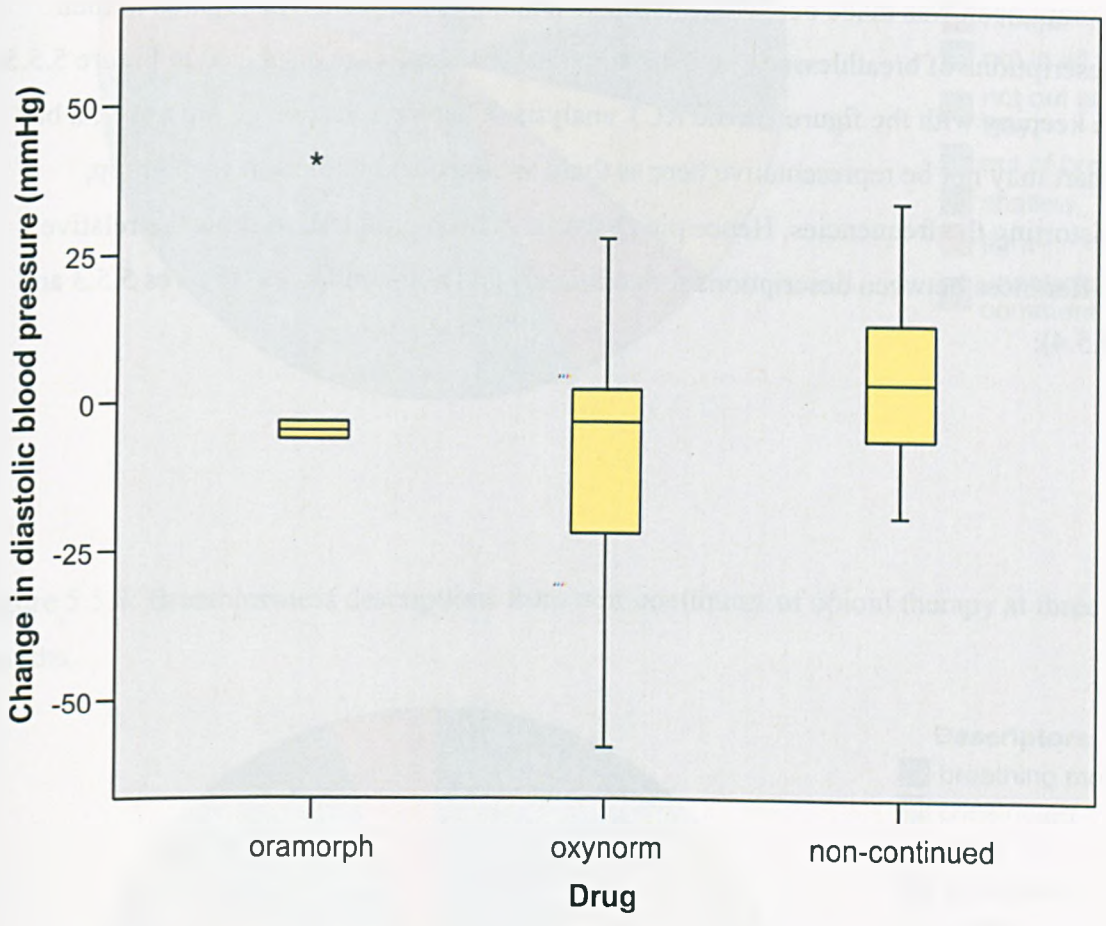
	Oramorph (n=6) mean change	Oxynorm (n=7) mean change	t statistic	Statistical significance
Pulse (beats per minute)	0.83 (1.45)	-1.29 (2.52)	-0.73	0.48
Systolic BP (mmHg)	-0.83 (7.42)	-3.86 (8.57)	-0.27	0.80
Diastolic BP (mmHg)	2.83 (7.25)	-10.29 (10.27)	-1.03	0.33*
Respiratory Rate (breaths per minute)	-2.00 (2.48)	0.57 (0.84)	0.98	0.36
O2 saturations (%)	-0.33 (0.78)	-0.57 (0.88)	-0.20	0.84

*Mann Whitney-U test more relevant to use, please see prose for explanation

Independent t tests were used for those values that were near normally distributed. For diastolic BP, the data was markedly positively skewed and therefore the non-parametric Mann Whitney U test should be used instead of t tests. From this analysis, the Z statistic is -7.14 with a significance value of p=0.48. On first appearance it would appear that the change for diastolic BP is markedly different for oxynorm than oramorph, with an apparent reduction of blood pressure of 12mmHg on oxynorm compared to oramorph. However, closer inspection of the data shows the skewness in the data, as evidenced by the boxplot below (Figure 5.5.2). This shows that the median difference is similar

between the two treatments and that the mean for oxynorm is distorted by lower outlying points, and the oramorph mean is higher due to a single high outlier.

Figure 5.5.2: Boxplot to show the medians and interquartile ranges for change in diastolic blood pressure at three months compared to baseline values for participants who did not continue on active therapy (n=20) and those that continued oramorph (n=6) or oxynorm (n=7).



5.4 Change in Karnofsky performance status at three months

Does a continuation of opioid therapy result in an improvement in performance status? Comparison was made between day 1 baseline and three month follow-up for continuers and non-continuers. Non continuers had a mean fall in Karnofsky status of 1.00 (SD 4.47) whereas continuers had a mean improvement of 2.31 (SD 5.59) over the three month follow-up period. The data was not normally distributed and non-parametric

testing revealed a trend towards improvement with active therapy but ultimately no statistically significant difference at the 5% level between continuers and non-continuers (Mann Whitney U test; Z= 1.77: p = 0.07)

5.5 Breathlessness descriptors at three months

Comparison was made between continuers and non-continuers with regards to their descriptions of breathlessness at three months. The results are displayed in Figure 5.5.5, in keeping with the figures in the RCT analysis (Chapter 4 Section 6). However, a bar chart may not be representative here as there are unequal numbers in each group, distorting the frequencies. Hence pie charts have been produced to show the relative differences between descriptions for continuers and non-continuers (Figures 5.5.3 and 5.5.4):

Figure 5.5.3: Breathlessness descriptions from participants who continued on opioid therapy at three months

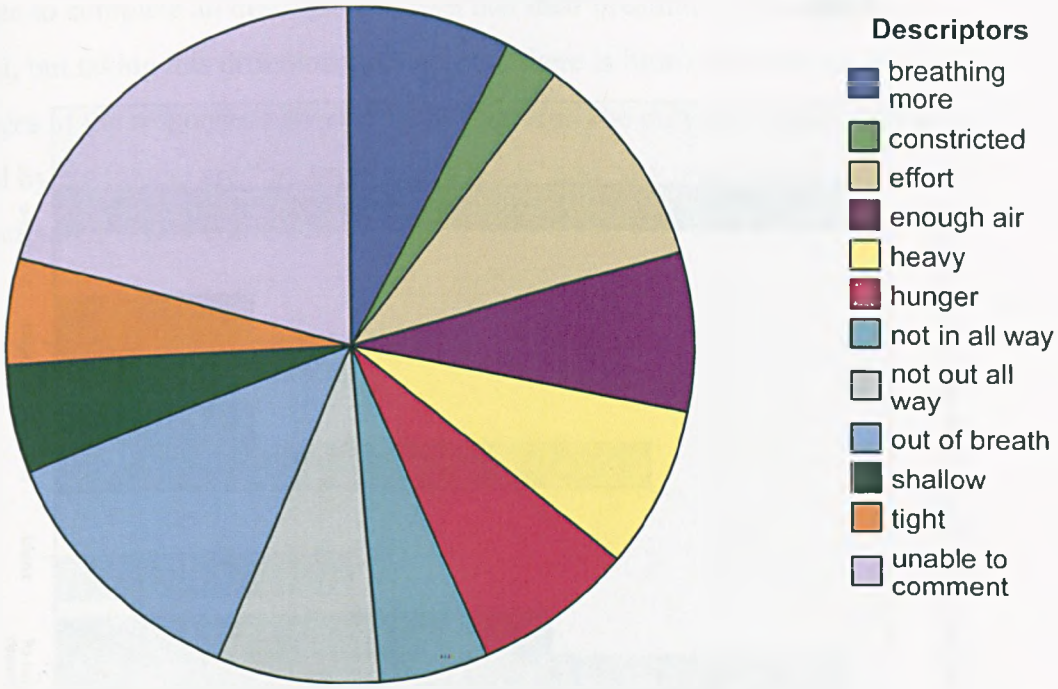


Figure 5.5.4: Breathlessness descriptions from non-continuers of opioid therapy at three months

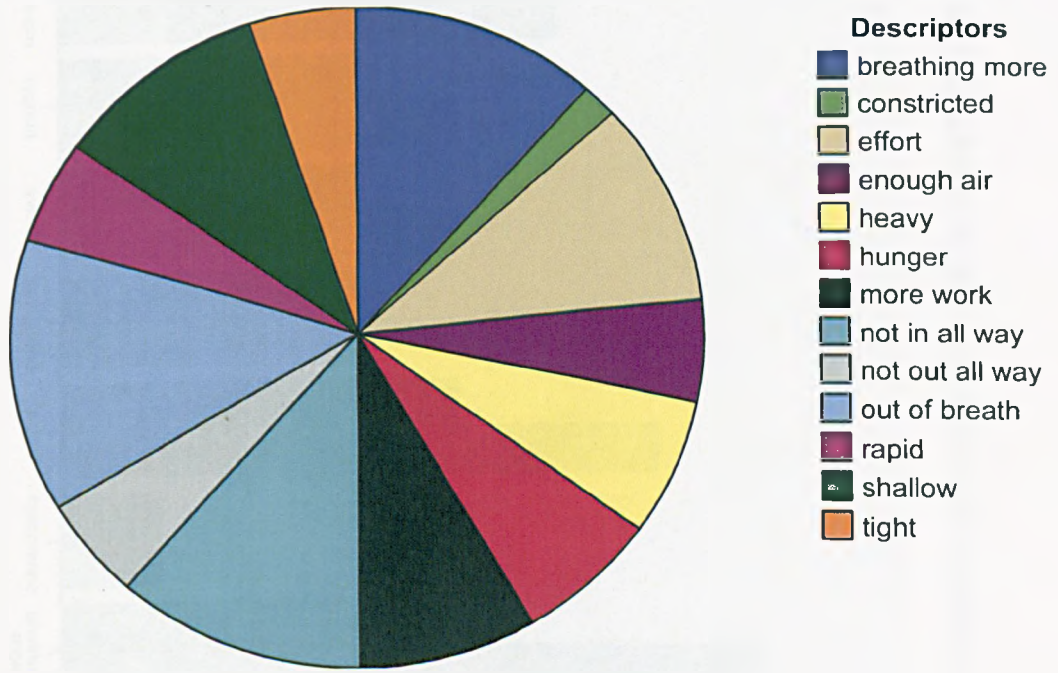
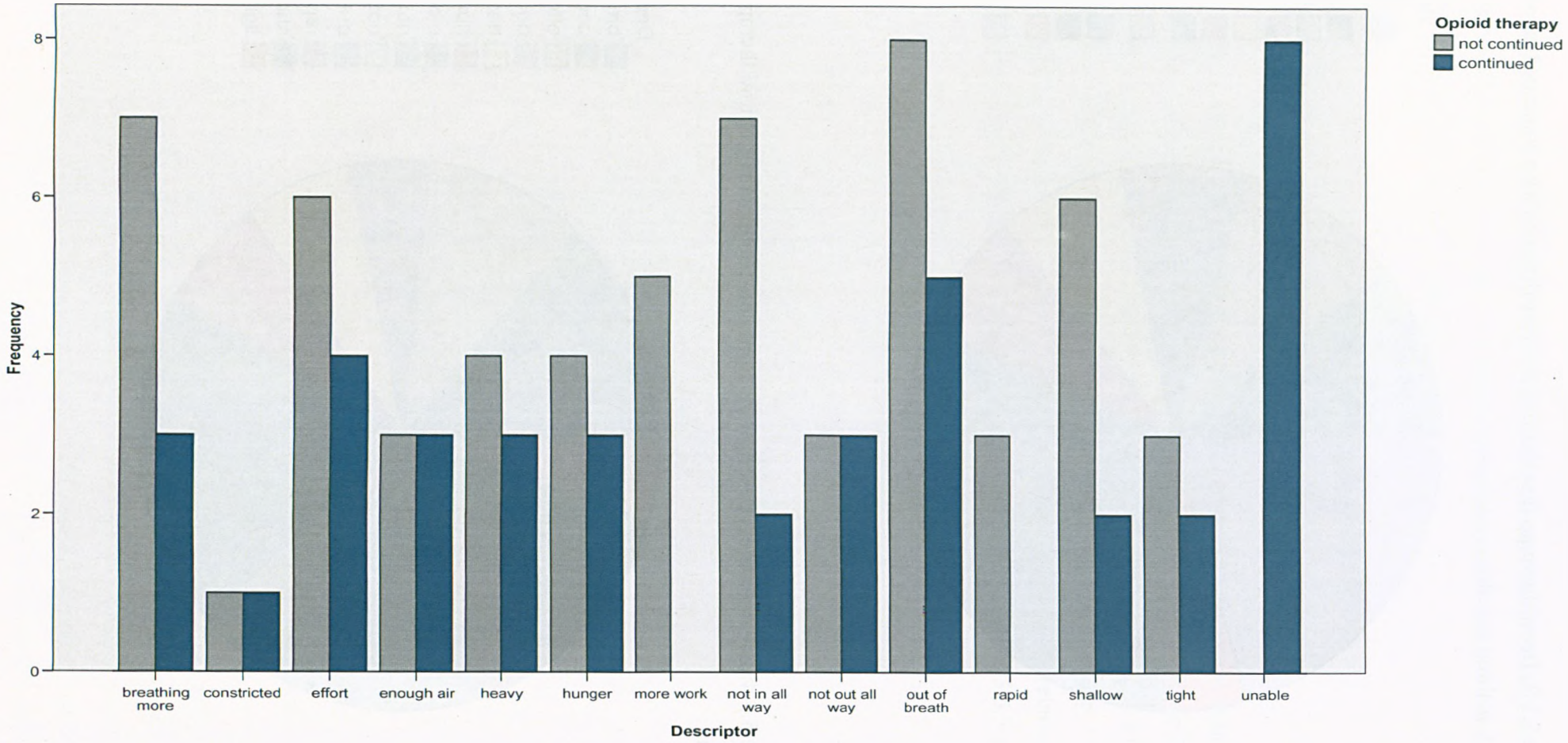


Figure 5.5.5: Descriptions of breathlessness at three months for those that continued opioid therapy and those that did not continue



As can be seen from both of these methods, there are minor differences between the types of descriptions noted by continuers and non-continuers. Some of those continuing felt unable to complete all descriptions given that their breathing had markedly improved, but taking this difference into account there is little difference in the percentages of the responses between the two groups. The only two responses that are not noted by continuers are "my breathing is rapid" and "my breathing requires more work" compared to non-continuers.

Section 6) Discussion: Demographic data and analytical points

The majority of randomised participants allowed open label follow-up assessment at three months. Two participants, one continuing treatment and one not continuing did not complete this three month assessment and therefore analysis proceeded with 33 participants only. Whilst this is not ideal, this represents a comparatively small level of withdrawal.

Not all participants continued therapy despite initially wanting to continue and not all of the remainder took the medication regularly. If one simply analysed the sample of those who continued on full treatment, not only would this potentially represent a biased sample but it would also reduce the number analysed. Although participants were not randomly assigned to intervention in this three month follow-up phase and were not blind to treatment (two of the major methodological drawbacks of the methodology of this three month extension), one can still analyse the results with other best practice principles in mind. By including all those who opted for continuation of treatment in one group, involving those that did not continue on regular medication, we are incorporating the principles of intention to treat analysis. Similarly, those not taking opioid medication ' as part of the trial may still be prescribed opioids by another health professional for another indication, yet they remain in the non-continuers group for intention to treat purposes.

It should be noted that self-selection of treatment continuation by participants, rather than randomisation to treatment as would occur in a properly constructed parallel group RCT, dilutes the relative importance of the three month results compared to the gold standard RCT methodology. In particular, the possibility of selection bias cannot be avoided. The three month follow-up results are nonetheless of interest, given that this has not been performed for opioids in CHF before, but a properly constructed parallel group RCT with a long follow-up period would be the preferential method of assessment of reaction to opioids on breathlessness over time.

Given the small numbers involved it was difficult to analyse the two opioids separately and compare their outcomes with each other given that there were only six and seven sets of results to compare for oramorph and oxynorm respectively. Where there was a statistically significant change with therapy compared to non-continuers, assessment of

the relative contributions of the two drugs towards that improvement were made. Otherwise, the two opioids were treated as one treatment entity. Independent t tests were used for analysis as unlike the RCT there was no paired data. Small numbers also prevented reasonable analysis of the participant characteristics of responders to treatment in those that continued active treatment over and above what had been documented earlier in the responders section of the RCT.

Table 5.3.1 reveals the demographic properties in those that continued treatment and those that did not. In the majority of factors, there were no differences between the two groups of participants (with respect to age, gender and aetiology for example). However, there was a significant difference in renal function as estimated by the GFR between those that continued opioid therapy and those that did not. Those continuing treatment had a lower mean GFR which suggests that their opioid treatment may have been cleared from the body less efficiently than those with higher GFRs. Opioids are removed by the renal system, which might indicate that some of those in the non-continuing group may have cleared their opioid treatment more readily than those that continued active treatment. This suggests that some of these participants might have received a comparative under-dosing of opioid treatment during the initial RCT, and they might have benefitted from a higher dose of opioid for breathlessness. Severity of CHF as measured by ejection fraction and BNP concentration was also different between groups, with participants with more severe CHF being more likely to respond and continue with opioid treatment, although this was a non-statistically significant finding.

In this three month open label extension, there appeared to be little difference in the median change in BNP between opioid continuers and non-continuers. Whilst there was a mean worsening of BNP concentrations for both groups, it can be seen in Figure 5.3.2 that the extreme negative outliers in both groups skew this data. Median values show very little difference, suggesting that BNP concentrations have been stable over this time period in this patient cohort. It is reassuring that opioid therapy has not caused a marked escalation in BNP values in the active therapy group on follow-up. However, a recent systematic review of the literature by Balion *et al.* (2008) indicated that NT-proBNP levels reduce in line with improving clinical outcomes in CHF, although they suggest that changing therapy simply by analysing the BNP results and adjusting treatment accordingly has not yet been shown to be beneficial. In an ideal situation BNP levels should improve with clinical outcomes on opioid therapy, whilst those not on active therapy at three months should demonstrate worsening BNP concentrations with disease

progression. Whilst this is the case with the median values, the values are so small that it is very unlikely that this is clinically significant.

The results demonstrate that assessment over three months noted an improvement in breathlessness with continuation of active therapy. Improvement with active therapy was not observed during the crossover RCT. This suggests that the initial period of treatment may not have been long enough to fully assess response to treatment. It also indicates that opioid therapy at the low doses involved in the study can be beneficial for some. In the crossover RCT, one of the potential reasons for no differences in breathlessness severity between active treatment and placebo was that the active treatment dose may have been too low. However, given the adverse effect profile and the improvement in breathlessness severity rating at three months, it is clear that the doses used could be adequate for some patients. Future studies in this area may wish to note these facts and have both a longer initial period of assessment in the RCT phase for perhaps 10 to 14 days rather than a maximum of 4 days and an escalation in dose in the absence of treatment or adverse effects for some of the participants. Withdrawals were low during this period and the doses well tolerated overall so a longer period in the RCT would be warranted.

Whilst participants were generally good at notifying any changes during the initial RCT, during the three month extension those on active treatment did not consistently discuss any changes in their medication. For example, some participants stopped the opioid medication and some reduced the dosage used without discussion. Although this was discussed a priori with the participant as acceptable, I considered that a three month follow-up was too long to maintain an awareness of the medication compliance in this period. Perhaps the addition of an initial one month telephone follow-up would be useful both for the participant to discuss any potential problems on treatment, compliance issues and for further assessment of change in breathlessness.

Three month comparison was made for those on treatment and those not on treatment on an open label unblinded basis. Participants could have selected their preferred week and remain blinded for the follow-up as they could have received placebo if this was selected. This kind of follow-up could have enhanced the robustness of the results from the three month follow-up period. However, some participants did not want to continue on treatment and might not have entered with the prospect of being in a three month study, rather than their perception of a three week study with extended optional follow-up. This

would also not be randomised as participants would choose their own treatment to continue. A properly constructed parallel group trial would probably be of more benefit to assess long term follow-up outcomes.

Section 7) Discussion: Primary outcome measure: Change in breathlessness severity at three months

7.1 Comparison with baseline NRS and Borg scores

Assessment was made for average and worst breathlessness scores for continuers and non-continuers between their day 1 treatment 1 baseline values and their three month follow-up scores to assess whether continued treatment with opioids resulted in an improvement in breathlessness compared to baseline. Participants could not make reference to their original baseline scores.

As expected from the previous comparisons of Borg and NRS scores, a greater magnitude of difference between continuers and non-continuers occurs for NRS compared to Borg scores. However, it can be seen for both NRS and Borg assessment of breathlessness for average and worst breathlessness that compared to the original baseline, those that continued therapy had an improvement in breathlessness rating at three months compared to those that did not continue. Non-continuers had little difference in Borg or NRS scores from baseline, whereas those that continued treatment had an improvement in all breathlessness parameters. A change in score of one on the NRS would be clinically significant (Booth et al 2006) and this change is observed for both average and worst scores. Scores for worst breathlessness in particular improved and this may relate to scores in those participants that continued active treatment on an as required basis only, as one might expect that opioid use only occurs in those participants at stages when their breathlessness is particularly troublesome. Change in NRS scores tended to show a near-normal distribution and tests of significance using parametric means reveal a statistically significant difference between active therapy and non-continuers for worst score at the 5% level and average score at the 10% level. Greater numbers for comparison might allow a greater confidence in these differences, but it is clear that there has been some response to opioids on breathlessness severity at three months.

7.2 Comparison with end of treatment scores

NRS and Borg scores for breathlessness severity have been shown above to improve from baseline for those continuing on active treatment. In the crossover RCT, all three interventions (oramorph, oxynorm and placebo) resulted in an improvement in breathlessness severity at day 4 (see Figures 4.4.2 and 4.4.3). Is this improvement in scores maintained for those that continued treatment? Comparison was made for the day 4 end of treatment scores and the subsequent three month NRS and Borg scores. Reference was made to oramorph and oxynorm continuers' day 4 scores on that therapy, whereas non continuers scores were compared with the day 4 placebo score. Although this comparison is not ideal, it was used to demonstrate whether there was a change in breathlessness over time on therapy.

Breathlessness severity measured on NRS and Borg ratings for active therapy showed a slight worsening over the three month period compared to the end of treatment score. The difference is small and lower than the comparative difference seen between day 4 on placebo and those not on opioid therapy at three months. This demonstrates that breathlessness has deteriorated over time for both groups, as one might expect with this patient cohort, but this deterioration on therapy is lower and some therapeutic effect appears to be maintained. This maintenance of effect is most marked for worst breathlessness scoring, perhaps again relating to those participants who took their opioid on an as required basis when moving. No differences were noted between individual opioid treatments and maintenance of effect, implying that oramorph is similar to oxynorm for relief of breathlessness.

7.3 Global impression of change at three months

Participants were asked to rate whether their breathlessness had changed at the three month assessment from their normal level prior to the start of the trial. Those that continued therapy noted a statistically significant improvement in breathlessness using this global impression of change measure for breathlessness. As one might expect, those not continuing on treatment noted a slight worsening of breathlessness over this period, with a mean difference of over three points between continuers and non-continuers using this 15 point scale. This outcome is encouraging for the use of opioids to manage breathlessness, however a degree of caution must be exhibited. Those in receipt of

therapy may note an improvement just because of the action of taking something additional for breathlessness, rather than actual clinical effects. This warrants further research but suggests that at three months participants consider that their breathing had improved from baseline with opioid therapy.

There was a trend towards a greater improvement in score for those that continued oramorph compared to those that continued oxynorm at three months. Although one could argue that the improvement with oramorph was twice as much as for that with oxynorm on the global change rating scale, the numbers of participants are small and definitive conclusions concerning this matter cannot be made. However, this possible difference may be explored further in future studies.

