University of Kent | School of Sport and Exercise Sciences

DIFFERENT APPROACHES TO IDENTIFYING DYSFUNCTIONAL BREATHING (DB) IN ATHLETES

The thesis is presented for the degree of Doctor of Philosophy at the University of Kent

by

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DECLARATION

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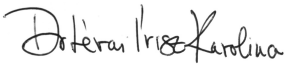
Signature:  Date: 29/09/2017

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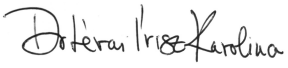
Signature:  Date: 29/09/2017

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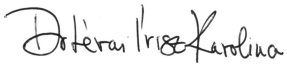
Signature:  Date: 29/09/2017

This thesis was supervised by *Dr John Dickinson* (School of Sport and Exercise Sciences, University of Kent), *Dr James Hull* (Department of Respiratory Medicine, Royal Brompton Hospital) and *Prof Greg Whyte* (Research Institute for Sport and Exercise Sciences, Liverpool James Moore University).

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It is common knowledge that getting a PhD is hard work and ridiculously difficult at times. It needs passion and patience. Nobody expects an easy ride.

The best way I can describe the past four years of my PhD journey is by comparing it to the first half-marathon I recently ran. I have been enjoying a nice jog in the mountains or alongside the beach, but running 21 km had been completely out of my comfort zone, it was definitely not something I would have ever considered enjoyable. I knew the race was going to be exhausting and tough, but the excitement of both the unknown and the completion of a such a big challenge had encouraged me deeply. As well as the picture in my head of me crossing the finish line. During the race, just like during the PhD, I tried to focus on how far I have come, rather than how far I have left to go. The only driver in the whole process was self-motivation: the motivation to begin; the motivation to continue; the motivation never to quit. The motivation that at times was incredibly hard to maintain.

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“Eventually all things fall into place. Until then, laugh at the confusion, live for the moments, and know EVERYTHING HAPPENS FOR A REASON.” (Albert Schweitzer)

ABSTRACT

Perceived exertional dyspnoea is reported to be the most common symptom among physically active individuals of all abilities and ages and/or performance in high level athletes, potentially impacting on performance and limiting enjoyment of sporting activities. Identifying the causes of the perceived symptoms requires careful assessment with a wide range of factors potentially contributing to the reported respiratory issues. The purpose of this thesis was to investigate different assessment approaches in the identification of breathing dysfunction in exercising adults.

Elite swimming and boxing require athletes to achieve relatively high minute ventilation. In Chapter 4 (Study 1 of this thesis), thirty-eight elite boxers and 44 elite swimmers completed a thorough respiratory assessment that revealed a nine-fold greater prevalence of exercise-induced bronchoconstriction in swimmers when compared with boxers. These results suggested that the combination of a sustained high ventilation and provocative training environment may impact the susceptibility of athletes to this condition.

Dysfunctional breathing may mimic and/or co-exist with exercise-induced bronchoconstriction. The use of specific questionnaires may improve the identification of this condition in athletes. In Chapter 5 (Study 2 of this thesis), 9% of the 428 healthy, physically active young adults who completed the Nijmegen Questionnaire had a score ≥ 23, suggestive of a dysfunctional breathing status. A separate cohort of 104 athletes underwent an indirect bronchoprovocation challenge and completed the Nijmegen questionnaire. The sensitivity, specificity, positive and negative predicted values suggested that the Nijmegen score was a poor predictor of a positive bronchoprovocation

challenge in athletes and therefore is not suitable to detect dysfunctional breathing in athletes.

The posture an athlete holds during exercise may alter breathing pattern and increase reported exercise induced respiratory symptoms. In order to investigate whether respiratory parameters are affected by different postural positions, in Chapter 6 (Study 3 of this thesis), 15 healthy male athletes performed a 10-minute, high intensity cycling test with normal shoulder position and with hunched shoulders. Results of this study showed that cycling with hunched shoulders at high intensities over a prolonged period leads to an increase in perceived dyspnoea and suggested that posture may contribute to reports of respiratory symptoms during exercise in the absence of cardio-pulmonary disease.

With the aim of investigating the effect of different postural positions on the ventilatory excursion, in Chapter 7 (Study 4 of this thesis), 15 healthy male athletes performed baseline spirometric measurements and 10-minutes cycling challenges with normal shoulder position and with hunched shoulders, while undergoing simultaneous data collection with optoelectronic plethysmography. The findings of this study suggested that respiratory excursion and lung volume compartmentalisation at both rest and during high intensity exercise are affected by the position of the shoulders.

In conclusion, athletes who train and compete in provocative environments at a sustained high ventilation have an increased susceptibility to airway dysfunction. No existing questionnaire is sensitive enough to identify dysfunctional breathing and differentiate it from other respiratory conditions, such as exercise-induced bronchoconstriction. Exercising for a prolonged period at high intensities with hunched shoulders triggers

increased abdominal contribution to vital capacity and a subsequent increase in perception of breathing sensation without a significant effect on physiological markers of respiratory function.

Further investigations should be undertaken in order to develop a new questionnaire that is more suitable for an athletic population and has higher accuracy in identifying symptoms associated with exercise induced breathing impairment. Precise detection of distortions between compartmental contributions in exercising individuals may play an important role in the differential diagnosis of dysfunctional breathing.

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ABBREVIATIONS

AB	Abdominal
AFB	Acid-fast bacillus
ANOVA	Analysis of variance
ARTP	Association for Respiratory Technology and Physiology
ASL	Airway surface liquid
ATS	American Thoracic Society
BbB	Breath-by-breath
BF	Breathing frequency
BHT	Breath holding time
BPD	Breathing pattern disorder
BTS	British Thoracic Society
°C	Celsius degree
C	Condition
CLE	Continuous laryngoscopy exercise
cm	Centimetre
CNS	Central nervous system
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
DB	Dysfunctional breathing
Dx	Previous diagnosis
E	Exercise phase
ECCS	European Community for Coal and Steel
EFL	Expiratory flow limitation

EIB	Exercise-induced bronchoconstriction
EIIS	Exercise-induced inspiratory symptoms
EILO	Exercise-induced laryngeal obstruction
EMG	Electromyography
EMGdi	Diaphragm electromyogram
ERS	European Respiratory Society
$ETCO_2$	End-tidal carbon dioxide
EVH	Eucapnic voluntary hyperpnoea
F	F-distribution (F-test)
FeNO	Fraction of exhaled nitric oxide
FET	Forced expiratory time
FEV_1	Forced expiratory volume in one second
FEV_1/FVC	FEV_1:FVC ratio
FSP	Forward shoulder position
FVC	Forced vital capacity
GB	Great British
GP	General practitioner
HR	Heart rate
HR_{peak}	Peak heart rate
HR_{max}	Maximum heart rate
HVS	Hyperventilation syndrome
IBM	International Business Machines
IR	Infra-red
kg	Kilogram
KMO	Kaiser-Meyer-Olkin

L	Litre
L/min	Litre per minute
La	Lactate
LNN	Lower limit of normal
LR	Likelihood ratio
m	Metre
MARM	Manual assessment of respiratory motion
min	Minutes
mg/l	Milligram per litre
MIP	Maximal inspiratory pressure
ml/min	Millilitres per minute
ml/kg/min	Millilitres per kilogram of body weight per minute
mmol/L	Millimoles per litre
MUAP	Motor-unit action potential
MVV	Maximal voluntary ventilation
N	Number
N_2	Nitrogen
NPV	Negative predicted value
NQ	Nijmegen Questionnaire
O_2	Oxygen
OEP	Optoelectronic plethysmography
p	Significance level
PAP	Peak aerobic power
PCA	Principal component analysis
PEF	Peak expiratory flow

ppb	Particles per billion
PPV	Positive predicted value
r	Reliability coefficient
RC	Rib cage
RCa	Abdominal rib cage
RCp	Pulmonary rib cage
RER	Respiratory exchange ratio
RIP	Respiratory induction plethysmography
RPE	Perceived exertion
RPM	Revolutions per minute
SD	Standard deviation
SEBQ	Self-Evaluation of Breathing Questionnaire
SEM	Mean standard error
SLP	Structured light plethysmography
SPSS	Statistical package for social sciences
TB	Tuberculosis
TiTo	Ratio between inspiratory time and total breath time
TLC	Total Lung Capacity
UK	United Kingdom
USA	United States of America
$\dot{V}_E$	Minute ventilation
$\dot{V}CO_2$	Carbon dioxide production
$\dot{V}O_2$	Oxygen consumption
$\dot{V}O_{2\ peak}$	Peak oxygen consumption
vs.	versus

VT	Tidal volume
W	Watts
WR	Work rate
X^2	Chi-squared
yr	Year(s)
β_2	Beta-2
ε	Degrees of freedom
µl	Microlitre
µm	Micrometre

Chapter 1. Introduction

1.1 Introduction

The health benefits of regular exercise and physical activity are well known, however frequent, repeated periods of high minute ventilation ($\dot{V}_E$) in certain environmental conditions might be disadvantageous to an individual's respiratory health (Hull et al., 2012). Respiratory symptoms (e.g. breathlessness, phlegm production, wheeze and cough) are common in athletes of all abilities. Turcotte et al. (2003) showed that one in four athletes has complaints of regular, troublesome respiratory symptoms. Moreover, primary care physicians in the UK see dyspnoeic athletes at a frequency of approximately one case per calendar month (Hull et al., 2012).

Many factors can limit pulmonary performance and produce symptoms of respiratory discomfort (Bussotti et al., 2014), the pathogenesis of which, is still not clearly understood. Currently, in the lack of objective, gold standard diagnostic methods and algorithms, diagnosis is often made solely on the basis of complaints and previous medical history alone. Moreover, the subjectivity of symptoms makes it difficult for the physicians to accurately identify and judge the severity of the underlying condition(s). These factors may contribute to a potential diagnostic delay and a possible failure to determine the specific cause of respiratory dysfunction, especially in those individuals whose symptoms are multifactorial.

In the absence of extensive differential diagnostic tools, healthcare professionals face with a major challenge when attempting to distinguish among the perception of symptoms that fall within a spectrum of what could be considered a normal physiological response to intense exercise (Hull et al., 2012), those indicating underlying cardiorespiratory

pathology and complaints linked to a non-pathological and/or non-organic problem or other contributing factors.

In healthy humans the structural characteristics of the respiratory muscles and the neural control of breathing are almost ideally designed and regulated to meet the demands for increased ventilation during exercise (Aliverti et al., 1997). However, although maximal expiratory flow rates are usually greater than the spontaneous flow rates reached during maximal exercise, endurance trained individuals with high maximal exercise ventilation may develop expiratory flow limitation (EFL) alongside a series of secondary manifestations such as dyspnoea, hypercapnia and consequent exercise limitation. Increased work of breathing during heavy sustained exercise may encroach on the capacity of the respiratory system by placing a load on the respiratory muscles (Harms et al., 2000, Dempsey et al., 2008). Fatigue of these muscles, particularly of the diaphragm, can have a vasoconstrictor effect on limb muscle vasculature compromising locomotory muscle blood flow, O_2 uptake and the overall performance (Bussotti et al., 2014, Dempsey et al., 2008, Harms et al., 1997).

Breathlessness is a complex set of symptoms that are often related to the strength or intensity of the sensation (sensory component) and how unpleasant the sensation feels (emotional component). Both components are influenced by the changes in ventilation, but they may operate independently (Faull et al., 2016). Moderate to severe breathlessness is well-recognised as a normal sensation during intense exercise in otherwise healthy individuals (Borg et al., 2010, Hamilton et al., 1996). The sensation of "being out of breath" is usually considered non-threatening due to precise matching between expectation and the actual ventilatory response to heavy exercise (Faull et al., 2016).

However, the increase in respiratory work may be perceived abnormal by those who experience discomfort and find that it limits their ability to perform to their expectations. It has been suggested that the affective components of breathlessness and the resultant anxiety when nearing maximal ventilation may be a key factor within the complex limitations of athletic performance in those, who are highly-trained (Faull et al., 2016, Harms et al., 1997, Harms et al., 2000). There might be an exaggerated perception of the intensity of breathlessness in individuals who, addition to the high levels of anxiety, experience multiple somatic complaints due to underlying pathological cardiorespiratory problems or non-organic issues.

Exercise-induced bronchoconstriction (EIB) is a common diagnosis in active individuals with complaints of dyspnoea, fatigue or poorer than usual performance during exercise (Smoliga et al., 2016). The occurrence of EIB is independent of age and fitness level and has a prevalence rate of about 10 to > 50% or greater in competitive athletes (Johansson et al., 2015, Parsons & Mastronarde, 2005). Exercise-respiratory symptoms such as cough, wheeze and chest tightness, however are not exclusive to only EIB; they can also be associated with exercise-induced laryngeal obstruction (EILO), hyperventilation syndrome (HVS) and dysfunctional breathing (DB) (Boulding et al., 2016). Although there exist well established guidelines for the diagnosis and management of EIB, due to the non-specific nature of the signs and symptoms, and the lack of gold standards to differentiate among the aforementioned conditions, it is frequently misdiagnosed in clinical practice (Smoliga et al., 2016) and as a consequence the underlying condition remain unrecognised and untreated.

Previous researches (Rundell et al., 2001, Parsons et al., 2011, Weiler et al., 2014, Simpson et al., 2015) have shown that the diagnosis of exercise-induced airway dysfunction using self-reported symptoms leads to a significant number of false-positive (17 - 39%) and false-negative rates (12 - 15%) (Rupp et al., 1992, Rupp et al., 1993) and such self-reports do not correlate with changes in airway calibre in athletes with EIB (Simpson et al., 2015). These findings highlight the importance of recognising the poor predictive value of symptoms and suggest to avoid basing a diagnosis on the evaluation of clinical features alone in order to protect athletes from the continuation or progression of symptoms. That could potentially lead to impaired performance and/or discontinuation of sport (Weiler et al., 2014).

Accurate identification of the causative factors contributing to the exercise-respiratory symptoms is crucial in order to ensure that optimum care is delivered to this specific population. This thesis therefore will attempt to investigate various diagnostic methods that would assist practitioners in identifying and differentiating between pathological and non-pathological causes and contributing factors of breathing dysfunction.

Specifically, investigations will be undertaken in order to explore whether environmental factors would affect the prevalence of airway dysfunction in high level sports and if the Nijmegen questionnaire is sensitive enough to distinguish between EIB and DB. It will also aim to study whether breath-by-breath analysis and/or optoelectronic plethysmography can detect physiological changes, if there exists any, when body position is altered during exercise.

In this current thesis, the term “physically active individual” will be used to describe those who exercise at least two times a week, a “recreational athlete” is somebody who exercises 2-5 times a week and competes regularly at regional and/or national level and “elite athletes” are those individuals who train 5-7 days a week, compete regularly in national and international competitions and are part of an elite sport squad.

Chapter 2. Literature review

2.1. Background

The act of breathing is unique in that it is considered as the only vital function that can be under both automatic and voluntary control (Gilbert, 1999, Butler, 2007, American Thoracic Society, 1999). It is regulated not only by automatic centres located in the brainstem, but also by sleep-wake cycles, environmental, emotional and volitional signals initiated in the cortex (Butler, 2007). The automatic and voluntary control nature of breathing is advantageous; enables complex and precise changes in breathing when speaking, eating or breath holding (Butler, 2007). Although most of the time individuals are unaware of their breathing, changes in the natural process of respiration due to physiological or psychological factors can affect an individual's sense of well-being (Gilbert, 1999).

Breathing is dependent upon the coordinated efforts of the breathing muscles (Benditt, 2006) and alterations in their function may reduce the effectiveness of ventilation (Ratnovsky et al., 2008). Posture, as a component of any position and every movement of locomotion, is considered to be an active, central nervous system (CNS) controlled maintenance of body segments against the action of external forces, from which gravity has the greatest impact (Chiba et al., 2016). Although the major function of the respiratory muscles is to contribute to inhalation and exhalation, they are also actively involved in postural movements of the torso (Butler, 2007). Disruption in one of these functions could negatively affect the other (Hodges et al., 2007) and as a consequence, individuals with poor posture may exhibit signs of faulty breathing mechanics in the absence of underlying cardio-respiratory diseases.

Breathing can be considered as an independent variable that affects emotion, cognition and behaviour, but also as a dependent variable that reflects changes in these parameters (Ley, 1994). Conscious or unconscious changes in breathing can affect both our feelings and thoughts. For example, breathing intensifies when an increased metabolic demand occurs (e.g. in exercise) but also due to an emotional impact (e.g. anger, fear or anxiety) (Ley, 1994). For instance, excessive breathing with an upper chest breathing pattern can be triggered by an acute stress reaction (e.g. anxiety) and generate unpleasant sensations such as dyspnoea, pain or chest tightness (Gilbert, 1999).

2.2 Breathing pattern

In this thesis, the term "breathing pattern" will exclusively be referring to the relationship of the thoraco-abdominal compartments to each other during an individual's breathing without considering any other parameters such as breathing frequency (BF) or volume.

Konno and Mead (1967) previously described the chest wall as a system of two moving compartments (ribcage and abdomen) with only one degree of freedom each. They suggested that when known air volume is inhaled and measured with a spirometer, volume-motion relationship can be expressed as the sum of the abdominal and rib cage displacements (Konno & Mead, 1967). Although the Konno-Mead model has been integrated in most available technology that aims to assess chest wall movements, its major limitation is that it disregards the axial displacements of the torso associated with postural movements of the spine and pelvis and only considers changes in the antero-posterior diameter of the chest wall, meaning that valuable information of the respiration may not be assessed.

To date, there are no standardised reference values of respiratory movements available (Kaneko & Horie, 2012). Previous studies show a wide range of variation in the ribcage contribution to the movement in healthy individuals (Verschakelen & Demedts, 1995), depending on whether they were assessed in a supine (20 - 45%), sitting (40 - 70%) or standing (50 - 70%) position (Lumb & Nunn, 1991, Courtney et al., 2008, Sharp et al., 1975, Vellody et al., 1978). A limitation in most of these studies is that they do not specify whether the participants are using any support for their upper body at the time the breathing pattern is measured. When sitting or standing with support, the diaphragm can focus more on the breathing than on the postural function (Price et al., 2014a).

Ribcage motion may decrease with increasing age (Kaneko & Horie, 2012), however this does not appear to influence any other parameters of breathing (Verschakelen & Demedts, 1995, Sharp et al., 1975, Ragnarsdottir & Kristinsdottir, 2006). Similarly, some studies indicate that males have lower percentages of rib cage movement than females (Kaneko & Horie, 2012, Ragnarsdottir & Kristinsdottir, 2006, Romei et al., 2010), however respiration appears not to be affected by gender (Verschakelen & Demedts, 1995, Sharp et al., 1975). The discrepancies that pertain to the effects of body position, age and gender might be related to the type of measuring instrument used in different studies (Kaneko & Horie, 2012). Regardless, a deviation away from the breathing pattern that is optimal for the given individual can affect the pressure, ventilatory volumes, stability and ultimately the work of breathing. Barker & Everard (2015) have previously claimed that once the maladaptive pattern is established, the impaired breathing movement becomes habituated and thus a self-perpetuating entity. As a consequence, these individuals develop symptoms of dysfunctional breathing that, by being intermittently or in some cases constantly present, contribute to a negative impact on everyday life.

2.3 Dysfunctional breathing (DB)

2.3.1 Description and definition

Dysfunctional breathing is a term used to describe a variety of breathing disorders where an inefficient breathing pattern is adopted and often results in reports of respiratory symptoms (e.g. dyspnoea, wheeze and chest tightness) and non-respiratory symptoms (e.g. anxiety, lightheadedness and fatigue) (Boulding et al., 2016).

Normal breathing, also known as diaphragmatic breathing, involves synchronised motion of the upper rib cage, lower rib cage, and abdomen (Bradley & Esformes, 2014) and requires adequate use and functionality of the respiratory muscles (Pryor & Prasad, 2008). Conversely, breathing dominantly with the upper chest results in abnormal or so called thoracic breathing, that involves greater upper rib cage motion compared to the lower rib cage (Gilbert & Chaitow, 2002). It has been suggested that both physiological and psychological factors can cause prolonged changes and deviation from the normal breathing pattern (Tobin et al., 1983). If abnormal breathing patterns are retained after the exclusion or treatment of the conditions that may have initiated their occurrence, is considered a DB pattern (Courtney, 2009). The extent of upper chest dominant breathing seems to be an important cause of accompanying symptoms such as breathlessness, dyspnoea and chest tightness (Courtney et al., 2011b), the presence of which can result in anxiety that may provoke further breathing irregularity (Ley, 1994).

The abnormal afferent proprioceptive input associated with upper chest dominant breathing can directly result in the perception of respiratory symptoms (Howell, 1997,

Thomas & Bruton, 2014). One hypothesis is that sensations of breathlessness and dyspnoea arise from mismatch between the brain's movement control (motor output) and sensory system (sensory input) resulting in dissociations between what the brain expects and what it receives from receptors in the respiratory muscles (Laviolette et al., 2014). In addition, an upper chest breathing pattern is generally associated with dynamic hyperinflation (Barker & Everard, 2015, CliftonSmith & Rowley, 2011, Gardner, 1996), which, due to the increases in the elastic recoil of the lungs and the chest, alongside an often increased breathing rate, leads to larger respiratory work. These processes, by reducing the economy of movement (e.g. flattening the diaphragm and shortening the muscle fibres), cause biomechanical changes that negatively affect the respiratory muscles (Lumb, 2016). As a result, symptoms of breathlessness, dyspnoea and chest tightness can occur (Simon et al., 1989).

2.3.2 Prevalence

Boulding et al. (2016) has previously claimed that in the absence of established diagnostic criteria, it is not possible to accurately interpret the reports of DB incidence rates. Thomas et al. (2001, 2005) previously suggested that DB affects 29% of asthmatics and 8% of those without asthma. They merged these two datasets to estimate the prevalence of DB in the general population, which they calculated was 9.5% (Thomas et al., 2005). Gender differences have been documented in relation to DB, with a study showing that in a non-asthmatic population, 14% of women but only 2% of men have symptoms suggestive of DB (Thomas et al., 2001). These percentages are increased among asthmatic adults with an incidence rate of 35% for women and 20% of men (Thomas et al., 2001), but remains similar in asthmatic children (13% females and 2% males)(de Groot et al., 2013).

2.3.3 Differential diagnosis of DB

Dysfunctional breathing can manifest alone or in association with other diseases (Courtney et al., 2011a). The symptoms of DB have similarities with other conditions such as hyperventilation syndrome (HVS), EIB and EILO (Table 2.1).

Table 2.1 Summary of the conditions that share symptoms with DB

	HVS (Gardner, 1996)	**EIB** (Hallstrand et al., 2013)	**EILO** (Røksund et al., 2016)
Presenting symptoms	• Breathlessness • Chest tightness • Dizziness • Light-headedness • Tingling sensation around mouth and in fingers	• Breathlessness • Chest tightness • Expiratory wheeze • Cough	• Breathlessness • Chest tightness • Throat tightness • Inspiratory stridor
Relation to exercise	Anytime during exercise	5-10 minutes after maximal exercise, peaks 5-20 minutes after stopping	Immediately with maximal exercise, resolves within 5 minutes of stopping
Suggestive mechanisms	Hemodynamic and chemical changes (e.g. decrease in $PaCO_2$) due to increased MVV.	Heat loss and consequent dehydration of the airways due to hyperventilation during exercise. Release of inflammatory mediators, along with airway dehydration, cause an exaggerated response that results in bronchoconstriction.	Airflow disturbance with laryngeal involvement, due to abnormalities of the epiglottis, the laryngeal cartilage-skeleton or its support, mucosal structures, muscular system or nerve supply. Various psychological characteristics (e.g. anxiety, depression and panic disorder) have been proposed to be implicated in this causal cascade.
Methods of diagnosis	Hyperventilation provocation test (HVPT)	(1) Vigorous exercise challenge test (2) Eucapnic voluntary hyperpnoea (EVH) challenge test (3) Mannitol dry powder test	Continuous laryngoscopy exercise (CLE) test

Due to the diversity of symptoms and clinical signs, patients with cardio-respiratory symptoms often undergo several investigations with negative results and remain undiagnosed (Jones et al., 2013). When screening for DB, it has been recommended to include biochemical measures (e.g. end tidal carbon dioxide ($ETCO_2$)), biomechanical measures (e.g. the evaluation of breathing pattern) and psychological features (e.g. the assessment of anxiety) as DB is proposed to have dimensions related to those functions of breathing (Courtney et al., 2011a, van Dixhoorn J, Folgering H., 2015). Respiratory symptoms and respiratory function should also be considered (Courtney et al., 2011a). All of the key diagnostic tests will be discussed in greater detail in Chapter 2.3.4 with regards to their clinical adequacy and limitations.

It is important to investigate whether DB occurs alone or in conjunction with other respiratory disorders, hence appropriate information and treatment can be provided. A clear link between DB and other respiratory diseases has not yet been described in the literature, however clinical studies suggest that a DB pattern does occur in patients with e.g. chronic obstructive pulmonary disease (COPD) and interstitial lung disease (Boulding et al., 2016). Nevertheless, the most widely recognised form of DB is HVS, which was first described over 70 years ago (Boulding et al., 2016, Kerr et al., 1938). This term is often also used synonymously with DB, whereas in fact it should be considered as a separate entity.

2.3.3.1 Hyperventilation syndrome (HVS)

Hyperventilation occurs when the rate and quantity of alveolar ventilation of carbon dioxide (CO_2) exceeds the body's metabolic requirements (i.e. CO_2 production) (Gardner,

1996) and results in hypocapnia. Hyperventilation is associated with an abnormality in respiratory control and may present with symptoms such as breathlessness, frequent sighing, dizziness, paraesthesia and palpitations (Kerr et al., 1938). The term "hyperventilation syndrome" was first used by Kerr et al. (1938) to describe patients with somatic symptoms of both hypocapnia and anxiety and the prevalence has previously been estimated to 6 - 10% (Lum, 1975).

Nevertheless, some symptoms associated with HVS have been shown to be unrelated to hypocapnia and may be due to other, rather psychological than physiological mechanisms (Courtney et al., 2011a, Howell, 1997, Hornsveld et al., 1996). Athletes, especially at elite levels, are typically exposed to a variety of stressors both in training and competition contexts and this might be the reason why they frequently experience symptoms of hyperventilation. High level athletes invest considerable time and effort in their sport and their performance may have profound consequences on their future career and life (Gustafsson et al., 2016, Conroy et al., 2001). As such, competitive athletes may perceive certain situations as threatening, challenging, or stressful (e.g., defeat, performance slumps, performing in a crucial competition) (Gustafsson et al., 2016), they often experience stress due to the pressure and challenges to win and progress (Conroy et al., 2007, Sagar et al., 2007, Sagar et al., 2010). Previous research has shown that fear of failure is related to anxiety and that psychological stress together with athletes "maladaptive coping responses to their fear of failure" might pose a risk of burnout (Gustafsson et al., 2016). It has also been proposed that high fear of failure is not only problematic when the athletes are young, but its impact can increase as the athletes get older (Conroy, 2001).

The term HVS has been used in so many different settings that its usefulness is questioned (Gardner, 1996). In a sport setting for example, the previously mentioned psychological factors can manifest hyperventilation as a symptom, however, it can also be an indirect response to the metabolic demands of exercise and therefore should not necessarily be considered as an abnormality.

2.3.3.1.1. Assessment for HVS

Hyperventilation syndrome can be assessed by a routine procedure called the hyperventilation provocation test (HVPT). The HVPT requires patients to voluntarily overbreathe for several minutes and is considered positive, if symptoms of HVS were reproducible (Boulding et al., 2016). Although it was previously assumed that HVPT, by inducing hypocapnia, reproduce hyperventilation symptoms, Hornsveld et al. (1996) showed that the mechanisms of most symptoms do not require a fall in PCO_2 and the attacks does not need to be associated with hypocapnia. These findings make the reliability of HVPT questionable.

2.3.3.2 Exercise-induced bronchoconstriction (EIB)

Exercise-induced bronchoconstriction is defined as a heterogeneous condition, usually characterised by a transient narrowing of the airways (Figure 2.1) that occurs in association with exercise and is reversible spontaneously or through the inhalation of β_2-agonists (Dickinson et al., 2006).

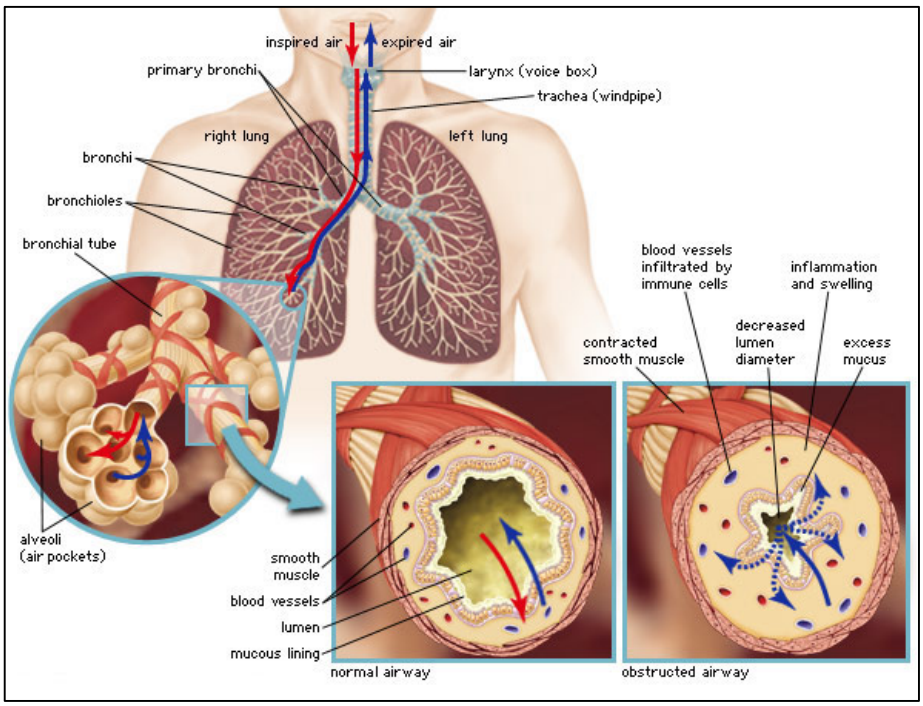

Figure 2.1 Anatomy of exercise-induced bronchoconstriction
Retrieved from: http://www.clivir.com/pictures/asthma/asthma_attack.jpg

Exercise induced bronchoconstriction has been estimated to occur in about 80-90% of asthmatics (Molphy et al., 2014). Respiratory symptoms and EIB are now recognised to be highly prevalent in certain groups of elite athletes (Price et al., 2013). Indeed, a greater prevalence of asthma related conditions has been reported in elite Great British athletes (21%) (Dickinson et al., 2005) when compared to the United Kingdom (UK) general population (approximately 10%) (National Asthma Campaign, 2001). This heightened prevalence of EIB in elite athletes (Dickinson et al., 2006, Dickinson et al., 2011) is thought to arise principally due to a combination of the deleterious impact of certain environmental exposures (e.g. pollution, swimming pool chemicals) and high ventilatory requirements necessitated by elite level sport (Dickinson et al., 2006, Bougault et al., 2009, Bougault & Boulet, 2012). Numerous studies have established a high prevalence of EIB in certain 'high-risk' sports, e.g. elite level swimming (41% - 55%) (Dickinson et al., 2005, Castricum et al., 2010).

The pathophysiology of EIB is not entirely understood, but it has been suggested that during strenuous exercise, hyperventilation and humidifying large volumes of unconditioned air to body temperature over a short period of time, causes a loss of heat (Anderson & Kippelen, 2005) and drying of the airways, leading to dehydration of the airway surface liquid (ASL) (Molis & Molis, 2010). Once the exercise is completed and ventilation returns to normal, airway cooling reverses as smaller bronchial vessels warm, creating a reactive hyperaemia (Anderson & Kippelen, 2005). This process triggers a cascade of events that includes (1) an increase in intracellular osmolarity, (2) initial water movement from the surrounding cells toward the airway lumen, (3) the shrinkage of subepithelial cells and (4) the release of bronchoconstrictive inflammatory mediators, including histamines, cytokines, and leukotrienes, among others (Hallstrand et al., 2013). These mediators, along with airway dehydration, cause an exaggerated response that results in bronchial smooth muscle contraction and consequently EIB (Hallstrand et al., 2013).

The water loss occurring at high ventilatory rates increases risk of airway inflammation and epithelial injury (Anderson & Kippelen, 2005). In the presence of allergenic stimulus, the repair mechanisms of the epithelium activate the airway smooth muscle, lead to alteration of their contractile properties causing hypersensitivity that can sustain a propensity to bronchoprovocation either during or following exercise (Anderson & Kippelen, 2008). A proposed mechanism underlying the relative high prevalence of EIB in athletes suggests repeated exposure to airborne irritants and sensitising agents (e.g. halocetic acids and trihalomethanes) that float just above the water surface can induce airway inflammation, smooth muscle hyperresponsiveness and remodelling processes that may lead to the development of asthma related conditions such as EIB (Bougault et

al., 2009, Bougault & Boulet, 2012).

Due to the similarities in symptoms, it is not uncommon that patients with DB are misdiagnosed and prescribed asthma medication unnecessarily (Lowhagen, 2005, Lowhagen, 1989, Marklund et al., 1999). It has been claimed by Ansley et al. (2012) that only half of the professional soccer players with a physician diagnosis of asthma/EIB had objective evidence of reversible bronchoconstriction. Rundell et al. (2001) demonstrated no association between the reporting of wheeze during usual training and the bronchial response to a sport/environment-specific field exercise challenge test; in approximately half of the athletes EIB did not explain the occurrence of symptoms. This underlines the importance of an objective bronchial challenge test to support a symptoms-based diagnosis of EIB in athletes prior to commencing pharmacological treatment.

