Is pacemaker-induced cardiac dysfunction progressive and reversible in patients receiving long-term pacemaker therapy?

Volume 1

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Intellectual Property and Publication Statements:

The candidate confirms that the work submitted is her own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

The following Chapters have resulted in jointly authored publications:

Chapter 2: **The detrimental effects of right ventricular pacing**

I performed and authored the literature review which was then reviewed and edited by Dr Klaus Witte prior to publication. I also co-authored the review of pacemaker battery longevity.

Relevant publications:

Rosling KB and Paton MF. Pacemaker longevity: understanding what drains the battery. British Journal of Cardiac Nursing. 2019;14(6):1-9.

Paton MF, Witte KK. Heart failure and right ventricular pacing–how to avoid the need for cardiac resynchronization therapy. Expert review of medical devices. 2019;16(1):35-43.

Chapter 6: Optimising pacemaker and medical therapy for heart failure in pacemaker patients – the OPT-PACE randomised trial

I co-ordinated and managed the study, as well as providing echocardiography and pacing investigations, data collection, blinding, assistance with statistical analysis and coding. I authored the trial methods article, and the results

manuscript which is under co-author review, and have presented preliminary findings.

Relevant publication:

Paton MF, Gierula J, Jamil HA, Lowry JE, Byrom R, Gillott RG, et al. Optimising pacemaker therapy and medical therapy in pacemaker patients for heart failure: protocol for the OPT-PACE randomised controlled trial. BMJ open. 2019;9(7):e028613.

Chapter 7: Personalised reProgramming to prevent Pacemaker associated left ventricular Remodeling (PPPR)

I designed and led the trial, performing day-to-day trial management. I undertook diagnostic investigations and patient assessment, data collection and data analysis. I was the lead author on the manuscript which is currently under peer review.

Relevant publications:

Paton MF, Gierula J., Lowry, JE., Cairns, DA., Bose Rosling, K., Cole, CA., McGinlay, M., Straw, S., Cubbon, RM., Kearney, MT., and Witte., KK. A randomised clinical trial of Personalised reProgramming to prevent Pacemaker-induced left ventricular Remodelling (PPPR). European Heart Journal 2020;Under Review.

Paton MF, Gierula J, Lowry J, Byrom-Goulthorp R, Cubbon R, Kearney M, et al. Reprogramming to Prevent Progressive Pacemaker-induced Remodelling. Journal of the American College of Cardiology. 2020;75(11 Supplement 1):314.

Dedication

This thesis is dedicated to my family; Michael and Caroline Paton, Annabel and Andy Daly, Norma Baguely and Jonathan and Bessie Boyes. Throughout my doctorate they have provided much needed love, support, perspective and laughter, for which I will be forever grateful.

I am also indebted to all my colleagues in the heart failure research team, particularly Dr Klaus Witte and Dr John Gierula, who from the beginning of my research journey, have shown great kindness in their donations of both time and support to channel my passion and help me build a career I love.

This year in particular has shown me the importance of family and friends, all of whom I wouldn't be in the position I am today without.

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Abstract

Permanent pacemakers remain the sole treatment for symptomatic bradycardia. There is consensus that pacemaker patients are at increased risk of adverse cardiac remodelling and heart failure (HF). Stratification of patients' risk of pacemaker-associated impairment, understanding progression and whether it is reversible, may allow life-extending treatment earlier.

An observational study was performed in 573 who participated in a baseline study between 2008-2012. During 74 months of follow-up, 45% of returning patients (164) experienced a worsening in their left ventricular ejection fraction (LVEF) of >5%. Patients who experienced a HF event (92(18%)) had more RV pacing, a lower ejection fraction, ischaemic heart disease, and higher incidence of atrial fibrillation.

Post-hoc data exploration on the surviving patients to investigate device and patient derived predictors of estimated pacemaker battery longevity revealed clinical characteristics had no bearing on estimated battery longevity, but that a number of device variables were predictive.

A prospective randomised trial of 1800 patients implanted with a bradycardia pacemaker assessed the efficacy on clinical outcomes of screening echocardiography to identify LV systolic dysfunction (LVSD). One third of patients had undiagnosed LVSD, and subsequently achieved optimal

medical management in a multi-disciplinary HF service. This has the potential for long-term favorable outcomes beyond standard care.

Finally, a randomised double-blind trial of 100 patients with bradycardia pacemakers allocated to personalised programming to reduce unnecessary right ventricular (RV) pacing, or usual care showed at 6 months, patients receiving personalised reprogramming had a reduction in RV pacing, improvements in LVEF and preserved battery longevity with no detriment to their quality of life.

In summary, RV pacing can cause or worsen LVSD, which can continue to decline, particularly in the presence ischaemic heart disease, atrial fibrillation, and high RV pacing burden. Personalised device prescription and programming can maximise device longevity, reduce RV pacing and improve LV function.

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Bibliography

Below is a list of publications I have authored or co-authored that are directly related to my doctoral research.

Paton MF, Gierula J., Lowry, JE., Cairns, DA., Bose Rosling, K., Cole, CA., McGinlay, M., Straw, S., Cubbon, RM., Kearney, MT., and Witte., KK. A randomised clinical trial of Personalised reProgramming to prevent Pacemaker-induced left ventricular Remodelling (PPPR). European Heart Journal 2020;Under Review.

Paton MF, Gierula J, Lowry J, Byrom-Goulthorp R, Cubbon R, Kearney M, et al. Reprogramming to Prevent Progressive Pacemaker-induced Remodelling. Journal of the American College of Cardiology. 2020;75(11 Supplement 1):314.

Paton MF, Gierula J, Jamil HA, Lowry JE, Byrom R, Gillott RG, et al. Optimising pacemaker therapy and medical therapy in pacemaker patients for heart failure: protocol for the OPT-PACE randomised controlled trial. BMJ open. 2019;9(7):e028613.

Rosling KB and Paton MF. Pacemaker longevity: understanding what drains the battery. British Journal of Cardiac Nursing. 2019;14(6):1-9.

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Chapter 1

Introduction to pacemaker therapy

1.1 Introduction

Cardiac implantable electronic devices (CIEDs) are valuable tools in the treatment of a variety of cardiac arrhythmias (Haghjoo, 2017). Permanent pacemakers are a specific type of CIED which have been the most effective treatment for bradycardia for at least four decades (Epstein et al., 2013). Around 350,000 people in the UK currently have an implanted pacemaker, with another 40,000 receiving a new system per year (NICOR, 2016). Pacemakers are most commonly implanted for sinus node disease (SND) and atrioventricular conduction disturbances (AVB) (Mond and Proclemer, 2011a). In developed countries the preferred system is a dual chamber device with both atrial and ventricular endocardial pacing leads positioned in the right atrium and in the right ventricular (RV) apex respectively (NICE, 2017).

Advances in both pacemaker hardware and software have improved implantation ease and long-term patient management (Mond, 1999, Berger et al., 2003, Murgatroyd et al., 2010, Savoure et al., 2005). As a result, complications arising from pacemaker insertion are low, but there is growing consensus that in addition to the long-term risks associated with pacemaker generator replacement and longer term lead failure, pacemaker patients are at higher risk than the normal population of adverse cardiac remodelling and

left ventricular systolic dysfunction (LVSD), associated with the development of heart failure and a worse clinical outcome (Thackray et al., 2003, Sweeney and Prinzen, 2006, Gillis, 2006, Sweeney et al., 2003, Wilkoff et al., 2002, Tops et al., 2006).

It has been hypothesised that the mechanism underlying the detrimental effect of pacemaker therapy is abnormal electrical and mechanical activation of the myocardium caused by RV apical pacing (Tse and Lau, 1997b, Lieberman et al., 2006, Prinzen et al., 1999). However, not all pacemaker patients develop LVSD, with most reports suggesting a prevalence of between 30 and 40% (Gierula et al., 2015). Moreover, most of these reports have been cross-sectional observational studies such that the incidence and progression of cardiac dysfunction are poorly understood. It is also unclear if any clinical variables may be used to predict the presence, onset or progressive deterioration of cardiac dysfunction. Identification of such clinical variables to allow risk stratification of pacemaker patients, would therefore create important opportunities to initiate targeted, personalised interventions to promote improved patient quality of life and survival.

1.2 Indications for bradycardia pacing

1.6.1 International Guidelines

Joint guidelines pertaining to the appropriate indications for pacemaker therapy are published by the American College of Cardiology (ACC), American Heart Association (AHA) and Heart Rhythm Society (HRS) (Kusumoto et al., 2019), and there are largely comparable guidelines from

the National Institute for Health and Care Excellence (NICE) (NICE, 2014b) and European Society of Cardiology (ESC) (Brignole et al., 2013b).

Recommendations	Class [a]	Level [b]	Ref. [c]
1) Sinus node disease. Pacing is indicated when symptoms can clearly be attributed to bradycardia.	I	B	1, 6–9
2) Sinus node disease. Pacing may be indicated when symptoms are likely to be due to bradycardia, even if the evidence is not conclusive.	IIb	C	-
3) Sinus node disease. Pacing is not indicated in patients with SB which is asymptomatic or due to reversible causes.	III	C	-
4) Acquired AV block. Pacing is indicated in patients with third- or second-degree type 2 AV block irrespective of symptoms.	I	C	-
5) Acquired AV block. Pacing should be considered in patients with second-degree type 1 AV block which causes symptoms or is found to be located at intra- or infra-His levels at EPS.	IIa	C	-
6) Acquired AV block. Pacing is not indicated in patients with AV block which is due to reversible causes.	III	C	-

Figure 1.1 – Indication for pacing in patients with persistent bradycardia (taken from (Brignole et al., 2013b) AV = atrioventricular; EPS = electrophysiological study; SB = sinus bradycardia. [a]Class of recommendation. [b]Level of evidence. [c]Reference(s) supporting recommendation(s)

The recommendations are endorsed with both a class of recommendation (COR), which demonstrates its strength in terms of the estimated benefit in relation to risk, and a level of evidence (LOE) which highlights the scientific quality of evidence supporting the suggestion.

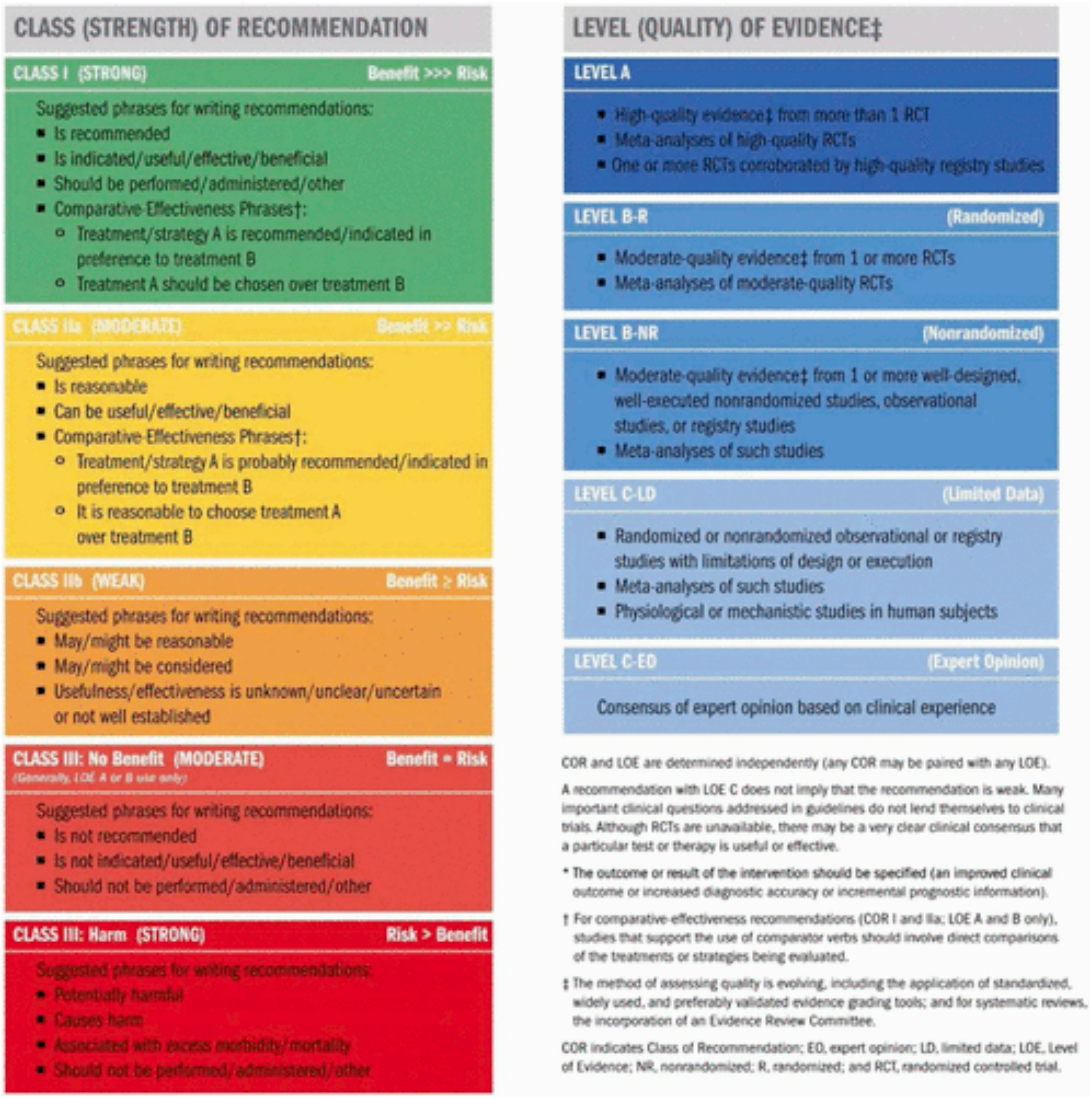


Figure 1.2. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, of Diagnostic Testing in Patient care (Updated August 2015) (taken from (Halperin et al., 2016)).

The guidelines are useful when determining the therapeutic options for bradyarrhythmia, but the clinical context should be taken into account. For example, in general, bradyarrhythmia is only an indication for pacing in the presence of symptoms which may become more frequent or severe with exertion (Brignole et al., 2013b). Inherently, the body of evidence surrounding pacing for bradyarrhythmia stems from historical research performed during the introduction of clinical pacing, therefore the effectiveness of pacing is sometimes inferred rather than confirmed in clinical trials (Breivik et al., 1979, Rasmussen, 1981, Sasaki et al., 1988).

1.2.2. Atrioventricular block

Untreated AVB can result in HF or death due to low cardiac output, or bradycardia-induced ventricular tachyarrhythmias or asystole (Ellenbogen et al., 2016). A number of observational studies and one randomised placebo-controlled trial have confirmed that pacemaker therapy counteracts syncope and improves survival (Edhag, 1969, Friedberg et al., 1964, Johansson, 1966) and is therefore recommended even in asymptomatic patients.

There is ongoing debate about the efficacy of dual chamber pacing in patients with prolonged first degree AVB and type 1 second degree AVB to normalise the PR interval, thereby reproducing atrioventricular synchrony. Some benefit has been suggested in limited uncontrolled trials (Barold, 1996, Brecker et al., 1992, Carroz et al., 2010). Although patients with extended QRS durations on their electrocardiogram (ECG) are more likely to

progress to more extensive AVB (Donoso et al., 1964, Ranganathan et al., 1972), the evidence remains inconclusive.

Ultimately, even though the evidence remains modest, there is strong expert consensus that patients with type two second degree or third degree AVB should receive cardiac pacing. In patients with type one second degree AVB, type one, there is less agreement and so the extent and correlation to symptoms should be contribute to the decision (Brignole et al., 2013b).

1.2.3. Sinus Node Disease

There is no proven survival benefit of cardiac pacing in patients with sinus node disease (SND). Pacing is currently indicated to relieve symptoms only (ESC), making it essential to establish a correlation between bradyarrhythmia and symptoms. However, one study has exposed a paradox of pacing for SND. In a controlled, prospective study of 470 patients over 60 years old with asymptomatic bradycardia compared to 2090 patients without bradycardia, pacemaker implantation occurred more frequently in those with symptomatic bradycardia, but didn't have an effect on all-cause mortality, which may suggest there may be a beneficial effect of pacemaker implantation (Goldberger et al., 2011).

Pacing as a treatment for SND should therefore be considered on an individual patient basis. For example, in a decision to undertake pacemaker implantation for SND, one needs to take into account the patient's level of training and heart rate limiting medical therapy.

1.3 Epidemiology of Pacing

Whilst there are degrees of variation geographically, pacemakers are the most commonly implanted electronic device worldwide (Brignole et al., 2013b). Due to the relationship between ageing and arrhythmia (mostly atrial fibrillation), and conduction system disease (Chow et al., 2012), rates of pacemaker insertion increase exponentially with age, with most (70-80%) implanted in people aged over 65 years old (Aronow and Gregoratos, 1999). Hence, in most Western societies with their ongoing ageing demographic (Gerland et al., 2014), pacemaker implantation rates have persistently risen (Figure 1.3) (Mond, 2001, Bradshaw et al., 2014a, Mond and Proclemer, 2011b, Raatikainen et al., 2015).

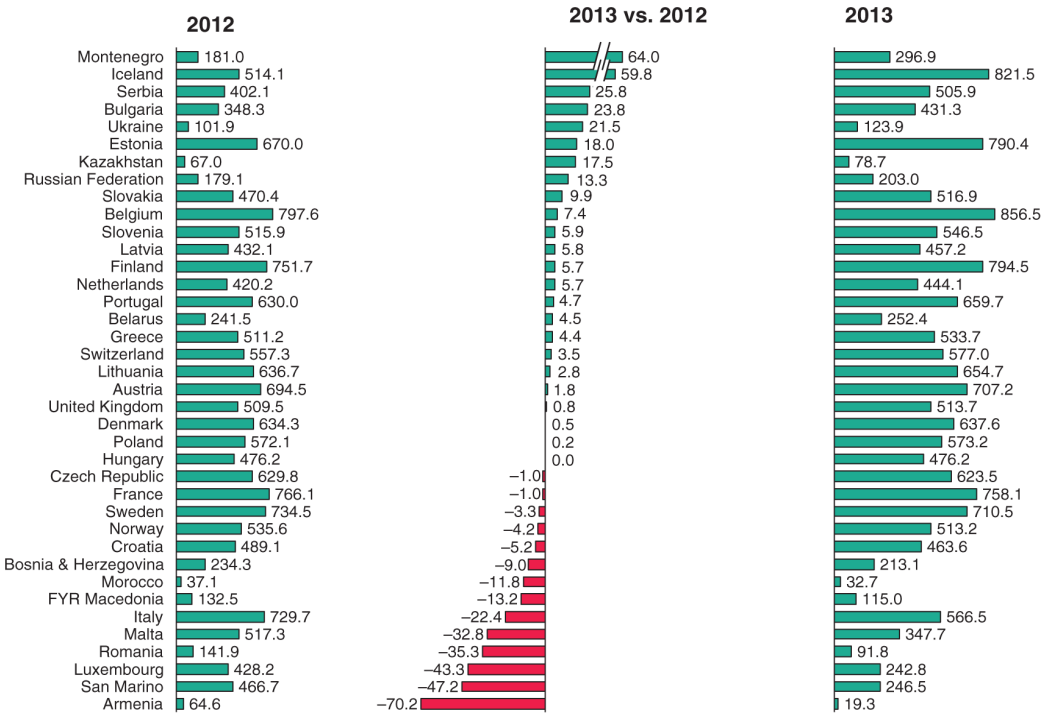


Figure 1.3 Change in the number of new pacemaker implantations per million inhabitants 2012 to 2013 in European Society of Cardiology countries (taken from (Raatikainen et al., 2015)).

Data from the United Kingdom (UK) national audit of cardiac rhythm management devices and ablation report (NICOR, 2019) describes that in England, 624 pacemakers are implanted per million population, equating to approximately 37,500 in 2016 to 2017. This is lower than in Germany, Italy, France, and Sweden, where rates are consistently greater than 700 per million (Mond and Proclemer, 2011b).

The consequence of increasing incidence of implantation rates, compounded by an ageing population with increasing longevity is that, the prevalence of patients with pacemakers is growing in the UK at around 8% per year (NICOR, 2019). This data also implies that above de novo implantations, the requirement for pacemaker generator replacements is also increasing, to around 10% per year. Population overall prevalence ranges from 469 per 100,000 adults in Western Australia in 2009 (highest for people aged 75 to 84 years old) (Bradshaw et al., 2014b) to 2600 per 100,00 for people aged 75 years or older in the United States of America (Silverman et al., 1995). In a typical European population (Denmark), the rates were lower, ranging from 1102 to 2454 per 100,000 across regions (Andersen et al., 1991).

Data collection for worldwide reports to assess trends in implantation rates remains challenging, and would benefit from more complete population level and person-based data. Some variation seen between countries demonstrates variance in demographics, disease prevalence and may also

reflect under-provision (Mond and Proclemer, 2011b). Nevertheless, some patients will receive pacing therapy despite not fulfilling the guideline criteria.

1.4 Device hardware

A pacemaker system typically comprises of a hermetically sealed can which includes the battery and circuitry, connected to the myocardial tissue by at least one pacemaker lead (Figure 1.4) (Kenny, 2005, Rajappan, 2009a, Wood and Ellenbogen, 2002). The leads can be attached to the myocardium by an “active” helix, or by “passive” tines which hook into the myocardial trabeculations (Rajappan, 2009a).

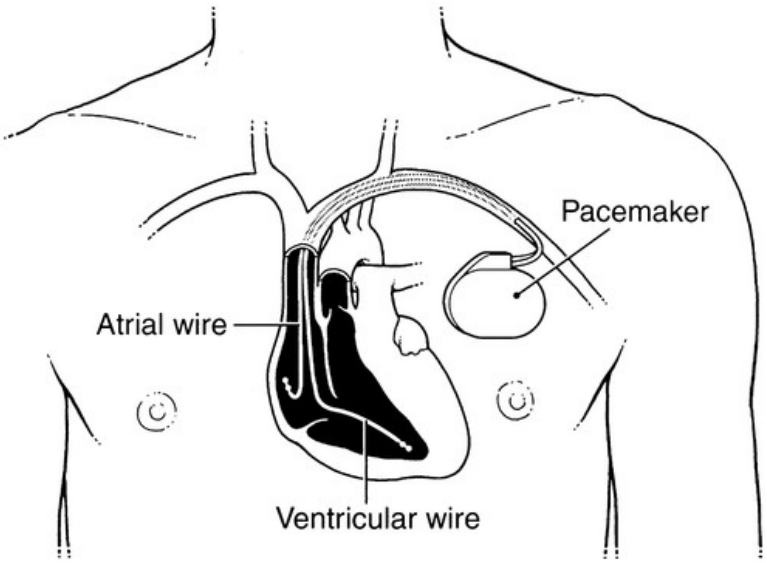


Figure 1.4 Diagram of a pacemaker system (taken from (Wood and Ellenbogen, 2002)).

A system with one lead, usually placed in the RV, is a single system, and those with two leads, typically one in the right atrium and one in the RV, are termed dual systems.

1.5 Pacemaker implant procedure

Pacemaker implantation requires appropriate informed consent of the patient prior to any procedural task. Key information includes the indications and the risks of the procedure; which are the risks of implantation, understanding the indication for implantation, and additional information such as driving restrictions (Rajappan, 2009a). Additional guidance should be given prior to the procedure regarding anticoagulant management (Goldstein et al., 1998). Pre-operatively, the patient should also receive antibiotics as per local protocol with all device interventions.

Local anaesthetic is administered prior to obtaining access to usually the left pectoral region via a small incision below the clavicle (Rajappan, 2009a). A pocket is formed initially in which the device will later be positioned. This is routinely subcutaneous but could also be submuscular (Rajappan, 2009a). Central venous access is obtained by cephalic cut down, subclavian puncture, or axillary puncture (Lau, 2007, Burri et al., 2005).

Via the venous access route, the RV lead is traditionally placed in the RV apex, although there are growing trends towards RV septal and RV outflow

tract positions (Victor et al., 1999, Stambler et al., 2003). Should a right atrial lead be required, this is placed second in the right atrial appendix or commonly the lateral wall if the appendage is not suitable (Rajappan, 2009b).

Once the leads are positioned, an intraoperative assessment of the lead measurements is undertaken in conjunction with the multidisciplinary team (BHRS, 2015). This should include an assessment of the lead sensing, impedance and output threshold as well as a stability assessment.

On successfully achieving suitable lead positions, the leads are inserted into the generator header and all set screws tightened before the generator is placed in the pocket curled with the leads curled behind the generator. Older approaches to position the header inferiorly have become less common due to the additional difficulties of lead binding in the bottom of the pocket during the generator replacement (Rajappan, 2009b). Finally, wound closure occurs using layered absorbable sutures with or without tissue glue (Haywood et al., 1991).

Increasingly, bradycardia pacemaker implantation is performed as a day case procedure (Haywood et al., 1991, Rajappan, 2009b). A chest radiograph should be obtained if subclavian access was utilised (Torres-Ayala et al., 2014).

1.6 Pacemaker programming

Pacemaker implantation is merely the initial phase in lifelong device therapy. Optimal, tailored follow-up patient management is the key to successful treatment.

1.6.1 Pacing Mode

Pacing mode is the most essential parameter to program on an CIED. In response to an intrinsic signal, the device can inhibit or trigger pacing, or pace in a different chamber after a timed delay (Mulpuru et al., 2017).

This function is described by a four letter code using A (atrium), V (ventricle), D (dual) or I (inhibit) (Kenny, 2005). The first position relates to the chamber paced, the second the chamber sensed, the third is the response to sensed events (inhibit, trigger or dual response), and the fourth is the presence of rate-adaptive pacing in response to either movement, ventilation, or changing intrathoracic impedance, with the specific aim of adapting to activity. The fifth position is reserved for indicating multisite pacing when used.

Inhibition refers to a scenario when a sensed events inhibits pacing and initiates a new timing cycle, whereas triggered pacing describes how a sensed event triggers pacing in the same chamber or more routinely, initiates pacing in an alternate chambers after a programmed delay (Kenny, 2005).

There have been several studies investigating the most effective mode of pacing, both in terms of hardware and programming between dual chamber and single chamber (ventricular or atrial) pacing in randomised trials (Nielsen et al., 2011, Connolly et al., 2000, Lamas et al., 2002, Toff et al., 2005), meta-analysis (Healey et al., 2006) and a systematic review (Castelnuovo et al., 2005). Overall, there is no evidence of particular benefit in terms of mortality or HF hospitalisation in either mode, but dual chamber pacing has been associated with reduced atrial fibrillation (AF) burden and stroke (Healey et al., 2006, Connolly et al., 2000, Lamas et al., 1998).

Hence, guidelines now recommended that patients with sinus rhythm AVB and SND should receive dual chamber pacing, although unnecessary RVP should be avoided where possible due to the risk of HF (Sweeney et al., 2007, Wilkoff et al., 2002). Patients in permanent atrial fibrillation require only single chamber ventricular pacing (Brignole et al., 2013b).

1.6.2 Rate-adaptive pacing

The aim of rate response is to enable patients with chronotropic incompetence to achieve target heart rates during episodes of physical activity to mimic physiological changes in heart rate.

Rate response provides dynamic increases in heart rate with sensor-based changes related to physical activity (Leung and Lau, 2000). As described,

there are a number of sensors in practice, including minute ventilation, stroke volume, accelerometers and devices with a combination of sensors (Kenny, 2005).

In patients with atrial fibrillation and a slow ventricular response rate, there is some evidence to suggest that rate responsive VVIR pacing is associated with better exercise capacity and quality of life measures (Padeletti et al., 2006, Sulke et al., 1991). However, this benefit of rate adaptive pacing is not seen in patients with DDD pacemakers, even in the present of chronotropic incompetence (Padeletti et al., 2006, Sulke et al., 1991). This lack of benefit also extends to patients with impaired left ventricular systolic function and includes those with and without sinus rhythm and with and without chronotropic incompetence (Jamil et al., 2016).

1.6.3 Mode switch

Mode-switch operations allow the device to change from a dual chamber tracking mode to a non-tracking mode during supraventricular tachycardia, avoiding over-pacing in the RV by decoupling atrial and ventricular sensing (Jiang et al., 2010). This protects the patient from rapid ventricular rates during supraventricular tachycardia. Through monitoring of the atrial beat-to-beat interval, mode switch then allows for normal mode re-initiation once the supraventricular tachycardia has terminated (Ellenbogen et al., 2016).

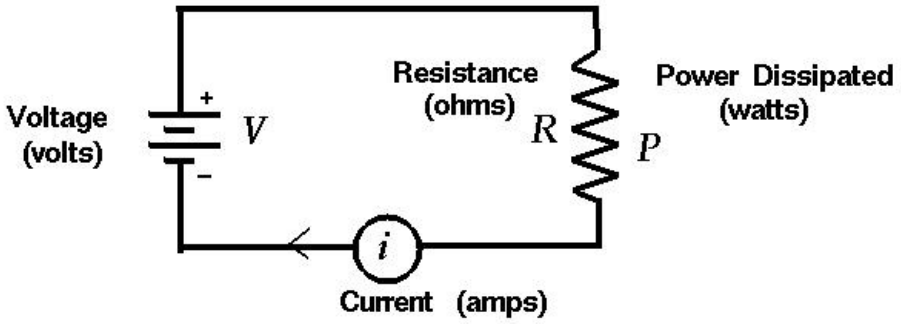
The clinical behaviour of mode switching algorithms differs between manufacturers and even pacemaker models. Generally, the algorithms use a programmable “cut-off” rate and a counter of beats to determine the presence of a supraventricular tachycardia (Kumar et al., 2016). The benefit of rate response during mode switch is not well known but the mode switch algorithm itself is considered to be useful when tailored to each patient (Kamalvand et al., 1997). In particular, although inappropriate mode-switching events can occur in the context of far-field R wave oversensing, mode-switch events (or atrial high-rate sensed events) may highlight the need for anticoagulant therapy if the event is thought to be true atrial fibrillation (Mulpuru et al., 2017).

1.6.4 Lead outputs

Electrical impulses generated by the device are transmitted via the leads to the myocardium. A certain amount of energy is required to stimulate an electrical response in the myocardium and begin a wave of depolarisation; known as the capture threshold. The ‘volume’ of energy delivered is a factor of the duration (width) and amplitude squared (voltage) of the pulse created divided by the resistance (Barold and Winner, 1976). For a given capture threshold therefore, a higher amplitude and shorter pulse width, or longer pulse width and lower amplitude could be chosen. For efficiency, an initial pulse width of approximately 0.4 or 0.5 milliseconds is reasonable (Stokes, 1985) , although this can be extended to save energy when the capture threshold at this pulse width requires an amplitude greater than the battery voltage. Usually the pulse width is kept stable and the amplitude is adjusted

to provide an adequate safety margin, considered to be double the minimum voltage required to produce an electrical stimulation of the myocardium (Ellenbogen et al., 2016).

The relationship between voltage, current and resistance is described by Ohm's Law (Irnich, 1975) (figure 1.5).



$$V = i\ R$$

$$P = i\ V = i^2 R$$

Figure 1.5 Ohm's graphical representation and formula (taken from (Hall, 2015))

As battery voltage is generally consistently around or just under 3.0Volts in permanent pacemakers, a higher resistance is favoured to reduce the current and preserve battery longevity (Nelson, 1993, Irnich, 1975). The capture threshold and programmed output are critical to generator longevity, since up to 50% of the pacemaker battery current drain is used for pacing (Lindemans and Denier Van Der Gon, 1978), hence the programmed output of the device, and the resistance of the leads' pacing configuration are important factors to consider during programming.

1.6.5 Base rate

The lower or base rate (BR) specifies the rate at which the pacemaker will pace the heart in the absence of intrinsic rhythm. Contemporary dual chamber pacemakers are commonly a hybrid of atrial and ventricular based timing as an improvement on historical pure atrial or ventricular based systems (Kenny, 2005).

There remains no consensus on the minimal BR applicable to all patients but a large amount of intrinsic activity is preferable, therefore, in the absence of SND, the BR could be kept low to allow for physiological left atrial activation and to preserve battery longevity. Avoiding right atrial pacing is important to maintain left atrial morphology, function and synchronicity, which has been shown to be negatively influenced by atrial pacing (Martens et al., 2020).

