The Assessment and Management of Dysfunctional Breathing in Children

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Abstract

Dysfunctional breathing (DB) is a respiratory disorder affecting children and adults. It can be defined as an alteration in the normal biomechanical patterns of breathing that results in intermittent or chronic symptoms. DB is characterised by irregular breathing patterns involving inefficient, excessive upper chest wall activity, and may or may not involve an upper airway abnormality such as paradoxical vocal cord dysfunction (pVCD).

DB is difficult to identify due to the similarity of presentation and co-existence with other respiratory disorders. There is also a lack of suitable assessment techniques , which impacts on diagnosis and the efficacy of treatment provided. Clinical experience indicates that breathing retraining reduces or ameliorates the substantial burden of morbidity associated with the condition. However, a systematic review revealed no evidence to support or refute this observation.

Studies were carried out to investigate whether respiratory sound analysis (RSA) and structured light plethysmography (SLP) could be used with children as tools for the diagnosis of pVCD and the assessment of DB as a whole. A third study investigated whether breathing retraining improved clinical outcomes and quality of life for children with DB.

These studies revealed that testing using RSA and SLP is well tolerated and that breathing retraining offers a positive and sustained benefit to children, both in terms of quality of life and symptoms experienced. However, while SLP can be used for the detailed assessment of breathing patterns, it cannot currently discern normal from abnormal patterns. RSA is a valid approach to the diagnosis of pVCD, but new technology is required to enable this to happen.

Further research is required to develop these approaches for the diagnosis and management of dysfunctional breathing, in conjunction with work to reach a consensus on the definition of DB and promote awareness of this important but under recognised condition.

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List of abbreviations

AB	Abdomen
AMED	Allied and complementary medicine database
AQLA	Asthma quality of life assessment
ATS	American Thoracic Society
AWR	Ambient wheeze rejection
BBT	Buteyko breathing technique
BP	Breath phase
BTS	British Thoracic Society
C-ACT	Childhood asthma control test
CENTRAL	Cochrane central register of controlled trials
CHSSS	Cochrane highly sensitive search strategy
CINAHL	Cumulative index to nursing and allied health literature
CLE	Continuous laryngoscopy during exercise
CO2	Carbon dioxide
CONSORT	Consolidated standards of reporting trials
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DB	Dysfunctional breathing
DI	Deep inspirations
ECG	Electrocardiogram
EMG	Electromyography
EMBASE	International biomedical database
EPAM	Exercise-induced paradoxical arytenoid motion
ERS	European Respiratory Society
ET-DB	Extra thoracic dysfunctional breathing
FEV_1	Forced expiratory volume in one second

FRC	Functional residual capacity
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GP	General practitioner
GRADE	Grading of recommendations assessment, development and evaluation
HEI	Higher education institution
HRQOL	Health related quality of life
HSRProj	Health services research projects in progress
HVPT	Hyperventilation provocation test
HVS	Hyperventilation syndrome
IE ratio	Inspiratory expiratory ratio
IQR	Interquartile range
IS	Inspiratory stridor
ISRCTN	International standard randomised controlled trial number
KM	Konno-Mead
LILACS	Latin American and Caribbean health sciences literature
MARM	Manual assessment of respiratory motion
Max Wz%	Maximum wheezeRATE
MCID	Minimal clinically important difference
MEDLINE	Medical literature analysis and retrieval system online
MeSH	Medical subject headings
NQ	Nijmegen questionnaire
NRES	National research ethics service
NRR	National research register
OB	Obliterative bronchiolitis
OEP	Optoelectronic plethysmography
OP	Overall phase

PA	Principle angle
PC	Personal computer
pCO_2	Partial pressure of carbon dioxide
PDB	Pattern disordered breathing
PedsQL	Pediatric quality of life inventory
PEEP	Positive end-expiratory pressure
PsycINFO	American Psychological Association database of abstracts
pVCD	Paradoxical vocal cord dysfunction
QOL	Quality of life
RC	Rib cage
RCT	Randomised controlled trials
RIP	Respiratory inductance plethysmography
RR	Respiratory rate
RSA	Respiratory sound analysis
SCH	Sheffield Children's Hospital
SD	Standard deviation
SEBQ	Self evaluation of breathing questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
SLP	Structured light plethysmography
Spr	Spread
TAA	Thoraco-abdominal asynchrony
T-DB	Thoracic dysfunctional breathing
Te	Expiratory time
Ti	Inspiratory time
Tr	Tracheal
Tr Exp	Tracheal sensor output during expiration
Tr Insp	Tracheal sensor output during inspiration

Tr Total	Combined inspiratory and expiratory tracheal sensor output
TV	Tidal volume breathing
USB	Universal serial bus
Wz%	WheezeRATE

1. Clinical overview of dysfunctional breathing

1.1. Thesis overview

The composition of this thesis has been chosen to ensure that dysfunctional breathing (DB) is considered from a holistic perspective. The chapters encompass aspects of the whole cycle of care for a patient, from diagnosis to long term outcomes, with a view to improving clinical outcomes and decreasing demand on health service resources. As the focus is a paediatric population, it is also important to consider the parental perspective, due to the impact that this condition can have on the family as a whole.

Whilst the recognition and understanding of DB in children remains challenging, the situation is improving with pockets of research and specialist services emerging. Currently, there is a lack of tools to enable the simple diagnosis of DB and only limited evidence to support current treatment techniques. However, when managed in a coherent fashion, the clinical outcomes for these children are very good. Effective research into the nature, objective diagnosis and management of dysfunctional breathing is required to progress the whole care pathway and avoid the present significant but often unrecognised levels of morbidity.

1.2. Chapter introduction

This review chapter brings together information from a wide variety of sources in order to provide clarity on diagnosis and management of the condition today, and give context for the research presented in this thesis. Dysfunctional breathing is introduced with the specific difficulties in defining the condition discussed. This is followed by an explanation of the two subgroups of dysfunctional breathing and their clinical features. Evidence is then presented to highlight the lack of appropriate diagnostic and assessment tools and is followed by the limited epidemiological and morbidity/mortality data available. The role of comorbidities in dysfunctional breathing is complex and important and this is discussed with particular respect to asthma, with which the condition is often confused. The chapter then introduces the historical and current treatments used in the management of dysfunctional breathing (including reassurance only, medical management and breathing therapies) and summarises their effectiveness. This background information provides the rationale for the work that forms chapters 3-6, and, finally, the aims and objectives of the thesis are explicitly stated.

1.3. Summary of current understanding

Dysfunctional breathing is clearly important as demonstrated by its inclusion in the British Thoracic Society/Scottish Intercollegiate Guidelines network (BTS/SIGN) asthma guidelines (1) and the Global Initiative for Asthma (GINA) guideline (2). Unfortunately, however, neither offers insight into the nature, diagnosis or treatment of the condition. In addition, the importance of dealing with the impacts of dysfunctional breathing was highlighted at the London 2012 Olympic Games, at which Physiotherapists were employed solely to treat athletes with DB (3). It has also received attention in an increasing number of publications

during the past decade, where it has been associated with various specialist areas and in reviews of specific problems such as '*the breathless athlete'* or *'pseudo asthma'* (4-11).

However, ambiguity in the use of the term, and the use of multiple terms to describe the same condition, has hampered our understanding of DB and created difficulties in objectively identifying it. Terms such as dysfunctional breathing (12-16), hyperventilation syndrome (17-25), disproportionate breathlessness (24, 26), behavioural breathlessness (27), anxiety related breathlessness (28), sighing dyspnoea (26, 29), psychogenic functional breathing disorders (30) and somatoform respiratory disorders (31) have all been used to describe what appears to be essentially the same problem. Many of the terms imply a significant psychological component, and this perceived link between psychological dysfunction and DB is one of the reasons physicians often avoid this area. Similarly, the relatively well characterised form of DB known as paradoxical vocal cord dysfunction (pVCD) (32-37) has been labelled factitious asthma, functional stridor, episodic laryngeal dyskinesia, hysterical croup and psychogenic stridor (33).

Consequently, lack of clarity regarding aspects such as aetiology, diagnosis and management means that many clinicians do not have a clear perceptual model on which to diagnose and manage the condition. Failure to diagnose DB not only deprives patients of effective therapy but also places them at risk of adverse events arising from mis-diagnosis.

1.4. A new definition for DB

A clear definition of DB is required and at the outset of this study we proposed it to be defined as:

'an alteration in the normal biomechanical patterns of breathing that result in intermittent or chronic symptoms which may be respiratory and/or non-respiratory'.

This definition provides greater clarity than previous definitions but it is very formal and, whilst it may be factually correct, it has become apparent throughout the time of this study that it is not particularly functional. It would be preferable to develop a definition that has greater clinical utility and helps guide clinicians towards an appropriate diagnosis. This could be achieved by incorporating typical presentations/symptoms into the definition, potentially alongside a scoring system. The practicalities of how to achieve this improved definition are investigated further in Chapter 7 as part of the discussion around future research and developments.

Regardless of the style of the definition, however, on review of the literature it would appear that the multitude of existing terms are describing, in essence, two forms of DB:

- Thoracic DB (T-DB) - alterations in the pattern of respiratory muscle activity (pattern disordered breathing), which may or may not be associated with hyperventilation
- Extra thoracic DB (ET-DB) - upper airway involvement (such as pVCD) in addition to pattern disordered breathing

Similarities in aetiologies and approaches to treatment suggest that both forms of DB should be considered together as related conditions. We would suggest that pattern disordered breathing (PDB) is the central component of DB, both for those patients with a) upper airway involvement b) no objective evidence of hyperventilation and c) in the minority of subjects who do hyperventilate during symptomatic episodes (10, 11). The rationale for this will be discussed below.

1.4.1. Functional vs. structural DB

The two types of DB can be further divided into functional and structural forms. With functional DB, structure and function is normal as opposed to structural DB which includes anatomical and neurological abnormalities. Figure 1 illustrates the relationship between the different forms. This schematic diagram is useful to support clinical rationale and decision making but is also an over simplification of the relationship between T-DB and ET-DB. As discussed above, pattern disordered breathing is the central entity of DB, and hence T-DB and ET-DB can coexist and may reflect a spectrum of the condition rather than finite groups. For example, a high level sporting individual may experience T-DB at moderate intensity exercise which then becomes ET-DB at high intensity exercise or in a more competitive situation.

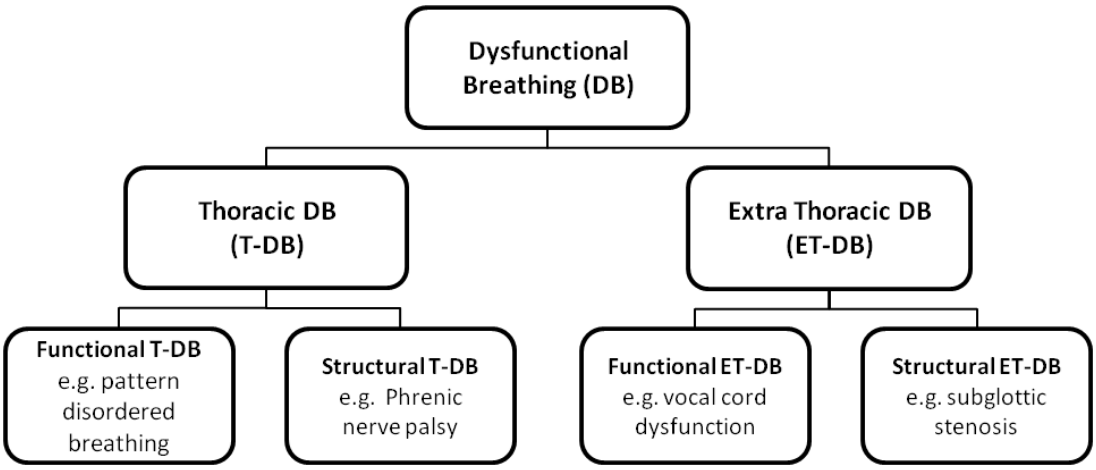


Figure 1: An overview of dysfunctional breathing

It is not the intention of this review to discuss structural DB, but examples are given here for completeness. These include phrenic nerve palsy, myopathy or an eventration of the diaphragm. Metabolic, cardiac and hepatic conditions, such as hepato-pulmonary syndrome may also be mis-diagnosed as DB, if a careful assessment is not undertaken when a patient complains of symptoms such as 'breathlessness'. For structural ET-DB the potential causes of symptoms include conditions such as unilateral cord palsy and subglottic stenosis (38).

1.5. Functional DB

1.5.1. Pathophysiology of functional DB

It appears that a central component of DB is pattern disordered breathing (PDB), in which the normal relaxed diaphragmatic breathing is replaced by a situation where the respiratory pump is largely being driven by upper chest wall and accessory muscles (15, 18, 39, 40). This is generally associated with mild hyperinflation, irregular rate and volume of respiration, and frequent sighing, and may be accompanied by an increase in rate (though this may not be dramatic). In some patients the minute volume increases sufficiently to induce hypocapnea (hyperventilation), either very transiently with the sighs that commonly accompany PDB, or more persistently during periods of stress. However, only a minority of patients with T-DB exhibit hyperventilation as defined by the presence of hypocapnea. The altered breathing pattern can be identified by experienced physiotherapists and other practitioners (40) from simple observation, however this is a skill lacked by many clinicians.

1.5.2. Relationship between hyperventilation syndrome and functional DB

DB is often equated with hyperventilation syndrome (HVS), and indeed much of the older literature in this area focuses on HVS. The term HVS was coined more than 75 years ago and there is no doubt that hyperventilation can generate significant metabolic effects resulting in a wide range of symptoms, many of which are apparently unrelated to the respiratory system.

Many, however, have suggested that HVS does not exist as a discrete entity (21-25). This is based on a failure to identify hypocapnea in the majority of subjects (including those with 'panic attacks') (23, 27, 41), the lack of specificity of the 'hyperventilation test' (21, 42, 43) and the observation that 'normal' individuals develop asymptomatic hypocapnea during normal activities (25). Significantly, it has been shown that breathing retraining focusing on diaphragmatic breathing can have a huge impact on symptoms, without significantly affecting a patient's partial pressure of carbon dioxide (pCO_2) (44). Older articles on HVS refer consistently to the 'characteristic' breathing pattern adopted by 'hyperventilators' with *'heaving of the upper sternum and lack of lateral costal expansion'* (17). These changes in the respiratory pattern (15, 17, 26, 45) suggest that DB was a core component of HVS, and that HVS describes one end of the T-DB spectrum.

There is no question that hyperventilation has discernible physiological and psychological effects, but when present in individuals with DB it is probably an additional, secondary component, rather than the primary abnormality. Additionally, there is little doubt that emotional and arousal states affect patterns of respiration (46-48). The similarities in response to heightened emotion, exercise and disease is reflected in one study, which found high levels of undiagnosed asthma in those presenting to an emergency department with 'hyperventilation' (49), while careful observation suggests that 'hyperventilation' is relatively common in asymptomatic asthmatics (50).

1.5.3. Aetiology of functional DB

Subjects develop symptoms when abnormal patterns become habitual or happen intermittently (e.g. when provoked by a psychological or physical stress). DB appears to co-exist with respiratory diseases such as asthma, though the nature of the relationship (causal or coincidental) remains unclear. The mechanisms leading to such characteristically 'abnormal' patterns of breathing are also unclear, though the condition does appear to be amenable to 'breathing retraining' where it is possible to exert a level of voluntary control over the pattern and rate of respiration.

Changes in breathing may also be affected by physiological and psychological influences, driven largely through the autonomic system. A degree of hyperventilation, which may be associated with increased sympathetic activity during periods of increased emotional arousal or stress, has potentially beneficial effects in increasing neuronal activity (15, 28). However, as with many physiological changes of potential benefit, excessive activity is counterproductive and further increases in ventilation, with increasing hypocapnea, result in reversal of this arousal and neuronal activity becomes depressed. Consequently, the individual moves from initial excitation to progressive exhaustion. Hyperventilation *per se* appears to reduce parasympathetic activity with associated sympathetic dominance, which may manifest as typical fight or flight signs. Similarity in physiological responses to both exercise and psychological stress has been demonstrated, where parameter response was not specific for either stimulus and there was considerable overlap. Overall, exercise had a greater impact on respiratory volumes while anxiety was associated with greater irregularity of breathing (46).

It has also been found that stress can alter function, with fluoroscopic studies showing that when a subject is exposed to emotional stress the diaphragm becomes flattened, hypertonic and relatively immobile (15). It is possible that similar changes taking place in the glottis may lead to the development of pVCD in some subjects. The alterations in breathing pattern, rate and regularity are normal responses to mental or emotional stress. From this perspective the development of DB can be seen as an unconsciously learnt, habitual change in the normal patterns of breathing, which may become apparent at rest or only when stressed. It would also explain the link between DB and psychological correlates. However, it must be remembered that, the pattern may have developed during a period of significant stress or heightened emotion, which may have resolved by the time patients present with symptoms.

In our experience of treating children and adolescents with DB, the driven individual is typical. These are often high-achieving perfectionists with obsessional traits who place themselves under stress (28) and presumably adopt a heightened readiness for 'fight or flight'. The trigger to move from intermittent, appropriate adoption of this pattern during periods of stress, to inappropriate maintenance of this pattern may be a specific episode (such as bereavement or an acute, life-threatening event). It appears to be common in an individual who sets themselves very high goals or standards, providing an internal source of stress. While the initial response may have been appropriate, DB might be seen as a failure to return to a baseline, efficient pattern of relaxed, slow abdominal breathing pattern (15).

DB frequently occurs in young sporting individuals but it also appears to be relatively common amongst musicians such as singers and wind and brass instrument players (51). However, this has not featured in literature to any great extent and the specific mechanism for the difficulties experienced by these performers has yet to be investigated. A possible explanation, that is common to these activities, is the degree of breathing control required. Patients experiencing problems with musical performance report difficulties in sustaining the length, volume and tonal quality/timbre of notes. These factors are controlled predominantly by the supporting column of air that the musician produces, which is generated by a good quality diaphragmatic inspiration and sustained by the coordinated activity of the abdominal and internal intercostal muscles. DB involves disruption of these normal breathing patterns, with predominance towards upper anterior chest wall activity, resulting in poor air column support and a poor or suboptimal musical performance. The situation can be further exacerbated by performance related anxiety and in the more extreme cases pVCD becomes evident.

pVCD (32-35, 52) has traditionally been viewed as having a psychological origin. Some early reports suggested that sexual abuse was a common antecedent, but this has not been borne out in more recent publications. There are reports of patients developing pVCD after severe life threatening asthma, or other severe respiratory events (such as acute severe allergic reactions involving the upper airway). It may be an exaggeration of the normal 'stress' response and the reported profile of many with pVCD appears to be very similar to those with T-DB again suggesting similar aetiology. It has been suggested that 'hypersensitivity' of the larynx (53, 54) is the initiating factor for many, and some authors have proposed that conditions such as gastroesophageal reflux and 'post nasal drip' are the triggers. However there are no studies convincingly correlating either trigger with pVCD. More importantly, the limited literature regarding treatment would suggest that therapy centred around breathing control, together with specific breathing techniques to abduct the vocal cords, produces much greater benefits than 'specific' treatment of these conditions (37, 55).

1.5.4. Prevalence

Most of the limited number of studies attempting to assess the prevalence of DB, both amongst those with respiratory diseases such as asthma and/or amongst the general population (as well as anecdotal reports), suggest that it is common (14, 17, 22, 30, 56). That the diagnosis is not made more often is probably attributable to a number of factors. For example, it is likely that many will not present to medical services because they have adapted their behaviour to avoid symptoms. In those with chronic respiratory disease the symptoms are often attributed to the underlying disease, resulting in a fatalistic acceptance or prescription for inappropriate treatment such as very high, and potentially harmful, doses of inhaled steroids. In others, symptoms are attributed entirely to anxiety, stress or other psychological conditions, without considering accompanying biomechanical components.

1.5.5. Clinical features

Patients with DB typically present to respiratory physicians with symptoms of 'difficult to treat asthma' or 'exercise induced asthma'. They also present to otolaryngologists when a laryngeal cause has been suspected. Many others without overt respiratory symptoms present to GPs and 'general' physicians with a variety of non-respiratory complaints. Table 1 shows a summary of the symptoms most commonly associated with the different types of DB, which are discussed in more detail below.

Table 1: Summary of symptoms associated with thoracic and extra thoracic forms of DB

Symptom	Key information	T-DB	ET-DB
Shortness of breath	At rest, with physical exertion or during performance	✓	✓
Wheeze/stridor	Predominantly inspiratory but can have an expiratory component	×	✓
Throat tightness	Commonly described as a choking sensation or throat closure	×	✓
Sighing	Generally frequent, deep or as yawning	✓	✓
Chest pain	At rest or with activity, can vary in location	✓	×
Difficulty breathing in	A sensation of not being able to get enough air in	✓	✓

1.5.5.1. Shortness of breath

Shortness of breath may occur at rest or with exertion. Those with DB often describe 'difficulty breathing in' at rest (such as when watching the television), though for others symptoms only manifest during exercise or in other specific situations.

The mechanisms contributing to an individual's perception of difficulty in breathing are complex (57-59). From a physiological perspective it involves a range of receptors in the chest wall and respiratory muscles, the lungs, carotid body and brainstem, together with intact pathways. A perception of dyspnoea may be generated by increased work of breathing, as seen in airways obstruction and interstitial diseases, but may also be experienced in the absence of any primary abnormality of the lungs and airways (for example in hypoxia due to a pulmonary embolus or imposed hypercapnea) (57).

Superimposed on this are factors such as anxiety, which heighten the sensation of distress experienced by an individual. Moreover the perception is significantly affected by a change from baseline, with considerable adaptation occurring in those with chronic disease.

1.5.5.2. Wheeze/stridor and tightness

'Wheeze' is often reported by subjects who have extra-thoracic forms of DB. On closer questioning the 'wheeze' is predominantly, or entirely, inspiratory. This, however, may be difficult for the patient to determine and is often more accurately described by an observer. Video captured using a mobile phone may be very helpful in this respect.

Subjects may also describe a 'choking sensation' or, less commonly, 'my throat seems to close'. In conjunction with this, when asked about 'chest' tightness, patients will commonly point to or place their hand over their throat or upper sternum. Clinicians should avoid gestures when asking about tightness to avoid influencing the response given, as it provides a key factor in diagnosis.

1.5.5.3. Sighing

Frequent or deep sighing is often cited as a prominent feature of DB (17, 26, 29, 60, 61) though why this is the case is unclear. Sighing can easily be measured using respiratory inductance plethysmography (RIP), where depth of sigh can be measured as well as rate. A normal sigh rate is considered to be 0-3 sighs in a 15 minute period. In one case study of 'disproportionate breathlessness', the baseline sigh rate increased with exercise from 18 to 60 sighs per 15 minute period (26). It is also of note that functional residual capacity (FRC) appears to be raised in those with DB and sighing (29, 61) and, clinically, a high propensity to yawning has also been observed.

DB is synonymous with the feeling of not being able to get enough air into the lungs (see section 1.5.5.5). This sensation may stimulate breath stacking, with a consequent rise in FRC, in an attempt to satisfy this need. Increased FRC and the resultant hyperinflation place the respiratory system at a mechanical disadvantage (with the ribs moving upwards and outwards) and stimulates the stretch receptors of the intercostal muscles. We would propose therefore that the sigh (or yawn) action serves to 'release' the respiratory system and allow the FRC to return to normal before the cycle starts again. Increased FRC can also be a product of anxiety and it may be that a combination of these factors contributes to the increased sighing associated with DB.

1.5.5.4. Chest pain

If present, chest pain is most commonly reported to occur during exercise, but can also be experienced during normal activities or at rest. Pain, often without associated shortness of breath, has certainly been one of the most common symptoms addressed by those with an interest in HVS (28), and hypocapnea has been evoked as a likely cause. It does seem, however, that the chest pain is likely to be musculoskeletal in origin in the vast majority of patients with DB (presumably due to muscle fatigue from inappropriate overuse of

respiratory muscles at rest, which is then exacerbated by increased muscle work associated with exercise). Breathing retraining appears to be valuable in addressing this symptom (62), supporting the suggestion that musculoskeletal dysfunction accounts for the discomfort in such cases.

'Chest pain' commonly induces significant anxiety in patients and their parents or relatives. Clearly it is important to eliminate organic causes such as asthma and costochondritis, and to consider other, rarer causes (including cardiac). However, accurate recognition that the musculoskeletal discomfort is attributable to abnormal biomechanical patterns of breathing is important, in providing both reassurance and appropriate therapy.

1.5.5.5. Difficulty breathing in

At face value this might be a useful symptom, particularly in the identification of ET-DB, and this symptom is frequently cited as almost pathognomonic. However, most asthmatics, when directly questioned, also describe breathing in as being more difficult than breathing out, even though most doctors consider asthma to cause more problems during exhalation (63). Hence, simply enquiring about whether breathing in is more difficult than breathing out is not helpful. Often it is more helpful to ask whether the patient can take a full breath in. The sensation that at the end of inhalation even greater effort is required to fill the lungs is a common symptom amongst those with DB and patients feel as if they cannot get enough air in to fill their lungs (18). This is only elicited if specific enquiries are made rather than simple asking 'do you find it difficult to breathe in?'

1.5.6. Impact on quality of life

The impact of the condition on individual's lives should not be underestimated. One study directly comparing patients with DB to those with controlled asthma found DB had a significantly greater impact on quality of life and activities (56) and represents a significant unrecognised burden of disease. However, whilst DB does have a direct impact on an individual's quality of life, it is important to recognise that some of the negative impact is the result of the attitude of clinicians when they dismiss symptoms as being '*all in the mind*', or diagnose a disease such as asthma and then fail to control symptoms with ever increasing therapy.

1.6. Clinical practice

1.6.1. Diagnosis

Both over- and under-diagnosis are likely and there is the potential for DB to swing from the current position of under-diagnosis to over-diagnosis if the true nature of the condition is not understood. It is important to be clear about an individual's particular problem if the appropriate therapy is to be offered, and a simple referral to the physiotherapist or speech therapist should not be seen as the 'easy option'.

1.6.1.1. Thoracic dysfunctional breathing

The lack of tools to objectively quantify the pattern of breathing has contributed to the lack of recognition of the importance of T-DB. Components of breathing pattern, such as the predominant type of breathing (i.e. abdominal vs. upper thoracic), unsteadiness and irregularity of breathing and frequent sighing, have traditionally been assessed subjectively through visual observation. However, when attempting to objectively monitor patterns of breathing it should be remembered that respiratory parameters can be influenced by a wide range of factors, including simply being observed (64), the respiratory patterns of others close by (65) and emotional state (18, 47, 48, 66, 67). Some have attempted to quantify the observations of skilled professionals using manual techniques such as 'MARM' (Manual Assessment of Respiratory Motion) (40, 68), but these have not been widely adopted. Similarly, powerful but relatively complicated techniques such as complex imaging and electromyography (EMG) (39) have remained largely a research tool used to study other disorders (69, 70). The majority of patients with dysfunctional breathing (in the absence of pulmonary disease) present with normal values for spirometry and, hence, this is rarely helpful.

Some studies have attempted to objectively assess respiratory patterns. In these studies, techniques used have included optical scanning methods (71-74), electromyography (69, 70), ultrasound (75) and respiratory inductance plethysmography (76). These measurement techniques have contributed to our understanding of normal respiratory patterns during quiet respiration, as well as changes during exercise and disease. However, their cost and complexity have largely prevented use in clinical practice and they have not been used to study DB. The absence of an easily applicable technique presents a significant limitation to objectively assessing important components of DB, but this may change with recent improvements in imaging technology.