2.3.3.2.1. Assessment for EIB

The assessment of EIB in athletes requires serial lung function measurements (e.g. FEV_1, FVC) before and after (1) vigorous exercise challenge test or a surrogate of exercise such as (2) eucapnic voluntary hyperpnoea (EVH) challenge or (3) mannitol dry powder test (Parsons et al., 2013, Anderson & Kippelen, 2012).

(1) The exercise challenge test involves a rapid increase in exercise intensity over about 2 to 4 minutes to achieve a high level of ventilation (for athletes $\dot{V}_E$ must be > 25 times the FEV_1) continued by exercise at that high level for an additional 4 to 6 minutes. Measurements of FEV_1 are made usually in duplicate at 3, 5, 10, 15, 20 and 30 minutes post exercise, and the higher of the two values is recorded. The criterion to diagnose EIB

using this assessment method is ≥ 10% fall in FEV_1 (Anderson & Kippelen, 2012).

When conducting on the field, monitoring the conditions (e.g. temperature, humidity) and having the right equipment available (e.g. spirometer, heart rate monitor) are challenging. In a laboratory setting, the greatest limitation is the wide variety of exercise protocols that are used, some of which are inadequate to provoke EIB. Due to the release of bronchodilation substances at low ventilation, exercise tests that start with a very low workload or uses a continuous increase in intensity for assessing maximum capacity may lead to false negative results (Anderson, 2011). Although a sports-specific exercise field test may simulate the exercise environment and demonstrate a reduction in airflow, due to its poor sensitivity for diagnosis and difficulty to perform reliably, this method of assessment has not been recommended as a first-line investigation in EIB (Dryden et al., 2010).

(2) Eucapnic voluntary hyperpnoea challenge is a 6-minute breathing test during which the individual inhales a dry gas containing, 21% O_2, 5% CO_2 and 74% nitrogen (N_2) at a ventilation equivalent to 30 times FEV_1 or more. After the test the lung function measurements are made at the same time interval as for exercise and a sustained ≥ 10% fall in FEV_1 is considered a positive test. This assessment method is said to be a surrogate for exercise, since the ventilation achieved voluntarily is higher than that achieved during maximum exercise, thus the rate of false-negative results is very low (Anderson & Kippelen, 2012).

(3) Dry powder mannitol inhalation increases the osmolarity of the airway surface and causes release of the same inflammatory mediators as exercise and EVH (Anderson &

Kippelen, 2012). The commercially available test kit contains pre-packed capsules containing 5, 10, 20 or 40 mg of mannitol and an inhaler device. The FEV_1 is measured in duplicate 60 seconds after each dose. A 15% fall in FEV_1 at ≤ 635 mg is considered a positive test result (Anderson & Kippelen, 2012).

Diagnosing asthma correctly requires detailed knowledge of the range of symptoms and the possible underlying conditions. This, however, does not seem to be the current practise. Some studies indicate that as many as one third of those with a diagnosis of asthma in developed countries do not actually have asthma (Marklund et al., 1999) and since there exist no validated protocols to confirm or exclude the condition in patients with previous physician diagnosis (that may or may not have been accurate), these patients may retain their "asthmatic status" for long years or in some cases for a lifetime (Luks et al., 2010). Inhaled corticosteroids (ICS), when properly used, improve quality of life and reduce the risk of asthma attacks and mortality. However, there is now evidence that they can cause mucosal immunosuppression and an increased risk of respiratory infections in adults. Additionally, the systemic absorption of ICS, and therefore the risk of developing side effects, is greater if the dose is inappropriately high for the degree of airway inflammation (Bush & Fleming, 2016).

On the other hand, a DB pattern such as dynamic hyperinflation without any bronchoconstriction has been proposed to be an important contributor to exaggerated dyspnoea in patients with asthma (Lougheed, 2007). Previous report (Marklund et al., 1999) showed that about 10% of patients diagnosed as asthmatics actually suffer from a "functional breathing disorder", which in the lack of diagnostic strategies may remain unrecognised and untreated.

2.3.3.3 Exercise-induced laryngeal obstruction (EILO)

Exercise-induced inspiratory symptoms (EIIS) may indicate an important differential diagnosis to EIB in otherwise healthy adolescents (Christopher & Morris, 2010, Roksund et al., 2009, Rundell & Spiering, 2003, Johansson et al., 2015). EIIS is most often linked to laryngeal abnormalities (Christopher & Morris, 2010, Roksund et al., 2009, Beaty et al., 1999, Bent III et al., 1996, Bittleman et al., 1994, Christensen et al., 2011, Dion et al., 2012) and if so, referred to as EILO (Dion et al., 2012, Hull et al., 2014, Christensen et al., 2015). Studies of athletes (Kenn & Balkissoon, 2011, Christensen et al., 2011) and of soldiers (Morris et al., 1999) in stressful situations have revealed high rates of EIIS. The magnitude of EILO has been addressed and objectivised in different ways, and the estimates therefore vary; however, in unselected populations EILO has been reported in 6 - 8% of adolescents (Johansson et al., 2015, Christensen et al., 2011).

Underlying mechanisms remain unclear, and a variety of structural and/or functional pathways have been proposed, such as abnormalities related to the epiglottis, the laryngeal cartilage-skeleton or its support, mucosal structures as well as the laryngeal muscular system or its nerve supply (Røksund et al., 2016, Maat et al., 2011). All these abnormalities might conceivably disturb the airflow on its way through the laryngeal inlet, increase the turbulence and the airflow resistance, and thereby set up a sense of dyspnoea and trigger the symptoms that are characteristic of EIIS (Templer et al., 1991). Additionally, various psychological characteristics (e.g. anxiety, depression and panic disorder) have been proposed to be implicated in this causal cascade (Maat et al., 2011) by triggering sufficient narrowing of the laryngeal space to cause breathing difficulties and a laryngoscopic image compatible with laryngeal obstruction to airflow.

EILO may be caused by adduction or collapse of supraglottic structures, inappropriate closure of the glottis, or a combination of these events (Røksund et al., 2016) (Figure 2.2). A validated grading scheme developed for the diagnosis of EILO has been used to assess obstruction both at the glottic and supraglottic level, and differentiates between obstructions occurring at moderate and maximal effort (Maat, 2011).

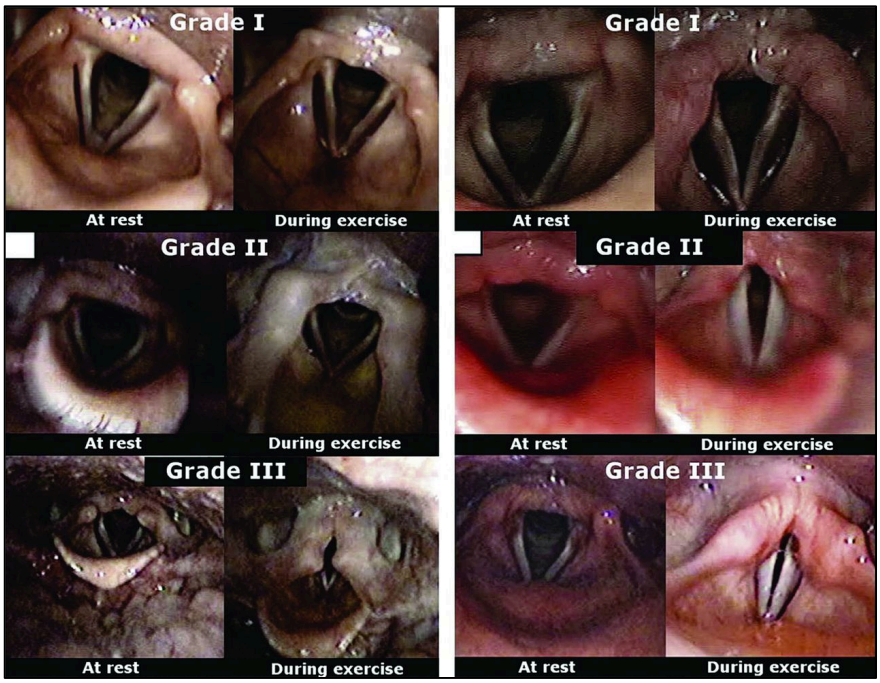

Figure 2.2 Glottic and supraglottic exercise-induced laryngeal obstruction
(Hall et al., 2016) Retrieved from: http://bjgp.org/content/66/650/e683/tab-figures-data

2.3.3.3.1 Assessment for EILO

The gold standard diagnostic test for EILO is called the continuous laryngoscopy exercise (CLE) test (Christensen et al., 2015) (Figure 2.3).

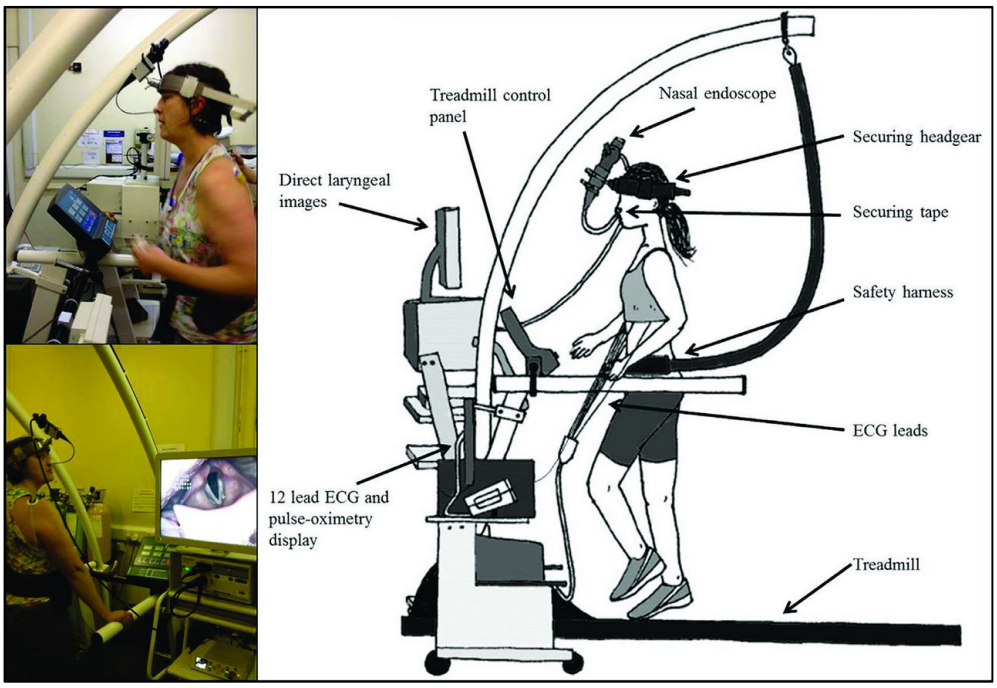

Figure 2.3 Continuous laryngoscopy exercise (CLE) test
(Hall et al., 2016) Retrieved from: http://bjgp.org/content/66/650/e683/tab-figures-data

This technique combines a full cardio-respiratory treadmill exercise set-up and uses flexible naso-endoscopy to provide a continuous image recording of the larynx throughout an exercise to the maximum, thereby enabling a dynamic recording of the movement of the laryngeal structures from start to stop. A camera and a microphone placed in front of the subject enable recording of simultaneous video images of the external upper part of the body as well as recordings of the respiratory sounds. The participant runs on a treadmill according to a standardised protocol, incrementing speed and/or grade every minute with the aim to obtain peak oxygen consumption ($\dot{V}O_{2\ peak}$) after 6 - 12 min of exercise. The test is considered completed, if the patient experience respiratory complaints, or indicate exhaustion, preferably supported by a plateau in oxygen consumption ($\dot{V}O_2$) and/or the heart rate (HR). All recordings continue until breathing returns to normal resting values (Heimdal et al., 2006).

Previous reports have concluded that EILO is more prevalent in young females when compared to males (Björnsdóttir et al., 2000, Smith et al., 1995, Gardner, 1996); Morris et al. (1999) reported a 2:1, whilst Brugman et al. (2003) found a 3:1 female predominance among their patients. One potential explanation of this is the difference in structural characteristics of the larynx between genders. According to observations from anatomical studies, the laryngeal inlet does not show significant gender differences when evaluated in pre-puberty, however considerable divergence in larynx dimensions occur during the development period (Maat, 2011). As such, in post-puberty "the male larynx enlarges considerably in comparison with that of the female; all the cartilages increase in both size and weight, the thyroid cartilage projects in the anterior midline of the neck, and its sagittal diameter nearly doubles" (Standring, 2015).

2.3.4 Assessment for DB

2.3.4.1 Nijmegen Questionnaire (NQ)

The most common method of diagnosing DB relies on a positive NQ (Boulding et al., 2016). The NQ was developed over 30 years ago as a screening tool to detect patients with hyperventilation complaints that could benefit from breathing regulation interventions (van Dixhoorn J, Folgering H., 2015). Although the NQ was developed and validated only in people with HVS, since the 1970s it has been used to identify and characterise DB in the general population (Courtney et al., 2011b), those with anxiety disorders (van Dixhoorn & Duivenvoorden, 1985) and patients with co-existing respiratory diseases e.g. asthma (Thomas et al., 2001, Thomas et al., 2003, Grammatopoulou et al., 2014). This self-completion questionnaire, developed by a group

in the Netherlands, comprises 16 items, that include symptoms common to both anxiety and asthma and related to different systems, such as cardiovascular, neurological, respiratory, gastro-intestinal, but also linked to psychological factors. For each of the 16 items, experience of the given symptom has to be rated on a five-point ordinal scale (where 0 is never and 4 is very often) (van Dixhoorn & Duivenvoorden, 1985). The NQ was shown to have a sensitivity of 91% and specificity of 95% in relation to the clinical diagnosis of HVS (van Dixhoorn & Duivenvoorden, 1985). A score of 23/64 or higher has been considered positive and suggestive of DB (van Dixhoorn & Duivenvoorden, 1985), although, in the validation study, this was calculated using a positive hyperventilation provocation test as the gold standard, which itself is no longer considered a reliable way of diagnosing HVS (Hornsveld et al., 1996).

The NQ has recently been validated in asthma patients. In this specific population the approximate prevalence of HVS was found to be 34% (Grammatopoulou et al., 2014). As many of the symptoms described in the NQ will occur in asthma the true prevalence of HVS in asthmatics is likely to be overestimated (Boulding et al., 2016). It has been previously reported by Demeter et al. (1986) that up to 80% of patients diagnosed with HVS may in fact have an underlying diagnosis of asthma (Demeter & Cordasco, 1986). Asthmatics with HVS tend to be female, have poor asthma control, frequent exacerbations and comorbid anxiety states (Agache et al., 2012).

2.3.4.2 Self-Evaluation of Breathing Questionnaire (SEBQ)

The SEBQ is a recently developed questionnaire that is aimed to evaluate the quality and quantity of uncomfortable respiratory sensations and the perception of breathing

(Chaitow et al., 2014d). It contains 25 items to be answered on a 3-point scale, ranging from never (counted as zero) to very frequently (counted as 3). Factor analysis showed that SEBQ can differentiate two distinct categories or dimensions commonly reported by patients with DB: the feeling of "lack of air" and the perception of "restricted breathing" (Courtney & Greenwood, 2009). The two dimensions were said to represent both biomechanical and biochemical mechanisms and also sensory and cognitive aspects of interoception (Chaitow et al., 2014d) contributing to DB, which have often been implicated in other studies (Harver et al., 2000). Research to establish normative values for the SEBQ has not been formally undertaken, however Courtney et al. (2011a) reported that individuals with NQ scores below 20 had a mean score of 11 for the SEBQ.

2.3.4.3 End-tidal capnography

End-tidal capnography is the non-invasive measurement of exhaled CO_2. Capnography measures average CO_2 partial pressure at the end of exhalation, known as end-tidal carbon dioxide ($ETCO_2$) and has good concurrent validity when compared to arterial CO_2 measures (Bradley & Esformes, 2014). Normal ranges were claimed between 35 - 40 mmHg, while values of < 35 mmHg were suggestive of HVS (Levitzky, 2003). Capnography can be used in endurance athletes whilst exercising on a bike or treadmill to isolate the anaerobic threshold. Feedback on the carbon-dioxide production ($\dot{V}CO_2$) can help athletes to recognise the signs of anaerobic metabolism (Chaitow et al., 2014b). When they are able to identify signs that suggest that anaerobic threshold is approaching, they can reduce their effort in order to prevent the threshold being crossed, allowing themselves to continue the exercise (Chaitow et al., 2014b). Study of Walsh et al. (2006) shows that athletes reach exhaustion 45 seconds sooner when they overbreathe before

exercising. Although capnography could potentially be used by athletes to make alterations to their respiration (e.g. breathing faster or slower, more or less volume) and by doing so reducing the effects of hyperventilation, it is not a useful diagnostic tool when the symptoms are triggered by inefficient breathing pattern, as seen in DB.

2.3.4.4 Depth and rate of breathing

Both depth and frequency of breathing are adjustable, independently from each other, depending on the body's metabolic need for air (Chaitow et al., 2014c). The combination of breathing volume and frequency is calculated by the brain to adjust air exchange. A mismatch of these variables due to abnormal control or execution of breathing, leads to altered $\dot{V}_E$ and consequently homeostatic imbalance (Chaitow et al., 2014c).

Compared to increasing frequency, increasing the depth of respiration is more effective for enhancing alveolar ventilation, but only to a certain extent. Increasing the depth of a breath is resisted by the elastic forces, which bring about exhalation; breathing faster is opposed by the friction of ventilating the airways (Chaitow et al., 2014c). Due to CO_2 deficiency, both increased frequency (Folgering, 1999) and increased breathing depth (Courtney & Cohen, 2008) cause respiratory alkalosis, that reduce cerebral circulation and interfere with neuro transmission resulting in confusion and dizziness (Gilbert, 1998).

The regularity or stability of the breathing cycle may reflect changes in appraisal of external demands as well as inner distractions and associations, therefore assessing these parameters may be beneficial in the evaluation of DB. Several assessments are available to practitioners to carry out these assessments.

2.3.4.5 Breath holding time (BHT)

Breath holding time is an indicator of an individual's ventilatory response to biochemical, biomechanical and psychological factors (Delapille et al., 2001). The precise mechanisms explaining breath-holding and causing the breath at breakpoint are unknown (Parkes, 2006). Some life situations (e.g. uncertainty about what action to take next, or waiting a moment for more information) are reflected in the breathing, as the brain switches between action preparation, focused attention and suppression (Chaitow et al., 2014d). When precise sensory attention is needed or when attempting to remain undetectable, the breathing may be suspended for a few seconds. If breathing is reduced or stopped for a short period, O_2 reserve slowly declines and there is an increase in CO_2 levels, which stimulates more breathing. This process lowers the increased CO_2 levels and the cycle starts over again (Chaitow et al., 2014d). While no standardised test yet exists, breath-hold times are recorded by many clinicians as part of HVS assessment. A shortened BHT may indicate abnormalities in respiratory control (Lin et al., 1974), and is commonly observed in individuals with inclinations towards hyperventilation and/or DB (Warburton & Jack, 2006).

Breath-holding time differs significantly depending on how and under what experimental conditions it is performed. It is affected by whether the hold occurs after inhalation or exhalation, but also depends on the initial lung volume. The most commonly used method for evaluating and monitoring DB is the Buteyko method that includes a post-expiratory breath hold (a.k.a. BHT control pause) at tidal volumes. It is performed either by holding the breath until the first urge to breathe or until the first involuntary motion of the respiratory muscles (Courtney & Cohen, 2008). Using this method, a short BHT (< 20

seconds) is considered an indicator of DB (Boulding et al., 2016, Gardner, 1996), however results should be interpreted with caution as breath-holds produce discomfort, which is not tolerated by all individuals the same way. Also, it is difficult to tell if the individuals tried equally hard to perform the assessment, therefore defining a cut off value is challenging. Although breath-holding ability reflects on breathing functionality, due to the number of limitations of the test, this assessment method was not used in this thesis.

2.3.4.6 Manual assessment of respiratory motion (MARM)

Manual assessment of respiratory motion is a tool used for assessing and quantifying the relative distribution of breathing motion between the upper and lower rib cage and abdomen (Boulding et al., 2016). The MARM is a palpatory procedure based on the examiners interpretation and estimation of motion perceived by their hands at the posterior and lateral aspect of the rib cage (Chaitow et al., 2014d) (Figure 2.4).

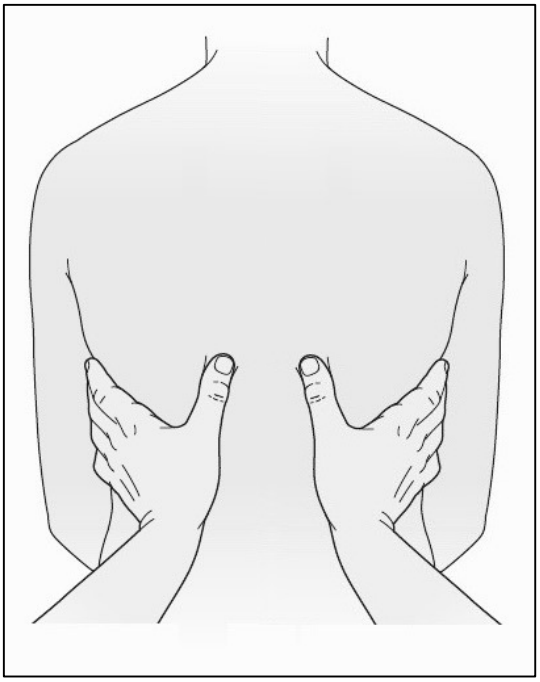

Figure 2.4 Performing the MARM (Chaitow et al., 2014e)

Although MARM has been shown to be a cost-efficient and easily applicable tool to assess breathing abnormalities with a good inter-examiner reliability as compared to plethysmography (Courtney et al., 2008), the assessment is limited to a still state and therefore its application in a sport setting is not feasible.

2.3.4.7 Respiratory induction plethysmography (RIP)

Respiratory induction plethysmography has been used as a tool to monitor ventilation and breathing patterns in multiple settings (e.g. in sleep studies or in critical care) (Brullmann et al., 2010). In this non-invasive respiratory monitoring method, the user wears an elastic band with inductance coils across the chest and abdomen to measure changes in respiratory excursion of the rib cage and abdomen during respiration (Figure 2.5) in order to distinguish between abdominal and thoracic breathing and to determine a "phase angle" (the relationship between chest and abdominal movements) as a measurement of asynchrony (Courtney et al., 2008). For movements that are perfectly synchronous (in phase), phase angle = 0°; for completely asynchronous (out-of-phase) movements phase angle = 180° (Brullmann et al., 2010).

Figure 2.5 Respiratory induction plethysmography: principle of measurement
Retrieved from: https://glneurotech.com/images/bioradio/wireless-resp-banner.jpg

Although RIP is a widely deployed method for non-invasive respiratory monitoring in adults, it has two major limitations: (1) its working principle is inherently sensitive to metallic or magnetic materials in the near surrounding of the subject and (2) for accurate recording that is free from motion artefacts, individuals are required to stay still during the assessment. The optimal conditions needed for the assessment are impossible to achieve in a laboratory, where athletes are tested during exercise and are surrounded by metal-containing devices (e.g. ergometer).

2.3.4.8 Structured light plethysmography (SLP)

Structured light plethysmography uses a visible or infra-red (IR) grid of light that is projected onto the chest and abdomen, allowing respiratory movements to be tracked or visualised by a digital camera system and respiratory data to be derived (Levai et al., 2012) (Figure 2.6).

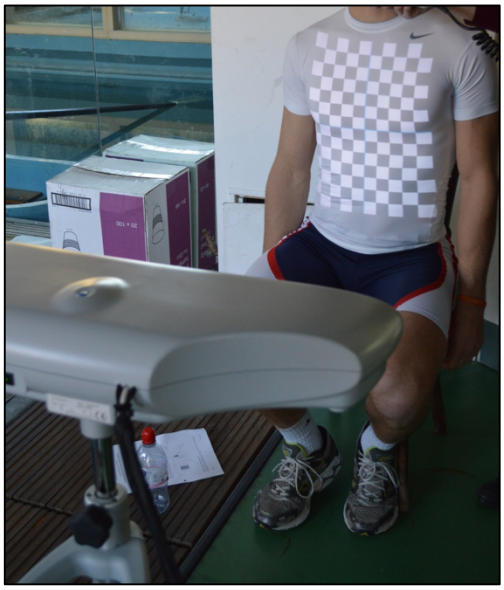

Figure 2.6 Structured light plethysmography: principle of measurement

Although this technology has a great advantage of allowing to measure ventilatory parameters in those whom conventional spirometry is difficult to perform (e.g. elderly people, children, immobile or surgical patients), it also has major limitations: (1) The projected grid is divided into equal portions by a blue cross in the middle, which allows the image to separate the chest and abdominal movements. Anatomically, the length of the chest and abdomen varies in every person, regardless of gender, age etc. and therefore projecting the grid to cover the torso from top to bottom will provide an unrealistic picture of the chest and abdomen contributions. (2) To ensure the grid is projected clearly, subjects need to wear a tight-fitting white T-shirt. If the T-shirt is not tight enough, particularly at the bottom, that causes creases and wrinkles on the T-shirt, which can affect the quality of the projection. Similarly, another problem occurs with regards to female subjects who have different body composition from men; lumps and bumps around the abdominal area and/or large breasts also affect the grid projections. (3) In the lack of fixed marker points (on shoulders, hip bone etc.), it is not possible to accurately project and position the exact same grid on a subject at different time points, hence the SLP measurements repeatability is questionable. (4) Some athletes may have breathing problems due to their posture/shoulder positioning and therefore it would be necessary to measure the upper part of their chest. However, it is not possible to cover the shoulder area with the grid during measurements, as this would result in the grid projection being lost to the side causing the overall results to be distorted. Also, due to some technical limitations an upward shoulder movement, which would be essential to be detected, will not appear in the 3D reconstruction. (5) As the device is very sensitive, any movement of the limbs or head can affect the results drastically making its application during exercise impossible.

2.3.4.9 Optoelectronic plethysmography (OEP)

Optoelectronic plethysmography is an innovative method of indirect measurement of pulmonary ventilation, capable of three-dimensional, real-time assessment of absolute lung volumes and their variations across the pulmonary ribcage, abdominal rib cage and abdomen (Parreira et al., 2012). It uses an optical reflectance motion analysis by computing the 3D coordinates of physical markers fixed on the chest and abdomen of the studied subject (Figure 2.7).

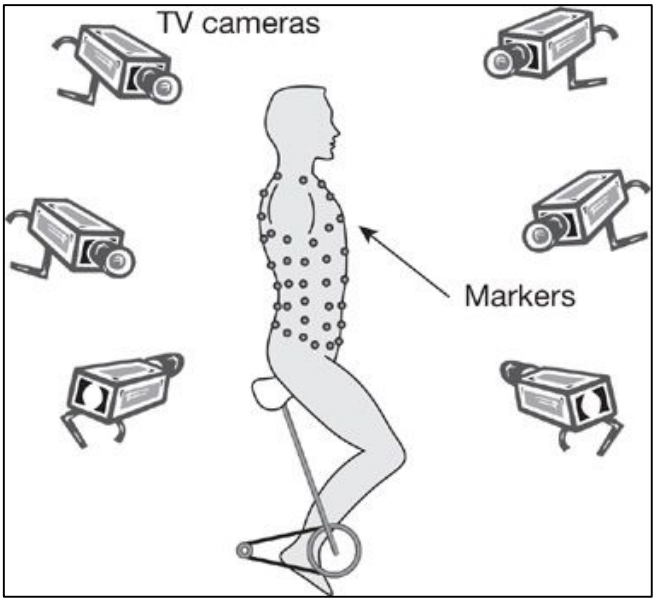

Figure 2.7 Optoelectronic plethysmography: principle of measurement (Vogiatzis et al., 2005)

Optoelectronic plethysmography has been shown to be a valuable and accurate assessment tool that can provide crucial information about chest wall mechanics including the measurement of variables of breathing pattern, breathing asynchrony, and contribution of each chest wall compartment and hemithorax to the tidal volume (Parreira

et al., 2012). Although OEP is able to measure volume variations with high accuracy and validity in different populations and experimental protocols, currently research is limited to healthy subjects and respiratory diseases such as COPD (Massaroni et al., 2017).

The large number (89 - 90) of markers used for the OEP assessment makes its employment in the daily clinical practice as an alternative tool for traditional flow-based instrument to assess respiratory parameters, very much challenging (Massaroni et al., 2017). In fact, the markers placement is time-consuming and in some cases complicated (e.g. in individuals in which the landmarks are difficult to identify). Moreover, at the moment the cost of an eight-cameras system OEP is very high.

Despite these limitations, OEP has several advantages. Compared to the previously mentioned assessment methods, OEP has the ability to simultaneously assess respiratory volumes and the biomechanical components of breathing (Massaroni et al., 2017). Special algorithms allow to obtain volume variations not only of the whole chest wall, but of the different compartments. It provides a better comprehension of the work of breathing without interventions using invasive instrumentation (Massaroni et al., 2017). Additionally, OEP is able to measure breathing patterns in any condition (at rest and during exercise) and it can be used to study respiratory kinematics and, if combined with pressure measurements, statics, dynamics and energetics. The use of this technology has its great potential in assessing breathing patterns in respiratory conditions that are difficult to diagnose objectively and therefore was the chosen assessment method to investigate DB in athletes in the present thesis.

2.4 Summary

Perceived exertional dyspnoea is reported to be the most common symptom, limiting performance and/or enjoyment of sporting activities among athletic individuals of all abilities and ages. Indeed, some describe the sensation of exercise breathlessness as the main barrier to participation in physical activity and/or high performance sport.

Exercise-respiratory symptoms such as cough, wheeze and chest tightness are not exclusive to only one condition; they can be associated with EIB, EILO and DB. Identifying and clarifying the cause of the perceived symptoms require careful assessment with a wide range of factors potentially contributing to the reported symptoms. In groups of elite athletes, estimates of rate of incorrect diagnosis of EIB have ranged between 20 - 50% (Ansley et al., 2012). The use of indirect airway challenges helps to reduce the chance of incorrect diagnosis, but research investigating the causes of exercise respiratory symptoms other than EIB is very limited.

Dysfunctional breathing is a term describing a group of breathing disorders, where chronic changes in breathing pattern result in dyspnoea and often non-respiratory symptoms in the absence, or in excess of, organic respiratory disease. Although accurate identification of the causative factors contributing to the exercise-respiratory symptoms is critical in order to ensure that optimum care is delivered to this specific population, in the lack of well-established differential diagnostic tools, healthcare professionals and team physicians face with a major challenge when attempting to distinguish among the perception of symptoms that may occur as a physiological response to exercise, those

indicating underlying cardiorespiratory pathology and/or complaints that are non-organic of origin.

Despite of its urgent need in clinical practice, several aspects of exercise respiratory problems in physically active individuals, such as effects of body position on respiratory performance and breathing pattern, remain unclear or have not been acknowledged in previous research. Therefore, the aim of this present thesis is to explore the identified gaps in the literature and investigate possible assessment methods that would assist practitioners in identifying and differentiating between pathological and non-pathological causes and contributing factors of breathing dysfunction.

Specifically, investigations will be undertaken in order to explore whether environmental factors would affect the prevalence of airway dysfunction in high level sports and if the Nijmegen questionnaire is sensitive enough to distinguish between EIB and DB in an athletic population. It will also aim to study the possible physiological and/or biomechanical changes associated with altered shoulder positioning during exercise. Attempts will be made to investigate whether breath-by-breath analysis techniques and optoelectronic plethysmography have the ability to assess the suspected changes.

2.5 Thesis aims and hypotheses

The overall purpose of this thesis was to investigate different assessment approaches for identifying DB in athletes. The following chapters presents a series of studies, which contribute to the overall aim of the thesis. The aims and hypotheses of each experimental chapter are as follows:

Chapter 4 - ENVIRONMENTAL INFLUENCE IN THE PREVALENCE AND PATTERN OF AIRWAY DYSFUNCTION IN ELITE ATHLETES

The aim of the chapter was to provide an 'up-to-date' evaluation of the prevalence of EIB in the Great British (GB) elite swimming squad but also, for the first time, to establish the prevalence of EIB in a cohort of screened elite-level boxers. A secondary aim was to compare the EVH challenge response and baseline fraction of exhaled nitric oxide (FeNO), as a surrogate of airway inflammation, between two sports with similar peak ventilatory demands, but with differing training environments.

H1 Athletes who train and compete at a sustained high ventilation in environments that are provocative for the airways (and carry the risk of triggering airway inflammation) have an increased susceptibility to airway dysfunction defined by higher baseline FeNO concentrations and greater reduction in lung function following an EVH challenge.

Chapter 5 - PREVALENCE OF DYSFUNCTIONAL BREATHING (DB) AND ITS RELATIONSHIP WITH AIRWAY DYSFUNCTION IN ATHLETIC INDIVIDUALS

The purpose of this study was to investigate the prevalence of NQ positive responses in a cohort of physically active, young adults. A secondary aim was to directly compare whether an NQ score was related to the outcome of an objective testing for EIB (EVH testing).

H1 In a physically active, young adult population, the prevalence of NQ positive responses is higher compared to reports of DB in non-athletic populations.

H2 There exists a poor relationship between the presence of symptoms on NQ and a diagnosis of EIB.

Chapter 6 - THE IMPACT OF UPPER THORACIC POSTURE ON RESPIRATORY PERFORMANCE AND SYMPTOMS DURING EXERCISE

The aim of this study was to investigate the effects of altered shoulder position on respiratory function and ratings of perceived exertion (RPE) and dyspnoea during high intensity exercise.

H1 Cycling with hunched shoulders at high intensities over a prolonged period leads to altered breathing mechanics and as a consequence, an increase in perceived exertion and dyspnoea.

Chapter 7 - OPTOELECTRONIC PLETHYSMOGRAPHY (OEP) IN THE ASSESSMENT OF DYSFUNCTIONAL BREATHING (DB) IN ATHLETES

The aim of this study was to investigate the effect of different postural positions on the respiratory system using OEP in conjunction with a spirometer and a breath-by-breath (BbB) analyser.

H1 Hunched shoulder position leads to increased abdominal motion to vital capacity and decreased lung volumes.