1.6.6 Rate hysteresis

In the presence of a gradual slowing of the heart rate, hysteresis is an algorithm that allows the patient's intrinsic rate to drop below the base rate before pacing is initiated (Brignole et al., 2013b). Hysteresis allows spontaneous sinus rhythm to emerge by slightly reducing the allowed lower rate after a sensed event to promote intrinsic sinus activity (Ellenbogen et al., 2016). If intrinsic ventricular conduction is not sensed, the pacemaker will continue to stimulate the heart at the base rate until a sensed event restarts this cycle (Kenny, 2005). Recently, many devices include a modified version of this that includes a search extension after a specified number of beats (Ellenbogen et al., 2016).

1.6.7 Rest rate

The aim of pacemakers is to mimic intrinsic activation wherever possible. In health, the heart rate decreases during rest or sleep (Kenny, 2005). Algorithms, somewhat similar in aim to hysteresis, have now been developed to permit a reduction in base rate more naturally, either by time-dependent base rates, or by utilising an activity sensor to detect periods of low activity and allowing a reduction in base rate automatically during these (Morris-Thurgood et al., 1994).

Automatic algorithms are largely considered preferable due to the benefits of not being dependent on clock times, having to be reset depending on time schedules and creating a more responsive, dynamic heart rate (Kenny, 2005).

1.6.8 Right ventricular pacing avoidance algorithms

RV pacing may be detrimental to some people. Induced cardiomyopathy rates with RV pacing are reported to be around 20%, therefore there is significant benefit in attempting to avoid RV pacing (Ellenbogen et al., 2016). Hence RV pacing avoidance algorithms, such as managed ventricular pacing, have become common due to increased recognition of the potentially harmful effects (Sweeney et al., 2005a, Stockburger et al., 2014). Simple approaches include longer AV delay programming, however, the use of excessively long fixed atrioventricular delays may lead to reductions in

cardiac output due to diastolic mitral regurgitation and thereby contribute to AF (Cheng et al., 2009b, Nielsen et al., 2012).

The overriding aim of RV pacing avoidance algorithms is to pace in the ventricle only when required by allowing AV delay extension to promote intrinsic ventricular conduction, but to automatically switch to DDD pacing with physiological AV delays if intrinsic conduction fails (Pascale et al., 2009).

There have been mixed findings with regards to the benefit of RV pacing avoidance algorithms and the incidence of AF, HF, and mortality from clinical trials (Gillis et al., 2006, Sweeney, 2007). Additionally, long AV delays could allow atrial contraction during diastole, resulting in “pseudopacemaker syndrome” or be proarrhythmic due to bradycardia (Pascale et al., 2009, Cheng et al., 2009a, Mansour and Khairy, 2012). Clinicians are still lacking clarity concerning optimal pacemaker programming for each individual.

1.6.9 Pacemaker programming conclusion

National and international guidelines are limited in their prescription for optimal programming (Fraser et al., 2000, Hayes et al., 2003). This results in variation in clinical practice and inadequate understanding of the optimal programming for patients with differing pacing requirements.

1.7 Pacemaker follow-up

1.7.1 In person Follow-up

Pacemaker follow-up is routinely performed in the United Kingdom by healthcare scientists holding national or international accreditation in cardiac rhythm management, in a secondary care environment (BHRS, 2015). The frequency of follow-up is variable, but usually consists of three phases: early surveillance, a maintenance period, and intensified monitoring (Roberts, 2005). During the early surveillance period, patients are usually followed up at 4 to 6 weeks post implantation, 6 months post implantation and 1 year post implantation. Thereafter patients are seen every 6 or 12 months (maintenance), and then more frequently approaching the end of the device battery life.

During in-person follow-up, a medical history should be taken to assess for any changes in the patient's symptoms as well as a review of their medical therapy. The pacemaker should be interrogated at every follow-up to assess the stored diagnostic information, to assess device and lead functionality and to optimise programming for the patients requirements at that time (BHRS, 2015). Finally, the patients pacemaker site should be checked for signs of infection (Kenny, 2005).

1.7.2 Remote Follow-up

With the advent of wireless technology including radiofrequency and Bluetooth communication, there have been changes in the mode of follow-

up. Automated communications occur between the patients pacemaker and a home monitor, which then transmits the reading to an internet based server should it fulfil specific alert criteria, for a scheduled automatic interrogation, or a manual, patient initiated transmission (Ellenbogen et al., 2016). The advantage of remote follow-up in this manner is the ability to undertake regular but less burdensome follow-up with the potential to identify device-related problems more readily (Mulpuru et al., 2017). Although interrogation can be performed remotely device reprogramming remains only available in-person due to substantial regulatory concerns.

1.8 Pacemaker longevity

Pacemaker battery longevity is not only the primary concern of patients but a key consideration for clinicians and institutions (Dean and Sulke, 2016). Battery technology and generator circuitry has developed considerably over the last 50 years to allow smaller devices with the same or greater functionality (Lau, 2017). Device longevity though continues to be limited; instead of utilising the additional capacity created to accommodate a larger battery with increased cell capacity, manufacturers have opted to reduce device size in favour of more discrete implantation profiles (Lau, 2017, Wild et al., 2004). As a consequence, technological improvements in device longevity have lagged.

Although research describing actual, and not predicted longevity is limited, according to a nationwide Dutch registry, dual chamber bradycardia

pacemakers have a typical longevity of 6.8years, and single chamber devices have 9.7years (De Vries et al., 2017). Variation is inherent between manufacturers, between models and on an individual patient level (Hauser et al., 2007, Gadler et al., 2014). It is the device predicted longevity which is utilised in clinical practice to inform patient follow-up and schedule pacemaker generator replacements (PGR), yet it is unknown which factors contribute to the longevity algorithm in each device. In fact, it has been suggested that there is a significant discrepancy between observed longevity values and estimated longevity values (Hauser et al., 2007).

Identifying all of the pacemaker variables that influence the battery longevity calculation would allow for more accurate assessment of battery longevity. The major components influencing longevity are the battery chemistry, internal architecture and cell capacity (Lau, 2017). Most pacemaker batteries are based upon lithium-iodine (Mallela et al., 2004). Battery capacity is the electric charge required to sustain a current for a given time period (Mallela et al., 2004). In theory, increasing the battery capacity leads to an increase in longevity, although there are limitations in practice as the chemical stability of the battery, which is paramount in clinical devices, can become unpredictable as the waste products of the chemical reaction accumulate in the sealed can (Lau, 2017, Mallela et al., 2004).

Energy is also used for ‘housekeeping functions’ of the device which include sensing the intrinsic rhythm, storing electrocardiograms and achieving radiofrequency connections (Paton et al., 2019). These functions necessitate

a small but continuous drain on the battery which accumulates to a notable reduction over the life of the device, however little work has been undertaken to reduce this, with manufacturers instead concentrating on software updates to improve device algorithms (Carlson et al., 2003).

RVP avoidance algorithms, which aim to minimise unnecessary RVP, have been shown to extend pacemaker longevity (J Moreno Planas, 2015, Benkemoun et al., 2012a), up to 14 months in one clinical trial (Stockburger et al., 2015). The extension to longevity translated into 23% fewer generator replacement procedures over the duration of the study. This evidence suggests pacemaker programming is important in maximising pacemaker longevity and that the programming is also integral to the battery longevity calculation.

Pacemakers can still occasionally deplete prematurely due to hardware issues or errors within the battery longevity calculation. One registry found 0.8% of devices were removed due to premature end of service (Gadler et al., 2014). This may in part be due to inefficient programming and patient management (Dean and Sulke, 2016), exacerbated by the lack of information regarding which pacemaker variables contribute to the longevity calculation, rendering it impossible to optimise programming specifically for longevity.

1.9 Pacemaker generator replacement

Patients require pacemaker generator replacements (PGR) when the device longevity approaches the elective replacement indicator (ERI), a safety feature which notifies the clinician that there are several months remaining of full device functionality at the desired pacemaker settings (Hauser et al., 2007). It remains true that most patients referred for PGR have reached routine ERI (Dean and Sulke, 2016, Hauser et al., 2007, Gadler et al., 2014, Deharo and Djiane, 2005), however, as population longevity extends, more patients require PGR procedures (Dean and Sulke, 2016). For example, over 50% of all pacemaker patients and 25% of those over 70 years old at their initial implant will require a PGR (Kindermann et al., 2001).

Even in the case of impending elective replacement indicator (ERI), as for any primary procedure, risk stratification of a PGR is important. At an infection rate of approximately 2-5% (Manolis and Melita, 2017, Uslan et al., 2012), PGR procedures have significantly greater rate of infection than that of an initial implant procedure (Uslan et al., 2012). It is therefore a concern that devices routinely fail to reach their estimated longevity (Hauser et al., 2007, Manolis and Melita, 2017, Kindermann et al., 2001), demanding of all healthcare teams that they maximise battery longevity.

Chapter 2

The detrimental effects of right ventricular pacing

2.1 Introduction

Although there is accumulating evidence to support the hypothesis that RV pacing results in deleterious effects on cardiac size and function (Wilkoff et al., 2002, Sweeney et al., 2008, Gierula et al., 2015), the direct impact and relationship between pacing therapy and LVSD in current practice remains ambiguous. Given the significant recent advancements in pacemaker therapy, for example, the addition of algorithms to minimise right ventricular pacing, an evaluation of outcomes of modern practice of bradycardia pacing is mandated. Thus, the purpose of this review is to evaluate contemporary evidence surrounding the effect of pacing therapy on cardiac function.

2.2 Literature review of right ventricular pacemaker associated left ventricular dysfunction

2.2.1 Literature search methods

A systematic literature search was conducted on studies investigating the effects of bradycardia pacing therapy on left ventricular function between 2000 up to the current day, in order to only include studies focussed on contemporary pacing parameters and practices. Cochrane library, Medline, and PubMed online databases were searched initially. Keywords entered were: cardiac pacing OR pacemaker AND left ventricular dysfunction, OR

LVSD, heart failure, remodel, NOT cardiac resynchronization. MeSH terms included were cardiac pacing, pacemaker, systolic heart failure, and left ventricular dysfunction. The search was limited to studies on humans. Hand searches of article reference lists were performed in addition to grey literature searches using Google, ASLIB and Opengrey and searches on the International Clinical Trials registry platform and Clinicaltrials.gov.

A total of 313 manuscripts were reviewed. After removal of duplications, manuscripts that were deemed outcome-based, from a peer-reviewed source and appeared to draw conclusions from data relevant to the relationship between pacing therapy and LVSD were included for analysis (44). Included manuscripts were then critically analysed using the appropriate CASP tool. 24 studies were deemed relevant and of a robust nature, with transparent methods and results and were included in the subsequent discussion with additional investigations identified from hand searches.

Initial review of the research available highlight that although the bradycardia pacing population is one commonly under-investigated, this relatively large evidence base (313 search results) epitomises the significance and longstanding debate surrounding the potential deleterious effects of right ventricular pacing.

2.2.2 Literature discussion

Initial review of the research available highlight that although the bradycardia pacing population is commonly under-investigated, the available evidence base epitomises the significance and longstanding debate surrounding the potential deleterious effects of right ventricular pacing.

The data are complicated not only by the technological advancements in pacemaker therapy, particularly over the last two decades, but the variability in outcome measures and lack of contemporary clinical trials. Therefore, the current evidence base as portrayed in this review, is inherently heterogeneous and careful interpretation of the findings is required.

2.2.2.1 The deleterious effects of right ventricular pacing on patient outcomes

A common animal model for dilated cardiomyopathy utilises rapid RV apical pacing to induce abnormal myocardial contraction causing reduced cardiac contractility(Armstrong et al., 1986, Duchenne et al., 2019). Whilst these findings had been detected in-vivo in pacemaker patients (Wiggers, 1925, Heyndrickx et al., 1985b), little clinical significance had previously been attributed to them.

Two prominent studies changed this paradigm. Firstly, the Dual-Chamber and VVI Implantable Defibrillator (DAVID) randomised trial (Wilkoff et al., 2002), which was designed to assess the hypothesis that dual chamber

physiological pacing would avoid bradycardia-induced ventricular tachyarrhythmias. The trial included 506 participants implanted with an internal cardiac defibrillator (ICD) for primary prevention who were randomly allocated to receive dual chamber pacing at a rate of 70 beats/minute with rate response activated, or to low base rate single chamber ventricular pacing at a rate of 40 beats/minute. The trial was stopped prematurely. At a mean of 1 year follow-up, there was a higher rate of congestive heart failure (CHF) or mortality in those allocated to dual chamber pacing (HR 1.61; 95% confidence interval 1.06-2.44) (Wilkoff et al., 2002). Sub-analysis suggested this was likely to be the consequence of higher RV pacing burdens seen in the dual chamber paced patients, disproving the hypothesis that physiological dual chamber pacing was beneficial to patient, yet initiating a discussion about the adverse effects of RV pacing. However, one key point often overlooked is that all patients in DAVID had severe LVSD, and an indication for an ICD at baseline. The findings of DAVID should therefore not be assumed to be immediately of relevance to pacemaker patients with normal function, or mild LVSD. Additionally, as a clinical outcomes study, no serial functional assessment was performed, so the investigators were unable to describe the direct effect of RV pacing on cardiac function.

The second practice-changing study published in 2003 was designed to test the hypothesis that dual chamber pacing would reduce atrial fibrillation in patients with sick sinus syndrome. A total of 2010 participants were randomly allocated to receive either single or dual chamber pacing with rate adaptive pacing activated (MOST trial) (Sweeney et al., 2008). After a mean

follow-up of 3 years, the study showed neutral results regarding the primary endpoint of incidence of atrial fibrillation, but post-hoc analysis revealed that patients with sinus node disease and high (unnecessary) RV pacing burdens were also at higher risk of hospitalisation for CHF (Sweeney et al., 2003). This association was found in patients paced in both dual and single chamber modes with a threshold of >40% RV pacing, above which there was a 2.5 fold increased CHF hospitalisation rate (Sweeney et al., 2003). These results indicated a loss of atrioventricular synchrony is less important than was initially suggested by the DAVID trial. Again, the MOST study was designed around clinical outcomes, and no serial functional assessment was performed in either study so the incidence of RV pacing induced LV remodeling is unknown.

More recent observational studies have reinforced the association found between RV pacing and adverse patient outcomes. Even in pacemaker patients without high grade AVB at baseline, hence with lower pacing requirements, worse clinical outcomes have been reported in both retrospective (Brunner et al., 2004, Jahangir et al., 1999, Shen et al., 1994, Jelić et al., 1992, Mayosi et al., 1999) and prospective studies (Zhang et al., 2008, Sweeney et al., 2008). Moreover, patients receiving atrial only pacing experience fewer HF events compared to patients paced only in the RV (Andersen et al., 1997).

Similar findings are described in large unselected bradycardia pacemaker populations whereby RV pacing is associated with CHF and cardiovascular

death risk (Udo et al., 2015). Previous nationwide observational studies investigating outcomes in patient with pacemakers, have suggested the likelihood of a CHF event is actually highest within the first 6 months post pacemaker implantation (Pap et al., 2012) however other risk factors for heart failure were not discussed.

Although these studies are unable to determine causative links and were mostly performed prior to programming advancements in pacemaker therapy, it is important to appreciate the uniformity in results.

2.2.2.2 Right ventricular pacing and left ventricular dysfunction: causation or association

More severe LVSD and third degree heart block requiring higher quantities of RV pacing have been shown to be predictors of mortality in pacemaker patients (Zhang et al., 2008, Brunner et al., 2004). It is notable that the highest prevalence of LVSD has been found in those with pre-existing cardiovascular disease (Gierula et al., 2015). Interestingly, strong relationships have also been described in cross-sectional studies between the degree of LVSD and the percentage of RV pacing, with the highest RV pacing percentage, particularly ≥40%, being related to the lowest LVEF (Gierula et al., 2015, Thackray et al., 2003), building on the findings of the DAVID and MOST studies.

Other relevant correlates to LVSD in pacemaker patients have been shown to be age, co-morbidities (chronic airways disease and diabetes mellitus) (Shukla et al., 2005, Tayal et al., 2019), QRS axis (Kim et al., 2014), paced QRS duration (Sweeney et al., 2005b) and the presence of atrial fibrillation (Sweeney et al., 2003). Taking into account these clinical confounders is challenging in a real-world study and requires a sufficient sample size to correct for these relationships.

It is now largely accepted that RV pacing is associated with greater incidence of LVSD and poor patient outcomes but there continues to be ambiguity surrounding causality; the evidence discussed suggests patients with more severe cardiac disease often have more severe conduction disease and necessitate higher percentages of RV pacing but is it the underlying cardiac disease or the RV pacing which causes LVSD?

Whilst research has attempted to describe the impact of pacing and LVSD, patient samples are often selective, the outcome measures used are often exclusive of either LVSD or clinical endpoints such as CHF hospitalisation or mortality and the analysis do not correct for the multiple interactions of relevant clinical features. For example, Nielson and colleagues (Nielsen et al., 2003) demonstrated a small reduction of LVEF of approximately 5% at a mean of 2.9years post implantation, yet the study population included patients with only sick sinus syndrome, hence excluding those potentially at higher risk of LVSD and high degrees of RV pacing.

In the latest Danish nationwide study, which included a comparison with age and gender-matched controls, showed that the highest risk of a HF event, with a hazard ratio of 5.98 (95% CI 5.19-6.90, p<0.01) was during the first 30 days post implantation and was minimally raised for pacemaker patients compared to age and sex matched controls after 180 days (Tayal et al., 2019). Male sex (HR 1.33, 95%CI 1.24-1.43), chronic kidney disease (HR 1.64, 95%CI 1.29-2.09), and previous myocardial infarction (1.77, 95% CI 1.50-2.09) were shown to be dominant variables associated with increased risk of HF in pacemaker patients, Additionally, patients implanted for atrioventricular block were more likely to experience a HF event (HR 1.25, 95%CI 1.15-1.35, p<0.001). Although, neither echocardiographic or pacing variables were collected, and patients with an existing diagnosis of CHF were excluded from this analysis. Therefore, whether pacing-induced LV remodelling is progressive and the causes of heterogeneity in clinical outcomes in response to RV pacing in all pacemaker patients remain unknown.

2.2.2.3 Adverse left ventricular remodelling

Left ventricular remodelling has been adopted as a surrogate endpoint in many clinical studies, particularly those investigating the effect of cardiac device therapy (Duchenne et al., 2019, Cvijic et al., 2017, Konstam et al., 2003). Interventions that have led to a 5% increase in mean LVEF at 1 year have been associated with an odds ratio of 0.86 (95% CI 0.77 to 0.96) for mortality (Kramer et al., 2010) and more specifically better clinical outcomes have been shown in patients receiving CRT with a ≥15% reduction in left ventricular systolic volume indexed to body surface area (Foley et al., 2009).

Exposure to RV pacing has also been related to abnormalities in myocardial blood flow (Simantirakis et al., 2003, Lee et al., 1994, Nielsen et al., 2000, Tse and Lau, 1997a) and myocardial thickness (Van Oosterhout et al., 1998) resulting in a redistribution of cardiac work to those regions activated late (Duchenne et al., 2019, Prinzen et al., 1999). These studies have collectively and consistently identified structural and functional changes in the septal and inferior and lateral free walls, which are reversible when research subjects were reprogrammed to atrial only pacing (Duchenne et al., 2019), even up to a duration of 22 months following RV pacing (Nielsen et al., 2000). All of these investigations involved pacing at settings to force RV pace to speedily induce any signs of LV remodelling. As a consequence, these studies have to date either not been performed in humans, or cannot now be further investigated or replicated in larger samples due to the requirement for unethical programming in patients given the greater risk of CHF.

2.2.2.4 Mechanisms of adverse left ventricular remodelling

Pacemaker associated LV remodelling and systolic dysfunction are caused by an interaction of multiple pathophysiological processes, genetics, and clinical co-morbidities. Acute RV pacing, particularly in the apical site, alters the electrical conduction and can induce dyssynchronous contraction in both ventricles, such as that witnessed with left bundle branch block (LBBB) (Auger et al., 2014, Freudenberger et al., 2008, Hayes et al., 2006, Hong et al., 2009, Saito et al., 2015, Sweeney et al., 2005b, Wolber et al., 2011). The electrical depolarisation produced through RV apical pacing propagates from the apex

through the myocardium, which is slower and heterogenous compared with intrinsic activation through the conduction system from basal LV to apex (Sarvari et al., 2017). In turn there is a long-recognised acute reduction in LV contractility (Wiggers, 1925, Heyndrickx et al., 1985b).

The propagation path of myocardial activation and therefore the QRS morphology, axis and consequent contraction pattern differ according to pacing site (Rubaj et al., 2010, Ng et al., 2009, Iorgulescu et al., 2014, Freudenberger et al., 2008). Further variability is introduced between individual patients, dictated by anatomical differences, areas of ischaemia, myocardial viability and cellular and mechanical properties (Ploux et al., 2013, Kroon et al., 2015, Eschalier et al., 2015). In general, QRS prolongation is universal with RV pacing, and this leads to reduced global stroke volume.

Regional structural changes can also occur and are a sign of abnormal stress vectors within the heart developed from the alterations in depolarisation cause by RV pacing and lead to myofibrillar disarray compared to non-paced controls (Adomian and Beazell, 1986). Not only do structural and functional changes occur, but there appears to be an acute change in genetic expression linked to longer term adverse remodelling (Arkolaki et al., 2015). Hence these pathophysiological changes may contribute in a cyclical process promoting ongoing LV systolic and diastolic functional decline (Bedotto et al., 1990, Betocchi et al., 1993).

Consistently though, pre-implant measures are not obtained and therefore there are no true baseline data to accurately define the impact of introducing RV pacing, leaving the dispute surrounding causation and association unanswered. One small observational study in eight patients awaiting pacemaker implantation undertook positron emission tomography (PET) prior to and 3 months after initiation of RV pacing. Findings suggested that myocardial blood flow remains relatively preserved but that glucose metabolism significantly decreases mainly within apical and inferior regions, near to the pacing stimulation site. Whilst these findings are interesting, the pathophysiological mechanism of reduced glucose utilisation in the context of normal perfusion remains ambiguous.

Many of these changes are not new concepts, yet they have been under-investigated in patient populations due to the inability to perform detailed assessments in-vivo. New advanced imaging technologies with improved access and the advent of MRI conditionality of devices are allowing more specialised analysis of the regions, layers and metabolic properties of the myocardium in these circumstances (Saunderson, 2019). For example, it is likely that there is an association between remodelling and the interplay between work load of the septal and inferolateral myocardium (Duchenne et al., 2019) and degree of myocardial scar (Saunderson, 2019). The extent to which LV remodelling is progressive, the causes of heterogenous functional responses, and the relationship to clinical outcomes are unknown in a real world population receiving long-term pacing therapy.

2.2.2.5 Preventing pacemaker-associated decline in left ventricular systolic dysfunction

2.2.2.5.1 Synchronous pacing

It is likely that RV pacing provides favourable outcomes in some patients whereby physiological atrioventricular delay maintenance is preferable to prolonged PR intervals which may exacerbate heart failure by leading to reduced cardiac output (Kutyifa et al., 2014).

More recent data from a multicentre randomised trial of 1030 patients implanted with internal cardiac defibrillation devices (ICDs) with sinus rhythm and without symptomatic bradycardia, allocated patients to atrial pacing with ventricular back-up at 60beats/min or ventricular back-up pacing only at 40beats/min. The authors showed patients with >230ms PR interval at baseline experienced worse hospitalisation and death rates in secondary exploratory analyses (Sweeney et al., 2010). They also reported a 3.4 fold increase in the risk of developing persistent atrial fibrillation in post hoc analyses (Ricci et al., 2015).

A sub-analysis of the MOST data demonstrated first degree atrioventricular block independently raised the risk of death, stroke or heart failure hospitalisation (HR 1.31, 95%CI 1.06-1.61, p=0.013) (Holmqvist et al., 2014). This may explain why RV pacing avoidance algorithms have been found to be non-inferior to fixed programming with shorter AV intervals in relation to clinical outcomes (4.9% mortality in the group receiving dual-chamber minimal pacing vs. 5.4% in the group receiving conventional dual-chamber pacing,

p=0.54) (Sweeney et al., 2007) . Whilst these findings suggest personalised programming taking into account each individuals electrocardiographic and functional clinic features is important, optimal pacing therapy investigations are limited.

A DAVID sub-analysis found patients <40% RV pacing randomised to dual chamber pacing at 70ppm with rate response activated, trended towards a educed composite endpoint of death or HF hospitalisation compared to those programmed to single chamber ventricular only pacing (p=0.07) (Sharma et al., 2005). These patients were mostly programmed with an atrioventricular delay of 170 or 150ms and it was hypothesised by the authors that this could be due to a reduction in rhythm disturbance, improvement in ventricular filling times and reduced degree of mitral regurgitation, all of which have been found to constitute pacemaker syndrome in investigations into patients with prolonged atrioventricular intervals (Barold and Levine, 2001, Barold and Herweg, 2012).

There seems to be a suggestion of two groups of patients; one with long PR intervals who do better with shorter, more physiological AV delays programmed on their pacemakers, and another group where the AV delay is reasonable and it may be better to avoid RV pacing and so they would benefit from a longer programmed AV delay. Potentially, this is because having a markedly long PR interval and continuing to avoid RV pacing is actually more detrimental than RV pacing. Currently, a randomised parallel prospective clinical trial of 50 patients is due to complete investigating the

effects of long fixed AV delays or short optimised AV delays on cardiac output, changes in functional status, and changes in patient sense of well-being (Feld, 2014). The study findings are awaited and may provide interesting insights into this hypothesis.

2.2.2.5.2 Alternate pacing site

There is widespread debate surrounding the contribution of the RV pacing site to the degree of LVSD. Septal pacing was initially introduced as a means of lessening the abnormal myocardial contraction produced by RV pacing, and has been the most investigated.

Multiple meta-analysis of apical versus non-apical positions have demonstrated a small but significant preservation in LVEF with non-apical positions of 3.58% (95%CI 1.8-5.35) at 6 month follow-up (Weizong et al., 2013) and 5.40% (95%CI 3.94-6.87) at 12 (2-120) months follow-up (Hussain et al., 2015). However, whilst Weizong and colleagues included all suitable studies, they grouped all non-apical positions in the intervention arm (RV septum, outflow tract and His bundle), so we cannot draw a conclusion as to which position is a better alternative clinically. Hussain and colleagues grouped studies into those that found a significant benefit of non-apical pacing, versus those studies that did not. This led to an over-emphasis of the benefit of non-apical pacing in their reported results. Although, an interesting point raised was that those studies reporting a benefit included more patients with <40% baseline LVEF, perhaps highlighting a subgroup who may benefit from RV apical pacing avoidance. The paradox that this raises is similar to

that discussed below regarding CRT. Many patients requiring high amounts of RV pacing with LVSD have conduction tissues disease, especially prolonging QRS duration, such that they could fall into a standard indication for CRT.

A multicentre, international randomised controlled trial which randomised 240 patients pacing at the RV apex or right ventricular high septum (PROTECT-PACE). Eligibility criteria stated patients had to have high-grade AVB requiring more than 90% ventricular pacing, with a preserved LVEF (>50%). The study found no additional protective effect of RV high septal pacing over apical pacing on LV function within the first 2 years post implant (LVEF 55% vs 54%; p=0.43) (Kaye et al., 2014). Whilst this was a robust investigation including only patients requiring >90% RV pacing, preserved LVEF at baseline was a recruitment criterion, so no conclusions can be drawn with regards to patients with LVSD prior to implant. Conversely, an earlier randomised cross-over trial of 28 patients implanted with both septal and apical RV leads showed that RV apical pacing caused a more substantial decline in LVEF than septal pacing (37±4% vs 42±5%; p<0.001) in patients with a baseline EF ≤45% after three months of follow-up.

An observational comparative study found patients with septal pacing had worse circumferential strain and more LV dyssynchrony than apical pacing on echocardiography (Ng et al., 2009). Conversely, in a small observational study exploring the acute haemodynamic effects of different pacing sites, RV outflow tract and dual RV site pacing did not offer any advantage over apical pacing

in patients with preserved baseline function, but for those with impaired LV function, RV outflow tract pacing was preferable than apical ($p<0.001$) (Rubaj et al., 2010).

One further, somewhat under-explored issue with alternative RV pacing sites is the technique and what constitutes a septal position. Fluoroscopic and ECG guided septal positioning leads to significant variation in anatomical placement (Ng et al., 2009). Within a single observational study of 50 patients, septal leads were classified as being in at least 3 different positions (Iorgulescu et al., 2014). A more systematic approach is necessitated to adequately describe lead position since it is possible that poor technique and inadequately placed leads have affected the outcomes of the studies. Hence, overall, despite enthusiastic initial uptake that persists in some centres, there is no consensus about the benefits of alternative RV pacing sites (Vijayaraman et al., 2017) and the search continues for substitutions.

Direct epicardial LV pacing, where a surgical approach places a lead directly onto the LV myocardium, is reserved for the post-surgery setting and, before leadless devices were available, for patients without venous access. Although compared with RV apical pacing, LV epicardial pacing has been associated with higher functional cardiac measures in a cross-sectional study of pacing for advanced heart block in children (<18 years old) (Van Geldorp et al., 2011), but due to the requirement for epicardial access, this option of LV pacing is not a viable method for patients apart from the situations described.

LV pacing has recently been revisited in adult patients using a fixed helix lead which accesses the LV endocardium by driving the lead through the interventricular septum. Early acute haemodynamic data suggest that whilst both RV apical and septal pacing reduced LV dP/dtmax, LV septal pacing maintained it in comparison to atrial only pacing (-7.1±4.1% vs -6.9±4.3% vs 1.0±4.3%; p=0.001) (Mafi-Rad et al., 2016). However, a bundle branch-like morphology was still induced with LV septal pacing and longer-term data are required to assess the potential complications.

His bundle pacing is an additional form of non-apical pacing which has gained recent popularity due to its ability to physiologically reproduce intrinsic ventricular activation. Investigations into the practicalities and reliability of His and para-His bundle pacing have increased with the advent of improved implant equipment. Studies continue to be predominantly observational in design and are focussed on the feasibility of implantation, with success rates quoted from 73-85%, and lead performance (Vijayaraman et al., 2017, Kronborg et al., 2011). However, these studies have included small samples with significant variation in patient co-morbidities and device selection (Occhetta et al., 2006) and larger randomised crossover trial results currently being undertaken in the HOPE-HF study are awaited (NCT number: 02671903).

2.2.2.5.4 Cardiac Resynchronisation Therapy

The growing epidemic of dyssynchony in pacemaker patients has encouraged investigators to consider alternate means of therapy. Whether de-novo cardiac resynchronisation therapy (CRT) could be a routine option for patients at high risk of adverse events due to requiring rate-supportive RV pacing, has been considered in two large trials and several smaller ones.

In the earliest prospective, double-blind, multicentre trial of 177 patients randomised to receive biventricular pacing or RV pacing, biventricular pacing demonstrated a preferential primary end point of LVEF at 12 months compared to those randomised to RV pacing (54.8% vs 62.2%) in a single trial (Yu et al., 2009). As enrolled patients had normal LVEF at baseline, the change in EF was minimal and still represented an EF within the normal range regardless of the reduction at 12 months. Unfortunately, the study was underpowered to assess the implications on clinical events hence the authors concluded by stating further work was required with larger samples and over longer study periods.

The COMBAT (Martinelli et al., 2010) prospective randomised double-blind cross-over study subsequently investigated the benefit of biventricular pacing over RV pacing in 60 patients with pacing indications for AV block with LVSD at implantation (LVEF <40%). All patients received a CRT device and were randomly allocated for 3 months to RV pacing-CRT pacing-RV pacing, or CRT pacing-RV pacing-CRT pacing. The investigators found biventricular pacing was beneficial to LVEF, LVESV and NYHA class in support of expanding the

indication for biventricular pacing to equivalent patients. Nevertheless, due to crossover design, clinical outcomes could not be fully assessed.