Section 8) Discussion: Secondary outcome measures at three months

8.1 Additional components of shortness of breath at three months

Not too surprisingly, participants who continued with active therapy had a greater improvement from initial baseline in satisfaction with their overall treatment for breathlessness at three months compared to those that did not. This was statistically significant at the 5% level, but one might expect this outcome as these participants were in receipt of what they considered was active therapy for breathlessness. De-blinding participants to allow open label therapy was necessary with the logistics of the trial at the time, but if active and control groups remained blinded one may have witnessed a different outcome. Change in coping with breathlessness and distress due to breathlessness over time were also better on therapy than in those not receiving opioids. This was not statistically significant, but demonstrated a trend for improvement in the active treatment group.

8.2 QOL change at three months

What would be the correct measure to use to assess quality of life in CHF? The SF-12 generic validated measure was compared to two of the more widely disease specific validated measures in CHF by Bennett *et al.* (2002) in 211 CHF patients. The Chronic Heart Failure Questionnaire (CHQ) was devised by Guyatt and colleagues (1989) following assessment of 88 patients with CHF who were asked what factors were most important to their quality of life. The most common responses were encompassed in the CHQ, allowing assessment of three domains: dyspnoea during daily activities, fatigue and emotional function. The (Minnesota) Living with Heart Failure Questionnaire (LHFQ) is a similar validated measure specifically for CHF. Comparisons between components of all three scores demonstrated a high degree of correlation between all three scales. Both disease specific scales, but not the SF-12 revealed either floor or ceiling effects of the scores provided. This can be problematic in analysing changes in health related quality of life. However, the SF-12 was not as useful as the disease specific questionnaires in determining NYHA class. This is not too surprising as NYHA class is derived from abilities that the patient is unable to achieve due to breathlessness, fatigue or other CHF symptoms, which are not directly enquired about by the SF-12 unlike the

two disease specific questionnaires. The SF-12 does not have categories for disease specific qualities of CHF, namely dyspnoea and fatigue, but this was not problematic for the RCT and three month follow-up as dyspnoea in particular was adequately covered by other measures (NRS, Borg and additional components of breathlessness). In addition, the SF-12 can be used to compare other aetiologies other than CHF, important for the small but expanding area of breathlessness research.

In this current study, the SF-12 was easy to use, with only a couple of questions posing problems with participant responses. In particular, participants were unlikely to be completing activities such as playing golf. Analysis of the SF-12 at first glance was complicated, with the need to reverse some responses, divide into eight different groups, convert to compare to a standardised normal population and finally calculate physical and mental component scores from all eight different groups given different weightings to divide into the two component groups. However, this process does allow direct comparison between different aetiologies.

Comparison of quality of life scores at three months showed a non-statistically significant improvement in both physical and mental components of QOL for those still receiving opioid therapy compared to those that did not. For those not continuing, mean scores were almost identical to baseline scores (28.15 and 47.24 at baseline to 29.65 and 47.1 at three months for physical and mental components). Whilst one might expect a slight reduction in mean QOL scores over time with disease, it is reassuring that these scores are consistent between these two time points. For those continuing opioid treatment there was a particular improvement in the physical rating components of QOL, which although non-significant warrants further investigation as to the improvement of QOL with opioid therapy. This improvement demonstrates that opioid treatment may be having more than just a psychological or emotional effect.

8.3 Observation data at three months

Opioids appear to be safe over the three month period in respect to cardio-respiratory parameters. Although there is a small reduction in blood pressure in continuers compared to those not continuing in relation to their original baseline values, these are unlikely to be clinically significant and are not statistically significant (due in part to the wide variability in the sample as evidenced by the large standard errors). In particular,

respiratory rate and oxygen saturations are not reduced significantly over time on opioids in CHF patients at these doses (less than half a percent reduction in oxygen saturation and less than one breath per minute in respiratory rate compared with baseline on treatment at three months). This demonstrates that at this level of opioid (equivalent to 5mg oramorph QDS) there are no adverse effects on respiratory function in particular with short to medium-term opioid treatment in CHF.

No statistically significant differences are seen between opioid treatments and overall mean values on treatment are comparable. This is slightly different to the initial day 4 values for all patients in the RCT, where oramorph appeared to cause a greater reduction in blood pressure than oxynorm. Simple comparison of the three month follow-up results for those continuing on therapy would suggest the converse effect. However, Figure 5.6.1 illustrating the change in diastolic blood pressure over time demonstrates the problems of using means for small skewed samples, in the fact that the oramorph mean value is affected by the single low outlier and the oxynorm mean value is affected by the (positive) skewness of the sample. Hence caution must be exhibited throughout the analysis of very small samples. As can be seen in the graph, both median values for active treatment, less influenced by outlying points, are similar, which would suggest little difference between opioid treatments on cardiorespiratory parameters at three months.

8.4 Change in physical function at three months

Change in Karnofsky status from initial baseline at three months was little different between opioid continuers and non-continuers. The three point difference between the two groups described is unlikely to be clinically significant and it should be remembered that Karnofsky status was determined by the observer, which may introduce bias as the observer at the time was unblinded. This measure of physical function is unlikely to detect the small physical changes that may occur with opioid therapy in CHF patients.

8.5 Breathlessness descriptors at three months

Descriptors of breathlessness were compared between groups at three months. Overall, the only main differences were that some participants who continued on treatment felt unable to complete the descriptions as they felt their breathing had improved too much to be able to describe problems with breathing. Descriptors such as breath not going in all the way, shallow breathing and the sensation of breathing more were comparatively less frequent in the group receiving opioid treatment and breathing being rapid and requiring more work were completely absent in this treatment group. Although one might not be able to predict from descriptors alone which participants may respond to treatment from these results it is interesting to note the relative changes in breathlessness.

However, only breathing requiring more work is part of the most common descriptions detailed in the CHF literature (see Chapter 5 Section 6 for the previous analysis of breathlessness descriptors in RCT). Other descriptors in the "work/effort" cluster (effort, feeling out of breath and inability to get enough air) are comparable at three months of treatment compared to baseline values for those continuing opioid therapy. Those descriptions that appeared to change with opioid therapy in the RCT, namely inability to get enough air and chest tightness, are comparable with baseline values at the three month follow-up. A slight improvement in opioid continuers of shallowness of breath at three months was observed, in keeping with the day 4 improvement with therapy.

Whether breathing changes with opioid therapy, enough to influence the patient experience and description of breathing, is impossible to tell from this small sample. An improvement in one of the key descriptors of breathlessness in CHF, namely breathing requiring more work, is encouraging. Unfortunately, other common descriptions in CHF are relatively unchanged with opioid therapy. However, descriptions of breathing that one might expect to observe with opioid therapy, namely reduction in frequency of breathlessness and taking deeper breaths with opioid therapy (Keats, 1985), do appear to be prominent in the treatment sample (such as absence of rapid breathing and reduction in frequency of shallow breathing and breath not going in all the way). This suggests that descriptions of breathlessness may be a useful tool in the response to therapy and perhaps in the understanding of how breathing modifications occur with opioids.

Section 9) Three month follow-up trial conclusion

This three month open label extension is the first reported study of opioids for breathlessness in CHF lasting greater than four days of opioid therapy. It also follows a pattern of treatment that is more aligned with that observed in clinical practice, whereby patients know they are receiving a drug that might have a symptom benefit, as opposed to the placebo controlled trial methodology. However, the trial extension potentially suffers from selection bias, meaning that results should be interpreted with some caution. The stability of the research population has been demonstrated with little change in performance status, BNP concentrations and QOL measures particularly in the participants not-continuing active therapy.

In contrast to the crossover RCT described in Chapter 4, the open label extension revealed a significant improvement in the rating of worst breathlessness on NRS between opioid treatment and no treatment. A mean change of two points from baseline for average breathlessness and over two for worst breathlessness was observed for continuers of opioid therapy compared to those that did not continue. Whilst breathlessness severity appeared to increase slightly from the equivalent treatment values at day 4 of the RCT for those that continued opioids, for those that did not continue there was a notable increase in breathlessness severity at three months compared to their day 4 placebo values. This suggests that any early improvement in breathlessness severity on treatment is maintained at the same dose over time, given that some treatment continuers did not take the full QDS therapy as they did in the trial.

Similarly, global impression of change scores were much improved for those continuing opioid therapy than those that did not. A change equating to a "moderate" improvement occurred on opioids, whereas non-continuers revealed a slight worsening in global change score. This difference between these two groups was statistically significant, rejecting the null hypothesis that there is no difference between opioid continuers and non-continuers on global impression of breathlessness change at three months. Unfortunately the sample of those that continued with opioid therapy was small and therefore differences between the opioids themselves with these outcomes was difficult to elucidate with any degree of reliability.

There was a slight improvement in performance status in those that continued opioid treatment compared to those that did not, however this difference was very small and

unlikely to be clinically significant. Quality of life scores at three months were also greater in the opioid continuing group, particularly in respect of physical components of QOL. In addition, although breathlessness descriptors were not found to predict the response to opioid treatment, as described in the RCT, those on opioid therapy over three months did note an absence in "rapid" breathing and "breathing requiring more work" descriptions compared to their baseline responses. The latter descriptor is one of the key descriptions noted in other studies of breathlessness in CHF and suggests a change in the participants' experience of breathlessness. It also may indicate that the mechanisms that are involved in the formation of breathlessness in CHF may be being subtly altered by opioid therapy over time.

In conjunction with the results on cardio-respiratory parameters in the RCT, opioids do not appear to cause significant respiratory depression or cardiovascular problems over a longer treatment course at these doses in CHF. BNP values taken to ensure that there was not a significant deterioration in cardiovascular function, revealed no differences between the opioid continuers and non-continuers. It would appear therefore that opioids are safe to use on an individual patient basis for the attempted relief of breathlessness in CHF.

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Chapter 6:

Qualitative Study:

Opiophobia: Attitudes to morphine in CHF patients

Section 1) Background: The importance of heart failure patient attitudes to opioids

Qualitative research seeks to find the meaning behind beliefs and attitudes seen in day-to-day life. It does not try to determine absolute values but to find meaning and application (Rogers *et al.*, 2002). This chapter will detail the qualitative study that was performed as part of this thesis. Firstly, the background of opioids in healthcare will be discussed alongside the expanding role of palliative and supportive care in Chronic Heart Failure (CHF) and the reasons why CHF patients may have greater exposure to these medications in the future. The aims of the research will be followed by the application of and reasons for the methodology employed in the research study prior to the interpretation and the implications of the data analysis. Considerations for future work in this area and key points from this study will form the conclusion to the piece. As documented previously in the thesis, the terms opioid, morphine and morphine-like medicines will be used interchangeably. Different terminologies will be used dependent on the situation, typically with "morphine" used when relating to patient experience and "morphine-like" medicines when patient-centred descriptions are being used.

1.1 Opioids in healthcare

Opioids or "morphine-like" medicines, traditionally considered as analgesics, conjure a variety of different thoughts in the minds of both medical and lay people. Many articles in the medical press and lay media suggest both positive and more frequently negative connotations regarding the use of opioids both in healthcare and recreationally. Historical medical associations of morphine with relaxation, sedation, respiratory depression and use at the end of life has left a legacy of consideration that opioids are harmful or even dangerous, particularly in a healthcare setting. Of course, a history of illicit use of morphine-like medicines may also form part of the consciousness of the populous. These associations may lead to patients eligible to receive opioid medications, and healthcare professionals, reluctant to consider opioids for medical conditions, where they may prove to be helpful. In particular, an association of morphine exists with the end of life, especially in patients with cancer (Blake *et al.*, 2007).

The Barriers Questionnaire (Ward *et al.*, 1993) was devised to demonstrate the reasons why patients were reluctant to report pain or use medicines such as opioids that are

utilised in more severe pain states. Themes that emerged from this and other studies in cancer patients included: addiction and tolerance to analgesics; saving a drug until the pain becomes much worse; medication side effects; fatalism (pain is to be expected); "good" patients don't complain; increased pain may indicate disease progression; discussing pain may detract from trying to cure the disease; strong painkillers require injections. Addiction and fear that opioids may mask important changes in a disease were the most common anxieties expressed in a 20 patient sample of palliative care patients with cancer (Lambert *et al.*, 2007). This questionnaire based study also highlighted that knowledge of opioids is generally quite poor and that most patients derive their knowledge about these medicines from their own experience rather than from patient information leaflets (Lambert *et al.*, 2007). Many articles have described why some healthcare professionals have a reluctance specifically for opioid prescribing (Elliott and Elliott, 1992, Zenz and Willweber, 1993, Zenz *et al.*, 1995, Wells *et al.*, 2001, Bennett and Carr, 2002) despite evidence that controlled use of these medicines is safe and effective (Hanks *et al.*, 2004).

Evidence exists to suggest that opioids are useful in the management of breathlessness and cough (Jennings *et al.*, 2001, Morice *et al.*, 2007). This expands the use of opioids in palliative medicine from the treatment of pain, typically in cancer patients, to the management of breathlessness and cough in both cancer and non-cancer patients, such as those with cardiac and respiratory disease. Currently there is no evidence as to the acceptability of "morphine" therapy to patients with CHF.

1.2 Palliative care and symptom control in heart failure

Palliative care should not be restricted to just oncology patients, but that a number of different life threatening chronic conditions (such as heart failure, chronic obstructive airways disease etc.) can be managed using palliative care principles as the condition advances. However, the patient experience for different diseases is not universally the same between different conditions.

CHF is a syndrome that impacts on many different systems in the body and requires a pharmaceutical approach to management to attempt primarily to modify further disease progression. This results in patients receiving multiple medicines as part of their standard therapy. In addition, these patients are often elderly and frequently have multiple other

co-morbidities, often resulting in further polypharmacy. It has been highlighted that knowledge about these medications is generally poor (Boyd *et al.*, 2004). To improve the approach to management of these patients, Heart Failure Nurse Specialist (HFNS) services have been devised to help co-ordinate services.

The presence of heart failure leads to a clinical spectrum of symptoms with progressive severity. In fact, this disease course has likened advanced heart failure to the malignant cancer disease process (Stewart *et al.*, 2001). Indeed, there has been growing recognition that the symptoms experienced in advancing disease should be better palliated (Department of Health, 2000, Hauptman and Havranek, 2005, Lewis and Stephens, 2005). A study of carers of CHF patients indicate that pain, dyspnoea and low mood impact on the quality of life of over half of patients with end stage disease (McCarthy *et al.*, 1996). In addition, quality of life is adversely affected by loss of activity and function due to CHF (Thornhill *et al.*, 2008, Europe and Tyni-Lenne, 2004, Martensson *et al.*, 1997). These factors have resulted in greater collaboration between cardiology, primary care and palliative medicine in some areas of the UK (Davidson *et al.*, 2004, Johnson and Houghton, 2006). However, symptom based research or assessment of quality of life and patient experience in CHF through qualitative methods has been lacking in the literature thus far.

1.3 Qualitative research in heart failure

Quantitative research involving multi-centre RCTs of drug therapy are prevalent in the CHF literature. Conversely, articles exploring meaning and the patient experience of heart failure are much less prevalent. Studies either involve small numbers of heart failure patients alone, or perform a comparison of the patient experience of different disease states involving common symptoms. For example, Murray *et al.* (2002) compared the experiences of 20 advanced lung cancer and 20 advanced heart failure patients through qualitative interviews. They demonstrated that heart failure patients tended to focus on the stresses of balancing and monitoring a complex drug regimen; had poor knowledge of diagnosis and prognosis; and experienced frustration, progressive losses and social isolation. This was in contrast to the lung cancer patients who were more pre-occupied with facing death and had greater access to social and financial resources. Rogers *et al.* (2002) confirm some of these themes using qualitative interviews in heart failure patients. They also found that patients generally had little knowledge

about the medications they were taking, and how use of the medications related to the symptoms they described. Willems *et al.* (2004) expanded on this work using semi-structured interviews in 31 advanced heart failure patients. They demonstrated that patients with advanced heart failure tended only to consider the prospect of dying during episodes of acute decompensation. It would therefore appear that heart failure patients may experience a loss of function due to health and might struggle more with coping with multiple medicines and acute changes in their condition than patients with other diseases. One might consider that other patient groups are more prepared for these changes due to the nature of their disease possibly due to an effort for greater communication from healthcare professionals. It has been noted that prognostication in heart failure is difficult (Lehman, 2006) and the disease trajectory for a condition such as cancer may be easier to communicate or understand. Indeed, Rogers *et al.* (2000) noted that there were barriers to effective communication between clinicians and heart failure patients. This finding is particularly important in the context of discussion of a medicine such as morphine between clinician and patient, particularly if that medicine is believed to have negative connotations attached to it. What has not been discussed in the literature is what preconceived ideas about morphine exist in heart failure and whether its use would be prevented by these connotations or through avoidance of a discussion by a clinician who might perceive it to be a difficult area to approach.

1.4 The importance for research regarding opioids in heart failure

It is likely in the next few years that opioids will be used more widely to manage pain, breathlessness and cough in advanced heart failure populations with increasing exposure to palliative care methods. As detailed previously, in the Department of Health guidelines for the management of heart failure, low dose opioids are suggested for the management of intractable breathlessness (Department of Health, 2000). To date, there is no evidence to describe how acceptable this will be to this patient population and what beliefs, attitudes and existing knowledge these patients have. Would heart failure patients find the use of opioid medication acceptable? What do patients already understand about their use? What fears or anxieties do CHF patients already have and how would information regarding opioid use be best targeted? The existing literature has not addressed these issues in CHF. The aims of the qualitative research performed are to explore the beliefs about and acceptability of opioid medication held by patients with heart failure. In particular:

- How acceptable is the use of opioids in the management of symptoms (especially breathlessness) to heart failure patients already in receipt of complex polypharmacy?
- What are the specific anxieties regarding potential opioid use in this patient group?
- What beliefs concerning the use of opioids already exist in heart failure patients? Does past experience of morphine alter attitudes?
- What hopes would heart failure patients have for opioid therapy?
- How has information about medicines (including opioids) been obtained by this patient group? Who would be best placed to provide information about opioids to patients?
- How are the daily lives of heart failure patients affected by their disease and can symptoms related to this be identified as having the potential for palliation with opioids?

1.5 Key points

- Attitudes to opioids in both medical and lay circles centre around a number of pre-conceived ideas, based on patient experiences that are often unfounded given the current clinical use of opioid medicines – leading to "opiophobia".
- Some physicians have a reluctance in the prescription of opioids despite evidence to suggest appropriate use for symptom control can be beneficial.
- Overall, knowledge about opioids in cancer patients currently or previously using these medicines is generally quite poor.
- When compared to cancer patients, heart failure patients have a poorer knowledge of their diagnosis and prognosis and their focus is directed towards monitoring a complex drug regimen.
- CHF patients may have a greater exposure to opioids for symptom control in future years.
- No studies have yet highlighted the acceptability of opioids in CHF or identified reasons that may preclude their use.

Section 2) Methodology for the qualitative study

2.1 Patient sample

A theoretical purposive sample of symptomatic chronic heart failure patients was used for this qualitative study. All potential participants were known to the Academic Department of Cardiology and classified in New York Heart Association (NYHA) Grades II, III or IV. This sample of symptomatic patients was chosen as they represent the most likely group to have prescription of opioids in the future and may have considered the potential use of medicines for symptoms. A theoretical sample allows the identification of a selection of cases that is able to produce as many categories as possible for that topic (Hammersley and Atkinson, 1995). This is performed by both reducing the differences between cases so that common basic properties of a category can be identified, and by subsequently increasing the differences between cases so that the properties of that category can be further developed (Hammersley and Atkinson, 1995). In this study, identification of symptomatic heart failure patients allows categories to be generated from the specific population of interest (purposive sampling).

Participants involved in the ongoing randomised controlled clinical trial involving opioids for breathlessness (Chapter 4) were not approached. These patients will have read the participant information sheet for this trial and may therefore have a different experience to those patients who have not be approached or enrolled into the RCT.

Heart failure patients were approached by invitation letter following identification and screening by use of the Academic Department of Cardiology computer database of heart failure patients. It may have been that these patients were also known through the Heart Failure Nurse Specialist (HFNS) Service and eligible patients could be approached with an invitation letter via these nurse specialists. Included in this correspondence was a copy of the participant information sheet and consent form for the patient to review.

The timing, people and context of the data collection is important in qualitative research (Hammersley and Atkinson, 1995). In this study, the timing of the interview coincided with the daytime attendance of the heart failure patient to the clinic, not performed out-of-hours or in the acute situation, where responses may be different. In addition, this would allow the minimum inconvenience to the participant. As an alternative, the interviews could occur on hospital wards or in the participants' home, whichever was

most convenient to the participant as long as a quiet area was found free from interruption. The setting of the interview was important, as changes in setting could affect the responses given. The context in which the data is collected is therefore important (Charmaz, 2004), for example the presence of a carer at the interview may affect what the interviewee thinks or feels within that social context. In addition, the physical location should be reported as data collected may be influenced by changes in the "ethnoarchitecture" (Atkinson and Delamont, 2004). The sample of patients studied involved people of different backgrounds and different severity of symptoms in order to maximise the data for each category formulated.

The logistics of contacting the potential participant, inviting them to discuss the study further and taking informed consent, then allowing the participant to return to complete the interview at least 24 hours after giving consent may have resulted in more inconvenience than was necessary for the participant given that this was a single interview study. At the ethics committee meeting I argued that to prevent this occurring, if the participants so wished they could give consent at the same time as performing the semi-structured interview. In this way, inconvenience to the participants was minimised if this suited them and the ethics committee agreed with this policy. It is recognised that this is a potentially frail population who may experience undue burden if repeated visits are necessary. However, in general, written informed consent was taken at least 24 hours after participant invitation.

No formal sample size was calculated for this qualitative study, in keeping with the qualitative methodological approach. Data collection was continued until theoretical saturation of both the coding and collection of data was achieved. It was originally considered that twenty participants involved in single semi-structured interviews was an adequate number considering the nature and scope of the of the topic, experience of the interviewers and quality of the data obtained (Morse, 2000). The topic guide for the interview had been reviewed by volunteers from the Scarborough-Whitby-Ryedale Heart Failure Patient Support Group. Review of the content is important to achieve by a peer group of the patient sample of interest. If the wording is too complicated, the participant may not understand what is being asked, or it may prevent a full answer being given if the participant feels pressure to answer in a manner they perceive as being appropriate. Topic questions that this patient group might feel uncomfortable in answering (such as a very personal question) should also be highlighted prior to the interview stage. This might allow the interviewer may ask this in a more sensitive fashion, or may structure the

question asked differently, or alternatively review whether this type of question is required at all to meet the objectives of the study.

2.2 Inclusion, exclusion and withdrawal criteria

Inclusion criteria

Patients who:

1) Were known to the Hull and East Yorkshire Academic Cardiology Heart Failure Service.
2) Had a diagnosis of NYHA grade II, III or IV heart failure of any aetiology.
3) Were aged 18 years and over.
4) Were able to complete written informed consent and semi-structured interview.

Exclusion criteria

Patients who:

1) Were unable to complete informed consent or semi-structured interview without assistance. Some patients may have found a long and intensive interview too demanding if they were acutely unwell or if they were particularly frail.
2) Had known true allergies to opioids (morphine-like medicines). It would not be correct to involve patients who were unable to take opioid medications due to known allergies and their experience of opioid medicine use is likely to be different due to their experience of adverse events not encountered by those not allergic.
3) Had been approached or are participating in the concurrent randomised controlled trial (RCT) involving opioids in heart failure. This would be selecting a different sample of patients that have read the patient information sheet about opioids which may influence their understanding of morphine use.
4) Had previously stated not be approached for consideration for research trials.

Withdrawal criteria

Participants were withdrawn from the study on either withdrawal of participant consent or withdrawal of the participant by the treating physician or medical researcher due to the patient no longer meeting the eligibility criteria. This was unlikely to happen if consent and interview occurred at the same visit.