Chapter 3. Respiratory assessment tests used in the thesis

In this current chapter, the respiratory assessment tests that were used for every experimental studies in this thesis will be discussed. The actual, extended method for each experiment can be find in the methodology section of each study chapter.

3.1 Spirometry

Spirometry is a medical test that measures the volume of air an individual inhales or exhales as a function of time (Miller et al., 2005). In the following collection of studies forced vital capacity (FVC) manoeuvres were performed exclusively. FVC is the maximal volume of air exhaled with maximally forced effort from a maximal inspiration (Miller et al., 2005). It is an effort dependent manoeuvre that requires cooperation between the test subject and the examiner, coordination and understanding by the participant. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) has published guidelines for the measurement of lung function (Miller et al., 2005), which were followed when spirometry measurements were performed.

3.1.1 Spirometer

Throughout the studies maximal flow volume loops were collected using either of the following turbine spirometers: SpiroUSB™ (Carefusion 234 Germany GmbH) or MicroLab® Spirometer (Carefusion 234 Germany GmbH).

When gas flows through a turbine flow meter it makes a vane turn; flow through the tube is proportional to the number of revolutions per unit of time: the higher the flow is, the faster the turbine rotates. An infrared detector detects the rate at which the light from the

infrared source is interrupted by the passing of the turbine (Chan, 2008). The volume of the air passing through the turbine is proportional to the total number of pulses generated and the flow is proportional to the frequency of the pulse generation (Newall et al., 2006).

3.1.2 Verification of spirometer

The volume accuracy of the spirometers was checked in accordance with ATS/ERS criteria (Miller et al., 2005) at least once for each day of testing and was repeated every 4 hours of use. A 3 litres syringe was used for the verification, during which expiratory and inspiratory manoeuvres were performed. The 3 litres volume was injected at low (0 - 0.9 litres/second), medium (1.6 - 4.5 litres/second) and high (7 - 12 litres/second) flow rates. The procedure was repeated three times at each flow rate and verification was accepted if the volume accuracy was within 3% at all flows.

3.1.3 Measurement of Maximal Flow Volume Loop

In preparation for the test, equipment safety was checked in accordance with manufacturer's instructions and guidelines of the Association for Respiratory Technology and Physiology (ARTP) and British Thoracic Society (BTS) (Hill & Winter, 2013). On the day of testing the equipment was checked for cleanliness and records of maintenance and was in working order. Prior to the test a clear and comprehensive description of the nature and purpose of the test was given to the participants who were able to ask questions about the testing procedure. All participants provided informed consent and completed a questionnaire that included questions about smoking habits, recent illness(es), past

medical history and medication use. Participants were assessed for contraindications (Table 3.1A and 3.1B) and allergies.

Table 3.1A Key contraindications of spirometry (Miller et al., 2005)

Absolute

- Active infection e.g. acid-fast bacillus (AFB) testing positive tuberculosis (TB) until treated for 2 weeks
- Conditions that may be cause serious consequences if aggravated by forced expiration such as dissecting /unstable aortic aneurysm, current pneumothorax, recent surgery including ophthalmic, thoracic, abdominal or neurosurgery

Relative

- Suspected respiratory infection in the last 4 - 6 weeks
- Recent pneumothorax
- Any condition which may be aggravated by forced expiration
  - Haemoptysis of unknown origin
  - Unstable vascular status such as recent (within 4 - 6 weeks) myocardial infarction
  - Uncontrolled hypertension or pulmonary embolism
  - History of haemorrhagic event (stroke)
  - Recent thoracic-, abdominal-, eye- or neuro-surgery (within 6 weeks)
- Cervical problems
- Communication problems such as learning disability or confusion
- Any other physical problem the patient may have that may be detrimental if/when performing spirometry

Table 3.1B Key contraindications of the EVH challenge
Retrieved from: http://emedicine.medscape.com/article/2094249-overview

Absolute

- Patients with known significant airway obstructions (FEV_1 < 50% of predicted or FEV_1 < 1.5 L)
- Recent severe acute asthma
- Recent myocardial infarct or stroke within 3 months
- Uncontrolled hypertension
- Known aortic aneurysm

Relative

- Patients with mild-moderate obstruction (FEV_1 < 75% of predicted)
- Spirometry-induced bronchoconstriction
- Pregnancy
- Patients using cholinesterase inhibitors
- Epilepsy

Participants body mass in kilograms (with minimal clothing and without shoes) and height in centimetres (without shoes and head in Frankfort plane position) were measured and entered into the spirometer alongside other details such as date of birth, gender and ethnicity. Participants were seated in a stable chair and asked to remain in the seated position throughout the whole manoeuvre. Breathing manoeuvres were explained and demonstrated to the participants. They were then asked to assume the correct posture (Figure 3.1), attach nose clips and inhale completely and rapidly until their lungs were full with a pause of no longer than 1 second at Total Lung Capacity (TLC).

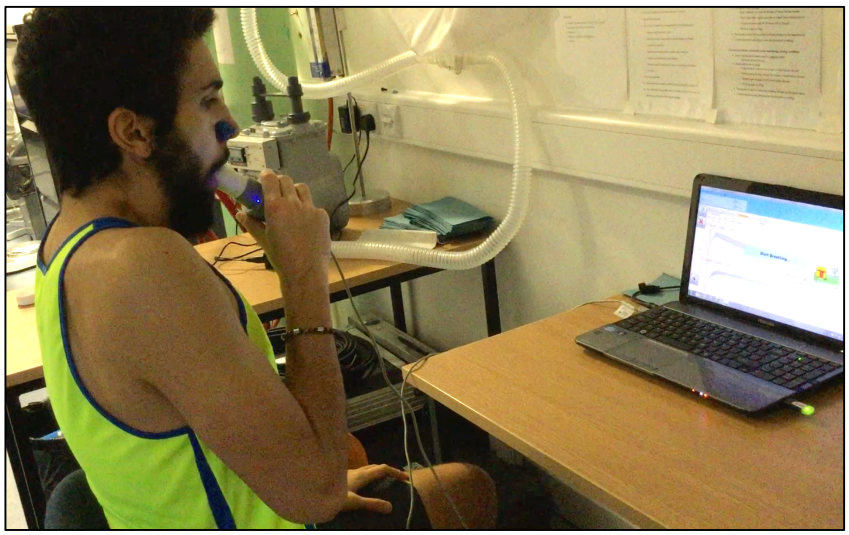

Figure 3.1 Spirometry measurement

Participant was instructed to place a mouthpiece in their mouth, seal lips around the mouthpiece and blow out as fast and far as possible until no more air could be expelled while maintaining an upright posture. When participants could not exhale out any more, they were asked to take a maximal breath in. Throughout the manoeuvres, the participants were given informative, fluent and encouraging instructions to ensure compliance with standardised methods (Miller et al., 2005). A minimum of three maximal flow-volume loops were recorded with a rest period of at least 30 seconds in between manoeuvres. Test repeatability (Table 3.2) was checked and if necessary more manoeuvres, up to a maximum of eight attempts, were performed. For each maximal flow-volume manoeuvre the following parameters were measured: forced expiratory volume in one second (FEV_1); peak expiratory flow (PEF); forced vital capacity (FVC); FEV_1:FVC ratio (FEV_1/FVC) and forced expiratory time (FET). The best of three technically acceptable measurements of FEV_1 and FVC were selected in accordance with the acceptability criteria laid down in Table 3.2.

Table 3.2 Criteria for acceptance of maximal flow-volume loops (Miller et al., 2005)

Within-manoeuvre criteria – Individual spirograms are "acceptable", if

1. They are free from artefacts
   - Leak
   - Poorly co-ordinated start/finish of the test (early termination or cut-off)
   - Cough during the first second of exhalation
   - Inadequate and/or incomplete inhalation/exhalation
   - Sub-maximal effort
   - Obstructed mouthpiece (tongue, teeth, loose dentures)
   - Additional breath taken during manoeuvre
   - Glottis closure that influences the measurement
2. They have good starts
   - Extrapolated volume < 5% of FVC or 0.15 L, whichever is greater
3. They show satisfactory exhalation
   - Duration of ≥ 6 second or a plateau in the volume-time curve or
   - If the participant/patient cannot or should not continue to exhale

Between-manoeuvre criteria

1. After three acceptable spirograms have been obtained, researcher applies the following tests
   - The two largest values of FVC must be within 0.15 L of each other
   - The two largest values of FEV_1 must be within 0.15 L of each other
2. If both of these criteria are met, the test session may be concluded
3. If both of these criteria are not met, researcher continues testing until
   - Both of the criteria are met with analysis of additional acceptable spirograms, or
   - A total of eight tests have been performed, or
   - The participant/patient cannot or should not continue
4. Researcher saves as a minimum, the three satisfactory manoeuvres

Predicted normal values were calculated as described by the European Community for Coal and Steel (ECCS) (Quanjer et al., 1994). All used consumables were disposed immediately after testing and equipment was left clean and ready for subsequent use.

3.2 Eucapnic voluntary hyperpnoea (EVH) challenge

The EVH challenge is an indirect bronchoprovocation test, a surrogate for exercise to identify EIB in athletes and defence force recruits with normal lung function at rest (Anderson, 2011). Lung function was considered normal if the following conditions were met: $FEV_1/FVC \geq 70\%$ of Lower limit of normal (LNN), $FVC \geq 70\%$ of LNN and the shape of the flow-volume curve indicated no airflow limitation (Pellegrino et al., 2005).

3.2.1 Participant preparation for the EVH challenge

Participants were required to withhold inhaled asthma medications prior to testing as indicated in Table 3.3.

Table 3.3 Medications and their required withholding times before the EVH challenge (Parsons et al., 2012)

Time to withhold medication	Medication
8 hours	Inhaled short-acting β_2-agonist *(e.g. salbutamol, fenoterol, terbutaline)*
48 hours	Inhaled long-acting β_2-agonist *(e.g. formoterol, salmeterol)*
96 hours	Leukotriene antagonists *(e.g. montelukast)* Inhaled corticosteroids *(e.g. beclomethasone, fluticasone)*

Participants were instructed to avoid high intensity exercise within 4 hours of the challenge as this may induce a refractory period (Parsons et al., 2013) and exert a protective effect against EIB (Edmunds et al., 1978). Due to the bronchodilator effects of caffeine (Duffy & Phillips, 1991), participants were asked to avoid consumption of caffeine-containing beverages and foods such as tea, coffee, cola, energy drinks and chocolate 4 hours before testing. On the day of the assessment participants completed a questionnaire stating any other medication they were using and whether they were suffering from any illness or injury (Table 3.1A). If an athlete was suffering from an illness that may limit the results of the test, they were asked to return when they were well and fit to complete the test.

3.2.2 Completing the EVH challenge

Prior to starting the EVH challenge, participants completed a minimum of three maximal voluntary flow-volume loops with the best FEV_1 being recorded as their baseline measurement. During the assessment (Figure 3.2) participants were asked to attain a target $\dot{V}_E$ of 85% of their predicted maximal voluntary ventilation (MVV) rate for 6 minutes, which was calculated by multiplying their baseline FEV_1 by 30 (Spiering et al., 2004).

Figure 3.2 Eucapnic voluntary hyperpnoea challenge

Inspired air during the EVH challenge consisted of 21% O_2, 5% CO_2 and 74% N_2 with inspired air temperature 19°C, and humidity < 2%. Note the 5% CO_2 concentration in gas to maintain eucapnia and prevent participant from the adverse effect of prolonged hyperventilation, such as dizziness and nausea. The gas was delivered to each participant through a mouthpiece attached to the EVH kit that contains a gas cylinder, a reservoir and a two-way valve (Figure 3.3).

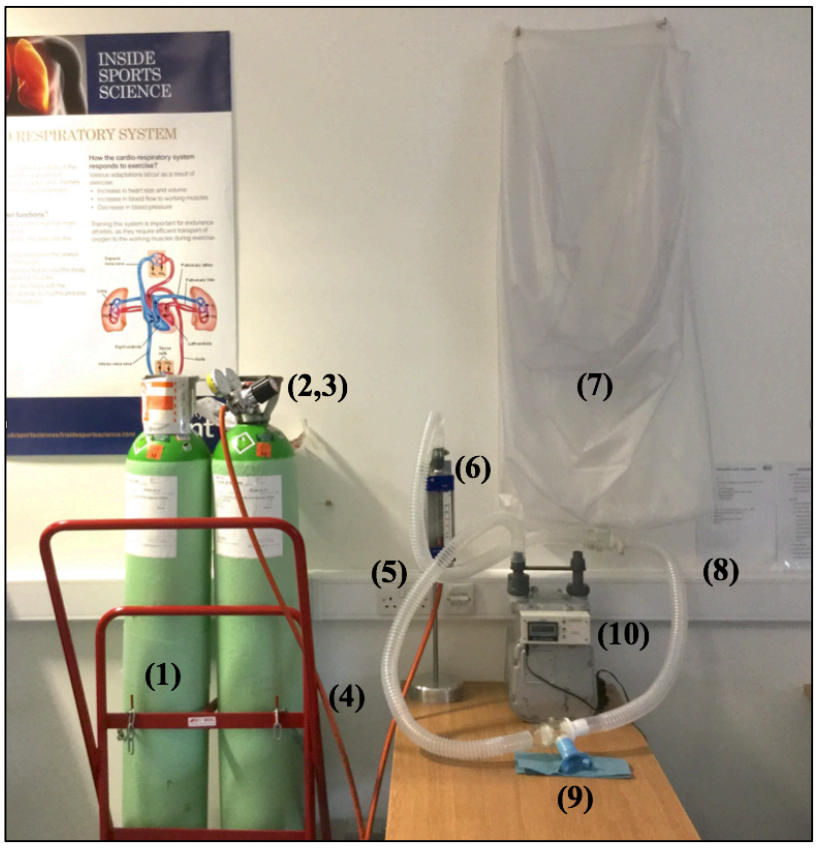

Figure 3.3 Equipment used to perform the EVH test
Gas cylinder (1), regulator (2), demand resuscitator 30-150 L/min (3) high pressure tubing (4), rotameter (5), three-way tap (6), Douglas bag (7), wide bore tubing (8), large low resistance low dead space two-way valve (9), gas meter (10).

During the EVH challenge verbal feedback was provided to the participant in order to encourage them to meet their target $\dot{V}_E$. After completing the EVH challenge, maximal voluntary flow-volume loops were measured at 3, 5, 7, 10 and 15 minutes at each time points. Two flow-volume loops were collected and the maximal flow-volume loop with the highest FEV_1 was recorded. The test was deemed positive, if the FEV_1 fell by at least 10% from baseline at two consecutive time points (Parsons et al., 2013). The severity of a positive EVH-challenge was graded as mild, moderate or severe if the percent fall in FEV_1 from baseline values were $\geq$ 10% but $<$ 25%, $\geq$ 25% but $<$ 50% and $\geq$ 50%, respectively (Parsons et al., 2013). Following the bronchoprovocation challenge

participants were not allowed to leave the laboratory until their FEV_1 was within 10% of their baseline FEV_1. Those individuals, who had not returned to within 10% of FEV_1 within 15 minutes after stopping the challenge were offered 400 μg inhaled Salbutamol to assess their reversibility to bronchoconstriction. Spirometry was performed 15 minutes post-inhalation of Salbutamol (Miller et al., 2005). A positive bronchodilator response (reversibility) was defined as an increase of ≥ 12% and 200 ml in post-EVH FEV_1 and/or FVC (Miller et al., 2005). Following the assessments, participants were given a detailed report of their respiratory health, and those who had a positive EVH challenge test were recommended to consult with their general practitioner (GP) or team doctor for further treatment.

Chapter 4. Environmental influence in the prevalence and pattern of airway dysfunction in elite athletes

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This is the first study to screen the entire elite Great British (GB) Swimming and Boxing teams using a eucapnic voluntary hyperpnoea (EVH) challenge. The findings support the notion that athletes who train and compete in provocative environments at sustained high ventilation have an increased susceptibility to airway dysfunction.

4.1 Abstract

Introduction: Elite swimming and boxing require athletes to achieve relatively high minute ventilation. The combination of a sustained high ventilation and provocative training environment may impact the susceptibility of athletes to EIB.

Aims and objectives: The purpose of the study was to evaluate the prevalence of EIB in elite GB Boxers and Swimmers.

Methods: Athletes from GB Boxing (N = 38, mean ± SD age: 22. ± 3 yr) and GB Swimming (N = 44, mean ± SD age: 21 ± 3 yr) volunteered. Athletes completed an exercise-induced respiratory symptoms questionnaire, baseline assessment of FeNO, maximal spirometry manoeuvres and an EVH challenge. EIB was confirmed, if FEV_1 reduced by ≥ 10% from baseline at two time points post-EVH challenge.

Results: The prevalence of EIB was greater in elite swimmers (30 of 44; 68%) than boxers (3 of 38; 8%) ($p < 0.001$). Twenty-two out of the 33 (67%) EVH-positive athletes had no prior diagnosis of asthma/EIB. Moreover, 12% (6 of 49) of the EVH-negative athletes had a previous diagnosis (Dx) of asthma/EIB. We found a correlation between FeNO and FEV_1 change in lung function post-EVH challenge in swimmers ($r = 0.32$; $p = 0.04$), but not in boxers ($r = 0.24$; $p = 0.15$).

Conclusion: The prevalence of EIB was nine fold greater in swimmers when compared with boxers. Athletes who train and compete in provocative environments at sustained high ventilation may have an increased susceptibility to EIB. It is not entirely clear whether increased susceptibility to EIB affects elite sporting performance and long-term airway health in elite athletes.

4.2 Introduction

Exercise-induced bronchoconstriction has been shown to be highly prevalent in certain groups of elite athletes (e.g. swimmers, cyclists, cross country skiers) (Dickinson et al., 2006, Dickinson et al., 2011, Fitch, 2012). It has been previously reported by Dickinson et al. (2005) that approximately a quarter of the Great British Olympic Team have asthma/EIB, i.e. more than double the national prevalence of asthma (National Asthma Campaign, 2001).

This heightened prevalence is thought to arise due to a combination of the deleterious impact of training and competition environmental exposures (e.g. pollution, swimming pool chemicals), coupled with the repeatedly high ventilatory requirements, necessitated by participation in elite level sport (Argyros et al., 1996). This combination may result in airway injury, (Anderson & Kippelen, 2005) leading to a greater propensity to bronchoconstriction, during or following vigorous exercise (Anderson & Kippelen, 2008). In order to investigate the effect of these aforementioned factors on the prevalence and pattern of airway dysfunction, sport teams with comparable peak physiological demands, but with differing training environments were to be studied. Although limited access to high level athletes made the recruitment process challenging, from all the available squads, GB Swimming and GB Boxing were the ones that fulfilled the inclusion criteria and therefore were selected to participate in the study. Both sports necessitate that athletes reach a similar peak heart rate (HR_{peak}) and $\dot{V}_E$ (Reis et al., 2012), however both the training environment and the duration athletes are exposed to these physiological demands differ significantly (Argyros et al., 1996, de Lira et al., 2013, Reis et al., 2012).

Elite level swimmers, appear to have an alarmingly high prevalence of EIB (41% - 55%) (Dickinson et al., 2005, Castricum et al., 2010). This heightened airway hyper-reactivity appears to resolve in retirement from competitive swimming (Helenius et al., 2002). It has been proposed that repeated exposure to airborne irritants and sensitizing agents (e.g. halocetic acids and trihalomethanes) may drive a sensitisation process and induce airway inflammation that increases a propensity to EIB (Anderson & Kippelen, 2008). Despite this, a clear relationship between EIB and airway inflammation has not been determined; with some studies demonstrating no difference in markers of eosinophilic inflammation between pool and non-pool athletes (Martin et al., 2012). In contrast, very little information is currently available on exercise associated respiratory problems in elite level boxing (de Lira et al., 2013, Smith, 2006).

This study therefore was undertaken with the aim of firstly providing an 'up-to-date' evaluation of the prevalence of EIB in the Great British (GB) elite swimming squad but also, for the first time, to establish the prevalence of EIB in a cohort of screened elite-level boxers. A secondary aim was to compare the EVH challenge response and baseline FeNO, as a surrogate of airway inflammation, between two sports with similar peak ventilatory demands, but with differing training environments.

4.3 Methodology

4.3.1 Study design and participants

Adult members (Age > 18 yr) of the elite GB Boxing and GB Swimming squads, competing regularly in international competition were recruited, as part of a screening study, to assess their airway health. Participants attended the laboratory on a single

occasion at various locations between July 2013 and September 2015. Participants were invited to take part in the testing regardless of previous diagnosis (Dx) of asthma/EIB.

Athletes were excluded if they had a chest infection within 4 weeks, did not withdraw from using their prescribed asthma medications or they had a current FEV_1 value of ≤ 70% predicted. The study was approved by the University Ethics Committee (Reference Number: Prop74_2012_13 and Prop82_2013_14) and all participants provided written informed consent.

4.3.2 Training environment

The boxing squad trained indoors in gymnasiums with moderate temperatures (19 - 21 °C) and relative humidity (40 - 50%) levels (Figure 4.1A). In contrast, the swimming squad trained in indoor pools with air temperatures of 29 °C with relative humidity above 60% (Figure 4.1B).

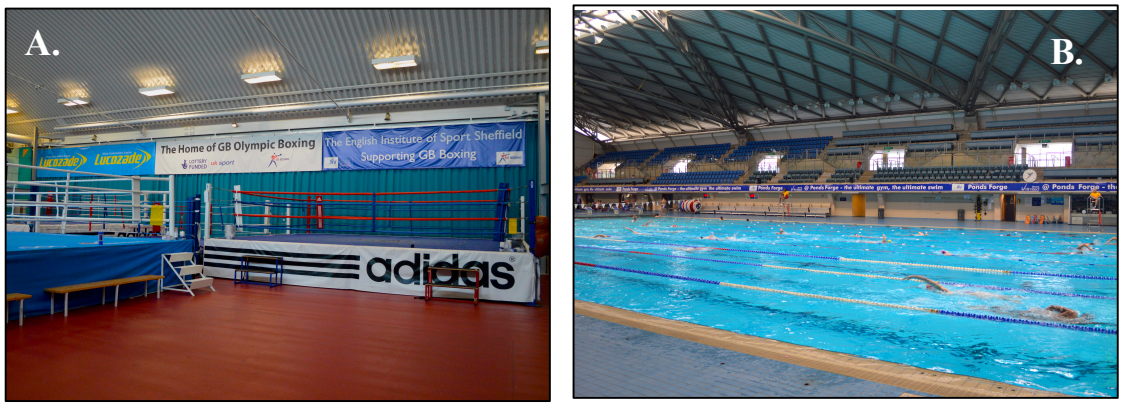

Figure 4.1 Training environment
Panel A shows the GB Boxing training gym and Panel B shows one of the swimming pools where GB Swimmers train

All pools that swimmers trained in followed WHO Guidelines (World Health Organization, 2006) for use of chlorine-based disinfectants. The free chlorine levels were maintained at 1 mg/l or below. Combined chlorine (chloramines) levels were never more than half the free chlorine, and never more than 1 mg/l.

4.3.3 Study measurements

Participants initially completed a questionnaire, addressing exercise respiratory symptoms and environmental triggers. They then completed measurements of FeNO and spirometry, followed by an EVH challenge. Participants were requested to avoid high intensity exercise and caffeine for four hours prior to the study. Participants with a Dx of asthma/EIB were required to withhold inhaled asthma medications according to recommendations (Parsons et al., 2007).

4.3.3.1 Fraction of exhaled nitric oxide (FeNO)

A NIOX analyser (NIOX MINO®, Aerocrine AB, Sweden) was used to measure FeNO in the exhaled breath at rest at a flow rate of 50 ml/min (Dweik et al., 2011). FeNO was performed prior to spirometry manoeuvres (Kharitonov et al., 1997) and taken as the mean of duplicate measures.

4.3.3.2 Spirometry

Using digital spirometers (Spiro-USB™ and MicroLab™, CareFusion, Germany), participants completed a minimum of three forced maximal flow-volume manoeuvres

(Miller et al., 2005). For each maximal flow-volume manoeuvre, the following measurements were recorded in accordance to ATS/ERS 2005 Guidelines (Miller et al., 2005): FEV_1, PEF, FVC and FEV_1/FVC.

4.3.3.3 EVH Challenge

EVH challenge was conducted in accordance to methods outlined by Anderson et al. (2001). Briefly, participants were asked to attain a target $\dot{V}_E$ of 85% of their predicted MVV rate for 6 minutes and maximal voluntary flow-volume loops were measured at 3, 5, 7, 10 and 15 minutes (Parsons et al., 2013). The test was deemed positive if the FEV_1 fell by at least 10% from baseline at two consecutive time points (Parsons et al., 2013).

4.3.3.4 Statistical analysis

Normally distributed data were expressed as mean ± SD unless otherwise stated. One-way analysis of variance (ANOVA) was performed to compare baseline spirometric indices between EVH-positive and EVH-negative participants. Chi-squared (X^2) analysis was used to evaluate the reported symptoms between EVH-positive and EVH-negative participants. To assess the efficacy of self-reported symptoms, sensitivity, specificity and diagnostic accuracy were calculated (Zhu et al., 2010). Assumptions of normal distribution of FeNO data could not be made therefore Spearman's correlation was used to demonstrate the strength and the direction of the relationship between mean FeNO values and the maximal fall in FEV_1 post-EVH challenge. The results were considered significant if $p \leq 0.05$. Statistical analysis was performed using statistical package for social sciences (SPSS, Version 22, IBM).

4.4 Results

4.4.1 Participant characteristics

Participant characteristics are shown in Table 4.1. Thirty-eight boxers (5 females; 26 Caucasians) and forty-four swimmers (19 females; 44 Caucasians) completed the study. Ten participants (12%) were excluded (N = 6, under age of 18 yr; N = 3 resting airflow obstruction; N = 1, equipment failure during testing).

Seventeen (21%) of the participants had a Dx of asthma/EIB. Of these, all were prescribed short-acting β_2-agonist for use pre-exercise, however in addition four (24%) were prescribed inhaled corticosteroid, six (35%) were prescribed an inhaled corticosteroid/long-acting β_2-agonist combination. One participant (6%) was not using any regular asthma medication.

At baseline, when compared against swimmers, boxers had lower baseline FEV_1, percentage predicted FEV_1, FVC, percentage predicted FVC and FEV_1/FVC (Table 4.1).

Table 4.1 Participant characteristics (mean ± SD)

	GB Boxing			GB Swimming		
	Total	**EVH-positive**	**EVH-negative**	**Total**	**EVH-positive**	**EVH-negative**
N	38	3	35	44	30	14
Gender Males	33 (86.8%)	3 (100%)	30 (85.7%)	25 (56.8%)	19 (63.3%)	6 (42.9%)
Females	5 (13.2%)	-	5 (14.3%)	19 (43.2%)	11 (36.7%)	8 (57.1%)
Age (yr)	22 ± 3	26 ± 2	22 ± 3	21 ± 3	21 ± 3.0	21 ± 2
Height (cm)	179.8 ± 11.5	183.3 ± 12.1	179.5 ± 11.6	180.4 ± 8.6	180.8 ± 7.4	179.7 ± 11.0
Weight (kg)	70.9 ± 16.1	74.7 ± 14.4	70.6 ± 16.4	74.5 ± 10.1	73.7 ± 9.4	76.2 ± 11.5
FeNO (ppb)	40.7 ± 40.9	99.0 ± 86.5 [a]	35.7 ± 32.5	28.1 ± 21.9	32.0 ± 25.0	19.6 ± 8.7
FEV_1 (L)	4.3 ± 0.7 [b]	4.5 ± 1.0	4.3 ± 0.7	4.8 ± 0.9	4.8 ± 1.0	4.9 ± 0.7
FEV_1 (% of predicted)	101 ± 14 [c]	102 ± 10	101 ± 14	113 ± 16	111 ± 15	118 ± 15
FVC (L)	5.1 ± 0.9 [c]	5.3 ± 1.2	5.1 ± 0.9	6.2 ± 1.1	6.2 ± 1.1	6.2 ± 1.1
FVC (% of predicted)	102 ± 12 [c]	103 ± 10	102 ± 12	124 ± 12	122 ± 13	128 ± 10
FEV_1/FVC (%)	83 ± 7 [c]	83 ± 3	84 ± 7	77 ± 6	77 ± 6	79 ± 8

[a] Different from EVH-negative boxers ($p < 0.05$); [b] Different from GB Swimmers ($p < 0.05$); [c] Different from GB Swimmers ($p < 0.001$)

4.4.2 Airway response to EVH Challenge and Dx of asthma/EIB

Eighty-two participants completed the EVH challenge, of which thirty-three (40%) had a positive EVH challenge. Twenty-two (67%) of these subjects (three boxers and nineteen swimmers) had no Dx of asthma/EIB. In contrast, six (12%) participants (all swimmers) with Dx of asthma/EIB had a negative EVH result.

Six (12%) EVH-negative athletes (six swimmers) and ten (30%) EVH-positive athletes (ten swimmers) reported having previously been diagnosed with asthma/EIB and were using one or a combination of short-acting β_2-agonists, long-acting inhaled β_2-agonists and inhaled corticosteroids.

The maximum fall in FEV_1 from baseline ranged from - 11.6% to - 21.3% in EVH-positive boxers and from - 12.4% to - 56.1% in EVH-positive swimmers. Two boxers and one swimmer presented with a FEV_1 fall from baseline of > 10% (- 10.1% and - 10.5% for the boxers and -10.1% for the swimmer) at only one single time point, deeming them EVH-negative. Of the thirty-three positive EVH challenges three (7.9%) were elite boxers and thirty (68.2%) were elite swimmers (Figure 4.2).

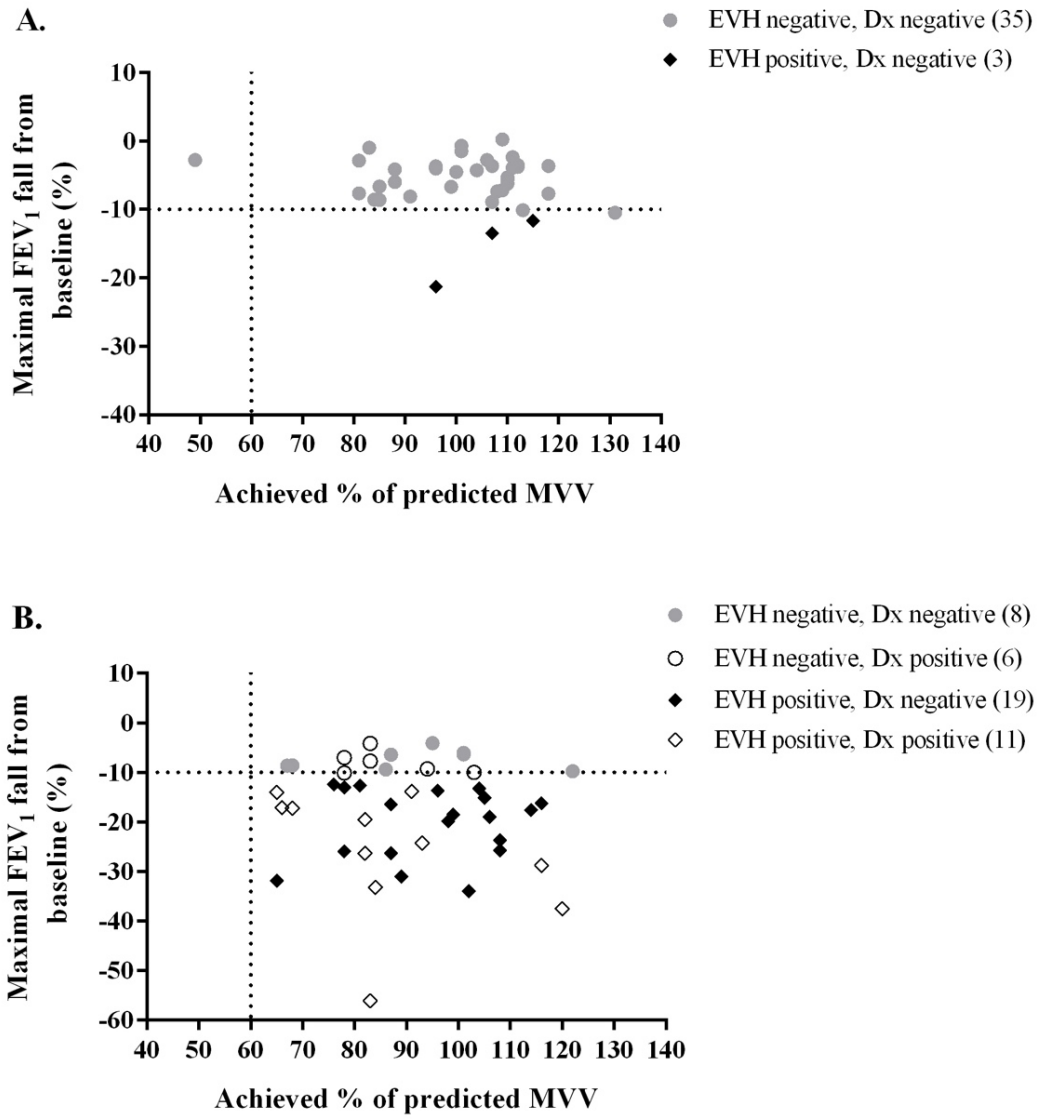

Figure 4.2 Maximal fall in FEV_1 post-EVH challenge showing tests that attained 60% MVV (vertical line) and tests, that were above and below the 10% fall in FEV_1 cut-off value (horizontal line) for a positive test.
Panel A represents GB Boxing and Panel B represents GB Swimming.

There was no difference in anthropometric characteristics between EVH-positive and EVH-negative participants (Table 4.1).

4.4.3 Symptoms

Of the EVH-positive participants, fourteen (43%; all swimmers) reported no exercise-associated respiratory symptoms. However, thirteen (93%) of the fourteen EVH-negative swimmers reported at least one exercise respiratory symptom.