The BLOCK-HF trial (Curtis et al., 2007) aimed to close the gap in the evidence. This was the largest multicentre, double-blind randomised study of patients with heart block and LVSD (LVEF ≤50%) with a class I or IIa indication for ventricular pacing. Participants were all implanted with a CRT pacemaker or defibrillator where indicated, and were randomly assigned to biventricular or RV pacing. The primary outcome was time to death for any cause, a greater than or equal to 15% increase in LVESV index, or an urgent care visit for heart failure. Although 918 patients were enrolled, only 691 were randomised and followed up for a mean duration of 37 months. The investigators reported an absolute reduction in in the combined primary endpoint (160 of 329 (45.8%) in the bi-ventricular pacing group vs 190 of 342 (55.6%) in RV pacing group, HR of 0.75; 95%CI 0.60 to 0.90), which was driven by increased LV remodelling and urgent HF care episodes (Curtis et al., 2013). Whilst the results were interesting, the trial suffered from a high crossover rate with 85 patients randomised to RV pacing going on to receive biventricular pacing, censoring a large subset from the primary endpoint analysis. Additionally, it may be argued there was no true comparator arm as all patients had CRT hardware implanted with a notable 6.4% complication rate, restricting the findings from being implemented clinically.

Finally, BIOPACE, a multicentre, randomised single-blind European trial of CRT versus RV pacing in patients with AV block and no significant LVSD was announced in 2014 (Blanc and Investigators, 2014). The trial had a prespecified combined primary endpoint of first heart failure hospitalisation or time to death. 1810 patients were recruited and randomised to CRT pacing or RV pacing. The patient demographics were mostly similar to BLOCK-HF with the main difference being patients within BIOPACE had a higher average LVEF of 55%. The preliminary results have only ever been presented in abstract form. 8 year follow-up data showed no benefit on clinical outcomes but true appraisal of these findings is limited whilst the findings remain unpublished.

2.2.2.5.4 Medical therapy

Despite there being well established medical therapies in the treatment of heart failure, there are no known published studies that have explored the use of medical therapy in the pacemaker population to prevent deterioration in cardiac function. In fact, in many early studies of heart failure therapy, including those testing beta-blockers and angiotension converting enzyme inhibitors, exclusion criteria often included patients with cardiac devices (Glick et al., 1995, TRIAL, 1999). In more recent studies investigating the efficacy of medical therapy, enrolled pacemaker patients remain a small proportion of participants (McMurray et al., 2013).

A single recent observational study investigated the effect of sacubitril/valsartan and LV reverse remodelling in patients with heart failure

due to reduced ejection fraction (Martens et al., 2019). 151 patients were included with an ICD or CRT and followed-up for a mean of 364 days. Analysis focussed on arrhythmia burden and the degree of reverse remodelling as assessed by echocardiography. The study found a lower incidence of appropriate arrhythmia therapy, PVC-burden, and a likely associated improvement in biventricular pacing delivered by CRT, compared to an ICD programmed to RV pace only. The authors also found a higher degree of reverse remodelling which was associated with a lower arrhythmia burden.

Whilst this study incorporates patients with CIED's, conclusions cannot be drawn for patients with standard bradycardia pacemakers and therefore the benefit of medical therapy to slow or prevent RV pacing associated LVSD remains unclear.

2.2.2.6 Conclusions on prevention and therapy

It is clear that further scientific investigations should be focussed on achieving enhanced understanding regarding the development of pacing associated LVSD in order to better identify patients in whom RV pacing is likely to be harmful. There is potential, should this be achieved, that CRT can be offered to these patients to mitigate the harmful effects of RV pacing from initial implantation in well-designed randomised controlled trials to assist evidence-based practice. Other approaches for bradycardia support remain experimental. Additionally, providing a blanket preventative strategy is problematic as not all patients develop LVSD, and even some that do will not

develop heart failure. Consequently, some patients could be sufficiently treated with standard RV pacing.

Future studies should aim to be more independent of industry support as there is a heavy influence within the literature base currently, and utilise the evolving nature of device technology by utilising advanced imaging techniques combined with clinical outcomes.

2.3 Pilot Data

2.3.1 Prevalence of LVSD

All patients listed for a pacemaker generator replacement in a single tertiary centre (Leeds Teaching Hospitals NHS Trust) were invited to attend for an assessment prior to procedure which involved documenting medical history, medical therapy, symptomatic status, pacing therapy information, diagnostic pacing data and an echocardiogram (Gierula et al., 2015). Observational data was collected on 491 patients, the demographics for which are shown below in table 2.1.

Table 2.1 – Baseline characteristics of 491 PGR patients (adapted from (Gierula et al., 2015))

Age (years)	76 (74-78)
Sex (% male [n])	56 [275]
Years since first implant	10 (9.6-10.4)
Age at implant (years)	66 (64-68)
Years of present generator	8.2 (7.6-8.8)

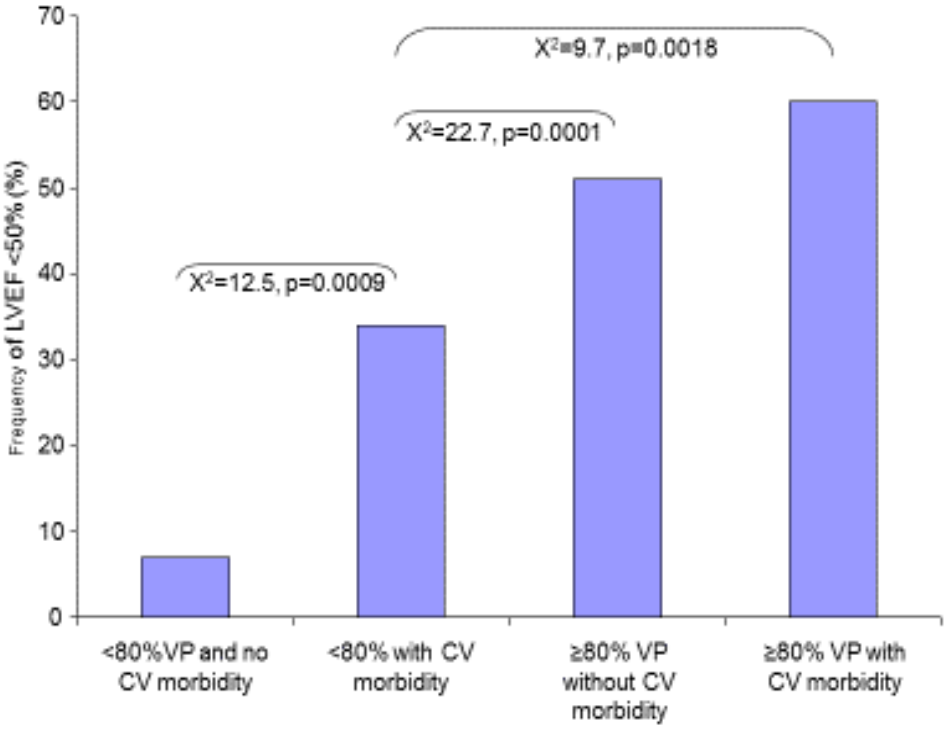
Baseline indication (% [n])	
Sinus node disease	54 [265]
AV-block	43 [211]
Other	3 [15]
Complete heart block at baseline (% [n])	27 [133]
Sinus rhythm at enrollment (% [n])	73 [358]
eGFR (ml/min)	57 (55-59)
Creatinine (µmol/L)	113 (109-117)
QRS width (ms)	161 (155-166)
Overt ischaemic heart disease (MI, PCI, CABG) (% [n])	15, 6, 22 [74, 29, 108]
Diabetes mellitus (% [n])	13 [64]
Hypertension (% [n])	44 [216]
B-blockers (% [n])	59 [290]
ACE-inhibitors (% [n])	68 [334]
Spironolactone (% [n])	10 [49]
Furosemide dose (mg/day)	20 (14-26)

AV-block – atrioventricular block; eGFR – estimated glomerular filtration rate; MI – myocardial ischaemia; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting; B-blocker – beta adrenergic receptor blockers; ACE-inhibitor – angiotension converting enzyme inhibitor.

40% of the cohort had an LV ejection fraction of <50%, which was much higher (59%) in those with >80% RV pacing ($p<0.001$) demonstrating that patients with RV pacemakers have a high prevalence of LV systolic dysfunction (Figure 2.1). In fact, after a mean follow-up time of 668 days, 56 patients (12%) had died or been hospitalised for heart failure.

Figure 2.1. Frequency of left ventricular systolic dysfunction in patients with or without cardiovascular co-morbidity (taken from (Gierula et al., 2015))

Multivariate analysis showed a number of simple clinical variables; high percentage RV pacing, high serum creatinine, and previous myocardial



infarction were independent predictors of LV systolic dysfunction (Table 2.2), and may be used to identify patients who may benefit from a more comprehensive review.

Table 2.2: Multivariable model of predictors of the presence of impaired left ventricular function (Gierula et al., 2015).

	Odds Ratio	95% confidence intervals of odds ratios		p-value
		Low	High	
Myocardial infarction (yes)	3.66	1.41	9.57	0.008
% ventricular pacing (per %)	1.03	1.02	1.04	<0.001
Creatinine (per μmol)	1.02	1.00	1.03	0.011

2.3.2 Pacemaker reprogramming

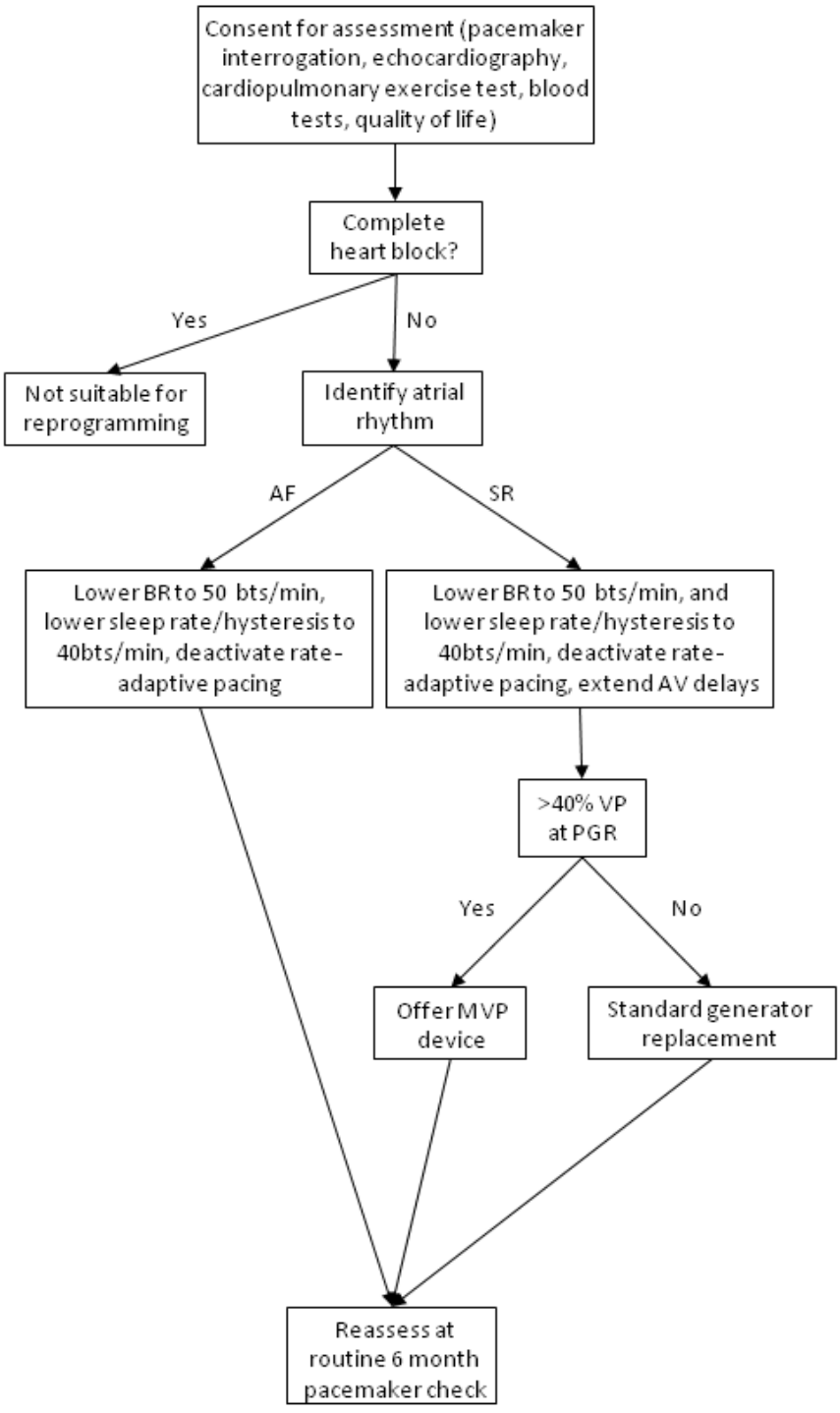
Pilot data were also taken from an observational cohort of 66 patients recruited consecutively from a single UK tertiary centre (Gierula et al., 2014). All patients had been referred for pacemaker generator replacement. Exclusion criteria included inability to consent, intrinsic complete heart block, life expectancy of <1year (clinician decision), presence of device-related complication, or those with LVEF less than 50%.

All patients underwent a thorough baseline assessment comprising of blood samples, echocardiogram, quality of life questionnaire, pacemaker interrogation, medical history, and if appropriate, a cardiopulmonary exercise test.

In patients with avoidable RV pacing, a pre-specified protocol was implemented to minimise this (Figure 2.2); base rate (BR) was reduced to 50 beats/min, nocturnal, rest or hysteresis rate to 40 beats/min, de-activation of rate-adaptive pacing. If paroxysmal heart block had been previously

documented, atrioventricular delays were extended or a device with RV pacing avoidance algorithms was implanted. The patients were re-assessed in 6 months.

Figure 2.2 RV pacing avoidance protocol (taken from (Gierula et al., 2014))



The primary endpoint was change in LVEF, calculated as an average over 3 non-paced beats using Simpson's Biplane method as per British Society of Echocardiography guidelines. Secondary endpoints were exercise capacity, inferred from peak oxygen consumption (pVO_2), NT-proBNP as a biomarker for cardiac dysfunction, and quality of life. Data were analysed as per intention to treat.

All but two patients tolerated the protocol, in whom rate-adaptive pacing was reactivated. On intention-to-treat analysis, utilisation of the protocol resulted in an absolute reduction in RV pacing percentage by a mean of 49% (95% CI: 41-57%; $p<0.001$), and a mean improvement in LVEF of 6% (95% CI: 2-8%; $p<0.001$). These changes occurred without a deterioration in exercise capacity, or quality of life, and without a change in NT-proBNP. There was an association between a reduction in RV pacing and the magnitude of change in LVEF ($p=0.04$) suggesting that the reduction in ventricular pacing burden, directly contributes to an improvement in LV systolic function.

2.3.3 Long-term LV remodelling

35 patients were invited for a thorough follow-up approximately 4.9 (SE 0.5) years since baseline visit and pacemaker generator replacement. 30 patients (86%) attended. Patients signed a consent form, had a pacemaker follow-up, transthoracic echocardiogram, blood tests and completed a quality

of life questionnaire. These data were compared to their previous visit. These patients had a mean (standard deviation) age of 72 (±2) years, had a pacemaker for a mean of 17 (±1) years, and a ventricular pacing burden of 48% (range 0-100). In this group, two thirds (n=23) experienced a reduction in LVEF (in 16, this was >5% absolute reduction) and there was a mean reduction from a baseline of 51(±2)% to 47(±2)% (p=0.017).

Patients with ≥40% RV pacing (n=18) had a reduction in LVEF of 5.3 (±2.1)%, whereas those with <40% RV pacing (n=12) had a reduction of 1.8(±2.1)% (p=0.28). There were also changes in LV dimensions (% change in LV end systolic dimension of 5.0±2.5mm vs. 2.8±6.9mm in those with ≥40% RV pacing and <40% RV pacing respectively. Finally, in patients with >15% increase in LVESV indexed to body surface area (LVESVi), nearly all had ≥40% ventricular pacing.

These data suggest there is a clinically significant progressive LV remodelling and a concomitant decline in function in long-term pacemaker patients that may be related, at least in part, to the patients' burden of RV pacing.

2.4 Aims and Hypotheses

The current thesis builds on the international literature and our group's pilot data to answer the following questions regarding pacemaker therapy for heart rate support.

2.4.1 The long-term relationship between right ventricular pacing and left ventricular systolic function

Question: Is right ventricular pacing-Induced left ventricular systolic dysfunction progressive?

Aim: To identify the long-term relationship between pacing therapy and left ventricular dysfunction; to determine if dysfunction occurs as an initial decline followed by plateau, or whether LVSD progressively worsens over time. Secondly to identify clinical factors with the potential to predict the onset and progression of LVSD in long-term pacemaker patients.

Hypothesis: Pacing associated LVSD progressively worsens over time in long-term pacemaker patients.

2.4.2 Determinants of pacemaker battery longevity

Question: Can estimated pacemaker battery longevity be predicted by clinical or pacing variables?

Aim: To explore potential clinical and pacemaker variables which may predict estimated battery longevity to assess if prior to implantation, we may identify patients at risk of reduced battery longevity in order to augment device prescription at implant.

Hypothesis: Clinical characteristics can provide additional information to highlight patients whom may benefit from pacemakers with large batteries.

2.4.3 Optimising pacemaker and medical therapy for heart failure in pacemaker patients – the OPT-PACE randomised trial

Question: Does optimising medical and device therapy improve the outcomes of patients with pacemaker for bradycardia?

Aim: To assess the effect of diagnosing and managing LVSD on clinical outcomes in pacemaker patients.

Hypothesis: Identifying LVSD, and subsequently optimising medical and device therapy improves outcomes for patients with pacemakers.

2.4.4 Personalised reProgramming to prevent Pacemaker associated left ventricular Remodeling (PPPR)

Question: Is pacemaker-associated left ventricular remodeling reversible?

Aim: To show in a single centre, phase II double-blind, randomised placebo-controlled trial that personalising pacemaker programming reduces unnecessary RV pacing, reverses LVSD and extends battery life.

Hypothesis: Minimising ventricular pacing improves adverse cardiac remodelling and left ventricular function alongside extending remaining battery life.

Chapter 3

Methodology

My investigations utilise predefined surrogate endpoints including echocardiographic variables, pacemaker variables and patient-orientated outcomes such as quality of life. In-vivo detection of pathophysiological modifications in left ventricular structure and function that are often prerequisites to CHF require accessible standardised imaging techniques to quantitatively measure the degree of change. In patients with pacemakers, these imaging modalities must be compatible with device technology and maintain functionality of the device throughout. Diagnostic information can be gained from a cardiac device, as well as functional pacemaker measures and programmed pacemaker variables. This chapter will discuss the methodology for all included endpoints and their prognostic value.

3.1 Transthoracic Echocardiography

3.1.1 Introduction

There are several available imaging modalities for patients with cardiovascular devices. Whilst cardiovascular magnetic resonance imaging is considered the gold standard for assessment of cardiac structure and function, it is not currently approved in all legacy pacemaker devices, repeated tests are not well tolerated in a significant number of patients (Saunderson, 2019) with high drop-out (Witte et al., 2016).

Echocardiography is an attractive alternate cardiovascular imaging modality

as it is freely available in UK hospitals, has no contraindications, delivers real-time images and is relatively inexpensive (Artis et al., 2008).

3.1.2 Test Overview

During a resting transthoracic echocardiogram, the patient is asked to lie on their side while a transducer is placed precordially in various positions and orientations on their chest. Ultrasound waves are formed by and directed towards the chest by the transducer. Once these mechanical waves come into contact with different structures they are reflected and are known as “echoes”. The echo is detected by the same transducer and transformed from mechanical energy into electrical data which are then processed into a still or moving image by software.

3.1.3 Echocardiographic imaging protocol

All echocardiographic assessments were undertaken by a highly specialised cardiac physiologist with British Society of Echocardiography accreditation. Full conventional transthoracic echocardiography was performed with grey scale images using harmonics to ensure optimal visualisation of the endocardial border. Images were obtained with the patient in a supine position on their left as per national guidelines (Wharton et al., 2015) and were acquired using commercially available scanners (3.5 MHz and 4D transducer Vivid E95 or Vivid S6, GE healthcare, Horten, Norway).

In addition to the minimum dataset suggested by (BSE) narrow sector acquisitions of the LV were recorded in apical 4, 2 and 3 chamber orthogonal views with a minimum frame rate of 90Hz in two-dimensional format. Three dimensional images were obtained where available with full volume acquisition of the left ventricle from the apex to atrioventricular valve.

Anonymised images were stored and analysed retrospectively on an offline digital imaging system (EchoPAC version 203, GE Healthcare), blinded to baseline assessment. The frame at the first deflection of the QRS complex on electrocardiogram (the ECG onset of the Q or R wave) was taken as end diastole, and the frame with the smallest cavity as end systole.

A secondary analysis was performed by the same sonographer and an additional independent fully qualified senior sonographer to allow assessments of inter- and intra-observer variability.

3.1.4 Measuring left ventricular size

3.1.4.1 Measures of diameter

Linear internal dimensions of cardiac chambers are the most commonly used parameters to quantify cardiac size. These measures of internal LV diameter and wall thickness, were made in parasternal long-axis view as with care taken to ensure the measures were perpendicular to the LV axis, at a level immediately below the level of the mitral valve leaflet tips (Lang et al., 2015) (Figure 3.1).

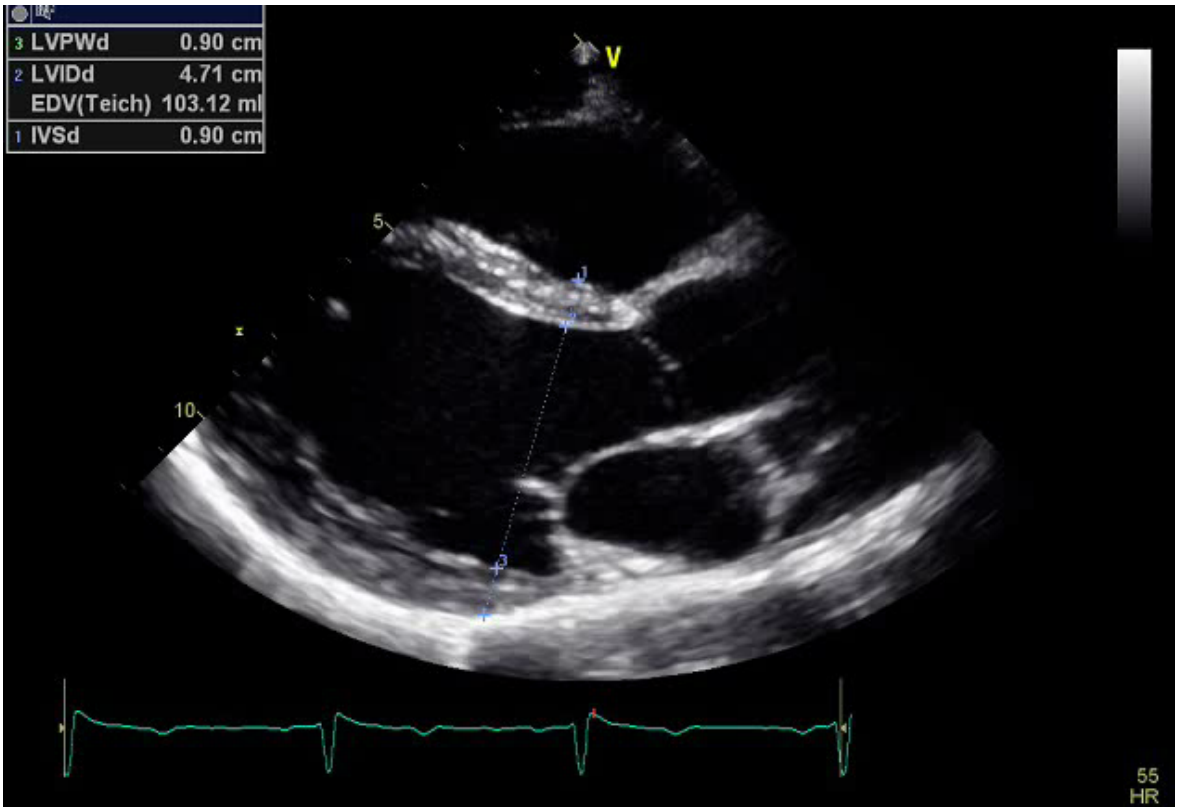


Figure 3.1 2D linear left ventricular cavity dimensions

Linear measurements are supported by a wealth of published data, however using single dimension images is unreliable when assessing LV volumes, unless the ventricle is normally shaped without regional wall motion abnormalities or dyssynchrony, in a patient with a normal echocardiographic window axis (Lang et al., 2015).

3.1.4.2 Measures of volume

In contrast, volumetric measures of LV size provide a degree of correction for shape distortions which are inherently neglected by linear measurements. In the presence of adequate endocardial borders, measurements can be obtained in most patients.

Throughout the following investigations, two-dimensional LV volumes were measured by the modified biplane Simpson method utilising apical four-chamber and two-chamber echocardiographic views taken from images with maximised LV area visualisation (Lang et al., 2015, Wharton et al., 2015) (Figure 3.2)

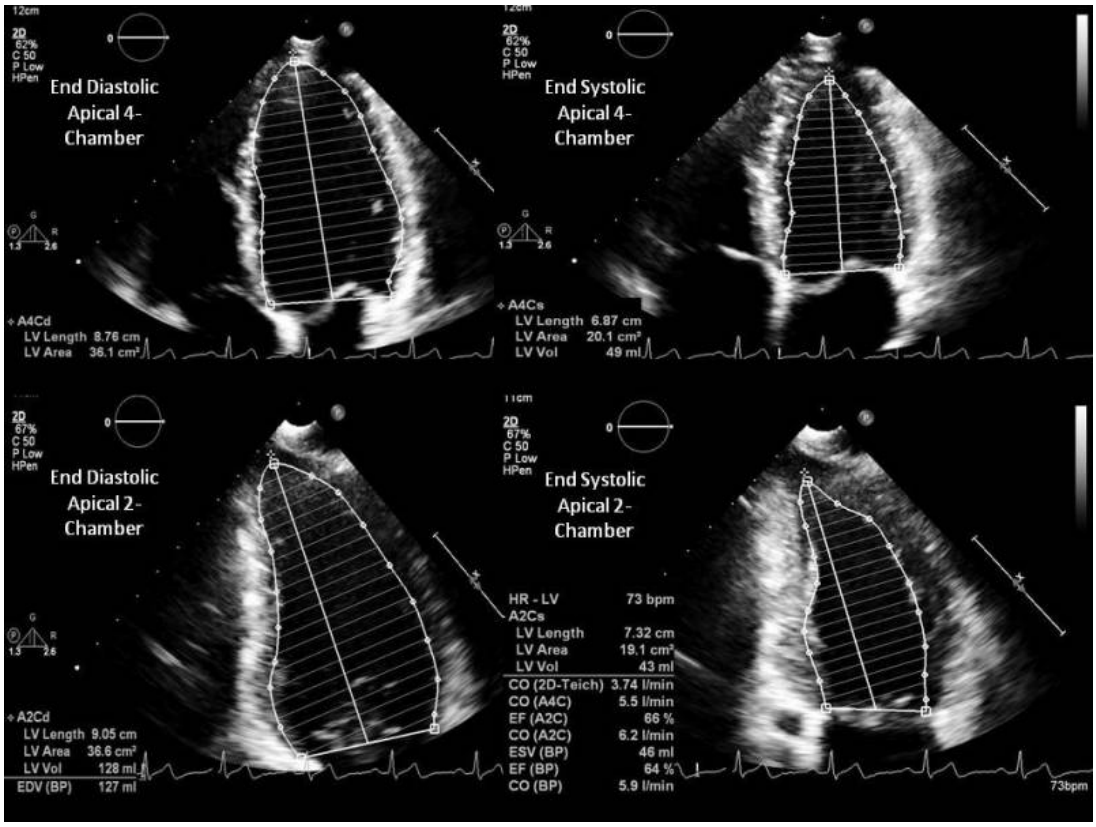


Figure 3.2 Biplane volumetric left ventricular cavity measurements.

However, although better than simple diameter measurements at describing volume and structure, two-dimensional volumes remain blinded to geometrical variations in the anteroseptum and posterior LV walls viewed in apical three-chamber. These limitations are overcome by three-dimensional

datasets which also have enhanced reproducibility (Dorosz et al., 2012), therefore three-dimensional volumes were acquired over a single cardiac cycle where feasible determined by image quality.

These measures were used to calculate LV end systolic volume indexed to body surface area (LVESVi) which is a powerful but simple echocardiographic sign of LV remodelling and has been shown to be a strong independent predictor of HF hospitalisation in patients with cardiac disease (McManus et al., 2009). A cut-off of change in LVESVi greater than 15% is frequently taken as clinically relevant (Foley et al., 2009, Curtis et al., 2007).

3.1.5 Measuring left ventricular function

3.1.5.1 Ejection fraction

Ejection fraction is a well-established measure of LV function. Calculation of ejection fraction occurred using the two-dimensional biplane disc or modified Simpson's method by tracing the endocardial border, excluding the papillary muscles as recommended by consensus of the European Association of Cardiovascular Imaging (Lang et al., 2015). The echocardiographic views utilised were the apical four and two chamber.

There remains some debate regarding the reference ranges for normal LV systolic function measured by ejection fraction. The largest European reference dataset suggests 55.5-73.9% (Kou et al., 2014), whilst most

frequently a cut off of <50% is used to distinguish heart failure with reduced ejection fraction (HFrEF) from heart failure with preserved ejection fraction (HFpEF) (Hogg et al., 2004, Owan et al., 2006). An LVEF <50% was defined as left ventricular systolic dysfunction (LVSD) in conjunction with national guidance (Harkness et al., 2020).

A greater than 5% decline in ejection fraction has been utilised previously in cardiovascular clinical trials as it correlates with clinical outcomes. Interventions resulting in a 5% increase in LVEF showed a reduction in the odds of 1 year mortality with an odds ratio of 0.86 (95% CI 0.77-0.96) (Kramer et al., 2010). Hence, a 5% reduction in LVEF was considered to show a clinically relevant decline in systolic function.

3.1.5.2 Longitudinal strain

Global longitudinal strain (GLS) is a measure of ventricular function derived from an average of eighteen mid-segmental regional measures of longitudinal strain usually assessed by speckle-tracking echocardiography (Figure 3.3) (Dalen et al., 2009, Voigt et al., 2014). Strain is defined as the change in length of an object along a direction relative to its baseline length (Marwick, 2006). These measurements are highly reproducible across serial assessments as they are angle independent and have established prognostic value (Potter and Marwick, 2018).