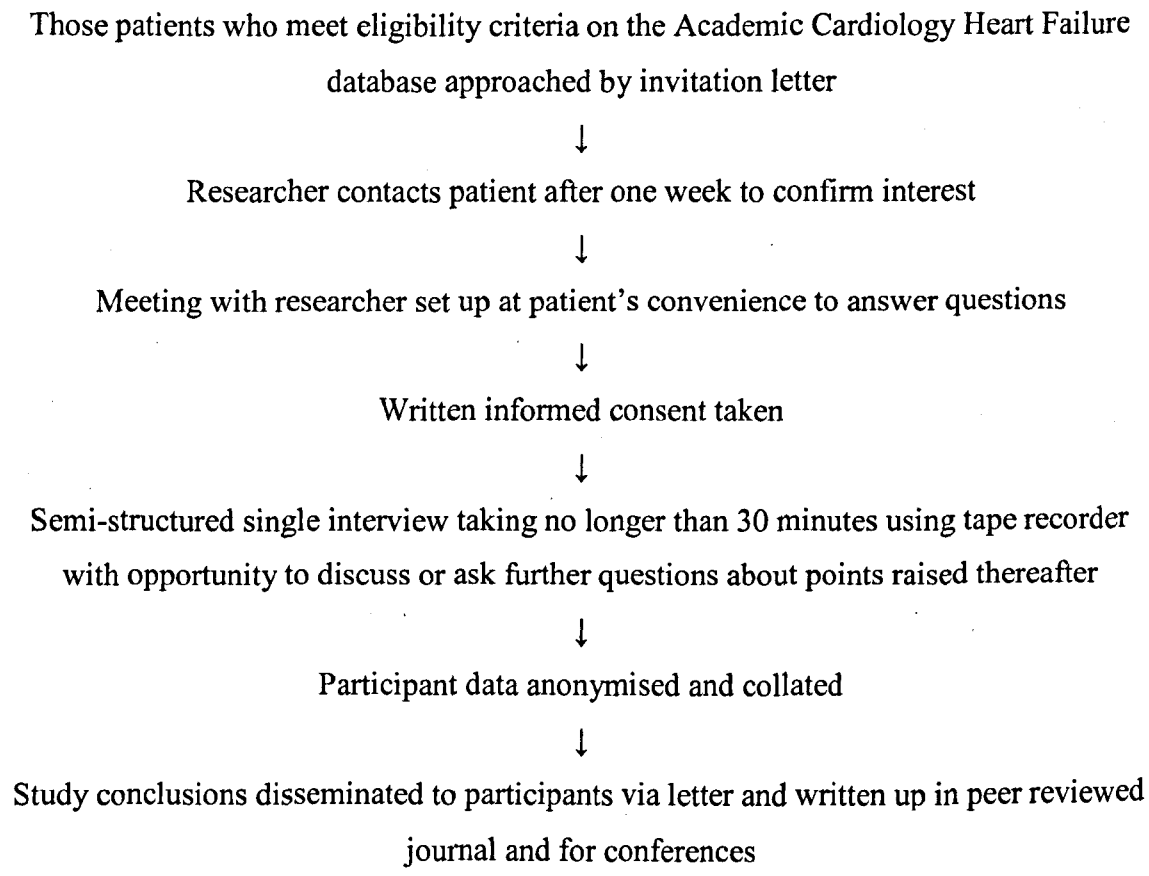
2.3 Sources of data and interview process

Once the participant had enrolled into the study, background data was collected. This included age, gender, NYHA status and date of diagnosis, taken from the Academic Cardiology Heart Failure database. The hospital notes for each participant were also obtained. Participants were each assigned a unique identification number for the trial, so that confidentiality could be maintained.

A topic guide was employed as a framework for the semi-structured interview to investigate themes that may be important to heart failure patients. Table 5.2.1 summarises the key points from the topic guide, which can also be found in Appendix 6. The interview itself was conducted in a quiet area and involved the participant and interviewer only, however a friend or family member was allowed to observe the interview if the participant so wished. It was made clear that the views of the participant alone are of interest to this current study. Provision was made after the interview to discuss any issues raised and at this point carers, friends or family could become involved in any subsequent discussions.

Interviews were tape-recorded and professionally transcribed verbatim. The transcriber did not have access to participant details except for the unique identification number assigned to that participant. Contemporaneous notes of any particular items of importance, conduct of the interview and physical characteristics not likely to be identified by voice alone were made immediately following the interview process by the interviewer. Both the taped interview transcript and notes taken regarding the conduct of the interview were drawn together to identify and gain consensus regarding the key themes that emerge. All interviewee responses and notes were anonymised and confidential. A summary of the study outline for the participant is detailed in Figure 6.3.1.

Figure 6.2.1: Study outline summary for the qualitative study



2.4 Data management plan

Data obtained from the interview process was analysed according to the principles of modified Grounded theory. One definition of Grounded theory is "theory that was derived from data, systematically gathered and analysed through the research process. In this method, data collection, analysis and eventual theory stand in close relationship to one another" (Strauss and Corbin, 1998). It is an inductive process, whereby categories are gradually obtained from the emerging data (Pope *et al.*, 2000). These methods allow the simultaneous collection and analysis of data, so that subsequent data collection is informed by the previous analysis (Charmaz, 2004). This is turn allows a dynamic ongoing refinement of the analysis, and so on. In this process, each item of data is identified and compared with other components of the data as a whole, allowing the emergence of analytical categories. This process is also known as a constant comparison approach (Pope *et al.*, 2000). It allows the researcher to take an interactive stance in the research process, allowing the researcher to remain close to the studied world (Charmaz,

2004). This is one approach that allows a systematic disciplined approach to data handling and management.

The data collected was broken down into component parts and given identifiable names (coding). Open coding of data was utilised to yield concepts and categories. Coding allows a close study of the data and gives a framework on which to derive concepts and categories for the data (Charmaz, 2004). Coding occurred alongside data collection in a dynamic manner to allow changes in emphasis in the topic guide as necessary. Data collected previously could then be re-analysed with knowledge of the codes to see if it allows further interpretation of previous data (Charmaz, 2004). Formal theory was generated from exploration of these concepts and categories which allowed the formation of subsequent hypotheses.

It is important that the data collection was thorough to provide accuracy to properly inform the subsequent analysis. In accordance with the process of modified Grounded theory, themes that emerge from the interview data were sought and subsequent participant interviews were refined to take any new concepts or themes into account. This "triangulation" of the data allows the review of inferences drawn from one interview alongside data from other interviews in different patients (Hammersley and Atkinson, 1995). Conclusions drawn from multiple sources of data leads to a greater confidence in the strength of that conclusion in the population under study (Hammersley and Atkinson, 1995). In addition to this, triangulation between researchers allows both a consensus to be made concerning the conclusions themselves through analysis of the codes and subsequent concepts and also confidence in the main outcomes of the study. This does not mean that the inferences made are correct, only that confidence in the conclusions is greater than analysis by a single researcher alone (Hammersley and Atkinson, 1995). It can also allow greater understanding of the data which can be categorised from different viewpoints dependent on the emphasis or previous experience of the reviewer. Triangulation between researchers did not happen as a part of this thesis to allow easier separation of the work done by student and supervisors. This will occur however for subsequent research publications in peer-reviewed journals as allowing this to happen in general is good practice.

Table 6.2.1: Key points from the topic guide (please see Appendix 6 for full topic guide)

Area of interest	**Example interview questions / probes**
Medicine use	Can you tell me about the medicines you take for your heart? Where do you go to get information about your medicines? How could your knowledge be improved?
General condition	How much does your heart failure trouble you? What do your symptoms prevent you from doing? If morphine could make you less breathless, would this benefit you?
Anxieties concerning opioids	What does the word "morphine" make you think of? Would you have any concerns about taking morphine? Would you worry about side effects?
Beliefs about opioids	What is your previous experience of morphine-like medicines? What was the setting as was it a good or bad experience? In what situations should morphine-like medicines be used for patients?
Hopes concerning opioids	Do you think morphine-like medicines have any helpful effects? Would this help you?

Section 3) Data Analysis

3.1 Participant characteristics

Of the seventeen patients were invited for interview, seven refused. Reasons given for refusal included the overall state of the patients' health and a consideration that the subject under review was not of relevance to their specific health. Ten male participants were interviewed in total. The mean age was 71.7 years (range 53 to 86 years). The mean number of types of medication each patient was receiving was nine (range 6 to 14 types). Three patients were in receipt of morphine-like medicines at the time of interview although one participant didn't realise that his solpadol was opioid based. None were taking strong opioids.

The interviews lasted between 17 and 43 minutes. Three patients were seen at their own homes; seven were interviewed in a hospital clinic room (not always post heart failure clinic). Three participants had their spouse present during the interview. Six patients were described as NYHA II, three were NYHA III and one NYHA IV. The participant characteristics are described in the table below.

Table 6.3.1: Study participant characteristics

Pt ID	NYHA	Age	Wife present	Location	Current opioids	No. of types of meds
1	2	75	N	Clinic	N	10
2	2	83	Y	Home	N	6
3	4	86	Y	Home	N	13
4	2	82	N	Clinic	N	7
5	2	53	N	Clinic	Y	9
6	3	65	Y	Clinic	Y	14
7	3	66	N	Clinic	N	6
8	2	70	N	Clinic	N	6
9	3	67	N	Clinic	N*	10
10	2	70	N	Home	N	12
Total	6xII 3xIII 1xIV	Mean age 71.7 years Range 53-86 years	3x Wife present	7xClinic 3xHome		Mean no. 9.3 types per patient Range 6-14

* Participant receiving solpadol on repeat prescription. Two others on codeine, none receiving "strong" opioids

Four key areas emerged from the analysis. These are also shown displayed in Figure 6.3.1 below:

- Medication use in CHF
- Symptomatic CHF
- Prior morphine experience
- Morphine attitudes, concerns and anxieties

These four areas are important in the context of starting morphine therapy in this patient group. Firstly, what is the impact of the existing medications? Do patients feel they are in receipt of too many medicines, which may prevent them from wanting to take any other ones? Morphine therapy may also involve the use of concomitant medicines such as antiemetics or laxatives, which may further add to the polypharmacy. What is their existing knowledge of their medications and who are they most likely to consult

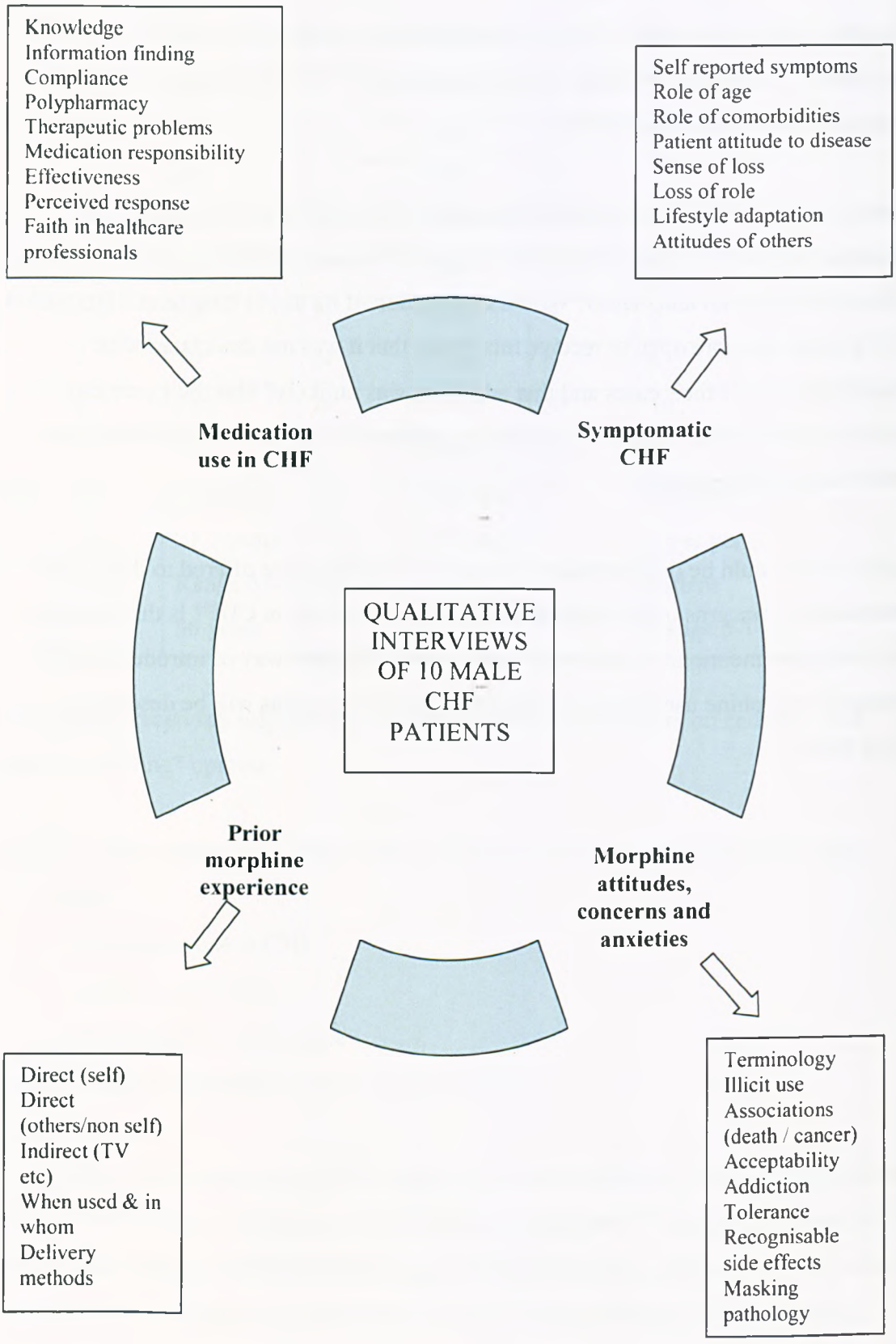
regarding starting a medicine like morphine? Would they trust the prescriber that recommended the use of additional medications?

Secondly, what is the impact of CHF and other factors on patients' daily lives and how may they be best served by using a drug like morphine? Which symptoms might it improve which would benefit them?

Thirdly, what has been their previous experience of morphine use and would this influence their use of it for symptomatic reasons? For many, morphine has connotations with addiction, death and cancer. Would explanation of its use in long-term illness allow CHF patients be more open to receive morphine; that it was not associated with impending death in their cases and that addiction was unlikely? Has their previous experience given them a positive or negative outlook on the use of opioids? Do they exhibit signs of opiophobia?

Lastly, what would be their attitude to take opioids if they were offered to them? Do patients have concerns or anxieties around the use of opioids in CHF? Is this shaped by the other areas mentioned already and how might be the best way of introducing the concept of morphine use in this patient group? These four areas will be described in detail below.

Figure 6.3.1 Key areas that emerged from the data analysis divided into themes and subthemes (boxed)



3.2 Medication use in CHF

3.2.1 Polypharmacy

All patients were taking some form of medication for their CHF, but most were also taking medications for other co-morbidities. Frequently, interviewed patients were receiving an average of nine different types of medication per day. Given this high number of tablets (four patients recognised the high level of tablets they were receiving), it was not surprising that some found this perceived polypharmacy was burdensome:

"You wouldn't believe it, five/six years I used to take nothing, the odd Paracetamol for a headache or anything, and now it's, it's like a pick and mix" Patient 5

The majority of the sample commented on the number of tablets they were taking. Of course, being in receipt of large amounts of medication made it more difficult to remember all the types of tablets taken, let alone what they're for and frequently patients found it difficult to remember all these tablets without writing a list.

3.2.2 Knowledge

Knowledge about the use and reason for their medications was variable; about half of the patients had a relatively clear understanding of what the medications were for; but similarly about half of the sample were happy to take the medications without having to understand why they were important:

"They're for me tick-tock but I don't know what they do." Patient 6

And in a similar response:

"I don't know a lot about my medicine at all and, quite frankly, if I did, I don't know how much it's going to help me. .. I'm happy as I am" Patient 3

3.2.3 Faith in the medical community

Similarly, some participants referred this lack of apparent knowledge about their medication to their faith of the greater knowledge of the medical profession:

"if there's anything wrong with my car I'll take it to a garage, and the mechanic who knows a lot more about the car will give me the right things to get it working right, and I

have the same trust in ... the clinicians here, that they know what they're doing." Patient 9

In this regard, most patients were deferential to the knowledge of the prescriber (typically a doctor). They felt assured that the medication would be helpful to them and would not interact with their other medications. They understood that the clinician had an initial reason why it had been administered, but could not necessarily remember the indication themselves.

All patients in the sample described their respect, trust or faith in the medical community which served them:
"You people (doctors) years ago when I was a boy used to be God, no-one dare speak to you or look up, you know, you was like the Dalai Lama at one time" Patient 1

Thankfully things have changed! This respect and faith in the doctors' knowledge was also expressed by another respondent in a referential but less spiritual tone:

"I believe when you say, trust me I'm a doctor, I'm a big believer in that and if you told me to take this and take this it would be better for me I will do that simply because as a layman I'm subject to your abilities." Patient 1

Faith in the doctors' ability and their use of medication was referred to by another:

"the specialists or the doctors must know they (the medications) work or else they wouldn't prescribe 'em" Patient 5

3.2.4 Finding further information

Information finding for the medications, their effects and adverse effects took a number of different routes. Some patients made enquiries directly to the prescriber, often the HFNS was involved in re-iterating the reasons for the medications and most found this helpful. Indeed, the HFNS was mentioned specifically in helping improve a patient's knowledge by five patients. Use of patient information sheets included with the medication was also discussed. Most patients said they had read these leaflets at some point, but that their usefulness was questionable. Some patients found the leaflets counterproductive, unhelpful or not relevant:

"sometimes when you read the notes to the, the medical notes, the .. bits of paper they put inside, this shouldn't be taken if you've got a heart problem. I thought hang on a minute, I've got a heart problem." Patient 5

Another respondent mentioned the potential conflict that the leaflets may create:

"I mean things start going through your mind and by the time you've finished reading that in your leaflet, you think I don't wanna take these, you know what I mean, what are the mind that plays tricks? You think oh why do they, why have they prescribed these for me, because according to them they don't work if I'm taking Aspirin or they don't work if I'm taking Paracetamol. But .. the specialists or the doctors must know they work or else they wouldn't prescribe 'em, and then you sit there and think .. oh you've frightened yourself to death over this lot but you didn't need to because the doctor was right" Patient 5

One interviewee could also see the contradictions provided by the information sheets:

"Q: Yes, yeah. The information sheets, are they...
A: Yes.
Q: ...helpful do you think?
A: They are providing you don't read the side effects...
Q: Yeah, right. (laughs)
A: ...or you'd never wish to take any of them." Patient 7

Conversely, two patients found the information sheets a useful prompt to discuss further with the prescriber:

"I was given Ramipril a few years ago and .. I was breathless after taking it, and I thought well may be this is a, an initial thing and I did read through the .. the list and it did say that could be one of the side effects. But after four days of taking it the breathlessness had got to a stage where I had to, well I had to ring up the .. Academic Cardiology and ask them if they could .. change it." Patient 7

And:
"when I got the leaflet out I saw some of the possible side effects and I thought no I'm not taking it, until I go and see him and then I'll ask him (the doctor)." Patient 8

Only one patient in the sample used the internet to obtain further information. He discovered that the same problems that beset the patient information sheets were also prevalent in cyberspace. The language was often too technical and conflicting information was portrayed. Most participants realised that their current medications were balanced and alterations in this regime could cause an upset to their control of disease. Other sources of knowledge therefore from information sheets or the internet tended to cause a tendency to worry or produced consternation that ultimately lead back to reassurance from the clinician.

3.2.5 Responsibility for medication

Many patients had lists of their medications which they kept on their person or developed routines to remember what to take and when. Those that had a partner or spouse found that they were useful in helping them to remember to take their medications. There was a strong belief in good compliance being related to having a routine to take their medications.

Responsibility for medication was not explored with all patients, but responses varied between full responsibility for medications lying with the individual and full responsibility being with the prescriber:

"All I go to is my doctor's and he says .. "I'm going to put you on so and so" so I say "All right"." Patient 4

Again, it was clear that faith in the clinician's skills allowed this participant to relinquish responsibility to the prescriber as described by the following quote:

"If they've (the doctors) got patients that have done well with these, they must think well it could work for him." Patient 5

3.2.6 Perceived effectiveness of existing medication

When it came to the perceived effectiveness of the medications which the patients were taking, some referred back to their faith in the medical staff who prescribed the therapy. Their perceptions of efficacy varied however with one patient described the fact that he had no discernable adverse events or side effects as an indication that the medication was

effective and one patient could not discern either any positive or negative effects, making it difficult to determine their effectiveness.

"I can't say anything about the tablets what I'm taking because nothing has happened. So, to me, they're doing me some good." Patient 4

3.3 Role of symptoms in CHF

3.3.1 Volunteered symptoms of CHF

The patients were asked what their main troublesome symptom was, in order to discuss whether an additional drug in the form of morphine would be useful. Specifically pain, cough and breathlessness were identified as symptoms that could be potentially improved by morphine therapy. Breathlessness was identified as the most troublesome symptom by five respondents, with three patients considering that the alleviation of pain would be most beneficial for their quality of life. One patient (patient 1) denied any symptoms attributable to heart failure during the interview, despite telling the doctor during his prior heart failure appointment that he was very symptomatic. Another patient (patient 2) described his main symptom was that of a cough, but that this was "natural" inferring that it wasn't related in any sense to his overall health or CHF.

3.3.2 Role of age with symptoms

A number of patients in the sample noted the effect of age on their own overall wellbeing and some even equated the majority of their symptoms on the fact that they were old rather than their CHF or co-morbidities:

"My only problem is, is that as I've got older the old Ano Domini has got hold of me" Patient 1

"Well I, I should imagine at my age .. I'm eighty-four this year, and .. anything could happen now, cos at present moment all our friends are all in that bracket of eighty, eighty-four, eighty-six including this year we've lost two of 'em already, but that's life, that's the way things are." Patient 2

"I'm eighty-six, you can't be, you can't be brilliant all your life, but .. you know, you try to do as best you can." Patient 3

One patient was also stoical when it came to the matter of what might happen in the future and had a sense of what little influence he might have over that:

"Well I, I should imagine at my age .. I'm eighty-four this year, and .. anything could happen now, cos at present moment all our friends are all in that bracket of eighty, eighty-four, eighty-six including this year we've lost two of 'em already, but that's life, that's the way things are." Patient 2

In response to the question "how much does your heart failure bother you", one patient said:

"If I'm gonna go I'm gonna go and there's nobody on this earth 'll stop me, will they? I mean even Kings die, oh they're millionaires, multi-millionaires, they all die." Patient 4
The implications of this will be discussed later.

3.3.3 Attitude to CHF

The patients' attitudes to their disease created a number of different responses in this male sample. Some patients denied the severity of their illness, or would attribute their symptoms to other co-morbidities or their age as described above. Two patients exhibited a type of "optimistic fatalism", cheerful at the fact that either things have been worse for them in the past, or that others are worse off than them:

"but you always turn to yourself and say there's always somebody worse off than you, you don't realise how .. lucky some things are." Patient 5

The other expressed it as:

"we're only on this place for once, aren't we, so make it a good one (laughs)." Patient 5

In addition, the variable nature of their symptoms meant that an "every day at a time" attitude was employed:

"It's a strange thing, you go to bed and feel reasonably comfortable and all the rest of it, go to sleep, and maybe about two o'clock you wake up feeling breathless" Patient 3

Another respondent noted the daily variability of symptoms, implying that it was difficult to plan ahead:

"when I get up in a morning I'm thinking mm, feel OK, and sometimes if you've had a bad night, you can't sleep and you're breathless and everything and you think mm, and some days you just can't be bothered to do anything." Patient 5

Similarly, this participant also discussed the inability to plan to do routine jobs due to daily variations:

"It, it very much varies, sometimes even, you know, but the whole, my whole condition seems to vary a lot. Sometimes I can be fine .. doing reasonably, you know, well .. oh cleaning and one thing and another, another day after I've bent down with the dustpan and brush to sweep up a few bits I can feel breathless." Patient 7

3.3.4 Loss of role and function

A sense of loss was displayed by virtually all respondents, both a loss of role and loss of function. Most patients revealed a functional loss, such as an inability to go dancing, do the gardening or other activities that they may have enjoyed in the past and might have looked forward to in retirement:

"I found that with the heart failure, you get to a point where it says stop and it means stop" Patient 6

In addition to the physical limitations of heart failure, others described a general lack of mobility due to their condition:

"because I'm aware that .. I'm limited now to what I can do, I mean I used to love doing gardening, but I can't do it now, I don't do it now, whether I could do it or I can't do it because I can't get about, but..." Patient 3

"Now, for instance, when we go dancing, we go, used to go dancing on a Tuesday afternoon, on a Friday night at the club, and .. when the dance band is playing the dances, they always play two records you see, but at the present moment I dance one, then I walk back off the floor, or come on to the second one you see, so as I don't .. get out of breath..." Patient 2

Inability to go dancing or complete other hobbies due to health was a common theme:

"I can't do no gardening, which I'm glad (laughs). I mean .. dancing, which .. I, I did like to dance and I can't. But, as I say .. I don't, I don't sit down and moan about it, you know what I mean?" Patient 4

"It's restricting. It .. I mean I have always been, up till my heart problems, a do-it-yourself fiend .. well no longer can I do the do-it-yourself work that I used to do. The frustrating thing, a lot of people will not understand it unless they're in the same position," Patient 9

Other than hobbies, other aspects of normal daily life can be disrupted:

"So I can't drive, that's taken one part of me life away" Patient 5

Secondary to this physical functional loss, was the impact on the inability to enjoy family events (e.g. playing with the grandchildren), or a sense of guilt with the loss of role that could be perceived as being a "male" role:

"last year me son took me to .. Hornsea and he said "Come on, I'll take you in the car" cos I was a bit, bit low on breathing, he said "Come on" he said "and I'll take you on a car and get some" just for the half day, well when I got to Hornsea I walked maybe say two or three hundred yards and then I had to sit down. They carried on walking and then they come back and said "Here we are" and picked me up again and that's how it was. But now I can go say from .. my house here to about, say, three minutes' walk across the road there, through the passageway, then out to the shop, we have a shopping centre, I can walk that and walk back again, and then of course I sit down." Patient 2

Actions that this patient performed to help in the household became difficult due to symptomatic disease:

"I used to take my wife shopping, you know, for the local grocers, well I can't now," Patient 3

Similarly, jobs or chores that are normally shared are difficult to perform:

"we've chucked papering and painting, you know, which we chucked it about .. about three month ago, and I said to our lass, I said "That's it, no more". But knowing our lass like, she'll say "Well I could do with that front bedroom doing"." Patient 4.