There was an inverse relationship between the maximal fall in lung function following EVH challenge and self-report of exercise-associated chest tightness ($r = - 0.25$; $p = 0.02$) and wheezing ($r = - 0.25$; $p = 0.02$) in EVH-positive participants. There was also an inverse relationship between the maximal fall in FEV_1 and reports of increased severity of symptoms ($r = - 0.35$; $p = 0.04$).

Ten (23%) swimmers reported increased respiratory symptoms due to "bad pool air and/or high chlorine concentrations" and three (7%) swimmers reported exacerbation of respiratory symptoms due to "hot, humid climate". There was no difference in likelihood of a positive EVH between these groups; i.e. five were EVH-positive and eight EVH-negative. Thus overall, the precision of symptoms for a positive EVH test in swimmers was poor; specificity values ranging from 19.2% (cough) to 29.4% (breathing difficulty).

4.4.4 Fraction of exhaled nitric oxide

Resting mean FeNO was similar between boxers and swimmers, 40.7 ± 40.9 ppb vs. 28.1 ± 21.9 ppb; $p = 0.08$, respectively. EVH-positive boxers had greater FeNO values when compared to their negative counterparts (99.0 ± 86.5 ppb vs. 35.7 ± 32.5 ppb; $p = 0.01$). There was no difference in FeNO values between EVH-positive and -negative swimmers

(32.0 ± 25.0 ppb vs. 19.6 ± 8.7 ppb; p = 0.08). There was a correlation between mean FeNO values and the maximal fall in FEV_1 post-EVH challenge in swimmers (r_s = 0.32; p = 0.04), but not in boxers (r_s = 0.24; p = 0.15).

4.5 Discussion

It is proposed that the combination of training and performing in noxious environments makes certain groups of elite athletes highly susceptible to the development of airway dysfunction (Price et al., 2013). The findings from this study supports this notion, confirming the very high prevalence of airway hyper-reactivity in elite level swimmers. Indeed, to our knowledge, this is the highest prevalence (68%) of airway dysfunction reported in an elite internationally-competitive squad of athletes, screened using an indirect stimulus for bronchial provocation. In contrast, in a cohort of athletes, who are not exposed to the environmental stress of the pool environment (i.e. boxers), the prevalence of airway dysfunction was found to be nine fold lower (8%).

The training and competition environment that elite swimmers are exposed to, clearly differs from that of elite boxers. In this respect, boxers train indoors in gymnasiums with relatively low levels of airborne irritants (e.g. allergens (5 - 10 μm) and ultrafine particles (< 0.1 μm)) (Rundell & Sue-Chu, 2013), moderate temperatures and moderate humidity levels. In contrast, the elite swimmers we studied trained in high temperature and humidity. Previous studies (Helenius et al., 2005, Bernard et al., 2009, Bougault et al., 2010, Seys et al., 2015) suggest that athletes who regularly attend indoor swimming pools are acutely and repeatedly exposed to high concentrations of inhaled surface irritants such as chlorine gas derivatives. Repeated exposure to airborne irritants and sensitizing agents

can induce an airway inflammation and remodelling process that may lead to the development of asthma/EIB (Anderson & Kippelen, 2008, Bougault et al., 2009). It has been suggested (Bougault & Boulet, 2013) that the increased occurrence of EIB in swimmers may be caused by the combined effects of the inhalation of by-products arising from disinfection and high number of training hours. The cohort assessed in this study may have had even greater exposure to triggers, as they were part of an elite squad, in contrast to other studies (Parsons et al., 2007, Molphy et al., 2014, Mannix et al., 2004) that have only tested well-trained and/or sub-elite athletes. Indeed, the prevalence of EVH-positive elite swimmers and boxers is notably greater than the only previous report of the prevalence of asthma and EIB in GB Olympic Swimmers (41%) (Dickinson et al., 2005). Although Dickinson et al. (2005) used similar methods to confirm asthma/EIB, they did not screen the entire 2004 GB Olympic Team, but only conducted indirect bronchoprovocation challenges with athletes who had a Dx of asthma/EIB or at the request of a team medical officer.

Recently, Haahtela et al. (2008) recommended distinguishing between two clinical phenotypes of asthma in athletes. The first phenotype is characterised by early onset in childhood, responsive to methacholine, atopy and signs of eosinophilic airway inflammation, and increased FeNO levels. The second one is described with a late onset of symptoms during sporting activity, bronchial responsiveness to eucapnic voluntary hyperventilation (EVH) but not necessarily to methacholine, with a variable response of atopic markers and FeNO (Bussotti et al., 2014). In the entire athletic cohort, no significant relationship was found between FeNO values and the maximal fall in FEV_1 post-EVH challenge. This is in keeping with prior publications (Voutilainen et al., 2013, Parsons et al., 2012) and indicates that FeNO is a poor predictor of airway hyper-reactivity

and clinical asthma in elite athletes. It also supports the hypothesis of Haahtela et al. (2008) that when respiratory distress is caused only by extreme exercise and severe airway cooling/drying, EIB may really be considered a physiological phenomenon. On the other hand, when this association was evaluated in swimmers alone, there was a correlation between FeNO and the maximal fall in FEV_1 post-EVH challenge, indicating that baseline airway inflammation may predict more severe response to EVH.

One of the key findings of this study is the high number of athletes (93%) who reported at least one exercise respiratory symptom, despite having been tested negative on the EVH challenge. The greatest benefit of the EVH test lies in its high ability to identify athletes who truly do not have EIB (Hull et al., 2016). Taking this into account, the high prevalence of symptomatic EVH negative athletes in this study suggests that asthma-like symptoms and exercise-induced respiratory discomfort are not inevitably caused by underlying pathology, but may be related to conditions that mimic EIB, such as DB, which, in the lack of diagnostic strategies, may remain unrecognised and untreated.

In total, 22 out of 33 (67%) EVH-positive athletes had no Dx of asthma/EIB. Sixty-three percent (19 of 30) of the EVH-positive swimmers had no previous history of EIB, whilst none of the EVH-positive boxers had a Dx of asthma/EIB. Moreover, reports of exercise-associated respiratory symptoms were not predictive for the presence of a positive EVH test. It is interesting to note that 26.09% (6 of 23) of the EVH-positive swimmers reported of experiencing no respiratory symptoms during or after training. These findings are in agreement with previous studies reporting impaired symptom recognition in athletes (Holzer et al., 2002, Bougault et al., 2009, Rundell & Jenkinson, 2002). Athletes may

consider their exercise-induced symptoms as a normal effect of high-intensity training, therefore they do not report them and their conditions remains unrecognised and untreated.

Additionally, there were six swimmers who had a Dx of EIB, but did not have a positive EVH challenge. Of these six athletes, four were using Salbutamol inhaler exclusively, one was also prescribed inhaled corticosteroid and one was prescribed an inhaled corticosteroid/long-acting β_2-agonist combination. Although athletes stopped using inhaler therapy prior to the EVH challenge (Parsons et al., 2012), this may not have been adequate and athlete may still have received some protection from inhalers. Furthermore, a negative indirect airway challenge does not confirm the absence of EIB. An alternate test, such as Mannitol or sport specific exercise, may be appropriate to confirm or reject diagnosis of EIB.

There is a lack of data to indicate whether initiating treatment in this context has a beneficial impact for health and performance (Price et al., 2014b) and indeed the relationship between a positive EVH result and 'in the field' airway dysfunction is not straightforward (Castricum et al., 2010). There has been (Castricum et al., 2010) reported a discrepancy between different bronchial provocation tests when they were compared to field based exercise challenge tests in the diagnosis of EIB in swimmers. At the current time initiation of treatment in asymptomatic EVH-positive athletes with no previous history of EIB must be taken on a case-by-case basis. The transient nature of EVH positivity can be reduced and/or normalised in swimmers when intense training has ceased for a period of at least 15 days (Bougault et al., 2011). These observations suggest that the results of bronchial challenges in swimmers may be dependent on training and resting periods.

4.6 Limitations

Although participants were encouraged throughout the test, seven athletes (9%) did not attain the minimum required percentage of MVV (60%) during the EVH challenge, outlined as a criterion for the acceptance of a valid test. This might have happened due to three reasons: (1) athletes did not push themselves to attain target $\dot{V}_E$ during the test and/or (2) did not feel comfortable breathing dry air at high $\dot{V}_E$ and/or (3) did not understand the test instructions. Despite these, the EVH challenge was able to identify positive responders even though they failed to reach the 60% criterion; four of the seven athletes had a significant fall in FEV_1 post EVH challenge confirming EIB. Those who did not provide a positive challenge should be offered another opportunity to complete the EVH challenge and achieve > 60% MVV. Alternatively, a different indirect challenge (e.g. mannitol challenge) or exercise may be preferred to use in order to rule out EIB in low-performing individuals, especially if they also present with co-existing indications of EIB (e.g. cough or environmental triggers) (Molphy et al., 2014).

Given the elite athletes have very strict schedule and do not all train at the same venue, testing days had to take place at various locations and at different times during the year. The athletes that demonstrated higher FeNO values in this study were tested during summer time. It has been previously reported that FeNO levels are influenced by several factors, such as environmental triggers (e.g. seasons), age, height, gender, allergen exposure and nitrate intake. The seasonal variation we detected in FeNO levels could be explained by the variation of ambient pollution or outdoor allergens.

4.7 Conclusions

The results of this study demonstrate a very high prevalence of airway dysfunction in elite swimmers and overall a nine-fold greater prevalence than elite boxers. The findings support the notion that athletes who train and compete, for prolonged periods, in provocative environments have an increased susceptibility to EIB. Additionally, a high proportion of athletes reported symptoms in the lack of objective evidence of airway dysfunction, highlighting the demand for a precise investigation of the causative factors contributing to the exercise-respiratory symptoms and the need for the development of an extended diagnostic algorithm in order to ensure that optimum care is delivered to this specific population. Future research should investigate whether a currently available, validated symptoms questionnaire have the sensitivity to identify athletes with a positive EVH challenge and/or distinguish these athletes from those who may suffer from a functional breathing disorder.

Chapter 5. Prevalence of dysfunctional breathing (DB) and its relationship with airway dysfunction in athletic individuals

5.1 Abstract

Introduction: Dysfunctional breathing may mimic and/or co-exist with EIB. The use of specific questionnaires could improve the identification of DB in athletes. The NQ has been previously used to identify DB across several populations, but not among athletes.

Aims and objectives: To report the prevalence of DB in a cohort of physically active, young adults. In addition, we investigated the factor structure of the NQ in a population of recreational athletes. A secondary aim was to evaluate the relationship between NQ score and the response to an indirect airway challenge.

Methods: Healthy, physically active young adults (N = 500) aged 18-35 years provided informed consent and completed the NQ. Participants responses to each of the 16 items was scored and a positive NQ score indicating DB was set at ≥ 23 out of 64. The participants NQ responses were used to investigate the construct validity through principal components analysis (PCA). A separate cohort of 104 athletes (mean ± SD age: 23 ± 4 yr.; N = 79 (76%) males; N = 63 (60.6%) elite athletes underwent an EVH challenge and completed the NQ. The cross-sectional and convergent validity of the NQ was tested through the Pearson's correlation between the NQ total score and baseline FEV_1 (% of the predicted value), FVC (% of the predicted value), FEV_1/FVC (%), MVV (%) and FEV_1 fall following the EVH challenge. A p value ≤ 0.05 was deemed significant.

Results: Of the 500 questionnaires distributed, 436 (87%) were returned and 428 (86%, N = 283 males) had complete data. Nine percent (9%) of the 428 participants had a NQ score ≥ 23, with female predominance. Fifty-two (50%) participants had a positive EVH challenge and 17 (16.4%) had a positive NQ score. The sensitivity, specificity, positive predicted value (PPV) and negative predicted value (NPV) of a positive NQ score predicting EIB were 15.38%, 82.69%, 47.06% and 49.43%, respectively. Principal

component analysis revealed a three factor solution with 11 items and 56.20% of explained variability.

Conclusions: The prevalence of athletes with a positive NQ score in athletic population is similar to reports in the general population. The NQ score was a poor predictor of identifying athletes who would present with a positive EVH challenge. The NQ does not appear suitable to detect DB in athletes; therefore, the development of an alternative questionnaire may better assist the identification of DB in this population.

5.2 Introduction

The results of Chapter 4 highlighted a very important problem surrounding the diagnosis of exercise respiratory conditions. From all EVH negative athletes, 93% had a complaint of at least one respiratory symptom and 12% had a previous diagnosis of EIB suggesting that reports of exercise-associated respiratory symptoms were not predictive for the presence of a positive EVH test. This finding supports previous studies (Hanks et al., 2012, Krieger, 2002) indicating that many athletes who report exercise respiratory symptoms have no objective evidence of bronchoconstriction, which is suggestive that their symptoms are not related to EIB.

Taken together the findings from Chapter 4 and the reports in the existing literature continue to confirm and underline the complex relationship between respiratory symptoms and the presence or indeed lack of airway dysfunction in athletes (Hull et al., 2012). Furthermore, it supports the notion that exercise respiratory complaints may occur in the absence of organic cardio-respiratory disease (Boulding et al., 2016).

The term dysfunctional breathing describes a maladaptive breathing behaviour that does not sit within the traditional clinical diagnosis and cannot be defined through the standard assessment methods, therefore remains having an abnormality. It can exist in isolation, as a condition without pathology or organic origin, but as an entity, it can also co-exist with apparent organic disease causing respiratory and non-respiratory complaints (Depiazzi & Everard, 2016).

Individuals with DB typically describe a myriad of respiratory symptoms including variable breathlessness, chest discomfort and an uncomfortable breathing sensation (e.g. being unable to 'obtain a satisfying breath'). Specifically, athletic individuals of all abilities, frequently report nociceptive and uncomfortable breathing sensations (Boulet et al., 2005, Price et al., 2016, Price et al., 2015). These symptoms are similar to those often reported by athletes with asthma related conditions (Hull et al., 2012, Price et al., 2015), hence it is not uncommon for symptoms of DB to be attributed to the presence of asthma or EIB and thus for inappropriate treatment to be prescribed, as seen in Chapter 4. Prior to diagnosis of DB, clinicians must first exclude, or adequately treat, organic disease and only then can dysfunctional breathing be considered (Morgan, 2002). It is therefore recommended that objective tests, such as indirect bronchoprovocation tests (e.g. EVH testing) are used in order to obtain a secure diagnosis of a bronchoconstriction related condition in athletic individuals (Parsons et al., 2013) and to exclude this organic cause as the trigger of exercise respiratory discomfort.

Identifying the cause of the perceived symptoms and distinguishing them from those originating from organic respiratory problems require careful evaluation, however, to date there exists no clear consensus on a gold standard differential diagnostic tool of this kind. Previous methods of diagnosis, however, include $ETCO_2$ measurement, BHT, MARM, the SEBQ, and the NQ (Boulding et al., 2016). Although, the latter has been the most frequently utilised method (Boulding et al., 2016) in assessing DB in the general population (Courtney et al., 2011b), those with anxiety disorders (van Dixhoorn & Duivenvoorden, 1985) and patients with co-existing respiratory diseases e.g. asthma (Thomas et al., 2001, Thomas et al., 2003, Grammatopoulou et al., 2014), there are no reports evaluating NQ outcomes in a cohort of physically active individuals and athletes,

among whom the symptoms are very prevalent.

This study was therefore undertaken to investigate the prevalence of NQ positive responses in a cohort of physically active, young adults. In addition, the specific symptom constellation most commonly reported by those with and without EIB was also evaluated. A secondary aim was to directly compare whether an NQ score was related to the outcome of an objective testing for EIB and whether a clear separation of DB from a genuine organic disease (EIB) can be made by the NQ.

5.3 Methodology

The study took place at the School of Sport and Exercise Sciences (SSES), University of Kent and was conducted between September 2014 and December 2015. The study was approved by the SSES Local Ethics Committee (Ethics Reference Number: Prop 104_2014_2015).

5.3.1 Study design and participants

Healthy participants (N = 500) aged 18-35 years and physically active were invited to participate in a cross-sectional study and complete the NQ. The principal components analysis (PCA) that was used to emphasise variation in the dataset, is a large sample procedure. Access to the (high) number of elite athletes, that satisfies the requirements of this type of statistical test, was not possible within the scope of this study. Therefore, participants were recruited from undergraduate and postgraduate sports science and sports therapy lectures and practical seminars or from the testing laboratory.

A separate cohort of elite (N = 13; cyclists, N = 49; swimmers) and recreational athletes (N = 42; from various sports), selected based upon access and availability, also completed the NQ, but in addition underwent an EVH challenge to diagnose EIB.

Participants from either of the studied groups were pre-screened for any diseases and history or suspicion of underlying respiratory conditions were not part of any inclusion criteria.

5.3.2 Questionnaire

The questionnaire completed by the participants consisted of two sections. The first section asked for demographic information such as gender, age, origin, and physical activity. The second section was the NQ.

5.3.2.1 Nijmegen Questionnaire (NQ)

The NQ is a useful tool to quantify and assess the normality of subjective sensations. Participants, differently from the standard, validated format of the NQ, were asked to rate their symptoms as experienced during bouts of exercise. The NQ consists of 16 items that include symptoms common to both anxiety and asthma and relate to different systems, such as cardiovascular, neurological, respiratory, gastro-intestinal and psychological factors. For each of the 16 items participants rated their experience of the symptom on a five-point ordinal scale (where 0 is never and 4 is very often). In keeping with previous literature a score of $\geq$ 23/64 was considered evidence of DB (van Dixhoorn & Duivenvoorden, 1985).

5.3.3 Spirometry and EVH challenge

Using a digital spirometer (Spiro-USB^{TM} and MicroLab^{TM}, CareFusion, Germany), participants completed a minimum of three forced maximal flow-volume manoeuvres. For each maximal flow-volume manoeuvre the following measurements were recorded in accordance to ATS/ERS 2005 Guidelines (Miller et al., 2005): FEV_1, PEF, FVC and FEV_1/FVC.

An EVH challenge was conducted in accordance to methods outlined by Anderson et al. (2001) Briefly, participants were asked to attain a target $\dot{V}_E$ of 85% of their predicted MVV rate for 6 minutes (calculated by multiplying resting FEV_1 x 30). After completing the EVH challenge, maximal voluntary flow-volume loops were measured at 3, 5, 7, 10 and 15 minutes. The test was deemed positive, if the FEV_1 fell by at least 10% from baseline at two consecutive time points (Parsons et al., 2013).

5.3.4 Statistical Analysis

The statistical package for the social sciences (SPSS Version 22) was used for data analysis. Normally distributed data were expressed as mean ± SD unless otherwise stated. The validity of the NQ was tested through construct validity using a PCA, in accordance with methods outlined by van Dixhoorn et al. (1985) and Grammatopoulou et al. (2014) Principal components analysis is a variable-reduction technique that is aimed to reduce a larger set of variables into a smaller set of 'artificial' variables (called principal components) in order to cluster the most highly related items of the questionnaire (Abdi & Williams, 2010) and thus, to exclude those questions that do not measure anything

clinically important in the particular study. To identify the number of extracted factors in the NQ, the following criteria were used: (1) Eigen values above 1.00, (2) scree plot, (3) percentage of explained variability (%) and (4) content of extracted factors. The criteria used to retain the respective items were high factor loading (> 0.30) and communality above 0.30. The sample adequacy was detected through Kaiser-Meyer-Olkin (KMO) measure and Bartlett's test of sphericity. Cronbach's Alphas were computed for each proposed scale to measure internal consistency. One-way ANOVA was performed in order to compare baseline spirometric indices between EVH-positive and -negative and NQ-positive and -negative athletes. The cross-sectional and convergent validity of the NQ was tested through Pearson's correlation between the NQ total score and baseline FEV_1 (% of the predicted value), FVC (% of the predicted value), FEV_1/FVC (%), MVV (%) and FEV_1 fall following the EVH challenge. Sensitivity, specificity and diagnostic accuracy were calculated.

5.4 Results

5.4.1 Part I – Prevalence of DB and construct validity of the NQ

Of the 500 questionnaires distributed, 436 (87%) were returned and 428 (86%, N = 283 males) had complete data. The majority of participants were students (N = 389, 91%) and Caucasian of origin (N = 278, 65%). The cohort had a mean ± SD age of 21 ± 4 yr.

Participants engaged in 49 different sports, of which the five most popular were football (41.1%), basketball (7.0%), strength and conditioning (6.5%), netball (5.4%), and running (3.5%). Slightly less than half of the cohort (47.7%) had participated in their main

sport for over 10 years. All participants included in the study considered themselves physically active; 256 (59.8%) trained one to two days a week, 127 (29.7%) trained three to four days a week and 45 (10.5%) trained five to seven days a week. Of the 428 participants, 110 (25.7%) reported to have a previous diagnosis of an asthma related condition at some point in their life, of which, 53 (12.4%) reported a current diagnosis of an asthma related condition.

The mean total NQ score was 11.1 ± 7.7 and ranged between 0 and 37. There was a difference in mean NQ score between females and males, with females scoring higher than males (13.1 ± 7.8 vs. 10.0 ± 7.5; $p < 0.001$). There was no relationship between NQ score and parameters such as age, ethnicity, type or length of sport engagement or weekly training time.

A positive NQ score (≥ 23/64) was found in 38 (8.9%) participants. When normalised against the total cohort more female (18/145; 12.4%) than male (20/283; 7.1%) participants scored above this threshold. There was no difference in mean age between NQ positive and negative respondents (20.5 ± 3.6 yr vs. 20.7 ± 3.8 yr; $p = 0.74$). Descriptors and component scores from the NQ are detailed in Table 5.1.

Table 5.1 Affirmative response rates to NQ components (%)

		TOTAL	NQ-negative	NQ-positive
N		428	390	38
NQ1	Chest pain	206 (48%)	168 (43%)	38 (100%)
NQ2	Feeling tense or agitated	236 (55%)	200 (51%)	36 (95%)
NQ3	Blurred vision	145 (34%)	113 (29%)	32 (84%)
NQ4	Dizziness	233 (54%)	197 (51%)	36 (95%)
NQ5	Confusion	74 (17%)	51 (13%)	23 (61%)
NQ6	Fast or deep breathing	302 (71%)	264 (68%)	38 (100%)
NQ7	Shortness of breath	279 (65%)	242 (62%)	37 (97%)
NQ8	Chest tightness	191 (45%)	154 (40%)	237 (97%)
NQ9	Bloated abdominal feelings	132 (31%)	108 (28%)	24 (63%)
NQ10	Tingling fingers	152 (36%)	120 (31%)	32 (84%)
NQ11	Cannot breathe deeply	128 (30%)	93 (24%)	35 (92%)
NQ12	Stiffness in fingers or arms	102 (24%)	79 (20%)	23 (61%)
NQ13	Stiffness around the mouth	47 (11%)	31 (8%)	16 (42%)
NQ14	Cold hands	193 (45%)	160 (41%)	33 (87%)
NQ15	Thumping of the heart	226 (53%)	188 (48%)	38 (100%)
NQ16	Anxiety	221 (52%)	185 (47%)	36 (95%)

In NQ-negative respondents, the symptoms with the highest response rates were fast or deep breathing (NQ6) (67.7%) and shortness of breath (NQ7) (62.1%). All NQ-positive participants reported having experienced chest pain (NQ1), fast or deep breathing (NQ6) and thumping of the heart (NQ 15; Table 5.1).

5.4.1.1 NQ structural analysis

In the present study, the recruited sample size (N = 428) was adequate to the pre-determined factor analytic criteria. To achieve a simple structure to the PCA; items that loaded into more than one component following the preliminary analysis, were removed.

The removed items were NQ1, NQ10, NQ11 and NQ14. One item (NQ9) in the third component had lower correlations than the other items in that set and was therefore also removed.

Inspection of the correlation matrix of the remaining 11 items showed that all variables had at least one correlation coefficient greater than 0.3. The sample adequacy was detected through KMO measure (KMO = 0.80) and Bartlett's test of sphericity ($p < 0.001$) indicating that the data was likely factorisable. A Varimax orthogonal rotation was employed to minimise the number of variables that have high loadings on each component and, as such, to aid interpretability.

Visual inspection of the scree plot (Figure 5.1) indicated that three components should be retained; these three components jointly accounted for 56% of the total variance.

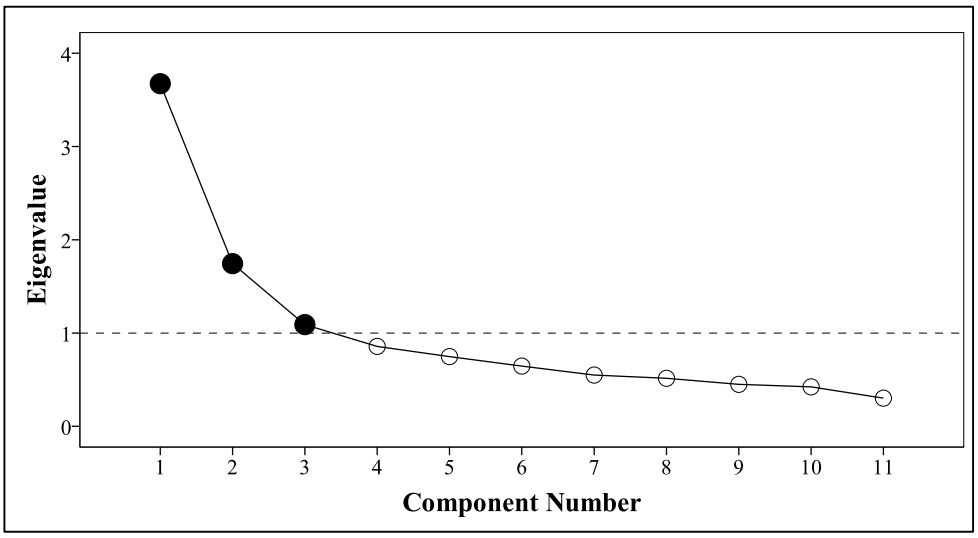

Figure 5.1 Scree plot of 3-component structure of the overall sample
The retained components are marked with a full dot.

The factor structure of the NQ, eigen values, the percentage of explained variance and Cronbach's alpha values of each component are shown in Table 5.2.

Table 5.2 Structure Matrix of the 3-component NQ

		Components		
		1	2	3
NQ7	Shortness of breath	**0.86**	0.11	-0.08
NQ6	Fast or deep breathing	**0.85**	0.04	0.02
NQ8	Chest tightness	**0.70**	0.20	0.10
NQ15	Thumping of the heart	**0.64**	0.23	0.18
NQ3	Blurred vision	0.07	**0.77**	0.07
NQ4	Dizziness	0.27	**0.72**	-0.09
NQ2	Feeling tense or agitated	0.22	**0.65**	0.20
NQ16	Anxiety	0.16	**0.60**	0.24
NQ5	Confusion	0.00	**0.59**	0.24
NQ13	Stiffness around the mouth	0.08	0.12	**0.84**
NQ12	Stiffness in fingers or arms	0.04	0.24	**0.79**
Eigen values		3.66	1.76	1.09
Variance explained (%)		33.28	15.96	9.90
Cronbach's alphas		0.78	0.73	0.60

Component 1 – Cardiorespiratory symptoms, Component 2 – Psycho-neurological symptoms, Component 3 – Exercise-induced fluid retention symptoms

5.4.2 Part II - Relationship between NQ and EIB

A separate cohort of 104 athletes underwent an EVH challenge (Tables 5.3 and 5.4). All participants were able to maintain $\dot{V}_E$ of > 60% predicted MVV to obtain a satisfactory test.

Table 5.3 Participants demographic characteristics

	TOTAL	EVH-positive	EVH-negative	NQ-positive	NQ-negative
N	104	52	52	17	87
Gender					
Male	79 (76.0%)	38 (73.1%)	41 (78.8%)	7 (41.2%)	72 (82.8%)
Female	25 (24.0%)	14 (26.9%)	11 (21.2%)	10 (58.8%)	15 (17.2%)
Ethnicity					
Caucasian	93 (89.4%)	47 (90.4%)	46 (88.5%)	17 (100%)	76 (87.4%)
Non-Caucasian	11 (10.6%)	5 (9.6%)	6 (11.5%)	-	11 (12.6%)
Age (yr)	23 ± 4	23 ± 4	24 ± 5	23 ± 4	23 ± 5
Height (cm)	179.27 ± 8.21	179.85 ± 6.97	178.69 ± 9.33	177.65 ± 8.02	179.59 ± 8.26
Weight (kg)	73.22 ± 9.77	72.21 ± 8.97	74.23 ± 10.49	71.65 ± 10.33	73.53 ± 9.69

Table 5.4 Participants respiratory characteristics (mean ± SD)

	TOTAL	EVH-positive	EVH-negative	NQ-positive	NQ-negative
N	104	52	52	17	87
FEV_1 (L)	4.64 ± 0.86	4.63 ± 0.91	4.64 ± 0.82	4.63 ± 0.90	4.64 ± 0.86
FEV_1 (% of predicted)	109 ± 14	108 ± 15	109 ± 13	115 ± 14 [c]	107 ± 14
FVC (L)	5.81 ± 1.10	6.00 ± 1.10	5.62 ± 1.09	5.81 ± 1.08	5.81 ± 1.12
FVC (% of predicted)	115 ± 14	118 ± 13 [a]	112 ± 15	124 ± 11 [c]	114 ± 14
FEV_1/FVC (%)	80 ± 8	77 ± 7 [b]	83 ± 7	79 ± 6	80 ± 8
Post-EVH FEV_1 (L)	3.97 ± 0.91	3.59 ± 0.85	4.34 ± 0.80	4.09 ± 1.03	3.94 ± 0.88
Post-EVH FEV_1 fall (%)	- 15 ± 11	- 22 ± 11	- 7 ± 3	- 13 ± 9	- 15 ± 12
MVV	125.59 ± 24.39	127.08 ± 23.93	124.10 ± 24.97	126.18 ± 22.43	125.47 ± 24.87
MVV (%)	90 ± 14	92 ± 15	87 ± 13	92 ± 16	89 ± 14
NQ	13 ± 9	13 ± 9	12 ± 10	28 ± 6	9 ± 6

[a] Significantly different from EVH-negative athletes ($p < 0.05$); [b] Significantly different from EVH-negative athletes ($p < 0.001$); [c] Significantly different from NQ-negative athletes ($p < 0.05$).

No participant had evidence of airflow obstruction at rest however fifty-two participants (50%; N = 43 elite, N = 9 recreational) had a positive EVH test (Figure 5.2).

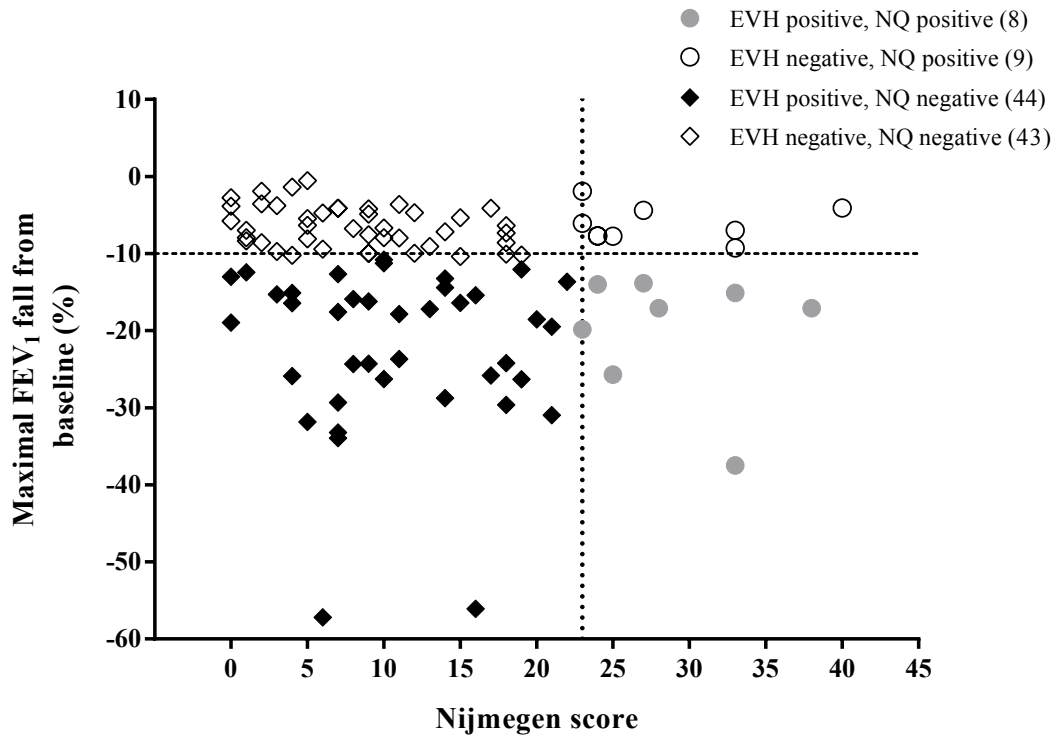

Figure 5.2 Relationship between EVH result and NQ total score

Maximal fall in FEV_1 post-EVH challenge showing tests, that were above and below the 10% drop in FEV_1 cut-off value (horizontal line) for a positive test and NQ total scores, that were above and below the 23 cut-off value (vertical line) for a positive total score. The number of participants in each group is presented in brackets.

The peak fall in FEV_1 from baseline ranged from - 11% to - 57% in EVH-positive and from - 0.6% to - 10% in the EVH-negative participants.

The mean total NQ score was 12.5 ± 9.3, a positive NQ score (≥ 23/64) was found in 17 (16.3%) participants, out of which, 15 (88%) were elite athletes. When normalised against the total cohort more female (10/25; 40%) than male (7/79; 8.9%) participants scored

above the cut-off threshold. There was a difference in mean NQ score between females and males, with females scoring higher than males (20.7 ± 8.6 vs. 9.9 ± 7.9; $p < 0.001$). We found no relationship between NQ score and parameters such as age or ethnicity.

Elite athletes scored higher on the NQ when compared to the recreational group (14.3 ± 10.4 vs. 9.8 ± 6.8; $p = 0.01$). The range of scores obtained by elite athletes (0 - 40) was also greater in comparison to the recreational respondents (0 - 27).