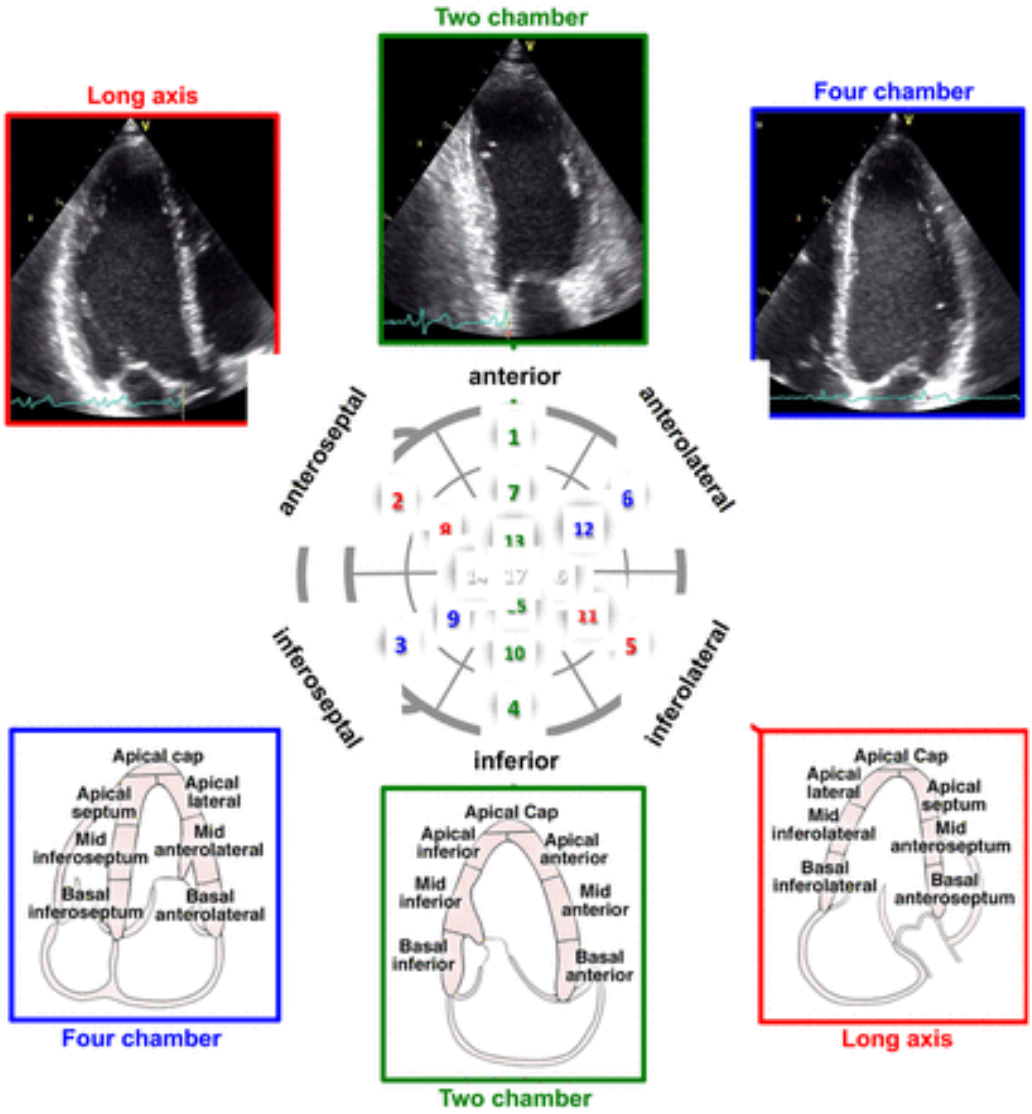


Figure 3.3 Orientation of apical four-chamber (A4C), apical two-chamber (A2C), and apical long-axis (ALX) views (taken from (Lang et al., 2015))

Two-dimensional speckle tracking was performed using apical four-chamber, two-chamber and three-chamber (long-axis) views utilising a frame rate of ≥60 frames per second. Opening and closing of the left heart valves were measured from spectral Doppler of apical long-axis view. As GLS calculation is intervendor and intersoftware variable, measurements were obtained using Echopac version 203, GE healthcare only.

Whilst evidence for the use of GLS in routine clinical echocardiography is less than that for ejection fraction, several studies have shown that it is a robust and reproducible measure (Yingchoncharoen et al., 2013) with potentially superior predictive value in the assessment of resting LV function (Mignot et al., 2010, Stanton et al., 2009). In fact, it has been shown that GLS has better prognostic value than LVEF in patients with acute heart failure and should be considered a standard measurement in all patients (Park et al., 2018).

Echocardiographic quantification of regional function is also achievable using speckle-tracking analysis. Deformation parameters such as strain and strain rate are more preferable for regional assessment as they are less influenced by the direction of cardiac motion relative to the transducer (Heimdal et al., 1998, Leitman et al., 2004, Stefani et al., 2007). Regional strain measures are however, highly dependent on the myocardial region under assessment, measurement methodology, vendor and sample volume definition (Voigt et al., 2014, Heimdal et al., 1998).

In regional analysis it is important not only to assess the degree of magnitude of strain, but also the temporal changes in deformation, both of which are the subject of ongoing research. The value of these measures is yet to be determined, but they have been reported to offer important information regarding regional functional homogeneity by identifying regional ischaemia or scar (Voigt et al., 2003, Voigt et al., 2009).

3.2 Pacemaker Interrogation

3.2.1 Introduction

Based on national guidance during the period of study, the suggested appointment schedule was yearly for patients with pacemakers implanted fewer than 7-10years, and 6 monthly thereafter until elective replacement indication was reached (BHRS, 2015). The aim of follow-up is to optimise the pacing system to the individual needs of the patient, ensure safe and adequate functioning of the device and to recognise any relevant clinical problems.

Nevertheless, it is recognised worldwide that detailed recommendations regarding the follow-up of patient with pacemakers are lacking (Wilkoff et al., 2008, Bernstein et al., 1994, Hayes et al., 2003) hence there is great variation in follow-up protocols between countries and centres and adherence to guidelines is variable (Udo et al., 2013). Perhaps as a consequence, although lead variables are reliably recorded, modifications to pacemaker programming after the first year post implant, occur in only 10-20% of visits (Udo et al., 2013).

3.2.2 Follow-up measurements

Device follow-up allows assessment of device function, the patient's clinical status and co-morbidities, and optimisation of device therapy and until the Spring of 2020, was performed with annual face-to-face visits in most pacemaker patients (BHRS, 2015, Udo et al., 2013). At each visit, routine

device checks should be performed along with a consideration of the diagnostic information presented by the device and patient symptoms (van Eck et al., 2008b). A visual assessment of the pacemaker site is also recommended to assess for signs of infection or erosion (Ellenbogen et al., 2016).

3.2.2.1 Battery measurements

Assessment of device-specific battery information (voltage, impedance, current drain) allow an appreciation of the rate of change in the battery longevity as well as the provided estimate of remaining longevity (Ellenbogen et al., 2016). The elective replacement indicator (ERI) marks the point at which the pacemaker has 90 days of full function remaining with the existing programmed settings. End of life (EOL) is the term used to express when the pacemaker battery has depleted and full functionality as programmed can no longer be reliably carried out.

Minimum estimated remaining battery longevity is most commonly used clinically to determine remaining longevity for safety and to compare devices (BHRS, 2015). The estimate is calculated by a manufacturer and model specific algorithm, which are not made available for critical appraisal (Paton et al., 2019). Minimum battery longevity estimates were used in the current work as a universal measure of battery longevity.

3.2.2.2 Lead measurements

It is recommended at every follow-up assessment, lead threshold, sensitivity and impedance measures are performed (BHRS, 2015) to detect sudden or gradual deterioration in lead integrity or displacement (Udo et al., 2013). The lead sensitivity refers to the minimum signal that can be detected as an intrinsic cardiac impulse. Usually, a sensing safety margin of twice that of the sensing threshold is adopted, but can be adjusted to account for over or undersensing. For example, if a sensitivity threshold of 4.0mV is obtained, the sensitivity would be programmed at 2mV.

Pacing threshold refers to the minimum required energy to initiate myocardial depolarisation (Kenny, 2005). Traditionally, output was fixed at twice the voltage threshold, or three times the pulse width threshold (Kenny, 2005). Many modern devices have the ability to perform this measurement intermittently and adjust the output accordingly. Although seemingly sensible, this automaticity brings challenges since the algorithm itself, designed with the over-riding aim of safety, uses energy, and sets the output at traditional and very safe levels above threshold. In patients with modest pacing requirements, with depleting and stable lead variables, when one is trying to delay box change, this automaticity might be a hindrance to optimal longevity.

Lead impedance is the resistance to current flow. Using Ohms law (Figure 1.5) to guide, it can be appreciated that a higher impedance is associated with lower power requirements and therefore battery drain is slower (Ellenbogen et al., 2016). However, a particularly high or low impedance at

implant or a rising or falling impedance at follow-up, can provide an early indication of lead failure (Kenny, 2005). High measurements (>1500 ohms) can be indicative of lead fracture, while low impedance measures (<500 ohms) are usually due to the electrical circuit having low resistance tissue rather than just the conductor, and may suggest lead insulation failure.

Throughout the present work, lead measures were documented at both baseline and follow-up.

3.2.3 Programmed parameters

Each of the pacing variables described contributes to battery longevity. Other pacemaker features play a critical role and should be used judiciously in a patient-orientated way to provide the patient with the bradycardia support they need but without the use of unnecessary or unproven technology that might contribute to accelerated battery drain. Hence a key but somewhat underappreciated objective of CEID follow-up is to deliver cost-effective care through prolonging the battery longevity by carefully adjusting pacemaker programming (Vardas et al., 2007). The most obvious is to adjust lead outputs (Crossley et al., 1996), but there remains no official guidance surrounding this. However, as patients age, their pacing indication and co-morbidities, or need for pacing support will change, requiring clinicians to adjust their pacing programming accordingly. For example, there is frequently no immediate quality of life of benefit of simplifying the pacing programming in an ageing patient, but avoiding a generator replacement can have significant benefits on the patient and the healthcare

system. Our aim to provide safe care incorporates prolonging battery longevity to avoid generator replacement given that this is the time of greatest risk for the patient (van Eck et al., 2008a).

This approach guided my activity throughout the upcoming investigations. The individual clinical setting was considered carefully before any programming changes were made within the research protocol. Programming was performed according to national guidelines released at the time (BHRS, 2015) and following the prespecified programming protocols where documented.

3.3 Blood Pressure

Blood pressure was measured manually using a sphygmomanometer and a standard stethoscope by an accredited cardiac scientist. Systolic blood pressure was recorded at the point where the first ‘tapping’ sound occurred for two; phase 1 of the Korotkoff sounds (Nutter, 1978). Diastolic blood pressure was taken as the measurement where all sounds disappeared.

3.4 Blood Sampling

Venepuncture was performed by a skilled healthcare professional on a peripheral vein using a tourniquet to encourage venous filling. All samples were collected using a vacuette system. Analysis of blood samples was performed at clinical pathology labs at Leeds Teaching Hospitals Trust,

Harrogate District Foundation Trust, or Bradford District Foundation Trust according to departmental protocols.

3.5 Quality of Life Measurement

Due to the high levels of associated mortality and morbidity, cardiovascular research has often included quality of life assessments, with exponential growth in their inclusion during the last decade (Morgan et al., 2007). Quality of life measures provide additional information to the clinical outcome (Zuluaga et al., 2010) and important insights from the patients perspective.

Whilst there are a range of condition-specific measures of quality of life available, the most widely utilised appears to be the Minnesota Living with Heart Failure Questionnaire (MLHF), used in 69% of studies assessed (Morgan et al., 2007) and received the highest rating by experts using a standard tool for assessing patient-reported outcomes (Garin et al., 2014). The MLHF questionnaire is also extensively validated (Riegel et al., 2002)

The EuroQol was initially developed as a disease independent tool which has since been extensively validated in general populations and multiple disease states The EuroQol quality of life measure was the only utility-based measurement observed in 233 studies between 1996 and 2005 and is widely used across disease groups (Morgan et al., 2007). It has been recently detailed that EuroQol is associated with echocardiographic CRT response and mortality (Nagy et al., 2017).

As it is important to select an instrument which allows for comparability, these two quality of life measures were adopted across the included studies. As part of the EuroQol there is also the visual analogue scale, which provides more continuous data.

3.6 Data Analysis

All statistical analyses were performed using the IBM SPSS Statistics program, version 22, for Windows. The Shapiro-Wilk test was used to determine whether parameters were normally distributed (parametric).

Continuous variables within and between groups were reported as either the mean and standard deviation (SD) if normally distributed, or as the median and interquartile range (IQR) if non-normally distributed (non-parametric). Categorical data were summarised as frequencies and percentages.

The paired t-test was used to compare continuous variables between baseline and follow-up for normally distributed variables. Analysis of covariance (ANCOVA) was used to assess change in variables between baseline and follow-up whilst adjusting for the baseline value. Categorical variables were analysed using the Chi-squared statistic.

Where statistical modelling was appropriate, linear regression was performed if the outcome variable was continuous, or logistic regression if the outcome was dichotomous.

For pre-specified tests I powered according to the precision and variance of measurements from known pilot data, described within the chapter methods, and utilised clinically significant differences in outcomes within the literature (Jones et al., 2003) and subsequently following rules of thumb for sample sizes where appropriate (VanVoorhis and Morgan, 2007). For post-hoc testing, a p-value of less than 0.05 was considered statistically significant. I did not correct for multiple testing, preferring to leave the data open to critical interpretation (Perneger, 1998) All numerical and graphical data was initially visually assessed for normality.

Chapter 4
The relationship between long-term right ventricular pacing and left ventricular systolic function

4.1 Introduction

Whilst there is some evidence to support the hypothesis that right ventricular (RV) pacing, particularly in the apex, results in deleterious effects on cardiac size and function, and that this can contribute to the development of left ventricular (LV) dysfunction and clinical heart failure (HF), the direct impact and relationship between pacing therapy and left ventricular systolic dysfunction (LVSD) remains ambiguous. Furthermore, it is unknown whether the deterioration is an acute decline preceding a plateau in left ventricular (LV) systolic function or is steadily progressive. Moreover, whether this occurs in all patients, or only those with risk factors is unknown. Currently, there is no accepted strategy to avoid RV pacing in guidelines, hence further understanding of the important relationship between pacing therapy, cardiac function and subsequent HF, could lead to improved risk stratification and preventative treatments in this cohort.

The aim of this study was therefore to describe the incidence of HF and all-cause mortality in a cohort of patients receiving long-term bradycardia pacemaker therapy. Secondary aims were to assess the rate and progression of long-term pacing associated LV remodelling and systolic dysfunction, and the association between clinical variables and LV remodelling, in an attempt to identify those patients most at risk.

4.2 Objectives

The objective of this study was to investigate the clinical outcomes in patients who have received long-term pacemaker therapy. This study also sought to describe the long-term relationship between RV pacing and LV remodelling.

4.3 Methods

4.3.1 Study Design

All surviving individuals previously recruited to a cross-sectional study describing the prevalence of LVSD in pacemaker patients at their elective pacemaker generator replacement between 1st April 2008 and 1st December 2012, were invited to attend the Cardiovascular Clinical Research Facility at Leeds Teaching Hospitals NHS Trust for a single additional visit. This attendance was approved through a substantial amendment to our previous study by the Local Ethics Research Committee and local authority (15/EM/0566, Appendices A and B).

4.3.2 Study Population

The defined historical cohort consisted of 572 patients recruited to the study described above between 1st April 2008 – 21st December 2012. These patients were assessed at the time of their elective pacemaker generator replacement (PGR) and the cohort equated to 97% of patients referred for generator replacement during the study period.

4.3.2.1 Inclusion Criteria

Surviving Patients recruited to the original observational cohort with long-term pacemakers between 2008 and 2012 with data and images available were eligible. Patients needed to be willing and able to give informed consent for the reassessment.

4.3.2.1 Exclusion Criteria

Patients who had been upgraded to cardiac resynchronisation therapy (CRT) devices at PGR ether as part of a study or routinely during the follow-up period were excluded from follow-up, although the clinical features for the upgrade were recorded.

4.3.3 Study Procedure

4.3.3.1 Initial baseline assessment (2008-2012)

Patients were recruited from 1st April 2008 – 21st December 2012 if they had a pacemaker already in situ for bradycardia, and had been referred for an elective PGR. Patients were assessed once informed written consent was gained, one week prior to their PGR procedure. All patients had been clinically referred for elective PGR due to achieving a minimum estimate battery longevity of between 3 and 6 months.

Baseline assessment included collecting a clinical history, physical clinical examination, mediation history, pacemaker interrogation and transthoracic echocardiogram. Collected data included pacemaker variables such as pacing systems, pacing utilisation, device function measures, as well as clinical variables (height, weight, blood pressure, symptomatic status, medical therapy, past medical history) and echocardiographic variables.

4.3.3.2 Follow-up assessment

Follow-up assessment consisted of a digital follow-up, recording clinical outcomes to the censor date (1/12/2017). The surviving patients who agreed to attend for a follow-up study visit provided written informed consent. At the follow-up study visit, patients underwent a repeat echocardiogram, pacemaker assessment, medical history and medication review, and blood tests (urea and electrolytes, full blood count, and NT-proBNP).

2D greyscale and tissue Doppler echocardiography images were recorded using harmonics to improve border definition. All datasets were obtained using a Vivid E95 General Electric echocardiography machine and stored on ‘echopac’ digital imaging program for offline analysis. Narrow sector acquisitions were recorded in apical four, two and three chamber views with a minimum frame rate of 90Hz. The frame at the peak of the R wave was taken as end diastole, and the frame with the smallest LV cavity size as end systole. It was documented whether the patient was in intrinsic rhythm or paced rhythm at the time of the ultrasound. No pacemaker reprogramming

occurred prior to the echocardiogram to ensure representation of real-world data.

To avoid observer bias, image analysis was performed blinded to baseline images by a British Society of Echocardiography accredited senior healthcare scientist. This ensured the robustness of the analysis, and reduced the bias of known clinical and pacing variables. Prior to any analysis, 10% of all scans were selected to be reported twice to enable an assessment of intra-observer reproducibility. 10% of all scans were also randomly selected to be reported by an additional sonographer to permit a description of inter-observer variability.

4.3.4 Outcome Measures

4.3.4.1 Primary Outcomes

The primary outcome was an assessment of changes in left ventricular size and function. A combined endpoint of greater than 5% reduction in left ventricular function, as determined by left ventricular ejection fraction (LVEF), or an increase in left ventricular end systolic volume indexed to body surface area (LVESVi) of equal to, or greater than 15% on echocardiography were pre-determined to present clinically relevant cut-offs for adverse LV remodelling.

4.3.4.2 Secondary Outcomes

Key secondary outcomes for the study included an assessment of the predictive value of baseline variables, such as pacing therapy indication, intrinsic rhythm, past medical history, RV pacing burden, age, and echocardiographic variables including 2D LV diastolic dimensions and volumes indexed to body surface area, in relation to echocardiographic markers of progressive remodelling at follow-up.

An additional secondary outcome involved time to event analysis of a combined endpoint of heart failure fatality, heart failure hospitalisation or CRT upgrade. The final censorship date was 12th January 2017. Morbid status and cause of death were recorded from the national SPINE database, as well as a local electronic health record. Cause of death was obtained from electronic coding, or via the death certificate where available. Hospitalisation data was collected from electronic clinical event databases detailing all admissions in the recruiting centre. All nonelective hospital admissions during the follow-up period, prior to death, were recorded and characterised as 1) heart failure hospitalisation, 2) other cardiovascular hospitalisation, 3) non-cardiovascular hospitalisation according to the admissions code.

4.3.5. Statistical Analysis Plan

Statistical analysis protocols followed guidelines described in STARD (Bossuyt et al., 2015) and TRIPOD (Collins et al., 2015) statements to ensure production of transparent and reproducible evidence which relates clinical and technical variables to markers of progressive LV remodelling.

4.3.5.1 Statistical testing

Data were analysed using the Statistical Package for the Social Sciences SPSS version 21 (IBM Corp., Armonk, New York), R: A Language and Environment for Statistical Computing version 3.2.3 (R Development Core Team, Vienna, Austria), and SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Normality for all continuous variables was tested using the Shapiro-Wilk test. Normally distributed continuous variables were reported as mean and standard deviation, and non-normally distributed continuous variables were reported as median and interquartile range. All statistical tests were 2-sided, and any p value <0.05 was called statistically significant.

4.3.5.1 Primary Outcome: Changes in left ventricular structure and function

A co-endpoint was chosen to provide a comprehensive picture of the potential detrimental effect of RV pacing on both LV structure and function.

As this produced a dichotomous outcome variable, logistic regression was utilised for statistical analysis.

4.3.5.2 Secondary Analysis

4.3.5.2.1 Predicting left ventricular remodelling

Univariate analysis was used to assess relationships between predictor variables and markers of LV remodelling. Assessments were then further developed to construct a more robust multivariable predictive model using logistic regression. This model was reliant on obtaining sufficient data to ensure all potentially relevant clinical variables were included.

4.3.5.2.2 Long-term heart failure risk

A secondary outcome was heart failure (HF) hospitalisation, upgrade to cardiac resynchronisation therapy (CRT), or fatal HF from baseline visit in the entire cohort of patients, assessed by event-free survival analysis. Patients were censored if they died due to a cause of death other than heart failure, including cardiovascular causes, without a preceding HF event within the follow-up period. Statistical modelling was undertaken using Kaplan Meier and Cox's proportional hazards regression.

4.3.5.3 Power calculation and Sample Size

A power calculation was performed to ensure adequate endpoints were obtained for key secondary analysis. Based upon pilot data, it was predicted

approximately one half (40-50%) of all returning patients would fulfil the binary cut-offs of greater than 5% reduction in LVEF or equal to or greater than 15% increase in LVESVi. It was assumed for each independent predictor variable under investigation that 10 ‘events’ (>5% reduction in LVEF or >15% change in LVESVi) were required. 9 predictor variables were collected, therefore allowing for drop-outs, withdrawals of consent, poor imaging subjects, and recognising that predictor variables were not likely to be independent of another, the conservative estimate necessitated 90 patients with ‘events’ to robustly estimate a model.

Of the original cohort of patients, 252 (49%) were deceased at the time of screening (12/01/2017), therefore all surviving patients were invited to re-attend for follow-up.

4.4 Results

The original cohort consisted of 572 patients listed for elective pacemaker generator replacement, which was 10 (±5) years after initial pacemaker implant. Within this group, 55 subsequently participated in an interventional research study, making them ineligible for follow-up assessment. Of the original cohort of patients, 253 (49%) were deceased at the time of screening (12/01/2017), 74 (IQR 59-92) months after baseline assessment, therefore all surviving 264 patients were invited to re-attend for follow-up.

Of the surviving patients, 164 consented to follow-up assessment at a median of 121 (IQR 104-132) months after baseline assessment. A total of 100 patients that had survived did not return due to an inability to consent (n=27) declined to attend (n=37), loss to follow-up (n=33) or upgrade to CRT (n=3) (Figure 4.1). Patients that survived but did not attend in-clinic follow-up were not different at baseline to those who did return in terms of age, pacemaker variables and co-morbidities.

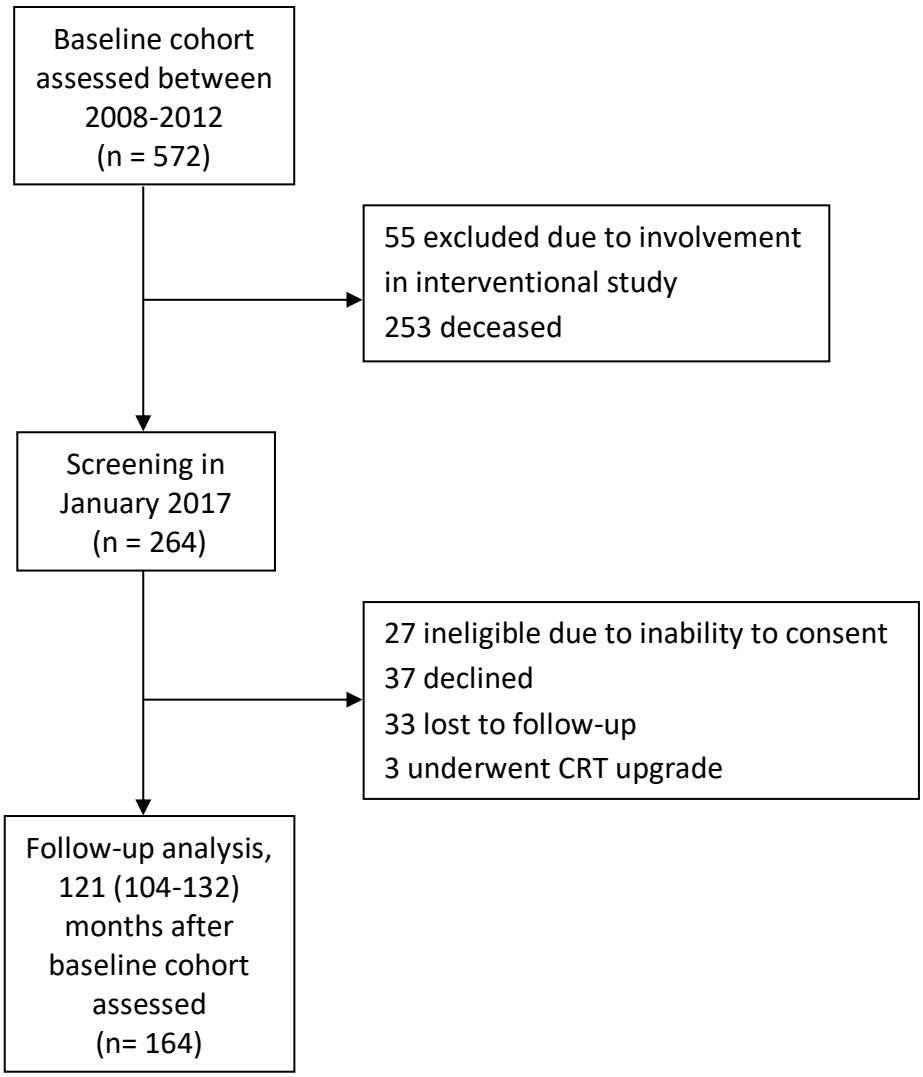


Figure 4.1 Is pacing-associated left ventricular dysfunction progressive? Study flow diagram

4.4.1 Differences between baseline and follow-up

After a decade, the rate of diagnoses of cardiovascular co-morbidity (ischaemic heart disease, diabetes mellitus, cerebrovascular event, hypertension) was markedly higher (n=38) (Table 4.1). At follow-up, patients also had a lower heart rate and systolic blood pressure, and were taking more cardiovascular medication than 10 years previously. More patients were paced in a mode with RV pacing avoidance, and there was significantly lower right ventricular pacing burden at follow-up than at baseline (12% vs 38%; p=0.01).

Table 4.1: Baseline characteristics of the 164 attending survivors of the cohort, at baseline assessment (2008-2012) and follow-up assessment (2017-2018).

	Baseline	Follow-up	p-value
Patient Demographics			
Age (years)	69 (11)	76 (11)	<0.001*
Sex (male)	98 (60)	98 (60)	1.000
Atrial Fibrillation	30 (18)	56 (35)	<0.001*
Clinical History Data			
Myocardial Infarction	12 (7)	15 (9)	0.368
Diabetes Mellitus	13 (8)	27 (17)	<0.001*
CABG	25 (15)	26 (16)	0.828
PCI	8 (5)	13 (8)	0.070
CVA	10 (6)	25 (15)	<0.001*
Haemodynamic data			
Systolic Blood Pressure (mmHg)	167 (14)	129 (22)	<0.001*
Resting Heart Rate (bpm)	77 (18)	69 (13)	<0.001*
Pacing data			
Atrial Pacing Burden (%)	43 (3-83)	23 (1-69)	<0.001*
Ventricular Pacing Burden (%)	38 (4-98)	12 (1-97)	<0.001*
Ventricular Pacing >80%	50 (30)	48 (29)	0.734
Pacing Mode			
DDD	113 (69)	51 (31)	<0.001*
DDI	19 (12)	6 (4)	<0.001*
VDD	8 (5)	8 (5)	1.000
VVI	23 (14)	53 (32)	<0.001*
RV pacing avoidance mode (AAI+)	1 (1)	46 (28)	<0.001*
Base Rate (bpm)	60 (9)	53 (8)	<0.001*
Echocardiographic Data			
LVEF (%)	53 (11)	48 (11)	<0.001*
LVEDD (mm)	47 (7)	48 (7)	0.143
LVEDV (mL)	112 (93-138)	109 (89-141)	0.805
LVESV (mL)	56 (40-71)	53 (42-75)	0.704
LVESVi (mL/m^2)	29 (22-36)	28 (23-38)	0.276
Medications			
Beta blocker	35 (21)	84 (51)	<0.001*
ACE inhibitor	40 (24)	79 (48)	<0.001*
Furosemide	11 (7)	33 (20)	<0.001*

Normally distributed continuous variables are shown as mean (standard deviation), non-normally distributed continuous variables as median (interquartile range), categorical variables are shown as n (%). CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention, CVA; cerebrovascular attack, RV; right ventricular, LVEF; left ventricular ejection fraction, LVEDV; left

ventricular end diastolic volume, LVESV; left ventricular end-systolic volume; ACE, Angiotensin-converting-enzyme. *denotes significance

4.4.2 Primary outcome: Long-term left ventricular remodelling among patients with a pacemaker

Of the patients seen at follow-up (164), 98 (60%) fulfilled the endpoint criteria of >5% change in LVEF or >15% change in LVESVi. This was driven by 73 (45%) patients attending follow-up experiencing a deterioration in LV systolic function >5% (Figure 4.2), and 52 (32%) patients having a >15% increase in LVESVi.

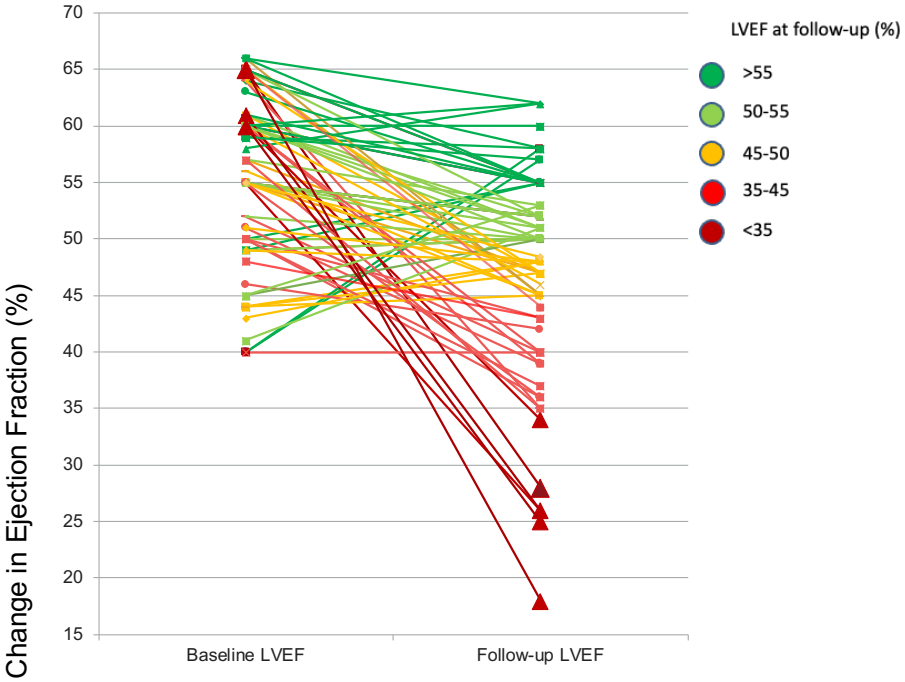


Figure 4.2 Change in LV ejection fraction per individual participant

4.4.3 Predictors of LV remodeling among patients with a pacemaker

There was no association observed between the presence of cardiovascular co-morbidities, seen in approximately 50% of the population, and clinically significant progressive adverse LV remodelling. Only baseline LVEF and

LVESVi at PGR were predictors of long-term adverse LV remodelling (table 4.2).

Table 4.2 Univariate logistic regression analysis of adverse left ventricular remodelling in the presence of right ventricular pacing after pacemaker generator replacement

Predictor	β	SE □	Wald's □2	*df*	*p*	Odds Ratio	95% CI of OR	
							Lower	Upper
Male sex (vs. Female)	0.148	0.341	0.187	1	0.665	1.159	0.594	2.263
Age (years)	0.007	0.015	0.215	1	0.643	1.007	0.978	1.037
MI	0.408	0.630	0.418	1	0.518	1.503	0.437	5.170
IHD	0.302	0.438	0.475	1	0.490	1.353	0.573	3.192
DM Type II	-0.580	0.689	0.710	1	0.400	0.56	0.145	2.160
Atrial fibrillation (vs Sinus Rhythm)	0.612	0.417	2.154	1	0.142	1.844	0.814	4.177
VP Burden (%)	-0.004	0.004	1.022	1	0.312	0.996	0.988	1.004
LVEF (%)	0.094	0.020	22.684	1	0.000*	1.098	1.057	1.141
LVESVi (mL/m2)	-0.057	0.016	12.815	1	0.000*	0.945	0.916	0.975

All categorical variables are stated as n (%). OR, odds ratio; MI, Myocardial infarction; IHD, Ischaemic heart disease; VP, Ventricular pacing; LVEF, left ventricular ejection fraction; LVESVi, Left ventricular end systolic volume index

4.4.4 Differences between surviving and deceased patients

Multiple important differences were observed in the baseline characteristics between patients who experienced all-cause mortality, and those who survived to the present follow-up study (Table 4.3). Surviving patients were younger (70±13 vs 81±9 years; p<0.001), fewer had atrial fibrillation (21 vs 36%; p<0.001), they required less ventricular pacing (44(4-99) vs 74(17-100)%; p0.001), were more likely to have their device programmed to dual-chamber mode (DDD) (64 vs 59%; p0.001), and had a higher LVEF (51±12 vs 49±11; p=0.036) at the initial recruiting visit (2008-2012).