An alternative approach to diagnosis used in a number of studies is questionnaires. The Nijmegen questionnaire (NQ), a 16 item list of complaints (scored on a 5 point ordinal scale), was designed to be an 'objective tool' for identifying patients with HVS (77). A score of 23 or above is considered to be indicative of HVS. However, many of the symptoms included in the questionnaire (such as chest pain) are probably related to DB as much as to hyperventilation. In addition, its use in asthmatic patients showed a negative correlation with the mini-Asthma Quality of Life Questionnaire (mini-AQLA) score (78); that is the NQ score increases as the mini-AQLA score fell, suggesting that the NQ was not specific for HVS. Conversely, there are reports of low scores on the Childhood Asthma Control Test (C-ACT) leading to the use of high doses of asthma medication in children who have DB but don't have asthma (79).

These observations reflect the significant overlap between symptoms associated with dysfunctional breathing, and those due to primary respiratory conditions such as asthma. A further study found that the dyspnoea sub-score of the NQ correlated closely with a manual assessment of DB. In the same study they observed that it was patients with DB and associated dyspnoea who benefited most from breathing retraining, as compared to

those with a comparable NQ score without DB or significant score on the dyspnoea sub-score (68).

The NQ may have some value in identifying symptoms of T-DB but its limitations, including the lack of any validation work in children or those with co- morbidities, should be recognised.

1.6.1.2. Extra-thoracic dysfunctional breathing

In those suspected of ET-DB it is important to make a positive diagnosis. Many with presumed exercise induced pVCD are found to have exercise-induced laryngomalacia (or exercise-induced paradoxical arytenoid motion or EPAM) (38, 80-86). This may profoundly alter the treatment options, as does the identification of other pathologies that may mimic the symptoms of pVCD.

Laryngomalacia and pVCD are not mutually exclusive, and in a proportion of those with pVCD the airway obstruction commences with abnormal supraglottic motion and collapse (with the vocal cord adduction, if it occurs, commencing after onset of the supraglottic collapse). The management is similar but recognition of EPAM has added the option of operative intervention by otolaryngologists, which to date has been largely undertaken in competitive athletes (36, 83).

As the obstruction in these conditions is extra-thoracic (supraglottic, glottic or subglottic), inspiratory flow volume loops may be helpful if the subject is symptomatic. However, if the subject is asymptomatic at the time of the test, results will generally be normal and it is uncommon to obtain diagnostic flow volume loops from these individuals (87).

Laryngoscopy during symptomatic periods is currently the gold standard method for diagnosing extra-thoracic forms of DB. The classic laryngoscopic findings during pVCD are adduction of the anterior vocal cords during inspiration with a 'diamond-shaped' aperture visible posteriorly (1, 2, 35-37, 55). As with spirometry, direct laryngoscopy is likely to be normal in the absence of symptoms and it is generally important to induce symptoms using the normal stimuli for a particular patient. In children and adolescents this is usually exercise, while in adults triggers such as perfumes and other 'irritants' are more common. A frequent experience is that symptoms can be induced by a period of exercise but, by the time a laryngoscope is passed following cessation of exercise, these symptoms, and hence characteristic appearances, can have resolved. For this reason some centres are adopting techniques that permit continuous laryngoscopy during exercise (CLE) (38, 81-86). The procedure involves the temporary siting of a fibre optic laryngoscope (usually via the nose) to visualize vocal cord motion. At present, this technique is limited to the study of adult patients.

1.6.2. Co-morbidities and differential diagnosis

It is important to recognise that dysfunctional breathing is often associated with, and can exacerbate, symptoms of respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD) and obliterative bronchiolitis, and that introduction of

appropriate therapy often produces significant benefits in terms of function and quality of life.

Recent studies using dynamic CT scans have confirmed that pVCD can be present during expiration amongst asthmatic subjects, and can contribute to the severity of reported symptoms (88, 89). Whether this is an unconscious mechanism for applying positive end-expiratory pressure (PEEP) analogous to breathing out through pursed lips, hence helping expiration at low lung volumes, is unclear. These studies have also confirmed that classical inspiratory pVCD and/or narrowing of the supraglottic area due to 'laryngomalacia' exist as co-morbidities in some subjects with difficult asthma.

The differential diagnosis of 'exercised induced asthma' in an individual who is experiencing significant exercised induced symptoms has been comprehensively reviewed recently by Carlsen and Weinberger, amongst others (4-11, 86, 90-92). In addition to straight forward exercise induced asthma, differential diagnoses include:

- Deconditioning with individuals having low levels of fitness
- Failure to recognise that a fit individual has reached their physiological limit
- Exercise induced tachyarrhythmia
- Forms of upper airways dysfunction (particularly supraglottic collapse during intense exercise and pVCD)
- Pattern disordered breathing (which may only induce significant symptoms during exercise)
- Exercise induced hyperventilation

All of these can co-exist with asthma or exist as a discrete entity masquerading as asthma. Hence comprehensive assessment may require full cardiorespiratory exercise testing, continuous laryngoscopy during exercise and assessment by experienced physiotherapists, in addition to a careful history.

Amongst those with 'brittle asthma' who develop attacks of apparently severe and poorly responsive symptoms, normal transcutaneous oxygen saturation is often a valuable clue that the patient has a form of DB.

1.6.3. Treatment

The evidence base for therapy for DB remains limited (as illustrated in Chapter 5); in part due to a lack of clarity surrounding diagnosis and lack of knowledge concerning aetiology, which translates to uncertainties surrounding therapy.

Common to most approaches for managing both thoracic and extra thoracic forms of DB is breathing re-training (15, 39, 59, 93-101). Breathing retraining is discussed in depth in Chapter 2 but an overview is presented here to illustrate its role within the other therapeutic options.

1.6.3.1. Thoracic dysfunctional breathing

Breathing retraining is used by physiotherapists, speech and language therapists, psychologists, 'alternative' therapists and some specialist nurses, and is recognised as a first line treatment for adults with DB (94). The aim of breathing retraining is to enable patients, over a period of time, to modify their breathing pattern with the ultimate goal of restoring and maintaining a normal diaphragmatic breathing pattern (44, 94-96). There is also a focus on normalising respiratory rate and/or tidal volume, in addition to education, relaxation and postural correction. Some have argued that simple explanation of the condition (sometimes with antidepressants) is sufficient (24). However, while acknowledging the patients concerns and fears together with supportive counselling is important, it is probably not sufficient in itself in most subjects (77).

A number of studies, primarily with adults, have suggested that breathing retraining can reduce respiratory symptoms, improve quality of life, alter breathing frequency and decrease levels of anxiety and depression (96-98). However, the mechanism for improvement in DB following breathing retraining is not fully understood, and more rigorous research is required to fully understand its role and effect. Despite this, the positive impact and benefit of this form of therapy appears to be sustained, as shown in a five year follow up study (102). This compares favourably with historical follow up studies which demonstrate that, without therapy, HVS amongst children and adolescents commonly persisted into adulthood (103).

1.6.3.2. Extra-thoracic DB

ET-DB is predominantly managed using the breathing retraining and supportive techniques outlined above, in association with specific techniques focusing on laryngeal 'hygiene' and function (33, 104-108). Techniques for suppressing cough and throat clearing can also be taught where habituation of these is a feature of a patient's symptoms (35).

Patients are taught various breathing techniques that are intended to provide immediate control over, or quick release from, paradoxical movement in the vocal folds. These include rapid inhalation through the nose ('sniffing') or mouth (109), depending on which the patient feels more comfortable with, and exhaling through a resistance (most conveniently pursed lips) for 2-3 seconds.

In addition, it has been observed that inspiration under resistance (sniffing through semi-collapsed nares or through a restricted oral aperture) causes the vocal cords to reflexively abduct, and, similarly, exhaling against a resistance is also believed to enhance cord abduction. These techniques can be used after the onset, or immediately prior to the onset, of symptoms to prevent them developing. As with the breathing retraining techniques, patients are encouraged to practice these techniques regularly.

As well as breathing techniques, there are anecdotal reports of anti-cholinergics prior to exercise (105), and heliox during acute episodes, being helpful (35). Interestingly, more invasive approaches such as intubation, tracheostomy and botox therapy are also described (55, 108). EMG with biofeedback has been used in both T-DB and ET-DB and

represents an alternative or complementary approach, but to date has not been widely adopted.

The role of more formal psychology and cognitive behavioural therapy will vary from patient to patient. In the majority of subjects this is not necessary, but as with almost any group of patients this may be required by some. The interested therapist, who spends significant time with patients during assessment and therapy, is likely to be best placed to identify those who may require more formal psychological help.

1.7. Conclusion

The literature reviewed above clearly demonstrates that there is little evidence available to health professionals on how to diagnose and manage dysfunctional breathing in children. The majority of the evidence that is available is drawn from adult studies, and is not necessarily applicable to children. This lack of appropriate evidence is at odds with the level of morbidity observed and the significant impact the condition has on these children and their families.

1.7.1. Thesis structure

Fundamental gaps in the knowledge and understanding of DB have been identified. Chapters 3-6 aim to generate new knowledge and understanding and promote further work into these important areas. The application of structured light plethysmography and respiratory sound analysis has been chosen for study as these technologies offer the potential for developing quantifiable and non-invasive testing and measurement methods. If successful, the simplicity of these tests for the patient makes them ideal for the paediatric population, and would provide levels of assessment not currently available.

Once correctly diagnosed, it is equally important to offer quality evidence based treatment to optimise the likelihood of good long term outcomes. The findings of both the systematic review and the observational study, will support clinicians in making informed decisions on the management of dysfunctional breathing.

Chapter 2 supports the work of the thesis by providing detailed information on the technologies, treatments and outcome measures that are pivotal to the studies presented.

The studies that form this thesis will help to build a body of knowledge and form a platform for future research. They will also raise awareness of this important but often under recognised condition.

1.7.2. Thesis aims and objectives

The primary aim of this thesis is to improve the care of children with dysfunctional breathing.

This aim will be achieved through the following objectives:

1. Appraise and summarise the current knowledge and evidence on the diagnosis and management of dysfunctional breathing in children

2. Investigate the use of structured light plethysmography as a method for the detailed assessment of dysfunctional breathing
3. Determine whether respiratory sound analysis can be used to identify vocal cord dysfunction in children
4. Systematically review the current evidence available on the treatment of dysfunctional breathing in children using breathing retraining
5. Investigate the short and longer term outcomes for children receiving breathing retraining for dysfunctional breathing in a specialist clinic
6. Raise awareness in health professionals of the condition and it's management by disseminating the newly generated knowledge

2. Introduction to technologies, treatments and outcome measures

2.1. Introduction

This chapter introduces the technologies, treatments and outcome measures that form the focus of this thesis.

It presents the background, development and potential benefit details of structured light plethysmography (SLP) and respiratory sound analysis (RSA). These technologies are explored in Chapters 3 and 4 respectively, as tools to objectively measure breathing patterns in children with dysfunctional breathing (DB), and for the non-invasive identification of paradoxical vocal cord dysfunctional (pVCD).

The chapter also explains the technique, and limitations, of nasendoscopy (an approach to visualising the upper airway) as, in this thesis, nasendoscopy is used as a gold standard for the diagnosis of ET-DB. Breathing retraining is examined through a systematic review and is the focus of Chapter 6, which examines the efficacy of this technique as a method of treatment for DB.

The chapter concludes with a discussion of outcome measures, in particular the Pediatric Quality of Life Inventory™, or PedsQL™ (a quality of life measure), and the Nijmegen questionnaire (used in this thesis as a symptom score). These measures are also a key component of Chapter 6.

2.2. Structured light plethysmography

2.2.1. Background

The ability to visualise and measure the chest using structured light is not a new concept. Similar concepts to structured light plethysmography (SLP) saw intense interest in the early and mid 1980's (110, 111), but were never taken forward into clinical practice. The reason for this loss of interest, and subsequent resurgence in awareness (whilst not stated implicitly), appears to relate to computational power and commercial viability.

The original development of a technique using light striping to measure respiration was carried out by a research team at the Royal Brompton Hospital (London) in conjunction with the computer giant, IBM. They developed an optical system for mapping the size and shape of the thoracoabdominal wall, and the change in its shape with breathing (110). The set-up involved two projectors (projecting stripes of light), two cameras and a steel reference frame, within which the patient would stand. At this time, the limited technology meant that only still images could be captured, but the equipment was assembled so that rapid repeated still frames could be used to obtain dynamic studies (110).

The outcome was an optical measuring technique that could relatively accurately and reliably measure the dimensions and volume of the chest. The applications, however, were limited by the cumbersome nature of the equipment and the inability to process the information on site. Significant computer resource was required and data had to be sent to

IBM for processing. This necessary outsourcing of data processing created a significant time lag between the test being performed and the results becoming available.

At a similar time, an alternative technique called rasterstereography was being developed. It shared many similarities with the light striping approach but instead of stripes used a grid of lines projected onto the subject. The crossed sections of the grid lines provided identifiable points, allowing a three-dimensional reconstruction of the surface being projected onto (112). The technique was originally developed for static measurements of problems such as spinal scoliosis (113), but had the capability of measuring moving objects. As with light striping, the use of rasterstereography for measuring the chest failed to emerge as a viable technique, because the complexity of the data captured outweighed the computational power available.

Although not successful at the time, light striping and rasterstereography appear to be the direct forefathers of structured light plethysmography. Proponents of SLP share the same aspirations as earlier researchers; to find a non-invasive, optical technique capable of quantifying different aspects of respiration.

2.2.2. The current situation

Technological advancements mean that where once computer power was the limiting factor, this is no longer the case. SLP, in the form of the Thora3Di™ (PneumaCare, Cambridge, England), has become commercially available in a portable system, where data capture and analysis happen almost simultaneously. The Thora3Di, which was initially designed to measure lung function, operates using a digital projector and two digital cameras connected to a laptop computer. The structured light is projected onto the person in the form of a checker board, as opposed to the original stripes or grids of lines. The intersections of the squares, however, act in a similar way, giving known reference points, and an internal auto-calibration system removes the need for the steel reference frame (114).

2.2.3. Potential benefits

The benefits of being able to measure the chest and respiration using SLP are significant. The system is non-invasive (i.e. with no patient contact), which allows people to be tested who cannot manage more traditional lung function testing (for example, a person with cerebral palsy who cannot achieve a seal around the mouthpiece of a pneumotachograph). This characteristic also minimises infection control risks associated with equipment, a cause for concern in patients with particular conditions (e.g. cystic fibrosis). Additionally, certain lung function parameters can be measured without the active involvement of the patient. This means that a wider population can be tested, particularly young children and those without the physical or mental ability to cooperate. The non contact nature of the device is also less likely to interfere with the breathing pattern being measured.

Whilst the potential benefits of SLP for lung function measurement are clear, the recent development of this equipment means that there is currently only a limited amount of evidence to support the technology. Pilot studies have been carried out, comparing

measurement of lung function using SLP and pneumotachography in terms of tidal volumes and forced expiratory manoeuvres (FEV_1) (115-117). The findings indicate that lung function measurements using SLP are consistent with measurements from the pneumotachograph. However, the primary means of disseminating findings from these studies has been in the form of abstracts, posters and verbal presentations, meaning the research methodology and results cannot be comprehensively examined.

The greatest value of SLP is not, however, in measuring lung function. New software developments offer a much wider range of applications. Peacock et al (110) identified that their structured light technique (striping) could determine the spatial distribution of each breath, allowing them to assess the relative contributions of rib cage and abdomen to breathing. SLP offers the same opportunity and early studies have been carried out in thoracic surgery patients, comparing breathing pre and post surgical procedure (118).

2.2.4. Key methodology: Konno-Mead loop analysis

Analysis of breathing by SLP is performed based on the Konno-Mead method (119). Konno and Mead proposed a two degree of freedom model of chest wall motion, where there is a direct relationship between rib cage (RC) and abdomen (AB) displacement and ventilation. Using complex algorithms, SLP measures rib cage and abdomen displacement during respiration and converts this movement into movement-time waveforms, individually for RC and AB and as a total body representation. The two individual waveforms (RC and AB) are then examined for phase relationship, and represented graphically by an XY-plot. Conventionally, AB is displayed on the X axis and RC on the Y axis. These plots are also known as phase plots or Konno-Mead (KM) plots. The same process that is used for RC and AB contribution can also be used to assess symmetry of breathing using left and right sided contributions. Furthermore, a combination of RC, AB, left and right can then be used to generate information pertaining to 'quadrants' of the chest.

As well as providing a graphical representation of breathing, the KM plot provides numerical information. The primary parameters that can be measured are overall phase (OP), breath phase (BP), spread (Spr) and principle angle (PA). Overall phase is based on the premise that RC and AB movement occur almost simultaneously, and in synchrony, during quiet tidal breathing in healthy individuals (120). The relationship of the phase between the two waveforms of the RC and AB signals can be analysed, giving a measure of synchrony. Synchronous breathing results in an overall phase angle verging on zero, which is represented on the KM plot by a straight line or very narrow loop at an angle of 45 degrees. An increasing overall phase value indicates increasing asynchrony of breathing.

Problems with the accuracy of overall phase can arise though if there is a drift in the signal or the breaths do not overlap perfectly on the KM loop. A solution to this is breath phase, where the phase for each individual breath is calculated and then averaged giving a potentially more accurate measurement.

In addition to numerical data, the shape of the KM loop itself is a useful measure of synchrony. Where the RC and AB movements are synchronous, the loop is very narrow or ellipsoid. As shown in Figure 2, the loop becomes more circular with increasing

asynchrony, until the signals are 90 degrees out of phase. It then narrows again until complete asynchrony is reached at 180 degrees out of phase. The narrow loop has a positive slope when breathing is synchronous and a negative slope when it is asynchronous. The loop shape can be described quantitatively using spread which is a ratio of the length of the secondary axis (the 'width') with the primary axis (the 'length') (see Figure 3). However, it is not possible to quantify the loop when a figure of eight pattern is produced. Figure of eight patterns, thought to be a result of biphasic abdominal motion (121), can occur in normal breathing, but are also seen in conditions such as neuromuscular disorders and obstructive airways disease (121, 122).

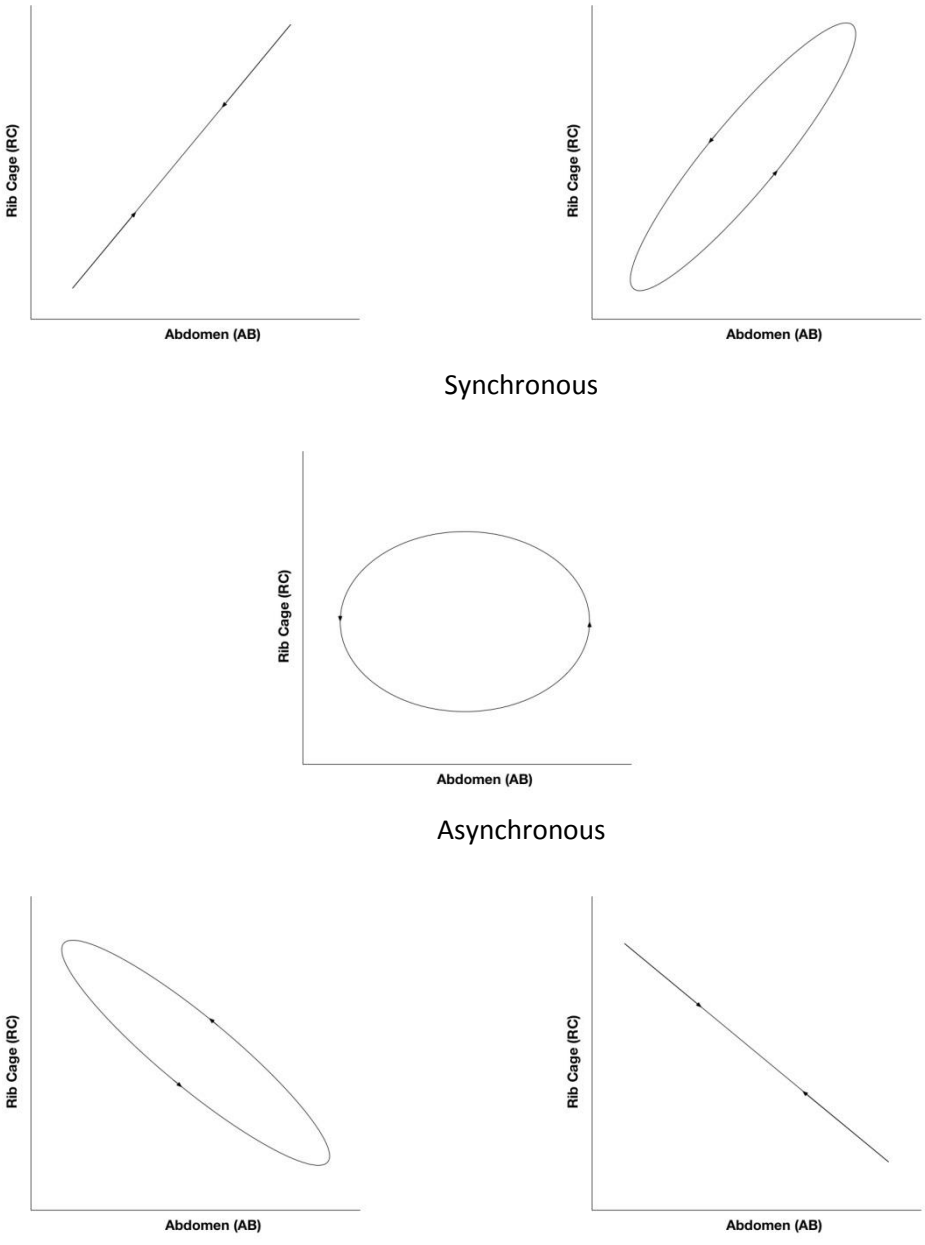


Figure 2: Graphical representations of phase relationship of abdomen and rib cage between 0 and 180 degrees

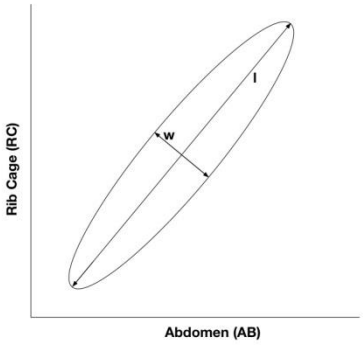
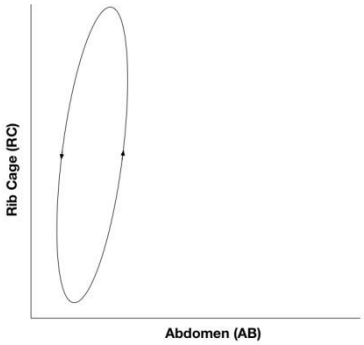
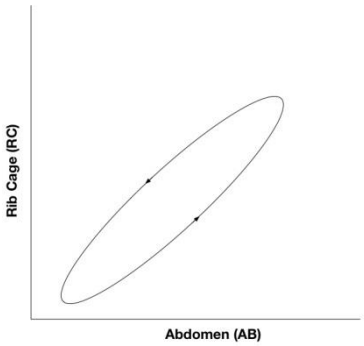


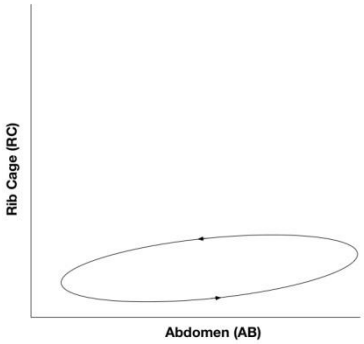
Figure 3: Calculation of spread using length and width of the loop



Rib Cage dominant breathing pattern



Equal Abdomen and Rib Cage contribution



Abdomen dominant breathing pattern

Figure 4: Graphs showing the loop angle associated with different breathing patterns

Principle angle, rather than an indication of synchrony, is a measure of contribution or dominance, and is the angle between the 'general direction' of the KM loop and the 45 degree line. Where contribution between RC and AB is equal, principle angle is zero. Proportionally greater RC contribution gives a positive principle angle. Conversely, a negative angle indicates a greater AB contribution. Figure 4 illustrates these three situations. Further information on the relationship between RC and AB is available from the direction of travel of the loop rotation. The direction of travel is dictated by the order in which the compartments RC and AB move. In normal breathing, and the majority of breathing disorders, the loop rotation is anticlockwise as AB leads RC. The exception to this situation is where there is diaphragmatic paralysis. Here, RC dominates and the loop rotation is clockwise (123).

2.2.5. Alternatives

2.2.5.1. Respiratory inductance plethysmograpy

KM loop parameters have been used previously as a means of measuring thoraco-abdominal asynchrony (TAA) in children with various respiratory disorders (124-126). The RC and AB signals have been generated almost exclusively using respiratory inductance plethysmography (RIP). RIP was developed about 25 years ago (127), and the most well known version is the LifeShirt^{TM}. The LifeShirt was originally created for the military and emergency services to monitor personnel in critical situations (by measuring and transmitting vital signs information). Initially, the system consisted of a RIP band round the chest, but more recent versions also include a band around the abdomen. The bands detect change in cross sectional area of the rib cage or abdomen. This information has primarily been used to calculate change in lung volume, but is also used to investigate breathing pattern (by detecting the relative contributions of the rib cage and abdomen to breathing) (127).

It is possible to use RIP with children; the only modification required is smaller sized bands. The technique is not, however, wholly suited as a tool for the assessment of breathing pattern in either adults or children. The movement of the chest wall during breathing is complex three-dimensional motion, which varies in the proportions of movement depending on factors such as activity levels and presence of disease or dysfunction. Whilst RIP can measure lateral expansion, it cannot detect vertical motion (40) – this means that some dimensions of breathing are not assessed. Furthermore, measurement error can occur if the bands move, or the subject makes a significant postural change (127).

2.2.5.2. Optoelectric plethysmography

The key difficulties in using RIP to assess breathing pattern have been overcome using optoelectric plethysmography (OEP). This is a technology originally intended for the analysis of gait, and involves the placement of reflective hemispherical markers on the chest wall (128). The position of these markers is recorded by strategically positioned cameras, and fed into a computer which translates them into three-dimensional coordinates as a function of time (72). The number of markers used for this technique ranges from 32 to 86, but it has been found that the degree of error is inversely

proportional to the number of markers placed. Cala et al (1996) found that the number of markers could be reduced from 86 to 58, but any further reduction resulted in an unacceptable level of error. When the optimal number of markers is used, OEP can accurately measure lung volumes as well as three-dimensional chest wall movement, including symmetry or asymmetry.

However, it is primarily the number of markers and degree of accuracy required to place them that prevents OEP from being adopted into routine clinical practice. The time required to prepare the patient for testing ranges from 30 to 45 minutes, plus 15 minutes for calibration of the equipment (129). Whilst this length of time may be manageable for adults participating in research, many children would find concentrating for this amount of time difficult (particularly if the measure is to be repeated on future occasions).

2.2.6. Summary

Breathing is a very personal activity and is easily interfered with by external factors. Contact with the chest during measurement has the potential to influence the very breathing pattern that is being assessed. RIP involves bands around the chest/abdomen and whilst OEP is less invasive, it still involves the placement of sensors on the chest wall. SLP was chosen for study, however, as it has the potential to offer a solution which can comprehensively measure the three dimensional nature of breathing without influencing the pattern of breathing by contact with the chest. It is quick and easy to perform, potentially suitable for all age groups, and, although the technology is still relatively unproven, the clinical benefits on offer provide a strong argument for its investigation.