Baseline spirometric indices were greater in the NQ positive group; specifically, FEV_1 (107 ± 14 % predicted vs. 115 ± 14 % predicted; $p = 0.05$) and FVC values (113.51 ± 14.27 L vs. 123.59 ± 10.78 L; $p = 0.01$).

There was no difference in ventilation achieved during the EVH test between NQ positive and negative athletes (126.18 ± 22.43 L/min vs. 125.47 ± 24.87 L/min; $p = 0.54$). The maximum fall in FEV_1 from baseline ranged from - 1.9% to - 37.5% in NQ-positive and from - 0.6% to - 57.2% in NQ-negative participants.

There was a weak relationship between average NQ score and the maximal fall in FEV_1 post-EVH challenge in the recreational group ($r = 0.32$; $p = 0.04$), however, in the elite athletes there was no statistically significant correlation ($r = - 0.80$; $p = 0.54$).

Sensitivity, specificity, PPV, NPV, and predictive values for the total screened population and for the specific groups are shown in Table 5.5.

Table 5.5 Discriminant validity.

A.	TOTAL	Elite athletes	Recreationals
Prevalence (%)	16.35	24.19	4.76
Sensitivity (%)	47.06	53.33	0.00
Specificity (%)	49.43	25.53	77.50
PPV (%)	15.38	18.60	0.00
NPV (%)	82.69	63.16	93.94
Accuracy (%)	49.04	32.26	73.81
Likelihood ratio (LR+)	0.93	0.72	0.00
Likelihood ratio (LR-)	1.07	1.83	1.29
B.	**TOTAL**	**Elite athletes**	**Recreationals**
Prevalence (%)	50.00	69.35	21.43
Sensitivity (%)	15.38	18.60	0.00
Specificity (%)	82.69	63.16	93.94
PPV (%)	47.06	53.33	0.00
NPV (%)	49.43	25.53	77.50
Accuracy (%)	49.04	32.26	73.81
Likelihood ratio (LR+)	0.89	0.50	0.00
Likelihood ratio (LR-)	1.02	1.29	1.06

Panel A shows the efficacy of the EVH challenge in predicting a positive NQ score. Panel B shows the efficacy of the NQ in predicting EIB.

In the assessment of the efficacy of the NQ in predicting a positive EVH challenge, sensitivity, specificity, PPV and NPV were 15.38%, 82.69%, 47.06% and 49.43%, respectively.

5.5 Discussion

This study reveals that approximately one in ten physically active, young adults report troublesome symptoms suggestive of DB. Despite asking our participants to respond the NQ specifically to exercise, the number of those that had a NQ positive score (≥ 23) was similar to that reported by Thomas and colleagues (Thomas et al., 2005). The estimated prevalence of NQ positive individuals in their adult population was 9.5%.

In our cohort of recreational athletes, females tended to be more likely to score higher on the NQ, which is similar to previous reports of female participants providing higher NQ scores when compared to males (12.4% vs. 7.1%, respectively) (Thomas et al., 2001, Grammatopoulou et al., 2014, Thomas et al., 2005). It has been demonstrated (Lamprecht et al., 2013) that females report more dyspnoea and cough when compared to males with the same degree of lung function impairment. One possible explanation may be a varying anatomy in the size of the lungs, airways and respiratory musculature between the two genders. These differences account for a relatively reduced maximum ventilatory reserve capacity, lower inspiratory and expiratory pressures and smaller laryngeal dimensions in females (Røksund et al., 2015, Lamprecht et al., 2013, Weiss & Rundell, 2009). In addition, neurobiological studies have demonstrated females have a higher intrinsic sensitivity to noxious somatic sensations, including dyspnoea (Lamprecht et al., 2013).

Athletes are more susceptible to EIB than the general population (Bonini & Palange, 2015) and as outlined above, the co-existence of DB may confound diagnostic accuracy. We therefore undertook a sub-study to evaluate the relationship between a common DB questionnaire and solid objective evidence of EIB, from an EVH challenge. In this study, thirty-five (74.5%) of the NQ negative athletes tested positive on the EVH. These findings are in line with previous reports (Rundell et al., 2001) that demonstrated that only half of athletes who had EIB reported any respiratory symptoms and that only 28.6% of symptomatic athletes could provide objective evidence of asthma (Lund et al., 2009). Furthermore, the NQ appears to have a low level of sensitivity (15.38%) but a greater degree of specificity (82.69%) in predicting a positive EVH challenge.

Eight (47.1%) NQ positive individuals (all elite athletes) had a positive result on the EVH challenge. In contrast, none of the NQ positive recreational athletes had a positive EVH challenge suggesting that to a certain extent, NQ may have a greater potential in differentiating EIB from DB in recreational athletes than in high level sports.

Killian et al. (1984) previously demonstrated a positive relationship between lung volumes and the perceived magnitude of respiratory effort and breathlessness within individuals. They found there was an increase in these parameters when the tension developed by the inspiratory muscle increased and when the muscle was weakened due to shortening of its operating length (Killian et al., 1984). A positive correlation, similar to those detected by Killian et al. (1984), was observed in this present study, however the finding was novel in that, this positive correlation was found between, rather than within individuals. Within-person variation shows whether and how quickly one is adapting to a transition or stressor, but in contrast, between-person variation reflects on individual differences. In this study, athletes with a positive NQ score had significantly higher lung function values when compared to their NQ negative counterparts, however, the clinical implication of this, if there exists any, is yet to be determined.

The PPV (47.06%) and NPV (49.43%) of self-reported symptoms on the NQ demonstrated only modest value in predicting clinical diagnosis, which might be due to impaired symptom recognition in elite athletes, especially in swimmers, who reportedly consider their exercise-induced symptoms as a normal effect of high-intensity training, therefore they do not report them (Turcotte et al., 2003). Additionally, symptoms (e.g. cough) may manifest in relation to cold air inhalation or only in provocative environments (e.g. chlorine exposure in swimming pools). Given the fact that the NQ in its current form

is “non-specific”, the aforementioned factors may have impacted the outcome of this study.

The construct validity of the NQ was originally reported for a relatively small sample of adults (N = 75) from the general population with and without HVS, with 16 items classified under three factors (shortness of breath, peripheral and central tetany) (van Dixhoorn & Duivenvoorden, 1985). In contrast, our sample size was adequately large for the PCA, as defined by Comrey and Lee (1992) and differently from previously studied populations, consisted of physically active, young adults. Therefore, by determining the dimensional structure of items included in the questionnaire, we aimed to establish whether the same factorial structure was evident for our sample of participants.

In comparison to previous reports, that aimed to investigate the efficacy of NQ in recognising HVS (van Dixhoorn & Duivenvoorden, 1985) and hyperventilation among asthmatics (Grammatopoulou et al., 2014), in the physically active young adult population assessed in this study, results showed a different pattern both in terms of dimensional structure and items loading. Principal component analysis in our cohort revealed three components, that differ from those described by van Dixhoorn et al. (1985). In this study, the first component comprised of four items, namely shortness of breath (NQ7), fast or deep breathing (NQ6), chest tightness (NQ8) and thumping of the heart (NQ15), which having been tightly linked to either the respiratory or cardiovascular system, we labelled as *‘Cardiorespiratory symptoms’*. Anxiety (NQ16) with the perception of feeling tense (NQ2) comprises the major asthma co-morbidity, increasing the risk of hyperventilation in the disease. Dizziness (NQ4) and confusion (NQ5) are symptoms related to disturbances in the nervous system and may be linked to anxiety and

hypocapnia. Blurred vision (NQ3) was previously reported by patients with asthma-like symptoms without physiological sign of asthma (Grammatopoulou et al., 2014). The second component was formed by these five items and due to the nature of these symptoms, they got labelled as *'Psycho-neurological symptoms'*. Prolonged sweating, excessive fluid consumption during exercise may result in an increase of total body fluid and a decrease in plasma sodium concentration leading to neurophysiological changes that may be responsible for the two items that loaded into the third component, namely stiffness around the mouth (NQ13) and stiffness in fingers (NQ12), which we labelled as '*Exercise-induced fluid retention symptoms'*. The third component only contained two items and had low reliability compared to the first two components, indicating that it may not reliably measure DB dimensions; this component could be improved in the future by adding more items to it to increase its internal consistency estimate.

In many cases the trigger of breathing discomfort, which can be related to a specific episode of stress such as excessive aerobic training (Courtney, 2009), initiates a transition from an intermittent, appropriate adoption of an altered breathing pattern to an inappropriate maintenance of disordered breathing. Altered motor recruitment pattern of the respiratory muscles can lead to increased workloads, reduced mechanical advantage and increased ventilatory requirements (Chaitow et al., 2014a). Consequently, an inefficient breathing pattern may lead to breathlessness that may be indicative of suboptimal function elsewhere than in the lungs and/or the larynx and may not even represent pathological condition (Johansson et al., 2015).

Dysfunctional breathing is thought to be a key cause of exertional dyspnoea, however, due to the lack of established gold standard diagnostic method for the differentiation of

DB from other, often co-existent respiratory diseases, difficulty arises when trying to untangle which conditions are contributing to a given individual's exertional symptoms. Many of the studies assessing the epidemiology of DB use the NQ as a method of diagnosis, however, we have shown that several NQ questions are not relevant for athletic populations. We used PCA to reduce the original set of variables into a smaller set of uncorrelated components in order to provide an adequate representation of the information in this specific cohort of participants, with a smaller number of variables constructed as linear combinations of the originals. Our analysis suggests, a shortened 11-item model of the NQ represents the information found in the original set of variables and shows a novel pattern in symptoms that are most likely related to exercise.

Although factor analysis suggested the possibility of reducing the NQ to 11 items, it would be premature to simply produce a shortened 11 item NQ for athletic populations. Additional items, such as psychosocial attributes and sport specific respiratory symptoms, should be added to make the NQ specific to exercise and reflective of all possible aspects of DB (e.g. origin, onset and manifestation of the condition). Based on the above, the obvious next step in this thesis would have been developing a new questionnaire, however in the absence of established diagnostic method for DB, it would not have been feasible to validate the questionnaire and evaluate whether it measures what it is supposed to measure and performs as it is designed to perform. Hence, a gold standard diagnostic tool for DB should be identified prior to undertaking further work towards the elaboration of a symptom assessment instrument.

5.6 Limitations

Self-reported questionnaires have a number of commonly recognised limitations that reduce their usefulness in a research or clinical setting. In particular, reports of symptom measures reflect subjective experience and symptom perception rather than objective health status; symptom reports do not necessarily reflect illness (van Wijk, Cecile MT Gijsbers et al., 1999). Under-reporting may also be a concern, as it relies on the recall of respondents, who although employ a wide range of cognitive processes in formulating their responses, may not pay attention as they answer the questions (Krosnick, 2000) or have trouble understanding the terms used in the questionnaire (Fricker et al., 2000).

Although the 16 items of the questionnaire remained unchanged, participants were asked to rate their symptoms as experienced during bouts of exercise, differently from the original questionnaire, in which specific circumstances related to symptom occurrence were not defined. Although this slight modification of the NQ presumably added clarity for respondents without sacrificing the questionnaire's psychometric properties, a validation study may need to be performed in the future to confirm this.

5.7 Conclusions

In this study, a DB prevalence of 9% was observed in an athletic population. Female athletes tended to be more likely to report symptoms of DB. The NQ score was a poor predictor of identifying athletes who would present with a positive EVH challenge. Although the development of a new questionnaire may enable a better recognition of DB and consequently lower the cost associated with inappropriate diagnosis and therapy, to

date, there exists no gold standard clinical assessment for DB to validate a new questionnaire against, without which, its application would not be clinically justified. Therefore, instead of focusing exclusively on symptoms, investigations should be undertaken in order to discern whether the presence of respiratory complaints of non-organic origin is accompanied by any physiological and/or biomechanical alterations and if so, to identify the best available clinical tools to assess these changes.

Chapter 6. The impact of upper thoracic posture on respiratory performance and symptoms during exercise

6.1 Abstract

Introduction: The posture an athlete holds during exercise may alter breathing pattern and increase reports of exercise induced respiratory symptoms.

Aims and objectives: The purpose of this study was to investigate the effect of different postural positions during high-intensity cycling on breathing frequency (BF), tidal volume (VT), ratings of perceived exertion (RPE) and dyspnoea.

Methods: Fifteen healthy male athletes (mean ± SD age: 26 ± 7 yr) performed a 10-minute cycling test at 70% of their peak power in two conditions, in a randomised order: with normal shoulder position (C1) and with hunched shoulders (C2). BF and VT were continuously monitored during exercise. RPE and dyspnoea were gauged by using Borg RPE and Borg-CR10 scales, respectively.

Results: BF and VT showed no significant difference between conditions at any time point, however an alteration in BF was observed in C2. Significant main effects of time emerged for BF, RPE and dyspnoea in both conditions (all p values < 0.001).

Conclusions: Cycling with hunched shoulders at high intensities over a prolonged period leads to altered breathing mechanics and as a consequence, an increase in perceived exertion and dyspnoea. These findings suggest that posture may contribute to reports of respiratory symptoms during exercise in the absence of cardio-pulmonary disease.

6.2 Introduction

Interest has increased in incorporating questionnaires into clinical practise, as they are a quick and more importantly cost-effective way of assessing medical conditions. They have strong evaluative and discriminative properties and if designed well, they minimise bias and maximise precision in the estimates of treatment effect within budget. Although using a questionnaire, as an assessment tool, would be beneficial in establishing an early diagnosis of DB, Chapter 5 highlighted that NQ in its current format is inadequate in identifying DB and/or differentiating it from other exercise-respiratory conditions and the development of a new questionnaire is not feasible due to current gaps in diagnostic measures. These findings suggest to shift the research focus from symptom recognition to the aetiology of DB by primarily exploring the physiological and biomechanical properties of the condition.

Exertional dyspnoea is reported to be the most common symptom, limiting performance and/or enjoyment of sporting activities among athletic individuals of all abilities and ages (Welsh et al., 2004). Indeed, some describe the sensation of exercise dyspnoea as the main barrier to participation in physical activity and/or high performance sport (Williams et al., 2008). It is often an interrelated symptom in athletes (Smoliga et al., 2016) and may manifest as hyperventilation, or symptoms that occur in association with hypocapnia and respiratory alkalosis (Boulding et al., 2016). It is likely to arise as the result of a complex interplay of factors including altered subjective awareness (Hayen et al., 2017).

Dysfunctional breathing (DB) is now thought to be a key cause of exertional dyspnoea and can be defined as an inappropriate breathing pattern, which is persistent enough to

cause symptoms without evidence, or despite optimisation of, any underlying organic cause, e.g. EIB (Bradley & Esformes, 2014). Currently there is no gold standard diagnostic method for the differentiation of DB from other, often coexistent respiratory diseases, and therefore difficulty arises when trying to untangle which conditions are contributing to a given individual's exertional symptoms.

Hodges & Gandevia (2000) previously reported that a deviation away from an optimal breathing pattern can affect the pressure, ventilatory volumes, stability and ultimately the work of breathing. They suggested that once the maladaptive pattern is established, the impaired breathing movement becomes habituated and thus a self-perpetuating entity (Hornsveld et al., 1996).

Anecdotally, athletes with DB often appear to ride in hunched aerodynamic position to minimise their frontal area in order to maximise speed. It has been shown that breathing efficiency is likely to be compromised in this position and has a negative impact on respiration and performance (Chaitow et al., 2014f).

In a recent study, Hayen et al. (2017) used functional neuroimaging to identify the neural correlates of the conditioned response to breathlessness and their modulation by the mu-opioid receptor agonist short-acting synthetic opioid analgesic drug. Their findings suggest that opioids palliate breathlessness through an interplay of altered associative learning mechanisms, independent of or in addition to effects on brainstem respiratory control (Hayen et al., 2017).

As described above, altered breathing patterns have immediate negative effects on postural stability. In many cases the trigger, which can be related to a specific episode of physical stress such as excessive aerobic training (Courtney, 2009), initiates a transition from a sporadic, altered breathing pattern to a sustained disordered breathing. Although exercising in sitting or supine positions, due to mechanical differences, have been reported to result in significant differences in $\dot{V}_E$ and VT (Takahashi et al., 1998), little is known as to whether a change in body position alters respiratory parameters or indeed perception of breathing. Thus Chapter 6 aimed to establish whether this phenomenon profoundly influence the physiology and perception of respiration during high intensity exercise. Specifically, the parameters of interest were VT, BF, $\dot{V}_E$, TiTo and Borg-CR10.

6.3 Methodology

6.3.1 Study design and participants

Based on observational experience, athletes with DB, regardless of the type of sport they are engaged in, are characterised by hunched shoulders with an anteriorly tipped shoulder blade and forward head, typically exhibiting wheeze and tightness of their upper chest when reaching high intensities during exercise. Due to the difficulties of recruiting a sufficient number of individuals of this kind, healthy participants were invited to take part in the study with the aim of reproducing an experimental set up, which is similar to that seen in real-life DB.

According to the original study plans, on an additional visit reflective makers would have been placed on the bare chest of the studied participants in order to investigate chest and

abdominal motion using OEP. It would have been technically more challenging to perform the assessment on females (due to markers placement and difficulty in recruitment), therefore only male participants were included in the study.

Recreational athletes, who exercised at least twice weekly, were invited to take part. To ensure that participants were at good respiratory health, inclusion criteria included a score less than 23 on the NQ and a negative response to the EVH test. Participants were excluded from study measurements, if they had a chest infection within 4 weeks, any other illnesses within 2 weeks prior to the tests, had any respiratory or cardiovascular problems, metabolic diseases, neurological conditions, they were injured or had any conditions that limited mobility.

On test days, participants were instructed to attend the laboratory in a rested state, having abstained from high-intensity exercise within the previous 24 hours, and abstained from food, alcohol, sports drinks or caffeine intake for the preceding 3 hours. Visits were separated by at least 48 hours but no longer than 1 week.

The study was approved by the University of Kent Ethics Committee (Ethics Number: Prop17_2013_14) and all participants provided written informed consent.

6.3.2 Experimental design

Participants attended the laboratory on four separate occasions within a 2-week period. On the first visit, participants completed the NQ and underwent spirometry measurements followed by an EVH challenge test (Anderson et al., 2001). On the second visit,

participants performed an exercise test to volitional exhaustion on a cycle ergometer to determine peak aerobic power (PAP) and $\dot{V}O_{2\ peak}$. The final two visits required participants to complete two 10-minutes cycling tests at 70% of their PAP in two randomly ordered cycling positions; either with normal shoulder position (C1) or with hunched shoulders (C2). Hunched shoulder positioning was chosen as an experimental condition in order to replicate the body posture observed in athletes with DB. An overview of the experimental design is provided in Figure 6.1.

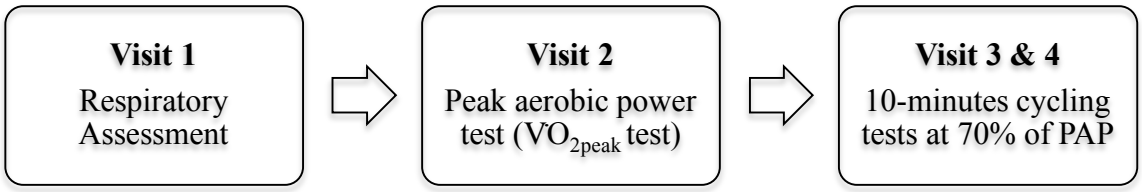

Figure 6.1 Overview of the experimental design

6.3.3 Study measurements

6.3.3.1 Nijmegen Questionnaire (NQ)

Participants completed the modified NQ questionnaire described in Chapter 5.

6.3.3.2 Spirometry and EVH challenge

Forced maximal flow-volume manoeuvres and the EVH challenge were conducted in accordance to methods outlined in Chapter 3.

6.3.3.3 Peak Aerobic Power (PAP) test

Participants performed a standardised incremental exercise test on a cycle ergometer (Lode - Corival, Groningen, The Netherlands) to volitional exhaustion in order to determine PAP. Expired air was analysed breath-by-breath using Cortex Metalyser 3b (CORTEX Biophysik GmbH, Leipzig, Germany). The exercise protocol was preceded with a 2-minute rest period followed by unloaded pedaling for 3 minutes. Power output was then increased by 25 W every minute; participants were instructed to maintain their preferred cadence throughout the test (range 60 - 90 RPM). The test was terminated upon volitional exhaustion or when the required cadence could no longer be maintained (i.e. dropped by > 10 RPM). Throughout the test participants' HR was monitored using a Polar RS400 watch (Polar Electro Oy, Kempele, Finland). Capillary fingertip blood samples (5 - 10 µl) were taken at rest and within 1 minute of exercise cessation. Perceived exertion and perceived dyspnoea were assessed at the end of each testing stage by using Borg ratings of perceived exertion (RPE) (ratings between 6 - 20) and Borg-CR10 scales (ratings between 0 - 10), respectively (Borg, 1998). The RPE scale is used to subjectively determine exercise intensity levels. In contrast, the Borg-CR10 scale is a general method for measuring most kinds of perceptions and experiences, including pain and other sensations (e.g. discomfort) (Borg, 1998). The scale is commonly used for measuring dyspnoea and other kinds of somatic symptoms.

All participants fulfilled ≥ 2 secondary criteria for a valid assessment of the maximal aerobic capacity, as reaching a RER ≥ 1.10, end-exercise blood lactate concentration ≥ 8 mmol/L and a RPE ≥ 17 (American College of Sports Medicine, 2013).

6.3.3.4 Exercise test at 70% of PAP

Participants performed an aerobic exercise test on a cycle ergometer (Lode - Corival, Groningen, The Netherlands). Protocol started with a 2-minute rest period followed by unloaded pedaling for 3 minutes. Participants were then asked to maintain a power output of 70% of the PAP for 10 minutes. During this period, participants were asked to maintain a self-selected cadence between 60 - 90 RPM. The protocol ended with a recovery period of 5 minutes with no resistance.

Participants completed the 10-minutes cycling challenge under two conditions: in natural shoulder position (C1) and with hunched shoulders (C2). Participants completed the exercise trials under C1 and C2 conditions in random order, assigned using simple randomisation procedures (computerised random numbers). The trials were performed at the same time of the day (within 2 hours) to minimise diurnal variation in exercise capacity. An overview of the experimental protocol of Visit 3 and 4 is provided in Figure 6.2.

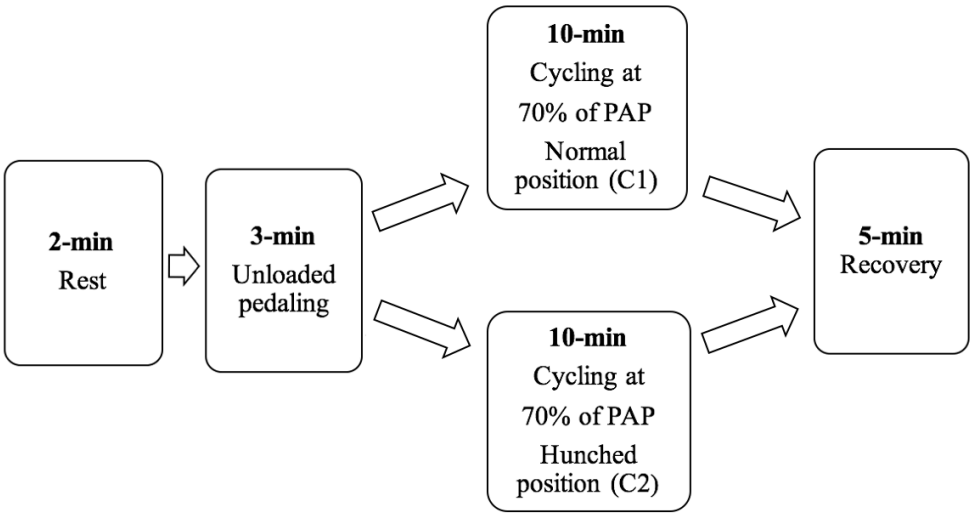

Figure 6.2 Overview of the experimental protocol (Visit 3 & 4)

Electromyographic (EMG) signals (Acknowledge, Version 4.1 for MP Systems, Biopac Systems Inc., Goleta, USA) were used to monitor muscular activity of shoulder region and provide biofeedback to the participants throughout the cycling tests (Figure 6.3).

Figure 6.3 Experimental set up during the 10-minutes cycling test
Panel A shows the participant sitting on the exercise bike and Panel B shows the computer screen with the EMG signals recorded during muscular contraction and relaxation

The electrodes were placed over the upper left and right trapezius midway between the acromion and vertebra prominents. Reference electrodes were placed on the mastoid behind the ears. Participants were instructed to monitor their shoulder movement on the computer screen connected to the EMG unit and placed in front of the cycle ergometer. When shoulders were relaxed and there was no muscle contraction, a flat line occurred and when shoulders were contracted, motor-unit action potentials (MUAPs) were displayed on the screen aiding the participants to perform the tasks (C1 and C2 conditions) as instructed.

Participants' HR was monitored using a Polar RS400 watch (Polar Electro Oy, Kempele, Finland). Capillary fingertip blood sample (5 - 10 μl) was taken at rest and within 1 minute after finishing exercise. Tidal volume, BF, $\dot{V}_E$, TiTo, $\dot{V}O_2$, $\dot{V}CO_2$, HR and RER were recorded by the BbB analyser. Perceived exertion, perceived dyspnoea and leg pain were assessed during exercise by using Borg RPE, Borg-CR10 and Pain scales (ratings between 0 - 10), respectively (Borg, 1998).

6.3.4 Statistical Analysis

Assumptions of statistical tests such as normal distribution and sphericity of data were checked. The dependent variables analysed were: VT, BF, $\dot{V}_E$, TiTo, $\dot{V}O_2$, $\dot{V}CO_2$, HR, RER, perceived exertion, perceived dyspnoea and leg pain. Paired t-tests were used to assess differences of the variables between conditions if normally distributed. Two-way repeated measures ANOVA were conducted to test the effect of the two conditions (C1, C2) and time (E3, E5, E7 and E10 of the 10-minute cycling test, where E3 represents the third, E5 the fifth, E7 the seventh and E10 the tenth minutes of the cycling test) on the dependent variables. Studentised residuals were used to assess normality and the presence of outliers (± 3 SD). Greenhouse-Geisser correction to degrees of freedom ($\varepsilon < 0.75$) was applied when violations of sphericity were present. Significant main effects of time with more than two levels and significant interactions and main effects were followed up with simple main effects of time or condition (pairwise comparisons) using Bonferroni adjustment. Significance was assumed if $p \leq 0.05$ (two-tailed) for all analyses. Statistical analysis was performed using Statistical Package for Social Sciences, Version 22 for Mac OS X (SPSS Inc., Chicago, IL, USA).

6.4 Results

6.4.1 Participants characteristics

Fifteen participants completed the study. Participants' demographics and respiratory parameters are shown in Table 6.1.

Table 6.1 - Participants demographics and physiological characteristics at rest (Visit 1)

Parameter (at rest) N = 15	mean ± SD
Age (yr)	26 ± 7
Height (cm)	178.5 ± 5.9
Weight (kg)	74.5 ± 12.7
NQ score	6 ± 5
FEV_1 (L)	4.59 ± 0.71
FEV_1 (predicted %)	106 ± 12
FVC (L)	5.45 ± 0.90
FVC (predicted %)	106 ± 14
FEV_1/FVC (%)	84 ± 6
Post-EVH change in FEV_1 (%)	- 5 ± 3

6.4.2 Participants characteristics at peak exercise

Participants' physiological and perceptual parameters assessed during the aerobic endurance test are shown in Table 6.2.

Table 6.2 - Participants physiological characteristics and perceptual parameters at the peak exercise (Visit 2)

Parameter (at maximal exercise) N = 15	mean ± SD
$\dot{V}O_{2\ peak}$ /kg (ml/kg/min)	49.6 ± 8.4
$\dot{V}O_{2\ peak}$ (L/min)	89.6 ± 14.3
$\dot{V}CO_2$ (L/min)	125.6 ± 24.4
HR_{max} (bpm)	181 ± 11
VE (L/min)	133.3 ± 21.8
VT (L)	3.0 ± 0.7
RER	1.23 ± 0.40
BF (/min)	46.7 ± 9.2
WR (W)	283 ± 47
RpM (/min)	71 ± 8
La (mmol/L)	11.01 ± 2.04
RPE	18 ± 2
Borg-CR10 scale	7.5 ± 1.9

6.4.3 Cycling trials at 70% of maximal aerobic power

6.4.3.1 Effects of posture on respiratory parameters (VT, BF, $\dot{V}_E$ and TiTo)

The C2 had no effect on any of the respiratory parameters (Table 6.3 and Figure 6.4). There was a significant time effect for BF, $\dot{V}_E$ and TiTo (all p values < 0.05), meaning that hunched position had a significant effect on the listed dependent variables over time.

Table 6.3 Physiological and perceptual parameters (mean ± SD) during the 10-minute cycling test (at minutes 3, 5, 7 & 10) in C1 and C2

	Normal position (C1)				Hunched position (C2)			
Response variables	**minute 3 (E3)**	**minute 5 (E5)**	**minute 7 (E7)**	**minute 10 (E10)**	**minute 3 (E3)**	**minute 5 (E5)**	**minute 7 (E7)**	**minute 10 (E10)**
VT (L)	2.6 ± 0.6	2.7 ± 0.7	2.7 ± 0.7	2.7 ± 0.8	2.7 ± 0.7	2.7 ± 0.7	2.7 ± 0.8	2.6 ± 0.8
BF (/min)	29.4 ± 6.4	33.2 ± 6.9	35.7 ± 8.0	39.6 ± 10.9	29.6 ± 6.2	33.5 ± 7.6	36.9 ± 8.9	42.1 ± 11.4
$\dot{V}_E$ (L/min)	74.3 ± 13.9	85.2 ± 13.2	92.2 ± 15.9	99.7 ± 20.3	75.1 ± 13.6	85.5 ± 12.9	93.9 ± 15.0	103.5 ± 15.9
TiTo (%)	47.7 ± 2.0	47.9 ± 2.6	48.3 ± 2.8	49.0 ± 2.6	47.1 ± 3.8	47.1 ± 3.6	47.8 ± 3.3	48.7 ± 3.2
HR (bpm)	147 ± 11	157 ± 12	164 ± 13	171 ± 14	149 ± 10	160 ± 11	167 ± 12	172 ± 12
$\dot{V}O_2$ (L/min)	2.7 ± 0.4	2.9 ± 0.4	3.0 ± 0.4	3.1 ± 0.4	2.7 ± 0.4	2.9 ± 0.4	3.0 ± 0.4	3.1 ± 0.4
$\dot{V}CO_2$ (L/min)	2.9 ± 0.5	3.2 ± 0.4	3.2 ± 0.4	3.3 ± 0.4	2.9 ± 0.5	3.1 ± 0.5	3.3 ± 0.5	3.3 ± 0.5
RER	1.11 ± 0.07	1.10 ± 0.05	1.08 ± 0.05	1.06 ± 0.04	1.11 ± 0.07	1.10 ± 0.06	1.08 ± 0.05	1.07 ± 0.04
Borg-CR10 score	3.1 ± 1.6	4.2 ± 1.7	5.1 ± 1.9	6.4 ± 2.4 [a]	3.3 ± 2.0	4.7 ± 2.0	5.8 ± 2.1	7.4 ± 2.2
RPE score	12 ± 3	13 ± 2	15 ± 2	15 ± 3	12 ± 2	13 ± 2	15 ± 2	16 ± 2
Pain score	3 ± 2	4 ± 2	5 ± 2	6 ± 2	3 ± 2	4 ± 2	5 ± 3	6 ± 3

[a] *Different from "C2" at corresponding time point (p = 0.05).*

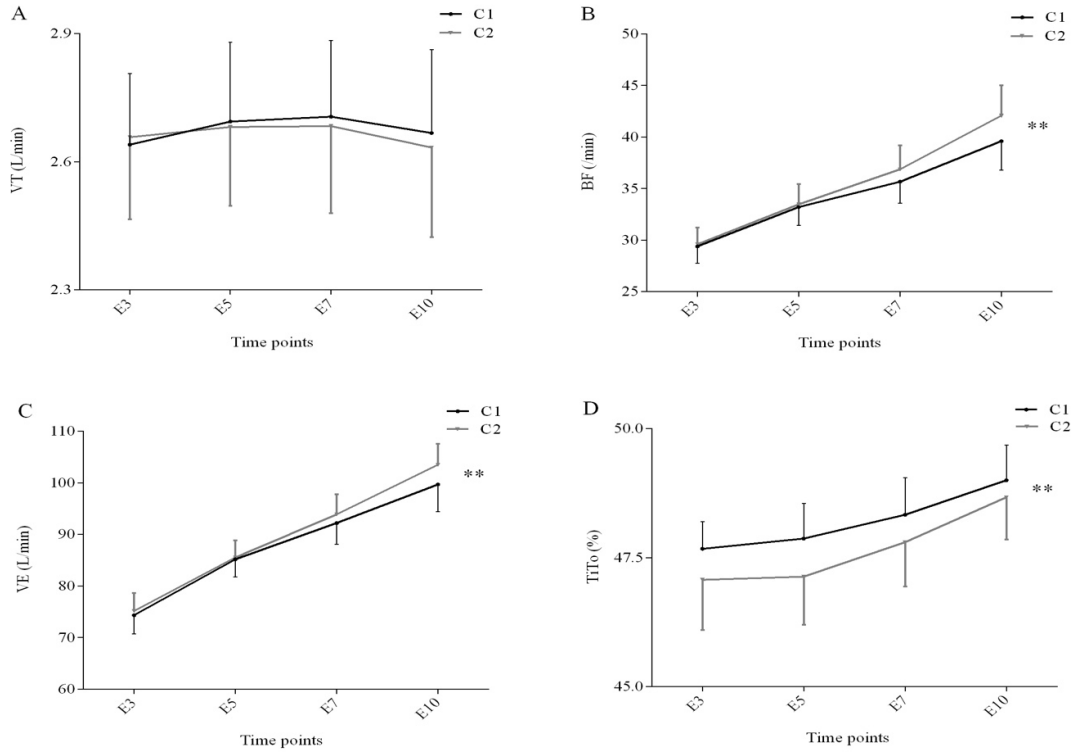

Figure 6.4 The effect of body position on respiratory parameters.
*Panels: tidal volume (A), breathing frequency (B), minute ventilation (C) and ratio between inspiratory time and total breath time (D). Data are presented as mean ± SEM. ** Significant main effect of time ($p < 0.001$). C1 represents 'Condition 1' (normal shoulder position) and C2 represents 'Condition 2' (hunched shoulder position). E3, E5, E7, E10 represent minutes 3, 5, 7 and 10 of the 10-minute cycling test.*

6.4.3.2 Effects of posture on heart rate and gas exchange parameters (HR, RER, $\dot{V}CO_2$, $\dot{V}O_2$)

Heart rate increased in a similar pattern over time in both conditions (Figure 6.5). HR, $\dot{V}CO_2$ and $\dot{V}O_2$ did not show any significant interaction or main effect of condition, however they changed significantly over time (all p values < 0.001) (Figure 6.5). There was a statistically significant mean difference in RER between the following time points: E3 and E10 (0.44 ± 0.12; p = 0.01), E5 and E7 (0.20 ± 0.06; p = 0.03) and E5 and E10 (0.34 ± 0.05; p < 0.001). Data are expressed as mean ± SEM.