Table 4.3: Baseline characteristics of the deceased compared to the survivors of the cohort

	Deceased (n=253)	Survivors (n=264)	p-value
Patient Demographics			
Age (years)	81 (9)	70 (13)	<0.001*
Sex (male)	144 (57)	143 (54)	0.537
Atrial Fibrillation	90 (36)	54 (21%)	<0.001*
Clinical History Data			
Myocardial Infarction	15 (6)	22 (8)	0.310
Diabetes Mellitus	15 (6)	19 (8)	0.479
CABG	35 (13)	27 (11)	0.417
PCI	12 (5)	7 (3)	0.352
CVA	15 (7)	14 (14)	0.095
Haemodynamic data			
Systolic Blood Pressure (mmHg)	163 (21)	165 (21)	0.520
Resting Heart Rate (bpm)	74 (14)	76 (19)	0.507
Pacing data			
Atrial Pacing Burden (%)	38 (1-83)	43 (3-86)	0.250
Ventricular Pacing Burden (%)	74 (17-100)	44 (4-99)	0.001*
Ventricular Pacing >80%	121 (49)	89 (34)	0.001*
Pacing Mode			
DDD	148 (59)	170 (64)	<0.001*
DDI	8 (3)	33 (13)	
VDD	12 (5)	11 (4)	
VVI	85 (34)	48 (18)	
RV pacing avoidance mode (AAI+)	0 (0)	2 (1)	
Base Rate (bpm)	62 (9)	61 (9)	0.300
Echocardiographic Data			
LVEF (%)	49 (11)	51 (12)	0.036*
LVEDV (mL)	109 (89-139)	111 (89-138)	0.941
LVESV (mL)	57 (43-75)	54 (41-72)	0.222
Prescribed Medications			
Beta blocker	45 (55)	60 (57)	0.883
ACE inhibitor	52 (62)	63 (59)	0.766
Furosemide	46 (55)	22 (23)	0.003*

Normally distributed continuous variables are shown as mean (standard deviation), non-normally distributed continuous variables are shown as median (interquartile range). Categorical variables are shown as n (%). CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention, CVA; cerebrovascular attack, RV; right ventricular, LVEF; left ventricular ejection fraction, LVEDV; left ventricular end diastolic volume, LVESV; left ventricular end-systolic volume. *denotes significance

4.4.5 Long-term heart failure risk analysis

At the end of the follow-up period, 92 (18%) patients had been hospitalised or died of HF. Median time to first HF event post PGR was 34 (15-58) months.

All-cause mortality was observed in 253 (49%) patients; 104 (20%) patients had fatalities confirmed as non-HF related, and cause was unknown in 68 (13%) of patients. A total of 81 (16%) patients died from chronic HF, which in 24 (31%) patients occurred without a preceding HF hospitalisation. 3 patients underwent upgrade to CRT, however all three experienced a HF hospitalisation prior to upgrade.

Factors associated with risk of HF in an unadjusted analysis are presented in figure 4.3. Patients who experienced a HF event were older (per year older HR 1.07, 95% CI 1.04-1.09), had worse LV function (per percent increase in LVEF HR 0.97, 95% CI 0.95-0.98), were more likely to have a history of atrial fibrillation (per percentage burden of AF, HR 2.83, 95% CI 1.88-4.28) and had more frequent right ventricular pacing (per percentage burden of RV pacing, HR 1.01, 95% CI 1.00-1.01) .

	95% CI	Hazard Ratio	P Value
Age (years)	(1.04-1.09)	1.07	<0.01
Sex (Male vs Female)	(0.44-1.04)	0.68	0.08
IHD	(0.56-1.75)	0.99	0.88
MI	(0.48-2.26)	1.05	0.91
Hypertension	(0.59-1.58)	0.96	0.97
Diabetes	(0.3-1.26)	0.61	0.68
Ventricular pacing burden (%)	(1.00-1.01)	1.01	<0.01
Atrial Fibrillation (%)	(1.88-4.28)	2.83	<0.01
LVEF (%)	(0.95-0.98)	0.97	<0.01

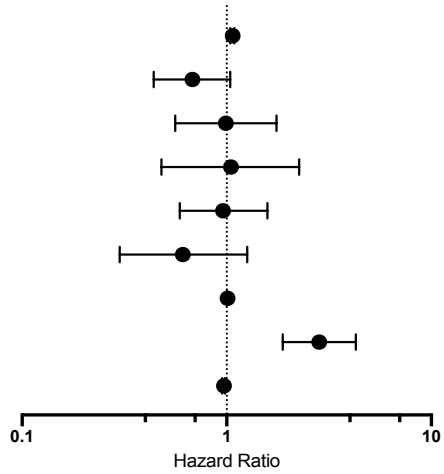
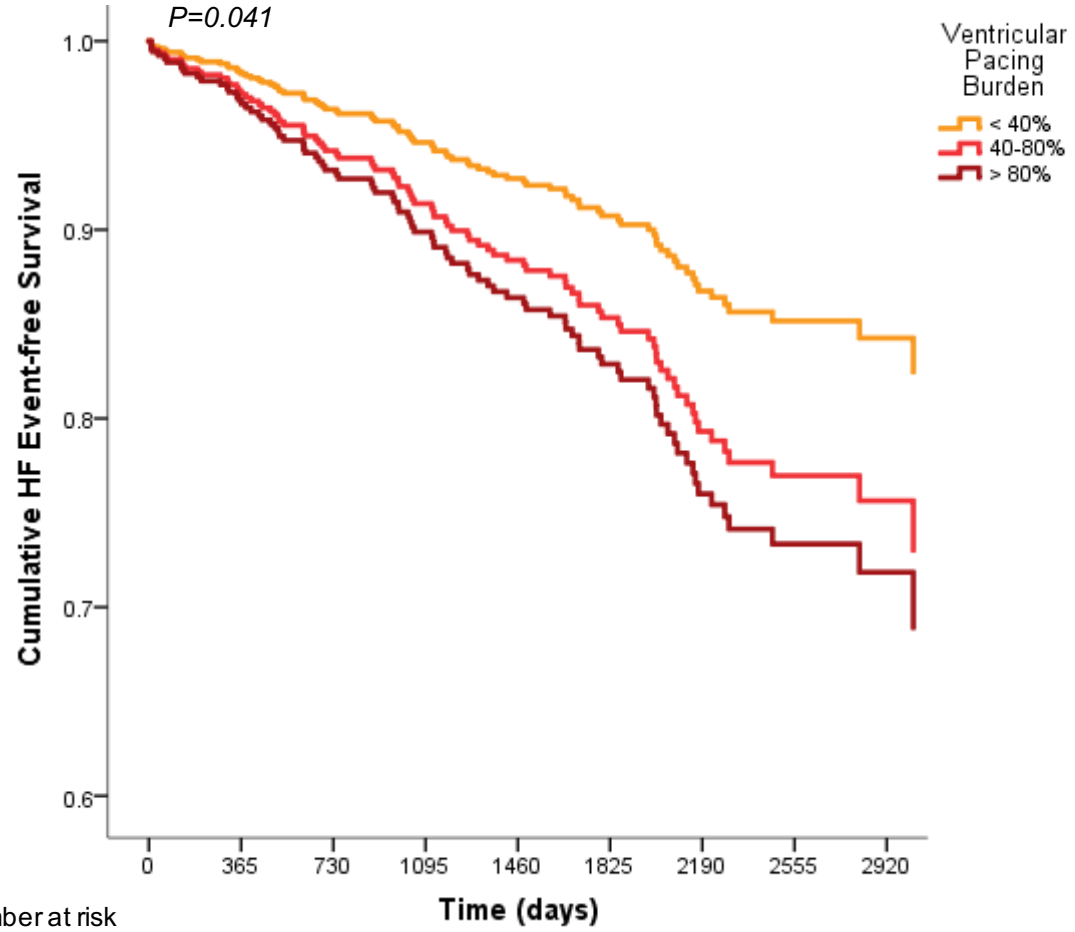


Figure 4.3 Forest plot showing factors associated with risk of heart failure death, heart failure hospitalisation and CRT upgrade amongst pacemaker patients after pacemaker

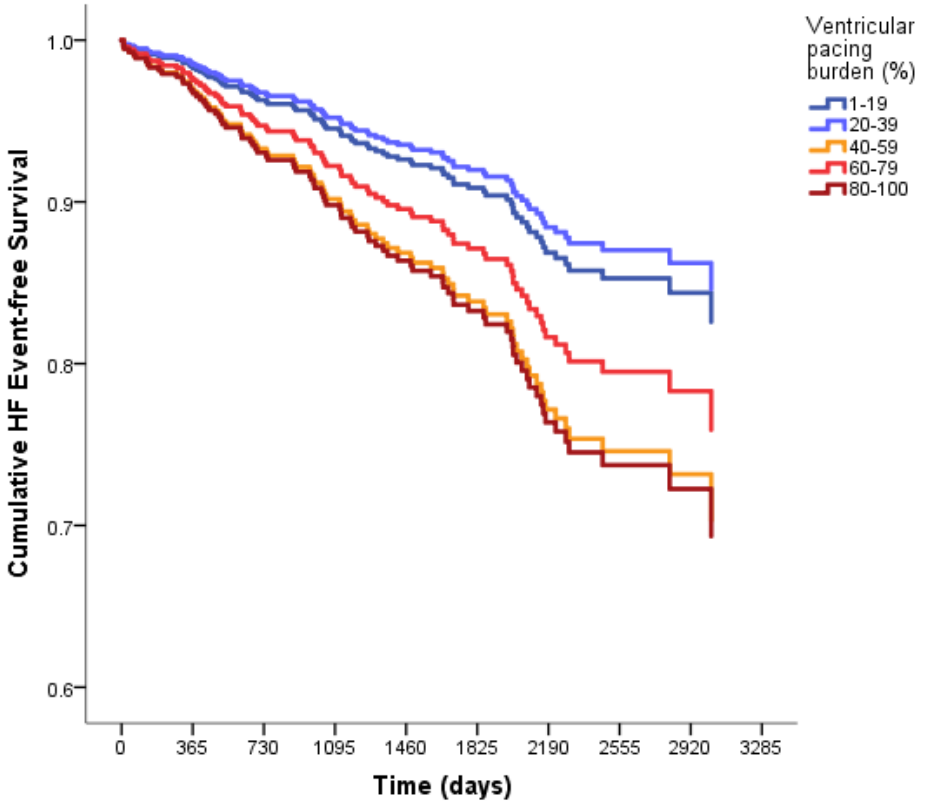
There was an association between the burden of RV pacing and HF event (hospitalisation or death) when adjusted for age and sex. RV pacing greater than 40% demonstrated an increased risk compared to patients with a RV pacing burden less than 40%, with the greatest risk observed in those paced greater than 80% (p=0.041) (Figure 4.4). Further analysis demonstrated a stepwise increase in the rate of HF events with RV pacing burden, but the association was non-significant (p=0.139) (Figure 4.5).

Figure 4.4 Kaplan Meier showing age and sex adjusted HF event-free survival according to baseline ventricular pacing burden.



Number at risk									
< 40%	207	196	181	164	147	118	80	51	23
40 - 80%	89	83	74	69	61	51	37	27	10
> 80%	209	189	166	142	124	96	70	47	19

Figure 4.5 Kaplan Meier showing age and sex adjusted HF event-free survival according to ventricular pacing burden (per 20%).



Number at risk									
0-19%	161	153	143	129	114	93	62	40	20
20-39%	41	37	32	30	29	23	17	11	3
40-59%	55	51	46	42	37	28	24	20	7
60-79%	37	36	31	30	26	25	13	7	3
80-100%	210	190	167	143	125	96	70	47	19

4.5 Discussion

The presented data are the first to investigate the long-term progression of adverse LV remodelling and HF syndrome in a contemporary cohort of patients receiving long-term pacemaker therapy. The novel findings are that LV size and function progressively worsen in this cohort, and that those patients in whom there is a change in LV function or remodelling, suffer a heightened incidence of HF events despite the competing risk of non-cardiovascular death for these elderly patients. Predictors of HF for patients post PGR may be somewhat different to those of patients undergoing de novo pacemaker implantation. Collectively, this extensive dataset of pacing, echocardiographic, clinical variables, and clinical outcomes, highlights the opportunities for optimising device prescription at PGR.

4.5.1 RV pacing and left ventricular remodelling

Of the surviving patients that consented to a follow-up assessment, over half experienced a clinically or prognostically significant deterioration in LV systolic dysfunction or LV dilatation over time, unrelated to newly diagnosed cardiac events. People developed LV remodelling even though they had already had their pacemaker for more than 7 years. Asymptomatic LVSD is a common finding in patients with permanent bradycardia pacemakers, although the incidence of 60% at follow-up found in this study is higher than in previous reports (Gierula et al., 2015, Ahmed et al., 2017), possibly related to the long duration of pacing in this group. The only clinical variables which independently predicted worsening LVSD were baseline LV size and function, with patients with higher LVEF at baseline and smaller LVESVi actually

predicting a higher likelihood of deterioration, perhaps because there is less scope for change in those patient with existing LV dilatation and LV impairment. Interestingly, it is important to also consider those in whom RV pacing has no detrimental effect; if LV remodelling or HF is not observed at least 10 years after pacing initiation, these patients are unlikely to be susceptible to the detrimental effects of RV pacing. Yet these findings may suggest that all patients, even those with preserved LV size and function at implant, may benefit from protective therapy.

Few longitudinal studies have described the long-term remodeling effects of RV pacing. For example Nielsen and colleagues examined regional blood flow in response to RV pacing (Nielsen et al., 2000). A total of 15 patients randomised to DDD pacing experienced a reduction in LVEF (SE) from 61 (0.09) to 56 (0.07)% at one year. In a second randomised study, there was a reduction in LVEF from 55 (3) to 47 (3)% after 18 months in 12 patients allocated RV apical pacing, which was seen alongside a significant increase in myocardial perfusion defects on myocardial scintigraphy (Tse et al., 2002). Finally, of 177 patients randomly exposed to either high (mean 90%) or low (mean 17%) rates of RV pacing, produced by pacing either DDDR with a fixed short or long AV delay, increases in LV end-systolic volumes of 11mL vs 3mL were reported with reductions in LVEF of 4% vs 3% respectively after 2.9 years (Nielsen et al., 2003). Crucially, all of these studies have concentrated on the change in LV function following RV pacing initiation after *de novo* device implantation. To our knowledge, no studies describe changes in

patients with existing devices limiting the real-world application to patients post PGR.

Hence, until now, it remained unclear if changes in LV function are pacemaker-induced or merely the result of ongoing cardiac co-morbidity and also whether the pattern of cardiac dysfunction in the presence of a pacemaker is characterised by an acute drop and stabilisation, or a chronic progressive decline. This critical finding has never been described previously and supports the requirement for ongoing review of patients beyond the initial implant period.

We did also however identify that patients experiencing a clinically significant reduction in LV function at follow-up, commonly had higher LV systolic function at baseline, than those without a clinically significant reduction in systolic function. This is true even in the presence of increased rates of medical therapy and reduced systolic BP's and heart rates. The current guidance for patient evaluation (Kusumoto et al., 2019, Brignole et al., 2013a) may therefore be suboptimal as these patients did not fulfil a clinical indication for CRT implantation, yet may have benefitted in the long-term from biventricular pacing rather than detrimental RV pacing.

4.5.2 Avoiding detrimental right ventricular pacing

Although our study did not examine the effects of pacemaker reprogramming, it reinforces that careful personalised programming to avoid RV pacing should be aimed for in all patients, especially those >40% RV pacing.

In fact it has been recommended additional clinical variables obtained readily from patients without complex investigations may form an easy method to indicate patients who could benefit from a more extensive review or additional therapy (Brunner et al., 2004). However, our data indicate to appropriately assess a patients' risk, clinicians need clinical history, pacing, and echocardiographic data to base a clinical decision on.

At the point of PGR, the clinician has evidence of the patients' historic pacing requirements, hence it is an opportune time to evaluate the patient to enable optimal device prescription. Our data could add to the discussion whether CRT upgrade should be considered for all patients with substantial RV pacing requirements without further reprogramming options regardless of LVEF at PGR. Further evidence is required in the form of randomised trials, although this study provides great insight into which data need to be collected.

4.5.3 Patient Survival

It is important to note that a large proportion of patients within the cohort did not survive to their next generator replacement. Those that did survive were typically younger, in sinus rhythm with a low ventricular pacing requirement and a higher LVEF at baseline. However, even those patients that survived

differed significantly at follow-up from their baseline information. Some had developed multiple co-morbidities, and medical therapy had changed with initiation or uptitration of cardiovascular medical therapy, with lower mean resting heart rates and systolic blood pressures than their first visit. Interestingly, the patients also showed less RV pacing burden, likely due to more patients having a pacemaker capable of utilising a RV pacing avoidance mode.

4.5.4 HF incidence in pacemaker device patients

In total, 98 (19%) patients experienced HF events during the follow-up period. Most of those (n=87(88%)) that suffered a HF event during the study period, did not survive to attend follow-up. This figure is higher than that observed in patients receiving their first device where a 10.6% incidence of HF has been documented, with the highest risk occurring within the first 30 days after implantation (Tayal et al., 2019). Whilst we cannot assess the impact of pacemaker use and underlying cardiac function as this was not assessed in the Danish cohort, our cohort had a higher incidence of cardiovascular co-morbidities, which is unsurprising given they had already received a decade of pacemaker therapy, and may in part explain these differences.

The patients in our cohort that experienced a HF event were older, had a lower LVEF at baseline, and were more likely to be in AF with a higher RVP burden, although the underlying cause of their deterioration is likely to be a combination of factors.

The heightened risk of HF in people with a cardiac device capable of right ventricular pacing, receiving an unavoidable high burden of pacing has stimulated clinical research in this area to explore alternative options.

Initially, this drove research into alternate RV pacing sites, such as the septum, which although carried out extensively and robustly in randomised clinical trials, routinely found no clinically significant benefit in terms of avoiding LV remodelling (Kaye et al., 2014, Da Costa et al., 2013, Saito et al., 2015)

There have since been limited trials examining the efficacy of cardiac resynchronisation therapy (CRT) as both initial device (BLOCK-HF) (Curtis et al., 2007) and as an upgrade (Gierula et al., 2013). The BLOCK-HF trial of CRT at initial implantation has been widely discussed but unable to change practice, in part due to the lack of true control group. Patients in the control group were programmed with a short atrioventricular delays, therefore encouraging RV pacing instead of intrinsic conduction, as is now routinely sought in clinical practice, which may have resulted in greater observed efficacy in the intervention arm due to worse than expected outcomes in the RV pacing arm.

The second study in which patients were randomly allocated to CRT upgrade or RV pacemaker at PGR, was a proof-of-concept study, thus has a small sample size and utilised surrogate endpoints (Gierula et al., 2013). Its findings warrant further investigation on a larger scale with hard outcomes.

One of the reasons data have to date been insufficient is likely the heterogenous response in cardiac function to pacemaker therapy. Evident from our previous work and reiterated in the present analysis, is that patients with an RV pacing burden of greater then 80% are most at risk of HF, whilst those with a burden of 40-80% also have an increased risk compared to those paced less than 40%.

However, most patients with a high degree of RV pacing do not develop clinical heart failure, and whilst RV pacing burden has been correlated with LV systolic function (Gierula et al., 2015), the presence of high grade atrioventricular (AV) block alone does not reliably predict ongoing RV pacing burden in those undergoing initial pacemaker device implantation (Kiehl et al., 2017), as 12% of patients experience late AV conduction recovery, with an associated significant reduction in RV pacing burden with appropriate pacemaker programming

Even in the era of RV pacing avoidance algorithms, our study continues to support the previous finding of DAVID (Wilkoff et al., 2002) that first described the increases in risk of death or HF hospitalisation of those paced above 40% and 80%.

As a result of lack of consistency, patient selection, cost, complexity, and the effect of confounders, the CRT approach and septal pacing have not become accepted but the search for a more protective therapy continues in the more contemporary forms of His bundle pacing and LV transeptal pacing, which

although technically challenging have shown some early promise in providing effective cardiac pacing whilst preserving cardiac size and function (Mafi-Rad et al., 2016, Occhetta et al., 2006, Vijayaraman et al., 2017).

4.6 Limitations

This is a single centre, small observational study but benefits from reflecting contemporary practice. It is possible that patients who have heart failure syndrome, but were not hospitalised for heart failure, and that didn't have echocardiographic signs of systolic dysfunction or cardiac remodeling, were underrepresented in the current study. Additionally, there was no non-heart failure control group to compare the rates of heart failure events, and therefore we cannot determine causality. We particularly focussed on the incidence of systolic dysfunction and remodelling in an attempt to understand those patients whom we may be able to offer additional therapeutic strategies. The study was therefore not powered to assess changes in adverse events and quality of life in patients with adverse LV remodelling compared to those without.

One of the main limitations of the study is that a large number of patients were deceased at the screening date and therefore we were unable to obtain measures of cardiac function or remodeling for this patient group. It can be inferred that these patients were the most at risk of adverse cardiac events from baseline data. More frequent follow-up periods may have allowed for better risk stratification.

Finally, confounders of cardiac disease may have been present in analysis, however, the study was conducted in real-world setting and is therefore typical of the clinical scenario clinicians experience routinely in this patient population.

4.7 Conclusion

In summary, we have shown for the first time that changes in LV structure and function in patients exposed to RV pacing are progressive. Moreover, we have also been able to describe the factors associated with susceptibility to RV pacing-associated LV dysfunction. These findings have critical clinical implications since they imply the need for ongoing review of cardiac function in people with a high burden of RV pacing and that updated programming, medical review and consideration of additional device therapy may be essential for the avoidance of the most serious complication of pacemaker therapy.

Whether pacemaker-induced remodelling is associated with mortality will now be the subject of further work.

Chapter 5

Patient and pacing determinants of pacemaker battery longevity

5.1 Introduction

Whilst improvements have been made in pacemaker longevity, (Lau, 2017), there are few studies investigating the factors that influence pacemaker battery longevity in long-term observations. Pacemaker longevity is the number one concern of patients, particularly as people are living longer with pacemakers and often require multiple pacemaker generator replacements (PGR) (Dean and Sulke, 2016). Yet PGR's carry a higher procedural risk than initial pacemaker implantation (Manolis and Melita, 2017, Uslan et al., 2012), and are also expensive; device costs alone are approximately £3000 (Wenzl and Mossialos, 2018) in addition to the equipment, staff and catheter lab time cost (Ferguson Jr et al., 1996). As a consequence, the increasing number of PGRs is likely to add to the financial burden on the National Health Service. Therefore, it is important that clinicians understand all factors which may influence pacemaker longevity.

Awareness of clinical variables which might indicate a patient is likely to utilise their battery more quickly, may allow for a better device prescription at implant, for example a device with a larger battery capacity. Previous data have also suggested that pacemaker battery longevity could be preserved through careful individualised programming (Gierula et al., 2014, Crossley et

al., 1996, Stockburger et al., 2015), thus knowledge of the pacing variables which effect longevity could permit optimal device programming more readily.

The purpose of this study was to ascertain the clinical and pacemaker variables that may govern the estimated longevity of bradycardia pacemakers.

5.2 Objectives

To explore patient and pacemaker derived variables for potential determinants of estimated remaining battery longevity to understand factors that may influence battery longevity.

5.3 Methods

5.3.1 Study design

This was a cross-sectional cohort study of pacemaker patients implanted for bradycardia, assessed at the time of routine PGR in a single tertiary centre between 2008 and 2012. The study received ethical approval by the Ethics Research Committee (15/EM/0566).

5.3.2 Study population

5.3.2.1 Baseline

All patients undergoing elective PGR with a pacemaker implanted for bradycardia were invited to attend the cardiology department one week prior to their procedure. Patients were excluded if they were unable to provide informed consent, were under 18 years of age, had a complex cardiac device (implantable cardioverter defibrillator or cardiac resynchronisation therapy) or had structural congenital heart disease.

Referral for PGR was generally based upon the device reaching minimum estimated battery longevity remaining of between 3 to 6 months dependent on the patient's clinical status and pacing requirements.

5.3.2.2 Follow-up

In January 2017 the cohort were digitally reviewed and surviving patients were invited to return to Leeds cardiovascular clinical research facility for an in-person follow-up between 2017 and 2018.

5.3.3 Study procedure

At baseline, patients received a transthoracic echocardiogram, clinical assessment including height, weight, resting heart rate and blood pressure, past medical history was taken as well as their medical therapy documented.

Body mass index (BMI) was calculated. Pacemaker information was collected to record the indication for pacemaker implantation and the number of PGR procedures undergone. The pacemaker was interrogated to document device manufacturer, base rate, atrioventricular delays, atrial and ventricular pacing burden (AP; VP), and pacing mode.

Blood tests were performed to assess full blood count, urea & electrolytes and N- terminal pro b-type natriuretic peptide (BNP). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease method. Each patient underwent two- dimensional transthoracic echocardiography (Vivid 7, Vingmed, USA) to assess left ventricular ejection fraction (LVEF), calculated using Simpson's biplane method (Ponikowski et al., 2016). Left ventricular end diastolic and systolic diameters (LVEDD; LVESD) were also assessed as measures of LV remodeling. Quality of life was assessed using the EQ-5D-3L questionnaire including a visual-analogue scale.

Hospitalisation and mortality data were collated on 12th January 2017 from both digital and paper records. All surviving patients were invited for an in-person follow-up assessment which included a repeat of all baseline measurements.

Additional pacing variables were documented on follow-up pacemaker interrogation with a particular focus on the use of a sleep, rest or hysteresis

mode, minimum estimated remaining battery longevity, lead impedances, thresholds and outputs, and number of years the device had been in situ.

5.3.4 Statistical analysis

Data analysis was undertaken using SPSS software (IBM SPSS Statistics Version 22). Continuous data is presented as the mean (± standard deviation (SD), with categorical variables presented as number (%). A sample size calculation was not undertaken as all patients were invited to return, with data collection governed by patient eligibility.

Linear regression analysis was used to determine the association of 14 clinical factors and 12 pacing factors on measured estimated minimum remaining battery longevity in a univariate fashion. Variables included age, BMI, heart rate, Sex, history of ischaemic heart disease (IHD), baseline LVEF, LVEDD and LVESD, intrinsic atrial rhythm, beta-blocker and ACEi prescription, AF, AP and VP burdens, presence of search AV, pacing mode, rate response programming, base rate, presence of sleep rate, PAVD, SAVD, atrial lead energy consumption and ventricular lead energy consumption. There was insufficient power to undertake multivariable linear regression due to the nature of the post-hoc analysis. Statistical significance was nominally set at $p<0.05$ but I have presented absolute values to allow a judgement to be made given the post-hoc nature of the study.

5.4 Results

5.4.1 Baseline Characteristics of Patients at Pulse Generator Replacement

A total of 572 patients were originally enrolled immediately prior to their PGR. This represented more than 95% of patients undergoing PGR during the study period (approximately 600). Of the cohort, 55 were involved in an interventional trial on pre-emptive CRT upgrade, or underwent pacemaker upgrade to CRT as part of routine clinical practice. The data on these patients were excluded from analysis due to potential differences in outcomes from programming and battery capacity.

After 74(59-92) months of follow-up, 253 patients had died, 37 declined to return, 27 were no longer capable of providing informed consent for the follow-up visit, 34 were lost to follow-up due to moving away from the area or not responding to either research or clinical communication, and 3 patients received clinically indicated upgrade to CRT.

Clinical factors associated with mortality and HF admissions have been described in chapter 4. Consequently, 164 surviving, eligible patients (79%) consented to return for follow-up 121 (104-132) months after their baseline visit and were included in the present analysis.

Table 5.1 summarises the patient characteristics and basic pacemaker data for the cohort at follow-up. Mean age of the cohort was 76 (±11) years and 60% were men. The cohort at follow-up demonstrated a similar proportion of people who had suffered a myocardial infarction (MI) and undergone coronary artery bypass grafting (CABG) (9% vs 7%; p=0.368, and 16% vs 15%; p=0.828 respectively), and a slightly higher proportion of people had received percutaneous coronary intervention (8% vs 5%; p=0.070) and type II diabetes (17%) compared to baseline. Consequently, more patients at the follow-up visit were taking beta blockers (51%), ACE inhibitors/ARBs (48%) and furosemide (20%) than at baseline. The mean quality of life score derived from the EQ-5D-3L visual-analogue scale was 69 (±22).

The distribution of basic programming mode was DDD (31%), AAI+ (28%) or VVI (32%). Very few had a basic mode of DDI (4%), or VDD (5%). Pacing burden at baseline in the right atrium was 23(1-69)% and ventricle was 12(1-97)%. The majority of patients (63%) required ventricular pacing less than 20% of the time, although a third (29%) had a ventricular pacing proportion of over 80%. Patients routinely had a base rate of 50bpm. The mean LVEDD was 48±7mm, with a mean LVEF of 48±11%. Clinical changes between baseline and follow-up for the returning patients were explored in Chapter 4.

Table 5.1: Characteristics of the 164 survivors that returned for follow-up

Patient Demographics and clinical history	
Age (years)	76 (11)
Sex (male)	98 (60)
Atrial Fibrillation	56 (35)
Myocardial Infarction	15 (9)
Diabetes Mellitus	27 (17)
CABG	26 (16)
PCI	13 (8)
CVA	25 (15)
Haemodynamic data	
Systolic Blood Pressure (mmHg)	129 (22)
Resting Heart Rate (bpm)	69 (13)
Pacing data	
Atrial Pacing Burden (%)	23 (1-69)
Ventricular Pacing Burden (%)	12 (1-97)
Paced >80%	48 (29)
Pacing Mode	
DDD	51 (31)
DDI	6 (4)
VDD	8 (5)
VVI	53 (32)
RV pacing avoidance mode (AAI+)	46 (28)
Base Rate (bpm)	50 (8)
Echocardiographic Data	
LVEF (%)	48 (11)
LVEDD (mm)	48 (7)
LVEDV (mL)	109 (89-141)
LVESV (mL)	53 (42-75)
LVESVi (mL/m^2)	28 (23-38)
Medications	
Beta blocker	84 (51)
ACE inhibitor/ARB	79 (48)
Furosemide	33 (20)
Quality of Life	
EQ-5D VAS	69 (22)

Normally distributed continuous variables are shown as mean (standard deviation), non-normally distributed continuous variables are shown as median (interquartile range). Categorical variables are shown as n (%). CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention, CVA; cerebrovascular attack, BP; blood pressure, LVEF; left ventricular ejection fraction, LVEDV; left ventricular end diastolic volume, LVESV; left ventricular end-systolic volume, LVESVi; left ventricular end-systolic volume index, ACE; Angiotensin-converting-enzyme, ARB; Angiotensin II receptor blockers, VAS; visual analogue scale. *denotes significance

5.4.2 Clinical characteristics associated with longevity

Table 5.2 contains the results of the analysis of clinical characteristics readily available at pacemaker implant.

Univariate analysis demonstrated that no single clinical characteristics were significantly associated with estimated remaining minimum pacemaker battery longevity.