He goes on to say:

"We'll get, get the family to do it (...). We .. normally we've done ourselves, but with .. if you're climbing the steps and that like, you've got to be careful, at my age anyway, this is what they always keep telling me like, at, you know, at your age."

Another man gave a clear account of lifestyle restriction with associated sense of loss of role and feeling of inadequacy:

"Q: OK. So did you find, by the sound of things, that you had to modify your lifestyle around how you were feeling with your heart failure?
A: Oh yeah, yeah, yeah, very much so, yeah.
Q: What sorts of things did you feel that you miss, miss out on, or missed out on?
A: Well I miss, I miss on, on general .. messing about with grandkids, any .. like normal.....normal exercise, like doing a bit of gardening, or doing, mending stuff. I just .. it's an effort to put a screw into, even, even with electric screwdriver, which I'm not supposed to use..... and it's frustrating watching your wife doing what you know that you ought to be doing. I mean you know why you're not doing it, but it does stop you feeling you're inadequate." Patient 6

One man in particular discussed his sense of loss in activities, his loss of role and how he perceived he was viewed by his wife:

"But I've always been used to doing the manly things, like carrying out the rubbish, the big black .. bin that's in, in the rubbish, now I have to watch her take that out. I have to watch her cut the grass, I have to watch her doing the heavy lifting and, you know, that, that drives me potty .. and every now and again, if she's not around, I lift something a bit too heavy that I know I shouldn't lift. I suffer for it, you know, virtually straight away I have to go and have a sit down, and she comes in and, she's like a bloody hawk "Who moved that for you?" you know, I, I'm caught, you know." Patient 9

And he goes on to describe:

"The, the manly bit, it, it makes you feel less of a man. It does for me .. I don't know how a woman would feel. .. But .. you try and make up for that by doing the jobs that you can do. Like I'll do the cooking, you know, which I never used to do. I mean .. I'd need a map to find the bloody kitchen (laughter). Now I know where everything is more than J {name} does, I know where, how much gear we've got, how much .. various things we've got, how many red kidney beans we've got, how many, you know, all that sort of stuff, because your responsibility .. circle has changed, you know. Where, where at one time I'd be able to tell you how many nails I've got, how many wood screws and what have you. I still do the odd bit of do-it-yourself, and I get a lot of enjoyment and satisfaction out of that, but doing some of the heavy stuff, like I built wardrobes and put in a new bathroom suite when we moved .. when we were in the south, I couldn't undertake that now, it's too heavy. And that annoys me as well, where I have to employ a bloody builder to come in and do things that I used to do, and then pass money over to him, and I know it only takes a couple of minutes, you know, it's just frustrating." Patient 9

And later:

"So I'm in a vicious circle at the moment. I can't exercise, I've cut down on me food .. because I know what'll happen if I don't exercise .. you know, I'll become pregnant again, so .. but I can't do anything about it at the moment .. and it's not an excuse .. although J {name} thinks it is an excuse. But it's just that I can't do it." Patient 9

3.3.5 Adaptation to CHF

Lifestyle adaptations were commonplace in this patient cohort, with a stoical attitude relating to the loss or inability to be able to perform what the patients perceive they should be able to do resulting in changing the day-to-day activity of the patients themselves:

"I had a big Rover, a lovely car, and .. well if we're gonna get me wife driving again it has to be smaller so it was swapped, swapped it for a little one." Patient 3

This sense of loss of ability due to health was remarked upon by another man:

"there's silly little things you miss, you know, you can't do, I can't bend down and tie my shoelaces, I can't, if I drop something on the floor I can't pick it up, I've got to have one of them handy Andy things to pick it up" Patient 5

And in another example of loss of ability and lifestyle adaptation:

"Well it's strange, I used to be .. I was off like the clapper, you know, walking, now if I go out anywhere, like me sisters, they're off, and I'm saying "Hang on it's, I can't keep up with you, I'm gonna stop" and they know he'll catch us up when, if they go shopping or anything, or if I go into places. I always have to make sure, if we're going anywhere, there's a lift .. " Patient 5

Even relatively simple everyday activities need to regulated according to health:

"At the, at the top of the stairs .. I have to stop normally .. and get a bit of breath. I have to be careful when I'm getting up off the settee that I don't automatically rush and go and do the job that I was gonna do. I have to sort of get up and familiarise myself with where I'm standing. Just a couple of minutes and it, then I don't get the out of breath. .. If I pick anything heavy up that's me knackered for about an hour, you know, I am really breathless. " Patient 9

One respondent commented on the need to have planned non-spontaneous activities with the option of having a strategy for getting home if his health deteriorates whilst going outside:

"A: I'm not too bad, cos I'm not going out just much now. But .. yesterday, for first time, I walked into, here into Brid to do a bit of shopping, just steady away. But I know all places where to stop where it's warm in shops, you know, Trading Post, it's warm in there...
Q: You've got like a route planned out?
A: Oh yeah, and then I know where seats are to sit down. But one or, once or twice I've been in town and it's been cold and I've flagged a taxi down and got home with a taxi, yeah. " Patient 10

3.3.6 Perception of others

Frightening experiences lead one respondent to consider the impact of their health on the thoughts of others around them:

"The one thing that does frighten us, I'm walking on a steep hill, I know what's gonna happen. It, it, it just doesn't like, I I've tried hills and I've tried steps, in fact other week I were shopping so I popped into Boyes in .. Bridlington, they have an upstairs. Well the queue for the lift was absolutely packed out so I thought I'd try and walk up the stairs. I didn't get very far, I had staff running out all over place and .. they wanted to send for an ambulance, I said "No just leave me alone, I'll take me spray" and I won't do that again, will I, when I'm by mesen, I'll make sure somebody's with me. It happened at me son's house, you see, when we go visiting him at Bradford, he lives in a big house and the bathroom and toilet's upstairs, so you have to go upstairs, and it's .. effort and it's a .. a worry, but what's more worrying is the look on people's face when you come back in room, cos they are absolutely taken aback aren't they?" Patient 9

Similarly, there may be a perception of what CHF patients think they are viewed as: *"to look at me, you know, and all, you'd think oh there's nowt wrong with him,"* Patient 10

3.4 Prior morphine experience

Patients reveal a wide range of experience and for the purpose of the results I have divided prior encounters with morphine-like medicines into those that directly been administered to the patients themselves and those effects that they have observed in others (friends, family and in the media). I have termed these observations as a direct (involving self), a direct (involving others like family or friends) and an indirect (media / television) patient experience. These terms are not designed to attach a greater importance or emphasis to one type of experience over another and frequently patients described both the effects of morphine-like medicines on themselves, on others and in the media. All of these types of prior experience are important in forming the views and ideas that patients may have about opioid therapy.

3.4.1 Direct experience involving self

The direct patient experience of morphine involving the patients themselves was at times difficult to elucidate from the patient sample. Four patients admitted that they had been administered opioid medications before and all of these were in injectable form. All four had received opioids during acute events such as myocardial infarctions or during surgery. In addition, three had received oral opioids for other conditions such as for

arthritic pain or angina pain. In general, use of opioids resulted in a positive experience in those interviewees, particularly when used to treat the pain of a myocardial infarction. What was interesting was their recall of what medical professionals had told them about taking these medications: this is detailed in the section of attitudes below, but some surprise was expressed as to the nature of the conversations lead by medical professionals as to the selective highly cautious approach taken for the use of opioid medications.

This leads on into those patients who denied having been given opioids in the past. These patients often had a similar history of myocardial infarcts and operations and it is likely that they have been in receipt of opioid medications at these times. Indeed case note review revealed three of these patients had received opioids at these times. The remaining patients notes did not include the events described and so use of morphine could not be corroborated in those patients.

3.4.2 Experience from observation of use in others

Interviewees had a wide range of experience of opioid use in other individuals. These included use for pain management in the majority of these cases in friends or family. The overall consensus of this use of opioids was, again, positive. Typically the underlying diagnosis in these examples was cancer and opioids were administered to relieve cancer pain. In addition, one patient had a son taking morphine for pain management following an accident – he "*wouldn't have the quality of life he has now without morphine*" and "*he's got life again, you know, so, which is great*" (Patient 9).

The only non-pain example volunteered was the use of opioids for breathlessness in a relative with COPD. This description was useful as the patient also had knowledge of the use of opioids for cancer pain in another relative. His insight on the situation was of interest as he didn't believe that the medication used for breathlessness was the "*powerful stuff*" used to treat cancer pain (Patient 5).

3.4.3 Indirect experience

Participants volunteered less information about what they had observed about morphine use in the media, such as on television programmes or in the press. One patient had knowledge of the use of morphine through being an avid reader of Charles Dickens: "*it is an opiate.. used for virtually any medical ailment & taken recreationally*" Patient 7

Another commented on the way that morphine was portrayed in the media:
"We don't see the medical side of it .. used properly. You see that illegal side of it" (on television) Patient 8

3.5 Morphine attitudes, concerns and anxieties

3.5.1 Associated adverse effects with opioids

Addiction, tolerance and side effects that interviewees were aware of were discussed. Surprisingly few responders discussed addiction and tolerance issues.

"Catch 22, if I take it and it does me any good, good if I take it but it don't do me any good, but I get addicted, is that good or bad?" Patient 5

"when people talk about morphine... you think of addicts" Patient 5 again

Side effects were also difficult to elucidate with many of the patients not sure of any side effects that they could think of to do with morphine use. One patient expected that morphine would give him side effects, even though he couldn't name any. Sleep and loss of concentration were the most commonly mentioned, with one respondent saying it had made someone that he had seen in hospital made "unrational" by therapy. Nausea, constipation and lightheadedness were the other adverse effects that were associated with morphine use.

3.5.2 Consideration for the use of opioid medicines in healthcare

The interviewees were asked, given their previous experience, in what sort of situations opioids should be used and in whom. Nearly all patients identified the use of morphine as a painkiller particularly in accidents, on the battlefield, in cancer or other painful conditions including, somewhat surprisingly, arthritis. Use for severe pain was expressed, often described as used to "kill" the pain interestingly. Three patients also noted that it could be used as a sedative. No patients had heard of its use in heart failure. Did morphine always have a negative connotation? Only two patients discussed its illicit use, and one of those had worked with heroin addicts in the past. Only one of the ten patients considered that the illness had to be sufficiently serious before morphine was considered for symptom control and that it should never be used prior to this point. Two respondents noted that morphine, when used properly and appropriately, could be a very useful

intervention. When discussing the subject of pain, one interviewee noted that his friends' quality of life had improved on therapy and another respondent had a novel way of thinking about pain management with morphine in his experience:

"I think it's just something like you put a plaster over your bleeding to stop it bleeding, and so it's, and that's how I look at Morphine," Patient 6

Connotations with illicit use still seem unavoidable for some. This patient discussed morphine's use as an illegal substance, without any prior prompting:

"I don't connect it at all with modern day people abusing acids and things that they've put into their bodies that are unnecessary. I purely mean it as a, it is a medicine, it's a medicinal factor and I treat it as, when you say Morphine to me, purely from a medicine point of view." Patient 1

Two other thoughts emerged from the discussions related to attitudes towards morphine. First, Patient 6 was concerned that morphine could potentially mask ongoing or worsening pathological or disease processes:

"The, the trouble with Morphine, it works very well at reducing pain, but I think it can also hide the pain that they ought, ought to be knowing about." And:

"you say how you feel, and I feel fine, well actually you're not cos it's something going on that you're .. you, you can't see and it's just not showing itself."

Another consideration expressed by some was the perception of the use of opioids at the end of life. Six patients in total noted the association, but not exclusivity, of morphine with the end of life. One patient noted how morphine was seen on television programmes when in the context of end of life care:

"helps them (patients) on if they give them a big dose..." Patient 10

The avid reader of Dickens volunteered the fact that he had never heard morphine used to hasten death, although this issue had not been prompted or had not been mentioned previously in our discussions, further illustrating the link of morphine with death. One respondent noted that morphine was associated with advancing illness if not death and

that their situation was "not so serious yet" for morphine (Patient 3). In converse, only one patient commented that one didn't have to be seriously ill to try morphine (Patient 6) and two others that suggested that morphine could be used to prolong or preserve life.

3.5.3 Attitudes to the terminology of morphine

Did the CHF patients find that the terminology of "morphine" was a problem and that calling it by another name might help it to become more accepted? Most responders found that the term "morphine" was acceptable to them, but realised that it may not be acceptable in a wider context or in the general population given its illicit connotations. One patient associated the word morphine with "relief".

Some patients also commented on the fact that use of morphine may be more or less acceptable to those treating the patients as well as themselves:

"funnily enough the doctors have various ideas about these things" Patient 3

One patient was given an oral form of morphine to help combat his angina pain, but was discouraged by his GP the prescriber when he was told not to take them "unless you could avoid it" and that if he did have to take if his chest pain was "really bad" he should "just take one". No repeat prescription was issued, although the morphine tablets were effective in symptom control when the patient had severe angina (Patient 10).

3.5.4 Attitudes to opioid prescription in CHF

The final question to be put to the patients was would they be prepared to try morphine if it was offered to them as a therapeutic intervention? Nearly all the respondents would be in favour, with certain caveats. Two patients considered that their situation was not so advanced or so serious to consider using morphine yet. It would have to be recommended by a doctor, with the benefits outweighing any potential side effects, in small doses initially for pain or breathlessness. Two would continue to take it if it help them feel more active or if it extended their lives. Overall, the general consensus is summed up by the following:

"I would not hesitate if it was Morphine, because I've seen the good that it does, and if somebody recommended it who I trusted, yeah, I'd take it. No problem"

Section 4) Discussion

4.1 General points

The 10 male interview participants collectively brought a wide range of experience to this qualitative research. This type of research attempts to provide accounts that give insights to the patients' experiences and are not necessarily representative of a wider population of patients. This single centre study reflects the local experience of CHF patients and experiences in other parts of the world may differ dependent on different treatment regimens. Limiting the sample by gender of course limits the findings to male patients, but given the time constraints placed on the study it would appear to be logical to follow this course to allow comparison with other gender-specific findings. Ideally, the sample size would have been large enough to allow comparison of male and female respondents, but this was not feasible given the time available.

Constant comparison of the data collected by myself allowed consideration to the point of saturation of the data collected. It is important ethically not to subject participants to procedures that are not necessary, however it is important to collect enough data to ensure that the findings in the other participants are meaningful. Ideally, coding of the data should occur with greater than one person. In addition, the role of the researcher should be considered in the analysis of the data and subsequent write-up. Having other people to review the research who may approach it from a different standpoint would be a useful process. Ideally this would have occurred and will be employed during the publication of the research away from the PhD process. I was aware throughout the interview process that participants may be responding to my role as a doctor. Of course, all researchers have different standpoints and previous experiences, but it is important that the role of my previous experiences and views as a researcher are considered in the research process as a whole. It was important to try to remain as objective as possible. I did not attempt to consciously pre-empt how a patient CHF would respond to the questions about morphine, but I suppose I did have some preconceived ideas, some of which have been confirmed and some of which have been disproved. The important point is to allow the participant to express their own thoughts and for the interpretation of those ideas to be performed as objectively as possible. Naturally, my past experience and ideas will influence what data is selected and what is reported as being of interest, and what is not. A lay person conducting the interviews may collect different data, or have a different emphasis on the data collected. Participants did not know my role as a previous palliative

care physician, as I did not want that to exaggerate any thoughts that opioids may be associated with death and dying. This makes the volunteering of information about this fact by the participants more interesting as it was not perceived by the interviewees as the focus of the interview, which it might have been given my background.

Patients known to have symptomatic CHF were approached to participate, with over half of those approached agreeing to take part. Of course, those patients not wishing to take part may have a different experience of morphine-like medications to those that do. In particular, these patients may have negative experiences, or associations with previous use that they do not wish to recant in an interview situation. Hence it must be appreciated that those taking part may either have a narrative to tell about morphine or might have had a positive experience that they wished to elaborate upon. After discussion with the participants, most involved wished to be interviewed if it helped to expand the research process in CHF rather than having such a vivid experience of morphine that they had to become involved in an interview based around opioid use.

Use of a topic guide was invaluable in the research process. It allowed discussions around subject areas of interest, but was flexible enough to allow respondents to express their own experiences. I would certainly be happy to use this method again. A purely open-ended question would allow complete flexibility in questioning, but may yield a great amount of data outside of the researchers' area of interest. Questionnaire based interviews would be specific for data collected to be within the area of interest, but may not allow the expression of ideas or concepts that are important to the participant and may be very relevant to the research in question, but are not volunteered by participants if they feel they are not relevant to the specific question asked. For example, direct questioning concerning the use of morphine in death and dying may have yielded a greater number of factual responses on that subject, but it may not be as interesting as the responses in those participants who volunteer the link without being prompted. Given that the interview process was designed to determine experience and feelings about morphine the use of a semi-structured interview would appear more appropriate than a questionnaire based approach, which is more suitable for determining factual information. Constant reflection of the previously collected data allowed refinement in questioning in areas of interest that were emerging which was useful to help streamline a large initial topic.

Attempts have been made to address issues of methodological quality in qualitative research and there have been many attempts to standardise criteria for quality. Mays & Pope (2000) have published guidelines for assessing the quality of qualitative studies and I have attempted to adhere to these suggestions in this study.

Respondent validation (also known as member checking) is a technique whereby the investigator's interpretation of the participant interviews are subsequently discussed with the participants themselves, allowing the participant to react to the analyses and add further comment which can then be incorporated into the analysis. This method can add further credibility to the study outcomes. Mays and Pope (2000) suggest that this method is useful, though they note it is a process to be used primarily to reduce the frequency of errors, rather than acting purely as an all encompassing credibility check. In future studies though I would consider it to be interesting to show the analysis in general to the contributors and incorporate any comments in the subsequent write-up.

Four distinct but interrelated areas emerged from the analysis and components of these will be discussed in detail:

- Medication use in CHF
- Symptomatic CHF
- Prior morphine experience
- Morphine attitudes, concerns and anxieties

4.2 Medication use in CHF

Prior to the consideration of any additional medication, including opioids, in CHF it is advisable to understand the perception of the medication currently taken and whether additional medication would be acceptable. An average of nine different types of medication were taken by these participants, which often equated to double the number of actual pills taken as many were on these medicines twice or three times a day. Initially I considered that this polypharmacy would be burdensome on patients. Often it occurred following an acute event, whereby patients were admitted with myocardial infarction or acute heart failure having been relatively fit and well and not having to take much in the way of regular medication.

Following such events, patients are frequently discharged on at least five different regular medications (aspirin, statin, beta-blocker, diuretic and ACE inhibitor in the case of myocardial infarction). Some patients joked about how many medications they were taking and although some realised that they were receiving a lot of medication, they felt that their medications were in a state of balance and were probably required. Participants remembered to take the medications by relying on a list, routine or by their spouse. The formation of a routine for taking medications is discussed by Reid *et al.* (2006) in their study of 50 CHF patients. They detail the formation of set routines, devised by the patients themselves out of necessity due to the high tablet burden which typically involves input from the spouse or main carer to maintain concordance with medications. Indeed, single CHF patients are more likely to be re-admitted or die after initial diagnosis necessitating hospital admission than non-single participants (Chin and Goldman, 1997), which in turn might be related to issues of medication compliance.

It has been noted that many CHF patients have coexisting cognitive impairment (Sloan and Pressler, 2009, Woo *et al.*, 2009, Sauve *et al.*, 2009). Indeed, one would imagine keeping track of all the medications, particularly when they were altered by their prescribers, would be difficult in any case. Knowledge about the medications and what they were for was variable, some good and some poor. This was interesting as those who had good knowledge tended to accept greater responsibility over their medications and overall health. Other studies detail a general lack of understanding as to the purpose of heart failure medications in CHF patients (Rogers *et al.*, 2002, Boyd *et al.*, 2004). However, I would consider that this is only part of the problem for the participants in our sample. Those with less apparent knowledge were more likely to suggest that they were only following what the prescriber had provided for them. This question of responsibility interlinks with polypharmacy, knowledge and cognitive impairment; those patients were less likely to question the approach by prescribers and were happy to be entirely guided by the medical profession.

It surprised me a little that the concept of "doctor knows best" still held true for a generation of CHF patients. I suspect that factors such as increasing complexity of the advancing disease process, increasing cognitive impairment and co-morbidities and increasing types of medication leads to a dependence on professionals who are considered to appreciate the nuances of the human condition. It also probably reflects the patient demographic in a relatively deprived area of the UK. Understandably trust in healthcare is already prominent given that the majority of patients had been in hospital

with acute events (MI or AHF) where they were acutely unwell, treated with appropriate therapy and discharged on a variety of medications that seek to prevent the re-emergence of these acute symptoms. Hence the patient experience is one of acute potentially life threatening illness followed by physician guided treatment preventing further episodes and hence the overall perception of the medical intervention is both positive and necessary for health.

Participants volunteered information about where they derived knowledge about their medications, with the heart failure specialist nurse service (HFNS) mentioned most frequently as a useful conduit for information. Frequently participants had their existing medications altered during admissions to hospital with the HFNS often involved with subsequent explanation of why this had occurred. It was unclear whether the changes had been fully discussed in hospital and this may be an interesting point to explore further comparing the experiences of hospital inpatients and outpatients as to their satisfaction of the way information has been translated to them about their condition.

The use of patient information sheets was discussed, with many patients feeling them unhelpful or counterproductive. They did not appear to be specific enough for patients with CHF and patients were discouraged from reading further when they realised either the nature of the side effects or the potential interactions there may be on other drugs that they were taking for CHF. This no doubt further emphasises or reinforces deference to the medical profession and responsibility for medication use shifts further away from the patients themselves to the prescriber. Rogers *et al.* (2002) documented that some CHF patients in their study were actually alarmed by the patient information sheets, particularly the list of contraindications or the magnitude of the doses prescribed. The authors highlight the potential for confusion with such patient information leaflets and that in general, information given to patients can be of poor quality. Undoubtedly, the information sheets can only provide a general approach whereas a medical professional can provide an individualised or tailored service. However, information sheets tailored to individual patient groups such as CHF or hypertension, in language that can be understood may be an appropriate compromise to allow patients to have greater involvement in their medication decisions.

4.3 Symptomatic CHF

Many patients limited their acknowledgement of the severity of their symptoms related to heart failure. Some considered that their increasing age was as much of a problem as the disease process and that some symptomatic changes were to be expected with advancing age. Was this just a case of male bravado? Their responses may have been different to a female interviewer; they may not have wanted to show health vulnerability to another male and it might be considered that reduction in role is more acceptable to link with age than health in male patients. Rogers *et al.* (2000) also comment that symptoms in CHF patients are attributed to the ageing process in a 27 patient sample of predominantly male participants with CHF.