2.3. Respiratory sound analysis

Respiratory sound analysis is a technique used to evaluate the acoustic properties of respiratory sounds (130), from which clinical conclusions can be drawn on their underlying cause and significance. It has also been called computerised acoustic analysis, lung sound analysis and computerised respiratory sound analysis. For the purpose of this thesis, the term RSA will be used (and will encompass all these common variations).

2.3.1. Background

Prior to the development of RSA, the only method available for listening to sounds generated by the respiratory system was the stethoscope. The stethoscope was introduced almost 200 years ago (131) and, even with the advent of RSA, is still used today. Although commonplace in our hospitals and clinics, and used by a variety of professions, the stethoscope is a less than ideal instrument, with a number of inherent problems.

Interpretation of respiratory sounds using this method is entirely subjective and there is a high degree of inter observer variability (132). Apart from the reliance on the skills of the user, and the qualitative nature of the information provided, the stethoscope selectively amplifies or attenuates the sounds detected dependent on their frequency (133). This means that the sounds heard by the stethoscope user are not necessarily the same as those generated by the patient. Furthermore, stethoscopes tend to be used because of

their apparent ease of use, but the brief technique commonly used, where only one or two breaths per area of the chest are listened to, can mean intermittent findings are overlooked.

RSA seeks to address the problems of the stethoscope and has developed in line with significant advances in computer technology. In its infancy, respiratory sounds were recorded on cassette tapes (134), whereas it is now possible to transmit the data wirelessly to a portable computer for real time processing, and almost immediate graphical representation. Initially, the parallel activities of different research groups, and the limitations of earlier computers, lead to the development of a variety of techniques using different equipment. Many of the groups fabricated their own equipment, which has led to difficulties in reproducing or comparing much of this earlier work.

2.3.2. The current situation

The majority of clinical studies carried out using RSA have investigated the detection of particular adventitious sounds, predominantly wheeze and crackles (131, 135, 136). It has been shown that different adventitious sounds have distinct acoustic properties, and that RSA can be used to differentiate between such sounds (135). Where sounds that are central to a condition can be identified and quantified, it becomes possible to use RSA to aid diagnosis and monitoring of that condition, as well as a means of assessing the benefits of interventions. This possibility has been investigated with asthma, where there is a relationship between wheeze and airway obstruction (136).

2.3.3. Potential benefits

Currently, airway obstruction is quantified using FEV_1 obtained through spirometry. Baughman and Loudon demonstrated that, in patients with asthma, there is good correlation between the proportion of the breath cycle occupied by wheeze (as measured using RSA) and FEV_1 at that time (134). This implies that RSA results could be used as a substitute measure of airway obstruction. This would be particularly useful in patient groups such as infants, who are unable to carry out the current forms of lung function testing. It also offers the benefit of continuous testing, e.g. for overnight studies of nocturnal asthma, where previously the patient would have to have been woken to perform spirometry, and results would have been periodic.

There are a number of conditions where diagnosis is difficult due to similar clinical presentations to other conditions, for example asthma and pVCD (137). The underlying mechanism of these conditions is very different; asthma classically presents with an expiratory wheeze, whereas pVCD presents with inspiratory stridor (IS). As the acoustic properties of these sounds are distinguishable, RSA offers a means of differential diagnosis. However, this apparently simple solution is complicated by the concurrent presentation of these conditions. In a cohort of 370 elite athletes, Rundell and Spiering demonstrated that, whilst 5% of this group presented with inspiratory stridor (indicative of pVCD), 53% of IS positive athletes also demonstrated exercise induced bronchospasm (138). The different acoustic profiles (with distinct patterns displayed in different parts of the breathing cycle) should however mean that both the pVCD and asthma related sounds remain identifiable.

The use of RSA as a non-invasive method for diagnosing pVCD has not been previously investigated. This may be related to a number of factors; a previous lack of easy to use, affordable equipment, and a possible lack of demand outside the discipline of elite sports performance. The increasing clinical need to accurately diagnose children potentially misdiagnosed with asthma, coupled with the availability of technologically advanced portable RSA devices, now makes the study of RSA for the diagnosis of pVCD not only important but also viable.

2.3.4. The PulmoTrack™

The Pulmotrack (KarmelSonix, Haifa, Israel) is a commercially available RSA device specifically designed for the identification, characterisation and quantification of respiratory sounds. The device consists of two acoustic sensors, a respiration belt and an external ambient microphone, all of which are connected to a wireless module. The wireless module is worn by the patient on a belt (or carried by a parent/assistant) and transmits signals via Bluetooth to a personal computer (PC). The signals are digitally processed using a Fast Fourier transformation algorithm, and then displayed on the computer screen in almost real time.

The acoustic sensors are placed on the right side of the chest wall (mid clavicular line at the second intercostal space) and on the right side of the trachea (anterior to the sternocleidomastoid muscle, midway between the laryngeal prominence and the sternal notch). The respiration belt is worn around the chest, over the lower ribs, and the external ambient microphone clipped to the patients shirt (in a position that is as close to the head as possible, whilst not being at risk of being obscured). The respiration belt is used for the measurement of breathing activity e.g. respiratory rate, phase and amplitude, as well as the inspiratory expiratory (IE) ratio. The external ambient microphone identifies and allows the removal of environmental noise (139).

The chest and tracheal acoustic sensors are capable of detecting respiratory sounds within the range of 75 to 4000Hz+, which is reasonably consistent with the range for normal lung and tracheal sounds (50-2500Hz and up to 4000Hz, respectively (140)). This small discrepancy in the very low frequency range should not impact significantly on the outcome of the thesis study presented in chapter 4, as this study focuses on analysing predominantly tracheal sounds (which constitute the higher frequency values). In addition, abnormal respiratory sounds tend to have a higher frequency band, when compared to normal respiratory sounds (132). The PulmoTrack has been compared to other RSA devices for sensitivity and specificity. It has been reported to have a sensitivity of 91% and a specificity of 89% for detecting wheeze (136) as compared to an overall sensitivity and specificity of 80% and 85% for other RSA devices (132).

The PulmoTrack presents RSA data graphically, numerically and audibly. The screen display (see Figure 5) divides the recorded information into four sections individually showing input from the two acoustic sensors, event/cough count and the respiration measures as described above. Bars on the acoustic sensor graphs represent wheezeRATE® (Wz%) for that episode of recording time, where Wz% = wheezing time/breathing time x

100. The bars are also subdivided by colour; red indicates inspiratory wheeze, blue expiratory wheeze and each bar represents 10 seconds of recording time. Clicking on an individual bar gives access to the related sonogram screen for that episode of recording, and individual sonograms are displayed for the two acoustic sensor outputs.

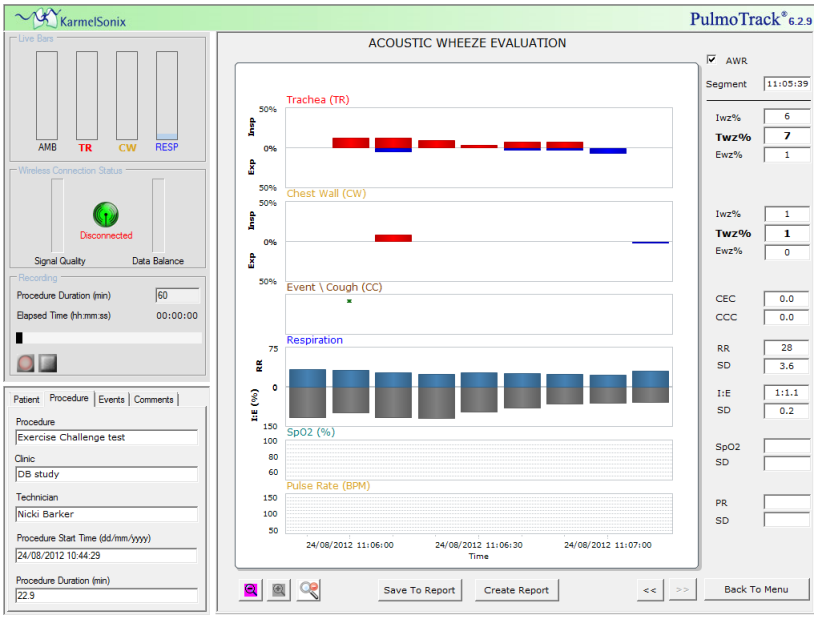


Figure 5: PulmoTrack screen display

It is possible to listen to the audio recordings separately, and these can be heard with and without ambient wheeze rejection (AWR). AWR eliminates audible wheeze-like sounds in the environment from the primary recording (141) isolating sounds that are generated by the patient for numerical analysis. Abnormal respiratory sounds, such as wheeze or inspiratory stridor, are seen graphically on the sonogram as horizontal lines, with harmonics as further horizontal lines above, as seen in Figure 6.

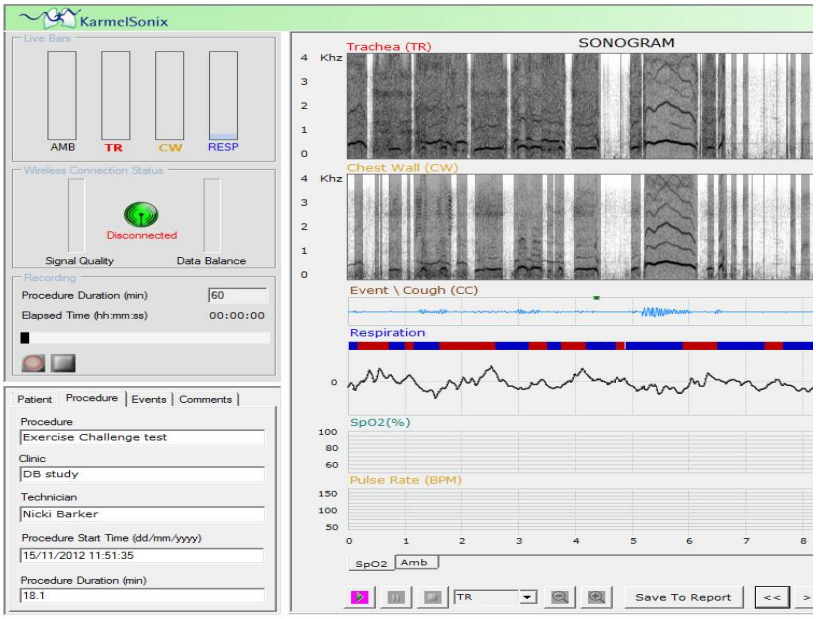


Figure 6: PulmoTrack screen display showing harmonics

2.3.5. The WheezoMeter®

The portable version of the PulmoTrack is the WheezoMeter, which has a more limited level of functionality compared to the PulmoTrack. It is a hand-held, battery-operated device that is held to the base of the neck to record respiratory sounds at the trachea. To achieve a successful recording, the WheezoMeter needs to be held in place for 30 seconds without significant movement of the device/neck, or interference from ambient noise. Loss of contact with the neck (as detected by a pressure sensor) or too noisy an environment leads to the recording being disregarded. Respiratory sounds are analysed using the same technology as the PulmoTrack and a Wz% is calculated and displayed on the built in display screen. As well as recording the extent of wheezing, the WheezoMeter can also record a 10 second voice event, which is saved alongside the sound recording and is useful to place the sound recording in context.

Data saved by the WheezoMeter can be downloaded to a PC using a USB cable and saved in individual patient files. Whether viewed on the display screen or downloaded, measurements are shown as Wz% (both with and without AWR). Once data has been downloaded it is possible to view sonograms for each measurement. The sonogram is divided into respiratory sounds and ambient noise, and both can be listened to as a whole recording, or digested in segments. Abnormal respiratory sounds are displayed graphically in the same way as for the PulmoTrack.

There is little information available regarding the sensitivity and specificity of the WheezoMeter. A study was registered by Wilson in 2010 with ClinicalTrial.gov, to determine whether Wz% and change in Wz% correlate with FEV_1 and change in FEV_1 in patients with asthma (142). No published or unpublished data is available from this study. A case report however demonstrates the use of the WheezoMeter in the assessment of a patient with asthma and possible paroxysmal vocal cord dysfunction (paroxysmal VCD). The study concluded that the WheezoMeter indicated the presence of paroxysmal VCD, but that further research was required to determine if it could provide a non-invasive method of differentiating paroxysmal VCD from asthma (143). Studies have suggested, that for both the WheezoMeter and the PulmoTrack, that a Wz% of less than 3% should be considered as normal for healthy individuals without wheeze, and that values greater than 3% are indicative of true wheeze (144-146).

2.4. Nasendoscopy

Nasendoscopy, also referred to as nasal endoscopy and laryngoscopy, is a well established technique in the care of both children and adults. It can be defined as 'the use of a flexible fiberoptic endoscope to evaluate upper airways' (147), where upper airways consist of the nasal passages, nasopharynx, oropharynx and the larynx.

2.4.1. Background

Forms of the procedure have been in use since the development of the endoscope during the 1700's and 1800's, where it was used for the inspection of the vagina and bladder, before progressing in the early 1900's to laparoscopy and thoracoscopy (148). Integration

of fiberoptics into the endoscope then led to it becoming suitable for many more purposes, including visualisation and assessment of the upper airway. Nasendoscopy can be performed in a person of any age and is usually carried out with the patient awake and in an upright sitting position.

2.4.2. The current situation

Upper airway assessment by nasendoscopy is used in the diagnosis and management of a diverse range of conditions, including chronic rhinosinusitis (149), epistaxis (150), obstructive sleep apnoea (151), voice disorders (152) and paradoxical vocal cord dysfunction (pVCD), where it is considered to be the gold standard method for confirming the diagnosis (137, 153). The procedure involves the introduction of a fibreoptic endoscope via the nose to visualise vocal cord motion. The classic endoscopic findings of pVCD are adduction of the anterior vocal cords during inspiration, with a 'diamond-shaped' aperture visible posteriorly (33).

Nasendoscopy at Sheffield Children's Hospital (SCH) involves the use of an Olympus ENFV2 endoscope, which is inserted nasally following the introduction of Lidocaine Hydrochloride 5% w/v and Phenylephrine Hydrochloride 0.5% w/v Topical Solution anaesthetic nasal spray. A full explanation of the procedure and what it will involve is made to the child and parents/guardians prior to the procedure and reassurance and positive reinforcement is given throughout. This process has been used when carrying out nasendoscopy with all children at SCH with DB and has been successful in all cases.

2.4.3. Considerations

Accurate diagnosis using nasendoscopy is not guaranteed. As with many investigations, success relies on the skill of the operator, and, in the case of pVCD assessment, also on the situation in which the test is carried out. Patients with pVCD are commonly asymptomatic at rest and, therefore, symptoms need to be provoked to allow the laryngeal changes to be observed (153).

2.4.3.1. Symptom provocation

The means used to provoke symptoms for nasendoscopy is important. A study by Perkins et al (154) included 10 subjects with pVCD confirmed previously by direct nasendoscopy. Nasendoscopy was repeated for the study pre and post methacholine challenge testing, and the results showed that 20% of these subjects presented with signs of pVCD prior to the challenge test. This number only increased to 40% after provocation indicating that there are notable differences in the results of nasendoscopy both within and between patients. In many young patients with pVCD the symptoms are most prominent during exercise. An exercise test is used in an attempt to simulate this situation. Studies investigating exercise tests as a means of provoking pVCD show similar results, however, to those using methacholine; exercise challenge testing can provoke pVCD but not in all patients (155, 156).

2.4.3.2. Procedure

There is also some debate about the exact procedure used during nasendoscopy. Clinical experience and evidence shows that, whilst it is a very useful procedure that has a high success rate (157), nasendoscopy can be quite uncomfortable (158). Discomfort is usually caused by resistance to the passage of the scope through the middle nasal meatus (the narrowest part of the nasal cavity), and the degree of discomfort experienced by the patient can impact on the outcome of the procedure (159).

A full and detailed assessment requires the patient to actively participate with the procedure, by performing activities such as sustained phonation, pitch glides and repetition of syllables (159). Where a patient is anxious or in pain they may not be able to fully cooperate with these activities. Certain preparations are sprayed into the nasal cavity prior to inserting the endoscope with a view to improving the comfort and tolerability of the procedure, especially for children. Studies have shown, however, that the use of a decongestant spray is just as effective as a topical anaesthetic, such as lignocaine, and that alternative measures for decreasing anxiety such as distraction should be used (160).

2.5. Breathing retraining

Experience indicates that dysfunctional breathing can have a significant impact on a young person's quality of life, but opportunities for treatment are rare. Where treatment is available, it is commonly based on the clinician's experience of *what works*, with strategies imported from the adult sector. Treatment approaches to breathing disorders in adults, however, have changed considerably over the years, possibly as a result of the changing opinions on the underlying cause or mechanism of the disorder.

2.5.1. The Buteyko Breathing Technique: origins of treatment

The origins of treatment for dysfunctional breathing lie in the use of breathing retraining for health benefits (both respiratory and general). An early champion of this was Konstantin Buteyko. In the 1960's he proposed a theory that hypocapnia, caused by hyperventilation, leads to numerous diseases by destabilising physiological systems and psychological states (161). His therapy, the Buteyko Breathing Technique (BBT) was, therefore, aimed at raising CO_2 levels through hypoventilation and breath holding.

2.5.1.1. Challenges

Significant challenges have been made in recent years to Buteyko's claims, due to findings that people with symptomatic hyperventilation syndrome can show normal levels of CO_2 (20). These have been supported by other authors, but it should be noted that the role of CO_2 levels in breathing disorders cannot be entirely rejected. Indeed, it has been suggested that fluctuating CO_2 levels are more likely than chronic hypocapnia, in the unstable breathing pattern of those with dysfunctional breathing (162).

Regardless of the mode of action of the BBT, there is a significant body of evidence to support the efficacy of this technique, particularly in the treatment of asthma (163-165). The paradox between the success of the technique, and the increasing scepticism of the

underlying principles, generates debate as to why the technique has proved to be so effective. Courtney (2008) suggests there are many possible mechanisms, including other biochemical changes, patient control, physiological effects of changing breath volumes, biomechanical alterations and the resetting of chemoreceptors. Further research is required to identify if any one, or a combination, of these factors contributes to the positive outcomes achieved.

2.5.2. Alternatives

Although the long term impact of Buteyko's ideas is undeniable, the wholesale adoption of his techniques was affected by some of his more extreme treatments, such as taping the mouth shut to enforce nose breathing. There are now a number of other breathing therapies in use in clinical practice, many of which are not as formalised as the BBT. The common focus tends to be on the normalisation of respiratory pattern, with regards to balance between the two compartments of the chest wall (the rib cage and the abdomen) and the respiratory rate (93). This breathing retraining is also often accompanied by education, relaxation and postural correction (97). However, in general, quality evidence for this type of breathing retraining is limited. For adults with dysfunctional breathing it is sparse (100), and for children with DB it is virtually non-existent (166).

2.5.2.1. Reassurance

Herman et al (1981) carried out a retrospective study into hyperventilation in children and adolescents examining long term outcomes (103). It is a relatively old study, with some methodological problems, but the general findings are of interest. The primary treatment modality offered was 'reassurance' that they were suffering from a benign disorder. In long term follow-up, it was discovered that 40% of the young people involved in the study still experienced episodes of hyperventilation in adulthood. With a lack of intervention, this study may demonstrate the natural course of the condition, but a more active intervention, such as breathing therapy, may have led to better long term outcomes. No intervention studies of this type have been performed with children.

2.5.2.2. Active retraining

Whilst not specifically in a population with dysfunctional breathing, a recent study investigating exertional dyspnea in otherwise healthy children looked at the effects of standardised breathing/reassurance therapy for managing similar symptoms to those seen in DB (167). The effect of therapy was measured on a nine point scale, ranging from -8 (deterioration) to +8 (improvement), and all children who received the intervention reported a positive response. The title given to this therapy, however, is misleading, as the sessions where not just focused on reassurance. Importantly they also consisted of education, diaphragmatic breathing and supervised exercise. Unfortunately, there was no long term follow-up in this study, so it is not known if the benefits were maintained.

Conversely, a five year follow-up study on the effects of breathing retraining in adults with DB did not present findings on the short term impact of this intervention (102). The intervention consisted of between one and four breathing retraining sessions, conducted

over a three month period and consisting of education of normal/abnormal breathing, self awareness and diaphragmatic breathing. Five-years post intervention, it was found that patients with DB had significantly fewer symptoms, improved health-related quality of life and fewer visits to hospital.

Two randomised controlled trials (93, 97) have been carried out in adults investigating the effectiveness of breathing retraining in dysfunctional breathing. Although effectively addressing the same question, the study designs and findings were quite different.

Thomas et al (2003) compared breathing retraining with a physiotherapist (75 minutes total contact) to a control group of asthma education with an asthma nurse (60 minutes total contact) (93). The control group was chosen to mitigate any effects from spending time with a health professional. The study may have benefitted from a third group exposed to routine care only; this would have given an understanding of any health intervention benefits (regardless of the content) and provided a baseline for the outcome without intervention. The findings of this study were that 50% of patients showed a clinically relevant improvement following physiotherapy intervention, but that only half of these patients maintained that improvement after 6 months.

In comparison, Holloway and West (2007) randomised patients into an intervention or control group (97). Participants in the intervention group received five one-hour sessions of treatment using the Papworth method (a breakdown of this method can be seen in Appendix 1). The study reports a statistically significant improvement in quality of life and Nijmegen scores, however sufficiently detailed data is not presented to allow a more complete analysis of these changes. Another parameter measured was end-tidal CO_2. For this there was no difference between the two groups or within groups at different time points. This finding is unexpected, as the Papworth method specifically aims to address hyperventilation in patients with DB. This may add more weight to the argument that low levels of CO_2 are not a key factor in dysfunctional breathing.

The differing levels of improvement with breathing retraining found by the two studies may be due to the level of intervention received. There is a marked difference between 75 minutes and five hours of contact time. A large scale study would be of value, comparing different types and lengths of breathing retraining interventions, to help clinicians plan services and ensure optimal outcomes. Such a study, however, cannot take place until the difficulties with the diagnosis, assessment and, hence, formalisation of outcome measures has been resolved.

2.5.3. The current situation

There is ongoing debate about why breathing retraining has beneficial effects when the rationale behind its development and application has been disputed. Whilst there is evidence showing the benefits of individual approaches (the BBT for example), there is little or no evidence available to guide the choice of therapeutic intervention, or to inform patients and healthcare professionals of the comparable benefits of these therapies.

Currently, research in this area is solely focused on adults and, considering the lack of clarity in this area, it is unsurprising that paediatrics has been largely ignored. Work not only needs to be done to provide information to guide treatment choices, and allow appropriate services to be provided, but also to stimulate research into treatments for children.

2.5.3.1. Study intervention

The breathing retraining method used in the observational study described in chapter 6, mirrors that described in the Papworth Method (97) as well as including elements from other approaches. The main focus of the intervention is a return to normal diaphragmatic breathing, with an associated reduction in upper chest and accessory muscle use. Diaphragmatic breathing is initially taught in supine, and then progressed through sitting, standing and into dynamic activities. The rationale for this is that the muscles of respiration have a dual role in posture and respiration (41, 168, 169). Therefore, retraining in supine allows the breathing pattern to be learnt with the minimum demands of gravity on those muscles prior to progression to positions with increased postural demands.

In-line with the Papworth Method, importance is also placed on nasal breathing (as opposed to mouth breathing). Nasal breathing performs the important functions of slowing the flow of air, whilst cleaning, warming and humidifying it. This is important for all children with DB, but may be particularly important for those with pVCD who may have laryngeal hypersensitivity (170). In addition to nasal breathing, exercises are also taught to improve posture, lengthen shortened muscles and promote relaxation when required.

Education is also a key element for improving symptoms of dysfunctional breathing in all affected patients. It needs to be age appropriate, and is equally important for the parents/carers as it is for the child. Whilst the style of delivery will change dependent on a child's age, topics always include information about the condition, why we breathe, how we breathe, how the child's breathing differs from the normal and that they can make it better. The education sessions are an exchange of information, which allows the therapist to recognise the child/families understanding of the condition and the impact that it has on them. This is very important in enabling the therapies to be targeted and effective. Practical education is also given in the form of advice and coping strategies. Examples of this are the short term management of shortness of breath, or symptom recognition to prompt the appropriate use of specialised breathing techniques (such as the sniff-blow-blow technique).

All exercises/activities need to be practiced frequently and a level of competence achieved whilst the child is asymptomatic. This then allows the child to implement the techniques successfully, when experiencing or about to experience symptoms. Over time, a suitable degree of breathing control is achieved, which is accompanied by a reduction and often complete amelioration of symptoms. No studies to date in either children or adults have reported any contraindications to breathing exercises, or have noted any adverse events.

2.6. Pediatric Quality of Life Inventory

2.6.1. Background

The Pediatric Quality of Life Inventory (PedsQL) is an instrument designed specifically for the measurement of health related quality of life (HRQOL) in children. It was first introduced in the late 1990's and is a modular system consisting of initially a 15, and then 23, item core measure of global HRQOL (the generic core scale), plus additional modules assessing specific symptom or treatment domains (171, 172). All versions are produced in both a child and parent report form. The child report versions are suitable for ages 5-18 years, and are divided in to young child (5-7 years), child (8-12 years) and adolescent (13-18 years). There is also a toddler version (2-4 years), which is completed by proxy by parents.

In most situations, the time taken to complete the questionnaires is less than five minutes and the scoring system is relatively simple to apply.

Since its introduction, PedsQL has become extremely popular in both research and clinical practice, and now includes a wide range of specific modules, such as diabetes, cerebral palsy, Duchenne muscular dystrophy and obesity (173-176). It has also been translated into over 60 different languages (177).

In the field of respiratory medicine, a specific module is available for children with asthma (178, 179), but modules are not available for conditions with more limited populations (such as dysfunctional breathing). Where a specific module is not available, the generic core scale can be used in isolation. The generic core scale is available in acute or standard formats; acute asks the recipient to consider the past seven days, and standard the past month.

It is also available in short or standard length formats, with the short format being shown to be as reliable as the full length version (180). The standard length format consists of four multidimensional scales, each consisting of a number of statements or items to which a response is required. The short format considers the same multidimensional scales, but has a reduced number of items in each dimension. The four multidimensional scales are shown in Table 2.

Table 2: PedsQL multidimensional scales

Dimension	Number of items (Standard format)	Number of items (Short format)
Physical functioning	8	5
Emotional functioning	5	4
Social functioning	5	3
School functioning	5	3

The PedsQL is administered using a standardised format (see Appendix 2) and the responses are scored using a standard scoring system (see Appendix 3), which involves a reversal of scores (e.g. a 0-4 scale becomes 100-0; i.e. 0=100, 1=75, 2=50, 3=25 and 4=0). The sum of each dimension is calculated, from which 3 summary scores are derived (total scale score, physical health summary score and psychosocial health summary score). Part of the calculation involves dividing the sum of a dimension by the number of items completed in that particular dimension. This allows for scores to be achieved, even if all items are not completed.

2.6.2. Application

The scores from the PedsQL can be used to distinguish between healthy children and children with health conditions, as well as distinguishing disease severity within a chronic health condition or indicating the effects of a treatment or intervention. This validity was determined using the known-groups method, both with healthy children and children with acute and chronic conditions (172, 181).

The reliability of PedsQL has been extensively examined, and it has been found that for the total scale score alpha is approximately 0.90. This was initially identified in a group of over 1,600 families, and then supported by a larger study involving more than 10,000 families (172, 181). The minimal clinically important difference (MCID) for total scale score is similar for child and parent proxy report, at a change of 4.4 and 4.5 respectively (172).

The PedsQL was chosen for use in this thesis above other measures of HRQOL due to a number of factors. It is specifically designed for children across a wide age range (2-18 years), there are both child and parent proxy report, the validity and reliability of the tool has been well demonstrated and it is easy to use.