Table 5.2: Univariate regression analysis of patient characteristics on minimum estimated remaining device longevity

Characteristic	B	Std. Err.	*β*	*t*	*p*	95% CI	
Age (years)	-0.032	0.021	-0.119	-1.525	0.129	-0.073	0.009
Sex (Male)	0.906	0.493	0.142	1.838	0.068	-0.067	1.879
Weight (kg)	0.016	0.012	0.107	1.281	0.202	-0.009	0.040
HR (bpm)	0.016	0.018	0.072	0.915	0.362	-0.019	0.051
IHD	0.576	0.660	0.068	0.874	0.383	-0.726	1.879
Pacing Indication	0.100	0.062	0.131	1.610	0.110	-0.020	0.221
Sinus Rhythm	0.319	0.634	0.039	0.504	0.615	-0.932	1.570
LVEF (%)	0.002	0.023	-0.006	-0.079	0.937	-0.048	0.044
LVEDV (mL)	0.001	0.004	0.027	0.339	0.735	-0.007	0.010
LVESV (mL)	-0.002	0.009	-0.021	-0.254	0.800	-0.020	0.015
BNP (pg/mL)	0.000	0.000	-0.017	-0.210	0.834	0.000	0.000
Beta Blocker	-0.817	0.485	-0.131	-1.686	0.094	-1.774	0.140
ACEi/ARB	-0.502	0.488	-0.081	-1.030	0.304	-1.465	0.460

HR; heart rate, IHD; ischaemic heart disease, BNP; Brain natriuretic peptide, ACEi; Angiotensin-converting-enzyme, ARB; Angiotensin II receptor blockers, VAS; visual analogue scale

5.4.3 The impact of pacing variables on longevity

Remaining battery longevity was negatively associated with increased base rate (-0.06, 95% CI -0.12, 0.00; p=0.047) and higher ventricular lead output amplitude (- 0.94, 95% CI -1.74, -0.13; p=0.024). A positive association was found with sleep or rest rate programmed on (1.75, 95% CI 0.67, 2.83; p<0.01). Additionally, pacing mode was associated with remaining longevity (AAI+ compared to DDD, VVI, DDI and VDD, OR of 0.37, 95% CI <0.01, 0.73, p=0.049), with devices programmed AAI+ and DDD showing the maximum estimated minimum battery longevities.

Higher atrial output amplitudes appeared to have a detrimental effect on battery longevity, although did not reach significance (-1.47, 95% CI -2.99, 0.06, p=0.059). Other variables such as paced and sensed atrioventricular delays, lead impedances, or the activation of an atrioventricular search algorithm or rate adaptive pacing had no effect on remaining minimum battery longevity.

Table 5.3. Univariate regression analysis of pacemaker characteristics on minimum estimated remaining pacemaker longevity.

Variable	B	Std. Err.	*β*	*t*	*p*	95% CI	
Years of Implant	-0.36	0.14	-0.23	-2.58	*0.011	-0.64	-0.84
Manufacturer (Medtronic vs St Jude Medical, Boston Scientific and Vitatron)	0.80	0.31	0.20	2.55	*0.012	0.18	1.41
System (Dual Chamber)	0.61	0.82	0.06	0.75	0.457	-1.01	2.24
AF burden (%)	0.01	0.01	0.07	0.84	0.401	-0.01	0.02
AP burden (%)	-0.14	0.01	-0.17	-1.80	0.074	-0.03	<0.01
VP burden (%)	<0.01	0.01	-0.05	-0.58	0.565	-0.02	0.01
AV Search (on)	0.12	0.50	0.02	0.24	0.809	-0.87	1.12
Mode (DDD)	0.37	0.19	0.15	1.99	*0.049	<0.01	0.73
Rate response (on)	-0.29	0.50	-0.05	-0.58	0.564	-1.27	0.70
Base rate(bpm)	-0.06	0.03	-0.16	-2.00	*0.047	-0.12	<0.01
Sleep/rest/hysteresis rate (on)	1.75	0.54	0.30	3.21	*0.002	0.67	2.83
PAVD (ms)	0.01	0.01	0.13	1.30	0.197	<0.01	0.02
SAVD (ms)	0.01	0.01	0.01	0.95	0.344	-0.01	0.02
Atrial impedance (ohms)	<0.01	<0.01	-0.10	1.05	0.298	<0.01	0.01
Ventricular impedance (ohms)	<0.01	<0.01	0.07	0.88	0.378	<0.01	<0.01
Atrial output (V)	-1.47	0.77	-0.19	-1.91	0.059	-2.99	0.06
Atrial output (PW)	-0.47	0.89	-0.05	-0.53	0.595	-2.23	1.29
Ventricular output (V)	-0.94	0.41	-0.21	-2.28	*0.024	-1.75	-0.13
Ventricular output (PW)	-0.43	1.63	-0.03	-0.27	0.792	-3.66	2.79

AF; atrial fibrillation, AP; atrial pacing, VP; ventricular pacing, AV; atrioventricular, PAVD; paced atrioventricular delay, SAVD; sensed atrioventricular delay.

5.5 Discussion

The present data are the first to investigate the relevance of clinical characteristics compared with programming options in predicting estimated pacemaker battery longevity. Although, due to the lack of transparency around the algorithms used by industry. a relatively large number of investigator-led studies have attempted to understand the pacing variables that contribute to pacemaker longevity estimates, few investigations have included clinical characteristics and their effect on pacemaker battery longevity.

5.5.1 The effect of clinical characteristics on estimated battery longevity

The results of my study suggest that at baseline, clinical characteristics of the patient are not a driver in regards to battery longevity utilisation, and that technological variables and programming are key drivers of estimated remaining minimum battery longevity.

Since pacemaker longevity is the primary issue for patients, it is essential that the device is selected carefully prior to the procedure and the programming options tailored immediately afterwards.

5.5.2 The impact of generator battery choice

As with defibrillators (Paton et al., 2019), pacemaker battery estimated longevities greatly between manufacturers. Differences in battery technology and chemistry, are likely to be contributors to this variability (Kenny, 2005). For most patients, the primary implantation is the only opportunity to carefully select the correct system and although this is usually focussed on leads and approach, consideration should be given to the battery features to prevent early reintervention.

5.5.3 The impact of basic programming mode

A surprising outcome was that device system (e.g. single or dual chamber) was not associated with estimated remaining battery longevity. In line with guidance (NICE, 2014b), patients in sinus rhythm were generally programmed to DDD mode, while most of those in AF were programmed VVI. Since battery size and therefore longevity is tailored to the number of leads (single chamber versus dual chamber devices), were programming always to reflect this, it might be expected that patients with DDD devices and VVI devices would have similar generator longevity. However, discrepancies occur since many patients with a DDD device for sinus node disease develop AF and are reprogramming to a ventricular only pacing mode such as VVI. Only 10% of patients with AF that returned to follow-up had a single chamber device implanted, suggesting they had longstanding AF, which was proven in chapter 4 to be a significant predictor of mortality in the original cohort, and therefore this patient group were underrepresented in this analysis on device longevity.

Dual chamber pacemakers are larger (Ellenbogen et al., 2016). The clinical scenario of a single functioning ventricular lead and a larger battery capacity means the subgroup of patients in AF with a dual chamber system programmed to VVI are likely to have augmented battery longevity. In fact, 27% of patients implanted at PGR with a dual chamber device were later programmed to VVI or VVIR.

VVI mode, previously demonstrated to prolong service time, also improves patient outcomes (Sharma et al., 2005). The DAVID trial (Wilkoff et al., 2002) found that patients paced in DDD mode with the aim to reduce pause-induced tachyarrhythmia's, were actually more likely to have ventricular pacing-induced electrical activation abnormalities. Currently there remains insufficient data to suggest a default programming of VVI, even in patients with SR, despite the potential benefits to the patients in terms of battery longevity and RV pacing avoidance. This is due to the non-physiological nature of VVI pacing.

5.5.3 Device programming to maximise longevity

Whilst clinical variables had little impact, some pacing variables had significant associations with estimated remaining battery longevity. The univariate analysis suggested for very beat per minute (bpm) of higher base rate, there is a loss in longevity of 0.06 years, equating to an approximate

reduction in estimated longevity of 3.6 months for every 5bpm increase. Whilst it is well documented that higher base rates result in more pacing and increase energy consumption, whether this relationship is linear and how therefore the range of base rates that could be chosen might be related to longevity warrants further investigation.

On balance, the data also suggest a relationship between longevity and atrial pacing burden (although this was not below my pre-specified significant cut-off for p values). It was expected that increasing pacing burden may cause a reduction in battery longevity since it requires additional energy (Kindermann et al., 2001).

I also found that programmed output, especially of the ventricular lead, is related to battery longevity. At higher pacing outputs, more energy is consumed to produce the programmed voltage (Lau, 2017). Whilst existing literature surrounding pacemaker battery preservation already focuses on the need for low but safe lead outputs (Zlatanovic et al., 2007, Tyers, 2011, Boriani et al., 2006), clinicians routinely follow historical advice on output safety margins due to the lack of contemporary advice in guidelines.

Continual adjustment of pacing output according to frequent automatic threshold measures have also been shown to improve device battery longevity (Crossley et al., 1996, H., 2014, Schwaab et al., 1998) by up to

4.25 (±2.14) years . In one observational study, over 8 years, 3% of patients with automated outputs vs 65% of those with fixed outputs underwent PGR (Crossley et al., 1996). However, consideration should be given to the efficacy of the algorithm which are different between manufacturers. Whilst some algorithms monitor the threshold on a beat-to-beat basis (Tyers, 2011), others perform the measurement once daily (Medtronic, 2020), leading to variation in the safety margin of the output provided. On the other hand, in the context of atrial fibrillation, autothreshold algorithms compromise battery longevity (Iglesias et al., 2014).

My data confirmed that sleep, rest rates or hysteresis are significantly associated with estimated remaining longevity and that activating these could extend battery longevity by up to 1.75 years. These algorithms were specifically introduced to reduce unnecessary pacing (Ellenbogen et al., 2016), but have perhaps inadvertently also improved battery longevity. These options are present in all modern pacemakers, but are infrequently activated partly because they are not part of manufacturer default ‘out of the box’ settings. Pacing at a higher base rate while the patient is sleeping or inactive is rarely necessary and may even be detrimental to patient’s wellbeing and morbidity (Jamil et al., 2016, Wilkoff et al., 2002).

Attention to these simple options could have a significant impact if applied routinely to a pacemaker population particularly when considering that the

potential extension of generator life could be even greater than found in my dataset if applied at the time of implantation.

Another potential contributor to improved generator longevity are the now commonplace RVP avoidance algorithms, activation of which is associated with an extension of pacemaker longevity and a reduction of PGR requirements (Dean and Sulke, 2016, Zlatanovic et al., 2007, Benkemoun et al., 2012b). In a randomised trial of usual care programming compared to the novel RVP avoidance algorithm, longevity was extended by 14 months, resulting in fewer PGR's in 23% of those patients in whom it was programmed on (Stockburger et al., 2015).

A focus on longevity could translate into fewer generator replacements and all possible energy-saving features should be assessed when programming modern cardiac devices, as combining those with potential is the approach most likely to have the greatest effect. Based on these findings from the present work, the greatest benefit is likely to come from optimising pacemaker lead outputs and automatic threshold and output algorithms, base rate, sleep, rest and hysteresis algorithms, and RV pacing avoidance.

5.6 Limitations

This was a real-world investigation of routine clinical practice. As such, the measure utilised for battery longevity was one applicable across all devices to avoid exclusion of a large number of patients, and readily utilised in practice. However, the longevity estimated is dictated by the pacemaker's internal algorithm, and may not reflect the true service time of the pacemaker. Nevertheless, the measure has been presented in many other studies investigating battery longevity (Zlatanovic et al., 2007, Crossley et al., 1996).

The present study, by necessity excluded the 252 patients (44% of the original cohort) who had died prior to the invitation to follow-up. Not surprisingly, the surviving patients had significantly different clinical characteristics at baseline compared to those that had died, potentially affecting the results of this analysis due to more severe disease and more extreme pacing characteristics. Whilst these patients' devices could have been interrogated post mortem, longevity estimates are likely to be unreliable as pacemaker use and variables will instantly change after death. The aim of this study though, was to provide long-term follow-up data of patients post PGR, and therefore the number of surviving patients was expected.

Additionally, it is unknown when programming changes were made between baseline and follow-up. Earlier changes will have had a greater effect on device longevity, whereas later changes will have had less effect on battery

longevity. However, these data somewhat represent a worst case scenario in that sense, as changes implemented at implant would have an even greater effect.

5.7 Conclusion

Pacemaker battery longevity cannot be estimated from patient clinical characteristics at device implant in this cohort. Device selection and programming variables are however important independent predictors of remaining longevity. It is crucial that clinicians select appropriate pacemaker systems at implant, and tailor pacemaker settings during follow-up to maximise battery longevity and minimise expensive and disruptive PGR procedures.

Chapter 6

Optimising pacemaker and medical therapy for heart failure in pacemaker patients – the OPT-PACE randomised trial

6.1 Introduction

HF is much more common in people with pacemakers than in the general population, with a prevalence of up to 50% (Thackray et al., 2003, Gierula et al., 2015), yet it is frequently overlooked even though it has a major effect on mortality and morbidity (Shen et al., 1996, Jahangir et al., 1999, Brunner et al., 2004). In particular, pacemaker patients with HF with left ventricular systolic dysfunction (LVSD) and a reduced ejection fraction (HFrEF) have been under-represented, excluded, or their inclusion unreported in many trials of medical therapy for HFrEF. As such, there is no clear treatment strategy for these patients in either current HF or pacemaker guidelines. In addition, there is no known evidence surrounding the benefit of screening for HF in this population.

The aim of this study therefore, was to assess the effect of diagnosing and managing LVSD in people with pacemakers to assess the effect of proactive management on clinical outcomes in a randomised controlled trial.

6.2 Hypothesis

Does screening for heart failure using echocardiography enable optimisation of medical and device therapy to improve clinical outcomes in people with pacemakers for bradycardia?

6.3 Methods

6.3.1 Study Design

The study was a multicentre, randomised, open-label parallel group design trial investigating the effectiveness echocardiography-guided management in improving 12 month clinical outcomes in bradycardia pacemaker patients. The trial was registered on ClinicalTrials.gov. The trial was conducted according to principles outlined in the Declaration of Helsinki and received full ethical approval by the Health Research Authority and local authority (South Yorkshire Research Ethics Committee: 12/YH/0487, Appendices C and D).

6.3.2 Study population

Participants were recruited from one tertiary centre (Leeds Teaching Hospitals Trust (LTHT)) and two district secondary hospital centres (Harrogate District Foundation Trust (HDFT) and Bradford District Hospital Foundation Trust (BDFT). Patients were eligible if they had an implantable pacemaker for bradycardia for at least 12 months due to any indication in current clinical guidelines (NICE, 2014a), and were able to give informed consent.

Patients were ineligible if they had an implantable cardioverter defibrillator or cardiac resynchronisation device, were less than 18 years old, pregnant, had known HFrEF, were awaiting heart transplantation or had a severe co-morbidity with life expectancy of <1 year. Patients with significant cognitive impairment and those already under the care of HF services were not eligible.

6.3.3 Allocation and Intervention

At their routine pacemaker follow-up appointment consecutive patients were provided with a printed patient information sheet by the clinical team, and if willing to participate were invited to attend for a research appointment where they signed a consent form, following which baseline investigations were undertaken, before being randomly allocated on a 1:1 basis to intervention or usual care (Figure 6.1) using a randomisation schedule derived by an independent statistician and accessed through a web-based system. Those randomised to intervention received a transthoracic echocardiogram (TTE) to assess LV function. Patients with normal resting LV function remained under usual care with standard pacemaker follow-up. Patients in the echocardiography arm, found to have reduced LV systolic function (LVEF<50%) received medical management according to accepted guidelines for LVSD via a care pathway stratified by recruitment centre.

Patients recruited in the tertiary centre were referred to a multidisciplinary outpatient HF clinic where they were assessed, prescribed optimal HF medical

therapy, and underwent dose-escalation where possible (optimised care), whereas the echocardiography results of participants recruited at the two district centres were forwarded to their primary care team who took the lead in further management which could include referral to a local HF service (enhanced care) (Figure 6.1).

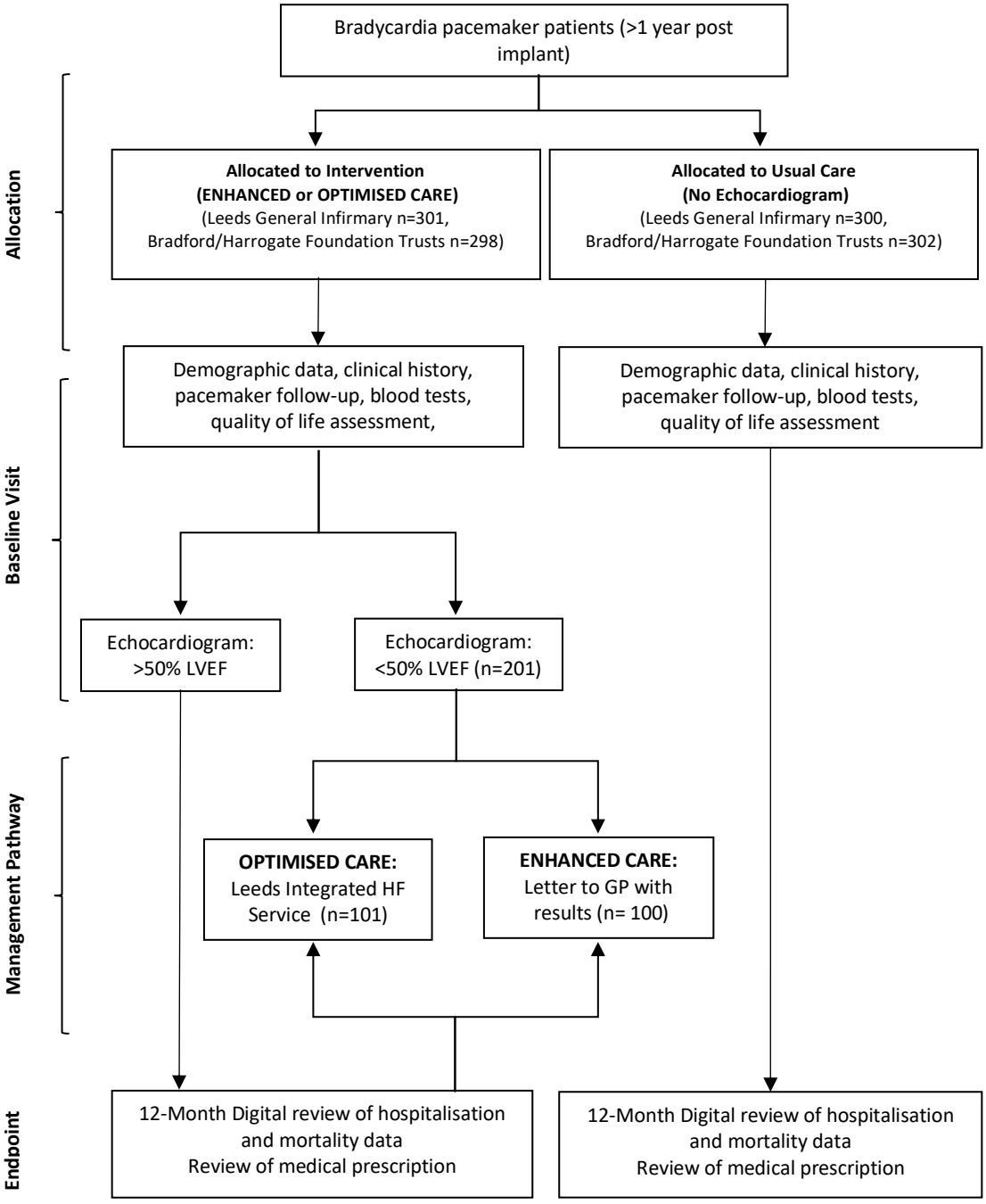


Figure 6.1: OPT-PACE CONSORT Flow Diagram

6.3.4 Outcome Measures

The primary outcome measure was a composite outcome of time from randomisation to date of first event of all-cause mortality or heart failure hospitalisation observed over a minimum follow-up of 12-months.
Secondary outcome measures included achievement of guideline-directed medications for HFrEF and quality of life as measured by the EuroQol (EQ5D) pre-randomisation and at 12-months.

6.3.5 Study Procedure

At baseline (pre-randomisation) each patient underwent a routine pacemaker follow-up, medical history, blood sampling for full blood count, renal function, and NT-proBNP, and quality of life assessment. In those allocated intervention, echocardiography was performed which included an assessment of LV function according to European Society of Cardiology criteria using Simpson's Biplane measures to determine LV ejection fraction (EF) (Lang et al., 2015). Electronic follow-up of all patients was performed at 12 months using hospital and primary care medical electronic patient records. Quality of life questionnaires were posted directly to patients.

6.3.6 Sample Size

OPT-PACE was powered to detect an absolute reduction in the primary event rate of 7.5% at one year in patients identified with cardiac dysfunction from 15% anticipated in patients randomised to the usual care pathway (Gierula et al., 2014). We assumed that one third of patients in both arms would have

cardiac dysfunction, and that a 7.5% reduction in clinical events in patients with LVSD would be diluted to an absolute 6% reduction in the intervention pathways. To detect a reduction in events from 15% to 9% (equivalent to a hazard ratio equal to 0.58) using log-rank analysis with an overall type 1 error rate of 0.05 (two-sided analysis) and a power of 0.90, required a total of 146 events to be observed in at least 1070 participants (assuming 18 month recruitment and 12-month follow-up). The target recruitment was inflated to 1200 patients in anticipation of drop-out.

6.3.7 Statistical Analysis Plan

Time to first HF hospitalisation or mortality was calculated from date of randomisation to date of event, or date of censor set at 31-Oct-2018 when all patients had minimum of 12-months follow-up. Event free survival estimates were calculated using the method of Kaplan-Meier compared across randomised groups using log-rank analysis. Secondary analysis of the primary outcome measure assessed the influence of patient baseline characteristics using multivariable Cox proportional hazards regression modelling reporting adjusted treatment effects. Variables considered for selection were age, previous history of myocardial infarction (MI), diabetes, coronary artery bypass grafting (CABG), or stroke (cerebrovascular attack, CVA), atrial rhythm, device technology, log of NT-pro BNP, pacemaker base rate, log of ventricular pacing burden and atrial fibrillation burden. Non-linear transformation of continuous covariates based on first degree fractional polynomials were considered. Planned exploratory subgroup analysis was based on resulting management of patients between optimized care (LTHT)

and enhanced care (Bradford and Harrogate) specified a priori. Quality of life data were scored and reported descriptively.

6.4 Results

6.4.1 Recruitment and baseline characteristics

A total of 1201 patients were recruited from the three centres between June 2013 and July 2017: 601 were recruited at the tertiary centre and 300 at each district centre. A total of 599 patients were randomised to intervention and received an echocardiogram, 602 were randomised to usual care. A single patient randomised to intervention had no diagnostic echocardiographic images obtainable.

Patient characteristics were balanced across randomised groups (Table 6.1). More than half (60%) were male and the mean (SD) age of participants was 75(12) years. Comorbidities included diabetes mellitus (21%), evidence of overt coronary artery disease (18%), history of coronary artery bypass grafting (CABG) (9%) and percutaneous coronary intervention (9%). Mean (SD) atrial and ventricular pacing percentages were 33(35)% and 40(42)% respectively with a mean base rate of 56 (7) bpm.

Table 6.1: OPT-PACE Patient demographics and Baseline at Randomisation

	Echocardiogram (n=599)	No Echocardiogram (n=602)	Total (n=1201)
Patient Distribution by Site			
District (Bradford)	148 (25%)	152 (25%)	300 (25%)
District (Harrogate)	150 (25%)	150 (25%)	300 (25%)
Tertiary (Leeds)	301 (50%)	300 (50%)	601 (50%)
Patient Demographics and clinical history			
Age (years)	74.9 (12.2)	75.5 (11.9)	75.2 (12.0)
Height (cm)	167 (13)	166 (14)	167 (14)
Weight (kg)	78 (16)	77 (17)	78 (17)
Atrial Rhythm			
Atrial Fibrillation	194 (32%)	162 (27%)	356 (30%)
Paced	46 (8 %)	62 (10%)	108 (9%)
Sinus Rhythm	359 (60%)	62.79 (63%)	737 (61%)
Myocardial Infarction No.(%)	105 (18%)	110 (18%)	215 (18%)
Diabetes Mellitus No.(%)			
Type 2	119 (20%)	128 (21%)	247 (21%)
Type 1	3 (0.5%)	3 (0.5%)	6 (0.5%)
CABG No.(%)	48 (8%)	57 (9%)	105 (9%)
PCI No.(%)	57 (10%)	50 (8%)	107 (9%)
CVA No.(%)	100 (17%)	90 (15%)	190 (16%)
Haemodynamic Data			
Resting Heart Rate (bpm)	69 (12)	69 (12)	69 (12)
Resting Systolic BP(mmHg)	138 (22)	138 (24)	138 (23)
Pacing Data			
Pacing indication N.(%)			
Atrioventricular block	213 (35.6%)	206 (34.3%)	419 (34.9%)
Sinus Node Disease	323 (53.7%)	320 (53.1%)	643 (53.5%)
Other	63 (10.7%)	76 (12.6%)	139 (11.6%)
Longevity of pacing (years)	7.2 (6.0)	7.2 (6.4)	7.2 (6.2)
Atrial Fibrillation burden (%)	30 (45)	28 (43)	29 (44)
Atrial Pacing burden (%)	32 (35)	33 (35)	32 (35)
Ventricular Pacing burden (%)	41 (43)	38 (42)	40 (42)
Base Rate (bpm)	56 (8)	56 (8)	56 (7)
Echocardiographic Data			
LVEF (%)	53 (9)		53 (9)
LVEDD (mm)	47 (7)		47 (7)
Medical Therapy Data			
Beta-blocker	264 (44)	264 (44)	528 (44)
ACEi/ARB	296 (50)	302 (50)	600 (50)
Loop Diuretic	136 (23)	125 (21)	261 (22)

Continuous data are expressed as mean (SD) or categorical data as n (%) as indicated. CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention, CVA; cerebrovascular attack, BP; blood pressure, LVEF; left ventricular ejection fraction, LVEDD; left ventricular end diastolic diameter; ACEi; Angiotensin-converting-enzyme inhibitor, ARB; Angiotensin II receptor blocker.

6.4.2 Prevalence of LVSD

Of 599 patients allocated intervention, 201 (34%) were identified as having LVSD; 101 of these received optimised care in HF clinics, and 100 received enhanced care informed by the echocardiogram via their primary care team (Figure 6.1). Patients had a mean (standard deviation) LVEF 53(9)% and LV end diastolic dimension 47(7)mm at randomisation. Patient and clinical characteristics were balanced across randomised groups.

6.4.3 Time to combined endpoint of all-cause mortality and HF hospitalisation

Patients were followed for a median of 30 months (inter-quartile range 22, 40) balanced across randomised groups. Of the 1201 patients' a total of 219 (18%) patients experienced a primary event of interest (first event being death in 158 patients, HF hospitalisation in 61). 12 month event-free estimates were 94% (95%CI: 92%, 96%) in intervention and 94% (95%CI: 91%, 95%) in usual care (Figure 6.2).

Table 6.2: Univariate estimates to event-free survival

Parameter	Parameter Estimate	Standard Err.	Wald χ^2 P-Value	Hazard Ratio (95%CI)	N
Echo					
Yes	-0.077	0.135	0.571	0.93 (0.71/1.21)	1201
Site					
Leeds	0.000	-	0.125	1.00 (-/-)	1201
Bradford	0.156	0.170		1.17 (0.84/1.63)	
Harrogate	0.328	0.161		1.39 (1.01/1.90)	
MI	0.568	0.152	< 0.001	1.77 (1.3/2.38)	1201
Diabetes Mellitus					
Type 1	0.126	1.003		1.13 (0.16/8.11)	
Type 2	0.429	0.151		1.54 (1.14/2.07)	
CABG	0.789	0.182	< 0.001	2.20 (1.54/3.15)	1201
PCI	0.149	0.225	0.508	1.16 (0.75/1.80)	1201
CVA	0.394	0.165	0.017	1.48 (1.07/2.05)	1201
Statin	-0.100	0.135	0.462	0.91 (0.70/1.18)	1199
Calcium Antagonist	-0.299	0.197	0.129	0.74 (0.51/1.09)	1199
Antiplatelet Therapy					
None	0.000	-	0.170	1.00 (-/-)	1198
Aspirin	0.159	0.151		1.17 (0.87/1.58)	
Aspirin + Clopidogrel	0.911	0.456		2.49 (1.02/6.07)	
Aspirin + Ticagrelor	0.240	0.584		1.27 (0.41/3.99)	
Clopidogrel	0.588	0.301		1.80 (1.00/3.25)	
Ticagrelor	-8.940	281.258		0 (0/.)	
Atrial Rhythm					
Sinus rhythm	0.000	-	< 0.001	1.00 (-/-)	1201
Atrial fibrillation	0.791	0.141		2.21 (1.67/2.91)	
Paced rhythm	0.111	0.262		1.12 (0.67/1.87)	
Technology	-0.747	0.151	< 0.001	0.47 (0.35/0.64)	1201
Age	-0.747	0.151	< 0.001	0.47 (0.35/0.64)	1201
Blood Na (*)	-0.092	0.025	< 0.001	0.91 (0.87/0.96)	872
Blood K	-0.030	0.064	0.638	0.97 (0.86/1.10)	870
Blood Ur	0.002	0.002	0.338	1.00 (0.99/1.01)	871
Blood Creatinine (*)	0.005	0.001	< 0.001	1.01 (1.00/1.01)	871
NT-proBNP	0.000	0.000	< 0.001	1.00 (1.00/1.00)	1108
Pacing Base Rate	0.022	0.006	< 0.001	1.02 (1.01/1.03)	1201
Ventricular Pacing Burden	0.005	0.002	0.003	1.01 (1.00/1.01)	1195
Atrial Fibrillation Burden	0.008	0.001	< 0.001	1.01 (1.01/1.01)	1197
	-0.000	0.002	0.958	1.00 (0.99/1.00)	978

Values are expressed as mean (95% Confidence Interval) or categorical data as n (%) as indicated. MI; myocardial infarction, CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention, CVA; cerebrovascular attack, Na; sodium, K; potassium, Ur; Urea, NT-ProBNP; Brain Natriuretic Peptide. * These variables were deemed significant but due to the high number of missing values, it was decided to not carry these variables forward.

There was no statistically significant difference between randomised groups in event-free survival (HR=0.94; 95% CI: 0.71, 1.21, χ^2_{LR}=0.32, p=0.57) (Figure 6.2). Estimated treatment effect adjusted by statistically significant

predictors did not alter results ($HR_{adjusted}$=0.95; 95% CI: 0.71, 1.26) (Table 6.2 and 6.3).

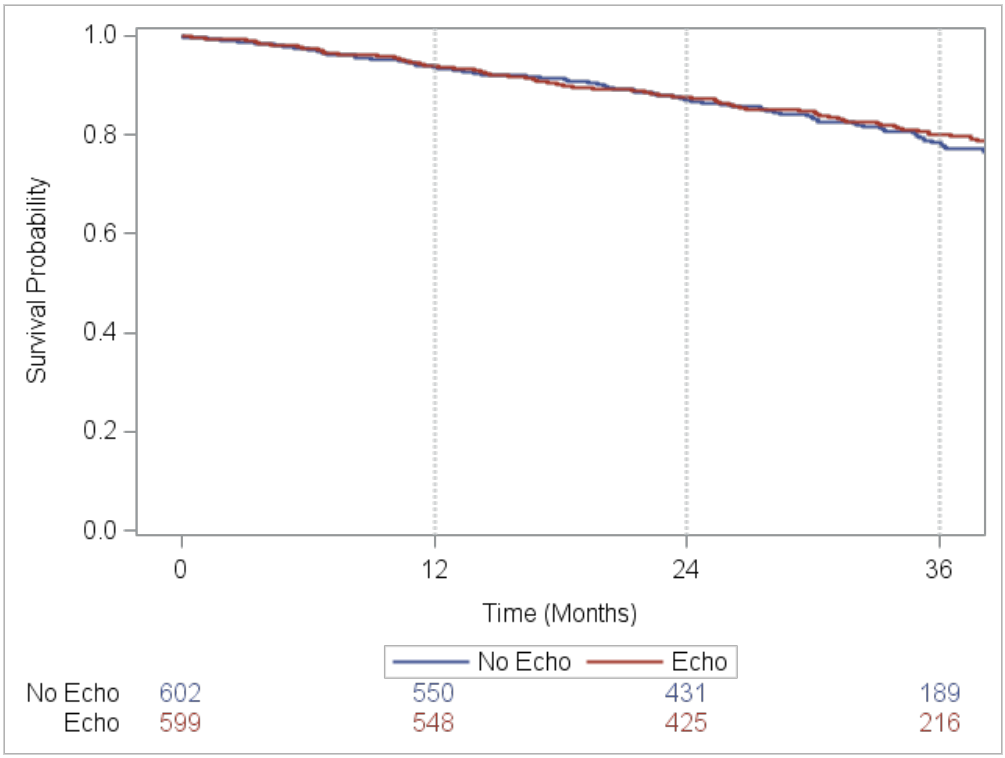


Figure 6.2 OPT-PACE Event Free Survival by Randomised Group

Table 6.3: OPT-PACE Multivariable Cox Proportional Hazards Model

Parameter	Parameter Estimate	Standard Error	Wald χ^2 P-Value	Hazard Ratio (95% CI)
Echo performed	-0.057	0.148	0.70	0.95 (0.71/1.26)
Site*				
Bradford	0.110	0.193	0.57	1.17 (0.76/1.63)
Harrogate	0.242	0.177	0.17	1.27 (0.90/1.80)
Age (years)	0.060	0.011	< 0.001	1.06 (1.04/1.08)
History of CABG	0.546	0.199	0.006	1.73 (1.17/2.55)
Log NT-pro BNP (pg/ml)	0.593	0.065	< 0.001	1.81 (1.59/2.05)
Base Rate (bpm)	0.015	0.007	0.045	1.02 (1.00/1.03)

Values are expressed as mean (95% Confidence Interval). CABG; coronary artery bypass grafting, PCI, NT-ProBNP; Brain Natriuretic Peptide.* Included as a stratification factor.