Some patients noted the points noted in the section above, notably that they had previously been very unwell with an acute event and that now even though they were describing limitations in life and health that they were better off than lying in a hospital bed. These patients realised the life-threatening nature of their condition and displayed stoicism relating to their condition. Comments such as "always someone worse off than you" and "everyones gotta go sometime" were a demonstration of a stoical attitude to health and disease. Again, this response may have been different in female patients. A qualitative study of predominantly male patients with advanced heart failure (Willems *et al.*, 2004) determined the perception of CHF patients about death and dying. Most of the 18 participant sample who wanted to discuss end of life issues did not consider their heart condition would result in a premature death, but considered if their overall condition was poor they would not want life prolonging treatment at all costs.

This attitude of stoicism was a developed response to the symptoms currently or previously experienced. Participants volunteered few symptoms related to CHF, but breathlessness, cough and chest pain were prominent among them. These were in keeping with those symptoms described in other studies of CHF (Rogers *et al.*, 2002, Seongkum *et al.*, 2006) although I had expected participants to volunteer many more symptoms. An open question was asked about symptoms in general, rather than specific questions concerning specific symptoms, which probably would have yielded more symptom descriptions. Two patients in particular denied any symptoms attributable to heart failure, even though they were selected for the interview because they were symptomatic as described by both themselves and their treating physicians. One patient denied symptoms when questioned, even though his prior clinic appointment that day

detailed him as being very symptomatic requiring medication changes. Another patient's cough was described as "natural", again playing down both the symptom itself and the impact it might have on daily life.

Do these patients not want to engage in discussion about symptom severity on tape or do they simply not want to appreciate the impact of these symptoms? Does a stoical attitude protect them from considering advancing disease and having to come to terms with morbidity and mortality? A positive outlook was considered important for maintaining a good quality of life in a predominantly male sample of 20 American CHF patients (Heo *et al.*, 2009). However, this view in male CHF patients is not supported by other studies of gender differences in living with CHF (Martensson *et al.*, 1997, Evangelista *et al.*, 2001) who might attach more negative meanings to their illness, though in the case of the Evangelista study (2001) this difference between gender is modest at best. Perhaps having a perceived experience of individuals with a worse condition to their own allows patients to maintain positivity. Why CHF patients need to maintain this positivity or why they think it is so important is not clearly understood and could form the basis for future research. Certainly the attitude of stoicism that is displayed in our sample links into this notion of positivity. Perhaps this attitude is a form of disavowal, described by Buetow *et al.* (2001) as a "selective perceptual blindness to unpleasant facts" considered by Yu *et al.* (2008) as another form of denial in coping with CHF, which is considered a negative trait. However, the Buetow article considers disavowal as a useful coping strategy between avoidance and acceptance in CHF. They consider some patients to acknowledge the reality of their situation, but to palliate that emotional burden they try to dissociate that awareness from its personal impact. Male patients in our sample may be describing this phenomenon as part of their stoical outlook on their condition. However, such stoicism may hide a degree of acceptance of their condition and realisation that they alone are unable to dramatically alter its course or outcome; the "one day at a time" strategy of coping with chronic illness, which is considered as a positive response to allow psychological adjustment to the effects of CHF.

Symptom variability was a key feature in the daily lives of some CHF patients. This did not allow the patient to plan the day ahead in some circumstances and left them having an approach of taking one day at a time (the old sporting cliché). This had two consequences; to perpetuate the stoical attitude about their disease, having the feeling that they have no choice but to carry on with what is expected of them despite their symptoms; and variability also leads eventually to reduction in activity as planned

activities may have to be cancelled on days where symptoms are at their worst. This withdrawal from activity might lead to a sense of loss as described below.

A sense of loss was noted in almost all participants, whether it was a sense of loss of functional capabilities, or as a result of this a sense of loss of role. Lack of independence and the need to reduce activity levels with symptomatic CHF has previously been described, again in a predominantly male sample of CHF patients (Thornhill *et al.*, 2008, Europe and Tyni-Lenne, 2004). The feeling of limitation due to disease both as a social and a physical restriction has been noted elsewhere in male CHF patients (Martensson *et al.*, 1997). A common group of activities that could no longer be achieved in our study was observed in less restricted participants such as dancing, gardening, DIY and driving. Similar reductions in the ability to perform hobbies has been noted elsewhere in the CHF literature (Edmonds et al 2005). Very restricted participants sometimes found it difficult to complete normal activities of daily living without help or observance by the family. This reliance on others may lead to a loss of personal identity as to the role played as part of the family unit and the wider community.

Days out away from the house were restricted, associated with a sense of loss of role either as a man (for example doing chores) or as a father or grandparent. The Hornsea day trip described by Patient 2 is a good example of a number of related concepts: a sense of guilt by slowing the family down; being left behind by the family whilst they did activities that the patient felt he could not; a stoical attitude to his health and the impact of it on both his physical and emotional behaviours; modifying his behaviour and activity in the confines of his disease; and being aware of his own limitations. How a patient with chronic disease might be viewed by others was touched on here and is continued by the remarks of patient 9. He describes how his family perceives him being unwell, elderly and possibly unable to cope and how this creates worry and apprehension in both the patient and family. In addition, there was guilt from his part on his spouse having to undertake jobs that he perceived as being traditionally male orientated. He was representative of other respondents. He had his spouse present in the interview, illustrating that he felt able to discuss these matters in front of his spouse. His wife's opinions on this would be interesting to gauge and it would be interesting in general to explore the impact of chronic disease on men and their families further in future studies.

Other respondents found the loss of function made them both guilty that someone else had to perform the task and frustrated that they were no longer able to accomplish it

themselves. This guilt concerning reliance on other family members has been documented in a focus group study in CHF (Fitzsimons *et al.*, 2007). No doubt this impacts on a patients' quality of life as both having the ability to perform tasks and having fulfilling relationships with family and others have been identified as important for a good quality of life from the patient perspective (Heo *et al.*, 2009). One can infer from our sample that quality of life will be adversely affected if patients perceive that they may be a burden on others given that they are more reliant on their family or carers, but future studies may address this point in more detail.

Lifestyle adaptations are a natural consequence of functional loss and interviewees described a number of changes. Allowing others, such as spouses or carers, to complete tasks was one feature that was common in the interviews. Men who lived on their own felt they had to carry out certain tasks themselves, leading to prior planning of events such as shopping to allow for concurrent health issues. Adaptations may be limitations in time out, shops visited, catching lifts or even ensuring enough money for a taxi home. This adaptation of course is not helped by the apparent variability of CHF symptoms. Adaptation to disease is also prominent in another study of 12 male CHF patients (Martensson *et al.*, 1997), though they purport that a strategy of avoidance is employed in their population, limiting the amount of physical and social activity through reduction of tasks and subsequent resignation to their plight. In our sample, adaptation appears to occur through necessity of functional impairment but the attitude is different for some participants where there is a realisation that a task must be done and adaptation occurs accordingly, rather than complete avoidance of the task.

4.4 Prior Morphine experience

Respondents described a number of experiences involving morphine administered to themselves (described as direct – self), friends and family (direct – others) and in the media. Surprisingly, few participants noted the perception of morphine use in the media. Most had direct experience of morphine use. Descriptions of this experience was difficult as some were unsure whether they had received morphine, even though I discovered written information in the notes on medication charts of its use, typically during acute events such as myocardial infarction or surgical procedures. Why could some participants not recall its use? Possibly, the acute nature of the event precluded discussion or recall of a discussion about therapeutic options. It is possible however, that

discussion of the use of morphine is avoided or deferred by some medical professionals. What is unclear is whether these clinicians believe it is not relevant to discuss with patients, or that patients might refuse to take it if discussion takes place. Some might see it as a therapeutic intervention, beneficial to the patients which therefore needs not to be covered in detail as part as an overall holistic approach to healthcare. As has been determined earlier, some patients are deferential to the skills of the clinician and are not particularly bothered about how improvements are going to be made, simply that an attempt to alleviate symptoms will be made. However, the research literature suggests that some professionals may avoid either use or discussion of the use of morphine due to perceived "opiophobia". This area is discussed further in the attitudes to morphine section.

In general, the direct experience of morphine use on themselves or on their friends and family was positive. Most experience involved morphine use for pain, particularly cancer pain, which is to be expected. Interestingly, the same patient who had seen beneficial effects of morphine in both a relative with end-stage COPD (for which morphine was used for breathlessness) and in a relative with pain related to cancer, considered that the cancer pain morphine was significantly stronger than that used for breathlessness. Unfortunately the types and doses of morphine are not known in these two clinical situations, but his insight appears to be that cancer pain necessitates strong analgesics as it is likely to be severe, whereas troublesome breathlessness does not necessarily require such radical intervention. Clinically patients with cancer pain are more likely to be prescribed higher doses of opioid than those with breathlessness, but frequently the same forms of opioid are used in both scenarios. Expansion of this concept would be interesting to analyse in future studies. Is there more acceptance of the use of morphine for cancer pain due to better education and dialogue? Is it because opioids are more commonly used for cancer pain, that the patient experience is greater and therefore there is greater acceptance of its use in therapeutic doses in such patients? Anxiety regarding the potential use of opioids is likely to be reduced with greater exposure to them in clinical situations with symptom improvement.

Less information came from the indirect experience of patients through media, television or further reading. This is partly due to the open-ended nature of the question about their experience and I attached greater priority to discovering their direct experiences. A future study could determine the possible juxtaposition of a positive direct experience with an often negatively portrayed experience of morphine in the media or on television; would

patients be reluctant to take morphine if the media frequently portrayed an unbalanced negative view of it, and how would their position change if a subsequent direct experience was positive?

4.5 Morphine attitudes, concerns and anxieties

Despite many participants having taken morphine in the past, few adverse events related to morphine were volunteered. Addiction and tolerance were infrequently mentioned in open questioning about side effects. These questions were discussed typically towards the end of the interviews, which may have had a bearing on the lower level of response given that most participants were elderly with a number of symptomatic chronic diseases. Fear of experiencing side effects was low, with one patient expecting to get side effects even though he could not detail what they might be.

Morphine use was associated typically with the control of pain during acute events or for the management of severe pain in cancer. Fewer patients than I expected discussed its use in an illicit sense. The majority noted its use at the end of life, whilst realising that morphine could be employed prior to the phase of imminent death. Only one deviant case from this analysis commented that morphine use should be restricted to very serious situations. Perhaps this was reflected in the patient sample; participants may have been more likely to enter an interview trial about morphine if they were more open to it potential uses. Use of an open question about the respondent's associations of morphine again may not have yielded specific information about illicit use, although having an open question allowed those that wished to discuss illicit connotations of morphine the opportunity to do so. However, even considering this, the potential use of morphine in these patients does not seem to be guided solely by advanced disease or end of life situations alone or by illicit non-prescriptive use.

This is not in keeping with the experience of morphine use in cancer patients for pain management. Reid *et al.* (2008) found that cancer patients who were to be commenced on morphine-like medicines for pain were frightened that it was being used as a last resort. This study is limited though by the nature of the study sample as participants were entered into a concurrent clinical trial of opioid analgesics and therefore may not constitute a representative sample. I had sought to avoid patients who had already considered entry into a clinical study of opioids as this may result in a biased sampling

strategy. That patient cohort was one of advanced cancer where thoughts of impending death may be interspersed with uncontrolled pain, linking morphine use with end-stage disease. The CHF cohort was symptomatic, but not necessarily reaching the point where end of life considerations are at an acute stage. It would therefore appear that early consideration of morphine in the trajectory of an illness, once patients are maintained on maximal standard conventional therapy, may increase its acceptability rather than leaving it to a very advanced stage with the inference that it can be only used at the end of life.

Prior to the study I anticipated that CHF patients might associate morphine with death and dying as evidenced in the literature (Blake *et al.*, 2007) and that this might preclude its use in these patients. It is true that the majority of the sample noted a link between use of morphine in the terminal phase, either through their own experience of family and friends or in the media as a cultural perception. This link however, did not appear to prevent many of these patients from considering the use of morphine in their own clinical situation. One person volunteered a link to death without any prompting, which shows that this association is held firmly by some individuals. It would seem that this link is not absolute for all forms of morphine and that lower doses or non-injectable forms may be acceptable away from the imminent death scenario. Only one patient volunteered that their situation did not warrant use of morphine for their symptoms as their disease was not so advanced yet. I had expected this level of response to be higher. The patients' perception of disease severity may differ from that of the treating clinician and it is only correct that it is the individual's right to choose or refuse therapy. Interestingly though this patient was the most severely affected by his CHF, so potentially might have the most to gain from additional symptom control based intervention. Perhaps the perception that morphine is only used in severe illness allows that patient to deny his own advanced disease, which is another feature of the stoical attitude seen in this cohort of CHF patients.

Attitudes towards the use of morphine are guided by past exposure to the drug, societal attitudes perpetuated by the media and perceived adverse events, all of which have been discussed in earlier sections. Other opinions included the fact that morphine use may mask a change in symptoms related to the disease process. This potential to mask pathologies is a feature in another study of cancer patients in a palliative care setting (Lambert *et al.*, 2007) and of papers involving the Barriers questionnaire, particularly noted by Gunnarsdottir *et al.* (2002). This questionnaire detailed reasons why there was a reluctance to report pain in cancer patients. Specific concerns included the fear of

addiction, tolerance or side effects with strong painkillers amongst others and the authors noted that large numbers of patients appeared to have misconceptions and concerns about using strong analgesics with may delay their presentation (Ward *et al.*, 1993). A further smaller study involving the questionnaire suggested that non-cancer patients may hold similar beliefs (Ward and Gatwood, 1994). Attitudes may have changed over the past 15 years since these studies with improving use of and education about morphine-like medicines. The term "morphine" itself was universally accepted, although respondents did realise that this terminology may preclude others from trying it due to its association with illegal or illicit use.

Patients attitudes may also be influenced by how they have seen morphine prescribed. The opiophobia of some medical professionals, not forgetting that they are held in such esteem and deference at times by these men, will certainly influence its use. Despite patients finding morphine use acceptable, particularly in acute or cancer pain states, it is notable that some prescribers find its use so daunting, at least in the eyes of their patients. Even when morphine has been successfully employed in severe symptomatic angina as in the case of patient 10, he was left with the impression that the drug should only be used very much as a last resort. This would seem unfortunate given that the patient would likely be on maximal tolerated therapy at that time, with morphine added in as a method of additional symptom control. Whilst no evidence is available specifically for cardiologists, which provides an avenue for future research, much qualitative research has been performed in oncologists and other healthcare professionals who can hold negative misconceptions of the use of morphine-like medications (Zenz and Willweber, 1993, Larue *et al.*, 1995, Pargeon and Hailey, 1999).

Finally and perhaps most importantly, would patients with CHF be prepared to take morphine? This concept had to take into account the noted polypharmacy that some participants had expressed, the negative connotations and positive experiences that some had witnessed and how it would be of potential benefit to them given symptoms of pain, breathlessness and cough. The general consensus was that morphine would be acceptable if it was prescribed by a trusted healthcare professional on a trial basis in a low dose initially to see if it would benefit them. In a way, this could be extrapolated for all drugs; prescribed correctly with benefits outweighing detrimental effects. Morphine prescription should be seen as being no different to this general model in CHF.

4.6 Implications for morphine use in CHF

Would CHF patients be amenable to accepting a prescription for morphine-like medicines if there was a potential symptom benefit? Despite considerable polypharmacy for some CHF patients, it would appear that the addition of a medication directed towards symptom improvement may be acceptable in the context of the disease modifying agents that patients are already accepting. Hence discussion of medications for symptom benefit is appropriate despite the co-prescription of multiple medications in this group. This discussion may also involve the patients' spouse or carer as from our sample it would seem that they are important in medication compliance issues.

The importance of symptoms attributable by the patients to age and other co-morbidities was of interest to myself as a palliative care physician, given that the importance of patient-centred symptom management is one of the key factors to good palliative and supportive care. It could be argued that the attachment of perception of the patient to specific disease aetiologies is less important than the acceptance of intervention for a given symptom as often symptoms such as pain or breathlessness can have multiple aetiologies in the same patient. The acceptance of palliative intervention for symptoms could therefore be argued as one of the more important factors in a symptomatic CHF patient. It would certainly appear that CHF patients in this sample would be agreeable to morphine-like medications for symptom control.

The knowledge of disease or the medications taken for CHF is variable in this and other samples of CHF patients. One can see from the participant testimonies in this sample that this knowledge is hampered by changing diagnoses, recurrent hospitalisations, changing treatments and different approaches by healthcare individuals. Unless the individual enquires about the details every drug change, the reasons for it and potential implications in relation to their other medications it is extremely difficult to understand what medications are for and why they are used. Frequently, acute events leading to hospitalisation results in a raft of changes in medications, some through necessity and some through the different approaches of the treating physician. If one combines these facts with the profound faith in healthcare professionals expressed in this sample and the lack of targeted sources of information, understandably CHF patients lose the ability to determine what their medications were for and why they were administered. In turn, these factors undermine a patients' understanding about their health and will reduce their ability to take more responsibility for their condition. In an age where patients are

generally encouraged to take more direct input into their health (Steinbrook, 2006), not only are CHF patients faced with having to be very perceptive and make detailed enquiries at every medication change, they also demonstrate significant symptom variability often necessitating short term treatment changes, such as transient increases in diuretic therapy for fluid retention for example. Ideally, patients with CHF should be able to monitor these changes themselves, through noticing weight gain and shortness of breath in the example of the transient increase in diuretic therapy. Early intervention in these matters may prevent further selaeque such as hospital admissions. This approach though would seem very difficult to institute in this patient sample who at times seem bamboozled by multiple medications and changing therapies. It is notable that the patients' appreciate the role of the heart failure specialist nurse, who has the time and ability to discuss the disease and current treatments on an individualised basis. These professionals may be the best to target with information about symptom relief with morphine-like medicines as they often describe the impact and implications of both changes in disease and changes in therapy. From this sample however, it would seem that doctors, in which these patients hold in such regard, would still need to prescribe morphine-like medicines as part of the overall therapeutic regimen. Given the patients' perception of physician opiophobia and from the literature in general (Zenz and Willweber, 1993, Larue *et al.*, 1995, Pargeon and Hailey, 1999), it would appear that a greater understanding of the use of morphine-like medicines for symptom benefit in CHF patients may be required in physicians to allow greater consideration of this type of therapy. One could hardly expect an open conversation about morphine-like medications with the patient if the treating physician was highly selective with the type of information given about morphine-like medications due to their own pre-conceived ideas or attitudes about this form of therapy. This potential physician reluctance in CHF could be explored with future studies.

It is currently unclear as to the nature of any potential benefit that morphine-like medications may provide for breathlessness in CHF. It is clear though that in this small patient sample a stoical attitude to health and physical limitations is demonstrated and there remains a distinct sense of loss of both activity and role. Patients adapt to their changing physical state by avoidance or reduction in physical activity. Interventions for breathlessness may not make a dramatic prolonged improvement in activities of daily living but CHF patients may appreciate the possibility of symptom intervention to allow them to try to participate in activities that they no longer appear to be able to perform. Pharmaceutically induced symptom improvement may provide an initial platform to

allow the cycle of inactivity and further physical deconditioning to be broken, thus empowering the patient to improve both activity and physical conditioning, leading to greater levels of activity and so on. This patient sample in general would appear to be receptive to a trial of symptom control therapy.

Section 5) Conclusion

The prevalence of CHF will increase in coming years, resulting in more patients with symptoms potentially amenable to opioid therapy. Such symptoms can markedly reduce physical function and adversely affect quality of life. Historical associations of morphine has allowed it to be viewed with suspicion by some lay and medical populations alike, leading to a reluctance in use of this potentially useful medicine. As demonstrated in this sample, male CHF patients are stoical in their outlook to CHF but are willing to accept symptom control measures if it has the potential to alter their loss of function or role. Hobbies restricted by breathlessness are prominent in the interviews of those that still enjoy a reasonable level of physical function. This would suggest that symptoms have an impact on the quality of life in earlier stages of CHF than simply end stage disease. The participants current pharmacotherapy is mostly directed to disease modification, with symptom control measures relatively neglected. Clearly, this needs some attention.

Are CHF patients opiophobic? This small sample of symptomatic male patients would suggest not. Morphine for symptom relief would be generally acceptable in this sample despite their concurrent polypharmacy. Many have already had direct experience of morphine use, which has generally not been a negative experience. End of life use of morphine or its use in cancer was not a barrier to accepting morphine as it was perceived that high doses were used in those situations. It would seem to have to be prescribed by a trusted physician following a dialogue about how their symptoms of pain or breathlessness might warrant to trial of therapy.

Patients would expect a discussion about risks, benefits and whether morphine therapy would affect their other medications that are seen to be in balance. Given the descriptions made by the participants in the study, maybe it is the physicians or medical professionals that are more at risk from opiophobia than CHF patients. Descriptions such as "strong", "use sparingly" and "severe" are reportedly attached to morphine by healthcare professionals in this sample. It cannot therefore be surprising that patients may be left with a biased view of morphine use; that it should be feared as a drug of abuse that might hasten death. Of course, morphine prescription should only be made on an individual basis for a specific identified reason in patients whose symptoms may not be palliated by other means, such as curative interventions or other medical therapies with lesser side effects or proven disease modifying benefit. However, this taboo of morphine use will

only be dispelled with greater and better dialogue of the risks and benefits of morphine use on an individual basis. Physicians may be apprehensive to approach such issues, but exposure to morphine is noted by many patients with chronic disease such as CHF and although there is some realisation that it is used at the end of life, that is not the sum total of its use in the experiences of CHF patients. It is clear that symptom control measures are required in CHF to address the loss of function experienced, and morphine is one such measure that deserves consideration.

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Chapter 7:

Opioids for breathlessness in heart failure: Past, present and future

Section 1) Opioids in heart failure: What has gone before

Opium-based compounds have been used for centuries to treat a variety of different ailments. We now understand that the administration of these exogenous compounds manipulates receptors that are involved in a naturally occurring "endogenous" opioid system within the body. In recent years, their use has been concentrated in pain management, typically in cancer patients. This has enabled a greater understanding of the opioid system, yielding the isolation of the three main opioid receptors, the endogenous opioid families and an appreciation of proposed methods of action and activation.

However, the opioid system is complex and may be involved in a whole range of body processes. In addition, endogenous opioid-like compounds have been identified that do not activate the main opioid receptors, opioid receptors that do not bind typical opioid compounds and there would appear to be a wide species variation regarding the site of specific opioid compounds or receptors. Even in humans there is a individual variation in response to the administration of exogenous opioids. Although there is a substantial body of work investigating the sites of endogenous opioids and their receptors relating to their proposed analgesic properties, relatively little research has involved sites of interest for the cardiorespiratory system and these studies have incorporated a number of different animal models rather than human subjects. Because little is understood regarding opioids in normal cardiorespiratory function, even less is known in diseased states, including CHF.

One of the historical associations of pharmaceutical opioids is the development of respiratory depression with increasing doses. This has allowed two bodies of opinion to develop. Firstly, opioid administration may be useful in smaller doses for regulating breathlessness in certain disease states. There has been some evidence to support this notion, mostly in non-CHF patients. Secondly, this detrimental effect of opioids indicates that these medicines are dangerous and should only be used with caution. This second point has led to the development of physician "opiophobia", where opioid use is viewed with suspicion, and secondly to an initial lack of opioid trials in CHF, in favour of the use of opioid antagonists that ultimately appeared to have little influence on cardiorespiratory function.

This thesis has investigated the potential role for opioids in the cardiorespiratory system and specifically in CHF. Endogenous opioids and opioid receptors have been isolated at sites involved in both cardiovascular and respiratory control in different animal species. Basic science and animal studies have identified the antagonism of opioid peptides to one of the key neurohormones involved in the development and propagation of CHF, namely norepinephrine. Endogenous opioids are raised in human CHF, however it is unclear whether this is a cause or effect of this disease. Far from being detrimental, potentiation of opioids may be beneficial, especially as another group of beneficial neurohormones, namely the natriuretic peptides, are degraded by one of the same enzymes as endogenous opioids (NEP). NEP inhibitors have been shown to have a beneficial effect in human CHF.