2.7. Nijmegen questionnaire

2.7.1. Background

In the 1980's a small team from Holland produced a key piece of work that would prove to be pivotal in the identification of hyperventilation syndrome (HVS). They developed a list of 16 complaints that were common to patients thought to have HVS, which became known as the Nijmegen questionnaire (182). A copy of this questionnaire, showing the 16 items that are scored on a five- point ordinal scale, can be found in Appendix 4.

The Nijmegen questionnaire (NQ) was subsequently validated by another Dutch group, and declared 'suitable as a screening instrument for early detection of HVS, and also as an aid in diagnosis and therapy planning' (77). It has gained popularity, been used widely and is the only validated measurement tool available for research and clinical practice into HVS.

2.7.2. The current situation

2.7.2.1. Problems

Despite this, developments in the understanding of DB mean that the NQ no longer offers the diagnostic solution it was once thought to. With the growing acceptance that HVS is only one aspect of DB, the NQ cannot be used to diagnose dysfunctional breathing (as it was not designed or validated in this setting).

The NQ has only ever been validated for adults but is used in studies investigating children (183), potentially due to the lack of suitable alternatives. There is no evidence to support this use and studies would be required to investigate aspects such as the suitability of language for different age groups. This would ensure that the information provided by the questionnaire is truly representative of a patient's condition. If this work was carried out, the NQ may become suitable for use with children, but would still be limited to those thought to present specifically with hyperventilation syndrome, rather than dysfunctional breathing.

2.7.2.2. Alternatives

The need for a questionnaire designed specifically for children has been recognised.

The SHAPE questionnaire (184, 185) was formulated using groups of French children and young people aged 4-11 and 7-20 years old, and, as with the Nijmegen questionnaire, involves respiratory and non-respiratory signs. The Sznajder study was performed as a pilot study, with plans to validate this questionnaire using a large prospective multi-centre trial. Personal communications with the authors have highlighted the difficulties, both in the two studies already completed and the proposed trial, in identifying the study cohort (as no gold standard exists to identify these children). The 2008 and 2009 studies used 'clinical diagnosis with favourable outcome with care' to classify children with HVS, but this is not felt to be a robust enough methodology for a more significant trial. Until this difficulty is resolved, validation of the SHAPE questionnaire cannot be achieved.

An alternative approach comes from the work of Osteopath Rosalba Courtney, who has embraced a more holistic interpretation of dysfunctional breathing. She proposes that dysfunctional breathing be considered as a multidimensional construct with three dimensions; biochemical, biomechanical (breathing pattern) and breathing related symptoms (186), as shown in Figure 7. The Nijmegen and SHAPE questionnaires, designed specifically for HVS, address primarily the biochemical dimension.

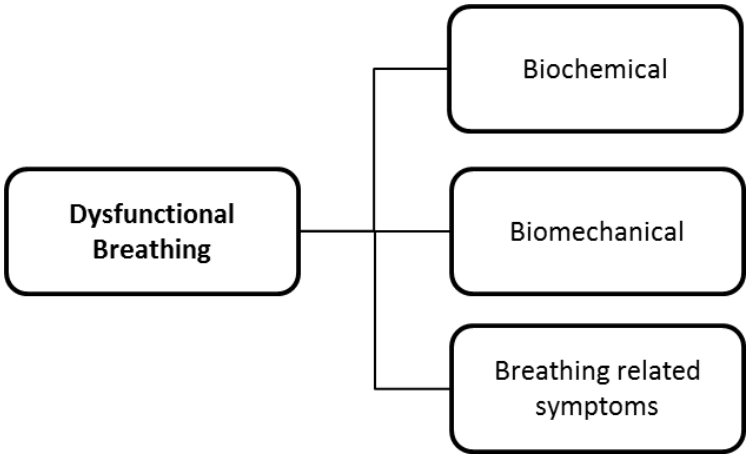


Figure 7: Representation of Courtney's multi-dimensional construct of dysfunctional breathing

As part of her recent work, Courtney has started developing a questionnaire designed specifically for DB (187). The Self Evaluation of Breathing Questionnaire (SEBQ) aims to capture the other dimensions of DB, and may give greater insight into the treatment approaches required to resolve the problem. The differences in questions posed can be seen from a copy of SEBQ in Appendix 5.

The SEBQ is still in the early stages of development and some problems are apparent. The questionnaire development was carried out using a group of people (n=83, average age 49 years) who volunteered to participate. The subjects didn't have a diagnosis of DB, and some of them had asthma. In addition, detailed demographic data is not presented, meaning it is not possible to assess the impact of this potentially diverse subject group on the questionnaire design. Furthermore, the SEBQ, like the Nijmegen questionnaire, is being developed with adults and will, therefore, still not be appropriate for use with children.

2.7.3. Application

Due to the limitations described above, the NQ used in Chapter 6 is not used as a tool for diagnosing dysfunctional breathing. It is implemented as a structured symptom score to identify change in symptoms, from baseline (pre treatment) to immediately post completion of treatment and then 6 months post completion of treatment. Whilst this is not a validated scoring system, clinical experience of using the NQ in this way with children indicates that it is consistent with other clinical measures, and is the most suitable alternative to use until a specially designed tool is available.

3. Quantification of dysfunctional breathing using structured light plethysmography

3.1. Introduction

As discussed in the introduction to this thesis, dysfunctional breathing (DB) can be defined as an alteration in the normal biomechanical patterns of breathing, which results in intermittent symptoms that may be respiratory or non-respiratory. The primary symptoms of DB (dyspnea, wheeze/stridor, chest pain and sighing) (8) are very similar to those of asthma. As a result, DB is often confused with asthma and a wrong or incomplete diagnosis given; this situation is further complicated as DB can coexist with asthma and other respiratory disorders (13, 93). Overlooking a diagnosis of DB, in favour of asthma, can lead to the prescription of medications that are either not needed, or at potentially harmful doses, in an attempt to control symptoms.

Dysfunctional breathing is characterised by breathing patterns and rate involving relatively inefficient, excessive upper chest wall activity (with or without accessory muscle use). Some attempts have been made to use these recognisable patterns as a means of diagnosing DB and a limited range of assessment techniques have been developed e.g. manual assessment of respiratory motion (MARM), respiratory inductance plethysmography (RIP) and optoelectric plethysmography (OEP). However, these techniques are not fully quantifiable, potentially interfere with a patient's breathing and have not been validated in children (40, 72, 127, 129, 188).

Recent technological developments in structured light plethysmography (SLP), as discussed in Chapter 2, address the above problems, whilst providing the opportunity to quantify respiratory motion, pattern, frequency and volume. The technique is entirely non-invasive and can provide quantitative data on breathing parameters, as well as three dimensional visual reconstructions of breathing, in almost real time. The use of SLP has been investigated in adults with chronic obstructive pulmonary disease (COPD) and thoracic conditions (118, 189) but has not been applied to dysfunctional breathing, either in children or adults.

The aim of this study, therefore, was to investigate whether structured light plethysmography can be used for the detailed assessment of abnormal breathing patterns found with dysfunctional breathing. It also sought to compare these patterns with those found in a normal population.

3.2. Methods

3.2.1. Participants

The study population was a convenience sample of 43 children aged 8 to 16 years, with 22 children in the condition group and 21 in the control group.

The condition group consisted of children with a clinical diagnosis of dysfunctional breathing (made by an experienced consultant or registrar specialising in respiratory

medicine) based on expert history taking and the exclusion or optimal management of other conditions. Children with dysfunctional breathing were recruited sequentially upon referral to the BreathWorks clinic (Sheffield) for physiotherapy based treatment, and all testing was carried out prior to the start of therapy. Children were not excluded from this group if they had a co-morbidity such as asthma, as long as the co-morbidity was well controlled.

Control group children were recruited via an e-mail advert to staff from Sheffield Children's Hospital (SCH) and staff and students at the University of Sheffield. These children were required to be free from a history of breathing problems, which was confirmed by the completion of a respiratory screening questionnaire prior to enrolment into the study. A copy of this questionnaire can be found in Appendix 6.

Children were excluded from either group if they lacked suitable cognitive or physical ability to follow study instructions and perform the exercise test, or the child or parents/guardians were not fluent in written and spoken English.

Parents/guardians attended all study sessions and gave written informed consent. Study participants gave written informed assent and the study was given ethical approval by the NRES Committee Yorkshire and The Humber – Sheffield.

3.2.2. Study design

Subjects from both groups followed the same study protocol (see Figure 8). The only deviation from this was those children in the DB group who had a diagnosis of suspected paradoxical vocal cord dysfunction (pVCD) and who were clinically required to have a nasendoscopy instead of the second light scan. Study sessions took approximately one hour per participant, and for condition group children were performed in conjunction with their routine exercise test. The spirometry and exercise tests were conducted by an experienced respiratory physiologist and supervised by a registrar level doctor. The SLP scans were carried out by the researcher (NJB).

Spirometry was performed using a pneumotachograph (MasterScreen PFT, Jaeger, Höchberg, Germany) and a standardised protocol following the ATS/ERS guidelines (190). All tests were performed standing whilst wearing a nose clip.

Prior to the SLP scan, participants were fitted with 10 ECG electrodes and leads (in readiness for the exercise test) and asked to put on a snug fitting white sports top. The purpose of the white top was to enhance the clarity of the image for the scan, and participants wore the top for the remainder of the session. SLP scans were performed with the subject seated on a straight backed chair, in a good upright position, with the arms in a relaxed position. Scans were taken using the SLP device the Thora3Di^{TM} (PneumaCare Ltd, Cambridge, England), with the device positioned 1-2 metres away from the participant to achieve an optimum fit of the projected grid of light on the chest and abdomen. Standardised instructions were given asking participants to breathe as they normally do, until asked to take six deep breaths and then return to breathing normally. Deep breaths were included in the protocol as it was hypothesised, from clinical experience, that the

breathing pattern abnormalities associated with DB would be more pronounced during this type of breathing. Once settled in front of the scanner, the measured tidal breathing prior to the deep breaths included at least six breaths for each participant. The ECG leads were in place during both pre and post exercise test scans to allow direct comparisons to be made between scans.

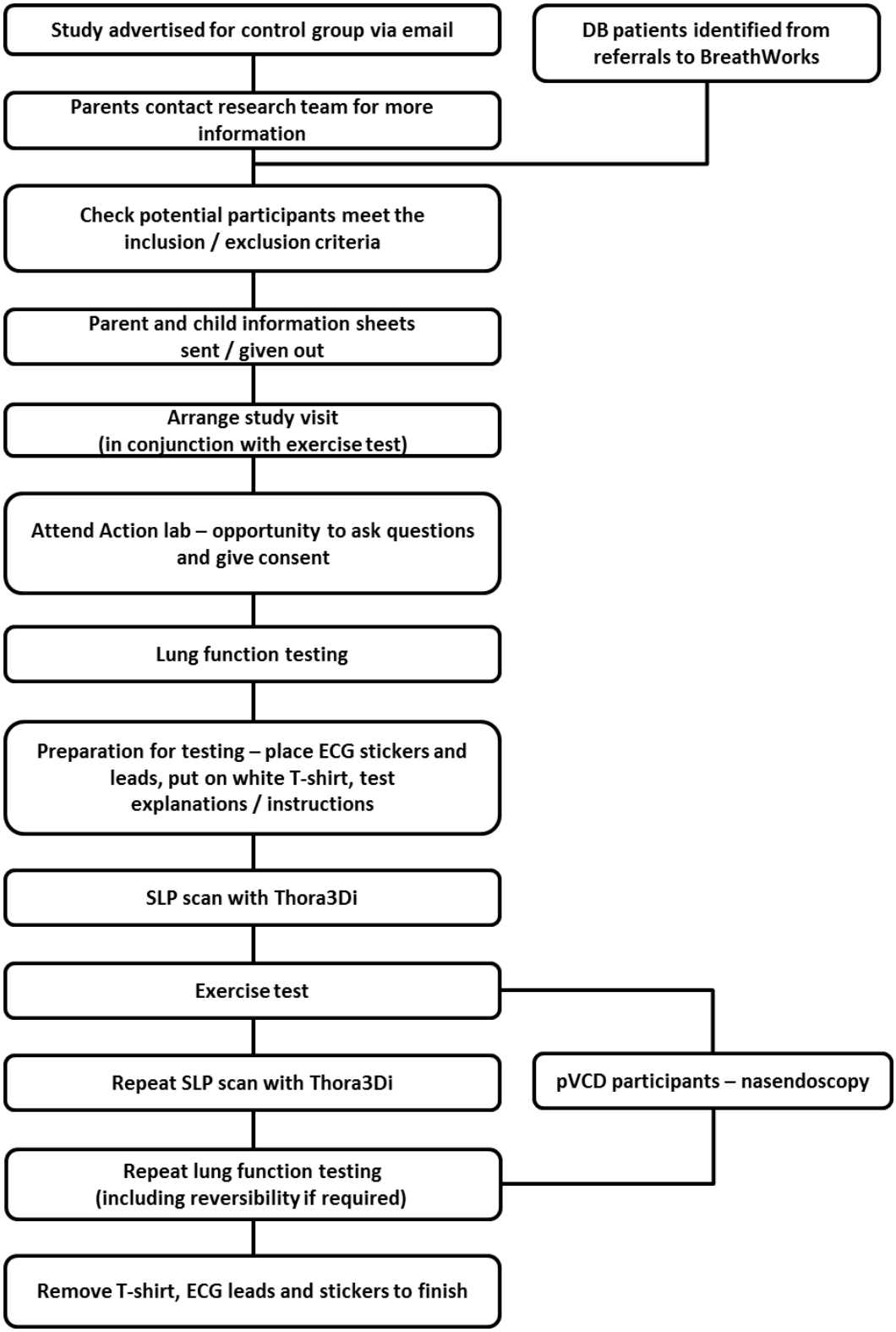


Figure 8: Study protocol for condition and control groups

The protocol for each treadmill based exercise test (JLab software, Jaeger, Höchberg, Germany) was determined on an individual basis by the respiratory physiologist. The tests predominantly used were Bruce (191, 192) or Houlsby (193) protocols (the Houlsby was chosen for the younger children due to the shorter time spent at each increment). A bronchoprovocation test (194) was used instead where it was also clinically necessary to investigate for exercise induced asthma. The standard operating procedures for exercise testing at SCH are presented in Appendix 7. Participants were encouraged verbally during the exercise test (in line with standard practice) and all children achieved heart rate levels that were indicative of a very good, if not exceptionally good, physical effort.

Repeat SLP scans were carried out immediately post exercise test using the same protocol as for the pre exercise test scan. Repeat spirometry was performed following the SLP scan, with the option to give an inhaled bronchodilator via a spacer device should bronchoconstriction be identified. In the presence of bronchoconstriction, spirometry would be repeated at five minute intervals (starting 20 minutes after the bronchodilator was given) until the participant had returned to their pre test lung function values. Bronchoconstriction was defined as a 15% or greater decrease in forced expiratory volume in 1 second (FEV_1) (195), compared to baseline, which reversed with 400mcg salbutamol via a metered dose inhaler and spacer.

3.2.3. Measured parameters

Demographic data in the form of age, gender, height and weight was collected, as well as FEV_1 and forced vital capacity (FVC) from spirometry. These measures allow a baseline comparison of groups, as well as the ability to identify any previously unknown or undetected lung disease (particularly in the control group). The measured parameters from SLP used to quantify breathing pattern were respiratory rate (RR), inspiratory time (Ti), expiratory time (Te), inspiratory expiratory (IE) ratio, overall phase (OP), principle angle (PA), spread (Spr) and breath phase (BP). These were derived from the Konno-Mead loops generated by the Thora3Di (as described in detail in Chapter 2). Each SLP capture was analysed by identifying and selecting the period of settled tidal volume breathing (TV) on the volume time graph, followed by the period of deep inspirations (DI). The start of settled TV was identified from breaths of similar amplitude and wavelength, and the DI breaths identified by a distinct increase in the amplitude of the waveform which was maintained for six wavelengths. The measurements for the two periods, TV and DI, were recorded separately.

3.2.4. Data analysis

All parameters apart from age, FEV_1 and RR were not normally distributed and, therefore, between group comparisons were carried out using the Mann-Whitney test. Differences in parameters for subjects pre and post exercise test were explored using the Wilcoxon signed rank test.

Statistical analysis was performed using GraphPad Prism 6.02 (GraphPad Software Inc, San Diego, USA) and statistical significance was accepted as $p<0.05$.

3.3. Results

Figure 9 shows the flow of the DB group participants through the study. Of the 22 participants with DB that enrolled in the study, two were excluded at the beginning of the study; one due to uncontrolled asthma and the other due to a previously undiagnosed fixed upper airway obstruction. A further 12 subjects were lost from the post exercise test analysis; one where no post test SLP data was available and 11 who required laryngoscopy for suspected pVCD (as identified in section 2.2), which prevented SLP from being performed. All of the 21 participants of the control group completed pre and post exercise test SLP, but in one subject post test SLP data were not available. In one further participant, only partial post test SLP data was available, as it was not possible to identify deep inspirations in this recording. Technical failure was the cause of the lack of availability of post test SLP data for the participants identified above in both groups.

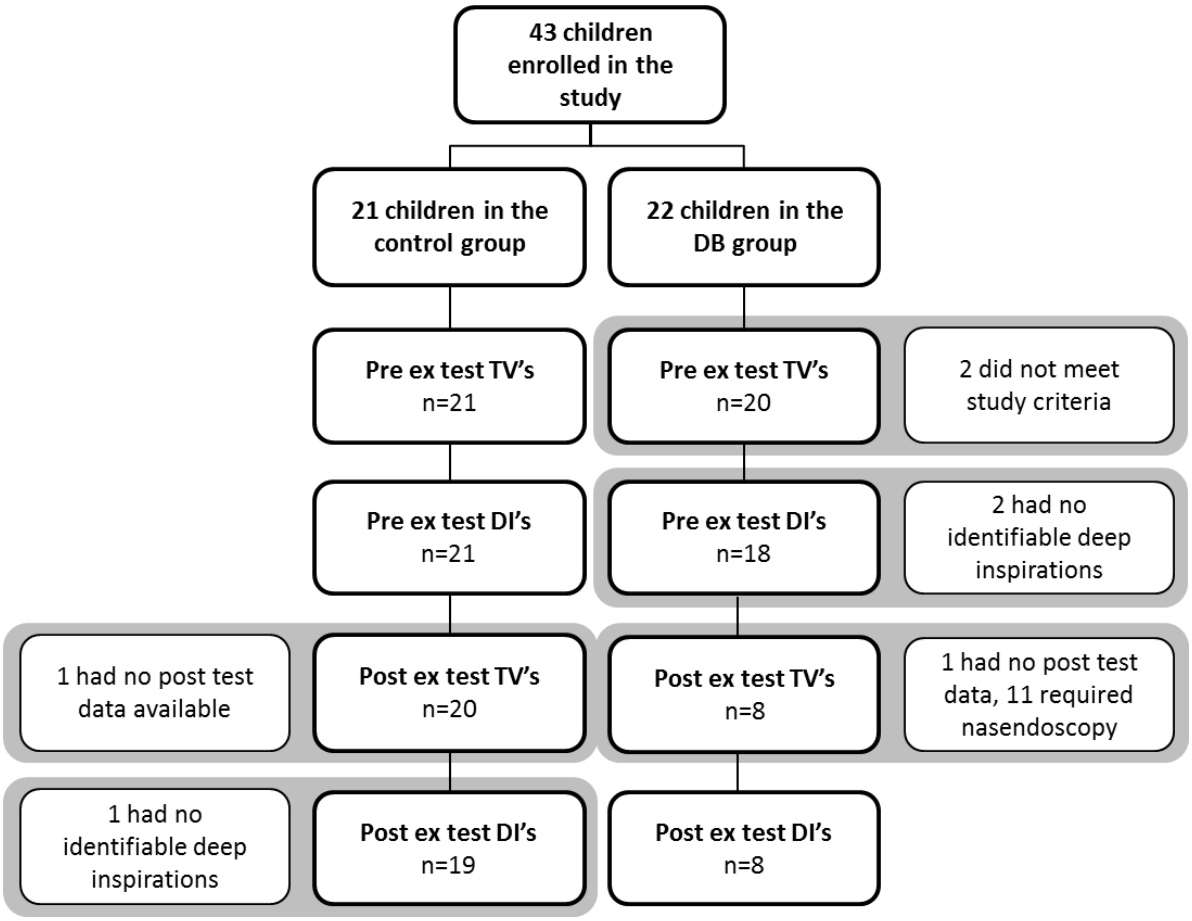


Figure 9: Flow of DB group participants

(where TV=tidal volume breathing and DI=deep inspirations)

Whilst the age range for the two groups was the same, both the mean and median age were greater in the DB group when compared to the control group. There was, however, no difference in lung function parameters (FEV_1 and FVC) between groups either before or after exercise test when considering either percent predicted or the potentially more sensitive Z score (see Table 3). There was also a similar ratio of males and females in each group.

Table 3: Demographic data expressed as median and interquartile range (IQR)

	Control group (n=21)	DB group (n=20)	P value
Age	10.5 (9.60-13.15)	13.55 (10.95-15.35)	P=0.0051**
Gender (M/F)	9/12	8/12	-
Pre test FEV_1	0.1 (-0.73-0.46)	-0.56 (-1.3-0.25)	P=0.10
Pre test FVC	-0.25 (-0.51-0.14)	-0.55 (-0.78-0.06)	P=0.15
Post test FEV_1	-0.015 (-0.62-0.31)	-0.55 (-1.4-0.08)	P=0.08
Post test FVC	-0.21 (-0.78-0.055)	-0.55 (-0.82- -0.13)	P=0.18

(where FEV_1 and FVC are expressed as Z score)

The scanning process was well tolerated in 100% of participants, with no scans failing due to the behaviour or non-compliance of the child. Of the 71 scans attempted, 97% (69) were successfully completed with the collection of meaningful data. Both of the two failures were due to technical problems resulting from suboptimal measurement setup.

Table 4: Pre exercise test tidal volume breathing data (median and IQR)

	Control group (n=21)	DB group (n=20)
Respiratory rate	23.3 (19.8-24.4)	19.8 (15.0-23.8)
IE Ratio	0.84 (0.76-1.01)	0.88 (0.7-0.97)
Inspiratory time	1.28 (1.05-1.46)	1.33 (1.14-1.73)
Expiratory time	1.46 (1.23-1.82)	1.66 (1.34-2.19)
Overall phase	26.1 (21.35-30.1)	23.25 (19.89-35.7)
Principle angle	6.4 (-6.2-13.15)	11.65 (5.08-17.05)
Spread	0.22 (0.18-0.3)	0.24 (0.19-0.32)
Breath phase	14.0 (9.5-20.4)	13.6 (6.48-18.83)

Table 4 shows the measured parameters from SLP (for tidal breathing prior to exercise test, expressed as mean and inter quartile range). There was no significant difference between groups ($p>0.19$) for any of the parameters when using data derived from captures of settled tidal volume breathing (TV). Figure 10 shows a TV segment chosen for analysis where the x-axis is time and the y-axis is breathing movement.

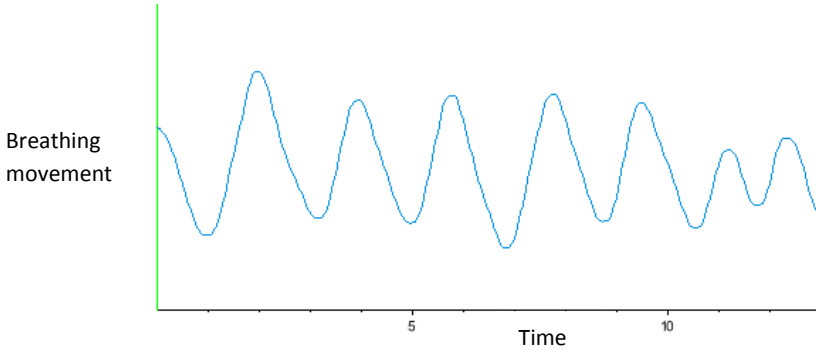


Figure 10: Example of settled tidal volume breathing chosen for analysis

There was also no difference between groups (p>0.32) for deep inspirations pre exercise test (Table 5).

Table 5: Pre exercise test deep inspirations data (median and IQR)

	Control group (n=21)	**DB group (n=18)**
Respiratory rate	18.70 (14.45-20.9)	17.4 (14.53-21.28)
IE Ratio	0.83 (0.74-0.94)	0.81 (0.71-0.89
Inspiratory time	1.55 (1.28-1.83)	1.54 (1.25-1.82)
Expiratory time	1.9 (1.5-2.45)	1.82 (1.63-2.32)
Overall phase	24.1 (21.65-32.2)	27.65 (17.7-38.83)
Principle angle	22.1 (15.7-29.85)	17.95 (13.38-26.3)
Spread	0.19 (0.15-0.32)	0.21 (0.17-0.77)
Breath phase	13.1 (10.55-32.85)	12.7 (9.52-27.25)

Statistical analysis was not performed on the post exercise test data, due to the small number of data sets (n=8) in the DB group at this stage of the study (196). Descriptive analysis of this data (Tables 6 and 7) does not indicate that particular differences would have been seen had statistical analysis been feasible.

Table 6: Post exercise test tidal volume breathing data (median and IQR)

	Control group (n=20)	DB group (n=8)
Respiratory rate	27.00 (21.35-33.43)	30.25 (25.75-35.55)
IE Ratio	0.87 (0.7-0.98)	0.93 (0.85-1.02)
Inspiratory time	0.99 (0.79-1.24)	0.86 (0.74-1.17)
Expiratory time	1.21 (0.92-1.62)	0.99 (0.69-1.26)
Overall phase	23.4 (17.38-29.43)	21.9 (13.05-38.95)
Principle angle	13.05 (-1.95-20.68)	12.85 (5.15-17.23)
Spread	0.21 (0.15-0.30)	0.19 (0.14-0.21)
Breath phase	11.4 (8.68-15.43)	10.0 (6.98-14.6)

Table 7: Post exercise test deep inspirations data (median and IQR)

	Control group (n=19)	DB group (n=8)
Respiratory rate	20.3 (15.7-24.9)	21.05 (18.6-26.9)
IE Ratio	0.88 (0.86-0.98)	0.86 (0.75-0.98)
Inspiratory time	1.42 (1.14-1.78)	1.29 (0.96-1.48)
Expiratory time	1.58 (1.3-2.08)	1.59 (1.35-1.66)
Overall phase	21.6 (13.9-34.4)	19.25 (12.45-38.5)
Principle angle	20.7 (13.5-27.9)	22.5 (15.3-24.95)
Spread	0.16 (0.12-0.21)	0.13 (0.1-0.35)
Breath phase	11.5 (9.2-21.2)	13.35 (8.9-25.65)

3.4. Discussion

This study is the first to investigate the use of SLP with children with dysfunctional breathing. It has shown that SLP can successfully be performed with both healthy children and those with DB.

Comparisons of breathing pattern, using SLP, were carried out between healthy children and those with DB. No significant differences in breathing pattern parameters were found between groups, at either tidal volume breathing or during deep inspirations. There is little data available with which to compare this finding, as no other studies have, using this technology, compared paediatric condition and control groups. Some studies have been carried out comparing the results of SLP to spirometry but these have been performed using a limited number of parameters (RR, TV, Ti and Te), and only in a small number of healthy adults (116, 197).