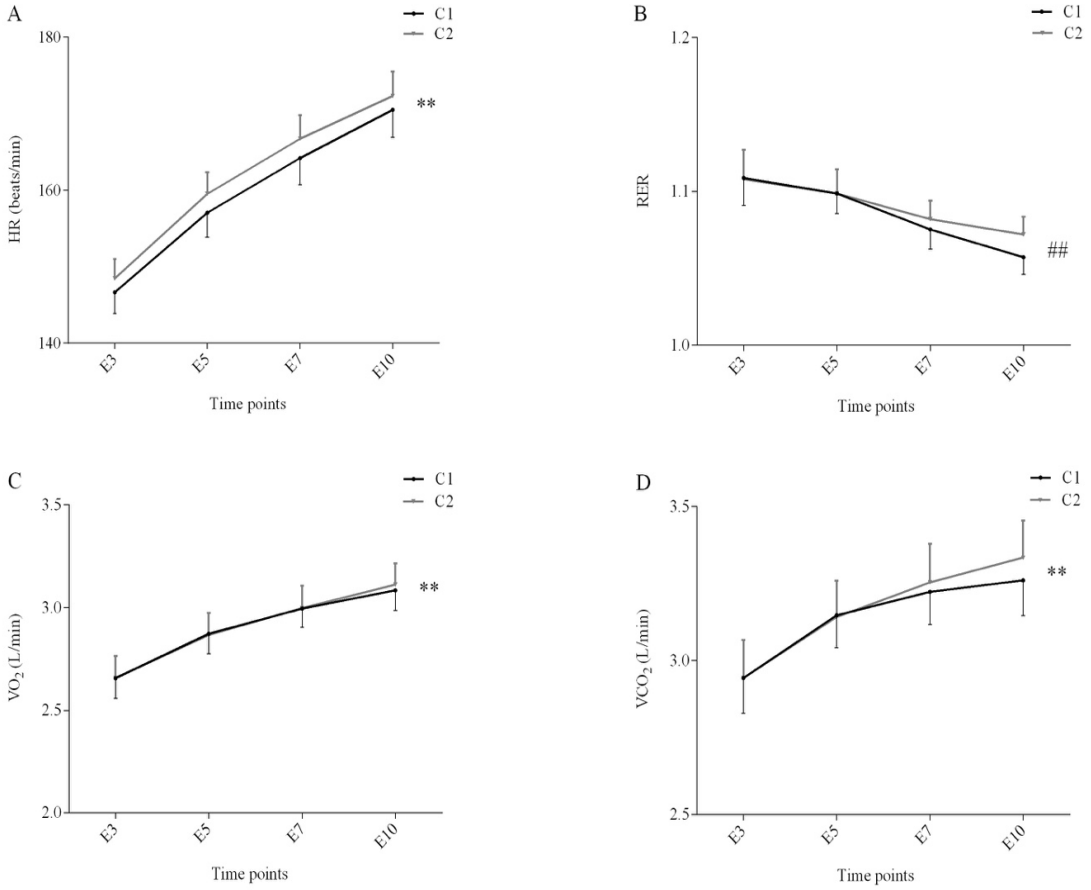

Figure 6.5 The effect of position on cardio and respiratory gas parameters
*Panels: heart rate (A), respiratory exchange ratio (B), oxygen uptake (C) and carbon dioxide output (D). Data are presented as mean ± SEM. ** Significant main effect of time ($p < 0.001$). ## Significant main effect of time ($p < 0.001$), except in C1 (E3, E5), (E3, E7) and (E7, E10). C1 represents 'Condition 1' (normal shoulder position) and C2 represents 'Condition 2' (hunched shoulder position). E3, E5, E7, E10 represent minutes 3, 5, 7 and 10 of the 10-minute cycling test.*

6.4.3.3 Effects of posture on perceptual parameters (perceived exertion, perceived dyspnoea, leg pain)

Ratings of perceived dyspnoea (as indexed by the Borg-CR10 scale) significantly differed in the two conditions in the final minute of the cycling test (6.4 ± 2.5 vs. 7.4 ± 2.3, in C1 and C2, respectively; $p \leq 0.05$) (Table 6.3), but RPE and Pain scores were not affected by the posture (Table 6.3, Figure 6.6).

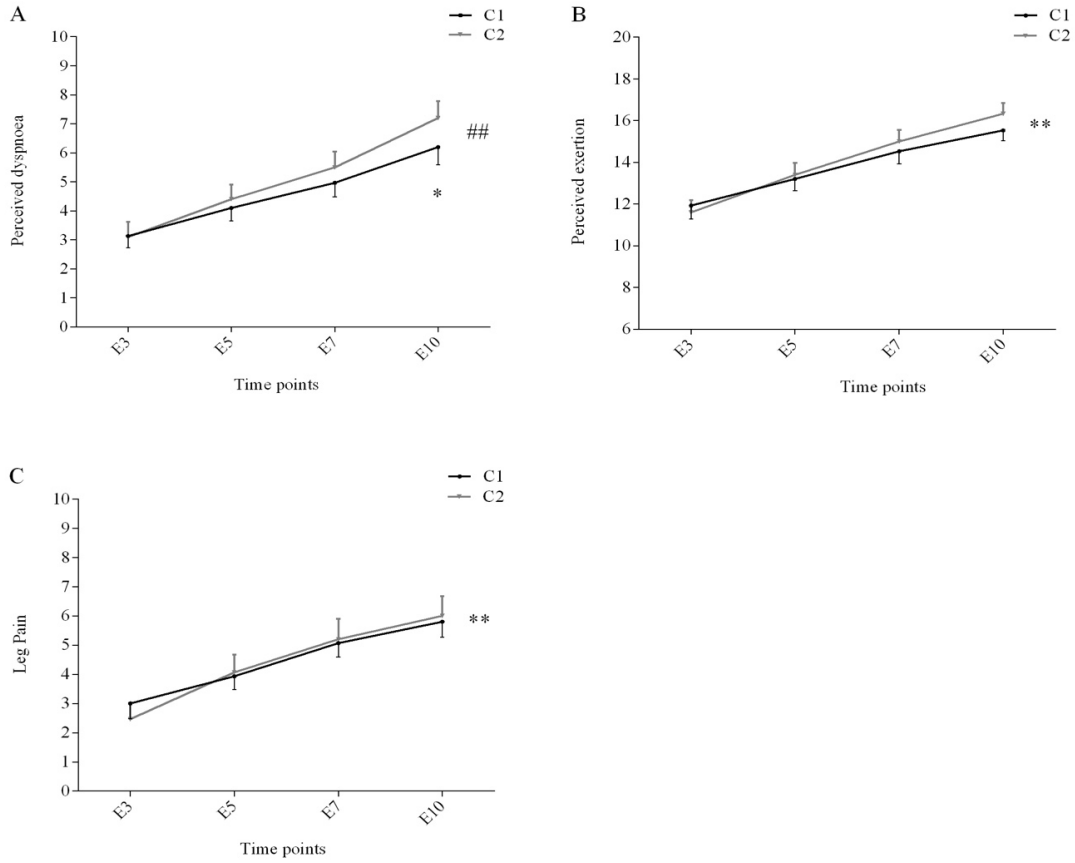

Figure 6.6 The effect of body position on perceptual parameters

*Panels: perceived dyspnoea (A), perceived exertion (B) and leg pain (C). Data are presented as mean ± SEM. * Significant difference between C1 and C2 ($p \leq 0.05$). ** Significant main effect of time ($p < 0.001$). ## Significant main effect of time ($p < 0.001$), except (E3, E5) and (E7, E10) in C1. C1 represents 'Condition 1' (normal shoulder position) and C2 represents 'Condition 2' (hunched shoulder position). E3, E5, E7, E10 represent minutes 3, 5, 7 and 10 of the 10-minute cycling test.*

There was a significant condition-time interaction between time across conditions and both perceived exertion ($F_{2.2, 30.5} = 3.529$; $p = 0.04$) and perceived dyspnoea ($F_{3, 42} = 3.753$; $p = 0.02$). The variable of interest was the difference between trials at minutes 3, 5, 7 and 10 (E3, E5, E7 and E10, respectively). There was a significant time effect for perceived exertion in both normal ($F_{3, 42} = 38.113$; $p < 0.001$) and hunched positions ($F_{3, 42} = 63.134$; $p < 0.001$) and for perceived dyspnoea in hunched position ($F_{1.4, 19.3} = 30.192$; $p < 0.001$). There was also a significant increase in perceived dyspnoea in normal condition but only between time points E3 and E7 (1.83 ± 0.28; $p < 0.001$), E3 and E10 (3.07 ± 0.51; $p =$

0.001), E5 and E7 (0.87 ± 0.17; p = 0.001) and E5 and E10 (2.10 ± 0.41; p = 0.01), where data are expressed as mean ± SEM.

6.5 Discussion

This study suggests that cycling for ten minutes with hunched shoulders does not result in a significant change in physiological markers of respiratory function, but it does lead to an increase in perception of breathing sensation, such as dyspnoea, assessed by using a Borg-CR10 scale in this study.

The development of exertional dyspnoea is multifactorial. It may derive from both physiological and environmental factors (Wahls, 2012), but psychological factors such as affective state or attentional focus have also been demonstrated to considerably impact the perception of respiratory symptoms (Von Leupoldt et al., 2010).

In this study, ratings of dyspnoea increased with the duration of the exercise in both C1 and C2, including the lowest work rate, where no increase in ventilation occurred. Towards the end of the cycling trial, an intensification of dyspnoea was observed in the C2 position when compared to C1. Previous studies (el-Manshawi et al., 1986a, Leblanc et al., 1988) have shown that in a healthy population, the increase in respiratory effort, assessed by oesophageal pressure measurements, represents the increase in motor command. Gigliotto et al. (2010) previously reported that the effort required to sustain any given power increases with the duration with which the activity is sustained. Although neural drive was not assessed in this study, the observed phenomenon may be a reflection of an increase in motor command and inspiratory muscle effort (Grazzini et

al., 2005) due to the decreased respiratory volumes and shortened inspiratory time detected in hunched position. Previous studies have shown that in healthy humans the increase in effort dictated by exercise is related to the length of the test and represents the increase in motor command (Grazzini et al., 2005). The effort required to sustain any given power increases the longer the activity is sustained (Grazzini et al., 2005).

Although it is important to assess the statistical significance of the differences between the evaluated conditions, another important factor to consider is, especially when investigating health and wellbeing, whether the findings provide information about the clinical relevance. With a large enough sample size, even the smallest, trivial differences between groups can become statistically significant. Although ratings of dyspnoea were statistically significantly higher in C2 condition in this study, it is not clear whether this difference is clinically important or meaningful to athletes or to their health support team.

Quantifying dyspnoea through specific scales is essential in order to describe the level of discomfort and also to assess changes after intervention. A minimal clinically important difference (MCID) shows whether an intervention provides a minimum level of perceived benefit and moves beyond the concept of statistical differences (Cook, 2008). Although the Borg-CR10 scale has been widely used to assess breathing discomfort and dyspnoea in a sport setting, its MCID has not yet been defined. As highlighted in the previous chapters, the presentation of DB and the perception of breathing discomfort varies among athletes and therefore they should be evaluated on a case-by-case basis. MCIDs however, are average estimates obtained in groups of patients and may not be accurate reflections of an individual's perceived benefits.

During exercise, an increase in VT generates an increase in end-inspiratory lung volumes, which forces the individual to breathe at higher volumes in the flat part of the pressure-volume curve, but also increases the inspiratory pressure per breath, that is a function of maximal inspiratory pressure (MIP) (el-Manshawi et al., 1986b, O'Donnell et al., 1997). At high lung volumes, the maximal pressure-generating capacity decreases with the increase in velocity of muscle shortening for any given lung volume. In turn, during progressive exercise, pressure per breath to maximal pressure-generating capacity ratio increases in proportion to the sense of effort (O'Donnell et al., 1997).

The results of this study show that in both conditions, the increase in ventilation was accomplished by increased respiratory frequency, however, in hunched position both the ventilation and the respiratory frequency reached a higher peak value. This could be explained by the biomechanics of the altered position. Cycling with hunched shoulders, by utilising the motor units that are best suited to the movements, may change the motor recruitment pattern of the respiratory muscles, which can possibly lead to increased respiratory work, and reduced mechanical performance of the respiratory system (Chaitow et al., 2014a). Consequently, an inefficient breathing pattern may lead to breathlessness that may be indicative of suboptimal function elsewhere than in the lungs and/or the larynx and may not even represent pathological condition (Johansson et al., 2015).

During spontaneous breathing normal inspiratory-expiratory ratio is 1:2, indicating that under normal circumstances the exhalation time is about twice as long as inhalation time (Van Diest et al., 2014). Increases in breathing frequency are brought about by reductions in both inspiratory and expiratory times (Tipton & American College of Sports Medicine,

2006). In this study, as expected, TiTo in both conditions increased slightly, but most of the total breath time remained in expiration and the inspiratory time was maintained at less than 50% of the total breath time.

6.6 Limitations

The non-significant differences observed between the two conditions may be due to one or a combination of the following three factors. Firstly, our participants were requested to maintain the altered body position throughout the cycling test, unlike in "real-life" DB, where athletes may only hunch their shoulders in the inspiratory phase of the breathing cycle. Secondly, the study was performed on a cycle ergometer, where athletes are placed in a position with prolonged back flexion and rounded shoulders compared to a treadmill test where upright posture is guaranteed. Adding to it, Costa et al. (2011) reported that simple arm elevation modifies ventilatory and postural muscle recruitment, therefore, altering the mechanics of the ribcage and abdominal compartments. They found that inefficient movement pattern of paradoxical breathing, due to the consequentially modified rib cage position, results in an alteration in respiratory function and intensification of exercise effort. Thirdly and most importantly, as differences were observed towards the end of the cycling trials, we presume, that it is possible that the length (10 minutes) of the cycling trial was not sufficient to trigger an alteration in VT and BF, therefore in future a time trial or prolonged exercise test would be preferable in order to see the differences between conditions increase and potentially become significant.

6.7 Conclusions

Cycling with hunched shoulders at high intensities, over a 10-minute period at 70% PAP is associated with higher ratings on the Borg-CR10 scale, however, the increased perception of dyspnoea was not accompanied by alterations in physiological markers of respiratory function. These findings suggest that the presence of respiratory discomfort may not be initiated by a ventilatory impairment, but likely to be related to the alterations of biomechanical properties caused by the distinctive body posture. Hence, a breath by breath gas analyser may not be useful as a diagnostic tool in the assessment of DB. Future studies should investigate whether altered shoulder positioning during exercise entails modifications in chest and abdominal motion and whether lung volume compartmentalisation techniques (e.g. OEP) can detect these changes.

Chapter 7. Optoelectronic plethysmography (OEP) in the assessment of dysfunctional breathing (DB) in athletes

7.1 Abstract

Introduction: Ventilatory pattern and thoracic excursion, can vary during exercise and impact on ventilatory performance. A deviation away from an optimal trunk lumbo-pelvic recruitment pattern may affect lung volumes, work of breathing and may be relevant in the development of exertional dyspnoea.

Aims and objectives: The aim of the study was to investigate the effect of different postural positions on the ventilatory excursion using OEP and a spirometer.

Methods: Fifteen healthy male athletes (mean ± SD age: 30 ± 7 yr) completed the study. Ninety reflective markers were placed on the chest, abdomen and back. Participants performed baseline spirometric measurements and 10-minutes cycling challenges at an RPE of 17 in two conditions, in a randomised order: (C1) with normal shoulder position or (C2) with hunched shoulders, while undergoing simultaneous OEP data collection. Forced vital capacity and FEV_1 were measured by the spirometer, whilst VT, BF and $\dot{V}_E$ were assessed by the BbB analyser and data was gathered on the chest wall volume (CW) and the compartmental volumes of the rib cage (RC) and the abdomen (AB) by OEP.

Results: The correlation between the two instruments in measuring FVC was good in both normal ($r^2 = 0.89$) and hunched ($r^2 = 0.84$) positions. FVC was significantly lower in hunched position during both spirometry (5.22 ± 0.69 L vs. 5.35 ± 0.69 L; p = 0.03) and OEP measurements (5.22 ± 0.62 L vs. 5.42 ± 0.69 L; p = 0.01). When volume contributions in the two conditions were compared, the RC/AB ratio was significantly lower in hunched position (1.84 ± 0.74 vs. 2.12 ± 0.79; p = 0.01). During the exercise challenge RC contribution was decreased and AB contribution was increased in C2 throughout the test, although significant difference between the two conditions were only observed at the fifth minute of the cycling trial (E5) with RC values of 59.06 ± 10.01 %

vs. 57.23 ± 9.38 %; p = 0.01; in C1 and C2 respectively and AB values values of 41.56 ± 10.32 % vs. 43.24 ± 9.33 %; p = 0.01; in C1 and C2 respectively.

Conclusions: These findings suggest that respiratory excursion and lung volume compartmentalisation at both rest and during high intensity exercise are affected by the position of the shoulders. Specifically, a hunched should position leads to increased abdominal motion to vital capacity and decreased lung volumes. OEP may be a useful tool to detect altered parameters associated with development of exertional dyspnoea.

7.2 Introduction

Chapter 6 suggests that cycling with hunched shoulders at 70% of PAP over a 10-minute period is associated with increases in the perception of dyspnoea, without any alterations in physiological markers of respiration. Our findings also highlighted that posture may contribute to development of heightened exercise respiratory symptoms in the absence of cardio-pulmonary disease.

The functional performance of the respiratory system during exercise is usually assessed with analysis of expired air to calculate BF, VT, $\dot{V}_E$, $\dot{V}O_2$ and $\dot{V}CO_2$. Although this method is commonly used and is valuable in the quantification of fitness status and diagnosis of a range of cardiovascular and respiratory diseases, (Albouaini et al., 2007) they provide no information of breathing pattern and/or lung volume recruitment, parameters, that may be of interest in the assessment of DB.

Until recently the movement of the chest and abdomen during exercise has not been considered in either the understanding of optimal breathing pattern or in relation to exercise respiratory diseases (Hull et al., 2009). Although non-contact (e.g. SLP) (Levai et al., 2012) and contact (e.g. Respiratory inductive plethysmography; RIP) breath measurement methods (Jensen et al., 2014) have been utilised in recent years, they have limitations, such as requiring individuals to remain very still during the measurements, which make their application in exercise challenging.

Optoelectronic plethysmography is an innovative method of indirect estimation of pulmonary ventilation, capable of breath-by-breath, three-dimensional, real-time

assessment of absolute lung volumes and their variations in the three compartments of the chest wall (pulmonary rib cage, abdominal rib cage and abdomen) (Parreira et al., 2012). Optoelectronic plethysmography uses an optical reflectance motion analysis by computing the 3D coordinates of physical markers fixed on the chest and abdomen of studied subjects and allows the measurement of variables of breathing pattern, breathing asynchrony, and contribution of each chest wall compartment and hemithorax to the tidal volume (Parreira et al., 2012). The OEP system has been used in a variety of conditions including COPD, neuromuscular diseases, following thoracic surgical interventions, but also in intensive care patients and in newborns (Massaroni et al., 2017). The literature available on the use of OEP in exercise related respiratory kinematics is currently sparse. Investigations using OEP during exercise may assist our understanding of the relationship between posture, chest wall movement and exertional dyspnoea not explained by cardio-pulmonary diseases.

The aim of this study was therefore to investigate the effect of different postural positions on the respiratory system using OEP in conjunction with a spirometer (during forced expiratory manoeuvres) and a BbB analyser (during exercise).

7.3 Methodology

7.3.1 Study design and participants

As previously mentioned, OEP measurements were planned to be undertaken as part of the study described in Chapter 6. However, an OEP system was not available at my department at the time and setting up a short-term rental agreement with the provider of

the motion capture system took considerable time. This resulted in a 6-month delay in the project, during which a good number of participants had dropped out of the study and had to be replaced with newly recruited volunteers. Similar to the study in Chapter 6, healthy male participants aged between 18 - 40 years, who took part in endurance exercise at least twice a week were recruited through emails and poster advertisement to take part in the study. Endurance exercise is defined as a physical activity that increases heart rate and breathing frequency, such as running, swimming and cycling. Inclusion criteria included a score less than 23 on the NQ and a negative response to the EVH test, i.e. no evidence of airways hyper-reactivity or symptoms of DB.

Individuals were excluded from the study if they had a chest infection within 4 weeks, any other illnesses within 2 weeks prior to the tests, had any respiratory or cardiovascular problems, metabolic diseases, neurological conditions, or if they were injured or had any conditions that limited mobility. On the test day, participants were instructed to come to the laboratory in a rested state, having abstained from high-intensity exercise within the previous 24 hours, and from food, alcohol, sports drinks or caffeine intake for the preceding three hours. The study was approved by the University Ethics Committee (Reference Number: Prop17_2013_14) and all participants provided written informed consent.

7.3.2 Experimental design

Due to the limited time available for the assessments (the OEP system was only loaned for a 2-weeks period) the study protocol used in Chapter 6 had to be modified in order to make its application feasible. Specifically, (1) participants did not have a pre-screening

visit, rather negative results on a previous EVH test, undertaken within one month, was accepted as a proof of airway health. (2) Participants did not perform a standardised incremental exercise test to determine PAP. Instead, a power output reached at an RPE 17 level was assumed to comply with 70% of PAP.

Participants attended the laboratory on a single occasion, during which they completed the NQ, and performed baseline spirometric measurements and 10-minutes cycling challenges at an RPE of 17. Both tests were performed in two different shoulder positions in a randomised order. Prior to starting the test, participants were given information on using the Borg 6 - 20 RPE scale. An overview of the experimental design is provided in Figure 7.1.

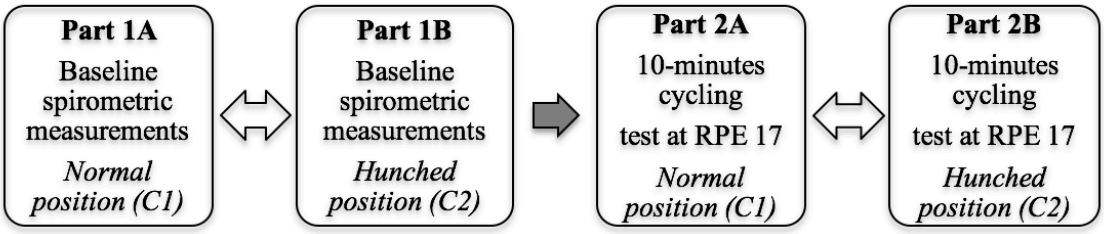

Figure 7.1 Overview of the experimental design

7.3.3 Study measurements

7.3.3.1 Optoelectronic plethysmography (OEP)

Ten IR cameras (Qualysis AB, Sweeden) were set up in a circular pattern over 360 degrees, between 1 - 3 m from the participant (Figure 7.2) to capture the breathing related chest wall motion during exercise (Massaroni et al., 2015, Cala et al., 1996).

Figure 7.2 Camera set up in the test laboratory

Using anatomical reference points defined previously by Aliverti & Pedotti (2002), 90 passive IR reflective markers with diameters of 6 and 9 millimetres were placed on the chest, abdomen and back. The markers were placed on a grid on the skin (Figure 7.3) using bi-adhesive hypoallergenic tape (Aliverti & Pedotti, 2014).

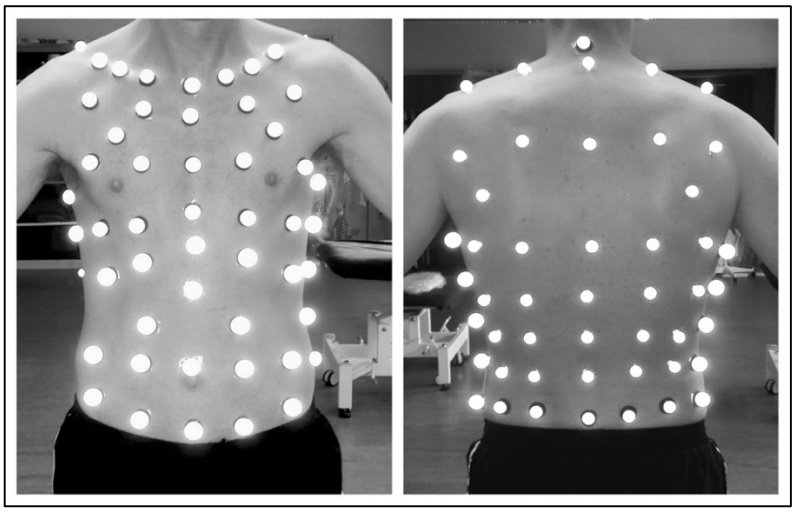

Figure 7.3 Reflective markers placement on the torso

The grid consisted of seven horizontal rows between the clavicles and the anterior superior iliac crest with additional bilateral columns in the mid-axillary line to create the anterior view. The rib cage (RC) was separated from the abdomen (AB) by the line of markers

placed on the lower edge of the chest. Seven posterior horizontal rows (between C7 and the posterior axillary lines) contributed to the coverage of the back (Layton, 2013).

The RC was subdivided into two main compartments, namely the pulmonary rib cage (RCp) and the abdominal rib cage (RCa), by the transverse section at the level of the xiphoid. RCp extended from the clavicles to the line of markers spreading transversely at the level of the xiphisternum, while RCa extended from this line to the lower costal margin. The AB division covered the caudal parts of the frontal torso, from the lower costal margin to the level of the anterior superior iliac crest (Layton, 2013).

Once the markers were positioned, the participant was seated on an upright cycle ergometer (Lode - Corival, Groningen, The Netherlands). Arms were positioned on supports at 90 degrees to the torso in the scapular plane in order to minimise upper body motion that could interfere with OEP data acquisition, and to maintain torso at 90 degrees of hip flexion. The IR cameras were positioned to ensure that all markers were visible by at least two infrared cameras, so the markers' three-dimensional position and displacement could be reconstructed for thoraco-abdominal volume calculations (Figure 7.4).

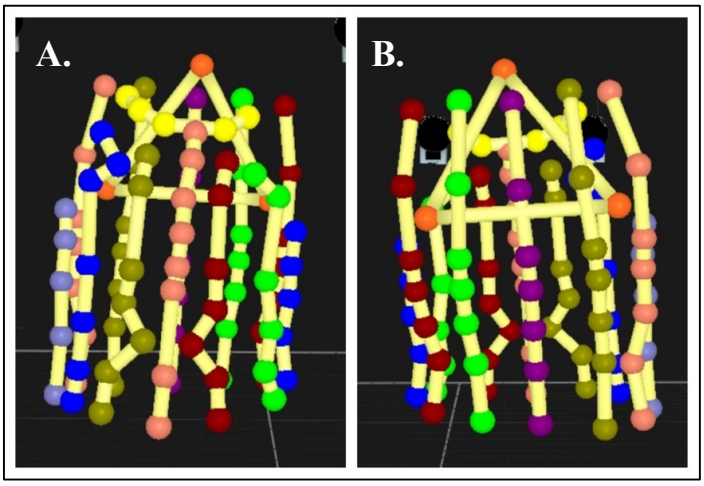

Figure 7.4 Three-dimensional markers placement
Panel A shows the markers placement on the front and Panel B shows the markers placement on the back of the torso

OEP breathing assessments were performed and respiratory parameters were measured during forced expiratory manoeuvres using a spirometer (Figure 7.5A) and a flow measuring BbB analyser (Metalyzer© 3B, Cortex Biophysik GmbH, Germany) (Figure 7.5B) and in the last 30 seconds of minutes 5, 7 and 10 of the 10-minutes cycling test at RPE 17 (Figure 7.5B).

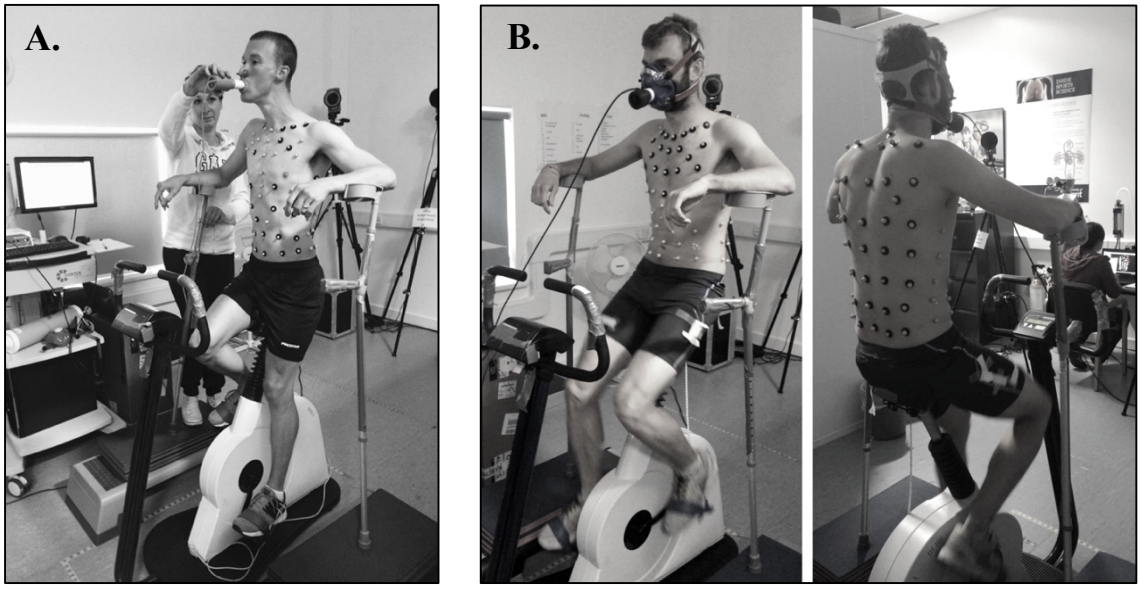

Figure 7.5 Study set up
Panel A shows the participant during simultaneous spirometry measurements and Panel B shows the participant during simultaneous breath-by-breath analysis

7.3.3.2 Spirometry

Using a digital spirometer (Spiro-USB^{TM} and MicroLab^{TM}, CareFusion, Germany 234 GmbH), participants completed a minimum of three forced maximal flow-volume manoeuvres (Miller et al., 2005). For each maximal flow-volume manoeuvre, the following measurements were recorded in accordance to ATS/ERS 2005 Guidelines (Miller et al., 2005): FEV_1 and FVC.

7.3.3.3 Compartmental measurements

The following indexes were used to evaluate the relationship between the different compartments of the torso: pulmonary rib cage and the abdominal rib cage (RCp/RCa),

the abdominal rib cage and the abdominal division (RCa/AB), the pulmonary rib cage and the abdominal division (RCp/AB) (Aliverti et al., 2004, Kenyon et al., 1997, Silvatti et al., 2012). A new index to measure distortions between the rib cage and the abdominal division (RC/AB) was also used.

7.3.3.4 Exercise test at RPE 17

Participants performed two aerobic exercise tests on a cycle ergometer (Lode - Corival, Groningen, The Netherlands). Participants were tested in two conditions; cycling with relaxed shoulders (C1; normal position) and cycling with lifted shoulders (C2; hunched position). The order of the cycling conditions was randomised.

The test started with a 2-minutes warm up exercise at 50 W. During the first of the two cycling trials, the power output displayed on the screen of the exercise bike was only visible for the research team and participants were asked to choose the resistance blinded. After the warm-up, participants (without being able to see the display screen, and therefore having relied solely on their perception of effort) were instructed to increase the power output to a resistance that equals to "Somewhat hard" exercise level (RPE 13). This stage lasted for 2 minutes, after which participants were asked to increase the power so they reached an exercise level of "Hard, Heavy" (RPE 15). They were instructed to cycle 2 minutes at this level, before they increased the power output again to a "Very Hard" exercise level (RPE 17). When participants reached this stage, they were instructed to cycle for 10 minutes at their previously set power output. The test ended with a 5-minutes recovery period. For the second cycling trial, the power outputs chosen by the participants in the first trial were used. Participants were instructed to maintain their preferred cadence

(60 - 90 RPM) throughout the test. Physiological markers of respiratory function were assessed throughout the test by using Metalyzer© 3B (Cortex Biophysik GmbH, Germany) BbB analyser. Taking simultaneous measurements was very much challenging. It required assistance: one person to operate the OEP system and another to run the CPET test, adjust the power output and ensure that markers were in place throughout the assessment. Also, prompt timing was crucial, in order to be able to sync the CPET data with the OEP output, the exact same time periods had to be recorded on both devices. Thus, it was not feasible to take any further measurements or collect any additional information (e.g. Borg-CR10 scores) during the cycling trials.

An overview of the experimental protocol of Visit 3 and 4 is provided in Figure 7.6.