A pre-specified subgroup analysis of the patients who had LVSD, comparing those patients who went to a HF clinic against those who had results forwarded to their primary care team, was conducted. Out of the 599 patients who were randomised to echocardiogram, 201 (34%) patients experienced LVSD, 101 then attended the HF clinic and 100 received primary care management. The analysis indicated potentially diverging curves by 36 months in favour of patients allocated to echocardiography subsequently managed through HF clinic (HR 0.90; 95% CI 0.86, 0.93).

6.4.4 Secondary outcomes: medical therapy and quality of life

There was a significant difference in medical management at 12 months in patients randomised to undergo an echocardiogram subsequently managed in HF clinic compared with those receiving an echocardiogram and managed in primary care or those randomised to usual care without an echocardiogram. Out of 903 patients with completed 12 month drug data (468 intervention, 435 usual care), 421 (90.0%) of 468 patients in the intervention arm received further medical management (118 diuretic, 247 beta blocker, 255 ACE) compared with 359 (82.5%) of 435 patients in the usual care arm (79 diuretic, 211 beta blocker, 214 ACE). Patients with LVSD managed through the HF clinic were almost three times more likely at 12 month follow-up to be prescribed further medical management for Beta blockers (OR= 2.92, 95%CI: 1.43, 6.00) and Spironolactone or Eplerenone (OR= 2.95, 95%CI: 1.01, 8.61). There was also a smaller effect for ACE inhibitor therapy (OR= 1.86, 95%CI: 0.96, 3.59) (Table 6.4).

Table 6.4: Drug therapy of patients with LVSD from 12 month OPT-PACE follow-up

Medical Therapy	**HF Clinic (n=83)**	**Primary care (n=73)**	**Odds Ratio (95% CI)**
Beta blocker	67	43	2.92 (1.43, 5.99)
ACEi or ARB	58	40	1.86 (0.96, 3.59)
Loop Diuretic	31	23	1.27 (0.65, 2.47)
Spironolactone or Eplerenone	15	5	2.95 (1.01, 8.61)
Statin	46	37	1.19 (0.62, 2.22)
Calcium Antagonist	7	7	0.84 (0.28, 2.53)
Anti-platelet	27	19	1.34 (0.67, 2.70)
Amiodarone	2	2	0.86 (0.12, 6.30)
Warfarin	35	34	0.85 (0.45, 1.61)
Digoxin	8	5	1.42 (0.44, 4.52)
Anti-Diabetic	13	16	0.65 (0.28, 1.44)

Values are expressed as mean (95% Confidence Interval) or categorical data as n (%) as indicated. ACEi; Angiotensin-converting-enzyme inhibitor, ARB; Angiotensin II receptor blocker.

1198 of 1201 patients completed Quality of Life questionnaires at baseline (randomisation) with 878 (73%) also completing questionnaires at 12-months follow-up. EQ5D scores were similar at baseline (0.77±0.25 and 0.76±0.24) for intervention and usual care respectively. Conditional on survival, there was

a small reduction in EQ5D scores at 12-months for intervention and usual care groups(0.76±0.24 and 0.73±0.31).

6.5 Discussion

The trial has firstly confirmed that around one third of people with long-term standard pacemakers have LVSD and that the risk is highest in those with a history of overt cardiovascular disease and those with a high proportion of right ventricular paced beats. Furthermore, the data show that simply embedding echocardiography into a pacemaker service does not lead to improved outcomes within the shorter term. However, our data demonstrate that improved medical management in patients with a pacemaker for bradycardia when adopting fully integrated care including a pathway that not only provides an echocardiogram but also reacts to the results of the scans with initiation and optimisation of guideline directed medical therapy where relevant in the context of a specialized heart failure clinic. There is potential for this improvement in management to result in improved longer term clinical outcomes.

6.5.1 Prevalence, associations and outcomes of LVSD in a pacemaker population

Patients with permanent cardiac devices have been repeatedly shown to be at increased risk of LVSD or overt heart failure with a reduced quality of life, increased rate of hospitalisations and poor overall prognosis. This is particularly common in people receiving a high proportion of right ventricular

pacing and has previously been demonstrated in prospective randomised trials of pacemaker settings. Post-hoc analysis of the Mode Selection Trial (MOST) (Lamas et al., 2002) revealed that patients exposed to high quantities of RV pacing were at higher risk of HF hospitalisation over the 3 year follow-up period. MOST was not designed primarily assess the effect of RV pacing and so neither serial echocardiographic assessment, nor medical intervention was performed.

The adverse effect of RV pacing seems to be especially great in people with underlying cardiovascular disease, especially pre-existing heart failure (Martinelli et al., 2010, Curtis et al., 2007). The Dual-Chamber and VVI Implantable Defibrillator (DAVID) trial (Wilkoff et al., 2002) showed in 506 patients with HF due to LVSD, that pacing in a dual chamber synchronous mode with rate adaptive pacing activated, and a base-rate of 70ppm, led to increased ventricular pacing burden, associated with worse survival and higher incident HF compared with ventricular only pacing (rate-adaptive pacing deactivated) at a base-rate of 40ppm. The DAVID II trial subsequently investigated the effect of atrial pacing versus back-up ventricular pacing at differing base rates and found rate was not to be an important contributor to adverse outcomes, however it is difficult to draw conclusions form this data compared to the DAVID trial given the substantial differences in pacing modes (Wilkoff et al., 2009).

More recently, observational studies have shown that RV pacing burden is directly related to degree of LVSD (Nielsen et al., 2003, Brunner et al., 2004)

and has a linear relationship to risk of HF and cardiovascular death (Udo et al., 2015) but were unable to determine causality. The development of device-based algorithms to limit unnecessary ventricular pacing developed as a result of these trials have provided additional ability to reduce RV pacing but not eradicated LVSD in this population.

Although the adverse effects of RV pacing on LV function, and the fact that many patients with standard pacemakers do have LVSD or HF, have now been appreciated for many years, the management of pacemaker-associated LVSD or HF is underinvestigated. Although most of the large phase III trials of medical therapy for HF did not actively exclude people with standard pacemakers, and around 9% of people with HF have a standard pacemaker (TRIAL, 1999, McMurray et al., 2013, DAVY et al., 2012), none reported subgroup analyses or even hazard ratios for outcomes with intervention in this subgroup. Optimal care including renin-angiotensin-aldosterone system blockers (Abdulla et al., 2007, Packer et al., 2001, Van de Ven et al., 2010) and beta-adrenoceptor blockade (Chatterjee et al., 2013) has favourable effects on left ventricular remodeling and delays the progression of, or reverses LV dilatation and dysfunction and thereby improves long-term outcomes in HF patients without cardiac devices (Cubbon et al., 2011). Consequently, it is feasible that the introduction and uptitration of these therapies could improve long-term outcomes for patients with LVSD and a bradycardia pacemaker. However, as a result of a lack of data, guidelines make no particular mention of the investigation and management of pacemaker patients at risk of or with proven HFrEF except to comment on the

potential benefits of upgrading standard pacemakers to cardiac resynchronisation therapy in the presence of symptoms, LVSD and a high requirement for ventricular pacing (Brignole et al., 2013b).

Furthermore, despite advances in pacemaker reliability and battery longevity, pacemaker follow-up services have remained resolutely technical with intervals based upon historical risk of pacemaker device failure rather than focusing on patient requirements and routine reviews or assessments to identify prevalent or future risk of HF.

In contrast, this was a randomised clinical trial of the effect of introducing TTE to routine pacemaker follow-up as a method of identifying LVSD with a view to offering subsequent optimal management in patients with permanent pacemakers for bradycardia and LVSD.

This trial demonstrates that previously undiagnosed HF is a key co-morbidity in people with pacemakers, and a coordinated screening program involving routine echocardiography will detect evidence of LVSD in 33% and that age, CABG, BNP and pacing base rate are features associated with a higher risk offering the opportunity of a tailored approach to screening (Gierula et al., 2015). Moreover, these features do not just help detect people who are more likely to have prevalent LVSD, but greater age, previous CABG, lower blood sodium, higher creatinine and pro-NT BNP and higher pacing base rate were also identified as significant independent predictors of adverse clinical events at 12 months.

6.5.2 Effect of echocardiography-guided care in a pacemaker population

Finally, this trial was designed not just to identify prevalence of LVSD, and markers of risk, but also to provide information on the potential benefit of incorporating a tailored screening echocardiography program into a routine pacemaker follow-up service. Moreover, there is limited evidence of the benefits of medical therapy in patients with pacemaker-associated with LVSD.

The primary outcome measure, a combined outcome of time to all-cause mortality or heart failure hospitalisation at 12 months was not different between the two arms (echocardiographic-guided care versus usual care). The addition of an echocardiogram to routine pacemaker follow-up did not improve short term clinical outcomes.

The trial was carried out in two hospital models of care in the UK. One half of all patients were enrolled from a pacemaker service at a tertiary teaching hospital centre, and the other half from two smaller district general secondary care hospitals. This design facilitated an ethically-appropriate exploration of the approach to management of patients found to have LVSD. The management for patients enrolled in the secondary care sites was coordinated by their primary care physician who received a letter describing the results of the echocardiogram with no specific management advice, but that onward referral to secondary care services could be considered. On the other hand,

participants enrolled in the tertiary centre found to have LVSD were directly referred to the hospital-based HF clinic and community HF services for optimisation of care.

Whilst there was no difference in 12-month event-free survival between echocardiographic-guided care and usual care overall and in those patients enrolled in the district secondary care centres, those patients enrolled in the tertiary centre appeared to have a lower event rate at 24 months. We also saw a higher uptake of guideline-directed medical therapy in this group compared to usual care, whereas there was no difference in medical therapy at 12m in those enrolled from secondary care pacemaker programs.

This trial has shown that identifying LVSD by embedding an echocardiography service into pacemaker follow-up services is not enough to improve 12-month patient outcomes. An enhanced pathway of care must also include access to a HF clinic offering tailored initiation and uptitration of medical therapy for people with LVSD.

6.6 Limitations

The trial was performed within a single region in the UK which limits generalisability particularly where international models of care of pacemaker patients differ. However, the study recruited from multiple centres of varying sizes within this region and the baseline table of demographic information suggests that our population was representative.

Digital data was extracted for follow-up. Access to clinical outcome data could not occur through a single data system and so patient admissions to other hospitals may not be complete. However, any bias regarding missed hospitalisations is likely to skew the data towards the smaller centres. Patients followed at Leeds Teaching Hospitals Trust are rarely admitted elsewhere. Furthermore, mortality is updated daily through national systems across all hospitals in the UK. Additionally, there is no data to date on the actions undertaken by patients referred with LVSD for primary care management and whether this led to secondary care HF specialist referral. This data is being collated.

There is known delay to the clinical effects of medical therapy for HFrEF which is longer for asymptomatic LVSD. Our primary end point of event-free survival at 12 months was therefore neutral. However, improvements were seen in medical therapy and longer term follow-up is therefore likely to show greater effects of optimised medical therapy for people with HFrEF. Currently though, there is no available long-term echocardiographic data to determine if medical therapy optimization reversed LVSD.

6.7 Conclusion

Around one third of patients with a standard pacemaker have undiagnosed LVSD. Introducing tailored echocardiographic assessment to routine pacemaker follow-up linked to a comprehensive multi-disciplinary HF service

ensures diagnosis, leads to the initiation of optimal medical management and has potential to lead to long-term favourable outcomes.

Chapter 7
Personalised reProgramming to prevent Pacemaker associated left ventricular Remodeling (PPPR):

7.1 Introduction

In response to the relationship between RVP and LVSD and HF events, pacemaker manufacturers have each developed largely automatic algorithms to avoid RVP, but these are variably applied with reprogramming occurring in only around 10% of all in-clinic follow-ups (Heidbüchel et al., 2008). It has previously been described in an observational cohort that careful individualised programming to limit RVP in people with pacemakers for bradycardia, can successfully reduce pacing requirements and leads to an improvement in LV function with no adverse effects on quality of life (Gierula et al., 2014). No prospective randomised controlled trial has ever explored the effects of reducing RVP on LV function and quality of life in patients without third degree heart block in the era of RVP avoidance algorithms.

The aims of this trial were to describe the effects of careful personalised reprogramming to limit RVP on echocardiographic and patient-orientated clinical outcomes in patients with avoidable RVP.

7.2 Hypothesis

Reducing unnecessary ventricular pacing has a beneficial effect on cardiac structure and function and extends pacemaker generator longevity without adversely affecting patient quality of life.

7.3 Methods

7.3.1 Study design

This was a 1:1 randomised, double-blind interventional study of personalised programming to avoid RV pacing versus standard care on LV size and function, quality of life, NT-pro-BNP levels and pacemaker generator longevity. The trial was approved by the National Research Ethics Committee (16/EM/0337, Appendix F), local authorities (Appendix G) and is registered on ClinicalTrials.gov (NCT03627585).

7.3.2 Study population

Patients were invited to attend at LTHT or HDFT if they fulfilled the inclusion and exclusion criteria, and were attending routine pacemaker clinic. Patients were sent a participant information sheet one week prior to their routine pacemaker follow-up. Those agreeing to participate attended the NIHR Cardiovascular Clinical Research Facility at either site and were consented by the investigator.

7.3.2.1 Inclusion Criteria

Participants were eligible if they had a chronic pacemaker device implanted greater than 24 months ago, that was capable of RV pacing (i.e. VVI or DDD pacemaker system implanted).

Participants had to be able and willing to give informed consent for the intervention after reading the information leaflet, and after having had the opportunity to ask any questions regarding the research.

7.3.2.2 Exclusion Criteria

Patients were excluded from the study if they had known significantly poor ultrasound images, although exclusion for this reason was recorded. Additionally, patients with complete heart block were excluded as the reprogramming options are limited.

7.3.3 Allocation and blinding

Using a simple random number generator patients were randomly allocated into one of two groups; either standard care or personalised reprogramming according to a predetermined protocol (Figure 7.1).

Randomisation, pacemaker assessment and reprogramming if allocated, was performed by an independent unblinded cardiac physiologist in order to ensure the primary investigator and patient remained blinded to their allocation according to the predetermined protocol.

7.3.4 Study protocol

Patients underwent a baseline assessment including collection of echocardiographic and pacemaker variables, a blood test to measure NT-pro-B-type natriuretic peptide (NT-pro-BNP), medical history including electrocardiographic and symptomatic indications for the device and co-morbidity assessment, and blood pressure. Quality of life assessment was undertaken using the EuroQol 5D-3L questionnaire. A pacemaker interrogation was performed to document baseline programming especially percentage atrial and ventricular pacing, programmed mode and remaining minimum estimated battery longevity which was also was collected at each interrogation.

Echocardiography was performed at the baseline visit on all patients in order to document baseline cardiac size and function. If allocated to personalisation of their pacemaker settings, this was performed at the same time as the patient's pacemaker follow-up, however, no reprogramming occurred prior to echocardiographic assessment. The patients rhythm was documented during echocardiography2 Pacemaker programming for those allocated into the intervention arm was carried out immediately at the baseline visit.

Patients received contact details for the research team at the baseline visit and were also contacted by telephone at one week. At that telephone call,

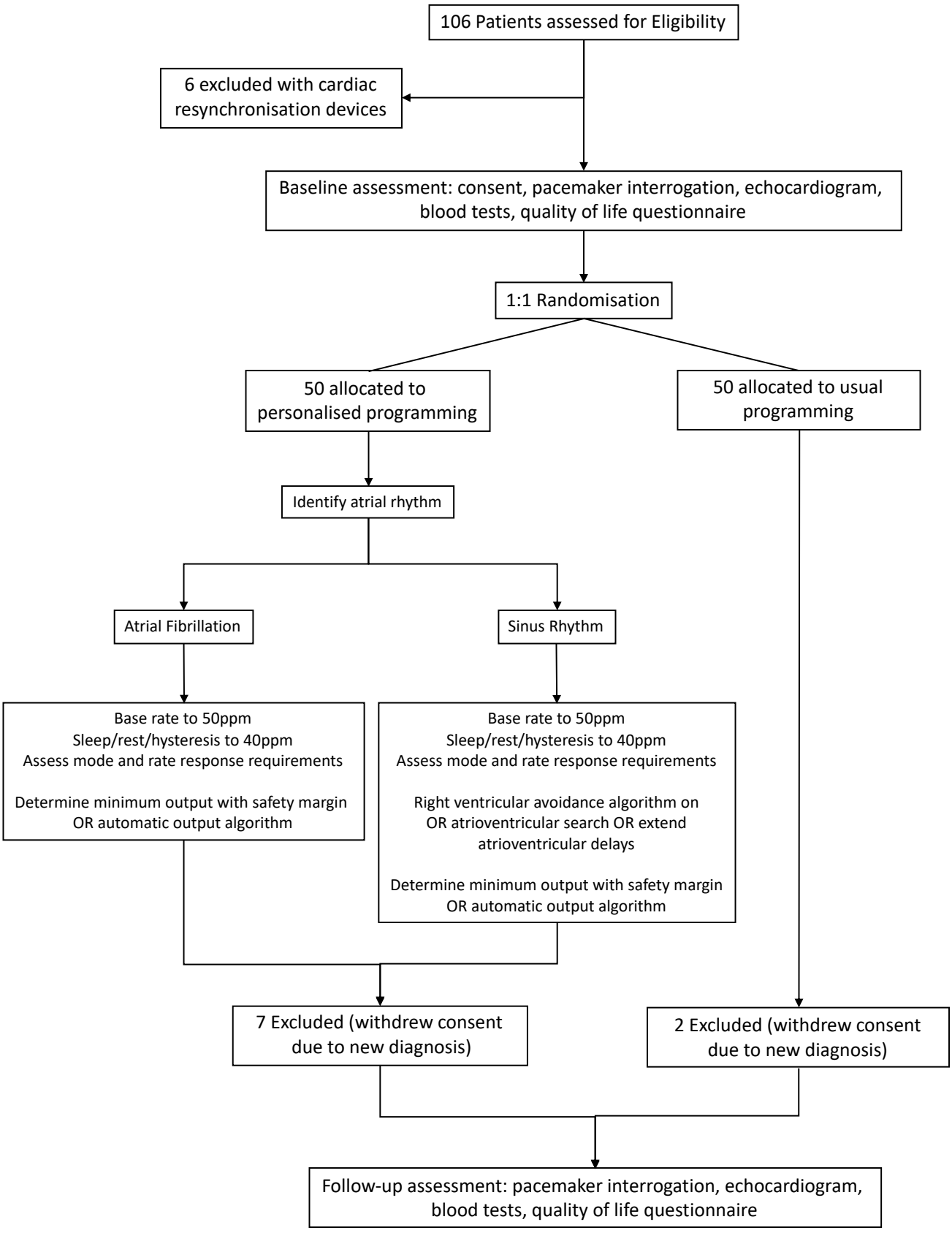
patients were asked about symptoms of dizziness, syncope or breathlessness. All participants were invited to return for a final visit at six months when all tests (echocardiogram, pacemaker check, quality of life assessment, and NT-pro-BNP blood test) were repeated.

7.3.5 Interventions

Usual care followed NICE guidelines (NICE, 2017) and British Heart Rhythm Society standards (BHRS, 2015) whereby patients underwent routine pacemaker follow-up with assessments to ensure device functionality, such as lead output thresholds and impedances, and interrogation of diagnostic information, for example atrial fibrillation burden.

Those randomised to the intervention arm received personalised pacemaker programming to avoid unnecessary RVP. The specific pacemaker variables assessed and modified were guided by our previously published RVP avoidance algorithm (Gierula et al., 2014) and included reducing day-time base rate (BR) to 50 beats per minute (and nocturnal or sleep rate (or hysteresis where available) to 40 beats/minute), deactivating rate-adaptive pacing, extending atrio-ventricular timing delays or activating pacing avoidance algorithms and reducing lead outputs (Figure 7.1).

Figure 7.1. PPPR CONSORT diagram



7.3.6 Outcomes

7.3.6.1 Primary Outcomes

The primary outcome was the difference in change in left ventricular ejection fraction (LVEF) measured by echocardiography between the two groups in the study.

7.3.6.2 Secondary Outcomes

1) Change in LV end diastolic and systolic volume index (LVEDVi, LVESVi) during the follow-up period between the two groups as additional measures of LV remodeling.

2) Quality of life measured using the EQ-5D-3L questionnaire between the two groups.

3) Change in minimum estimated pacemaker battery longevity between the two groups during the follow-up period.

4) Reproducibility of echocardiographic parameters within the trial.

7.3.7 Statistical Considerations

This study was a phase II pilot trial randomising 100 patients 1:1 to intervention and control arms.

7.3.7.1 Sample size and power calculation

This was a single-centre phase II trial. The sample size was influenced by pilot data (Gierula et al., 2014) and the guidelines for pilot and feasibility studies (Eldridge et al., 2016). Considering this, it was estimated randomising 70 patients 1:1 to intervention and control arms permitted an estimate a 95% confidence interval for the difference in mean LVEF at 6 months post randomisation. This allowed for the drop-out of 6 patients (approximately 10%). Furthermore, although this trial was not powered primarily to show a significant difference, this number of patients still allowed 50% power at a 5% significance level to detect a difference of 6 % in mean LVEF; from 45% in the control arm to 51% in the intervention arm.

The pilot sample was extended to 100 participants due to widespread interest in participation shown by people from the patient and public involvement group, granted by the Health Research Authority (Appendix E). The trial intended a priori and achieved, recruitment of 100 participants.

7.3.7.2 Statistical Analysis Plan

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 21 (IBM Corp., Armonk, New York), R: A Language and Environment for Statistical Computing version 3.2.3 (R Development Core Team, Vienna, Austria), and SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Normality for all continuous variables was tested using the Shapiro-Wilk test. Normally distributed continuous variables were reported as mean and standard deviation, and non-normally distributed continuous variables were reported as median and 25^{th}-75^{th} percentiles. Categorical variables were presented as count and percentages. Subsequently, differences between interventional groups' baseline characteristics were assessed using the 2-sample Student t test for normally distributed data and the Mann-Whitney U test for non-normally distributed data, whilst categorical variables were compared using the χ^2 test. A one-way ANCOVA was conducted to determine statistically significant differences between groups for all outcome variables controlling for baseline measures. Intraclass correlation coefficient (ICC) was estimated to assess the inter-observer agreement between two blinded echocardiographic readers. All statistical tests were 2-sided, and any p value <0.05 was deemed statistically significant.

7.3.8 Patient and public involvement

The research question was prompted by patients with pacemakers presenting to local HF clinics with symptoms suggestive of CHF, a deterioration in cardiac function and a high burden of RVP. The study was initially discussed with a well-established local patient and public involvement (PPI) advisory group (AG) consisting of people with cardiovascular disease and their families. The AG advised on suitable follow-up periods and study procedures. They were particularly enthusiastic to know the potential effect on battery longevity of the intervention as their primary concern was the number of generator

replacements required over a lifetime, particularly for an increasingly frail population.

Once the final protocol was established, it was reviewed along with the patient information sheets by the PPI-AG to ensure clarity and context. Discussions surrounding effective means of dissemination to patients are ongoing.

7.4 Results

A total of 100 patients were recruited from two centres between January 2017 and September 2018. Participants were randomised 1:1 to intervention or standard care. Of the 100 patients, 9 withdrew due to serious illness, all of which were non-cardiovascular, with no patients reporting changes to their medical therapy during the study period. No patient randomised to intervention reported adverse effects from device reprogramming.

Patients were followed for a median of 189 days (interquartile range 176, 230), similar between intervention groups. Personalised pacemaker programming successfully achieved a reduction in RVP burden compared to standard care (-6.5, 95% confidence interval -11.45 to -1.60%; p=0.01).

7.4.1 Baseline characteristics

Patient and clinical characteristics were similar between intervention groups for age, sex, baseline RVP burden, LVEF, NT-proBNP and pacemaker battery longevity (Table 7.1). More than half (71%) were male with a mean age of 76 (standard deviation ±9) years. Co-morbidities included diabetes mellitus (31%), history of myocardial infarction (13%), percutaneous coronary intervention (10%), coronary artery bypass grafting (8%). Patients had a median atrial pacing burden of 27 (3-67)% and RVP burden of 9 (1-58)% with a mean resting heart rate of 69 (±12)bpm. Mean LVEF was 50 (±9)% and median NT-proBNP of 1423 (±3783)pg/ml.

Table 7.1: PPPR Patient Characteristics at Baseline

	Total	Interventional Group		p-value
		Personalised Programming	Usual Care	
	(n=100)	(n=50)	(n=50)	
Patient Demographics				
Age (years)	76 (9)	75 (10)	76 (9)	0.579
Sex (male)	71 (71)	35 (70)	36 (72)	0.368
Height (cm)	169 (15)	170 (10)	167 (19)	0.376
Weight (kg)	82 (19)	84 (19)	80 (20)	
Atrial Rhythm				
Atrial Fibrillation	39 (39)	22 (44)	17 (34)	0.450
Paced	3 (3)	2 (4)	1 (2)	
Sinus Rhythm	58 (58)	26 (52)	32 (64)	
Clinical History Data				
Myocardial Infarction	13 (13)	6 (12)	7 (14)	0.766
Diabetes Mellitus	31 (31)	20 (40)	11 (22)	0.052
CABG	8 (8)	3 (6)	5 (10)	0.461
PCI	10 (10)	4 (8)	6 (12)	0.505
CVA	18 (18)	9 (18)	9 (18%)	0.962
Haemodynamic Data				
Resting Heart Rate (bpm)	69 (12)	69 (12)	69 (12)	0.150
Resting Systolic BP(mmHg)	138 (23)	138 (22)	138 (24)	0.158
Pacing Data				
Pacing indication				
Atrioventricular block	30 (30)	15 (30)	15 (30)	0.602
Sinus Node Disease	69 (69)	34 (68)	35 (70)	
Other	1 (1)	1 (2)	0 (0)	
Time receiving pacing (years)	11 (7)	12 (8)	11 (5)	0.317
Atrial Pacing burden (%)	27 (3-67)	25 (4-69)	31 (3-68)	0.796
Ventricular Pacing burden (%)	10 (1-58)	9 (1-73)	11 (2-42)	0.841
Echocardiographic Data				
LVEF (%)	50 (9)	49 (10)	50 (9)	0.732
LVEDV (mL)	107 (78-122)	106 (66-122)	107 (77-124)	0.802
LVESV (mL)	47 (37-60)	47 (37-60)	44 (37-60)	0.924
LVESVi (mL/m^2)	24 (15-31)	24 (20-31)	23 (20-33)	0.710

Continuous normally distributed data are expressed as mean (SD), non-normally distributed continuous data as median (IQR) or categorical data as n (%). CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention, CVA; cerebrovascular attack, BP; blood pressure, LVEF; left ventricular ejection fraction, LVEDV; left ventricular end diastolic volume, LVESV; left ventricular end-systolic volume, LVESVi; left ventricular end-systolic volume index.

7.4.2 Primary outcome: Left Ventricular Systolic Function

There was a significant improvement in the primary endpoint of LV systolic function, measured by LVEF, at 6 months in patients randomised to receive personalised pacemaker programming compared to those receiving standard care (mean difference +3.09, 95% Confidence interval 0.48 to 5.70%; p=0.02] (Table 7.2 and Figure 7.2).

Table 7.2: Change in primary and secondary outcome variables in patients following 6 months of personalised pacemaker programming v standard care, intention-to-treat analysis

Endpoint	Randomised treatment	Mean at follow-up [95% Confidence Interval]	Mean difference [95% Confidence Interval	Significance Level
Primary outcome				
LVEF (%)	Reprogramming	51.05 [49.15, 52.94]	**+3.09 [0.48, 5.70]**	**0.02***
	Usual care	47.96 [46.16, 49.75]		
Secondary outcomes				
LVEDV (mL)	Reprogramming	104.30 [96.99, 111.61]	-4.81 [-14.72, 5.11]	0.34
	Usual care	109.10 [102.41, 115.80]		
LVESV (mL)	Reprogramming	52.99 [49.20, 56.78]	-5.08 [-10.26, 0.11]	0.06
	Usual care	58.07 [54.44, 61.60]		
LVEDVi (mL/ m^2)	Reprogramming	53.33 [49.72, 56.97]	-2.88 [-7.83, 2.07]	0.25
	Usual care	56.22 [52.85, 59.59]		
LVESVi (mL/m^2)	Reprogramming	26.95 [24.99, 28.90]	**-2.99 [-5.69, -0.29]**	**0.03***
	Usual care	29.93 [28.08, 31.79]		
NT-proBNP (pg/mL)	Reprogramming	1136.22 [768.02, 1504.43]	-87.83 [-450.95, 626.61]	0.75
	Usual care	1224.05 [831.08, 1617.02]		
Battery Longevity (years)	Reprogramming	6.15 [5.98, 6.32]	**+0.38 [0.14, 0.62]**	**<0.01***
	Usual care	5.77 [5.60, 5.93]		
EQ5D	Reprogramming	0.69 [0.38, 1.02]	+0.19 [-0.25, 0.62]	0.40
	Usual care	0.51 [0.22, 0.81		
EQ-VAS	Reprogramming	74.44 [68.97, 79.90]	-0.03 [-7.60, 7.54]	0.99
	Usual care	74.47 [69.25, 79.69]		

Values are mean change [95% confidence intervals]; 95% significance shown in bold, *Denotes significance (P<0.05).LVEF; left ventricular ejection fraction, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end systolic volume, LVESVi; left ventricular end systolic volume index, NT-proBNP; N-terminal pro-B-type natriuretic peptide, EQ5D; Euro-quality of life score -5 questions, VAS; visual analogue scale.

7.4.3 Secondary outcomes: Left Ventricular Remodelling

There was a non-significant mean reduction in LVEDVi of -2.88 (-7.83 to 2.07; p=0.249) mL/m2 in those allocated to personalised care, compared to those receiving usual care when corrected for baseline LVEDVi. Moreover, there was a significant difference in LVESVi between the groups with those allocated personalised programming showing a greater reduction than those in the usual care arm (-2.99, -5.69 to -0.29 mL/m^2; p=0.03) (Figure 7.2 and Table 7.2). Of those allocated personalised programming, 8 (30%) experienced a clinically significant (Foley et al., 2009) reduction in LVESVi by greater than 15% compared to 2 (7%) patients randomised to usual care (p=0.02).