Clinical experience observing the breathing patterns of children with DB would lead us to expect a difference in parameters between the two groups. Children with DB frequently present with an observable increase in upper chest wall motion, and in some cases a paradoxical breathing pattern. It is possible that no difference was found as healthy children may also breathe with an 'abnormal' pattern, but are rarely carefully observed in this way. According to Konno and Mead (119), in terms of breathing parameters, normal breathing pattern would have an overall phase of zero, a spread of almost zero and a principle angle of zero. This would indicate that breathing was synchronous and that the contributions of the abdomen and rib cage were equal. In comparison to this, the figures from Table 4 show that, whilst the two groups are similar, they are very different from the theoretical normal; a situation that doesn't change whether the children are asked to breathe naturally, take deep breaths or exercise. The symptoms of DB are commonly experienced during, or exacerbated by, exercise. It would therefore be expected that the parameters (particularly principle angle as a measure of contribution) would become more abnormal for the DB group following exercise. Table 4 illustrates that this change was not seen. The work of Konno and Mead, however, was based on an adult model and hence it is not known whether the expected normal pattern of breathing for a child (expressed in terms of these parameters) is the same as that of an adult.

There are a number of other explanations for why the study findings differed from those expected.

With a new technology such as SLP it is important to understand the current strengths and weaknesses of the testing procedure. The strengths have been described above, but the optimal capture required to get a true assessment of breathing pattern has yet to be established. This is clearly demonstrated by an analysis of different segments selected from the same participant data.

In this study, data was analysed from a single segment of settled tidal breathing for each participant once their breathing had stabilised. On average, these segments were approximately 18 seconds in duration. If, however, the segment was chosen from the beginning of the capture to immediately before the deep inspirations (a slightly longer and less controlled period) the outcome of the data analysis is quite different. A significant difference in breath phase is revealed between the two groups on pre exercise test tidal breathing ($p=0.03$). The direction of the relationship, however, is unexpected, with the DB group values being significantly lower (i.e. more normal) than those of the control group. This finding is in opposition to a study of elite rowers (198), where the rowers were found to have a more complex, less synchronous breathing pattern than the non-rowers (with multiple sections of the chest moving separately). The Levai study, however, used a three compartment model of respiration (pulmonary rib cage, abdominal rib cage and abdomen) as opposed to the more traditional two compartment model (rib cage and abdomen) used in this study. Table 8 illustrates the difference in recorded values for an individual participant depending on the segment of capture chosen.

Table 8: Variation in breathing parameter values for a single subject

	RR	IE	Ti	Te	OP	PA	Spr	BP
Settled TV only	22.6	1.0	1.38	1.28	6.9	16.7	0.11	6.4
All TV	21.5	1.05	1.44	1.38	10.9	19.8	0.12	2.9

(where RR=Respiratory rate, IE=Inspiratory expiratory ratio, Ti=Inspiratory time, Te=Expiratory time, OP=Overall phase, PA=Principle angle, Spr=Spread and BP=Breath phase)

The variation of outcomes, depending on the segment of the capture chosen, could be overcome by increasing the length of the capture. By doing this the breathing pattern included in the segment would be more representative of the participant's usual breathing. Current thinking (which has yet to be proven) is that a three minute capture would be required to accurately reflect a person's breathing pattern.

A dysfunctional breathing pattern is often described as being 'unstable' (199) which may be caused by the increased sighing and altered FRC described in Chapter 1.5.5.3. Technologically, the longer capture would allow the pattern to be analysed for entropy, where entropy is a measure of variation (on a breath-by-breath basis) of the metric that it is applied to. The appropriate metric to investigate the potential involvement of sighing as a factor in the unstable breathing pattern would be principle angle. The rationale for this is that principle angle is a measure of contribution or dominance of the rib cage or abdomen and, with a sigh, a larger volume rib cage dominated inspiration would be expected prior to the prolonged expiration. The sigh would then be seen as an increased principle angle compared to the preceding and following breaths, leading to an increase in entropy of that measurement.

A single study comparing adults with COPD and healthy controls found that people with COPD exhibited a particularly chaotic breathing pattern when compared to the healthy individuals (189). It therefore may be the case that the instability of the DB breathing pattern is more important, or characteristic, than the absolute deviation from the normal. The study described in this chapter similarly made an attempt to compare the breathing patterns associated with a condition with that of healthy individuals. Attempting to do this with children, however, poses significant additional difficulties. It is well known that the mechanics of breathing in children is different to that of adults and that the change to an adult breathing pattern occurs gradually over time. It is not known though when changes occur, particularly with reference to the parameters measured by SLP. To overcome this problem it would be necessary to compile comprehensive reference data for healthy children to enable comparison with particular conditions. The reference data would need to be generated from a large number of children, of both genders, and across the complete age range to ensure that changes with age were captured. Also, it is known that ethnicity affects lung function measurements and hence it would be prudent to consider whether ethnicity has an effect on breathing patterns and therefore whether it would need to be taken into account in the reference data.

Other factors that potentially affect the study outcomes are related to the study sample. Participants for the DB group were selected based on a high level of clinical experience, coupled with elimination or optimisation of other respiratory conditions. The diagnosis of DB, however, for these children was not made by a single clinician, opening up the possibility of some variance within the diagnosis. A diagnostic test or tool would ideally be used to identify the population, but such a tool (apart from for those with extra thoracic DB) has yet to be developed. Further heterogeneity may have been introduced to the group by the combination of participants with thoracic DB and extra thoracic DB. Ideally, the DB group would have been divided into these two subgroups, as underlying differences in the physiology of the conditions could predispose children to adopt different breathing patterns. The small sample size, particularly post exercise, did not allow this to be done in this study. The sample size also limited the conclusions that could be drawn about breathing pattern post exercise, either in comparison to the control group or as a within group comparison pre and post exercise.

A further potential factor was the presence of asthma as a co-morbidity in a proportion of the participants in the DB group. The lack of difference between the DB group and control group for lung function parameters indicates that, where asthma was present, it was well controlled. However, it is not known whether the pathophysiology of asthma causes a change in breathing pattern with or without the presence of DB.

This study did, however, demonstrate that testing using SLP is extremely well tolerated by children. The high tolerance level (100%) is likely to be due to the simple, non-invasive nature of the scan, the short time it takes (approx. five minutes per child) and the limited demands placed on the subject. The scan is also relatively straightforward for the tester/clinician to perform as demonstrated by the low technical failure rate (3%). Technical failures were due to suboptimal measurement setup, of which common causes were low grid contrast (caused by too much light in the room) or a creased, or loose-fitting t-shirt. The failure rate could be further reduced by a brief check of the scan immediately after it had been performed, allowing the scan to be repeated if the quality of the capture was poor. In practice scans can be repeated as necessary, as there are no additional cost or radiation implications.

3.5. Conclusion

This study has shown that structured light plethysmography can be used for the detailed assessment of breathing patterns in healthy children and those with dysfunctional breathing. The technique is both easy to perform and well tolerated. No significant differences were found in the measured breathing parameters using this study protocol, but differences are likely if future studies analyse longer captures (allowing parameters such as entropy to be investigated) and include greater participant numbers.

4. Non-invasive diagnosis of vocal cord dysfunction

4.1. Introduction

The importance of exercise in children and child health is becoming increasingly important, especially now that, in some countries, up to one third of the paediatric population is considered to be overweight or obese (200). There are a group of children, however, who wish to exercise but are limited in their ability to do so due to disproportionate shortness of breath and other symptoms such as wheeze and throat tightness (8, 33). These symptoms are precipitated by exercise and caused by paradoxical vocal cord dysfunction (pVCD), a form of extra thoracic dysfunctional breathing (ET-DB) that is characterised by incorrect vocal cord adduction, primarily during inspiration (35).

The current 'gold standard' means of diagnosing pVCD is by nasendoscopy (156) to visualise the abnormal vocal cord motion, which restricts inspiratory airflow and is typical of this condition. However, nasendoscopy is invasive and needs to be performed whilst symptoms are provoked, as the majority of people with pVCD are asymptomatic at rest. For these reasons, children can find the procedure difficult to tolerate and it is limited to specialist centres.

Alternative methods for diagnosis have been suggested, such as specific lung function tests. However, evidence has shown that in patients with proven pVCD, lung function testing has very low sensitivity when being used to identify pVCD (87).

A non-invasive means of testing offers clear benefits; significantly improved tolerability and the potential for early accurate diagnosis.

Recent developments in technology offer opportunities for addressing the above difficulties. Airway narrowing due to inappropriate vocal cord activity causes abnormal respiratory sounds such as stridor and modern respiratory sound analysis (RSA) devices (the PulmoTrack™ and Wheezometer®, KarmelSonix, Haifa, Israel) are now available that can detect these sounds. These record and analyse breath sounds both in the respiratory function laboratory and in the community respectively. This allows the recording of patient's symptoms in their natural environment for later analysis by their health professional, and comparison with laboratory elicited symptoms.

These RSA devices have primarily been used with patients with asthma where RSA has been shown to offer potential as a surrogate measure of airway obstruction (131, 134, 136). Detection of abnormal sounds within the inspiratory phase of breathing, however, should be strongly indicative of pVCD and it was proposed that computerised RSA could be used for the non-invasive diagnosis of paradoxical vocal cord dysfunction.

The primary aim of this exploratory study therefore was to determine whether respiratory sound analysis (RSA) (using PulmoTrack or WheezoMeter) can be used to identify paradoxical vocal cord dysfunction (pVCD) in children who have nasendoscopically-proven pVCD. A secondary aim of this study was to investigate whether RSA results differ

depending on whether the information is recorded during laboratory based exercise or during the patient's normal sporting activity or exercise.

4.2. Methods

4.2.1. Participants

The study population was a convenience sample of 43 children aged between eight and 16 years (condition group n=22, control group n=21). The condition group consisted of children with clinically-diagnosed dysfunctional breathing (DB) where the diagnosis was made by an experienced consultant or registrar specialising in respiratory medicine, based on expert history taking and the exclusion or optimal management of other conditions. Children were not excluded from this group if they had a co-morbidity such as asthma, as long as the co-morbidity was well controlled. The group was divided into thoracic DB (n=11) and extra thoracic DB (n=11) with the extra thoracic DB group being identified by a history indicative of pVCD (e.g. performance symptoms, difficulty breathing in, throat tightness, stridor). All children with DB were recruited sequentially upon referral to the BreathWorks clinic (Sheffield) for physiotherapy based treatment, and all testing was carried out prior to the start of therapy.

The control group were healthy volunteers with no history of breathing problems, which was confirmed by the completion of a respiratory screening questionnaire prior to enrolment into the study. A copy of this questionnaire can be found in Appendix 6. They were recruited via an e-mail advert to staff from Sheffield Children's Hospital (SCH) and staff and students at the University of Sheffield.

Children were excluded from either group if they lacked suitable cognitive or physical ability to follow study instructions and perform the exercise test, or the child or parents/guardians were not fluent in written and spoken English.

Parents/guardians attended all study sessions and gave written informed consent. Study participants gave written informed assent and the study was given ethical approval by the NRES Committee Yorkshire and The Humber – Sheffield.

4.2.2. Study Design

This exploratory study involved three groups of children (thoracic dysfunctional breathing (T-DB), extra thoracic dysfunctional breathing (ET-DB) and control group) performing spirometry prior to being fitted with the PulmoTrack system and carrying out a treadmill based exercise test. Repeat spirometry was performed post exercise test. In addition to this, children in the ET-DB group underwent nasendoscopy at the beginning of the testing session and immediately after the exercise test to confirm the diagnosis of pVCD. They were also issued with a WheezoMeter to provide recordings made in the natural environment (eg whilst doing sport) for comparison with those made during the laboratory based exercise test.

Nasendoscopy was performed by an experienced otolaryngologist using an Olympus ENF-V2 (Olympus Corporation, Tokyo, Japan), with subjects in a seated position as described in

Chapter 2. Pre and post exercise test spirometry was carried out to identify any participants who may generate added sounds due to bronchoconstriction, rather than upper airway obstruction. Bronchoconstriction was defined as a 15% or greater decrease in FEV_1 (195), compared to baseline, which reversed with 400mcg salbutamol via a metered dose inhaler and spacer. Spirometry was performed using a pneumotachograph (MasterScreen PFT, Jaeger, Höchberg, Germany) and a standardised protocol based the ATS/ERS guidelines (190). All tests were performed by an experienced respiratory physiologist with subjects standing and wearing a nose clip.

The two respiratory sound analysis acoustic sensors and the respiration belt of the PulmoTrack system (KarmelSonix Ltd, Haifa, Israel) were attached to each participant by the researcher (NJB), following the manufacturer's instructions (see Chapter 2 for details). The wireless module was held by the parent rather than hung on a belt during the exercise test to avoid interference with the low posterior ECG electrodes.

The exercise tests were treadmill based (JLab software, Jaeger, Höchberg, Germany) and were conducted by an experienced respiratory physiologist and supervised by a specialist registrar level doctor. The protocol for each exercise test was determined on an individual basis by the respiratory physiologist. The tests predominantly used were Bruce or Houlsby protocols, where the Houlsby was chosen for the younger children due to the shorter time spent at each increment (191-193). A bronchoprovocation test was used where it was also clinically necessary to investigate for exercise induced asthma (194). Participants were encouraged verbally during the exercise test (in line with standard practice) and all children achieved heart rate levels that were indicative of a very good, if not exceptionally good, physical effort. The standard operating procedures for exercise testing at SCH are presented in Appendix 7.

Children in the ET-DB group were issued with a WheezoMeter (KarmelSonix Ltd, Haifa, Israel) and given standardised instructions on how to use it. This group were chosen to make WheezoMeter recordings as they were the group most likely to generate abnormal sounds, which could be compared to the sounds on the corresponding PulmoTrack recordings. They were instructed to make a minimum of three recordings when feeling well and three recordings when symptomatic. They were also asked to make a voice recording for each sound recording identifying the situation that the recording had been made in, e.g. at rest or following a particular type and duration of exercise. A test recording was made at the time of issue of the WheezoMeter to ensure that the child and parents understood how to operate the device. The WheezoMeter recordings were downloaded from the device by the researcher and analysed in conjunction with the PulmoTrack recordings following the completion of data collection. All recordings were analysed numerically for wheezeRATE from the standard report.

Analysis of the PulmoTrack numerical data was carried out using the output from the tracheal (Tr) sensor with ambient wheeze rejection (AWR) off. This particular stream of data was chosen as pVCD is a problem of the upper airway and therefore abnormal sounds would most likely be heard at the level of the trachea. pVCD is also primarily present during inspiration but can occur during expiration therefore output from the tracheal

sensor during inspiration, expiration and a combined total (Tr Insp, Tr Exp and Tr Total) were all considered.

The audio recording and sonogram from each PulmoTrack recording was simultaneously analysed by NJB and, using this combined information, a decision was made for each as to whether true abnormal respiratory sounds were heard during the exercise test. The recording for the tracheal sensor was listened to in all cases and the ambient recordings were considered if it was not clear whether a sound was from the participant or an external source, e.g. an equipment alarm. Abnormal sounds were also divided depending on whether they occurred in the inspiratory or expiratory phase of respiration.

4.2.3. Data Analysis

A full descriptive analysis of all variables collected was performed. Continuous variables are summarised with the mean and standard deviation, or median and interquartile range as appropriate. Categorical variables are summarised as proportions observed in each category. The primary data for analysis was maximum wheezeRATE® (Max Wz%) from the tracheal sensor during inspiration, expiration and as a combined total (Tr Insp, Tr Exp and Tr Total), where Wz% is wheezing time/breathing time x 100.

Statistical analysis is not appropriate due to the study design and the small amount of data available for the condition groups. However, the data from this exploratory study could potentially be used to inform a power calculation for a larger study in the future.

4.3. Results

Twenty one healthy children were recruited to the control group and RSA recordings were successfully made for all children in this group. Demographic data for this group and the DB groups is displayed in Table 9.

Table 9: Characteristics of the study population

	Control group (n=21)	**T-DB (n=11)**	**ET-DB (n=11)**
Age (mean & SD)	11.18 ±2.29	13.05 ±2.43	13.03 ±1.99
Gender (M/F)	9/12	2/9	7/4
Presence of co-morbidity	0	7	5

Of the 11 children recruited into each of the DB groups, seven complete recordings were achieved in the T-DB group and 9 in the ET-DB group (see Figure 11). Four recordings were not attempted due to participants not meeting the inclusion/exclusion once the protocol had been started (e.g. uncontrolled asthma), or due to the presence of pVCD on nasendoscopy prior to the exercise test. The two participants with evidence of pVCD pre

exercise test were not reporting symptoms but the exercise tests were cancelled as the role of the test was to provoke the pVCD, which was technically already present. Eight out of the 11 participants of the ET-DB group clinically diagnosed with pVCD had abnormal cord movement on nasendoscopy.

Additionally, in two cases, the study protocol was performed but complete recordings were not achieved due to technical failures with the PulmoTrack system. In no cases were failures to achieve recordings due to tolerance, as all 39 attempted recordings were well tolerated by the children and the protocol was completed in all cases.

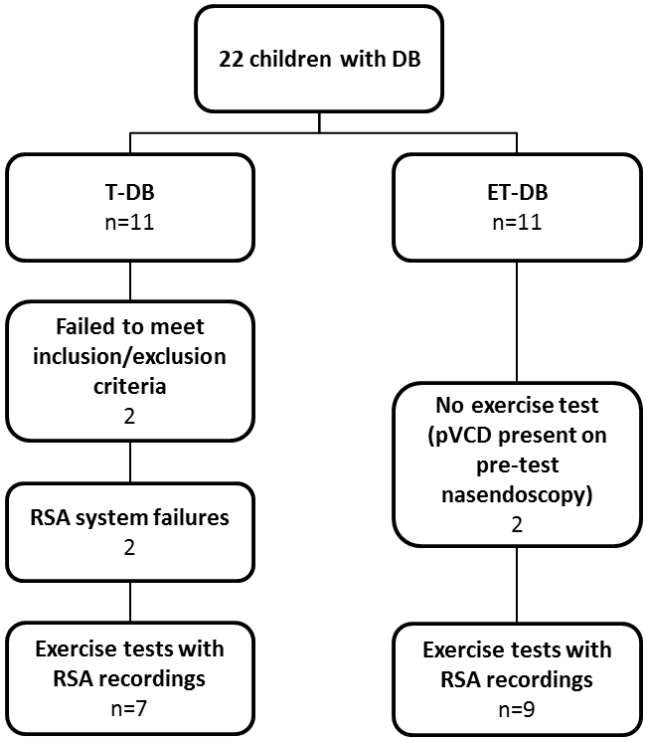


Figure 11: Flow of thoracic and extra thoracic DB group participants

Pre and post exercise test lung function data for participants that completed exercise tests with RSA recordings is shown in Table 10. Note that n=20 in the control group and n=8 in the ET-DB group due to the lung function tests of one participant from each of these groups not being reproducible.

Table 10: Pre and post exercise test lung function data (median and IQR)

	Control group (n=20)	**T-DB (n=7)**	**ET-DB (n=8)**
Pre test FEV_1	102.2 (93.10-106.0)	104.0 (85.30-111.6)	91.75 (82.65-99.50)
Post test FEV_1	99.85 (92.15-103.9)	101.1 (80.60-108.0)	87.25 (78.8-97.33)
Pre test FVC	97.15 (93.90-102.3)	95.80 (93.80-107.6)	92.45 (90.90-98.63)
Post test FVC	97.10 (90.55-100.9)	92.60 (90.40-104.2)	91.10 (90.55-97.08)

(where FEV1 and FVC are expressed as percent predicted)

4.3.1. PulmoTrack numerical data

Apart from ET-DB Tr Exp and Tr Total data, all RSA data was either not normally distributed or the data sets were too small to be assessed for normality. Data collected for the three groups, from the PulmoTrack standard report with ambient wheeze rejection (AWR) off, is summarised in Table 11 and presented as median and inter quartile range (IQR).

Table 11: Maximum wheezeRATE (Max Wz%) data from the tracheal sensor

	Control group (n=21)	**T-DB (n=7)**	**ET-DB (n=9)**
Tr Insp	3.0 (2.0-4.0)	1.0 (0.0-3.0)	2.0 (0.0-5.0)
Tr Exp	3.0 (2.0-4.5)	4.0 (1.0-4.0)	3.0 (2.0-6.0)
Tr Total	5.0 (3.0-9.0)	5.0 (2.0-12.0)	7.0 (2.0-12.0)

4.3.2. PulmoTrack audio and visual data

Abnormal respiratory sounds were identified in each of the three groups. In all cases where abnormal respiratory sounds were detected, they were heard at some point during the recording in both phases of respiration. Table 12 shows the proportions of participants in each group who were positive for abnormal respiratory sounds. Two figures are given for the ET-DB group showing the proportion for the group as a whole and those who presented with abnormal cord movement on nasendoscopy (i.e. nasendoscopically-proven pVCD). The proportion of participants who were positive for abnormal sounds increases from 56% to 67% when only those with nasendoscopically-proven pVCD are included (i.e. more than double the proportion of either the control or T-DB groups).

Table 12: Abnormal respiratory sounds present during exercise

	Control group (n=21)	**T-DB (n=7)**	**ET-DB (n=9)**
Percentage	24	29	56/67

4.3.3. WheezoMeter data

WheezoMeters were issued to nine of the 11 children recruited into the ET-DB group; one child declined to take the device home and on one occasion a WheezoMeter was not available to be issued. Of the nine WheezoMeters issued, no participants were successful in making all of the six requested recordings (three when asymptomatic and three when symptomatic). Five participants made some recordings however, only one of these participants managed recordings during activity whilst the rest were carried out at rest. Three participants attempted, but did not achieve, successful recordings and one participant did not attempt to make any recordings.

4.4. Discussion

This study has demonstrated that it is possible to use RSA (using the PulmoTrack system) with children when investigating pVCD. The children were comfortable with the equipment and 100% of the 39 tests that were attempted using the PulmoTrack were completed. Data was continuously captured for 37 of these 39 tests, giving a technical success rate of 95%.

This high success rate however indicates that data was captured, but does not give an indication of the reliability or validity of this data. Statistical analysis is not appropriate due to the study design and small numbers in the condition groups, where at least 12 subjects would have been required in each group (196). The descriptive statistics however offer some insight into the meaning of the data collected and the possible interpretation of this, along with some of the limitations identified, is discussed below.

4.4.1. PulmoTrack numerical findings

It would be expected that, in the presence of pVCD, the ET-DB group would present with higher values (particularly for Tr Insp) due to inappropriate cord adduction causing airway obstruction, which generates abnormal inspiratory sounds. Whilst the Tr Total and the 75th percentile values are highest in the ET-DB group, the overall trend from the descriptive analysis does not suggest a marked difference between groups when measured in this way.

There are factors, however, that impact on the accuracy of these figures. AWR is designed to eliminate all audible wheeze-like sounds in the environment from the primary recording (141). The benefits of this are clear, as it serves to reduce the amount of ambient noise that is inappropriately attributed to the participant, however AWR is unable to differentiate between genuine ambient sounds and audible wheezes/stridor generated by the patient. Hence, if the AWR is on, all recorded respiratory sounds that are also audible will be removed from the numerical analysis, returning incorrectly low figures. Conversely, setting AWR to off returns incorrectly high figures due to the inclusion of environmental ambient sounds.

This problem can only be resolved by developments in the PulmoTrack technology, to allow differentiation between participant-generated and ambient sounds. The AWR feature of the PulmoTrack essentially performs a basic form of sound signal separation by subtracting sound signals from the ambient microphone from those detected by the tracheal and chest sensors. Achieving an effective level of signal separation requires significantly more sensitive signal processing technology than is currently available. The technology will require the ability to 'learn' which signals heard in the ambient array, e.g. stridor, are patient generated and therefore should not be excluded from the analysis.

In this study, data was therefore analysed with AWR off as it was deemed most important to not eliminate any genuine respiratory sounds.

4.4.1.1. PulmoTrack audio and visual findings

The combined audio and visual data shows a similarity between the control group and T-DB group, with abnormal respiratory sounds present in 24% and 29% of the participants

respectively. These groups provide data on what sounds are generated within the respiratory system in children who have no history of upper airway obstruction.

The figures for both these groups, however, are higher than would have been anticipated. This may indicate that there was an element of pVCD in the non-pVCD groups that had not been identified either by patient history (for the T-DB group) or via the respiratory screening questionnaire (for the control group). The solution to this would have been to perform pre and post test nasendoscopy in all of the participants. This was not carried out, however, in this study due to the ethical issues surrounding performing an invasive procedure in children where there would be no real or perceived benefit for the child.

The ET-DB group presented with a much higher proportion of participants with abnormal respiratory sounds during exercise (56% or 67% depending on how the figure is calculated). There is the possibility that some or all of the children from the ET-DB group, who were negative for abnormal cord motion on post test nasendoscopy, did have pVCD. The abnormal cord motion associated with pVCD can resolve very quickly on cessation of exercise meaning that it is possible for normal cord motion to resume prior to the post test nasendoscopy, even if the procedure is carried out as soon as possible. The only way to avoid this potential for false negative diagnoses is to use continuous laryngoscopy during exercise (CLE), where the cords are observed throughout the test (82). This is currently not possible in children as suitable equipment is not available.

Regardless of method, these increased figures indicate that there is a difference in the abnormal sounds produced between the ET-DB group and the other two groups (as the only other group variables are comorbidity, age and gender). Compared to the control group, a high proportion of the children in the ET-DB and T-DB groups had a diagnosis of asthma, but this is unlikely to have impacted on the results as the pre and post exercise test lung function for these (and the other) group remained consistent. As shown in Table 2, all groups had a small decrease (<5%) in both FEV1 and FVC when comparing pre and post exercise test values. This change is not clinically significant (195) and is likely to be due to fatigue following the exercise test.

The mean age of the ET-DB group is greater than that of the control group, but similar to that of the T-DB group, whereas gender is more equally distributed in the control group, predominantly female in the T-DB group and approximately two thirds male in the ET-DB group. The gender distribution in the ET-DB group is in opposition to the historical view that pVCD affects more females than males (201) but in the current study is based on small numbers. It would be possible in a study of large numbers to investigate further the relationship between age, gender and pVCD and whether these factors have an impact on respiratory sounds generated during exercise.

4.4.1.2. Technological problems

Analysis of the audio data and the sonogram highlighted a variety of interference that potentially introduced an uncontrolled variable to the study. The most common form of interference was from speech, either from participants, parents or the study team. It was most predominant at particular stages of the exercise test, namely in the early stages of the

test (whilst getting the child settled with the moving treadmill) and towards the end of the test when verbal encouragement is needed to ensure that the child makes the level of physical effort required to induce symptoms if present. Stipulating a quiet room during the exercise test would reduce this type of interference but would risk false negatives (where children did not exercise hard enough to elicit symptoms).

Interference was also heard from equipment alarms, ringing telephones and passing emergency vehicles, but in the majority of cases the PulmoTrack system was able, potentially from the pattern of harmonics, to successfully identify these as being non-patient related.

There were also occasions when patient related abnormal respiratory sounds were heard outside of the period of the exercise test. These were predominantly identified to be associated with forced maximal inspiration and expiration during lung function testing, and were eliminated from the audio and visual analysis. It was not possible though to remove them from the numerical analysis but as all participants performed pre and post exercise test lung function these additional sounds should affect all groups equally. There is the possibility, however, that the forced manoeuvres required for spirometry provoked abnormal cord motion in patients with pVCD. It has been suggested that some patients with pVCD present with flattened inspiratory loops on spirometry (156, 202), but it has not been considered whether this abnormality is an indicator of the presence of pVCD or whether the manoeuvre provokes the pVCD.