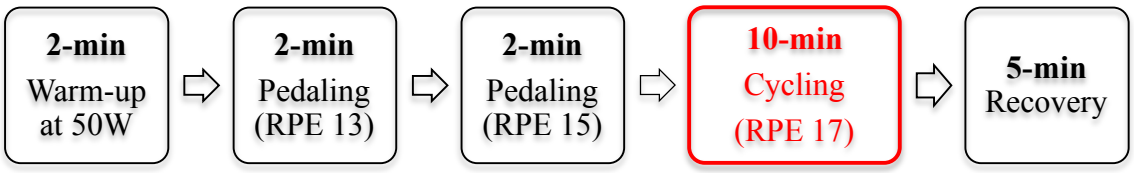

Figure 7.6 Overview of the experimental protocol (C1 & C2 conditions)

7.3.4 Statistical Analysis

Data was assessed for normal distribution and sphericity of data were checked and parametric or non-parametric tests applied thereafter, as appropriate. The dependent variables analysed were: (1) Spirometer: FEV_1, FVC; (2) BbB analyser: VT, BF, $\dot{V}_E$, TiTo, $\dot{V}O_2$, $\dot{V}CO_2$, RER and (3) OEP: RC, RCp, RCa and AB. Paired t-tests were used to assess differences of the variables between conditions. Statistical analysis was performed using statistical package for social sciences (Version 22 for Mac OS X SPSS Inc.,

Chicago, IL, USA). Normally distributed data were expressed as mean ± SD unless otherwise stated. The results were considered significant if $p \leq 0.05$.

7.4 Results

7.4.1 Participant characteristics

Fifteen male participants (N = 13 Caucasians) completed the study. Participant characteristics are presented in Table 7.1.

Table 7.1 Participant characteristics

Parameter N = 15	mean ± SD
Age (yr)	30 ± 7
Height (cm)	178.5 ± 5.8
Weight (kg)	73.0 ± 7.5

7.4.2 Lung volumes and compartmental contributions during forced expiratory manoeuvres

Mean FVC values showed a difference between the normal (C1) and hunched (C2) shoulder positions with higher values in C1 (5.35 ± 0.69 L vs. 5.22 ± 0.69 L; $p = 0.03$). During the forced expiratory manoeuvres, RC and AB contributions differed between conditions; RC showed lower values (66.24 ± 7.48 % vs. 63.85 ± 8.01 %; $p = 0.01$) and AB showed higher values (33.76 ± 7.48 % vs. 36.15 ± 8.01 %; $p = 0.01$) in C2 when compared to C1 (Table 7.2). When RC compartments were examined separately, RCp

contributions differed between conditions and showed lower values in C2 (42.20 ± 7.55 % vs. 39.75 ± 7.94 %; p = 0.01) (Table 7.2).

Mean FEV_1 values did not differ between conditions, however RC contribution was lower (65.76 ± 9.77 % vs. 62.15 ± 11.18 %; p < 0.001) and AB contribution higher (34.23 ± 9.77 % vs. 37.85 ± 11.18 %; p < 0.001) in C2 (Table 7.3). When RC compartments were examined separately, we found that RCp contributions differed between conditions and showed lower values in C2 (41.17 ± 9.32 % vs. 38.85 ± 10.66 %; p = 0.04) (Table 7.2).

Table 7.2 FVC and FEV_1 values and related compartmental contributions (mean ± SD) during the forced expiratory manoeuvres in C1 and C2

	Normal position (C1)	**Hunched position (C2)**
FVC (L)	5.35 ± 0.69 [a]	5.22 ± 0.69
OEP Contributions		
RC (%)	66.2 ± 7.5 [a]	63.9 ± 8.0
RCp (%)	42.2 ± 7.6 [a]	39.8 ± 7.9
RCa (%)	24.0 ± 4.1	24.1 ± 5.1
AB (%)	33.8 ± 7.5 [a]	36.1 ± 8.0
FEV_1 (L)	4.36 ± 0.65	4.35 ± 0.71
OEP Contributions		
RC (%)	65.8 ± 9.8 [a]	62.2 ± 11.2
RCp (%)	41.2 ± 9.3 [a]	38.8 ± 10.7
RCa (%)	24.6 ± 4.6	23.3 ± 5.3
AB (%)	34.2 ± 9.8 [a]	37.8 ± 11.9

[a] *Different from "C2" (p ≤ 0.05)*

7.4.3 Lung volumes and compartmental contributions during exercise

VE and BF increased in a similar pattern over time in both conditions with slightly higher values in C2 (Table 7.3). When the two conditions were compared, VT was lower in C2 at the measured time points, however the difference was only significant at E5 (2.80 ± 0.65 L vs. 2.68 ± 0.58 L; $p = 0.01$, in C1 and C2 respectively). Shoulder positioning had no effects on gas exchange parameters (Table 7.3).

Table 7.3 Physiological parameters (mean ± SD) during the 10-minute cycling test (at minutes 5, 7 & 10) in C1 and C2

	Normal position (C1)			Hunched position (C2)		
Response variables	**minute 5 (E5)**	**minute 7 (E7)**	**minute 10 (E10)**	**minute 5 (E5)**	**minute 7 (E7)**	**minute 10 (E10)**
VT (L)	2.8 ± 0.7 [a]	2.7 ± 0.7	2.7 ± 0.6	2.7 ± 0.6	2.6 ± 0.6	2.6 ± 0.6
BF (/min)	33 ± 8	37 ± 9	39 ± 9	35 ± 8	39 ± 9	42 ± 10
$\dot{V}_E$ (L/min)	89.4 ± 17.9	96.9 ± 19.6	100.3 ± 23.2	91.7 ± 20.2	98.9 ± 20.5	103.8 ± 24.9
TiTo (%)	49 ± 5	48 ± 3	49 ± 3	49 ± 3	49 ± 3	49 ± 3
$\dot{V}O_2$ (L/min)	2.8 ± 0.4	2.9 ± 0.4	3.0 ± 0.5	2.9 ± 0.5	3.0 ± 0.5	3.0 ± 0.5
$\dot{V}CO_2$ (L/min)	3.0 ± 0.5	3.1 ± 0.5	3.1 ± 0.5	3.0 ± 0.5	3.1 ± 0.5	3.1 ± 0.5
RER	1.05 ± 0.05	1.04 ± 0.05	1.03 ± 0.04	1.04 ± 0.05	1.03 ± 0.04	1.02 ± 0.05

[a] *Different from "C2" at corresponding time point ($p \leq 0.05$)*

RC contribution was decreased and AB contribution was increased in C2 throughout the test, although significant difference between the two conditions were observed only at E5 with RC values of 59.06 ± 10.01 % vs. 57.23 ± 9.38 %; $p = 0.01$; in C1 and C2 respectively and AB values values of 41.56 ± 10.32 % vs. 43.24 ± 9.33 %; $p = 0.01$; in C1 and C2 respectively (Table 7.4). At this time point, both RCp (39.90 ± 8.59 % vs. 36.64 ± 8.36 %; $p < 0.001$, in C1 and C2 respectively) and RCa (19.16 ± 3.21 % vs. 20.59 ± 3.37 %; $p = 0.02$, in C1 and C2 respectively) differed significantly between conditions with RCp contributing less to the RC in C2 (Table 7.4).

At E7, both RCp (39.90 ± 8.59 % vs. 36.64 ± 8.36 %; $p < 0.001$, in C1 and C2 respectively) and RCa (19.16 ± 3.21 % vs. 20.59 ± 3.37 %; $p = 0.02$, in C1 and C2 respectively) differed significantly between conditions, however this difference did not affect their contribution to the RC in either C1 or C2 (Table 7.4).

Table 7.4 Compartmental contributions (mean ± SD) during the 10-minute cycling test (at minutes 5, 7 & 10) in C1 and C2

	Normal position (C1)			Hunched position (C2)		
	minute 5 (E5)	**minute 7 (E7)**	**minute 10 (E10)**	**minute 5 (E5)**	**minute 7 (E7)**	**minute 10 (E10)**
Compartments						
RC (%)	59.06 ± 10.01 [a]	57.38 ± 9.92	60.58 ± 8.92	57.23 ± 9.38	57.31 ± 9.70	57.97 ± 10.29
RCp (%)	39.90 ± 8.59 [a]	38.99 ± 8.24 [a]	40.83 ± 8.18	36.64 ± 8.36	37.08 ± 7.71	37.14 ± 8.05
RCa (%)	19.16 ± 3.21 [a]	18.89 ± 3.36 [a]	19.76 ± 3.11	20.59 ± 3.37	20.24 ± 3.75	20.83 ± 4.31
AB (%)	41.56 ± 10.32 [a]	42.69 ± 9.90	40.06 ± 8.99	43.24 ± 9.33	43.73 ± 10.60	42.54 ± 10.44
Indexes						
RCp/RCa	2.11 ± 0.44 [a]	2.10 ± 0.46 [a]	2.10 ± 0.49	1.82 ± 0.49	1.87 ± 0.43	1.83 ± 0.48
RCa/AB	0.50 ± 0.17	0.47 ± 0.16	0.52 ± 0.16	0.50 ± 0.16	0.50 ± 0.19	0.53 ± 0.21
RCp/AB	21.21 ± 8.96 [a]	21.83 ± 8.60 [a]	20.79 ± 9.44	26.50 ± 13.11	25.25 ± 11.62	25.38 ± 12.40
RC/AB	1.56 ± 0.61 [a]	1.46 ± 0.54	1.65 ± 0.57	1.42 ± 0.52	1.43 ± 0.56	1.38 ± 0.69

[a] *Different from "C2" at corresponding time point ($p \leq 0.05$)*

7.5 Discussion

The results of this study suggest that there is a difference in measures of spirometric indices and compartmental contributions between the two shoulder positions with a significant decrease in FVC and RB motion when subjects hunching their shoulders. This phenomenon was seen not only during maximal lung function assessments but also captured during exercise.

The reduced vital capacity measured in hunched position indicates that athletes may achieve larger lung volumes during expiratory manoeuvres when in normal body position with straight back and relaxed shoulders. These results are in line with previous research of Chang et al. (2005), who demonstrated that an increase in energy expenditure due to hypertonic respiratory muscles may reduce ventilatory capacities. Our finding of reduced lung volumes is also in agreement with literature where McKeough et al. (2003) reported that arm movements could alter lung volumes; they suggested that arm position may change RB expansion and affect respiration.

Forward shoulder position (FSP) is described as abduction and elevation of the scapula and a forward position of the shoulder, giving a caved-in appearance of the chest (Savadatti & Gaude, 2011). It can result from shoulder being pulled forward by overdeveloped, shortened and tight respiratory muscles such as the serratus anterior, pectoralis minor and intercostals or other shoulder girdle muscles, such as pectoralis major and upper trapezius muscles (Savadatti & Gaude, 2011). Our findings also support the results of the studies conducted by Ghanbari et al. (2008) and Savadatti et al. (2011) who found there was a significant correlation between FSP and respiratory values; respiratory parameters decline with increasing FSP degree (Ghanbari et al., 2008). They

suggested that FSP may decrease the expansion of the RC during inspiration (Ghanbari et al., 2008), increase the energy expenditure and the inability of the diaphragm to descend (Savadatti & Gaude, 2011) and reduce the compliance of the respiratory system (Ghanbari et al., 2008).

Haas et al. (1982) and Appel et al. (1986) reported that altering the orientation of accessory muscles of respiration (as seen in FSP) has marked effects on the operating length and function of the diaphragm. Our results differ from these findings in that RCa did not change by the altered shoulder position, suggesting that either the diaphragmatic region was not affected by the change in upper body posture in our experimental set up or the upright cycling position with arms positioned on supports at 90° to the torso might have placed the participants in such an altered body position that the difference in compartmental contributions could not be detected between 'normal' and hunched conditions. Diaphragm electromyogram (EMGdi) is a valuable technique for the recording of electrical activity of the diaphragm (Estrada et al., 2016). The analysis of the EMGdi signal amplitude is an alternative approach for the indirect quantification of neural respiratory drive, which reflects the load on the respiratory muscles (Estrada et al., 2016). Using this method during the exercise tests in order to confirm diaphragmatic activity would have been beneficial and recommended for future studies.

In this study, ventilation increased in a similar pattern over time in both conditions. The ventilation in hunched position was achieved at a slightly reduced VT and a higher BF without any alterations in gas exchange parameters. The breathing motion in C2 is similar to that assessed in restrictive lung disease, where due to the reduced compliance, the work of breathing increases and individuals have to work harder to ventilate the lungs (Brown

et al., 2006).

RC and AB contributions were significantly different in hunched position at the first assessed time point (E5), but not at later stages of the test. When RC contribution was divided into RCp and RCa, both parameters differed significantly between conditions, however RCp contributed less to the total RC volume in hunched position. This phenomenon may be explained by previous work of Illi et al. (2013) who reported that in altered body posture, the inspiratory and expiratory RC muscles have greater activation when compared to the diaphragm (Illi et al., 2013). At E7, both RCp and RCa differed significantly between conditions, however this difference did not affect their contribution to the total RC volume in neither of the cycling trials. No further differences were observed between conditions during the test, which might be due to the limitations described in 7.6.

Although results were not conclusive, the percentage contributions and the coordination between compartments during breathing are assumed to be clinically and diagnostically relevant in DB, especially when the focus of interest is the optimisation of breathing mechanics in order to resolve symptoms. It is important to highlight, that each individual possesses their own characteristic breathing pattern, therefore when DB is suspected, assessment should be carried out on a case-by-case basis and treatment should aim to achieve breathing pattern that is optimal for the given individual.

7.6 Limitations

Although OEP provides important physiological information regarding chest wall motion and therefore it is the most promising approach in the assessment of DB, the technique has a number of limitations. (1) Marker placement is extremely time consuming, especially in individuals, in which landmarks are difficult to identify. (2) Although markers are attached to the skin using bi-adhesive tape, due to the extensive motion (especially at high intensities) and a consequent sweating during exercise, markers often fall off and are difficult to be physically replaced. (3) In our setup, in order to acquire optimal data with all markers visible for the duration of the test, participants were required to sit completely upright with arms in the scapular plane. Most participants found this position unnatural and difficult to maintain during prolonged, high intensity exercise. As a consequence, critical markers were blocked from camera view, resulting in data that was unable to be reconstructed and requiring virtual markers to be used. This unnatural position did not represent normal breathing, hence the difference between C1 and C2 may have been greater had we been able to allow the arms to move their natural way.

7.7 Conclusions

These findings suggest that respiratory excursion and lung volume compartmentalisation are affected by the position of the shoulders. Specifically, a hunched shoulder position leads to increased abdominal motion to vital capacity and decreased lung volumes. OEP, despite of its limitations, may be a useful tool to detect altered parameters associated with development of exertional dyspnoea and sub-optimal breathing mechanics.

Chapter 8. General Discussion

8.1 General Discussion

It is clear that the findings from this thesis contribute to the limited available literature surrounding DB and highlight particular areas that warrant further research. Specifically, the main results of this thesis were threefold: (1) Chapter 4 demonstrated a very high prevalence (68%) of airway hyper-reactivity in elite level swimmers and revealed that a high proportion of athletes experiences exercise-induce respiratory symptoms in the lack of objective evidence of airway dysfunction. (2) Chapter 5 showed that the NQ, which at present is the most commonly applied diagnostic method for DB, has a low sensitivity in predicting a positive EVH challenge and differentiating EIB from DB in athletes. (3) Chapter 6 and 7 suggested that cycling for a prolonged period at high intensities with hunched shoulders does not result in significant changes in physiological markers of respiratory function, but triggers increased abdominal contribution to vital capacity and a subsequent increase in perception of breathing sensation.

Athletes are particularly liable to injuries to the airway epithelium when they are requested to sustain high level exercise, with consequent high ventilation demand, especially when additionally exposed to unfavourable environmental conditions (i.e. cold dry air or chlorinated indoor pools) (Carlsen et al., 2008, Weiler et al., 2007, Moreira et al., 2011, Fitch, 2012, Dickinson et al., 2005). The findings from Chapter 4 support this notion, confirming the highest prevalence (68%) of airway dysfunction reported in elite swimmers. In contrast, in elite boxers, who are not exposed to the environmental stress of the pool environment (high concentrations of inhaled surface irritants such as chlorine gas derivatives), the prevalence of airway dysfunction was found to be nine fold lower (8%). It is important to note, that our cohort may have had greater exposure to triggers,

as they were part of an elite squad, in contrast to other studies (Parsons et al., 2007, Molphy et al., 2014, Mannix et al., 2004) that have only tested well-trained and/or sub-elite athletes. It is also possible that some athletes, with a positive EVH test on the day of testing, could have a negative EVH result on a subsequent or second test. This acknowledged, the majority of the athletes tested positive had a fall in FEV_1 > 15% (N = 24; 73%) and in prior studies, test repeatability is improved in those with a fall of this severity or above (Price et al., 2015).

It is claimed that dyspnoea is a prominent and disabling clinical characteristic of exercise-induced airways dysfunction, such as EIB (Parsons et al., 2011). Although it can be diagnosed and managed effectively, the care that athletes suffering from this condition receive is often suboptimal. In this respect, it is apparent that the diagnosis of EIB is often made without objective evidence and in order to improve symptoms, athletes may be advised to reduce exercise intensity. At elite levels, this can result in withdrawing from competitive events and ultimately ending one's sports career.

Research in the past 20 years has highlighted an important, yet often overlooked fact, that there exists a weak association between the presence of conventional airway-centric symptoms (e.g. cough, wheeze and dyspnoea) and objective test confirmation of EIB (Rundell et al., 2001, Ansley et al., 2012, Nielsen et al., 2013). This poor relationship has been reinforced by the results of Chapter 4, that demonstrated a high prevalence of athletes, who reported respiratory complaints, despite having been tested negative on the EVH challenge. The fact, that half of these symptomatic EVH negative athletes had a previous diagnosis of asthma/EIB and were using one or a combination of short-acting β_2-agonists, long-acting inhaled β_2-agonists and inhaled corticosteroids, highlights an

important problem that health professionals, who encounter athletes with unexplained respiratory symptoms or symptoms that are "refractory" to treatment, face with and warns about the 'danger' of using solely a symptom-based method for diagnosis. The reason for this discrepancy has not yet been fully understood, but may relate to conditions that mimic EIB and not inevitably caused by underlying pathology.

Identifying the cause of the perceived symptoms and distinguishing them from those originating from organic respiratory problems require careful evaluation, however, to date there exists no clear consensus on a gold standard assessment of this kind. In Chapter 5, when evaluating the diagnostic performance of the NQ in distinguishing DB from EIB, self-reported symptoms on the NQ demonstrated only modest value in predicting clinical diagnosis. Three quarters of those athletes who scored under the cut-off value on the NQ, tested positive on the EVH challenge. One explanation for this might be an impaired symptom recognition including faulty perception of dyspnoea in elite athletes, especially in swimmers, who reportedly consider their exercise-induced symptoms as a normal effect of high-intensity training and consequently fail to report them (Turcotte et al., 2003). Additionally, symptoms such as cough, wheeze and chest tightness may manifest in relation to cold air inhalation or only in provocative environments (e.g. chlorine exposure in swimming pools). Nearly half of all NQ positive individuals had a positive result on the EVH challenge, all of whom were elite athletes. In contrast, none of the NQ positive recreational athletes tested positive on the EVH challenge suggesting that to a certain extent, NQ may have a greater potential in differentiating EIB from DB in recreational athletes than in high level sports.

Although many of the studies assessing the epidemiology of DB use the NQ as a method of diagnosis, the questionnaire in its current form is "neither disease or population-specific". The analysis in Chapter 5 has revealed a novel pattern of principal components both in terms of dimensional structure and items loading in physically active adolescents and suggested the possibility of removing five of the original questions from the questionnaire. In order to make the NQ specific to exercise and presumably more sensitive in identifying DB in athletes, a new questionnaire should be developed based on the previously described shortened version of the NQ and with the addition of questions related to psychosocial characteristics and sport specific respiratory symptoms.

In order for a questionnaire to become clinically useful, it is important to assure that the instrument consistently measures what it purports to measure, when properly administered (Del Greco et al., 1987). When the focus of interest is in determining whether the scores satisfy a diagnosis, the questionnaire has to be assessed against a well-established existing standard, a specific diagnostic criterion (e.g. objective evidence of a condition). In this context, to ensure that a newly developed symptoms questionnaire has the ability to predict DB in athletes, it should be stack up against another instrument or predictor. However, due to the lack of gold standard diagnostic tool for the identification of DB, a validation procedure of this kind is currently not possible. These findings suggest that, instead of symptom recognition, assessments should initially focus on the evaluation of the physiological and biomechanical characteristics of DB and the establishment of a gold standard diagnostic method.

As highlighted in previous chapters, a high proportion of young athletes present with a breathing abnormality, which does not sit within the traditional clinical diagnosis and

cannot be defined through the standard assessment methods. In recent years, it has been proposed that certain triggers (e.g. high intensity aerobic exercise) can initiate a transition from a sporadic, altered breathing pattern, to a sustained disordered breathing, causing symptoms that are similar to those seen in EIB, but not linked to underlying pathology.

It has been previously suggested (David et al., 2012) that stability of the body may be compromised in situations, in which respiratory demand increases and requires voluntary control. David et al. (2012) claimed that a functional link may exist between ventilation and posture control centres. They reported that an increase in tidal volume and breathing frequency during hyperventilation, is much more likely to change mass repartition of the trunk and to disturb posture. Although these findings suggest that voluntarily hyperventilation induces a wide range of posturographic perturbations, it is not known what happens to the respiratory parameters when an altered breathing pattern is maintained for a longer period of time. Thus Chapter 6 aimed to establish whether an alteration in body positioning profoundly influences breathing function and respiratory effort, when ventilatory requirements are increased.

The results of Chapter 6 demonstrated that body posture during cycling at high intensity levels for a set period of time, has no significant effect on physiological markers of respiratory function, however it may lead to an increased perception of breathing sensation, such as dyspnoea. The intensified awareness of breathing detected in this study in the lack of physiological disturbances, may be indicative of suboptimal function elsewhere than in the respiratory tract and may not even represent pathological condition (Johansson et al., 2015). Inefficient breathing pattern with increased workloads, reduced mechanical advantage and increased ventilatory requirements may occur due to changes

in the optimal motor control of the respiratory muscles (O'Donnell et al., 2017), but detecting these alterations using breath by breath gas analysis techniques has proven not to be feasible and suggested that assessing the movement pattern changes related to body posture during exercise by using lung volume compartmentalisation techniques may be a better way to detect DB.

Until recently the movement of the chest and abdomen during exercise has not been considered in either the understanding of optimal breathing pattern or in relation to exercise respiratory diseases (Hull et al., 2009, Massaroni et al., 2017). Although both non-contact (Levai et al., 2012) and contact (Jensen et al., 2014) breath measurement methods have been utilised in recent years, they have limitations, such as requiring individuals to remain very still during the measurements, which make their application in exercise challenging. In the last decade, OEP has taken the lead in the use of investigating chest wall kinematics and volume changes in the three compartments of the torso (Massaroni et al., 2017). This technique allows the study of both breathing volumes and biomechanical indexes for a better comprehension of the work of breathing without interferences using invasive instrumentation (Massaroni et al., 2017).

Chapter 7 demonstrated that spirometric indices and compartmental contributions differ when body position is altered; a significant decrease in FVC and rib cage motion was observed when participants hunched their shoulders during the assessment. This phenomenon was seen not only during the maximal lung function tests but also captured during exercise. Furthermore, a significant difference in rib cage and abdominal contributions was detected when shoulders were hunched during cycling. Illi et al. (2013) previously reported that in altered body posture, the inspiratory and expiratory rib cage

muscles have greater activation when compared to the diaphragm. This phenomenon was supported by our findings at the beginning of the assessment. When rib cage contribution was divided into two compartments (pulmonary and abdominal rib cage), we found that they both changed significantly with the alteration of body position, with the pulmonary rib cage contributing less to the total rib cage volume in hunched position. At a later stage, the motion of both rib cage compartments differed significantly between conditions, however this difference did not affect their contribution to the total rib cage volume in neither of the cycling trials. These findings suggest that respiratory excursion and lung volume compartmentalisation are affected by the position of the shoulders. Specifically, a hunched shoulder position leads to increased abdominal motion to vital capacity and decreased lung volumes. Although OEP provides important information regarding chest wall motion and therefore it is the most promising approach in the assessment of DB, the technique has a number of limitations, which must be resolved or at least reduced prior to undertaking further work in this field.

8.2 Future directions

Precise detection of distortions between compartmental contributions in exercising individuals may be a key element in the identification of DB and could potentially contribute towards the establishment of a gold standard diagnostic tool in this condition. Future research may want to consider the inclusion of additional cameras in order to assess individuals in a more natural cycling position and by doing so to allow the precise detection of distortions between compartmental contributions. Additionally, in order to support the easy application of the setup and reduce the processing time, a new marker set with lower number of markers would be beneficial to be developed.

Once a gold standard diagnostic method is established for the identification of DB, research could focus on the development of a DB specific symptom recognition instrument. This new questionnaire should be designed to have higher accuracy in identifying symptoms associated with exercise induced breathing impairment and to be more suitable for an athletic population.

8.3 Conclusions

Athletes who train and compete in provocative environments at a sustained high ventilation have an increased susceptibility to airway dysfunction. Additionally, a high proportion of athletes reports exercise-induced respiratory symptoms in the lack of objective evidence of airway dysfunction. Although NQ is currently the most commonly used diagnostic method for DB, it has a low sensitivity in predicting a positive EVH challenge and differentiating EIB from DB in athletes. Cycling with hunched shoulders at high intensities over a prolonged period does not result in significant changes in physiological markers of respiratory function, but leads to altered breathing mechanics and a consequential increase in the sensation of dyspnoea, without the presence of cardio-pulmonary disease. Due to the nature of the alterations, it has been concluded, that DB may be best assessed by using lung volume compartmentalisation techniques, such as OEP.

References

Abdi, H. & Williams, L.J. (2010). Principal component analysis. *Wiley Interdisciplinary Reviews: Computational Statistics,* 2, 433-459.

Agache, I., Ciobanu, C., Paul, G. & Rogozea, L. (2012). Dysfunctional breathing phenotype in adults with asthma-incidence and risk factors. *Clinical and Translational Allergy,* 2, 18.

Albouaini, K., Egred, M., Alahmar, A. & Wright, D.J. (2007). Cardiopulmonary exercise testing and its application. *Heart (British Cardiac Society),* 93, 1285-1292.

Aliverti, A. & Pedotti, A. (2002). Opto-electronic plethysmography. Opto-electronic plethysmography. *Mechanics of Breathing* (pp. 47-59). Springer.

Aliverti, A. & Pedotti, A. (2014). Optoelectronic Plethysmography: Principles of Measurements and Recent Use in Respiratory Medicine. Optoelectronic Plethysmography: Principles of Measurements and Recent Use in Respiratory Medicine. *Mechanics of Breathing* (pp. 149-168). Springer.

Aliverti, A., Cala, S.J., Duranti, R., Ferrigno, G., Kenyon, C.M., Pedotti, A., Scano, G., Sliwinski, P., Macklem, P.T. & Yan, S. (1997). Human respiratory muscle actions and control during exercise. *Journal of Applied Physiology (Bethesda, Md.: 1985),* 83, 1256-1269.

Aliverti, A., Stevenson, N., Dellaca, R.L., Lo Mauro, A., Pedotti, A. & Calverley, P.M. (2004). Regional chest wall volumes during exercise in chronic obstructive pulmonary disease. *Thorax,* 59, 210-216.

American College of Sports Medicine (2013). *ACSM's Guidelines for Exercise Testing and Prescription,* 9th edn. Philadelphia, PA: Thompson Wolters Kluwer/Lippincott Williams & Wilkins.

American Thoracic Society (1999). Dyspnea. mechanisms, assessment, and management: A consensus statement. *American Journal of Respiratory and Critical Care Medicine,* 159, 321-340.

Anderson, S.D. & Kippelen, P. (2005). Exercise-induced bronchoconstriction: Pathogenesis. *Current Allergy and Asthma Reports,* 5, 116-122.

Anderson, S. (2011). Bronchial challenge tests: Usefulness, availability and limitations. *Breathe,* 8, 53-60.

Anderson, S.D., Argyros, G.J., Magnussen, H. & Holzer, K. (2001). Provocation by eucapnic voluntary hyperpnoea to identify exercise induced bronchoconstriction. *British Journal of Sports Medicine,* 35, 344-347.

Anderson, S.D. & Kippelen, P. (2012). Assessment and prevention of exercise-induced bronchoconstriction. *British Journal of Sports Medicine,* 46, 391-396.

Anderson, S.D. & Kippelen, P. (2008). Airway injury as a mechanism for exercise-induced bronchoconstriction in elite athletes. *The Journal of Allergy and Clinical Immunology,* 122, 225-35; quiz 236-7.

Ansley, L., Kippelen, P., Dickinson, J. & Hull, J. (2012). Misdiagnosis of exercise-induced bronchoconstriction in professional soccer players. *Allergy,* 67, 390-395.

Appel, M., Childs, A., Healey, E., Markowitz, S., Wong, S. & Mead, J. (1986). Effect of posture on vital capacity. *Journal of Applied Physiology (Bethesda, Md.: 1985),* 61, 1882-1884.

Argyros, G.J., Roach, J.M., Hurwitz, K.M., Eliasson, A.H. & Phillips, Y.Y. (1996). Eucapnic voluntary hyperventilation as a bronchoprovocation technique: Development of a standarized dosing schedule in asthmatics. *Chest,* 109, 1520-1524.

Barker, N. & Everard, M.L. (2015). Getting to grips with 'dysfunctional breathing'. *Paediatric Respiratory Reviews,* 16, 53-61.

Beaty, M.M., Wilson, J.S. & Smith, R.J. (1999). Laryngeal motion during exercise. *The Laryngoscope,* 109, 136-139.

Benditt, J.O. (2006). The neuromuscular respiratory system: Physiology, pathophysiology, and a respiratory care approach to patients. *Respiratory Care,* 51, 829-37; discussion 837-9.

Bent III, J.P., Miller, D.A., Kim, J.W., Bauman, N.M., Wilson, J.S. & Smith, R.J. (1996). Pediatric exercise-induced laryngomalacia. *Annals of Otology, Rhinology & Laryngology,* 105, 169-175.

Bernard, A., Nickmilder, M., Voisin, C. & Sardella, A. (2009). Impact of chlorinated swimming pool attendance on the respiratory health of adolescents. *Pediatrics,* 124, 1110-1118.

Bittleman, D.B., Smith, R.J. & Weiler, J.M. (1994). Abnormal movement of the arytenoid region during exercise presenting as exercise-induced asthma in an adolescent athlete. *Chest,* 106, 615-616.

Björnsdóttir, U.S., Gudmundsson, K., Hjartarson, H., Bröndbo, K., Magnússon, B. & Juliusson, S. (2000). Exercise-induced laryngochalasia: An imitator of exercise-induced bronchospasm. *Annals of Allergy, Asthma & Immunology,* 85, 387-391.

Bonini, M. & Palange, P. (2015). Exercise-induced bronchoconstriction: New evidence in pathogenesis, diagnosis and treatment. *Asthma Research and Practice,* 1, 1.

Borg, E., Borg, G., Larsson, K., Letzter, M. & Sundblad, B. (2010). An index for breathlessness and leg fatigue. *Scandinavian Journal of Medicine & Science in Sports,* 20, 644-650.

Borg, G. (1998). *Borg's Perceived Exertion and Pain Scales.* 2nd edn. Champaign, IL: Human kinetics.

Bougault, V., Turmel, J. & Boulet, L. (2010). Bronchial challenges and respiratory symptoms in elite swimmers and winter sport athletes: Airway hyperresponsiveness in asthma: Its measurement and clinical significance. *CHEST Journal,* 138, 31S-37S.

Bougault, V. & Boulet, L.P. (2013). Airways disorders and the swimming pool. *Immunology and Allergy Clinics of North America,* 33, 395-408, ix.

Bougault, V. & Boulet, L.P. (2012). Airway dysfunction in swimmers. *British Journal of Sports Medicine,* 46, 402-406.

Bougault, V., Turmel, J. & Boulet, L.P. (2011). Airway hyperresponsiveness in elite swimmers: Is it a transient phenomenon? *The Journal of Allergy and Clinical Immunology,* 127, 892-898.

Bougault, V., Turmel, J., Levesque, B. & Boulet, L.P. (2009). The respiratory health of swimmers. *Sports Medicine (Auckland, N.Z.),* 39, 295-312.

Boulding, R., Stacey, R., Niven, R. & Fowler, S.J. (2016). Dysfunctional breathing: A review of the literature and proposal for classification. *European Respiratory Review: An Official Journal of the European Respiratory Society,* 25, 287-294.

Boulet, L.P., Turcotte, H., Langdeau, J.B. & Bernier, M.C. (2005). Lower airway inflammatory responses to high-intensity training in athletes. *Clinical and Investigative Medicine.Medecine Clinique Et Experimentale,* 28, 15-22.

Bradley, H. & Esformes, J. (2014). Breathing pattern disorders and functional movement. *International Journal of Sports Physical Therapy,* 9, 28-39.

Brown, S.P., Miller, W.C. & Eason, J.M. (2006). *Exercise Physiology: Basis of Human Movement in Health and Disease,* Lippincott Williams & Wilkins.

Brugman, S. (2003). The many faces of vocal cord dysfunction: What 36 years of literature tell us. *Am J Respir Crit Care Med,* 167, A588.

Brullmann, G., Fritsch, K., Thurnheer, R. & Bloch, K.E. (2010). Respiratory monitoring by inductive plethysmography in unrestrained subjects using position sensor-adjusted calibration. *Respiration; International Review of Thoracic Diseases,* 79, 112-120.

Bush, A. & Fleming, L. (2016). Is asthma overdiagnosed? *Archives of Disease in Childhood,* 101, 688-689.

Bussotti, M., Di Marco, S. & Marchese, G. (2014). Respiratory disorders in endurance athletes - how much do they really have to endure? *Open Access Journal of Sports Medicine,* 5, 47-63.