A variety of mechanisms for the formation of generalised breathlessness have been proposed. Trials in intractable breathlessness as a whole suggest that opioids are beneficial, though trials are small and tend to involve cancer or COPD patients. Typically, exogenous opioids that predominantly activate mu receptors have been utilised in these studies. Antagonism of the sympathetic nervous system by opioids suggests that opioids may have an additional effect on breathlessness in CHF as sympathetic activation is implicated in some of the mechanisms of dyspnoea in CHF. The small trials of the assessment of opioids for breathlessness in CHF have been discussed, showing a small positive benefit for opioid use. Participant numbers in these studies are small and there is only one documenting repeat doses of opioid, as would occur in normal clinical practice. Additionally, opioid compounds that activate kappa receptors as well as mu receptors may have an additional effect on breathlessness in CHF as kappa receptors may be involved in inhibiting fluid retention. Oxycodone is such an opioid, with mu and kappa activating properties. Therefore, there was a need to investigate whether repeat dosing of opioids for breathlessness in CHF was actually beneficial; to corroborate the safety of opioids in CHF; to identify patient factors such as aetiology, stage of disease or level of sympathetic blockade that might influence response to opioids; and to assess whether CHF patients would be accepting of such an intervention.

Section 2) Opioids in heart failure: Present study findings

This thesis involves a double blind crossover randomised controlled trial (RCT), a three month open label study and a qualitative study of CHF patient attitudes to opioids. This is only the second multiple dose study in CHF of opioids for breathlessness following the first involving ten participants. It is the first to compare two opioids with placebo and the first to include oxycodone as an opioid. It adds to the evidence base that low-dose opioids are safe in CHF. No detrimental impact was observed on cardiovascular or respiratory parameters and overall opioids were well tolerated.

The RCT did not reveal any statistically significant improvement with either opioid for breathlessness severity versus placebo, but did show that at baseline breathlessness appeared to be a significant problem in this patient sample. This may have been in part related to the large placebo response seen in some participants, indicating possible regression to the mean, or the short treatment period. Overall oxycodone was better tolerated than oramorph at equivalent doses. A variety of breathlessness measures were used, some of which appeared to reflect the participant experience better than others. For the first time, Borg and NRS measures of breathlessness were compared to each other in CHF with the development of formulas for conversion between rating scales. Types of descriptions of breathlessness concurred with the other small trials in CHF, adding to the evidence base. This study is the first to document the effect of opioids on breathless descriptors and the first to investigate breathlessness severity with individual descriptors.

This work incorporates the first published open-label treatment follow-up of opioids for breathlessness in CHF. In contrast to the RCT, a statistically significant improvement was seen on breathlessness severity with opioids on the NRS worst breathlessness scale. This difference approximated to a moderate improvement in breathlessness severity on global impression of change scores compared to those not continuing with opioid therapy. The open-label design approximates more closely to the actual clinical situation of opioid prescription, so this finding is important. It also demonstrates that opioids at these low doses were effective for breathlessness, rather than consideration of higher doses given the neutral RCT results.

Overall, no difference between opioid treatments on breathlessness severity was observed. However, those that responded to one opioid may not respond to the other,

suggesting that opioid switching might be appropriate if initial success in breathlessness management was not forthcoming. No association was observed with dose of beta-blocker for opioids in general, hence no link with sympathetic inactivation due to opioids could be made. Markers of disease severity, such as BNP or ejection fraction, also did not correlate to response with opioids. In general, the effect on breathlessness severity was maintained from the initial improvement observed after four days of treatment in those that continued opioid therapy, with a marked deterioration in breathlessness severity from end of placebo treatment in those that did not continue. This suggests that the effects of opioids are maintained over time, whereas breathlessness markedly worsens with time if no opioid treatment is taken. Continuation of opioid therapy also resulted in an improvement in quality of life scores in both physical and mental (psychological) domains compared to those not continuing treatment, suggesting that therapy does not just improve symptoms through a psychological response alone.

A separate group of symptomatic CHF patients were interviewed regarding their attitudes to CHF and the possibility of morphine treatment for breathlessness. This study was the first to assess the attitudes of CHF patients to the potential for morphine use. Perhaps surprisingly, most participants thought that morphine would be acceptable, as breathlessness was a troublesome symptom and they had some experience of morphine use before. This work also corroborates other studies in CHF regarding the importance of functional loss due to physical restriction and subsequent adaptation. It is the first work to concentrate on factors affecting male patients with CHF as a separate group. Despite acceptability in patients often with complex pharmacotherapy, attention needs to be focussed on prescribers that may restrict use due to opiophobic tendencies. In addition, the use of mixed methodological techniques has a synergistic approach in understanding in this area.

Section 3) Opioids in heart failure: Future directions

This thesis illustrates the potential role of opioids in the management of breathlessness in CHF. Future studies should expand upon this work. Firstly, a definitive multi-centre RCT is warranted. A greater number of centres are required to increase the number of potential participants. The inclusion and exclusion criteria should be relatively broad, as in the current RCT, as it is clear that many patients will not fit stricter eligibility criteria. A longer treatment phase should be employed, perhaps up to fourteen days as an example, to allow more standardisation of clinical variation. As documented in this thesis, NRS scores appear to be more flexible at lower levels of breathlessness and change in NRS should be documented as the primary outcome measure. Borg scores can always be used as a comparative measure. NRS rating scores could be taken simply at the end of each treatment period in conjunction with global impression of change rating of breathlessness as these measures may reflect the patient experience better than change in scores from baseline. It is also clear that current rating scores may not be as descriptive as average or worst ratings for these patients. Following the crossover part of the RCT, and extended follow-up period could be initiated. This could follow similar lines to the three month follow-up in this thesis, but additional assessments, for example at one, two, three and six months could derive more useful information. In addition, if this follow-up period was blinded to intervention, this would improve the robustness of the study. Participants could select the treatment they felt most benefitted them (first, second or third), then continue on this open label, even if it was the placebo. This would eliminate some of the potential criticisms of the follow-up period, as all participants would be receiving a treatment.

Opioid doses should be based on the equivalent doses utilised in the RCT, however in the absence of side effects the dose could be increased incrementally in those whose breathlessness does not respond. This would allow a dose range for breathlessness to be investigated, as some participants may only respond at higher doses than the ones previously quoted. As demonstrated in the results in Chapter 5, some of those participants that did not respond to opioid therapy in the initial RCT may have tolerated much higher doses as their renal function was good and the trial drugs may have been cleared more rapidly than in those that responded to opioid treatment. Increasing the dose in these participants may allow more to respond to treatment. Oxycodone should be the choice of opioid if only one were to be investigated in this fashion, as adverse effects

were lower compared to oramorph. Drug delays and placebo manufacture caused difficulty in the RCT, so sourcing commercial manufacturers of investigational medicinal products should be a priority prior to trial commencement.

From the existing literature it is still unclear as to the relationship of sympathetic activation, endogenous opioids and level of breathlessness. Using beta-blocker prescription as a proxy measure for sympathetic activation is not ideal. Measurement of serum concentrations of norephinephrine as an approximation for sympathetic activity may be more accurate. Serum norepinephrine and circulating endogenous opioid concentrations could then be measured against breathlessness rating to elucidate whether high norephinephrine concentrations and low endogenous opioid levels correlate with high levels of breathlessness. In addition, given that sympathetic overdrive is associated with breathing disorders in CHF such as periodic breathing, cheyne-stokes respiration and sleep-disordered breathing, measurement of these breathing patterns in a sub-section of enrolled participants would be of interest. The effect of opioids over time on these abnormal breathing patterns can then be assessed. One quality of symptomatic CHF that should also be measured in conjunction with this would be an assessment of sleep and whether this is improved with opioids both through improvement in breathing patterns and from the drug's adverse effect profile.

Opioid therapy would appear to be acceptable in advanced heart failure and discussion about the potential role of this therapy should be encouraged. Whilst patients may not exhibit opiophobic tendencies, what is unknown is whether their treating cardiologists may have preconceived ideas about opioid use. The possibility of CHF physician opiophobia should be explored in future studies in order to allow appropriate prescription of opioids for symptoms. There is a sense that cancer patients are more willing to consider morphine and this point should be explored further; does greater information about morphine improve the willingness of patients to consider its symptomatic use?

The stoical outlook of patients and their possible sense of disavowal should also be further explored, with comparison between groups of patients with different aetiologies. Further comparison of the attitudes to disease between genders should also be encouraged, with a similar study involving the attitudes of women to CHF. The sense of how CHF patients feel they are perceived by carers and the wider community was only partially explored in the thesis, but this again would provide an interesting avenue for future qualitative research.

The use of mixed methodological techniques involving both quantitative and qualitative design in this thesis has allowed a synergistic improvement in the understanding of opioids in CHF. An adequate understanding of the previous work undertaken, an assessment of treatment efficacy and an appreciation of the potential role for therapy from a patient's perspective has provided a more complete picture than the use of these techniques in isolation. Future studies should have an appreciation of all these separate areas of research importance with a view to providing more studies of good quality mixed methodology.

Appendix 1) Glossary of terms

Acute Heart Failure

The sudden onset of a physiological state in which cardiac output is insufficient to meet the body's needs, typically caused by sudden events such as myocardial infarction or cardiac rhythm disturbances. Pulmonary oedema is a key feature and is treated acutely with diuretic therapy

Afferent neurons

Carry nerve impulses from sensory receptors or organs towards the central nervous system

Afterload

The systolic load on the left ventricle after it has started to contract. If this occurs chronically and increased afterload is sustained the left ventricle must hypertrophy to compensate for the increased pressure

Agonist

A compound or drug that binds to a receptor of a cell and triggers a response by that cell

Antagonist

A drug that blocks the action of an agonist on a cell

Atria

Chambers of the heart that receive blood from the venous systemic circulation (right atrium) or pulmonary circulation (left atrium) to pump into the cardiac ventricles

Autonomic

Pertaining to the autonomic nervous system, part of the peripheral nervous system and comprising of sympathetic and opposing parasympathetic components. It has sensory and motor properties.

Baroreceptors

Sensory receptors that monitor the pressure of blood flowing through blood vessels and feed this information back to the central nervous system

Bruce protocol

A standardised method of exercise testing in cardiac patients to monitor cardiac function with exercise using a treadmill

Cardiomyopathy

A general term indicating disease of cardiac muscle, causing dilatation of heart muscle, hypertrophy of heart muscle or restriction in heart muscle function dependent on aetiology

Central Nervous System

Neurons of the brain and spinal cord

Chemoreceptors

Sensory receptors that detect chemical stimuli in the circulation and relate the information to the central nervous system. Peripheral chemoreceptors exist in the aortic and carotid bodies, whereas central chemoreceptors occur near the medulla oblongata in the brain. Collectively they can detect changes in carbon dioxide, oxygen concentrations and pH.

Cheyne-Stokes

An abnormal breathing pattern involving periods of alternating hyperventilation and apnoea

Chronic Heart Failure

The gradual onset of a physiological state in which cardiac output is insufficient to meet the body's demands. Can occur after periods of acute heart failure or due to ongoing myocardial damage. Chronic heart failure is seen as a stable condition, with periods of decompensation where acute signs and symptoms can occur (acute decompensated heart failure).

Efferent neurons

Also known as motor neurons, carry nerve impulses from the central nervous system to effector organs (e.g. muscles)

Ejection fraction

The fraction of blood pumped out of the left ventricle with each heart beat

End-diastolic volume

The volume of blood in a ventricle at the end of diastole (filling). Increases in this volume increases the pre-load on the heart and subsequently the volume of blood ejected from the ventricle during systole.

Haemodynamic

Relating to the circulation of the blood

Hypercapnea

An excess of circulating carbon dioxide in the blood

Hypoxia

Deprivation of adequate oxygen supply (hypoxaemia – abnormally low oxygen concentration in the arterial blood is one such cause)

Ischaemia

Insufficient blood supply to a tissue or organ

Ischaemic Heart Disease

A condition characterised by reduced blood supply to heart muscle, usually due to coronary artery disease

Inotropic

Drugs or factors that increases the strength of contraction of heart muscle (positively inotropic). Negative inotropes reduce cardiac contractility

Ligand

Molecule that binds to a receptor forming a complex

Mechanoreceptors

Sensory receptors that respond to mechanical stimuli and relate information to the central nervous system

Myocardium

Striated muscle of the heart (individual muscle cells known as myocytes)

Naloxone

An opioid receptor antagonist, inhibiting opioid transmission at relatively low doses across all receptor subtypes

Neurohormonal

Pertaining to neurohormones, any hormone-like protein produced and released by neurons (including but not exclusively into the circulation)

Noradrenaline

See norephinephrine

Norepinephrine (noradrenaline)

A hormone released by the adrenal glands and neurotransmitter in the central nervous system and sympathetic nervous system where it acts as an agonist for sympathetic activity

Oedema

The abnormal accumulation of fluid in skin, soft tissues or body cavities

Oramorph

A short acting oral liquid form of morphine, predominantly a mu opioid receptor agonist

Oxynorm

A short acting oral liquid form of oxycodone, a mu and kappa opioid receptor agonist

Parasympathetic nervous system

Modulates vital functions with the sympathetic nervous system, for which it is continually in a state of balance. Parasympathetic activity tends to oppose the actions of the sympathetic system by returning body functions to their resting state.

Parenchyma

Typically used to describe lung components, including alveoli and bronchioles

Parenteral
Route of administration through the skin or mucous membranes (examples include intravenous and subcutaneous)

Periodic Breathing
An abnormal breathing pattern characterised by intervals of apnoea within periods of normal breathing

Peripheral Nervous System
The neuronal connection between the central nervous system and the organs. It is divided into somatic and autonomic types.

Post synaptic
Occurring in neurons after a nerve junction (synapse) with another neuron

Pre synaptic
Occurring in neurons prior to a nerve junction (synapse) with another neuron

Step 2 analgesics
"Weak" opioid medicines (codeine, tramadol as examples) used for moderate pain as the step 2 of the traditional World Health Organistion analgesic ladder. Their use is limited by ceiling dose effects

Step 3 analgesics
"Strong" opioid medicines (morphine, oxycodone, fentanyl as examples) used for severe pain as the step 3 of the traditional World Health Organisation analgesic ladder

Stroke volume
The volume of blood pumped from one ventricle with each heart beat (calculated from subtracting the end-systolic volume from the end-diastolic volume)

Sympathetic nervous system

Modulates vital functions with the parasympathetic nervous system, tending to promote a "fight or flight" response, increasing heart rate, heart muscle contractility, blood flow to skeletal muscles, dilates lung alveoli and coronary blood vessels. One of its principle neurotransmitters is norepinephrine.

Vasoconstriction

Narrowing of blood vessels through muscular vessel wall contraction, resulting in reduced blood flow due to an increase in vascular resistance. It is part of the mechanism that regulates arterial pressure

Ventricles

Chambers of the heart that receives blood from the atria to pump around the pulmonary circulation (right ventricle) or systemic circulation (left ventricle)

Appendix 2) List of abbreviations

ACEI	Angiotensin Converting Enzyme Inhibitor
ADH	Anti-Diuretic Hormone
ANP	Atrial Natriuretic Peptide
ARB	Adrenoreceptor blocker
ATII	Angiotensin II
BP	Blood pressure
BNP	B type Natriuretic Peptide
CHD	Coronary Heart Disease
CHF	Chronic Heart Failure
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
DCM	Dilated Cardiomyopathy
ECG	Electrocardiogram
EF	Ejection Fraction
FEV_1	Forced Expiratory Volume in one second
GFR	Glomerular Filtration Rate
HFNS	Heart Failure Nurse Specialist
ICD	Implantable Cardioverter Defibrillator
IHD	Ischaemic Heart Disease
LVEF	Left Ventricular Ejection Fraction
LVSD	Left Ventricular Systolic Dysfunction
NT-ProBNP	N-terminal Pro-B type Natriuretic Peptide
NYHA	New York Heart Association (functional classification)
ON	Once nightly (omni nocte)
PCR	Polymerase Chain Reaction
PEFR	Peak Expiratory Flow Rate
QDS	Medicine taken four times a day (quater die sumendus)
QOL	Quality of Life
RAAS	Renin Angiotensin Aldosterone System
RCT	Randomised Controlled Trial
SD	Standard Deviation
SE	Standard Error
TDS	Medicine taken three times a day (ter die sumendus)

Appendix 3) RCT study protocol

OPIOIDS IN THE MANAGEMENT OF BREATHLESSNESS IN ADVANCED HEART FAILURE PATIENTS

S Oxberry 25/09/07

M Johnson, D Torgerson, J Cleland, A Clark

This proposal has been developed by Dr Stephen Oxberry and Dr Miriam Johnson in collaboration with the York University Trials Unit (Professor David Torgerson) and the Hull Academic Unit of Cardiology (Professor John Cleland and Dr Andrew Clark).

1.0 Introduction

1.1 Background

Breathlessness is a defining symptom of heart failure and forms the basis of the New York Heart Association (NYHA) grading. In addition to the physical burden, it is a cause of patient distress and has a significant impact on quality of life, which is thought to be poorer than some patients with incurable cancer (1). Heart failure has become a common chronic disease in the developed world and thus this represents a large symptom burden that impacts greatly on health resources. The prevalence of heart failure is increasing with the increasing age of the population (2). Patients with advanced heart failure can still be limited by breathlessness, despite the development of therapies currently used in standard clinical practice.

The precise mechanism of breathlessness in various disease states remains unclear, though there are a number of different hypotheses (3). In addition to general mechanisms of breathlessness, it has been shown that some chronic heart failure patients also demonstrate abnormal breathing patterns (such as Cheyne-Stokes breathing or Periodic breathing) {4}. In heart failure, there is also a chronic activation of the sympathetic nervous system which is considered to be detrimental to the failing heart (5).

It has been noted that opioid receptors are located within the sympathetic nervous system, heart, lungs and brainstem (6) that may influence the sensation of breathlessness

in heart failure. Endogenous opioids are released in acute and chronic heart failure but their role is somewhat unclear. In general, opioids have an inhibitory role and it has been suggested that they may balance the sympathetic overactivity seen in heart failure (7).

Opioids or "morphine-like medicines" have been used for years in the management of pain and have a good safety profile when administered appropriately by trained healthcare professionals (8). The side effect profile is well described and can include nausea, vomiting, drowsiness, impaired concentration, constipation and itch (9). Respiratory depression, tolerance and addiction are considered to be rare particularly at low doses when prescribed appropriately (8). Parenteral administration of naloxone is considered as the treatment of overdose due to opioids if respiratory depression is sufficient to compromise respiratory function.

Opioids like morphine and oxycodone are metabolised by the liver and excreted via the kidneys. They bind to the 3 types of opioid receptor that are distributed in the body, but it is considered that morphine preferentially binds to mu-opioid receptors, whereas oxycodone has a greater affinity for kappa as well as mu receptors (10). Both the oral morphine and oxycodone preparations proposed in the study are termed immediate release, but sustained release preparations of opioids are available.

Opioids have also been used clinically in the management of breathlessness in advanced disease. A Cochrane review of 18 small placebo controlled double blind randomised trials in advanced disease populations (116 participants in total) revealed improvement in the severity of breathlessness when opioids were given by oral or parenteral administration (11). Only one of the included trials involved heart failure patients specifically (the majority of patients had cancer or chronic obstructive pulmonary disease).

Unlike breathlessness in cancer where there have been a number of studies evaluating the effects of opioids, there has only been one small pilot study of repeat dosing in heart failure patients by Johnson et al. (12). The safety of diamorphine in heart failure patients during exercise has also been demonstrated in a small study (13). Weak opioids have been shown to improve the abnormal breathing patterns seen in some heart failure patients in a pilot study (14). The paucity of research into opioids and heart failure has

been noted (15, 16). Current clinical practice either involves the prescription of morphine for breathlessness or a reluctance to use morphine without efficacy studies.

We aim to conduct a double blinded cross-over study to compare the effects of two opioids against placebo for the relief of breathlessness in advanced heart failure. Oral morphine (Oramorph) and oral oxycodone (Oxynorm) have been chosen as they do not have ceiling doses like weaker opioids (such as codeine or tramadol) and are used the most widely in clinical practice. The doses considered for oral morphine and oral oxycodone are considered to be clinically equivalent (9). Oral morphine has been chosen because of the previous pilot study and because Oramorph is specified as an unlicenced indication for the management of breathlessness in the British National Formulary (9). Oxycodone has been chosen as a common alternative to morphine in palliative medicine that has a different morphine receptor profile in humans and may have less side-effects in a patient group who may not have consistent optimal renal function (10).

Key points:

- Breathlessness is a common problem in heart failure patients which affects their quality of life.
- Opioids are already used, albeit inconsistently, in the management of breathlessness for cancer patients and COPD.
- A pilot study indicates that morphine relieves breathlessness in heart failure patients.

1.2 Primary research question:

Do morphine and oxycodone relieve breathlessness in patients with NYHA grade III/IV heart failure receiving optimal medical therapy?

2.0 Study objectives

Primary objective:

- To assess the relative benefits of oral morphine and oral oxycodone in the management of breathlessness in advanced heart failure.

Secondary objectives:

- To monitor any subsequent changes in distress caused by breathlessness, physical function, coping with breathlessness and satisfaction with treatment.
- To assess the impact of morphine or oxycodone on quality of life in heart failure.
- To confirm tolerability of therapy in this patient population and to assess relative merits of morphine versus oxycodone.
- To explore the characteristics of breathlessness in heart failure patients.

3.0 Overview of design

3.1 Design and summary treatment plan

This study is a 3-arm prospective, double-blind, randomised, placebo controlled, cross-over study involving patients with NYHA Grade III/IV heart failure receiving optimal medical therapy. The two intervention arms consist of oral morphine sulphate (5mg) and oral oxycodone (2.5mg) administered four times a day for a total of four days. At the end of the study, patients will be asked their preference, and if this is an opioid rather than placebo, they will be able to continue taking this medication after the study.

The four day intervention period is chosen to allow drug to reach steady state given that the half life of oral morphine (oramorph) and oral oxycodone (oxynorm) is between 1.5 and 4 hours. It will also allow the placebo benefit and adverse effect of sedation to return to baseline as indicated by the pilot study (12). Thereafter a three day washout period will occur before the next intervention / control to avoid a sequence effect. A generous wash out period is planned as both opioids are renally excreted.

Participants will be randomly allocated using a Latin-square pattern to receive oral morphine, oral oxycodone or placebo. All of the study drugs will be dispensed in liquid form. A schematic representation is detailed in section 3.2. A cross-over design has been chosen to reduce the number of study participants required; it is recognised that it is difficult to recruit to palliative care studies. The disadvantage of crossover studies in palliative care is that it is necessary for the patients to be stable for the duration of the study to avoid a period effect and this can be a problem with malignant disease. However, is thought that heart failure patients are more likely to be stable over the study time period.

3.2 Schedule summary

Key: A = morphine, B = oxycodone, C = placebo, W = washout period

Patient identification by treating physician or from database

↓

Eligibility criteria fulfilled

↓

Informed consent

↓

Baseline data collection

↓

Simple randomisation to 1 of the 6 following groups

↓

Days 1-4	A	A	B	B	C	C
(Daily assessment*)	↓	↓	↓	↓	↓	↓
Days 5-7	W	W	W	W	W	W
	↓	↓	↓	↓	↓	↓
Days 8-11	B	C	A	C	A	B
(Daily assessment*)	↓	↓	↓	↓	↓	↓
Days 12-14	W	W	W	W	W	W
	↓	↓	↓	↓	↓	↓
Days 15-18	C	B	C	A	B	A
(Daily assessment*)	↓	↓	↓	↓	↓	↓
Days 19-21	W	W	W	W	W	W

↓

Day 28 Follow-up / open label therapy

*Daily assessment of the patient will occur during this period with the first and last days requiring completion of face-to-face assessments with the remaining two days as telephone assessments. Please refer to section 5.5 for further details of the schedule of assessments.

3.3 Endpoints

Primary: Change in severity of breathlessness as measured by the validated Borg score and Numerical Rating Scale (NRS) for breathlessness (average and worse over past 24 hours and current level).

Secondary:
1) Distress from breathlessness as measured by the NRS score for distress.
2) Satisfaction with treatment of breathlessness and coping with breathlessness as measured by the NRS scores for satisfaction and coping with breathlessness.
3) Assessment of the overall change in breathlessness severity as measured by the Global rating of change score.
4) Assessment of the characteristics of breathlessness in heart failure patients by using the descriptors for breathlessness.
5) Adverse effects as measured by NRS scores for nausea and drowsiness, constipation assessment, use of concomitant medications and identification through self report of other events that may or may not be attributable to study drug.
6) Quality of life scores as measured by the validated SF-12 Quality of Life Questionnaire.
7) Change in validated Karnofsky performance scale of physical activity.