4.4.2. WheezoMeter findings

The secondary aim of this study was to investigate whether similar abnormal respiratory sounds are generated in children with pVCD, depending on if they are provoked in the participant's natural environment, e.g. doing sport, or provoked in a laboratory environment using an exercise test. This was to be carried out by comparing recordings captured by the WheezoMeter outside of the laboratory with the recording from the PulmoTrack during the exercise test. Eight out of the nine children who were issued with WheezoMeters actively attempted to make recordings but the success rate was very low, especially during activity, and was attributed to unresolvable equipment failure that did not improve when the WheezoMeters were replaced. Whilst the small number of recordings captured cannot be used as comparisons to the PulmoTrack recordings in this study, the successful recordings indicate that there is merit in exploring this question in the future using more robust technology.

4.5. Conclusion

Data from this study supports the possibility of using respiratory sound analysis as a non-invasive means of diagnosing pVCD. However it is not possible to do this using the technology that is currently available. RSA systems would need to be specifically designed to incorporate the degree of sensitivity required and the ability to differentiate between patient generated audible sounds and ambient noise. Systems that could be used both in the laboratory and out in the 'field' would enable better investigation of the relationship between symptoms and the means of provocation.

5. Breathing exercises for dysfunctional breathing/hyperventilation syndrome in children

This Cochrane Review is published in *the Cochrane Database of Systematic Reviews* 2013, Issue 12. Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the *Cochrane Database of Systematic Reviews* should be consulted for the most recent version of the Review.

Reference: Barker NJ, Jones M, O'Connell NE, Everard ML. Breathing exercises for dysfunctional breathing/hyperventilation syndrome in children (Review). Cochrane Database of Systematic Reviews 2013, Issue 12. Art.No.: CD010376. DOI: 10.1002/14651858.CD010376.pub2. http://dx.doi.org/10.1002/14651858.CD010376

5.1. Chapter abstract

5.1.1. Background

Dysfunctional breathing (DB) is described as chronic or recurrent changes in breathing pattern causing respiratory and non-respiratory symptoms. It is an umbrella term that encompasses hyperventilation syndrome, vocal cord dysfunction and pattern disordered breathing. Dysfunctional breathing affects 10% of the general population. Symptoms include dyspnoea, chest tightness, sighing and chest pain which arise secondary to alterations in respiratory pattern and rate. Little is known about DB in children. Preliminary data suggest 5.3% or more of children with asthma have DB and that unlike in adults it is associated with poorer asthma control. It is not known what proportion of the general paediatric population is affected. Breathing training is recommended as a first-line treatment for adults with DB (+/- asthma) but no similar recommendations are available for the management of children. As such, breathing retraining is adapted from adult regimens based on the age and ability of the child.

5.1.2. Objectives

1. To determine whether breathing retraining in children with dysfunctional breathing has beneficial effects as measured by quality of life indices.
2. To determine whether there are any adverse effects of breathing retraining in young people with dysfunctional breathing.

5.1.3. Search methods

We identified trials for consideration using both electronic and manual search strategies. We searched CENTRAL, MEDLINE and EMBASE. We searched the National Research Register (NRR) Archive, Health Services Research Projects in Progress (HSRProj), Current Controlled Trials register (incorporating the meta-register of controlled trials and the International Standard Randomised Controlled Trial Number (ISRCTN) to identify research in progress and unpublished research. The latest search was undertaken in October 2013.

5.1.4. Selection criteria

We planned to include randomised, quasi-randomised or cluster randomised controlled trials. We excluded observational studies, case studies and studies utilising a cross-over design. The cross-over design was considered inappropriate due to the purported long-lasting effects of breathing retraining. Children up to the age of 18 years with a clinical diagnosis of DB were eligible for inclusion. We planned to include children with a primary diagnosis of asthma with the intent to undertake a subgroup analysis. Children with symptoms secondary to cardiac or metabolic disease were excluded.

We considered any type of breathing retraining exercise for inclusion in this review, such as breathing control, diaphragmatic breathing, yoga breathing, Buteyko breathing, biofeedback-guided breathing modification and yawn/sigh suppression. We considered programs where exercises were either supervised (by parents and/or a health professional) or unsupervised. We also considered relaxation techniques and acute episode management as long as it was clear that breathing exercises were a component of the intervention.

Any intervention without breathing exercises or where breathing exercises were not key to the intervention were excluded.

5.1.5. Data collection and analysis

We planned that two authors (NJB & MJ) would extract data independently using a standardised form. Any discrepancies would be resolved by consensus. Where agreement could not be reached a third review author (MLE) would have considered the paper.

5.1.6. Main results

Two hundred and sixty four potential trials and reviews were identified from the search. Following removal of duplicates, 224 papers were screened based on title and abstract. Six full text papers were retrieved and further evaluated but did not meet inclusion criteria. There were, therefore, no studies suitable for inclusion in this review.

5.1.7. Authors' conclusions

The results of this systematic review are unable to inform clinical practice as no suitable trials were identified for inclusion. Therefore, it is currently unknown whether these interventions offer any added value in this patient group or whether specific types of breathing exercise demonstrate superiority over others. Given that breathing exercises are frequently used to treat DB/HVS, there is an urgent need for well designed clinical trials in this area. Future trials should conform to the CONSORT statement for standards of reporting and use validated outcome measures. Trial reports should also ensure full disclosure of data for all important clinical outcomes.

5.2. Background

5.2.1. Description of the condition

Dysfunctional breathing has been described as chronic or recurrent changes in breathing pattern, causing respiratory and non-respiratory complaints (13). It is an umbrella term that encompasses more traditionally recognised breathing disorders such as hyperventilation syndrome and vocal cord dysfunction.

Dysfunctional breathing affects almost 10% of the general population. It is more common in women than men and three times more likely in those with asthma (14). Whilst there is some debate as to the accuracy of these figures (13), it is clear that dysfunctional breathing affects a wide range of people, from those with chronic obstructive pulmonary disease (COPD) through to elite athletes. Apart from the overt symptoms of dyspnoea, chest tightness, sighing and chest pain, people with dysfunctional breathing present with observable alterations in respiratory pattern and rate, which can deviate significantly from the norm.

Much less is known about the condition in children, including its prevalence. It is difficult to establish prevalence as dysfunctional breathing is not well defined and there are no standardised assessment tools available. However, preliminary data indicate that 5.3% of children with asthma have dysfunctional breathing and that, unlike in adults (56), it is associated with poorer asthma control (183). A more recent study of children with hyperventilation syndrome suggests that prevalence may be much higher, with 18.6% of non-asthmatic and 55% of asthmatic children affected (203).

Dysfunctional breathing can be a partner to, or separate from, respiratory conditions such as asthma (14); this often leads to it being overlooked or misdiagnosed. Clinical observations indicate that where misdiagnosis of asthma is made, young people receive medications that are either not needed or at a higher dose than is required to control the asthma element of their presentation. In addition to the unnecessary risks this poses for the child, there are significant implications for health service resources: costly repeat attendances at hospital clinics, emergency departments and general practices could be replaced by the provision of appropriate therapy preventing long-term sequelae.

5.2.2. Description of the intervention

Breathing training is carried out routinely with children in the United Kingdom (UK) and other countries for a variety of respiratory disorders (204, 205). There is, however, very little formal guidance for this breathing training in children, and the majority of regimens are taken from the treatment of adults and adapted where necessary depending on the age and ability of the child. Breathing training is recommended as a first-line treatment for adults, with or without asthma, who suffer with disordered breathing (94) but no similar recommendations are available for the management of children.

The multi-dimensional model of dysfunctional breathing reported in Courtney 2009, consisting of the three key elements of biochemical, biomechanical and breathing-related symptoms, promotes approaches to breathing training from different perspectives (187). The Buteyko breathing technique is a formalised programme of breathing retraining based on a hypothesis that biochemical disturbances contribute to dysfunctional breathing. The technique is aimed at 'normalising' carbon dioxide levels by hypoventilation and breath holding techniques (163).

The Papworth Method and other more modern retraining programmes differ from the Buteyko breathing technique in that they focus on the biomechanical and breathing-related symptoms of dysfunctional breathing. The focus is on normalisation of respiratory pattern with regards to balance between the two compartments of the chest wall (the rib cage and the abdomen) and the respiratory rate (93). Diaphragmatic breathing is central to these programmes and is often accompanied by education, relaxation and postural correction (97).

Whichever breathing retraining approach is taken, techniques are commonly consolidated by an individualised home programme tailored to each patient's needs (206).

5.2.3. How the intervention might work

Breathing retraining programmes encourage patients gradually to alter their breathing pattern with the ultimate goal to restore and maintain a normal diaphragmatic breathing pattern. Emphasis is also placed on reducing respiratory rate, tidal volume or both (94). Historically it was thought that breathing retraining reprogrammed the respiratory centre to trigger inspiration at a higher level of carbon dioxide, but this is now a source of debate (44, 161) and the exact mechanism for improvement is currently unknown. It has also been suggested that breathing retraining may work by impacting on the possible neurological and psychological causes of dysfunctional breathing (186).

5.2.4. Why it is important to do this review

Currently, no systematic review exists evaluating breathing retraining interventions for the management of dysfunctional breathing in children. Whilst treatment opportunities for children with dysfunctional breathing are less freely available than for adults, the core treatments delivered are still centred around breathing retraining even though the breadth and quality of the evidence base is unknown. Performing this systematic review with regard to children will offer insight into the evidence that is available, highlight any significant gaps in the evidence base and allow the following objectives to be met.

5.3. Objectives

1. To determine whether breathing retraining in young people with dysfunctional breathing has beneficial effects as measured by quality of life indices.
2. To determine whether there are any adverse effects of breathing retraining in young people with dysfunctional breathing.

5.4. Methods

5.4.1. Criteria for considering studies for this review

5.4.1.1. Types of studies

We planned to include randomised, quasi-randomised or cluster-randomised controlled trials. We excluded observational studies, case studies and studies utilising a cross-over design. The cross-over design was considered inappropriate due to the purported long-lasting effects of breathing retraining.

5.4.1.2. Types of participants

Children up to the age of 18 years with a clinical diagnosis of dysfunctional breathing were eligible for inclusion. We planned to include children with asthma, with the intention of undertaking a subgroup analysis. Children with symptoms secondary to cardiac or metabolic disease were excluded.

5.4.1.3. Types of interventions

We considered any type of breathing retraining exercise for inclusion in this review, such as breathing control, diaphragmatic breathing, yoga breathing, Buteyko breathing, biofeedback-guided breathing modification and yawn/sigh suppression. We considered programmes where exercises were either supervised (by parents or a health professional, or both) or unsupervised. We also considered relaxation techniques and acute episode management as long as it was clear that breathing exercises were a component of the intervention.

Any intervention without breathing exercises or where breathing exercises were not key to the intervention were excluded.

We planned to include trials with the following comparisons:

1. Breathing retraining versus another intervention
2. Breathing retraining versus no intervention
3. Breathing retraining in addition to a control intervention versus the control intervention alone

5.4.1.4. Types of outcome measures: primary outcomes

Quality of life measured by any respiratory disease-specific or generic instrument.

5.4.1.5. Types of outcome measures: secondary outcomes

- Nijmegen questionnaire (whilst not formally validated in paediatrics, this is used in clinical practice as no other validated options currently exist. The scale provides a score between 0 and 64 with higher scores indicating more severe hyperventilation symptoms (77))

- Ventilation (measured by minute volume, tidal volume, respiratory frequency, end tidal carbon dioxide (CO_2) or transcutaneous CO_2)
- Exercise capacity (e.g. measured by shuttle walking test, six-minute walk; all exercise capacity tools were considered)
- Dysfunctional breathing specific tests (e.g. breath hold test or hyperventilation provocation test (HVPT))

5.4.2. Search methods for identification of studies

We identified trials for consideration using both electronic and manual search strategies. For the Ovid MEDLINE search, we ran the subject search with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision) as referenced in chapter six and detailed in box 6.4c of the *Cochrane Handbook for Systematic Reviews of Interventions (207)*. The search strategies and filters used to search MEDLINE and the other databases are presented in Appendix 8. They include a combination of controlled vocabulary (MeSH) and free-text terms.

5.4.2.1. Electronic searches

We searched:

- Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*): all years in Issue 9, 2013
- MEDLINE (Ovid): 1946 to October week 1 2013
- EMBASE (Ovid): 1974 to week 1 2013
- AMED (EBSCO): 1985 to October week 1 2013
- PsycINFO (Ovid): 1967 to October week 2 2013
- CINAHL (EBSCO): 1982 to October week 1 2013
- LILACS: 1982 to October 2013

We searched all databases from their inception to the present, with no restriction on language of publication. Non-English papers were assessed and if necessary, translated with the assistance of a native speaker.

5.4.2.2. Searching other resources

We searched reference lists of all relevant primary studies and review articles for additional references. We planned to contact authors of identified trials and ask them to identify other published and unpublished studies. We handsearched abstracts from scientific meetings and respiratory journals.

5.4.2.3. Unpublished data

We searched the National Research Register (NRR) Archive, Health Services Research Projects in Progress (HSRProj), Current Controlled Trials register (incorporating the *meta*Register of Controlled Trials and the International Standard Randomised Controlled Trial Number (ISRCTN)) to identify research in progress and unpublished research.

5.5. Data collection and analysis

5.5.1. Selection of studies

Two authors (NJB and MJ) independently checked search results for eligible studies. We screened the titles or abstracts (or both) of identified studies. If it was clear from the study title or abstract that the study was not relevant or did not meet the selection criteria, it was excluded. If it was unclear, then we retrieved the full paper and assessed it along with all studies that appeared to meet the selection criteria. We aimed to resolve disagreement between review authors through discussion and consensus. Where resolution was not achieved the paper(s) in question were to be considered by a third review author (MLE). We kept a full record of decisions made and their rationale.

5.5.2. Data extraction and management

We planned that two authors (NJB and MJ) would extract data independently using a standardised form. We planned that discrepancies would be resolved by consensus. Where agreement could not be reached a third review author (MLE) would have considered the paper. We planned to extract information on the following domains:

- Risk of bias
- Country of origin
- Study design
- Study population (duration of symptoms; age; gender; prior management)
- Sample size (intervention and control groups)
- Intervention (breathing exercise type/approach)
- Outcomes reported
- Results for the outcomes defined above (short-term - at completion of the intervention; intermediate - less than one to six months following the intervention; long-term - greater than six months following the intervention)
- Adverse effects (nature and frequency)

Where insufficient data were presented to enter a study into the meta-analysis, we planned to contact study authors to request access to the missing data.

5.5.3. Assessment of risk of bias in included studies

We planned to assess risk of bias using the Cochrane 'Risk of bias' assessment tool outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (207). We planned to allocate studies with an overall rating of high, low or unclear risk of bias based on the Cochrane criteria. Specifically, if we judged a study as being at high risk of bias for one or more criteria then that study would have received an overall assessment of high risk of bias. Where we judged a study as being at unclear risk of bias for one or more criteria then that study would have received an overall assessment of unclear risk of bias.

We planned to assess the following criteria for parallel study designs (using yes/no/unclear judgements):

- Adequate sequence generation
- Adequate allocation concealment
- Adequate blinding of assessors
- Incomplete outcome data adequately assessed
- Free of suggestion of selective outcome reporting
- Free of other bias

Since it is not possible to blind therapists or clinicians in studies of this kind of intervention these criteria were not assessed but we planned to discuss the potential impact of incomplete blinding in the discussion of the results. We planned that two authors (NJB and MJ) would independently assess risk of bias for each included study. Disagreement between review authors would have been resolved through discussion. Where resolution was not achieved the paper(s) in question would have been considered by a third review author (MLE). Where the risk of bias of trials was unclear, we would have attempted to contact the authors for clarification.

5.5.4. Measures of treatment effect

For continuous variables, we planned to enter the mean (and standard deviation) post-intervention difference between groups into the meta-analysis using RevMan 5. Where these data were unavailable, we planned to record the mean (and standard deviation) change from baseline for each group. For continuous outcomes, we planned to enter mean difference as the measure of effect size where different studies utilise a common outcome measure. Where a variety of measures were employed across studies we planned to use the standardised mean difference to pool results. For dichotomous outcome measures we planned to use the risk ratio.

5.5.5. Unit of analysis issues

We planned to include the results of cluster-randomised trials in any meta-analysis; we would have performed a sensitivity analysis to assess whether their inclusion had an influence on the pooled effect size.

5.5.6. Dealing with missing data

We planned to contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible.

5.5.7. Assessment of heterogeneity

We planned to assess heterogeneity and its impact using the Chi^2 test and the I^2 statistic. The significance level for heterogeneity would have been accepted at alpha $P < 0.1$.

5.5.8. Assessment of reporting biases

We planned to consider the possible influence of publication/small study biases on review findings through checking for asymmetry of funnel plots and applying Egger's test.

5.5.9. Data synthesis

Where adequate data existed, we planned to pool results using RevMan 5 using a random-effects model. This model would be chosen because, in therapy trials, it is very rare for different trials to assess the same intervention in the same group of people. Therefore, the assumptions of the fixed-effect model are unlikely to be met. As such, it was likely that any proposed pooling of data would have included a range of similar but essentially different effect estimates. However, we planned to perform a sensitivity analysis using a fixed-effect model in order to investigate the influence of this choice.

Where inadequate data were found to support statistical pooling, we planned to report a narrative synthesis of the evidence using the GRADE system (208).

5.5.10. Subgroup analysis and investigation of heterogeneity

Where significant statistical heterogeneity ($P < 0.1$) was present, we planned to explore subgroup analysis. Where adequate data allowed we planned to perform the following subgroup analyses:

1. type of breathing exercise intervention (subgroups: yoga-based/conventional breathing control/Buteyko breathing)
2. amount of treatment provided (multiple treatment versus single treatment studies)
3. presence versus absence of asthma
4. specific diagnosis of vocal cord dysfunction

5.5.11. Sensitivity analysis

Where sufficient data were available, we planned to conduct sensitivity analyses to investigate the influence of including trials at high or unclear risk of bias (across all 'Risk of bias' criteria) and the effect of including cluster trials on pooled effect size.

5.6. Main results

5.6.1. Description of studies

5.6.1.1. Results of the search

In January 2013, we undertook electronic and manual searches which identified 264 potential trials and reviews; this included 40 duplicate papers. We initially screened the 224 unique papers based on title and abstract. Review author NJB identified eight trials which were unclear and required discussion. Review author MJ identified two trials which were unclear and required discussion. Following discussion between the two review authors (NJB, MJ), four trials were considered not to be relevant as they did not meet the inclusion criteria for the review. However, we retrieved six full-text papers and further evaluated

these but they did not meet the inclusion criteria for this review (8, 44, 93, 96, 209, 210). A repeat search undertaken on 16 October 2013 identified an additional six titles but none met the inclusion criteria for this review. Figure 12 shows a flow chart of the search screening process.

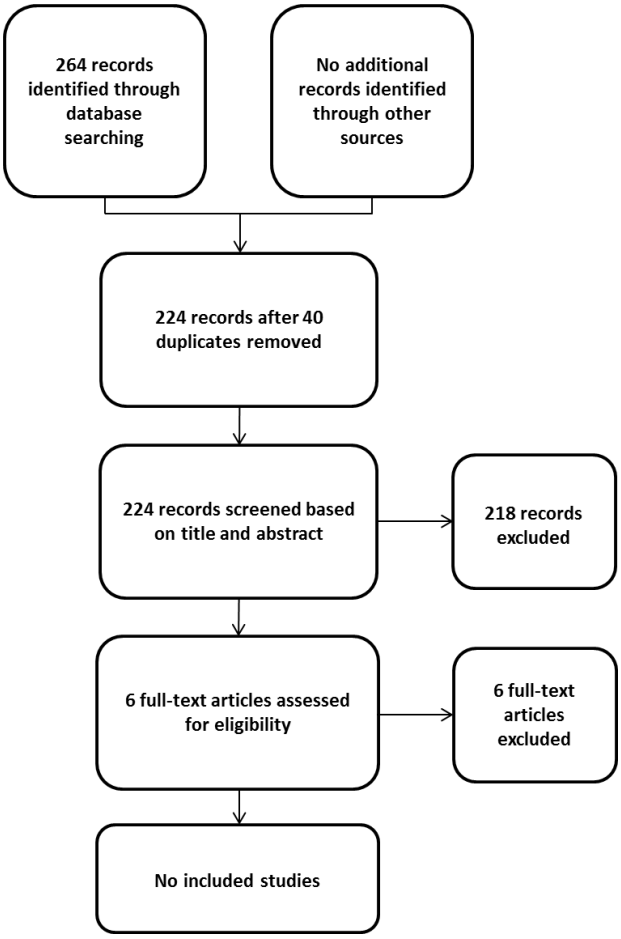


Figure 12: Flow diagram of the search screening process

5.6.1.2. Included studies

No suitable studies were identified that met the inclusion criteria for this review.

5.6.1.3. Excluded studies

Six studies were excluded and the reasons for their exclusion are detailed in Appendix 9. Three of these papers were excluded as they were not randomised controlled trials (RCTs) (8, 44, 210). Monday 1995 was a RCT including 18 participants with chronic hyperventilation syndrome and compared three non-pharmaceutical approaches to treatment (209). However, this study contained only one participant under the age of 18 years and the control group received verbal education on breathing techniques and therefore could not be considered a true control group. Kraft 1984 undertook a controlled trial in 40 adults, examining which of four therapeutic interventions could be considered the most effective treatment for hyperventilation syndrome (211). However, no participants were under the age of 18 years. Thomas 2003 undertook a RCT comparing

breathing retraining with asthma education in 33 people with asthma and dysfunctional breathing (93). Patients aged 17 years and above were screened for the study but no paediatric data were included.

5.6.1.4. Risk of bias in included studies

There were no included studies and hence risk of bias is not applicable.

5.6.2. Effects of interventions

There were no eligible studies for this review.

5.7. Discussion

We identified no studies that could provide evidence on whether breathing retraining is effective in the management of children with dysfunctional breathing. The primary cause of this lack of evidence was the absence of studies carried out in children, with four out of the six studies identified from initial screening containing only adults (44, 93, 209, 211). It is not clear from the one study that did include children (from aged 13.5 years) (210) how many children were involved, however we did not seek further information on this from the authors as the comparison group was not considered to be suitable.

Clinical experience indicates that children with dysfunctional breathing are receiving and benefiting from breathing retraining. The four adult-based studies eliminated from this review (44, 93, 209, 211), whilst not considered to offer quality evidence, support the benefits of breathing retraining for dysfunctional breathing. Conversely, Stanton 2008 (210) found no evidence of change in outcomes for patients with dysfunctional breathing but it is unclear whether this is related to study design or reflects a true lack of change. These studies are, however, carried out predominantly with adults and are not a substitute for good-quality controlled trials.

5.7.1. Potential biases in the review process

We have undertaken a comprehensive and systematic search for relevant trials pertinent to the objectives of this review. However, it may be argued that the exclusion of non-randomised studies, or studies that included adults, may have led to the exclusion of important data. We excluded non-randomised studies since they are at a higher risk of bias (207) and because it should be possible to investigate the effectiveness of these interventions through RCTs. We excluded studies that recruited adult participants because the physiology of children is significantly different to that of adults and hence the evidence for interventions should be considered separately. In addition to this, studies involving adults with dysfunctional breathing have been thoroughly considered in another Cochrane review and no credible evidence found (100).

5.7.2. Agreements and disagreements with other studies or reviews

No suitable studies were found to provide evidence on the efficacy of breathing retraining in children with dysfunctional breathing. This finding is consistent with the recent review of

breathing exercises for dysfunctional breathing/hyperventilation syndrome in adults (100). The adult review identified one study suitable for inclusion in the review but this study was not robust or detailed enough to allow recommendations to be based upon it.

5.8. Conclusions

5.8.1. Implications for practice

There is currently no evidence to support or refute the efficacy of breathing retraining in children with dysfunctional breathing. There is also no evidence from the studies reviewed of any adverse events or outcomes from the use of breathing retraining with children. We would therefore suggest that current practice is not changed either through the introduction or removal of breathing retraining until quality evidence becomes available.

5.8.2. Implications for research

It is currently unknown whether breathing exercises offer any added value to children with dysfunctional breathing or whether specific types of breathing exercise demonstrate superiority over others. Given that breathing exercises are frequently used to treat dysfunctional breathing, there is an urgent need for well-designed clinical trials in this area. The difficulties in diagnosing children with dysfunctional breathing should be recognised and addressed to ensure that the outcomes of these trials are valid and clinically useful. Future trials should conform to the CONSORT statement for standards of reporting and use validated outcome measures. Trial reports should also ensure full disclosure of data for all important clinical outcomes.

6. Current outcomes of physiotherapy for children with dysfunctional breathing

6.1. Introduction

Dysfunctional breathing (DB) is a respiratory disorder characterised by abnormal breathing patterns (15, 39, 40). These breathing patterns and the associated symptoms (shortness of breath, chest pain, wheeze/stridor etc.) have a significant impact on quality of life which has been shown to be more impaired than for those with asthma (56).

Clinical experience, and feedback from patients and their families, indicates that young people with DB experience significant improvements in both physical health and quality of life following a course of physiotherapy where breathing retraining is the key element of therapy.

However, a recent Cochrane review of DB in children (presented in Chapter 5) demonstrates that no studies have been carried out investigating the value of breathing retraining for children with dysfunctional breathing (166). This means that there is little or no evidence available to clinicians to guide assessment techniques, choose therapeutic interventions or assess outcomes (8).

The aim of this study was to explore the hypothesis that a structured, but individualised, program of physiotherapy interventions improves clinical outcomes and quality of life for young people with dysfunctional breathing, and that the improvement would be maintained following cessation of treatment.

6.2. Methods

6.2.1. Study design and participants

This observational study was performed at the BreathWorks clinic for young people with dysfunctional breathing at Sheffield Children's Hospital, Sheffield, England. All children that started treatment at the clinic between April 2011 and March 2013 were prospectively included, unless they presented with one or more of the exclusion criteria. The criteria for referral to the clinic are that patients have a clinical diagnosis of dysfunctional breathing (made by an experienced Consultant or Registrar specialising in Respiratory Medicine based on expert history taking and exclusion or optimal management of other conditions) and that they are aged between 7 and 16 years at the time of referral. Children were excluded from the study if:

- they lacked suitable cognitive ability to follow instructions
- the child or parents/guardians were not fluent in written and spoken English
- they had a co-morbidity where the relationship between that co-morbidity and DB is not yet understood
- they did not complete the course of treatment

Ethical approval was not required as all children involved were receiving standard routine care, as provided by this institution, and it would not be possible to identify participants from the data generated.

6.2.2. Intervention

All children received breathing retraining and education as their key interventions. The breathing retraining method used was based on the Papworth Method (97) where the main focus of the intervention was a return to normal diaphragmatic breathing, with an associated reduction in upper chest and accessory muscle use. This was done in conjunction with nasal breathing and was adjusted for children with the use of age appropriate language.

Treatment programmes were also individualised and, where appropriate, included one or more of the following additional interventions:

- postural correction
- thoracic mobility exercises
- airway clearance techniques
- shortness of breath management strategies
- exercise advice/physical exercise
- sniffs and vocal fricatives
- inhaler advice
- relaxation

6.2.3. Measures

In line with the normal clinical procedures, each child and family completed quality of life (QOL) and symptom questionnaires at the start of treatment (time point 1), at the end of the course of treatment (time point 2) and six months after the completion of treatment (time point 3) as shown in Figure 13.

Quality of life was measured using the Pediatric quality of life inventory (PedsQL), parent proxy and child report versions, (172, 181) and symptoms using the Nijmegen questionnaire (NQ) (77, 182). Both of these measures are described in detail in Chapter 2. The questionnaires for the first two time points were completed in the clinic environment and the six month follow-up questionnaires were posted out (with a stamped addressed envelope to optimise return rate). No contact was had with the children or their families between time points 2 and 3.