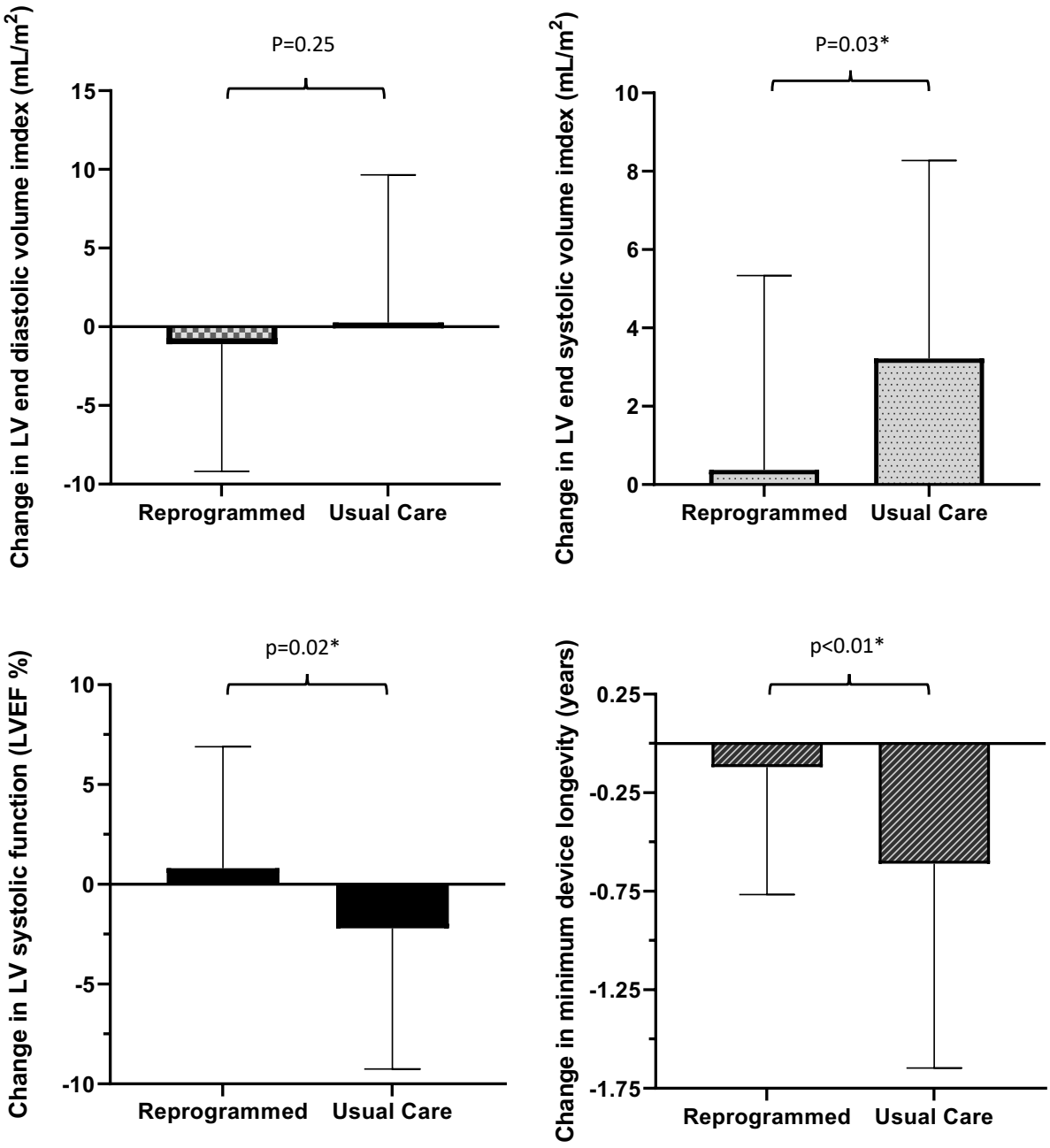


Figure 7.2 Mean change and standard deviation in left ventricular (LV) diastolic and systolic volume index, LV ejection fraction (LVEF) and minimum device longevity over 6 months compared between patients receiving personalised programming and usual care

7.4.4 Secondary outcomes: Quality of Life

Personalising pacemaker settings to avoid unnecessary RVP had no detrimental effect on quality of life as measured by EQ5D-3L (+0.19, -0.25 to

0.62; p=0.402) and visual analogue scale (VAS) (-0.03, -7.60 to 7.54; p=0.99] when adjusted for baseline.

7.4.5 Secondary outcomes: Device Battery Longevity

Personalisation of the pacemaker settings led to a preservation in the remaining minimum battery longevity by approximately 5 months compared to usual care (+0.38, 0.14 to 0.62; p<0.01) (Figure 7.2 and Table 7.2). This was achieved through personalised assessment and manipulation of the base rate (in 44%), sleep, rest or hysteresis rates (68%), mode (8%), rate-response (38%), atrioventricular search (4%), automatic thresholds (36%), lead outputs (74%) and electrocardiogram storage (10%) as appropriate.

7.4.6 Secondary outcomes: Echocardiographic reproducibility

Echocardiographic outcome measurements demonstrated strong inter-observer agreement for LVEF [ICC 0.968 (0.948 to 0.980)], LVEDV [ICC 0.955 (0.931 to 0.975)], and LVESV (ICC 0.964 (0.941 to 0.979)].

7.5 Discussion

The present study is the first to provide evidence that personalising pacemaker programming to limit RVP can successfully lead to an improvement in LV systolic function, without an adverse effect on quality of life, whilst simultaneously preserving battery longevity in an unselected

population of patients with a pacemaker for bradycardia without third degree heart block.

7.5.1 Predicting pacing-associated LV dysfunction

RVP has a longstanding association with an acute reduction in LV contractility (Wiggers, 1925, Heyndrickx et al., 1985a). Longer term effects on LV function are reported to include abnormal myocardial perfusion (Lee et al., 1994, Nielsen et al., 2000, Tse and Lau, 1997a, Tse et al., 2002), structural (Van Oosterhout et al., 1998) and histological abnormalities (Adomian and Beazell, 1986) and abnormal gene expression (Arkolaki et al., 2015) thought eventually to contribute to the development or progression of LVSD and CHF.

In two separate cross-sectional studies we have described and validated that the degree of LV function is strongly related to the amount of RV pacing, and that this relationship is enhanced by the presence of cardiovascular disease (Gierula et al., 2015, Thackray et al., 2003). Whether remodelling is progressive in patients with long-term pacemakers and the underlying mechanisms behind the heterogeneity in functional response to RVP are unknown. In this thesis I have described that remodelling in response to RV pacing is progressive such that careful attention to avoiding this driver of progression could have longer-term benefits on important clinical and surrogate outcomes.

7.5.2 Does RV pacing-induced LV dysfunction affect outcomes?

In patients with LVSD, RVP is associated with adverse outcomes (Wilkoff et al., 2002). We have previously described that the presence of LVSD is the most powerful determinant of medium-term survival (Thackray et al., 2003). Retrospective (Brunner et al., 2004, Jahangir et al., 1999, Shen et al., 1994, Shen et al., 1996, Jelić et al., 1992, Mayosi et al., 1999) and prospective (Zhang et al., 2008, Sweeney et al., 2008) studies in patients without clinical heart failure at baseline have also shown increased heart failure associated deaths and hospitalisation rates. Although these studies could not prove causation, it is notable that the most consistent feature in each of these studies was that cardiac dysfunction at baseline and complete heart block as an indication (necessitating high RVP burden) were important markers of mortality (Zhang et al., 2008, Brunner et al., 2004). Age, coronary artery disease, co-morbidities (chronic airways disease and diabetes mellitus), paced QRS (Shukla et al., 2005), and atrial fibrillation were also relevant (Sweeney et al., 2003).

These studies have been supported by subsequent work showing that patients with sick sinus syndrome receiving only right atrial pacing have fewer CHF events, fewer strokes and less atrial fibrillation than those paced only in the right ventricle (Andersen et al., 1997). Specifically, it has been suggested that high RVP is related to 2.5-fold increases in CHF hospitalisation rate following pacemaker implantation (Sweeney et al., 2003). More recently it has been suggested the risk of CHF is highest within the first 6 months post-pacemaker implantation (Pap et al., 2012). However, these latter studies were

observational and no assessment of cardiac function was done at baseline or at follow-up and other risk factors for heart failure were not described.

7.5.2 Can RV-pacing be avoided and what effect does this have?

In experimental models, reducing RVP seems to correct *pacing-induced* left ventricular systolic dysfunction (Nielsen et al., 2000, Tse et al., 2002, Duchenne et al., 2019). Whether cardiac function improves by reducing RVP in humans in clinical practice was unknown.

We previously undertook an observational study in 66 patients with long term pacemakers to determine whether reducing RVP in a chronically implanted patient cohort had effects upon LV function (Gierula et al., 2014). The programming changes were tolerated in all but two patients. Both of these patients had atrial fibrillation and were reprogrammed back to their original settings. The protocol reduced mean RVP percentage by 49% (95% CI 41 to 57%; $p<0.0001$) from baseline, and there was an improvement in LVEF of 6% (95% CI 4 to 8%; $p<0.0001$) and a reduction in LV dimensions.

Currently various national guidelines offer limited advice regarding pacemaker programming (Fraser et al., 2000, BHRS, 2015) therefore clinical practice often relies on local policy. Our data provide evidence that a simple RVP avoidance protocol can guide clinicians to successfully reduce unnecessary RVP to improve or prevent a worsening of LV systolic function.

7.5.3 Left ventricular remodelling

LV remodelling is an accepted surrogate endpoint in clinical studies (Konstam et al., 2003) due to a close relationship between therapy-related changes in echocardiographic variables (in HF patients) and subsequent findings in morbidity and mortality studies of the same interventions (Kramer et al., 2010). Interventions that led to a 5% increase in mean LVEF were associated with an odds ratio of 1 year mortality of 0.86 (95% CI 0.77-0.96) (Kramer et al., 2010).

LV end diastolic volume (LVEDV) also demonstrated a reliable link to mortality outcomes. A decrease in 10ml was associated with an OR of 0.95 for mortality at one year (95% CI 0.94 to 0.97) and a 1.9-fold (95% CI 1.2 to 3.2) increase in the odds that an intervention would show a favourable outcome. A decrease in LVESV of 10ml was associated with a relative OR of 0.96 (95% CI 0.93 to 0.98) for mortality. In one study of cardiac resynchronization therapy (CRT), a reduction in LVESV of >10% had a sensitivity and specificity of >70% each for all-cause mortality and 87 and 69% for cardiovascular mortality (Yu et al., 2005).

Similar data apply to LVESV. A reduction in LVESVi of ≥15% is associated with better outcomes in recipients of cardiac resynchronisation therapy (CRT) (Foley et al., 2009) and this cut-off has been used as an endpoint in CRT studies previously (Curtis et al., 2007). Our data suggest therefore, that a long-term application of personalised pacemaker therapy could improve outcomes. These relationships are not seen with changes in 6-minute walk distance

datasets, or for changes in peak oxygen consumption or natriuretic peptide levels (Wessler et al., 2011).

7.5.4 The opportunity to improve device longevity

Device longevity is the most important aspect of pacemaker therapy to patients (Wild et al., 2004) and has featured in the medical and the lay press (Dean and Sulke, 2016). We have previously shown that extending longevity by as little as twelve months could avoid a pacemaker generator replacement procedure entirely in around 20% of patients (and therefore eliminate its 1-5% complication rate in these people) (Uslan et al., 2012). The amount of pacing the device has to perform is the major drain on battery current (Paton et al., 2019).

The products formed from the chemical reaction cannot be vented as in normal batteries, and eventually hinder the reaction itself, hence merely increasing battery size, although acceptable to patients (Wild et al., 2004), is of limited benefit. On the other hand, the amount of pacing required is the major drain on battery current (Paton et al., 2019).

The results of this study therefore provide the first data from a randomised, placebo-controlled trial that personalised programming can significantly preserve battery longevity and have important implications. It is likely that addressing programming earlier in the life of a pacemaker battery will have cumulative effects upon device longevity.

7.5.5 Safety and patient tolerability

Our protocol was well-tolerated with no patients returning with or reporting symptoms and no detriment to their quality of life. In particular, de-activating rate-adaptive pacing led to significant reductions in pacing and preservations in battery longevity without affecting quality of life. Rate-adaptive pacing in pacemaker patients without CHF is associated with a greater cardiac output rise during exercise (McMeekin et al., 1990) and although studies have shown improvements in exercise capacity ranging from the marginal (Batey et al., 1990, Carmouche et al., 1998) to the dramatic (Capucci et al., 1992), there is no consistency on measures of quality of life (Lau et al., 1989, Trappe et al., 1988, Haywood et al., 1993). Hence, the present data are consistent with the literature, that rate-adaptive pacing is of little benefit in most patients with standard pacemakers and especially those with LVSD (Jamil et al., 2016).

7.6 Limitations

This trial was performed within a single region in the UK limiting generalisability, particularly as international pacemaker programming may differ. However, baseline demographic data indicates that our population was representative of a pacemaker recipient population.

Whilst our end points showed small but significant benefits from personalised programming, these are likely to be cumulative. Longer term follow-up in a

larger multi-centre trial would allow for further sub-analysis to understand which programming modifications show the greatest effect.

7.7 Conclusions

Personalised reprogramming in patients with standard right ventricular pacemakers to avoid unnecessary RV pacing can improve LV function and extend battery longevity, and is safe and acceptable to patients.

Chapter 8
Discussion

8.1 Introduction

Pacemakers have been an effective, safe and cost-effective life-saving treatment for many people requiring cardiac rhythm support for bradycardia for over four decades. Contemporary devices consist of reliable hardware supported by sophisticated software allowing for smaller devices with better battery longevity and greater functionality.

There is consensus based upon solid evidence from clinical trials, that right ventricular (RV) apical pacing is associated with adverse cardiac remodelling thereby causing or exacerbating left ventricular systolic dysfunction (LVSD), and clinical heart failure events including data from DAVID, MOST, BLOCK-HF, PROTECT-PACE. Nevertheless, as a result of its otherwise great safety profile, ease and reliability for sensing and capture, right ventricular (RV) apical pacing remains the most common method of delivering pacemaker therapy,

Whilst the trial and observational cohorts stimulated industry partners to develop new pacemaker algorithms aimed at minimising RV pacing and provoked clinicians to begin investigating alternative methods for delivering cardiac pacing, few approaches have produced overwhelmingly supportive data, and subsequently advice from guidelines remains somewhat non-

committal and routine clinical practice, apart from the appearance of the new algorithms, remains somewhat indifferent to a comprehensive drive to limit RV pacing. This heterogeneity of uptake is probably due to the broad spectrum of risk in the pacemaker population as a whole, the fact that despite this indifference, most patients with a pacemaker do not develop clinical heart failure (HF), and a lack of understanding of the pathophysiology and poor knowledge of which patients to target for intensive attention.

This thesis delivers original observational and trial data demonstrating that RV pacing contributes to the progressive development of LVSD and HF in patients receiving long-term pacemaker therapy. I have shown that this can be detected by routine echocardiography and that responding to changes in LV structure and function through a comprehensive device-orientated HF service can lead to improved uptake of protective medical therapy and optimised programming. I have also shown that LVSD can at least in part be reversed by careful personalisation of pacemaker programming to avoid unnecessary RV pacing, which has the added benefit of preserving the pacemaker battery.

8.2 LVSD is progressive in pacemaker patients

My studies include the first to describe the progressive impact on LV size and function in patients exposed to long-term contemporary RV pacing (chapter 4). I have shown that nearly half of all pacemaker patients experience a deterioration in left ventricular function and that almost one fifth

(18%) experienced at least one HF event. I have described that those at highest risk of a clinical event had a higher percentage of RV pacing, a lower ejection fraction at baseline, had a history of ischaemic heart disease, and a higher incidence of atrial fibrillation. These data suggest that we may be able to identify patients at higher risk of pacing associated progressive LVSD or HF and therefore which patients may require ongoing review of cardiac function in order to tailor patient management.

8.3 Device battery longevity

In chapter 5 I described that pacemaker battery longevity cannot reliably be estimated from patient clinical characteristics at device implant in this cohort, but that device selection and programming variables are important independent predictors of longevity. This highlights the importance of the device prescription at implant, and optimising pacemaker programming at every follow-up.

8.4 Trial 1: Screening for LV dysfunction and optimising medical therapy

Chapter 6 presents data from the largest multicentre randomised double blind trial of 1200 patients at least 2 years after their initial pacemaker implantation. The study aimed to assess the efficacy of introducing tailored echocardiographic assessment to routine pacemaker follow-up to direct optimal medical management. I proved that introducing echocardiography led

to a diagnosis of LVSD in around one third of patients with a standard pacemaker and that subsequent management in a multidisciplinary specialist HF service leads to the introduction of optimal medical therapy with the potential to lead to long-term favourable clinical outcomes.

8.5 Trial 2: Personalising pacemaker programming

Chapter 7 discusses the first randomised controlled trial of personalised pacemaker reprogramming in patients with standard right ventricular pacemakers to avoid unnecessary RV pacing compared to usual programming. I proved that personalised pacemaker programming can improve LV function and extend battery longevity, and is safe and acceptable to patients.

8.6 Conclusions

Routine pacemaker follow-up is focussed on the functional assessment of the pacemaker system. My doctoral programme of research indicates that a pacemaker patients' clinical status is often dynamic. This warrants in-person follow-up be utilised as an opportunity to provide a holistic review of the patients' pacemaker indication, current clinical status, device programming, cardiac function and medical therapy in order to ensure the best quality of life and prognosis for our patients.

My data have contributed to new national standards from the British Heart Rhythm Society (BHRS, 2020) by formulating a guide for pacemaker optimisation and pacemaker patient management for all clinicians. Widespread adoption of the standards developed from this evidence has significant clinical implications by potentially reducing expensive upgrade procedures and generator replacements, by preserving pacemaker battery longevity and reducing heart failure hospitalisations.

List of Abbreviations

Atrial Fibrillation	AF
Atrioventricular	AV
Atrioventricular block	AVB
Base rate	BR
Beta-Blocker	BB
Cardiac Resynchronisation Therapy	CRT
Cardiopulmonary Exercise Test	CPX
Complete Heart Block	CHB
Diabetes Mellitus	DM
Ejection Fraction	EF
Electrocardiograph	ECG
EuroQol 5-Dimension	EQ-5D
Heart failure with reduced ejection fraction	HFrEF
Heart failure with preserved ejection fraction	HFpEF
Hypertension	HTN
Implantable Cardioverter Defibrillator	ICD
Ischaemic Heart Disease	IHD
Left Bundle Branch Block	LBBB
Left Ventricle	LV
Left Ventricular Ejection Fraction	LVEF
Left Ventricular Systolic Dysfunction	LVSD
Myocardial Infarction	MI
New York Heart Association	NYHA
N-terminal prohormone of Brain Natriuretic Peptide	NT-proBNP
Pacemaker Generator Replacement	PGR
Peak Oxygen Consumption	pVO2
Percutaneous Coronary Intervention	PCI
Right Ventricle	RV

Sick Sinus Syndrome	SSS
Sinus Rhythm	SR

Appendix A: The relationship between long-term right ventricular pacing and left ventricular systolic function - Ethical Approval

NHS
Health Research Authority
East Midlands - Nottingham 1 Research Ethics Committee
Royal Standard Place
Nottingham
NG1 6FS

18 February 2016

Miss Maria Paton
LICAMM
UoL
LS2 9JT

Dear Miss Paton

Study title:	**Is pacemaker-related cardiac remodelling progressive?**
REC reference:	**15/EM/0566**
IRAS project ID:	**189942**

Thank you for your letter of 18.02.2016. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 09 December 2015

Documents received

The documents received were as follows:

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		
GP/consultant information sheets or letters [GP letter]	1.0	27 October 2015
IRAS Checklist XML [Checklist_17022016]		17 February 2016
Participant consent form	1.1	27 January 2016
Participant information sheet (PIS)	1.1	27 January 2016
REC Application Form [REC_Form_30112015]		30 November 2015
Research protocol or project proposal [Protocol]		12 November 2015
Summary CV for Chief Investigator (CI) [CV Witte]		30 October 2015
Summary CV for student		30 October 2015

You should ensure that the sponsor has a copy of the final documentation for the study. It is

the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

15/EM/0566	**Please quote this number on all correspondence**

Yours sincerely

Teagan Allen
REC Assistant

E-mail: NRESCommittee.EastMidlands-Nottingham1@nhs.net

Copy to: *Miss Maria Paton*
Mrs Amanda Burd, LTHT R+I

Appendix B: The relationship between long-term right ventricular pacing and left ventricular systolic function
LTHT R&I Approval

The Leeds Teaching Hospitals NHS
NHS Trust

Date: 18/02/2016

Our Ref: Amanda Burd

Research & Innovation Department
34 Hyde Terrace
Leeds
LS2 9LN

Tel: 0113 392 0162
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www.leedsth.nhs.uk/research

Dr Klaus Witte
Consultant Cardiologist
Department of Cardiology
LIGHT Laboratories
University of Leeds
LS1 3EX

Dear Dr Klaus Witte

Re: **NHS Permission at LTHT for: Establishing the remodelling effect of long-term right ventricular pacing**
LTHT R&I Number: CD15/401:
REC: 15/EM/0566

I confirm that *NHS Permission for research* has been granted for this project at The Leeds Teaching Hospitals NHS Trust (LTHT). NHS Permission is granted based on the information provided in the documents listed below. All amendments (including changes to the research team) must be submitted in accordance with guidance in IRAS. Any change to the status of the project must be notified to the R&I Department.

The study must be conducted in accordance with the *Research Governance Framework for Health and Social Care*, ICH GCP (if applicable), the terms of the Research Ethics Committee favourable opinion (if applicable) and NHS Trust policies and procedures (see http://www.leedsth.nhs.uk/research/) including the requirements for research governance and clinical trials performance management listed in appendix 1 and 2 . NHS permission may be withdrawn if the above criteria are not met including the requirements for clinical trials performance

The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority ""Clinical Negligence Scheme for NHS Trusts"" for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers with an employment contract (substantive or honorary) with the Trust. The Trust only accepts liability for research activity with NHS Permission

The Trust therefore accepts liability for the above research project and extends indemnity for negligent harm. Should there be any changes to the research team please ensure that you inform the R&I Department and that s/he obtains an appropriate contract, or letter of access, with the Trust if required.

Yours sincerely

Anne Gowing
Research Governance Manager

Appendix C: Optimising pacemaker and medical therapy for heart failure in pacemaker patients – the OPT-PACE randomised trial Ethical Approval

Health Research Authority
NRES Committee Yorkshire & The Humber - South Yorkshire
Millside
Mill Pond Lane
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LS6 4RA

Telephone: 0113 3050122
Facsimile: 0113 8556191

31 October 2012

Dr Klaus Witte
Senior Lecturer and Consultant Cardiologist
University of Leeds
LIGHT building,
Clarendon Road
Leeds
LS2 9JT

Dear Dr Witte

Study title: **Optimising pacemaker therapy (OPT-PACE)**
REC reference: **12/YH/0487**

The Research Ethics Committee reviewed the above application at the meeting held on 25 October 2012.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of

the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

The participant information sheet should have references to vitamin D removed and should state the correct Research Ethics Committee.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Evidence of insurance or indemnity		
GP/Consultant Information Sheets	1.0 - Leeds - new implant study	24 September 2012
Investigator CV	Witte K, abbreviated CV	12 January 2012
Other: GP letter	1.0 - Leeds	24 September 2012
Other: GP letter	1.0 - Bradford	24 September 2012
Other: GP letter	1.0 - Harrogate	24 September 2012
Other: OPT-PACE flow chart	1.0	24 September 2012
Participant Consent Form: OPT-PACE	1.0	24 March 2012
Participant Consent Form: OPT-PACE (Bradford)	1.0	24 March 2012
Participant Consent Form: OPT-PACE (Harrogate)	1.0	24 March 2012
Participant Information Sheet: new implants	1.0	24 September 2012
Participant Information Sheet: Leeds WP2	1.0	24 September 2012

Participant Information Sheet: Bradford WP2	1.0	24 September 2012
Participant Information Sheet: Harrogate WP2	1.0	24 September 2012
Protocol	1.0	24 September 2012
REC application		

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/YH/0487 **Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

pp
Ms Jo Abbott
Chair

Email: nrescommittee.yorkandhumber-southyorks@nhs.uk

Appendix D: Optimising pacemaker and medical therapy for heart failure in pacemaker patients – the OPT-PACE randomised trial OPT-PACE LTHT R&I Approval

The Leeds Teaching Hospitals NHS
NHS Trust

Ref: Amanda Burd

12/04/2013

Research & Development
Leeds Teaching Hospitals NHS Trust
34 Hyde Terrace
Leeds
LS2 9LN

Tel: 0113 392 2878
Fax: 0113 392 6397

r&d@leedsth.nhs.uk
www.leedsth.nhs.uk

Dr Klaus Witte
Consultant Cardiologist
University of Leeds
LIGHT building,
Clarendon Road
Leeds
University of Leeds
LS2 9JT

Dear Dr Klaus Witte

Re: NHS Permission at LTHT for: Optimising pacemaker therapy (OPT-PACE)
LTHT R&D Number: CD12/10554 (116334/WY)
REC: 12/YH/0487

I confirm that *NHS Permission for research* has been granted for this project at The Leeds Teaching Hospitals NHS Trust (LTHT). NHS Permission is granted based on the information provided in the documents listed below. All amendments (including changes to the research team) must be submitted in accordance with guidance in IRAS. Any change to the status of the project must be notified to the R&D Department.

Permission is granted on the understanding that the study is conducted in accordance with the *Research Governance Framework for Health and Social Care*, ICH GCP (if applicable) and NHS Trust policies and procedures available at http://www.leedsth.nhs.uk/sites/research_and_development/.

This permission is granted only on the understanding that you comply with the requirements of the *Framework* as listed in the attached sheet "Conditions of Approval".

If you have any queries about this approval please do not hesitate to contact the R&D Department on telephone 0113 392 2878.

Indemnity Arrangements

The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority 'Clinical Negligence Scheme for NHS Trusts' for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers with an employment contract (substantive or honorary) with the Trust. The Trust only accepts liability for research activity that has been managerially approved by the R&D Department.

The Trust therefore accepts liability for the above research project and extends indemnity for negligent harm to cover you as investigator and the researchers listed on the Site Specific Information form. Should there be any changes to the research team please ensure that you inform the R&D Department and that s/he obtains an appropriate contract, or letter of access, with the Trust if required.

Yours sincerely

Dr D R Norfolk
Associate Director of R&D

Approved documents
The documents reviewed and approved are listed as follows

Document	*Version*	*Date of document*
NHS R&D Form	3.4	12/02/2013
SSI Form	3.4	06/01/2013
Directorate Approval		20/03/2013
REC Letter confirming favourable opinion		31/10/2012
Insurance with Indemnity		N/A
Protocol	1.0	24/09/2012
Patient information sheet (REC approved) Implants	1.1	24/09/2012
Consent form (REC approved)	1.1	31/10/2012
Patient Information Sheet - Leeds	1.1	31/10/2012
Flow Chart	1.0	24/09/2012
GP/Consultant information sheets (REC approved)	1.0	24/09/2012

Appendix E: Personalised reProgramming to prevent Pacemaker associated left ventricular Remodeling (PPPR) Health Research Authority Approval

NHS
Health Research Authority

Dr Klaus Witte
LIGHT building
UoL
Leeds
LS2 9JT

Email: hra.approval@nhs.net

26 October 2016

Dear Dr Witte,

Letter of HRA Approval

Study title:	**Reprogramming to Prevent Progressive Pacemaker-induced Remodelling**
IRAS project ID:	**211016**
REC reference:	**16/EM/0337**
Sponsor	**University of Leeds**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details

IRAS project ID	211016

and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators",* issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

IRAS project ID	211016

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **211016**. Please quote this on all correspondence.

Yours sincerely

Miss Lauren Allen

Assessor

Email: hra.approval@nhs.net

Copy to: *Mrs Amanda Burd, LTHT R+I (Lead NHS R&D contact)*

Appendix F: Personalised reProgramming to prevent Pacemaker associated left ventricular Remodeling (PPPR) Ethical Approval

NHS
Health Research Authority

East Midlands - Leicester Central Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

30 August 2016

Dr Klaus Witte
LIGHT building
UoL
Leeds
LS2 9JT

Dear Dr Witte

Study title:	**Reprogramming to Prevent Progressive Pacemaker-induced Remodelling**
REC reference:	**16/EM/0337**
IRAS project ID:	**211016**

Thank you for your letter of 23 August 2016 , responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Ellen Swainston, nrescommittee.eastmidlands-leicestercentral@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of

recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*	
Covering letter on headed paper [Ethics resubmission]	1.0	22 August 2016	
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity certificate UoL]			
GP/consultant information sheets or letters [GP letter]	1.1	22 August 2016	
IRAS Application Form [IRAS_Form_25072016]		25 July 2016	
IRAS Checklist XML [Checklist_25072016]		25 July 2016	
Participant consent form [Consent form - LGI]	1.0	20 June 2015	
Participant consent form [Consent form - Harrogate]	1.0	20 June 2016	

Participant consent form [Consent form]	1.1	22 August 2016	
Participant consent form [Consent form Harrogate]	1.1	22 August 2016	
Participant information sheet (PIS) [Patient information sheet]	1.0	20 June 2016	
Participant information sheet (PIS) [PIS]	1.1	22 August 2016	
Research protocol or project proposal [Protocol for reprogramming study]	1.0	20 June 2016	
Summary CV for Chief Investigator (CI) [Short CV KW]		20 June 2016	
Summary CV for student [Summary CV]		30 October 2015	
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Consort diagram of how the present project fits into a fellowship (workstream 2)]	1.0	20 June 2016	
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Reprogramming protocol]	1.0	20 June 2016	
Validated questionnaire [EQ5D questionnaire]			
Validated questionnaire [Minesota Living with Heart Failure Questionnaire]			

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/EM/0337	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp. K. Sroczyk

Mr Ken Willis
Chair

Email: nrescommittee.eastmidlands-leicestercentral@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mrs Amanda Burd, LTHT R+I*

Appendix G - Personalised reProgramming to prevent Pacemaker associated left ventricular Remodeling (PPPR) LTHT R&I Approval

The Leeds Teaching Hospitals NHS
NHS Trust

Ref: Amanda Burd

Research & Development
Leeds Teaching Hospitals NHS Trust
34 Hyde Terrace
Leeds
LS2 9LN

Tel: 0113 392 2878
Fax: 0113 392 6397

r&d@leedsth.nhs.uk
www.leedsth.nhs.uk

Dr Klaus Witte
Consultant Cardiologist
University of Leeds
LIGHT building,
Clarendon Road
Leeds
University of Leeds
LS2 9JT

Dear Dr Klaus Witte,

Re. Preventing progressive pacemaker induced remodelling, R&I No: CD16/86332.

This email confirms that the Leeds Teaching Hospitals NHS Trust has the capacity and capability to deliver the above research study, based upon Protocol version 1.0 (20/06/2016). You may now begin the study at this organisation.

Please find attached:

- agreed statement of activities
- agreed schedule of events

It is the responsibility of the principal investigator to ensure that the study is conducted in accordance with the terms of the Health Research Authority approval and Leeds Teaching Hospitals NHS Trust policies and procedures including the requirements for research governance and clinical trials performance management. These are available at http://www.leedsth.nhs.uk/assets/Uploads/PI-responsibilities-v1.3-210716.docx

New requirement

Please note: If your study will involve the testing or use of an **interventional procedure which is new to LTHT** you must obtain the approval of the New Interventional Procedures Group (NIPG). Details and application form are available from Jason Dunne, secretary to NIPG, telephone 0113 - 206 6951 or email jason.dunne@nhs.net If your study will involve an interventional procedure which is new to you as an individual (but not to LTHT) you must ensure you have agreement from your clinical director, clinical lead and general manager

Important

As an NHS Provider, for clinical trials we must submit information regarding performance in initiating clinical research to the Department of Health. One of the data points we require is **the date this study is ready to start** i.e., recruit study participants, provide data or tissue. Therefore please either copy us into any "green light" emails you receive or send us a separate email with this date when it is confirmed with the sponsor.

If you have any queries please do not hesitate to contact the R&I team at leedsth-tr.lthtresearch@nhs.net.

Best wishes,

Anne Gowing
Research Governance Manager, Research & Innovation Department

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