At the end of the study, the participants will be asked which of the three arms they prefer most and will be given the opportunity to continue that treatment in consultation with the physician on an open-label basis if an active drug is identified. Participants will be invited to return three months after cessation of the study for a repeat BNP blood sample and repeated assessment measures but this will not be compulsory. Overall, the study itself will be deemed to have finished following the final visit of the last participant.

4.0 Study population

The Academic Department of Cardiology in the Hull and East Yorkshire NHS Trust maintain a database of heart failure patients to facilitate patient screening. Patients attending heart failure out-patient clinics and in-patients will also be screened. Patients with NYHA grade III/IV heart failure on optimal medical therapy will form the study population. This group has been selected where the impact of breathlessness is high and therefore may have the most to gain from improved breathlessness management. The Academic Department is run by Professor John Cleland.

4.1 Inclusion criteria

Patients with:

- Heart failure grade NYHA III/IV with Left Ventricular (LV) dysfunction confirmed by echocardiography.
- Heart failure from any aetiology with stable NYHA status for at least one month.
- Optimal (and unchanged over previous one month) medical management of their heart failure (diuretic and ACE inhibitor/AII antagonist).
- Adequate renal clearance (using Cockroft and Gault: GFR>30ml/min)
- Aged 18 years or over.
- Provided written informed consent and able to complete patient assessments.
- An estimated prognosis of more than eight weeks.

4.2 Exclusion criteria

Patients who:

- Are unable to complete patient related information on entry.
- Have significant co-existing lung disease (e.g. COPD, Asthma, Lung fibrosis) contributing significantly to the patients' breathlessness i.e. PFR <150.
- Have co-existing malignant disease if this would affect the study in the investigators' opinion.
- Have significant renal impairment (Using Cockcroft and Gault GFR<= 30ml/min).
- Are unable to provide informed consent.

- Are involved in other medicinal trials currently.
- Have used morphine-based medications within the last month.
- Have known true morphine allergies.
- Have conditions contraindicated in the Summary of Product Characteristics (SmPCs) for Oramorph and Oxynorm, namely:
  Respiratory depression, obstructive airways disease, acute and chronic bronchial asthma, cor pulmonale, hypercarbia, acute hepatic disease, moderate to severe hepatic impairment, acute alcoholism, acute abdomen, delayed gastric emptying, chronic constipation, head injury, coma, convulsive disorders, raised intracranial pressure, paralytic ileus, severe renal impairment, known hypersensitivity to product constituents and those receiving Mono-amine Oxidase inhibitors (MAOIs) or within 2 weeks of cessation of these drugs.
- Are planning to undergo a surgical or interventional procedure, those taking a medicinal product with a known interaction with opioid based compounds, and women who are pregnant or lactating will also be excluded.

4.3 Withdrawal criteria

Patients will be withdrawn from the study on:

- Withdrawal of patient consent.
- Withdrawal of the patient by the treating physician or medical researcher due to the patient no longer meeting the eligibility criteria.

5.0 Method and procedures

5.1 Recruitment

Eligible patients will be approached following identification from the Academic Unit of Cardiology Heart Failure database. Only patients who have expressed a wish to participate in clinical trials previously or have expressed an interest when seen in clinic will be approached. An invitation letter will be sent out with details of the trial and contact details of the researcher included in the patient information sheet in the first instance. Eligible patients may also be assessed by the researcher if the treating physician

has approached the patient for possible entry into the study during routine heart failure clinic visits or on hospital wards. At a time and place that is convenient to the patient, the researcher or research nurse will be available to discuss the study further and to answer any questions that may arise from the patient information sheet. Each subject will be adequately informed of the aims, methods, anticipated benefits, potential hazards and discomforts the study may entail. The subjects' right not to participate and the right to withdraw at any time, without the need to give an explanation and without detriment to their overall treatment will be clearly stated.

Once a patient has accepted the invitation to take part, written consent will be obtained by the researcher. At least 24 hours should elapse between receipt of the patient information sheet and giving informed consent. It will be made clear that the participant will be able to withdraw consent at any time should they wish. All consent forms will be documented and stored in accordance with local Hull and East Yorkshire NHS requirements. A copy of the consent form will be given to the participant, one copy will be entered into the patients hospital notes and the original will be kept in the study file in the Academic Unit of Cardiology. The consent form for participants must be completed prior to study entry and this form contains a section requiring consent to inform the patients GP regarding entry into the study. A GP letter regarding the study and copy of the Participant Information Sheet will be sent to the GP following the consent procedure.

5.2 Randomisation

Simple randomisation of the six possible combinations of receiving treatment will occur in the Calderdale and Huddersfield NHS Trust hospital pharmacy. This is following statistical advice from Professor Martin Bland. Randomisation will usually take place at the same visit as completion of the consent form.

5.3 Blinding

This crossover study involves two active medications (oral morphine and oral oxycodone) and placebo. It is important that the participant is unaware of the order that these medications are taken in as this knowledge may bias the subsequent results. It is also important the assessor of the participant outcomes is also blinded to the order so that potential bias in recording the results can be prevented. Therefore neither the researcher,

participant or research nurse will be aware of the order of treatments. Calderdale and Huddersfield NHS Trust hospital pharmacy will be aware of the order of treatments but will label the medications so that the order cannot be deduced by the research team or participant. A copy of the randomisation codes will be kept locally in Hull and East Yorkshire NHS pharmacy so that local access to the randomisation sequence for each participant can be obtained for the purposes of de-blinding should the need arise due to adverse events. Both pharmacies will be independent to the study process.

5.4 Intervention

In this crossover trial all participants will receive oral morphine (5mg), oral oxycodone (2.5mg) and oral placebo. All of these compounds will be administered in liquid form. Given the difference in the concentrations of the interventions used each patient will take 2.5ml of liquid four times a day (morphine, oxycodone or placebo). The oral liquid placebo will be manufactured in accordance with MHRA guidelines by Calderdale and Huddersfield NHS Trust pharmacy manufacturing unit (MHRA site number: 11706). The placebo will have very similar characteristics to the active medications (a clear, colourless liquid with the same viscosity and similar taste). The formula of the placebo mixture is as follows:

Syrup BP	15% v/v
Methyl Hydroxybenzoate	0.1% w/v
Propyl Hydroxybenzoate	0.01% w/v
Citric Acid 5% soln	q.s
Distilled water	to 100% v/v

The liquid placebo will be manufactured in the Calderdale and Huddersfield NHS Trust Pharmacy Manufacturing Unit (Non-sterile product) at Huddersfield Royal Infirmary. The method of production is detailed as follows:

1. Make up the citric acid 5% solution
2. Dissolve the Methyl and Propyl hydroxybenzoate in 200ml of boiling distilled water
3. When dissolved add to the syrup in a 1 litre measure
4. Make up to volume with distilled water. Mix well. Check the pH (needs to be between 4-5). Reduce the pH using the Citric Acid solution above.

5. Pack, cap and label in a 500ml amber glass bottle with Clic Loc tamper evident cap.

For a more detailed process of manufacture and monitoring please refer to the Pharmacy Manufacturing Sheet produced by Calderdale and Huddersfield NHS Trust Pharmacy, Huddersfield Royal Infirmary, Acre Street, Lindley, Huddersfield HD3 3EA.

Placebo and active medications will be labelled by Calderdale and Huddersfield NHS Trust hospital pharmacy and transported as packs of 50ml bottles of oral oxycodone, oral morphine and placebo. Each pack will contain one bottle of each of the three medications to be taken in a randomised sequence and one pack will be given to each participant. The bottles will be placed in a plastic minigrip bag and labelled according to the guidance in Annex 13 for the Manufacture of Investigational Medicinal Products (IMP). Both the immediate containers and the outer packaging will be labelled.

Click-locked bottle adapters and tamper evident seals will be employed. These medication packs will be dispensed by Hull and East Yorkshire NHS hospital pharmacy from the controlled drug register. An expiry time of 90 days will apply to each medication pack (in accordance with the manufacturers guidelines). Opened bottles will be collected every week following use and residual medication will be measured to assess compliance.

In addition, Domperidone 10mg prn (an antiemetic) and Senna 7.5mg prn (a laxative) will be co-prescribed at the start of the trial to ensure that participants have appropriate medications in case of side effects to take as required. Eleanor Dakkak (Chief Clinical Pharmacist) and Vicki Lowthorpe (Senior Pharmacy Technician, Hull Royal Infirmary) will help us in this regard.

5.5 Measurements

Baseline assessments will be carried out by the researcher or research nurse. Some of these variables can be derived from information on the Academic Unit of Cardiology heart failure database at the discretion of the researcher. These assessments will include:

- Age and gender

- Aetiology of heart failure
- NYHA Grade
- Current medication
- Left Ventricular dysfunction on echocardiography
- Peak Flow Rate
- Serum Urea and Creatinine
- BNP (B-type Natriuretic Peptide) measurement

A blood sample will be required at baseline to assess the participants' BNP level (BNP is released by the cardiac ventricles and is raised in proportion to heart failure severity) and renal function if not done within the last month. Blood samples for BNP will be stored at -80^{O}C in the freezer in the Academic Unit of Cardiology, Castle Hill Hospital, Hull. Samples will be identified by unique trial number and participant initials. Once the study is complete, these will be transferred to Anne Anderson in the Immunoassay section of the Pathology department in Hull Royal Infirmary, Hull. The blood sample for renal function assessment will be analysed directly by the pathology laboratories in Hull Royal Infirmary. The results of these tests will be inputted onto the Academic Cardiology computer database.

Participants will be directly observed by the investigator (Dr Stephen Oxberry) for one hour after the first administration of each compound (oramorph, oxynorm and placebo). Measurements will be taken at baseline (pre-administration) and at one hour on Day 1 to assess effect and side effect profile as detailed below. The one hour observed period for each compound is to ensure that participant safety is maintained after the first dose. With this in mind, participants will be telephoned for assessments on the following two days on treatment, with a further face to face assessment on Day 4. When the researcher is not present the participant will be given a number to contact in case of any questions, queries or problems.

Palliative care patients are frequently commenced on opioid based medication on an outpatient basis without a period of observation by the clinician. This is part of routine clinical practice. The previous pilot study involving oramorph by Johnson et al (12) allowed for a similar period of one hour of observation of the trial participant. The time to clinical effect for oral oxynorm and oramorph will be observed within the first hour following administration.

As part of the study, participants will be assisted in completion of a diary card at baseline (pre-treatment), 1 hour, day 2, day 3 and day 4 for each of the three study medication periods (morphine, oxycodone and placebo). Daily assessments will occur whilst on treatment (Days 1 to 4 in each treatment period). These daily assessments include:

- Borg score for breathlessness (worst, average and current)
- 11 point Numerical rating scale of breathlessness severity (worst, average and current) and distress caused by breathlessness
- 11 point Numerical rating scale for side effects (drowsiness, nausea)
- Assessment of constipation (Do you feel constipated?: Yes/No)
- Enquiry into any further side effects
- Change in medication or use of concomitant medication

The SF-12 Quality of life score, Karnofsky performance score and physical measurements (pulse, blood pressure, respiratory rate and oxygen saturation) will be taken on days 1 and 4 of each treatment period. The requirement of additional medications (such as anti-emetics or laxatives) will be monitored and supplies of these concomitant medications will be prescribed by the medical researcher to be used as necessary. Global impression of change in breathlessness due to the study medication will be assessed on day 4 of each treatment period. A summary table of the schedule of assessments is outlined below.

Schedule of assessments

	Day 1 Baseline	Day 1 1 hour	Day 2	Day 3	Day 4
Data collection	*Visit*	*Visit*	*Phone*	*Phone*	*Visit*
Pulse Blood pressure Respiratory rate Oxygen saturation	X	X			X
NRS* breathlessness, distress, satisfaction, drowsiness, nausea	X	X	X	X	X
Constipation	X		X	X	X
Borg score**	X	X	X	X	X
SF-12***	X				X
Breathlessness descriptors****	X				X
Karnofsky performance status†	X				X
Global rating of change in breathlessness††					X
Concomitant medication	X		X	X	X
Adverse events	X	X	X	X	X

Key:

*11-point Numerical rating scale (NRS) of average breathlessness over the past 24 hours (anchored with "not breathless" and "worst breathlessness imaginable"):

0 1 2 3 4 5 6 7 8 9 10

Not breathless Worst Breathlessness Imaginable

11-point NRS of distress caused by breathlessness (17), satisfaction, drowsiness and nausea will also be completed by the participant. In addition, daily assessments of bowel function will be made.

** The Borg score, a self-assessment instrument validated for use in breathlessness (18) will be completed.

*** The SF-12 validated Quality of Life (QoL) score version 2 (19) will be assessed at baseline (pre-treatment) and day 4 for each of the three study arms.

****Breathlessness descriptors (20) used to describe the quality of a participants' breathlessness from a fifteen item questionnaire. These 15 items will be presented in a random order.

† The validated Karnofsky performance status scale (21). This scale incorporates the components of physical activity, work and self care of patients.

†† The Global rating of change score is a measurement of response to treatment (22). Participants are asked if their breathlessness has changed and if so by how much on a verbal rating scale.

Given the nature of the patient population, we have tried to incorporate the minimum number of assessments and measurements necessary so not to inconvenience the participant unduly but to monitor the effects of treatment closely. The length of the trial overall (three weeks), the nature of assessments (face to face on days 1 and 4 and via telephone on days 2 and 3) and the flexibility of the researcher in the place of assessment (clinic, hospital ward or home) reflects the consideration for participants that we have tried to incorporate into the study. We will ensure that we adhere to the Good Clinical Practice guidelines for the reporting of adverse events as set out by the Hull and East

Yorkshire NHS Trust R&D department standard operating procedures. In particular, all serious and unexpected adverse reactions (SUSARs) will be reported to the sponsor (Hull and East Yorkshire NHS Trust) who will subsequently inform co-investigators, local ethics committee and the MHRA as per guidelines. According to local policy guidelines from the sponsor (Hull and East Yorkshire {HEY} NHS Trust), a serious adverse event becomes a SUSAR (suspected unexpected serious adverse reaction) if the event is suspected (possibly, probably or definitely) to be related to the IMP and unexpected i.e. not previously documented in any of the product information (e.g. SmPC) or protocol. Within 24hrs of knowledge of event, an initial SUSAR reporting form is to be completed by the investigator, faxed to HEY Trust R & D department (01482 622368) keeping the original form in the Trial Master File. An additional SAE/SUSAR follow-up form is then to be completed by the investigator within 5 days of knowledge of event. It is the sponsors responsibility to record these details and report them as soon as possible to the licensing authority and ethics committee (not later than seven days after the sponsor was first made aware of the adverse reaction if it is lifethreatening). As sponsor, the HEY R&D department has responsibility for informing the relevant regulatory authorities.

An optional invitation to have a repeat blood test for BNP and repeat assessments (Borg score, NRS for breathlessness and side effects, breathlessness descriptors, SF-12 quality of life questionnaire and assessment of additional medications) will be made for all participants approximately three months after cessation of the initial study whether they have or have not continued to take active medication on an open label basis. Participants will be able to attend this follow-up without having to complete any participant information and the follow-up is on a purely voluntary basis.

6.0 Data management plan

A formal monthly assessment of recruitment into the study and six-weekly meetings with the research nurse to check study documentation will occur between the researcher (Dr Stephen Oxberry) and the Academic Supervisors (Dr Miriam Johnson and Professor David Torgerson). This will allow issues concerning the study to be addressed at the earliest opportunity. Reasons will be sought for missing data and recurring problems will be solved where feasible. Professor Torgerson will also arrange a Research Advisory Group at York University which will convene every six months.

6.1 Analysis plan

Primary outcome measures:

- Change in worst and average NRS- and Borg-rated breathlessness severity over the previous 24 hours and current breathlessness at time of assessment.
- Change in global rating of breathlessness at the end of each inetervention

Secondary outcome measures:

- Distress and Quality of Life.
- Change in physical function.
- Between drug comparison of effect on breathlessness.
- Between drug comparison of adverse effects.

For a description please refer to assessment schedule in section 5.5 above. The Medical Research Council (MRC) Clinical Trials Unit and the Cicely Saunders Foundation have recently recommended a one point change in Borg score or 10% improvement in Visual Analogue Score (VAS) as significant (23). In pain measurement it has been shown that a Numerical Rating Score (NRS) is easier for patients to understand and complete than a VAS (24). In breathlessness it has been shown to be highly correlated with VAS scores and more repeatable (17, 25).

6.2 Sample size

Initial assessment by a statistician of sample size using modelling techniques from the morphine pilot study suggested that a sample size of 33 evaluable patients would be required to determine a one point change in breathlessness score ($\alpha = 0.05$; $\beta = 0.8$). Further discussions with Professor Martin Bland, Professor of Statistics in Healthcare at York University led to a feasible aim for recruitment of 48 participants in order to achieve enough data for analysis allowing for a generous withdrawal rate of over 30%. This is important to allow for in studies with patients with advanced disease where withdrawal rates may be quite significant.

6.3 Statistical considerations

The clinical trial will be reported according to the CONSORT guidelines for clinical trials. Baseline data (gender, age, diagnosis distributions etc.) will be presented in tabular form. Data will be analysed according to intention to treat criteria. Statistical comparisons will compare the measurements of primary and secondary outcomes between individuals for each treatment. As the results from a crossover trial are not independent, this is likely to involve the use of non-parametric methods of comparison of outcomes between treatments, for example the Wilcoxon Signed Rank test for continuous data. Paired t-tests will be used if the data is normally distributed. McNemars test will be used for any paired dichotomous data. All of these statistical tests do not allow for period effects, as we suspect that participants will remain relatively stable over a 3 week period and the sequence of medications to be taken has been randomised. Statistical help with this crossover trial will be accessed through Professor Bland.

Missing data is a well recognised problem in longitudinal studies, particularly with patients with advanced disease. We aim to handle missing data by using extreme values. By making the assumption that the missing value is the worst it could be for the intervention and the best it could be for the placebo, if there remains a statistically significant difference between active treatment and placebo then one can be sure that the results are robust. Other techniques that we have considered involve building a regression equation to predict the value of the missing data from the baseline characteristics from patients with no missing values or the use of other imputation techniques. We will take expert statistical advice from Professor Martin Bland.

7.0 Ethical considerations

The patient population under study is a potentially vulnerable group and care should be taken not to introduce further physical, psychological or financial burden with entry into studies. However, this must be balanced with the need for good research to identify practices that are potentially beneficial or prevent practices that are unhelpful or unduly burdensome. In order to try to address some of these concerns, this study:

- Will follow Good Clinical Practice consenting and follow-up procedures
- Is being performed by a Palliative Care registrar (Dr Stephen Oxberry) as the principle researcher, with supervision by Dr Miriam Johnson (Consultant in Palliative Medicine). These physicians have considerable experience of opioid management in frail patients
- Incorporates flexibility to review participants in the setting of their choice and incorporates the use of telephone follow-up
- Re-imburses reasonable travel costs
- Is comparatively short in length (three weeks on treatment in total with optional three month follow-up) for a Cardiology study
- Will withdraw patients from the study if they become too unwell due to progression of disease or intercurrent illness
- Allows for any additional medical treatment as necessary
- Allows continuation of the treatment of most perceived benefit to that patient on an open label basis once follow-up has been completed
- Will obtain Ethics committee and Research and Development approval prior to commencement

8.0 Dissemination of findings

It is intended that the results will be disseminated in peer reviewed journals, through the local cardiology network and at national and international meetings in both palliative care and cardiology. Participants will also have the opportunity to ask for the treatment that they found most beneficial and will continue this on an open label basis.

9.0 Anticipated costs

Projected costs are as follows:

- Research nurse (F grade 3 sessions per week for 18 months) salary /superannuation /employer's NI contribution = £13,033

- Travel (patients' taxi fares, and research nurse / researcher mileage) = £4000 (this assumes 48 x 6 for taxi fares at £15 each and assumes that some assessments will be at the participant's home and mileage for the researcher / research nurse may be cheaper)
- Paper and telephone costs = £800
- MHRA application fee = £2607
- Annual MHRA service fee = £234
- Calderdale & Huddersfield Pharmacy trial set-up charge = £1400
- Pharmacy Archiving = £25
- Randomisation / medication labelling = £150
- Batch release of medication packs (based on 9 packs per batch every 3 months) = £600 = £600x5 batches = £3000
- Delivery = £30 per batch = £30x5 = £150
- Medication costs = £9.43 for oral oxycodone (oxynorm) liquid plus £1.87 for oral morphine (oramorph) liquid = 48 x 11.3 = £542
- Laxative and anti-emetic costs = to be confirmed
- Hull pharmacy storage and release fee = to be confirmed
- Cost of placebo ingredients = to be confirmed
- B-type natriuretic peptide (BNP) test and analysis = 48 x £15 = £720
- SF-12 registration and authorisation = $90US = £50

Total estimated cost = £ 26711. This will be funded through the Clinical Research Fellowship study budget.