Age, gender and presence/absence of a co-morbidity was also recorded.

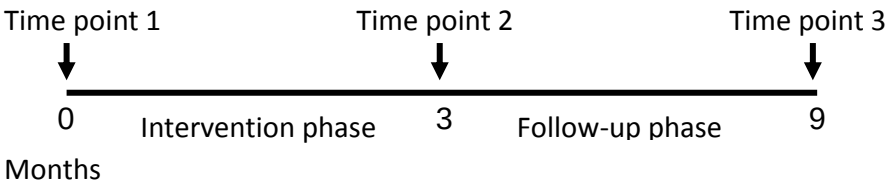


Figure 13: Study timeline illustrating time points and study phases

6.2.4. Data analysis

Study data are presented as median and interquartile range to allow for some data not being normally distributed.

The Wilcoxon signed rank test was used to compare data where only information from time points 1 and 2 were available. In the cases where data was available from all three time points, the Freidman's test followed by Dunn's test was employed. The decision was made to use nonparametric tests for all data sets (including those that were normally distributed) to allow comparison of the various statistical analyses.

All statistical analysis was performed using GraphPad Prism 6.02 (GraphPad Software Inc, San Diego, USA) and statistical significance was accepted as $p<0.05$.

6.3. Results

Of the 36 children referred to BreathWorks during the study period, two were excluded due to the presence of obliterative bronchiolitis (OB), as little is known about the relationship or interaction between DB and OB. Eleven children either did not complete the intervention, or the second questionnaires, and a further 10 children did not return the final questionnaires.

This left 23 sets of data that were analysed by Wilcoxon signed rank test and 13 sets for analysis using the Freidman's test (Figure 14).

Twelve of the 23 children included at time point 2 were girls (52%) and the cohort mean ± SD age was 13.43 ± 2.11 years. The mean number of interventions received was four over an average period of three months and 14 of these children had a recognised co-morbidity, e.g. asthma. The symptom score as measured by the Nijmegen questionnaire reduced in 91% (21/23) of the subjects, when comparing scores before and after the intervention (time point 1 to time point 2). For the same time period, child-reported QOL improved in 91% of the children and an improvement in the child's QOL was reported by 100% of the parents/guardians. These differences were all significant with $p<0.0001$ (see Table 13).

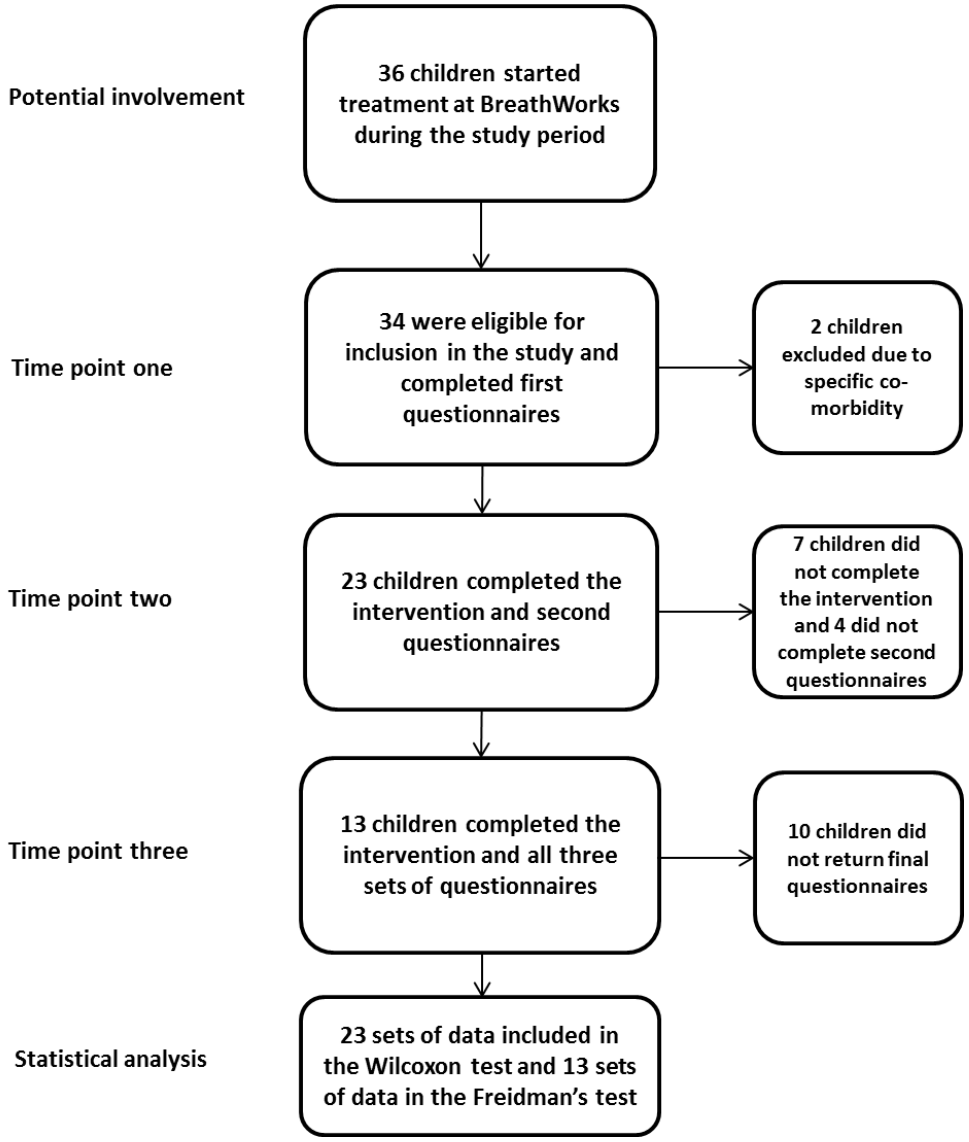


Figure 14: Flow diagram showing participant involvement at different stages of the study

Table 13: Comparison between the measures at time points 1 and 2

	Time point 1	Time point 2	P value
PedsQL child (n=23)	70.60 (55.40-77.10)	84.70 (75.00-90.20)	<0.0001
PedsQL parent (n=23)	58.60 (50.00-67.30)	82.60 (72.80-90.20)	<0.0001
NQ (n=23)	25.00 (18.00-32.00)	12.00 (8.00-17.00)	<0.0001

Data from the 13 children who completed all three sets of questionnaires showed that, whilst there was a significant difference in scores between time points 1 and 2 ($p<0.003$), there was no significant difference in the same scores (NQ, PedsQL child and PedsQL

parent) between time points 2 and time points 3 ($p>0.05$). There was also therefore a significant difference in scores between time points 1 and 3 ($p<0.05$). Figure 15 shows summary data for each measure at each of the three time points.

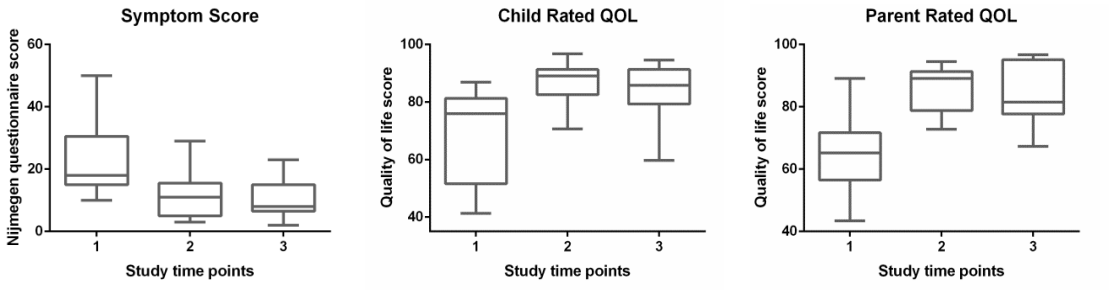


Figure 15: Box and whisker plots of the measures at each time point

6.4. Discussion

This study is the first to specifically investigate the short and medium term outcomes of breathing retraining for children with dysfunctional breathing. The results demonstrate that both quality of life and symptom scores are significantly improved following the intervention, and that this improvement is maintained for at least six months after the course of treatment has ended.

The observational nature of the study, however, has an impact on the strength of the study findings and consequent recommendations.

The lack of a control group means that it is not known what the outcome for these children would have been had they not been exposed to the intervention, i.e. the natural course of the condition. Older studies into hyperventilation syndrome in children and adolescents show that, where no intervention was given apart from reassurance, symptoms persisted in 40% of cases into adulthood (103). In comparison to this, the current study indicates that the outcomes following active intervention are much improved. Holloway and West (2007) carried out a RCT in adults with DB (97) which compared breathing retraining to no intervention and the findings of this study also support the use of breathing retraining with statistically significant improvements seen in quality of life and Nijmegen score. The lack of follow-up past six months in the current study, however, leads to a lack of knowledge of the long term outcomes following breathing retraining for dysfunctional breathing in children. A longitudinal study would be required to investigate the long term outcomes of this treatment approach.

Due to the small sample size, there is a risk of overestimating the effect size or the reproducibility of results (212). The very small p values ($p<0.0001$) however support the likelihood of it being acceptable to reject the null hypothesis that a structured but individualised program of physiotherapy interventions does not improve clinical outcomes and quality of life for young people with dysfunctional breathing. Conversely, the large p values for the difference in means for measures between time points two and three

indicate that the null hypothesis for maintenance of effect could also be rejected even in the face of small sample size.

The questionnaires were administered following the standard format for the clinic; the first two administrations were carried out in the clinic setting and the third by postal survey. There are some weaknesses in this approach when used as a basis for research. The clinic administered questionnaires are supervised by the therapist. This potentially introduces an element of bias as the therapist could influence the child or parent/guardian responses. The third questionnaire should be free from bias, as it was completed unsupervised in the patients home, however there was a relatively low return rate, leading to fewer data being available for analysis of outcomes at the six month time point (time point 3). In reality, the return rate for this study was 57% which is higher than average for this type of short survey (213). Measures such as addressing questionnaire cover letters personally and including stamped addressed return envelopes were taken to optimise the response rate, but this may have been further improved by the offer of incentives or sending the questionnaires recorded delivery (214).

Both parent proxy and child report versions of the Pediatric quality of life inventory (PedsQL) were used as measures of the child's quality of life. Study data shows (see Table 13) that parents consistently rated the QOL of their child to be poorer than the child themselves reported. Whilst parents were specifically asked to rate the child's QOL, it is possible that parents, either consciously or subconsciously, took into account the affect the child's condition had on themselves and/or the wider family leading to a lower score. The impact of DB on parents and family is currently unknown but could be investigated through the use of the PedsQL Family Impact Module.

There are also more global issues related to the study of dysfunctional breathing. As highlighted in previous chapters, dysfunctional breathing is currently diagnosed based on clinical experience and by exclusion/optimal management of co-morbidities. There is no specific diagnostic tool with which to identify dysfunctional breathing (either in adults or children), which may lead to heterogeneity in study populations and affect the ability to apply findings to a wider population.

The relative newness of dysfunctional breathing as an accepted condition also leads to a lack of condition-specific validated outcome measures. The generic scales of the PedsQL were chosen as they are well validated (172, 181), but no validated measure of symptoms is available. The Nijmegen questionnaire (NQ) was chosen as the most suitable alternative, but it is important to recognise that it has been used in this context purely as a symptom scoring tool, rather than the indicator of hyperventilation syndrome that it was originally designed to be (77, 182).

Future studies investigating interventions for dysfunctional breathing would need to take all of the above identified limitations into consideration. Larger, multi centre trials are required where the diagnosis of DB is based on criteria that can be consistently applied at the different centres. The design will need to include a control group to allow the natural course of the condition to be identified and compared with the outcome following intervention. Longer term follow-up of participants will provide information on the

longevity of improvements with intervention but will need to be assessed using measures that are appropriate for a variety of age groups.

6.5. Conclusion

Overall, this study indicates that breathing retraining, as a key part of physiotherapy intervention, offers a positive benefit to children both in terms of quality of life and symptoms experienced.

It supports the need for well-designed prospective clinical trials to investigate the short, medium and long term effects of this intervention, with a view to optimising treatment and ameliorating the significant morbidity experienced by children with dysfunctional breathing.

7. Conclusions and future work

This final chapter will draw together the key points and conclusions from the preceding chapters to give a succinct overview of what has been learned about dysfunctional breathing from these studies, and how this information compares with previous work. It will also make suggestions on which lines of research need to be developed further and highlight where new research opportunities lie.

7.1. Key findings

This thesis, and the current and subsequent papers derived from it, progresses our knowledge and understanding about the overall management of dysfunctional breathing (DB). This can broadly be divided into two areas; technological advancements in the assessment and diagnosis of DB, and breathing retraining as a therapeutic approach to the amelioration of symptoms. Table 14 highlights the key findings of the thesis which are discussed in more detail below.

Table 14: Key findings of the thesis

	Key finding
1.	SLP can be used to measure breathing patterns in children with or without a respiratory condition but further work is required before adoption into routine clinical practice
2.	RSA is a valid approach to the non-invasive diagnosis of pVCD, but new technology needs to be developed to allow this to happen
3.	Breathing retraining offers significant positive benefits in terms of symptoms and quality of life to children with DB, both in the short term and for up to at least six months following completion of treatment

7.1.1. Technological advancements

The studies presented in Chapters 3 and 4 investigated whether structured light plethysmography (SLP) and respiratory sound analysis (RSA) could be used, respectively, for the objective assessment of breathing patterns in children with both forms of DB and the non-invasive diagnosis of paradoxical vocal cord dysfunction (pVCD). It was demonstrated that testing using both technologies can practically be performed in children of the age group investigated (8-16 years), who either had DB or were healthy. 100% tolerance was achieved with no tests in either study failing to be completed for this reason. Neither technology has previously been used before with this, nor a similar, population and hence no comparison data for tolerance is available.

The exception to this successful application of technology, however, was the portable form of RSA, the WheezoMeter. Participants attempted to make recordings but very little usable data was obtained. It has not been possible to discover the reason for this failure of the equipment to record data, as a similar situation occurred when the equipment was replaced. It is possible that the size and shape of the children's neck/throat may have been

incompatible with the WheezoMeter, even though it was designed for use with children. The WheezoMeter is subsequently being removed from the market and replaced with the analogue SonoSentry™ and the digital, smartphone-based AirSonea™ devices (215).

Investigating applications of existing technologies and developing new technologies can bring significant benefits. Prior to these studies, there was no comprehensive method for objectively measuring breathing pattern, either in children with DB or any other respiratory condition. Although SLP was originally developed for the measurement of lung function, we have investigated the application of this technology for quantifying breathing patterns in children. We have found that SLP, using the Thora3Di device, can be used to measure breathing patterns in children with or without a respiratory condition. The additional benefits of using this method, apart from providing a range of measured parameters (RR, Ti, Te, IE ratio, OP, PA, Spr and BP), are its acceptability to the patient (as discussed above), ease of use and speed of use. Our technical failure rate, which could be improved upon, was 3%. Tests that can be carried out in a short period of time are important for all patient groups, but particularly in paediatrics where concentration spans can be limited. Additional benefits of using SLP are that, due to the non-invasive nature of the technology (using ordinary light), breathing pattern changes caused by testing are less likely and the test can be repeated as often as required. This allows SLP to be used as an outcome measure of change as well as a more diagnostic assessment.

This study did, however, highlight that further development of how SLP is used is needed before it is ready to be implemented in routine clinical practice. The Thora3Di has built-in calibration (removing the need for this), but a robust protocol for achieving reliable results has yet to be developed. Differences in the length of capture, and which breaths are chosen from the capture for analysis, lead to differences in the product of the resultant breathing pattern analysis. Validation will be challenging, however, as there is no gold standard to use for this process. Furthermore, the system relies on participants to be wearing an appropriately-fitted t-shirt and for the light levels in the room to be suitably dim. If the t-shirt is either too loose or too tight, wrinkles are formed in the fabric of the shirt, leading to a recording failure. The Thora3Di has become more tolerant of higher light levels as it has developed, but ideally needs to be able to function well regardless of the level of ambient light. The system also currently requires the subject to be still which limits the applications of the test.

As with SLP, the results of the study into RSA for the diagnosis of pVCD (presented in Chapter 4) promise future benefits for patients. The current gold standard technique for the diagnosis of pVCD, nasendoscopy, is highly invasive and challenging for children to cope with. The procedure can be uncomfortable and there is a reasonable risk that children may refuse to take part. It also needs to be performed by an experienced person in an appropriate environment. RSA is minimally invasive, with the current technology only requiring sensors to be temporarily attached to the skin using specially designed stickers and an elastic belt to be placed around the chest. The two additional sensors are a minimal addition to the 10 electrocardiogram (ECG) electrodes that are required for the safe performance of an exercise test. Whilst the RSA test is no quicker than the current

alternative, it can be performed by a wider range of staff and the equipment required is significantly less expensive than the cost of a nasendoscope.

Our study found that, in principle, RSA could be used for the non-invasive diagnosis of pVCD, but not using the technology that is currently available. The PulmoTrack was unable to distinguish between ambient sounds emanating from the patient and those truly recorded from the environment. This situation is manageable in the assessment of asthma-related wheeze, where the sounds are generated in the small airways, but not for pVCD, where there can be significant audible upper airway induced stridor. Technological developments would need to overcome this problem before further progress can be made using RSA as a diagnostic technique.

7.1.2. Breathing retraining

The systematic review presented in Chapter 5 clearly demonstrated the lack of evidence to support or refute the use of breathing retraining for the treatment of dysfunctional breathing in children. However, clinicians involved in the management of this condition witness the benefits of breathing retraining experienced by the children and their families, and it was these clinical experiences that highlighted the need to investigate this therapy. The study presented in Chapter 6 set out to explore whether a structured, but individualised, program of physiotherapy interventions (with breathing retraining as the key intervention) would improve clinical outcomes and quality of life for young people with dysfunctional breathing. It also aimed to investigate whether any improvements achieved would be maintained following cessation of treatment. The study found that breathing retraining offers positive benefits in terms of symptoms and quality of life to children with DB, both immediately following the completion of the intervention and up to at least six months later.

7.1.2.1. Benefits to patients

The work described in Chapter 6 shows that breathing retraining promises to offer an effective long term solution to dysfunctional breathing that places the control of the condition with the child and family, empowering them to manage symptoms should they reoccur in the future. Clinically, families report a reduction or removal of the need for inhaled medication, however it was not possible to investigate changes in medication as part of this study due to the small numbers. What was clear, though, was the practical implications of the reported improvements in symptoms and quality of life; children and their families have been able to resume normal family life, whether that be sporting activities, musical hobbies or just being able to walk to school.

7.1.2.2. Benefits to health care services

Currently, there are very few services offering treatment to children with dysfunctional breathing nationally. This may be partially due to the difficulties in diagnosing the condition, but will almost certainly be due to the lack of data to support the commissioning of such services. Studies such as this one provide the beginnings of the evidence required for the provision of specialist breathing retraining services for children.

As it stands, without access to these services, many patients are reduced to repeat attendances to their general practitioner (GP) or hospital clinic, where they are prescribed increasing and inappropriate doses of, primarily, inhaled medications in a vain attempt to control symptoms. Breathing retraining, as a non-pharmacological long-term solution, should decrease the pressure on health service resources as the need for unnecessary prescriptions and repeat attendances is removed.

In addition to this, the study findings support clinicians to offer breathing retraining as a treatment option, promote such services and to get involved with future research projects to further define the benefits of breathing retraining.

7.2. Study limitations

Whilst these studies represent significant developments in the field of dysfunctional breathing, there are limitations that need be acknowledged to avoid overstatement of the study findings.

Primarily, the numbers of participants studied were small, affecting the power of the studies, and the study designs were pragmatic. The approach taken combined routine clinical visits/procedures with research activities, in an effort to reduce the burden of participating in research on the participants and their families. Whilst the pragmatic study design allowed recruitment targets to be met, this has implications for the outcome of the studies. An example of this can be seen in the SLP study of Chapter 3. A higher than anticipated number of children clinically required nasendoscopy post exercise test, resulting in very small numbers of SLP scans being available for analysis at this time point in the study. The limited number of children with DB available within the study timescale prevented the inclusion of further participants. Conclusions could therefore not be drawn about breathing pattern changes post exercise, either within or between groups.

7.3. Future research and developments

The studies presented in this thesis progress the field of dysfunctional breathing, but also generate many new questions which need to be answered. A cohesive research strategy uniting the strands detailed below is required to further the understanding, diagnosis and management of dysfunctional breathing in children.

Themes for further investigation that have emerged from the work of this thesis include;

- the need for a functional definition of DB and a tool/s to enable accurate diagnosis
- the use of continuous laryngoscopy during exercise (CLE) testing to improve the diagnosis of ET-DB
- the use of RSA to supersede the nasendoscopic diagnosis of ET-DB
- the further development of SLP as an assessment tool for both types of DB
- the controlled evaluation of breathing retraining as a treatment technique.

7.3.1. Definition and diagnosis

An important consideration for all current and future studies is the means of diagnosing dysfunctional breathing. Extra thoracic dysfunctional breathing (ET-DB) can be confirmed using nasendoscopy, but thoracic dysfunctional breathing (T-DB) is currently diagnosed based on exclusion/optimisation of co-morbidities combined with expert history taking. An alternative to this, 'clinical diagnosis with favorable outcome with care', has been used in other studies (184, 185) but the subjective nature of the diagnosis remains a problem. For large scale or multi centre studies to be performed in any of the aspects of DB being investigated, a diagnostic tool or objective measure of T-DB needs to be developed, to allow patients to be identified in a standardised manner. This would require the condition to be better characterised and consensus to be reached on what constitutes dysfunctional breathing.

Progress can be made in this area through the organisation of national conferences bringing professionals interested in DB together to discuss and debate the issues. Work has been started on this with the organisation of the 1st and 2nd Sheffield Dysfunctional Breathing Conferences and will continue at this year's forthcoming 3rd event. These events also foster relationships which will allow future collaborations to take place. A prime example of such collaboration would be in the use of the Delphi technique to formulate and agree a definition for dysfunctional breathing. The Delphi technique is commonly used to establish a consensus on a complex problem whilst allowing all voices in the process to be heard equally and without risk of derision or ridicule. This approach would be suitable as there are many factors that will need to be taken into account when agreeing a definition of DB, for example the differences in presentation of the condition depending on whether the individual is a child or an adult.

Once a clear definition and appropriate diagnostic tool becomes available for DB it becomes possible to establish the prevalence of the condition in the paediatric population. This is important as it is currently not known how many children and young people are affected or the true level of morbidity associated with DB. Knowledge of the true prevalence and impact of the condition will also aid the success of future research funding applications as it will enable the economic cost of the condition to be understood and the value of effective assessment tools and interventions to be calculated.

7.3.2. CLE testing

A limitation identified in Chapter 4 was the weakness of the gold standard method, nasendoscopy, to accurately diagnose pVCD when used pre and post exercise test. The visual abnormal vocal cord motion can subside very quickly, meaning that the lack of abnormality seen on post test nasendoscopy can realistically be a false negative (rather than a true absence of the condition).

Inconclusive diagnosis is very frustrating for both patients and clinicians and the problem could be solved using continuous laryngoscopy during exercise (CLE) testing. CLE testing is currently performed in a single centre with adults in the UK, but has yet to be investigated as a procedure in children in the UK. Some children aged 14 years and above have been

involved in studies of CLE in Norway and Denmark but separate paediatric data is not presented and younger children have not been investigated (82, 86).

Development of this technique will involve the innovation of a new device needed to mount the scope on a child followed by studies to investigate the feasibility of the technique and its validity and reliability. The first stage of this program has been completed at Sheffield Children's Hospital, in collaboration with the University of Sheffield, resulting in technical proof of principle and a concept prototype. An application to fund the next stage of the program has been made by a collaborative team from Sheffield Children's Hospital, the University of Sheffield and Design Futures (Sheffield Hallam University). This collaboration brings together clinical, engineering and design expertise and plans to realise the aim of creating a fully functioning device that will enable the accurate diagnosis of pVCD in children within the next two years.

7.3.3. Respiratory sound analysis

Whilst the development of paediatric CLE testing will improve the diagnostic capabilities of nasendoscopy for ET-DB, it remains an invasive procedure with all its associated problems (as discussed in Chapters 1 and 4). Respiratory sound analysis offers a potentially viable, non-invasive alternative (where modern technology using multiple micro sensors at the throat could triangulate sounds from the upper airway). Patterns of sound could then be compared between groups of healthy individuals and those with a variety of fixed or dynamic upper airway abnormalities, including pVCD, and validated by correlation studies using nasendoscopy. As well as being non-invasive, this approach could provide continuous data during exercise and the technology required to perform the sound analysis could easily be wireless. Wireless technology would allow future testing to be performed in a sport or environment specific setting, which would enhance the reproducibility of symptoms.

The primary problem to overcome will be the elimination of background noise and this should be possible using advanced signal separation techniques. A multidisciplinary project team with members from the NHS, higher education institutions (HEIs) and the HEI/industry interface has been formed and a cohesive research strategy for investigating this technique, with both children and adults, has been developed. Preliminary work is already underway investigating the hardware/software requirements for such an acoustic based device as well the development of methods for translating visual images into signals that can be compared directly with sound signals. Successful development of this signal translation technique will allow the new non-invasive acoustic device to be compared in the clinical environment with the gold standard CLE test.

7.3.4. Structured light plethysmography

Structured light plethysmography has been shown to have significant potential for the objective measurement of breathing patterns, but improvements need to be made both in the technology itself and in how the technique is applied.

Testing using SLP is currently limited to situations where the patient can remain static for the duration of the capture. As the symptoms of DB are frequently experienced during exercise or activity, it would be beneficial to be able to monitor the breathing pattern in these situations (when symptoms are maximal and hence breathing pattern is most likely to be abnormal). Significant advancements will need to be made to the Thora3Di technology to allow measurements to be taken whilst a patient has a degree of movement, as, currently, a static reference is required to allow the parameters of respiration to be calculated.

In the shorter term, however, studies are required to investigate the optimal length of capture period to generate reliable breathing pattern data from SLP. It is estimated that capture duration of three minutes is required, but this needs to be investigated in both healthy subjects and those with breathing disorders. This is a relatively simple process and we have incorporated it into the design of future studies.

An equally simple but larger undertaking is the need to create comprehensive paediatric reference data for SLP parameters (as discussed in Chapter 3). This study would involve large numbers of children, who would ideally be tested in the school environment to enable this scale of testing to be performed. The requirement for each child to be provided with a fresh, white, sports top for testing, however, makes large scale testing more challenging in terms of the expense involved in an otherwise economical study.

Once reliable reference data has been obtained, SLP can be used both as an initial assessment tool and as an outcome measure to monitor progress in the treatment of dysfunctional breathing.

7.3.5. Breathing retraining

More robust evidence for the treatment of DB needs to be generated. A multi-centre controlled trial is required to investigate the efficacy of breathing retraining for dysfunctional breathing on a larger scale. The design of this study would need to include a control group, as it is currently not known what the natural course of the condition is without intervention. It would also need to investigate changes in medication use and, potentially, with greater numbers involved, could investigate whether the benefits of breathing retraining vary depending on whether a patient has T-DB or ET-DB

The involvement of a control group for such a study, however, is challenging particularly in geographic areas where breathing retraining has become the accepted treatment of choice and is offered as normal routine clinical care. In this situation, randomising children to either a treatment or control group involves withholding treatment for a period of time for those allocated to the control group. Alternative study designs need to be considered to avoid this ethical dilemma. It is not possible to carry out crossover design studies where breathing retraining is the intervention due to the purported long term effects of the intervention and inability to 'unlearn' the breathing techniques. The solution identified in Sheffield for this problem is for participants to act as their own control whilst on the waiting list for treatment. This allows the natural course of the condition to be investigated without the need to deliberately withhold intervention.