10.0 Revised project milestones

Finalise protocol:	May 2007
Finalise study documentation:	May 2007
Confirm placebo preparation details:	May 2007
Apply to Eudract / MHRA:	July 2007
Submission to ethics and R&D committees:	July 2007
Recruit research nurse:	July 2007
Complete updated literature review:	July 2007

Research nurse commence and training given:	September 2007
Commence patient screening and entry:	September 2007
Patient recruitment at 1-2 per week:	by Sept 2008
Data entered and cleaned:	September 2008
Data analysed and written:	November 2008
Dissemination of data:	December 2008

11.0 Study reference and contact numbers

Hull And East Yorkshire Hospitals NHS Trust R&D trial number:	RO452
Eudract number:	2006-06718-13
Funding reference number (HYMS):	ZNA-502
ISRCTN:	ISRCTN85268059
Calderdale and Huddersfield NHS Trust Pharmacy reference numbers for placebo manufacture:	MIA (IMP) 19055 MHRA site 11706

Contact details for the study are as follows:

Dr Stephen Oxberry (Principle Investigator):

Carolyn Medlam (Clinical Trials Secretary) 01482 675102

Dr Miriam Johnson (Academic Supervisor): 01723 351421

Hull NHS Pharmacy 01482 675939

Hull Royal Infirmary (HRI) 01482 328541

HEY R&D department 01482 622681

Emergency Contact Number: Dr Stephen Oxberry 07949 109726

Ward 8, HRI 01482 674347

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Appendix 4) RCT sequence of events for each participant

Generate list of patients coming to NHS outpatients and screen them for eligibility

↓

Approach those patients who appear to fit the criteria on this list and assess

↓

If patient displays interest given patient information sheet

↓

Patient contacted by telephone >1 day after

↓

If agreeable, consent date arranged with opportunity to ask questions

↓

Consent date: written informed consent taken, eligibility check and BNP blood test

↓

GP letter sent, patient number assigned and prescriptions sent to pharmacy

↓

Patient notes obtained and trial documentation added to them

↓

Trial patient registered on NHS heart failure database and in Trial Master File

↓

Prescriptions collected and signed for on Week 1 Day 1 of trial & given to patient

↓

3 week trial commences – 2 days of patient visits and 2 days of telephone follow-up each week (see Appendix 5 for example of a day 1 assessment) followed by 3 day washout for each intervention

↓

Patient written folders completed alongside entries into patients hospital notes with attention to adverse events (specific procedures to follow for serious adverse events and serious unexpected adverse reactions

↓

Trial Access database completed with patient entries

↓

Progress documented on NHS heart failure database

↓

Medication bottles collected in and signed for

↓

Open label therapy to start if patient agreeable – arrange prescriptions and inform GP

↓

3 month optional follow-up for all patients (letter, visit, BNP test)

↓

Ensure all documentation (patient folders, Access database, NHS database, TMF) completed

↓

Repeat process for all patients

↓

Ensure all documentation up to date for regulatory authority inspections and complete annual assessment reports and end of trial documentation

Study number: Date:
Trial week / Visit number:

Thesis Appendix 5) Example of day 1 assessment booklet

Case Report Form (CRF): Front page

Participant ID:

Inclusion criteria check: (tick boxes to confirm)

Heart failure grade NYHA III/IV with LV dysfunction confirmed by echo ☐
Heart failure from any aetiology with stable NYHA status for at least one month ☐
Optimal (and unchanged over previous one month) medical management of their heart failure (diuretic and ACE inhibitor/AII antagonist) ☐
Adequate renal clearance (using Cockroft and Gault: GFR>30ml/min) ☐
Aged 18 years or over ☐
Provide written informed consent and able to complete patient assessments ☐
An estimated prognosis of more than eight weeks ☐

Exclusion criteria check: (tick boxes to confirm none apply)

Are involved in other medicinal trials currently ☐
Have used morphine-based medications within the last month ☐
Have known true morphine allergies ☐
Have significant co-existing lung disease (e.g. COPD, Asthma, Lung fibrosis) contributing significantly to the patients' breathlessness i.e. PFR <150 ☐
Have co-existing malignant disease if this would affect the study in the investigators' opinion ☐
Have conditions contraindicated in the Summary of Product Characteristics (SmPCs) for Oramorph and Oxynorm, namely:

Respiratory depression, obstructive airways disease, acute and chronic bronchial asthma, cor pulmonale, hypercarbia, acute hepatic disease, moderate to severe hepatic impairment, acute alcoholism, acute abdomen, delayed gastric emptying, chronic constipation, head injury, coma,

convulsive disorders, raised intracranial pressure, paralytic ileus, severe renal impairment, known hypersensitivity to product constituents and those receiving Mono-amine Oxidase inhibitors (MAOIs) or within 2 weeks of cessation of these drugs ☐

Are planning to undergo a surgical or interventional procedure ☐

Taking a medicinal product with a known interaction with opioids ☐

Pregnant or lactating women ☐

Study inclusion? **Included / Excluded**

If excluded, why? (sign & date)

Blood samples taken and dates:

Renal function:		**Date taken:**
Sodium (mmol/l)	=	
Potassium (mmol/l)	=	
Urea (mmol/l)	=	
Creatinine (micromol/l)	=	
eGFR (if available)	=	

Cockcroft and Gault calculation of GFR:

Men:

$$\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 1.23}{\text{Plasma Creatinine}}$$

Women:

$$\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 1.04}{\text{Plasma Creatinine}}$$

Calculated GFR in subject =

Study number: Date:
Trial week / Visit number:

BNP: **Date taken:**

Visit dates:

Date	**Purpose (initial / follow-up / open label visit / 3/12 follow-up)**	**Study Status (completed / ongoing / withdrawn)**	**Assessor**

Study number: Date:
Trial week / Visit number:

Eligibility assessment booklet

Study Number:

Date:

OPIOIDS IN THE MANAGEMENT OF BREATHLESSNESS IN HEART FAILURE PATIENTS

For researcher use:

Age ☐ **Heart failure aetiology** ☐

Sex ☐ **NYHA grade** ☐

Echocardiogram **Date:** ☐

Ejection fraction: ☐

Reported severity: ☐

Peak flow rate ☐ **Date:** ☐

Serum urea and creatinine ☐ **Date:** ☐

Calculated GFR (ml/min) ☐

BNP measurement ☐ **Date:** ☐

Medication

Medication	Dose	Indication	Date started if < 7 days ago

Other relevant treatment

Baseline (day 1) assessment booklet:

Trial week: (1st/2nd/3rd) ☐

Study Number: ☐

Date: ☐

OPIOIDS IN THE MANAGEMENT OF BREATHLESSNESS IN HEART FAILURE PATIENTS

Study number: Date:
Trial week / Visit number:

Section 1: For researcher use:

Resting Pulse

Blood pressure

Respiratory rate

Oxygen saturation

Medication

Medication	Dose	Indication	Date started if < 7 days ago

Other relevant treatment or concomitant medication use

Other events

Study number: Date:
Trial week / Visit number:

Section 2: To be completed by participant with assistance from researcher

Please could you give the following a score from 0 -10 by circling the number that best describes how you feel.

1. **How bad has your breathlessness felt *on average* over the past 24 hours?**

Not breathless at all	0	1	2	3	4	5	6	7	8	9	10	The worst imaginable breathlessness

2. **What is the *worst* that your breathlessness has been over the past 24 hours?**

Not breathless at all	0	1	2	3	4	5	6	7	8	9	10	The worst imaginable breathlessness

3. **How bad is your breathlessness *right now*?**

Not breathless at all	0	1	2	3	4	5	6	7	8	9	10	The worst imaginable breathlessness

4. **How much *distress* has your breathlessness caused you on average over the past 24 hours?**

No distress at all	0	1	2	3	4	5	6	7	8	9	10	The worst imaginable distress

5. **How well have you *coped* with your breathlessness on average over the past 24 hours?**

I have not coped at all	0	1	2	3	4	5	6	7	8	9	10	I have coped very well

6. **How *satisfied* have you felt with the treatment you have received for your breathlessness?**

Not satisfied at all	0	1	2	3	4	5	6	7	8	9	10	Completely satisfied

Study number: Date:
Trial week / Visit number:

7. How bad has any nausea been *on average* over the past 24 hours?

No nausea at all | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The worst imaginable nausea

8. How bad has any drowsiness/sleepiness been *on average* over the past 24 hours?

No drowsiness at all | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The worst imaginable drowsiness

9. Do you feel constipated?

Yes / No

10. Is there anything else you would like to mention that has not been covered already?

Borg scale (1)

Please circle the number that best describes your shortness of breath *at its worst* over the past 24 hours

0	**Nothing at all**
0.5	**Very, very slight (just noticeable)**
1	**Very slight**
2	**Slight**
3	**Moderate**
4	**Somewhat severe**
5	**Severe**
6	
7	**Very severe**
8	
9	**Very, very severe (almost maximal)**
10	**Maximal**

Study number: Date:
Trial week / Visit number:

Borg scale (2)

Please circle the number that best describes your shortness of breath, on average, over the last 24 hours.

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Borg scale (3)

Please circle the number that best describes your shortness of breath *at this moment*

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Study number: Date:
Trial week / Visit number:

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please tick the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

		Yes, limited a lot	Yes, limited a little	No, not limited at all
A	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
B	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

Study number: Date:
Trial week / Visit number:

3. **During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Study number: Date:
Trial week / Visit number:

6. **These questions are about how you feel and how things have been with you <u>during the past week</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past week</u>...**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Study number: Date:
Trial week / Visit number:

Breathlessness descriptors

Please tick THREE of the following statements that BEST reflect how your breathing feels *right now*. Carefully consider the three statements that apply most. Please do not choose more than three.

1. My breathing is shallow
2. My chest is constricted
3. I feel out of breath
4. My breathing requires effort
5. My chest feels tight
6. My breath does not go in all the way
7. My breath does not go out all the way
8. I feel hunger for more air
9. I feel that I am suffocating
10. My breathing requires more work
11. I cannot get enough air
12. I feel that my breathing is rapid
13. I feel that I am being smothered
14. I feel that I am breathing more
15. My breathing is heavy

Study number: Date:
Trial week / Visit number:

Karnofsky Performance Scale:

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most of their needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalisation necessary; active supportive treatment is necessary
20	Very sick; hospitalisation necessary; active supportive treatment is necessary
10	Moribund; fatal processes developing rapidly
0	Dead

OPIOPHOBIA – ATTITUDES TO MORPHINE IN HEART FAILURE PATIENTS

Authors: **Dr Stephen Oxberry**
Dr Lesley Jones
Dr Miriam Johnson

Contents:

OPIOPHOBIA – ATTITUDES TO MORPHINE IN HEART FAILURE PATIENTS

15th January 2008

1. Overview:

This protocol proposal has been produced by Dr Stephen Oxberry with assistance from Drs Miriam Johnson and Lesley Jones at Hull York Medical School and Professor David Torgerson at the University of York. It will form part of a PhD project funded by a Clinical Research Fellowship by Hull York Medical School awarded to Dr Oxberry. Opioid ("morphine-like") medications are increasingly being used for symptom management in non-malignant conditions. We intend to discover whether heart failure patients would find the use of opioid medication acceptable, what patients already understand about their use and what fears or anxieties they may have, and how information regarding their use can be best targeted.

2. Background:

Opioids in healthcare

Opioids or "morphine-like" medicines conjure a variety of different thoughts in the minds of both medical and lay people. Opioid use can be associated with addiction, dependence, side effects and thoughts of the consequences of non-prescription opioid drugs such as heroin. These ideas can often prevent the clinical use of opioids by medical professionals (Bennett and Carr 2002) despite increasing evidence that controlled informed use of these medicines is both justified and has a good safety profile.

Opioids are most commonly employed in the sphere of pain management, particularly with advancing disease. The Barriers Questionnaire (Ward et al. 1993) was devised to demonstrate the reasons why patients were reluctant to report pain or use medicines such as opioids that are utilised in more severe pain states. Themes that emerged from this and other works in cancer patients included: addiction and tolerance to analgesics; saving a drug until the pain becomes much worse; medication side effects; fatalism (pain is to be

expected); "good" patients don't complain; increased pain may indicate disease progression; discussing pain may detract from trying to cure the disease; strong painkillers require injections. From our own work in palliative medicine patients with cancer, we noted that addiction and fear that opioids may mask important changes in a disease were the most common anxieties expressed. This small pilot questionnaire based study also highlighted that knowledge of opioids is generally quite poor and that most patients derive their knowledge about these medicines from their own experience rather than from patient information leaflets (Lambert et al. 2007). Many other articles have described why some healthcare professionals have a reluctance specifically for opioid prescribing ((Elliott and Elliott 1992; Zenz and Willweber 1993; Zenz et al. 1995; Wells et al. 2001).

However, the role of opioids in symptom management is changing. There is increasing evidence to suggest that opioids are useful in the management of breathlessness and cough (Jennings et al. 2001; Morice et al. 2007). This expands the use of opioids in palliative medicine from the treatment of pain typically in cancer patients, to the management of breathlessness and cough in both cancer and non-cancer patients, such as those with cardiac and respiratory disease.

Palliative care and heart failure

It has been recognised that palliative care should not be restricted to just oncology patients, but that a number of different life threatening chronic conditions (such as heart failure, chronic obstructive airways disease etc.) can be managed using palliative care principles as the condition advances. The prevalence of heart failure is increasing (Thomas and Rich 2007) and the prognosis of heart failure patients is likened to that of many advanced cancers (Stewart et al. 2001). Heart failure patients with chronic advancing disease often experience a multitude of physical symptoms, including breathlessness, pain and fatigue, in addition to non-physical symptoms including loss of role/independence, reduced quality of life and mood disturbances (Barnes et al. 2006). The disease trajectory is often difficult to predict with acute exacerbations of symptoms punctuating a variable chronic disease course. The impact of heart failure on daily physical function is assessed by the New York Heart Association (NYHA) grading of

heart failure severity. It assesses the restriction of patient activity by breathlessness and fatigue (Grade 1 indicating no limitation on activity, Grade 4 indicating symptoms at rest).

Murray et al (2002) compared the experiences of 20 advanced lung cancer and 20 advanced heart failure patients through qualitative interviews. They demonstrated that heart failure patients tended to focus on the stresses of balancing and monitoring a complex drug regimen; had poor knowledge of diagnosis and prognosis; and experienced frustration, progressive losses and social isolation. This was in contrast to the lung cancer patients who were more pre-occupied with facing death and had greater access to social and financial resources. Rogers et al (2002) confirm some of these themes using qualitative interviews in heart failure patients. They also found that patients generally had little knowledge about the medications they were taking, and how use of the medications related to the symptoms they described. Willems et al (2004) expand on this work using semi-structured interviews in 31 advanced heart failure patients. They demonstrated that patients with advanced heart failure tended only to consider the prospect of dying during episodes of acute decompensation. Rogers et al (2000) noted that there were barriers to effective communication between clinicians and heart failure patients.

It is likely in the next few years that opioids will be used more widely to manage pain, breathlessness and cough in advanced heart failure populations. To date, there is little evidence to describe how acceptable this will be to this patient population and what beliefs, attitudes and existing knowledge these patients have.

Key points:

- Attitudes to opioids in both medical and lay circles centre around a number of pre-conceived ideas, based on patient experiences that are often unfounded given the current clinical use of opioid medicines – leading to "opiophobia".
- Overall, knowledge about opioids in cancer patients currently or previously using these medicines is generally quite poor.
- When compared to cancer patients, heart failure patients have a poorer knowledge of their diagnosis and prognosis and their focus is directed towards monitoring a complex drug regimen.

3. Research Aims:

To explore the beliefs about and acceptability of opioid medication use held by patients with heart failure. In particular:

- How acceptable is the use of opioids in the management of symptoms (especially breathlessness) to heart failure patients already in receipt of complex polypharmacy?
- What are the specific anxieties regarding potential opioid use in this patient group?
- What beliefs concerning the use of opioids already exist in heart failure patients?
- What hopes do heart failure patients have for opioid therapy?
- How has information about medicines (including opioids) been obtained by this patient group?

4. Design:

Qualitative data will be derived from the use of semi-structured interviews in twenty heart failure patients. A topic guide of key themes will be used to guide the researcher during the interview. This is outlined in the Appendix.

4.1 Sample:

A theoretical sample of symptomatic chronic heart failure patients will be used for this qualitative trial. All potential participants will be known to the Academic Department of Cardiology and classified NYHA Grades II, III or IV. This sample of patients has been chosen as they are the most likely group to have prescription of opioids in the future and may have considered the potential use of medicines for symptoms. Participants involved in the ongoing randomised controlled clinical trial involving opioids for breathlessness will not be approached. These patients will have read the participant information sheet for this trial and may therefore have a different experience to those patients who have not be approached or enrolled into the RCT.

Heart failure patients will be approached by invitation letter following identification and screening by use of the Academic Department of Cardiology computer database of heart failure patients. It may be that these patients are also known through the Heart Failure Nurse Specialist Service and eligible patients can be approached with an invitation letter via these nurse specialists. Included in this correspondence will be a copy of the participant information sheet and consent form for the patient to review. Potential participants will have the opportunity to contact the research team or Academic Department of Cardiology trials secretary directly if they express an interest or if they wish to decline the invitation. If this has not occurred within one week, the researcher will contact the potential participant by telephone to find out if the patient requires any additional information or if they wish to discuss the study in more depth. At all times during this process the researcher will be available to answer questions either via telephone or face to face.

It is anticipated that participants will be asked to perform the semi-structured interview during their next heart failure clinic attendance. This will allow the minimum inconvenience to the participant. Alternatively, the interviews can occur on hospital wards or in the participants' home, whichever is most convenient to the participant as long as a quiet area is found free from interruption.

Informed consent may be taken on the day of the interview to minimise inconvenience to the participant if it is deemed appropriate by the researcher. It is recognised that this is a potentially frail population who may experience undue burden if repeated visits are necessary. However, in general, written informed consent will be taken at least 24 hours after participant invitation. The original consent form will be kept in the trial site study file, with copies of the signed consent form given to the participant and entered into the participants' hospital notes. It will be made clear to the participant they will be free to withdraw consent at any time.

No formal sample size has been calculated for this qualitative study, but we suspect that theoretical saturation of both the coding and collection of data will be achieved with twenty participants. It is considered that twenty participants involved in single semi-structured interviews is an adequate number considering the nature of the topic,

experience of the interviewers and quality of the data obtained (Morse 2000). The topic guide for the interview has been reviewed by volunteers from the Scarborough-Whitby-Ryedale Heart Failure Patient Support Group.

4.2 Inclusion, exclusion and withdrawal criteria:

Inclusion criteria:

Patients who:

Are known to the Hull and East Yorkshire Academic Cardiology Heart Failure Service.

Have a diagnosis of NYHA grade II, III or IV heart failure of any aetiology.

Are aged 18 years and over.

Are able to complete written informed consent and semi-structured interview.

Exclusion criteria:

Patients who:

Are unable to complete informed consent or semi-structured interview without assistance.

Have known true allergies to opioids (morphine-like medicines).

Have been approached or are participating in the concurrent randomised controlled trial (RCT) involving opioids in heart failure.

Have previously stated not be approached for consideration for research trials.

Withdrawal criteria:

Participants will be withdrawn from the study on:

Withdrawal of participant consent.

Withdrawal of the participant by the treating physician or medical researcher due to the patient no longer meeting the eligibility criteria.

4.3 Sources of data:

Once the participant has been enrolled into the study background data will be collected. This will include age, gender, NYHA status and date of diagnosis. This demographic data will be obtained from Academic Cardiology Heart Failure database. Participants will each be assigned a unique identification number for the trial. Dr Stephen Oxberry will hold the list of numbers matched to each participant and this information will remain confidential.

A topic guide will be used by the researcher as a framework for the semi-structured interview. The interview itself will be conducted in a quiet area and will involve the participant and interviewer only. If the participant wishes, a friend or family member will be allowed to observe the interview, however it will be made clear that the views of the participant alone are of interest to this current study. Provision will be made after the interview to discuss any issues raised and at this point carers, friends or family can become involved in any subsequent discussions should the participant wish. Interviews will be tape-recorded and professionally transcribed verbatim. The transcriber will not have access to participant details except for the unique identification number assigned to that participant. Contemporaneous notes of any particular items of importance, conduct of the interview and physical characteristics not likely to be identified by voice alone will be made immediately following the interview process by the interviewer. Both the taped interview transcript and notes taken regarding the conduct of the interview will be drawn together by the research team to identify and gain consensus regarding the key themes that emerge. All interviewee responses and notes will be anonymised and confidential. The audio tape interviews will be retained in a locked storage unit in the Department of Academic Cardiology, Hull and East Yorkshire NHS Trust once transcription of the interview has occurred. These audio tapes will be kept for the duration of the study and then deleted. Transcripts of the interviews will not be sent to the participant, but an executive summary of the key points raised by the study will be sent out by post to the participant. A summary of the study outline for the participant is detailed below:

Those patients who meet eligibility criteria on the Academic Cardiology Heart Failure database approached by invitation letter

↓

Researcher contacts patient after one week to confirm interest

↓

Meeting with researcher set up at patient's convenience to answer questions

↓

Written informed consent taken

↓

Semi-structured single interview taking no longer than 30 minutes using tape recorder with opportunity to discuss or ask further questions about points raised thereafter

↓

Participant data anonymised and collated

↓

Study conclusions disseminated to participants via letter and written up in peer reviewed journal and for conferences

5. Data management plan:

A formal monthly assessment of recruitment into the study and six-weekly meetings to check study documentation will occur between the researcher (Dr Stephen Oxberry) and the Academic Supervisors (Dr Miriam Johnson, Dr Lesley Jones and Professor David Torgerson). This will allow issues concerning the study to be addressed at the earliest opportunity. Professor Torgerson has also arranged a Research Advisory Group at York University which meets every six months as part of the overall PhD project incorporating the RCT, Qualitative work and Thesis production.

Data obtained from the interview process will be analysed according to the principles of modified Grounded theory. One definition of Grounded theory is "theory that was derived from data, systematically gathered and analysed through the research process. In this method, data collection, analysis and eventual theory stand in close relationship to one another" (Strauss and Corbin 1998). The topic guide has been produced to investigate themes that we consider may be important to heart failure patients. However, in accordance with the process of Grounded theory, themes that emerge from the interview data will be sought and subsequent participant interviews may be refined to take any new concepts or themes into account.

The data collected will be broken down into component parts and given identifiable names (coding). Open coding of data will be utilised to yield concepts and categories. Coding will occur alongside data collection to allow changes in emphasis in the topic guide to be made where necessary. Formal theory will be generated from exploration of these concepts and categories allowing the formation of subsequent hypotheses by the researcher and Academic supervisors.

6. Dissemination:

Results from the study will be disseminated locally in the Academic Cardiology Department in Hull, in peer reviewed Cardiology or Palliative Medicine literature and at national and international conferences. Participants will have the opportunity to ask questions of any topics that emerge at the time directly after the interview. In addition, a short summary sheet of the findings of the research will be posted out to the participants to their home address at the completion of the study.

7. Ethical issues:

The patient population under study is a potentially vulnerable group and care should be taken not to introduce further physical, psychological or financial burden with entry into studies. However, this must be balanced with the need for good research to identify issues that may enhance or inhibit good patient care. In order to try to address some of these concerns, this study:

- Will follow Good Clinical Practice consenting procedures
- Is being performed by a Senior Palliative Care registrar (Dr Stephen Oxberry) as the principle researcher, with supervision by Dr Miriam Johnson (Consultant in Palliative Medicine). These physicians have considerable experience of both opioid management and sensitive discussions with frail patients
- Incorporates flexibility to review participants in the setting of their choice as long as confidentiality can be maintained and the setting is as free from potential interruption as possible

- Re-imburses reasonable travel costs
- Is a single 30 minute interview rather than a series of lengthy interviews or questionnaires
- *Will withdraw patients from the study if* they request
- Will obtain Ethics committee and *Research and Development approval prior to* commencement

8. Project milestones:

Finalise protocol	October 2007
Complete updated literature review	September 2007
Ethics submission	January 2008
Commence patient recruitment	March 2008
Complete patient recruitment	March 2009
Complete write-up	May 2009
Dissemination of results	June 2009

9. Project team:

Dr Stephen Oxberry: Cardiology Clinical Research Fellow / Specialist Registrar in Palliative Care / PhD student at Hull York Medical School.
Email oxbs@yahoo.co.uk; Mobile 07949 109726.

Dr Miriam Johnson: Senior Lecturer in Palliative Medicine, Hull York Medical School, Hull University.
Prof David Torgerson: Director York Clinical Trials Unit, York University.
Dr Lesley Jones: Senior Lecturer in Social Sciences, Hull York Medical School, York University.

10. Anticipated costs:

Written transcription costs of each interview:	20 x £15 = £300
Travel costs (patient taxi fares / researcher mileage):	20 x £15 = £300
- assumes taxi fares at £15 return	
Paper & telephone costs	£200

These costs will be funded through the Clinical Fellowship research budget.

11. References:

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Appendix:

Topic guide:

Medicine use

Probes: Tell me about the medicines you're taking for your heart / heart failure

Where do you go to get information about your medicines? (Doctor, nurse, media, friends, family, internet?)

How could your knowledge about medicines be improved (and would this be of benefit to you)?

Would you regard yourself as being good at taking medicines everyday? Why?

What would prevent you from taking a medicine every day?

General Condition

Probes: How much does your heart failure trouble you?

Is breathlessness / pain / cough a particular problem? What do they prevent you from doing if anything?

If morphine could help people feel less breathless, would this be useful for you? Why, what difference would it make to you?

Anxieties concerning opioids

Probes: What does the word "morphine" make you think of?

Does the term or word "morphine" put you off?

Would you have any concerns about taking morphine if it was offered?

Would you worry about side effects? What sort of side effects have you heard of?

Would you be concerned to receive morphine-like medicines on a long term basis if you found them helpful?

Is there anything that might stop you from taking morphine even if you thought it might help you?

Beliefs regarding opioids

Probes: What is your previous experience of morphine-like medicines? (Own, Family & Friends). Have you come across morphine medicines before, either yourself or someone you know?

What was the setting and was it a good or bad experience?

Do you think morphine medicines should be used for patients... if so – in what situations?

Have you ever thought that morphine-like medicines could be helpful in heart failure?

Hopes concerning opioids

Probes: From what you know about morphine-like medicines, do you think they would have any helpful effects? Would this help you?

Close

Any questions or comments

Thanks

Appendix 7) Financial costs of the trials: Estimated and Actual

Expediture	Predicted cost (£)	Actual cost (£)
Research nurse salary through Academic Cardiology	*13033*	5097
Travel: taxi's researcher mileage	*3500* *500*	290 2457
Paper / Telephone / Postage / Laptop / Documents	*1000*	873
Study equipment (Pulse oximeter, SF-12 purchase)	*215*	219
MHRA application & ISRCTN registration	*2996*	2810
Huddersfield Pharmacy manufacture (set-up fee, archiving, randomisation, batch release, delivery, drug constituents)	*4875*	2835
Hull pharmacy costs (dispensing fee, set-up fee, temperature recording, concomitant medications)	*830*	830
BNP laboratory analysis	*720*	1020
Transcription costs for qualitative trial	*300*	489
Archiving	*0*	150
Total	*27969*	17070

Please see the protocols for a more complete analysis of expected costs prior to study commencement. The researcher's salary was not included in the study budget and is therefore excluded. The study budget was generously donated as part of the clinical trial fellowship through Hull York Medical School. Trial costs were less than predicted, mostly due to the savings in nurse salary and Huddersfield manufacturing costs. Research nurse time was invaluable for maintenance of study procedures, but more assessments than originally predicted were performed by the researcher. In addition, medication delivery delays meant that a significant saving was made in these costs, as a reduction in these prices was negotiated.