Funding has been secured to carry out a feasibility study for a multi-centre controlled trial designed to investigate whether physiotherapy improves outcomes for children with dysfunctional breathing; an important step towards providing robust and clinically useful evidence.

7.4. Final conclusion

Dysfunctional breathing is common, frequently unrecognised and responsible for a substantial burden of morbidity. Interest has grown in this condition, particularly in paediatrics, primarily due to frustration when misdiagnosis results in lack of health improvement. There is an increasing demand for evidence based healthcare from diagnosis through to treatment. The studies that constitute this thesis provide a foundation for the development of this evidence base and provide recommendations for future work.

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Appendices

1. Summary of the Papworth method (Holloway and West, 2007)

The PM integrates five components, the principal one being specific breathing training:

- Breathing training, including teaching of appropriate minute and tidal volume and the development of a pattern of breathing suitable to current metabolic activity. Elimination of dysfunctional breathing, including hyperinflation and hyperventilation patterns is discussed. A specific Papworth method diaphragmatic breathing technique is taught to replace the use of inappropriate accessory muscles of respiration.[5 22] Emphasis, when relaxed, is placed on calm slow nasal expiration. Patients are encouraged to "nose-breathe" rather than "mouth-breathe" and eradication or reduction of habits such as yawning, sighing, etc is taught and practised.
- Education, with the emphasis on the recognition and physical management of stress responses and specifically the interaction with breathing patterns.
- Relaxation training, specific and general.
- Integration of "appropriate" breathing and relaxation techniques into daily living activities. Initially the techniques are taught in a semi-recumbent position progressing to sitting, then standing and during daily living activities. Finally, the integration of breathing and relaxation techniques into speech is taught and practised.
- Home exercises with an audiotape or CD containing reminders of the breathing and relaxation techniques are supplied at the third treatment. Encouragement is given to practise at least once a day with the tape.

2. PedsQL administration guidelines

The following guidelines are intended for use by individuals trained in the administration of standardized questionnaires. The PedsQL™ administrator is crucial in developing rapport with the respondents, emphasizing the importance of the questionnaire, addressing concerns, and ensuring that the PedsQL™ is completed accurately and confidentially.

General Protocol

1. Create a procedure for assigning identification numbers that will allow for parent/child
   comparisons as well as comparisons of baseline/follow-up data.
2. If feasible, the PedsQL™ should be completed *before* the respondents complete any other health data forms and *before* they see their physician or healthcare provider.
3. The parent/child should first complete the PedsQL™ Generic Core Scales and then complete any additional PedsQL™ Module.
4. Parents, Children (8-12) and Teens (13-18) may self-administer the PedsQL™ after introductory instructions from the administrator. If the administrator determines that the child or teen is unable to self-administer the PedsQL™ (e.g., due to illness, fatigue, reading difficulties), the PedsQL™ should be read aloud to the child or teen. For the Young Child (5-7), the PedsQL™ should be administered by reading the instructions and each item to the young child word for word. At the beginning of each subscale repeat the recall interval instructions (one month or 7 days) to remind the young child to respond only for that specific recall interval. Use the separate page with the three faces response choices to help the young child understand how to answer. When reading items aloud to a child, intonation should be kept neutral to avoid suggesting an answer.
5. If a child has difficulty understanding the age-appropriate PedsQL™, the preceding age group version may be administered to the child (e.g., administering the Young Child (5-7) Self-Report version with the three faces response choices to an 8 year old). However, if a child presents with severe cognitive impairments (as determined by the administrator), the PedsQL™ may not be appropriate for that child. In such cases, only the Parent-Proxy Report should be administered to the child's parent.
6. The parent and child must complete the questionnaires *independently* of one another. Discourage the parent, child, or other family members from consulting with one another during the completion of the questionnaire. Let them know that they can feel free to discuss their answers following completion of the questionnaires, but that it is important to get both the parent's and the child's *individual* perspectives. If you are administering the questionnaire to the child, the child should be facing away from the parent.
7. If the child or parent has a question about what an item means or how they should answer it, do not interpret the question for them. Repeat the item to them verbatim. Ask them to answer the item according to what *they think the question means*. If they have trouble deciding on an answer, ask them to choose the response that comes closest to how they feel. The child and/or the parent has the option of not answering a question if they truly do not understand the question.

8. If a parent/child asks you to interpret the responses, tell her/him that you are not trained to interpret or provide a score for the answers given. If the PedsQL™ is being used for a clinical study, let the parent/child know that their answers will be combined with other participants' answers and analyzed as a group rather than as individual respondents.
9. Document all reasons for refusals and non-completions of the PedsQL™.

Administering the PedsQL™

1. The following scripts have been developed as a guide to introduce the PedsQL™ to the child and his/her parent(s). Modify the language to a style that is most appropriate for you and the respondent.

   For the child:

   The PedsQL™ asks you questions about how you feel and what you think about your health. It is not a test, and there are no right or wrong answers. It takes about 5 minutes to complete. If you have any questions, please let me know.

   For the parent:

   The PedsQL™ is a questionnaire that assesses health-related quality of life in children and adolescents. It contains questions about your child's physical, emotional, social, and school functioning ***in the past one month (****or for the Acute version****, in the past 7 days)****.*

   The PedsQL™ is brief and typically takes less than 5 minutes to complete. It is not a test, and there are no right or wrong answers. Please be sure to read the instructions carefully and choose the response that is the closest to how you truly feel. Please do not compare your answers with your child's responses. We are interested in your and your child's ***individual*** *perspectives. However, feel free to discuss the questionnaire with your child* ***after*** *you have both completed it and returned it to me. If you have any questions, please let me know.*

2. Provide the respondent with a pen or pencil and a solid writing surface. If a table is not available, the participant should be provided with an item such as a clipboard. Remain nearby should questions or concerns arise.
3. When the parent/child returns the PedsQL™, look it over and check to see that all answers have been completed. Verify that no item has more than one response. If any responses are incomplete, illegible, or there are multiple responses for an item, please ask the parent or child to indicate their response.
4. Ask the participants if they had any difficulties completing the questionnaire or if they have any other comments regarding the questionnaire. Document any important feedback.
5. Thank the parent and child for taking the time to complete the questionnaire. If the study design involves following up with these respondents, let them know that they may be asked to complete the PedsQL™ again at another time. Indicate when they can expect to be contacted again if known.

3. PedsQL scoring system

Item Scaling	5-point Likert scale from 0 (Never) to 4 (Almost always) 3-point scale: 0 (Not at all), 2 (Sometimes) and 4 (A lot) for the Young Child (ages 5-7) child report
Weighting of Items	No
Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100
Scoring Procedure	**Step 1: Transform Score** Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1-75, 2=50, 3=25, 4=0 **Step 2: calculate Scores** Score by Dimensions: • If more than 50% of the items in the scale are missing, the scale scores should not be computed • Mean score=Sum of the items over the number of items answered Psychosocial Health Summary score = Sum of the items over the number of items answered in the Emotional, Social and School Functioning Scales. Physical Health Summary Score = Physical Functioning Scale Score **Total score:** Sum of all the items over the number of items answered on all the Scales.
Interpretation and Analysis of Missing Data	If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: Impute the mean of the completed items in a scale.

4. Nijmegen questionnaire

Please ring the score that best describes the frequency with which you experience the symptoms listed below:

	Never	Seldom	Some-times	Often	Very Often
Chest pain	0	1	2	3	4
Feeling tense	0	1	2	3	4
Blurred vision	0	1	2	3	4
Dizziness	0	1	2	3	4
Confusion or loss of touch with reality	0	1	2	3	4
Fast or deep breathing	0	1	2	3	4
Shortness of breath	0	1	2	3	4
Tightness across chest	0	1	2	3	4
Bloated sensation in stomach	0	1	2	3	4
Tingling in fingers and hands	0	1	2	3	4
Difficulty in breathing or taking a deep breath	0	1	2	3	4
Stiffness or cramps in fingers and hands	0	1	2	3	4
Tightness around the mouth	0	1	2	3	4
Cold hands or feet	0	1	2	3	4
Palpitations in the chest	0	1	2	3	4
Anxiety	0	1	2	3	4

5. Self evaluation of breathing questionnaire (SEBQ)

Order	Item	Never	Occasionally	Frequently	Very frequently
1	I get easily breathless out of proportion to my fitness.	0	1	2	3
2	I notice myself breathing shallowly.	0	1	2	3
3	I get short of breath reading and talking.	0	1	2	3
4	I sigh yawn or gasp.	0	1	2	3
5	I feel I cannot get a deep or satisfying breath.	0	1	2	3
6	I notice myself breathing irregularly.	0	1	2	3
7	My breathing feels stuck or restricted.	0	1	2	3
8	My ribcage feels tight and can't expand.	0	1	2	3
9	I notice myself breathing quickly.	0	1	2	3
10	My clothing feels tight and uncomfortable around my chest.	0	1	2	3
11	I get breathless when I am anxious.	0	1	2	3
12	I find myself holding my breath.	0	1	2	3
13	I feel breathless in association with other physical symptoms.	0	1	2	3
14	I have trouble co-ordinating my breathing when I am speaking.	0	1	2	3
15	I can't catch my breath.	0	1	2	3
16	I feel that the air is stuffy, as if not enough air in the room.	0	1	2	3
17	I get breathless even when I am resting.	0	1	2	3

6. Respiratory screening questionnaire

Sheffield Children's NHS
NHS Foundation Trust

Study number:

Non-invasive assessment of dysfunctional Breathing in children
Respiratory Screening Questionnaire

Complete this questionnaire by putting a ring around the answer you want to choose. If you don't understand any of the questions, please ask for them to be explained.

Have you ever been told by a doctor that you have asthma?

Yes/No

Have you been given inhalers or 'puffers' to take for your chest?

Yes/No

Have you had an unexplained cough, wheeze or shortness of breath when exercising in the last 6 months?

Yes/No

7. Standard operating procedures for exercise testing

STANDARD OPERATING PROCEDURE FOR:

Exercise Testing

Referral

Requests for this test must come from a consultant or have been reviewed by a respiratory consultant.

The consultant may have already determined which exercise protocol is appropriate and if test to be performed on or off treatment.

Roles

Respiratory consultant/registrar and physiologist required to perform this test.

Clinician

- explains test to patient
- obtains relevant patient history prior to testing
- operates JLab software (treadmill) during testing
- monitors ECG during testing
- determines start and end of test
- completes Exercise Test Pro Forma pre, during and post test

Physiologist

- Prepares all testing equipment & software ready for testing
- Explain test to patient with regards to the protocol to be used, ie. Gradient & speed increments etc
- Performs spirometry
- Sets up ECG
- Encourages patient throughout procedure
- Ensures patient safety at all times throughout procedure

Equipment required

- Treadmill
- JLab system
- *Masimo* Oximeter
- Spirometer
- Stadiometer
- Weighing scales
- Exercise Report sheets
- ECG components
- Salbutamol + Space device
- Stop Clock

Pre test preparation

Treadmill

- Press button at rear of device, on right hand side to switch ON

JLab system

- Boot up the software
- Allow 15 minutes to fully warm up
- If an error message pops up relating to 'Bicycle Init Failed' – click to ignore this if you are doing a test that requires treadmill only. If you are doing a CPET, the bicycle must be switched on (in which case you don't get the 'Bicycle Init Failed' message).
- Ensure System Check is OK
- Once System Check complete it should bring up JLab automatically

Ensure all equipment, eg Spirometer, is calibrated as per the Quality Control SOP.

Contraindications

- If the patient is from a respiratory referral the baseline FEV_1 must be >75% predicted.
    - If the patient is usually below this value and an exercise test is required, the referring consultant should specifically record that they have acknowledged this and still wish the exercise test to occur.
    - If the patient on the day has an FEV_1 <75% but are usually above this value, the exercise test should not go ahead.

Testing

Measure patient height and weight.

Perform spirometry

- Obtain baseline FEV_1, FVC as per the guidelines for Spirometry. Check *Contraindications*.

Attach 12 lead ECG to patient as per Lab guidelines

Prepare Treadmill

- If the patient is of a height that they cannot hold on to the treadmill handlebar suitably then attach the portable handlebar (located at the front of the treadmill). Use Allen key to tighten the bar to the treadmill.

JLab software

- Click on 'Patient Data'
- Type the patient's surname, then first name and Identification (ID number without the C – e.g. C123456 would just be 123456). Then press the tab button on keyboard.

- If the patient has performed the test before, the rest of the information should become automatically populated. If the patient has not done the test before, manually enter their date of birth and select whether they are Male or Female.
- You will also need to input the patient's height and weight (once they have been measured).
- Press F12 to exit to main module selection screen

Pre Exercise

Instruct patient to stand on the treadmill.

Connect ECG control cable to ECG signal box.

Attach the Radical oximetry probe to patient finger. Ensure patient does not grip onto handlebar too tight.

Provide patient with general safety advice regarding treadmill.

- Hold on to bars but not lean on them
- Avoid looking down at feet, or behind.
- Stay in the middle of the treadmill track
- Keep straight posture whilst treadmill moving
- Ensure oximetry/ECG cables do not cause trip hazard
- Ensure patient shoelaces do not cause trip hazard

Test

Operator to Click on 'Stress ECG' and then select the required exercise protocol.

IMPORTANT: If the last test performed was on the Bike and you need the Treadmill (or vice versa) you will need to select the other modality. You can do this in 'Stress ECG' by selecting 'Setup' icon on the right hand side (the icon looks like some dials). When this opens, select 'Protocol Editor' tab and then select the Treadmill or Bicycle, i.e. testing method you want to use.

Bruce Sheff

- Automated by software.
- Increments gradient and speed every three minutes. Exercise until patient cannot continue. Ie too breathless/leg fatigue

Bronchoprov

- Automated for first minute then manually controlled by operator thereafter.
- First minute gradual exercise and automated.
- During the second minute clinician and physiologist manually change the speed/gradient to achieve maximal BPM for patient. Ie. 180-190. NB: Increasing gradient, rather than speed is regarded as a more practical and successful method of achieving higher levels of BPM in most patients.
- The following 6 minutes should attain a BPM of 180-190 for patient, which can be achieved by the operator adjusting gradient & speed accordingly.

Houlsby

- Automated.
- Gradient and speed are increased every 2 minutes automatically by software.
- Patient encouraged to continue to exercise until they stop due to breathlessness/leg fatigue.
- NB: This protocol commonly used if patient is likely to be unable to endure the 'Bronchoprov' protocol, ie particularly the younger or unsteady patients.

Patient is continually motivated during the exercise phase of the test. In the case of the Houlsby and Bruce protocol, they are encouraged to exercise for as long as they can until:

- They can no longer exercise due to breathing
- They can no longer exercise due to leg fatigue
- Clinician decides to terminate exercise phase
-

Upon termination of the treadmill movement the patient should sit down on chair which the physiologist places behind them. Allow at least 2 minutes of recovery time or until HR has returned to acceptable rate.

End of Test

Detach ECG cable from ECG box. Detach oximeter probe from finger.

Start stop clock.

Perform post exercise spirometry post exercise at the required intervals.

Check the post exercise FEV1 change from baseline by selecting the 'Exercise SP' template in SentrySuite. Inform clinician of this.

If drop of 15% or more from baseline then administer Salbutamol via MDI and volumatic spacer. Repeat blows after 15 minutes to ensure return to baseline.

Completion of test

Detach ECG stickers and ECG connection box from patient.

Allow time for patient to completely recover before leaving hospital premises.

Print out spirometry baseline results and the 'Exercise SP' report. File along with completed 'exercise report' proformas.

Clean equipment, return to usual place.

Last Modified: [15/01/2014]

Authors: Karen O'Donnell, Royston Andrew

8. Database search strategies

8.1. CENTRAL search strategy

#1 MeSH descriptor: [Hyperventilation] explode all trees

#2 hyperventilat*

#3 MeSH descriptor: [Respiration Disorders] this term only

#4 (breath* or respirat*) near/5 (dysregul* or dysfunction*)

#5 over-breath* or overbreath* or "over breath*"

#6 air* near/3 hunger*

#7 MeSH descriptor: [Panic Disorder] explode all trees

#8 panic* near/3 (attack* or disorder*)

#9 {or #1-#8}

#10 MeSH descriptor: [Breathing Exercises] this term only

#11 (breath*) near/3 (exercis* or retrain* or train*)

#12 buteyko*

#13 diaphragm* near/3 breath*

#14 breath* near/3 control*

#15 relax* near/3 breath*

#16 tidal* near/3 breath*

#17 MeSH descriptor: [Respiratory Therapy] explode all trees

#18 physiotherap*

#19 "physical therapy"

#20 yawn*

#21 sigh*

#22 {or #10-#21}

#23 #9 and #22

#24 MeSH descriptor: [Child] explode all trees

#25 MeSH descriptor: [Infant] explode all trees

#26 MeSH descriptor: [Adolescent] explode all trees

#27 MeSH descriptor: [Pediatrics] explode all trees

#28 paediatric* or paediatric* or child* or adolescen* or infant* or young* or preschool* or pre-school* or newborn* or new-born* or neonat* or neo-nat*

#29 {or #24-#28}

#30 #23 and #29

8.2. MEDLINE (Ovid) search strategy

1. exp Hyperventilation/

2. hyperventilat$.ti,ab.

3. Respiration Disorders/

4. ((breath$ or respirat$) adj5 (dysregul$ or dysfunction$)).ti,ab.

5. over$breath$.ti,ab.

6. (air adj3 hunger).ti,ab.

7. Panic Disorder/

8. (panic adj3 (attack$ or disorder$)).ti,ab.

9. or/1-8

10. Breathing Exercises/

11. (breath$ adj3 (exercis$ or retrain$)).ti,ab.

12. buteyko.ti,ab.

13. (diaphragm$ adj3 breath$).ti,ab.

14. (breath$ adj3 control$).ti,ab.

15. (relax$ adj3 breath$).ti,ab.

16. tidal breath$.ti,ab.

17. Respiratory therapy/

18. physiotherap$.ti,ab.

19. physical therapy.ti,ab.

20. yawn.ti,ab.

21. sigh.ti,ab.

22. or/10-21

23. 9 and 22

24. exp Child/

25. exp Pediatrics/

26. exp infant/

27. exp adolescent/

28. (paediatric$ or paediatric$ or child$ or adolescen$ or infant$ or young$ or preschool$ or pre-school$ or newborn$ or new-born$ or neonat$ or neo-nat$).tw.

29. or/24-28

30. 23 and 29

31. (clinical trial or controlled clinical trial or randomised controlled trial).pt.

32. (randomised or randomised).ab,ti.

33. placebo.ab,ti.

34. dt.fs.

35. randomly.ab,ti.

36. trial.ab,ti.

37. groups.ab,ti.

38. or/31-37

39. Animals/

40. Humans/

41. 39 not (39 and 40)

42. 38 not 41

43. 30 and 42

8.3. EMBASE (Ovid) search strategy

1. exp hyperventilation/

2. hyperventilat$.ti,ab.

3. breathing disorder/

4. ((breath$ or respirat$) adj5 (dysregul$ or dysfunction$)).ti,ab.

5. over$breath$.ti,ab.

6. (air adj3 hunger).ti,ab.

7. exp panic/

8. (panic adj3 (attack$ or disorder$)).ti,ab.

9. or/1-8

10. breathing exercise/

11. (breath$ adj3 (exercis$ or retrain$)).ti,ab.

12. buteyko.ti,ab.

13. (diaphragm$ adj3 breath$).ti,ab.

14. (breath$ adj3 control$).ti,ab.

15. (relax$ adj3 breath$).ti,ab.

16. tidal breath$.ti,ab.

17. respiration control/

18. physiotherap$.ti,ab.

19. physical therapy.ti,ab.

20. exp physiotherapy/

21. yawn.ti,ab.

22. sigh.ti,ab.

23. or/10-22

24. 9 and 23

25. child/

26. infant/

27. adolescent/

28. exp pediatrics/

29. (paediatric$ or paediatric$ or child$ or adolescen$ or infant$ or young$ or preschool$ or pre-school$ or newborn$ or new-born$ or neonat$ or neo-nat$).tw.

30. or/25-29

31. 24 and 30

32. Randomized Controlled Trial/

33. randomisation/

34. Controlled Study/

35. Clinical Trial/

36. controlled clinical trial/

37. Double Blind Procedure/

38. Single Blind Procedure/

39. Crossover Procedure/

40. or/32-39

41. (clinica$ adj3 trial$).mp.

42. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).mp.

43. exp Placebo/

44. placebo$.mp.

45. random$.mp.

46. ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).mp.

47. (crossover$ or cross-over$).mp.

48. or/41-47

49. 40 or 48

50. exp ANIMAL/

51. Nonhuman/

52. Human/

53. 50 or 51

54. 53 not 52

55. 49 not 54

56. 31 and 55

8.4. PsycINFO (Ovid) search strategy

1. exp hyperventilation/

2. hyperventilat$.ti,ab.

3. ((breath$ or respirat$) adj5 (dysregul$ or dysfunction$ or disorder$)).ti,ab.

4. over$breath$.ti,ab.

5. (air adj3 hunger).ti,ab.

6. exp panic disorder/

7. exp panic attack/

8. exp Panic/

9. (panic adj3 (attack$ or disorder$)).ti,ab.

10. or/1-9

11. (breath$ adj3 (exercis$ or retrain$or technique$)).ti,ab.

12. buteyko.ti,ab.

13. (diaphragm$ adj3 breath$).ti,ab.

14. (breath$ adj3 control$).ti,ab.

15. (relax$ adj3 breath$).ti,ab.

16. tidal breath$.ti,ab.

17. exp physical therapy/

18. physiotherap$.ti,ab.

19. physical therapy.ti,ab.

20. exp yawning/

21. yawn.ti,ab.

22. sigh.ti,ab.

23. or/11-22

24. 10 and 23

25. exp pediatrics/

26. (paediatric$ or paediatric$ or child$ or adolescen$ or infant$ or young$ or preschool$ or pre-school$ or newborn$ or new-born$ or neonat$ or neo-nat$).tw.

27. 25 or 26

28. 24 and 27

8.5. CINAHL (EBSCO) search strategy

S1 (MH "Hyperventilation+")

S2 hyperventilat*

S3 (MH "Respiration Disorders")

S4 (breath* or respirat*) N5 (dysregul* or dysfunction* or disorder*)

S5 over* N1 breath*

S6 air* N3 hunger*

S7 (MH "Panic Disorder")

S8 (MH "Breath Holding Attacks")

S9 panic* N3 (attack* or disorder*)

S10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9

S11 (MH "Breathing Exercises")

S12 breath* N3 (exercis* or retrain* or technique*)

S13 buteyko*

S14 diaphragm* N3 breath*

S15 breath* N3 control*

S16 relax* N3 breath*

S17 tidal* N1 breath*

S18 (MH "Respiratory Therapy")

S19 (MH "Physical Therapy+")

S20 physiotherap*

S21 "physical therap*"

S22 (MH "Yawning")

S23 yawn* or sigh*

S24 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23

S25 S10 AND S24

S26 (MH "Child")

S27 (MH "Adolescence")

S28 (MH "Pediatrics")

S29 paediatric* or paediatric* or child* or adolescen* or infant* or young* or preschool* or pre-school* or newborn* or new-born* or neonat* or neo-nat*

S30 S26 OR S27 OR S28 OR S29

S31 S25 AND S30

S32 (MH "Clinical Trials+")

S33 random*

S34 placebo*

S35 clinical* N3 (trial* or study or studies)

S36 (single* or double* or triple*) and blind*

S37 S32 OR S33 OR S34 OR S35 OR S36

S38 S31 AND S37

8.6. AMED (EBSCO) search strategy

S1 (DE "HYPERVENTILATION")

S2 hyperventilat*

S3 (breath* or respirat*) N5 (dysregul* or dysfunction* or disorder*)

S4 over* N1 breath*

S5 air* N3 hunger*

S6 panic* N3 disorder*

S7 panic* N3 attack*

S8 S1 or S2 or S3 or S4 or S5 or S6 or S7

S9 (DE "BREATHING EXERCISES") OR (DE "BREATHING THERAPIES")

S10 breath* and (exercis* or retrain* or train* OR technique*)

S11 buteyko*

S12 diaphragm* N3 breath*

S13 breath* N3 control*

S14 relax* N3 breath*

S15 tidal* N3 breath*

S16 physiotherap*

S17 "physical therapy"

S18 (DE "PHYSIOTHERAPY")

S19 yawn*

S20 sigh*

S21 S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20

S22 S8 and S21

S23 (DE "CLINICAL TRIALS")

S24 (DE "RANDOMIZED CONTROLLED TRIALS")

S25 randomised or randomised

S26 placebo

S27 randomly

S28 clinical* and (trial* or study or studies)

S29 (single* or double* or triple*) and blind*

S30 S23 or S24 or S25 or S26 or S27 or S28 or S29

S31 S22 and S30

S32 (DE "PEDIATRICS")

S33 (DE "CHILD")

S34 (DE "INFANT")

S35 (DE "ADOLESCENT")

S36 paediatric* or paediatric* or child* or adolescen* or infant* or young* or preschool* or pre-school* or newborn* or new-born* or neonat* or neo-nat*

S37 S32 OR S33 OR S34 OR S35 OR S36

S38 S31 AND S37

8.7. LILACS search strategy

(hyperventilat* or hiperventilación or hiperventilação or "Respiration Disorders" or "Trastornos Respiratorios" or "Transtornos Respiratórios" or ((breath*) and (dysfunction* or dysregulat* or disorder*)) or over-breath* or "over breath*" or air-hunger or "air hunger" or panic or Pánico or Pânico) and (((breath*) and (exercis* or retrain* or technique* or control* or relax* or diaphragm* or tidal*)) or "Ejercicios Respiratorios" or "Exercícios Respiratórios" or buteyko* or yawn* or sigh* or "Respiratory Therapy" or "Terapia Respiratoria" or "Terapia Respiratória" or physiotherap* or "physical therapy" or Fisioterapia) and (random* or aleatoria or "Ensayo Clínico" or "Ensaio Clínico" or estudio or estudios or trial)

9. Characteristics of excluded studies

Study	Reason for exclusion
de Groot 2011	Review article rather than a controlled trial
Han 1996	Prospective cohort study examining the effect of breathing retraining on 92 adults with hyperventilation syndrome. The study was not a controlled trial and did not include children
Kraft 1984	Controlled trial in 40 adults examining which of 4 therapeutic interventions could be considered the most effective treatment for hyperventilation syndrome. A control group was present but no participants were under the age of 18 years
Monday 1995	Randomised controlled trial in 18 participants with chronic hyperventilation syndrome comparing 3 non-pharmaceutical approaches to treatment. The study contained only 1 participant under the age of 18 years and the control group received verbal education on breathing techniques and therefore could not be considered a true control group
Stanton 2008	Prospective cohort study in 102 people aged 13.5 to 83 with asthma, examining the effect of breathing control therapy on Nijmegen and Mini-AQLQ scores as well as parameters measured by progressive exercise testing. The comparison group differed by more than 1 variable; participants were deemed not to have dysfunctional breathing and did not receive breathing control therapy
Thomas 2003	Randomised controlled trial comparing breathing retraining with asthma education in 33 people with asthma and dysfunctional breathing. Patients aged 17 years and above were screened for the study but no paediatric data were included