Butler, J.E. (2007). Drive to the human respiratory muscles. *Respiratory Physiology & Neurobiology,* 159, 115-126.

Cala, S.J., Kenyon, C.M., Ferrigno, G., Carnevali, P., Aliverti, A., Pedotti, A., Macklem, P.T. & Rochester, D.F. (1996). Chest wall and lung volume estimation by optical reflectance motion analysis. *Journal of Applied Physiology (Bethesda, Md.: 1985),* 81, 2680-2689.

Carlsen, K.H., Anderson, S.D., Bjermer, L., Bonini, S., Brusasco, V., Canonica, W., Cummiskey, J., Delgado, L., Del Giacco, S.R., Drobnic, F., Haahtela, T., Larsson, K., Palange, P., Popov, T., van Cauwenberge, P., European Respiratory Society & European Academy of Allergy and Clinical Immunology (2008). Exercise-induced asthma, respiratory and allergic disorders in elite athletes: Epidemiology, mechanisms and diagnosis: Part I of the report from the joint task force of the european respiratory society (ERS) and the european academy of allergy and clinical immunology (EAACI) in cooperation with GA2LEN. *Allergy,* 63, 387-403.

Castricum, A., Holzer, K., Brukner, P. & Irving, L. (2010). The role of the bronchial provocation challenge tests in the diagnosis of exercise-induced bronchoconstriction in elite swimmers. *British Journal of Sports Medicine,* 44, 736-740.

Chaitow, L., Bradley, D. & Gilbert, C. (2014a). Breathing pattern disorders and the athlete. In CliftonSmith (Ed.), *Recognizing and Treating Breathing Disorders: a multidisciplinary approach* (pp. 216). Elsevier Health Sciences.

Chaitow, L., Bradley, D. & Gilbert, C. (2014b). Capnography assessment. In McLaughlin (Ed.), *Recognizing and Treating Breathing Disorders: a multidisciplinary approach* (pp. 147-149). Elsevier Health Sciences.

Chaitow, L., Bradley, D. & Gilbert, C. (2014c). Interaction of psychological and emotional variables with breathing dysfunction. In Gilbert (Ed.), *Recognizing and Treating Breathing Disorders: a multidisciplinary approach* (pp. 81). Elsevier Health Sciences.

Chaitow, L., Bradley, D. & Gilbert, C. (2014d). Questionnaires and manual methods for assessing breathing dysfunction. In Courtney & Van Dixhoorn (Eds.), *Recognizing and Treating Breathing Disorders: a multidisciplinary approach* (pp. 140-141). Elsevier Health Sciences.

Chaitow, L., Bradley, D. & Gilbert, C. (2014e). Questionnaires and manual methods for assessing breathing dysfunction. In Courtney & Van Dixhoorn (Eds.), *Recognizing and Treating Breathing Disorders: a multidisciplinary approach* (pp. 142). Elsevier Health Sciences.

Chaitow, L., Bradley, D. & Gilbert, C. (2014f). The structure and function of breathing. In Chaitow, Bradley & Gilbert (Eds.), *Recognizing and Treating Breathing Disorders: a multidisciplinary approach* (pp. 27-29). Elsevier Health Sciences.

Chan, Y.K.A. (2008). Flow transducers. Flow transducers. *Biomedical Device Technology: Principles and Design* (pp. 104). Springfield, Illinois: Charles C Thomas Publisher Ltd.

Chang, A.T., Boots, R.J., Brown, M.G., Paratz, J.D. & Hodges, P.W. (2005). Ventilatory changes following head-up tilt and standing in healthy subjects. *European Journal of Applied Physiology,* 95, 409-417.

Chiba, R., Takakusaki, K., Ota, J., Yozu, A. & Haga, N. (2016). Human upright posture control models based on multisensory inputs; in fast and slow dynamics. *Neuroscience Research,* 104, 96-104.

Christensen, P.M., Thomsen, S., Rasmussen, N. & Backer, V. (2011). Exercise-induced laryngeal obstructions: Prevalence and symptoms in the general public. *European Archives of Oto-Rhino-Laryngology,* 268, 1313-1319.

Christensen, P.M., Heimdal, J.H., Christopher, K.L., Bucca, C., Cantarella, G., Friedrich, G., Halvorsen, T., Herth, F., Jung, H., Morris, M.J., Remacle, M., Rasmussen, N., Wilson, J.A. & ERS/ELS/ACCP Task Force on Inducible Laryngeal Obstructions (2015). ERS/ELS/ACCP 2013 international consensus conference nomenclature on inducible laryngeal obstructions. *European Respiratory Review: An Official Journal of the European Respiratory Society,* 24, 445-450.

Christopher, K.L. & Morris, M.J. (2010). Vocal cord dysfunction, paradoxic vocal fold motion, or laryngomalacia? our understanding requires an interdisciplinary approach. *Otolaryngologic Clinics of North America,* 43, 43-66.

CliftonSmith, T. & Rowley, J. (2011). Breathing pattern disorders and physiotherapy: Inspiration for our profession. *Physical Therapy Reviews,* 16, 75-86.

Comrey, A. & Lee, H. (1992). A first course in factor analysis. *Hillsdale, NJ, Lawrence Eribaum Associates Inc.*

Conroy, D.E. (2001). Fear of failure: An exemplar for social development research in sport. *Quest,* 53, 165-183.

Conroy, D.E., Coatsworth, J.D. & Kaye, M.P. (2007). Consistency of fear of failure score meanings among 8-to 18-year-old female athletes. *Educational and Psychological Measurement,* 67, 300-310.

Conroy, D.E., Poczwardowski, A. & Henschen, K.P. (2001). Evaluative criteria and consequences associated with failure and success for elite athletes and performing artists. *Journal of Applied Sport Psychology,* 13, 300-322.

Cook, C.E. (2008). Clinimetrics corner: The minimal clinically important change score (MCID): A necessary pretense. *Journal of Manual & Manipulative Therapy,* 16, 82E-83E.

Costa, D., Cancelliero, K.M., Ike, D., Laranjeira, T.L., Pantoni, C.B.F. & Borghi-Silva, A. (2011). Strategy for respiratory exercise pattern associated with upper limb movements in COPD patients. *Clinics,* 66, 299-305.

Courtney, R. (2009). The functions of breathing and its dysfunctions and their relationship to breathing therapy. *International Journal of Osteopathic Medicine,* 12, 78-85.

Courtney, R. & Cohen, M. (2008). Investigating the claims of konstantin buteyko, MD, ph. D.: The relationship of breath holding time to end tidal CO2 and other proposed measures of dysfunctional breathing. *The Journal of Alternative and Complementary Medicine,* 14, 115-123.

Courtney, R. & Greenwood, K.M. (2009). Preliminary investigation of a measure of dysfunctional breathing symptoms: The self evaluation of breathing questionnaire (SEBQ). *International Journal of Osteopathic Medicine,* 12, 121-127.

Courtney, R., Van Dixhoorn, J. & Cohen, M. (2008). Evaluation of breathing pattern: Comparison of a manual assessment of respiratory motion (MARM) and respiratory induction plethysmography. *Applied Psychophysiology and Biofeedback,* 33, 91-100.

Courtney, R., Cohen, M. & van Dixhoorn, J. (2011a). Relationship between dysfunctional breathing patterns and ability to achieve target heart rate variability with features of "coherence" during biofeedback. *Alternative Therapies in Health and Medicine,* 17, 38-44.

Courtney, R., van Dixhoorn, J., Greenwood, K.M. & Anthonissen, E.L. (2011b). Medically unexplained dyspnea: Partly moderated by dysfunctional (thoracic dominant) breathing pattern. *The Journal of Asthma: Official Journal of the Association for the Care of Asthma,* 48, 259-265.

David, P., Laval, D., Terrien, J. & Petitjean, M. (2012). Postural control and ventilatory drive during voluntary hyperventilation and carbon dioxide rebreathing. *European Journal of Applied Physiology,* 112, 145-154.

de Groot, E.P., Duiverman, E.J. & Brand, P.L. (2013). Dysfunctional breathing in children with asthma: A rare but relevant comorbidity. *The European Respiratory Journal,* 41, 1068-1073.

de Lira, C.A., Peixinho-Pena, L.F., Vancini, R.L., de Freitas Guina Fachina, R.J., de Almeida, A.A., Andrade Mdos, S. & da Silva, A.C. (2013). Heart rate response during a simulated olympic boxing match is predominantly above ventilatory threshold 2: A cross sectional study. *Open Access Journal of Sports Medicine,* 4, 175-182.

Del Greco, L., Walop, W. & McCarthy, R.H. (1987). Questionnaire development: 2. validity and reliability. *CMAJ : Canadian Medical Association Journal = Journal De L'Association Medicale Canadienne,* 136, 699-700.

Delapille, P., Verin, E., Tourny-Chollet, C. & Pasquis, P. (2001). Breath-holding time: Effects of non-chemical factors in divers and non-divers. *Pflügers Archiv European Journal of Physiology,* 442, 588-594.

Demeter, S.L. & Cordasco, E.M. (1986). Hyperventilation syndrome and asthma. *The American Journal of Medicine,* 81, 989-994.

Dempsey, J.A., McKenzie, D.C., Haverkamp, H.C. & Eldridge, M.W. (2008). Update in the understanding of respiratory limitations to exercise performance in fit, active adults. *Chest Journal,* 134, 613-622.

Depiazzi, J. & Everard, M.L. (2016). Dysfunctional breathing and reaching one's physiological limit as causes of exercise-induced dyspnoea. *Breathe (Sheffield, England),* 12, 120-129.

Dickinson, J., McConnell, A. & Whyte, G. (2011). Diagnosis of exercise-induced bronchoconstriction: Eucapnic voluntary hyperpnoea challenges identify previously undiagnosed elite athletes with exercise-induced bronchoconstriction. *British Journal of Sports Medicine,* 45, 1126-1131.

Dickinson, J.W., Whyte, G.P., McConnell, A.K. & Harries, M.G. (2006). Screening elite winter athletes for exercise induced asthma: A comparison of three challenge methods. *British Journal of Sports Medicine,* 40, 179-82; discussion 179-82.

Dickinson, J.W., Whyte, G.P., McConnell, A.K. & Harries, M.G. (2005). Impact of changes in the IOC-MC asthma criteria: A british perspective. *Thorax,* 60, 629-632.

Dion, G.R., Eller, R.L. & Thomas, R.F. (2012). Diagnosing aerodynamic supraglottic collapse with rest and exercise flexible laryngoscopy. *Journal of Voice,* 26, 779-784.

Dryden, D.M., Spooner, C.H., Stickland, M.K., Vandermeer, B., Tjosvold, L., Bialy, L., Wong, K. & Rowe, B.H. (2010). Exercise-induced bronchoconstriction and asthma. *Evidence Report/Technology Assessment,* (189), 1-154, v-vi.

Duffy, P. & Phillips, Y.Y. (1991). Caffeine consumption decreases the response to bronchoprovocation challenge with dry gas hyperventilation. *Chest,* 99, 1374-1377.

Dweik, R.A., Boggs, P.B., Erzurum, S.C., Irvin, C.G., Leigh, M.W., Lundberg, J.O., Olin, A.C., Plummer, A.L., Taylor, D.R. & American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications (2011). An official ATS clinical practice guideline: Interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *American Journal of Respiratory and Critical Care Medicine,* 184, 602-615.

Edmunds, A.T., Tooley, M. & Godfrey, S. (1978). The refractory period after exercise-induced asthma: Its duration and relation to the severity of exercise. *The American Review of Respiratory Disease,* 117, 247-254.

el-Manshawi, A., Killian, K.J., Summers, E. & Jones, N.L. (1986a). Breathlessness during exercise with and without resistive loading. *Journal of Applied Physiology (Bethesda, Md.: 1985),* 61, 896-905.

el-Manshawi, A., Killian, K.J., Summers, E. & Jones, N.L. (1986b). Breathlessness during exercise with and without resistive loading. *Journal of Applied Physiology (Bethesda, Md.: 1985),* 61, 896-905.

Estrada, L., Torres, A., Sarlabous, L. & Jané, R. (2016). Improvement in neural respiratory drive estimation from diaphragm electromyographic signals using fixed sample entropy. *IEEE Journal of Biomedical and Health Informatics,* 20, 476-485.

Faull, O.K., Cox, P.J. & Pattinson, K.T. (2016). Psychophysical differences in ventilatory awareness and breathlessness between athletes and sedentary individuals. *Frontiers in Physiology,* 7, 231.

Fitch, K.D. (2012). An overview of asthma and airway hyper-responsiveness in olympic athletes. *British Journal of Sports Medicine,* 46, 413-416.

Folgering, H. (1999). The pathophysiology of hyperventilation syndrome. *Monaldi Archives for Chest Disease = Archivio Monaldi Per Le Malattie Del Torace,* 54, 365-372.

Fricker, P., Gleeson, M., Flanagan, A., Pyne, D., McDonald, W. & Clancy, R. (2000). A clinical snapshot: Do elite swimmers experience more upper respiratory illness than nonathletes? *Clinical Exercise Physiology,* 2, 155-158.

Gardner, W.N. (1996). The pathophysiology of hyperventilation disorders. *Chest Journal,* 109, 516-534.

Ghanbari, A., Ghaffarinejad, F., Mohammadi, F., Khorrami, M. & Sobhani, S. (2008). Effect of forward shoulder posture on pulmonary capacities of women. *British Journal of Sports Medicine,* 42, 622-623.

Gigliotti, F. (2010). Mechanisms of dyspnea in healthy subjects. *Multidisciplinary Respiratory Medicine,* 5, 1.

Gilbert, C. & Chaitow, L. (2002). Interaction of psychological and emotional effects with breathing dysfunction. *Multidisciplinary Approaches to Breathing Pattern Disorders,* 11-130.

Gilbert, C. (1999). Breathing and the cardiovascular system. *Journal of Bodywork and Movement Therapies,* 3, 215-224.

Gilbert, C. (1998). Emotional sources of dysfunctional breathing. *Journal of Bodywork and Movement Therapies,* 2, 224-230.

Grammatopoulou, E.P., Skordilis, E.K., Georgoudis, G., Haniotou, A., Evangelodimou, A., Fildissis, G., Katsoulas, T. & Kalagiakos, P. (2014). Hyperventilation in asthma: A validation study of the nijmegen questionnaire--NQ. *The Journal of Asthma: Official Journal of the Association for the Care of Asthma,* 51, 839-846.

Grazzini, M., Stendardi, L., Gigliotti, F. & Scano, G. (2005). Pathophysiology of exercise dyspnea in healthy subjects and in patients with chronic obstructive pulmonary disease (COPD). *Respiratory Medicine,* 99, 1403-1412.

Gustafsson, H., Sagar, S. & Stenling, A. (2016). Fear of failure, psychological stress, and burnout among adolescent athletes competing in high level sport. *Scandinavian Journal of Medicine & Science in Sports.*

Haahtela, T., Malmberg, P. & Moreira, A. (2008). Mechanisms of asthma in olympic athletes–practical implications. *Allergy,* 63, 685-694.

Haas, F., Simnowitz, M., Axen, K., Gaudino, D. & Haas, A. (1982). Effect of upper body posture on forced inspiration and expiration. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology,* 52, 879-886.

Hall, A., Thomas, M., Sandhu, G. & Hull, J.H. (2016). Exercise-induced laryngeal obstruction: A common and overlooked cause of exertional breathlessness. *The British Journal of General Practice: The Journal of the Royal College of General Practitioners,* 66, e683-5.

Hallstrand, T.S., Altemeier, W.A., Aitken, M.L. & Henderson, W.R.,Jr (2013). Role of cells and mediators in exercise-induced bronchoconstriction. *Immunology and Allergy Clinics of North America,* 33, 313-28, vii.

Hamilton, A.L., Killian, K.J., Summers, E. & Jones, N.L. (1996). Quantification of intensity of sensations during muscular work by normal subjects. *Journal of Applied Physiology (Bethesda, Md.: 1985),* 81, 1156-1161.

Hanks, C.D., Parsons, J., Benninger, C., Kaeding, C., Best, T.M., Phillips, G. & Mastronarde, J.G. (2012). Etiology of dyspnea in elite and recreational athletes. *The Physician and Sportsmedicine,* 40, 28-33.

Harms, C.A., Babcock, M.A., McClaran, S.R., Pegelow, D.F., Nickele, G.A., Nelson, W.B. & Dempsey, J.A. (1997). Respiratory muscle work compromises leg blood flow during maximal exercise. *Journal of Applied Physiology (Bethesda, Md.: 1985),* 82, 1573-1583.

Harms, C.A., Wetter, T.J., St Croix, C.M., Pegelow, D.F. & Dempsey, J.A. (2000). Effects of respiratory muscle work on exercise performance. *Journal of Applied Physiology (Bethesda, Md.: 1985),* 89, 131-138.

Harver, A., Mahler, D.A., Schwartzstein, R.M. & Baird, J.C. (2000). Descriptors of breathlessness in healthy individuals: Distinct and separable constructs. *CHEST Journal,* 118, 679-690.

Hayen, A., Wanigasekera, V., Faull, O.K., Campbell, S.F., Garry, P.S., Raby, S.J., Robertson, J., Webster, R., Wise, R.G. & Herigstad, M. (2017). Opioid suppression of conditioned anticipatory brain responses to breathlessness. *NeuroImage,* 150, 383-394.

Heimdal, J.H., Roksund, O.D., Halvorsen, T., Skadberg, B.T. & Olofsson, J. (2006). Continuous laryngoscopy exercise test: A method for visualizing laryngeal dysfunction during exercise. *The Laryngoscope,* 116, 52-57.

Helenius, I., Rytilä, P., Sarna, S., Lumme, A., Helenius, M., Remes, V. & Haahtela, T. (2002). Effect of continuing or finishing high-level sports on airway inflammation, bronchial hyperresponsiveness, and asthma: A 5-year prospective follow-up study of 42 highly trained swimmers. *Journal of Allergy and Clinical Immunology,* 109, 962-968.

Helenius, I., Lumme, A. & Haahtela, T. (2005). Asthma, airway inflammation and treatment in elite athletes. *Sports Medicine (Auckland, N.Z.),* 35, 565-574.

Hill, S. & Winter, R. A Guide To Performing Quality Assured Diagnostic Spirometry. Retrieved from http://www.artp.org.uk/en/professional/artp-standards/index.cfm/QADS%20Apr%202013. Last Accessed: 01/03 2016.

Hodges, P., Sapsford, R. & Pengel, L. (2007). Postural and respiratory functions of the pelvic floor muscles. *Neurourology and Urodynamics,* 26, 362-371.

Hodges, P.W. & Gandevia, S.C. (2000). Changes in intra-abdominal pressure during postural and respiratory activation of the human diaphragm. *Journal of Applied Physiology (Bethesda, Md.: 1985),* 89, 967-976.

Holzer, K., Anderson, S.D. & Douglass, J. (2002). Exercise in elite summer athletes: Challenges for diagnosis. *Journal of Allergy and Clinical Immunology,* 110, 374-380.

Hornsveld, H., Garssen, B., Dop, M.F., Van Spiegel, P. & De Haes, J. (1996). Double-blind placebo-controlled study of the hyperventilation provocation test and the validity of the hyperventilation syndrome. *The Lancet,* 348, 154-158.

Howell, J.B. (1997). The hyperventilation syndrome: A syndrome under threat? *Thorax,* 52 Suppl 3, S30-4.

Hull, J.H., Ansley, L., Price, O.J., Dickinson, J.W. & Bonini, M. (2016). Eucapnic voluntary hyperpnea: Gold standard for diagnosing exercise-induced bronchoconstriction in athletes? *Sports Medicine,* 46, 1083-1093.

Hull, J.H., Ansley, L., Robson-Ansley, P. & Parsons, J.P. (2012). Managing respiratory problems in athletes. *Clinical Medicine (London, England),* 12, 351-356.

Hull, J.H., Hull, P.J., Parsons, J.P., Dickinson, J.W. & Ansley, L. (2009). Approach to the diagnosis and management of suspected exercise-induced bronchoconstriction by primary care physicians. *BMC Pulmonary Medicine,* 9, 29-2466-9-29.

Hull, J.H., Selby, J. & Sandhu, G. (2014). "You say potato, I say potato": Time for consensus in exercise-induced laryngeal obstruction? *Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery,* 151, 891-892.

Illi, S.K., Hostettler, S., Aliverti, A. & Spengler, C.M. (2013). Compartmental chest wall volume changes during volitional hyperpnoea with constant tidal volume in healthy individuals. *Respiratory Physiology & Neurobiology,* 185, 410-415.

Jensen, W., Andersen, O.K. & Akay, M. (2014). *Replace, Repair, Restore, Relieve–Bridging Clinical and Engineering Solutions in Neurorehabilitation: Proceedings of the 2nd International Conference on NeuroRehabilitation (ICNR2014), Aalborg, 24-26 June, 2014,* Springer.

Johansson, H., Norlander, K., Berglund, L., Janson, C., Malinovschi, A., Nordvall, L., Nordang, L. & Emtner, M. (2015). Prevalence of exercise-induced bronchoconstriction and exercise-induced laryngeal obstruction in a general adolescent population. *Thorax,* 70, 57-63.

Jones, M., Harvey, A., Marston, L. & O'Connell, N.E. (2013). Breathing exercises for dysfunctional breathing/hyperventilation syndrome in adults. *The Cochrane Library.*

Kaneko, H. & Horie, J. (2012). Breathing movements of the chest and abdominal wall in healthy subjects. *Respiratory Care,* 57, 1442-1451.

Kenn, K. & Balkissoon, R. (2011). Vocal cord dysfunction: What do we know? *The European Respiratory Journal,* 37, 194-200.

Kenyon, C.M., Cala, S.J., Yan, S., Aliverti, A., Scano, G., Duranti, R., Pedotti, A. & Macklem, P.T. (1997). Rib cage mechanics during quiet breathing and exercise in humans. *Journal of Applied Physiology (Bethesda, Md.: 1985),* 83, 1242-1255.

Kerr, W.J., Gliebe, P.A. & Dalton, J.W. (1938). Physical phenomena associated with anxiety states: The hyperventilation syndrome. *California and Western Medicine,* 48, 12-16.

Kharitonov, S., Alving, K. & Barnes, P.J. (1997). Exhaled and nasal nitric oxide measurements: Recommendations. the european respiratory society task force. *The European Respiratory Journal,* 10, 1683-1693.

Killian, K.J., Gandevia, S.C., Summers, E. & Campbell, E.J. (1984). Effect of increased lung volume on perception of breathlessness, effort, and tension. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology,* 57, 686-691.

Konno, K. & Mead, J. (1967). Measurement of the separate volume changes of rib cage and abdomen during breathing. *Journal of Applied Physiology,* 22, 407-422.

Krieger, B.P. (2002). When wheezing may not mean asthma: Other common and uncommon causes to consider. *Postgraduate Medicine,* 112, 101-111.

Krosnick, J.A. (2000). The threat of satisficing in surveys: The shortcuts respondents take in answering questions. *Survey Methods Newsletter,* 20, 4-8.

Lamprecht, B., Vanfleteren, L.E., Studnicka, M., Allison, M., McBurnie, M.A., Vollmer, W.M., Tan, W.C., Nielsen, R., Nastalek, P., Gnatiuc, L., Kaiser, B., Janson, C., Wouters, E.F., Burney, P., Buist, A.S. & BOLD Collaborative Research Group (2013). Sex-related differences in respiratory symptoms: Results from the BOLD study. *The European Respiratory Journal,* 42, 858-860.

Laviolette, L., Laveneziana, P. & ERS Research Seminar Faculty (2014). Dyspnoea: A multidimensional and multidisciplinary approach. *The European Respiratory Journal,* 43, 1750-1762.

Layton, A.M. 2013, *Ventilatory Mechanics in Endurance Athletes*, Columbia University.

Leblanc, P., Summers, E., Inman, M.D., Jones, N.L., Campbell, E.J. & Killian, K.J. (1988). Inspiratory muscles during exercise: A problem of supply and demand. *Journal of Applied Physiology (Bethesda, Md.: 1985),* 64, 2482-2489.

Levai, I., Sidoroff, V. & Iles, R. (2012). An introduction to the non-invasive non-contact assessment of respiratory function. *Respiratory Therapy,* 7, 43.

Levitzky, M.G. (2003). *Pulmonary Physiology,* McGraw-Hill Medical Publishing.

Ley, R. (1994). An introduction to the psychophysiology of breathing. *Biofeedback and Self-Regulation,* 19, 95-96.

Lin, Y.C., Lally, D.A., Moore, T.O. & Hong, S.K. (1974). Physiological and conventional breath-hold breaking points. *Journal of Applied Physiology,* 37, 291-296.

Lougheed, M.D. (2007). Variability in asthma: Symptom perception, care, and outcomes this paper is one of a selection of papers published in this special issue, entitled young investigators' forum. *Canadian Journal of Physiology and Pharmacology,* 85, 149-154.

Lowhagen, O. (2005). Asthma - a disease difficult to define. patients can receive correct treatment by means of differential diagnosis criteria. *Lakartidningen,* 102, 3872-3878.

Lowhagen, O. (1989). Functional respiratory disorders as significant differential diagnosis in asthma. *Lakartidningen,* 86, 57-59.

Luks, V.P., Vandemheen, K.L. & Aaron, S.D. (2010). Confirmation of asthma in an era of overdiagnosis. *The European Respiratory Journal,* 36, 255-260.

Lum, L. (1975). Hyperventilation: The tip and the iceberg. *Journal of Psychosomatic Research,* 19, 375-383.

Lumb, A.B. (2016). *Nunn's Applied Respiratory Physiology,* Elsevier Health Sciences.

Lumb, A.B. & Nunn, J.F. (1991). Respiratory function and ribcage contribution to ventilation in body positions commonly used during anesthesia. *Anesthesia & Analgesia,* 73, 422-426.

Lund, T.K., Pedersen, L., Anderson, S.D., Sverrild, A. & Backer, V. (2009). Are asthma-like symptoms in elite athletes associated with classical features of asthma? *British Journal of Sports Medicine,* 43, 1131-1135.

Maat, R.C. (2011). Exercise-induced laryngeal obstruction. diagnostic procedures and therapy.

Maat, R.C., Hilland, M., Roksund, O.D., Halvorsen, T., Olofsson, J., Aarstad, H.J. & Heimdal, J.H. (2011). Exercise-induced laryngeal obstruction: Natural history and effect of surgical treatment. *European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : Affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery,* 268, 1485-1492.

Mannix, E.T., Roberts, M.A., Dukes, H.J., Magnes, C.J. & Farber, M.O. (2004). Airways hyperresponsiveness in high school athletes. *The Journal of Asthma: Official Journal of the Association for the Care of Asthma,* 41, 567-574.

Marklund, B., Tunsater, A. & Bengtsson, C. (1999). How often is the diagnosis bronchial asthma correct? *Family Practice,* 16, 112-116.

Martin, N., Lindley, M.R., Hargadon, B., Monteiro, W.R. & Pavord, I.D. (2012). Airway dysfunction and inflammation in pool- and non-pool-based elite athletes. *Medicine and Science in Sports and Exercise,* 44, 1433-1439.

Massaroni, C., Schena, E., Saccomandi, P., Morrone, M., Sterzi, S. & Silvestri, S. 2015, "Evaluation of optoelectronic plethysmography accuracy and precision in recording displacements during quiet breathing simulation", *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*IEEE, , pp. 1291.

Massaroni, C., Carraro, E., Vianello, A., Miccinilli, S., Morrone, M., Levai, I.K., Schena, E., Saccomandi, P., Sterzi, S., Dickinson, J.W., Winter, S. & Silvestri, S. (2017). Optoelectronic plethysmography in clinical practice and research: A review. *Respiration; International Review of Thoracic Diseases,* 93, 339-354.

McKeough, Z.J., Alison, J.A. & Bye, P.T. (2003). Arm positioning alters lung volumes in subjects with COPD and healthy subjects. *Australian Journal of Physiotherapy,* 49, 133-137.

Miller, M.R., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., Crapo, R., Enright, P., van der Grinten, C.P., Gustafsson, P., Jensen, R., Johnson, D.C., MacIntyre, N., McKay, R., Navajas, D., Pedersen, O.F., Pellegrino, R., Viegi, G., Wanger, J. & ATS/ERS Task Force (2005). Standardisation of spirometry. *The European Respiratory Journal,* 26, 319-338.

Molis, M.A. & Molis, W.E. (2010). Exercise-induced bronchospasm. *Sports Health,* 2, 311-317.

Molphy, J., Dickinson, J., Hu, J., Chester, N. & Whyte, G. (2014). Prevalence of bronchoconstriction induced by eucapnic voluntary hyperpnoea in recreationally active individuals. *The Journal of Asthma: Official Journal of the Association for the Care of Asthma,* 51, 44-50.

Moreira, A., Delgado, L. & Carlsen, K. (2011). Exercise-induced asthma: Why is it so frequent in olympic athletes? *Expert Review of Respiratory Medicine,* 5, 1-3.

Morgan, M.D. (2002). Dysfunctional breathing in asthma: Is it common, identifiable and correctable? *Thorax,* 57 Suppl 2, II31-II35.

Morris, M.J., Deal, L.E., Bean, D.R., Grbach, V.X. & Morgan, J.A. (1999). Vocal cord dysfunction in patients with exertional dyspnea. *CHEST Journal,* 116, 1676-1682.

National Asthma Campaign (2001). Out in the open: A true picture of asthma in the UK today. *J.Asthma,* 6, 3-14.

Newall, C., Evans, A., Lloyd, J., Shakespeare, J. & Carter, R. (2006). Chapter 3: Performance of measurement and interpretatation. In Cooper, Billings, Newall, Roberts, Evans & Watts (Eds.), *ARTP Spirometry Handbook* (pp. 57). Birmingham: Association for Respiratory Technology and Physiology.

Nielsen, E.W., Hull, J.H. & Backer, V. (2013). High prevalence of exercise-induced laryngeal obstruction in athletes. *Medicine and Science in Sports and Exercise,* 45, 2030-2035.

O'Donnell, D.E., Elbehairy, A.F., Berton, D.C., Domnik, N.J. & Neder, J.A. (2017). Advances in the evaluation of respiratory pathophysiology during exercise in chronic lung diseases. *Frontiers in Physiology,* 8, .

O'Donnell, D.E., Bertley, J.C., Chau, L.K. & Webb, K.A. (1997). Qualitative aspects of exertional breathlessness in chronic airflow limitation: Pathophysiologic mechanisms. *American Journal of Respiratory and Critical Care Medicine,* 155, 109-115.

Parkes, M. (2006). Breath- holding and its breakpoint. *Experimental Physiology,* 91, 1-15.

Parreira, V.F., Vieira, D.S., Myrrha, M.A., Pessoa, I.M., Lage, S.M. & Britto, R.R. (2012). Optoelectronic plethysmography: A review of the literature. *Revista Brasileira De Fisioterapia (Sao Carlos (Sao Paulo, Brazil)),* 16, 439-453.

Parsons, J.P., Craig, T.J., Stoloff, S.W., Hayden, M.L., Ostrom, N.K., Eid, N.S. & Colice, G.L. (2011). Impact of exercise-related respiratory symptoms in adults with asthma: Exercise-induced bronchospasm landmark national survey. *Allergy Asthma Proc,* 32, 431-437.

Parsons, J.P. & Mastronarde, J.G. (2005). Exercise-induced bronchoconstriction in athletes. *CHEST Journal,* 128, 3966-3974.

Parsons, J.P., Cosmar, D., Phillips, G., Kaeding, C., Best, T.M. & Mastronarde, J.G. (2012). Screening for exercise-induced bronchoconstriction in college athletes. *The Journal of Asthma: Official Journal of the Association for the Care of Asthma,* 49, 153-157.

Parsons, J.P., Hallstrand, T.S., Mastronarde, J.G., Kaminsky, D.A., Rundell, K.W., Hull, J.H., Storms, W.W., Weiler, J.M., Cheek, F.M., Wilson, K.C., Anderson, S.D. & American Thoracic Society Subcommittee on Exercise-induced Bronchoconstriction (2013). An official american thoracic society clinical practice guideline: Exercise-induced bronchoconstriction. *American Journal of Respiratory and Critical Care Medicine,* 187, 1016-1027.

Parsons, J.P., Kaeding, C., Phillips, G., Jarjoura, D., Wadley, G. & Mastronarde, J.G. (2007). Prevalence of exercise-induced bronchospasm in a cohort of varsity college athletes. *Medicine and Science in Sports and Exercise,* 39, 1487-1492.

Pellegrino, R., Viegi, G., Brusasco, V., Crapo, R.O., Burgos, F., Casaburi, R., Coates, A., van der Grinten, C.P., Gustafsson, P., Hankinson, J., Jensen, R., Johnson, D.C., MacIntyre, N., McKay, R., Miller, M.R., Navajas, D., Pedersen, O.F. & Wanger, J. (2005). Interpretative strategies for lung function tests. *The European Respiratory Journal,* 26, 948-968.

Price, K., Schartz, P. & Watson, A.H. (2014a). The effect of standing and sitting postures on breathing in brass players. *SpringerPlus,* 3, 210.

Price, O.J., Ansley, L. & Hull, J.H. (2015). Diagnosing exercise-induced bronchoconstriction with eucapnic voluntary hyperpnea: Is one test enough? *The Journal of Allergy and Clinical Immunology.in Practice,* 3, 243-249.

Price, O.J., Ansley, L., Levai, I., Molphy, J., Cullinan, P., Dickinson, J. & Hull, J.H. (2016). Eucapnic voluntary hyperpnea testing in asymptomatic athletes: 979 board #295 june 1, 2: 00 PM - 3: 30 PM. *Medicine and Science in Sports and Exercise,* 48, 280-281.

Price, O.J., Ansley, L., Menzies-Gow, A., Cullinan, P. & Hull, J.H. (2013). Airway dysfunction in elite athletes--an occupational lung disease? *Allergy,* 68, 1343-1352.

Price, O.J., Hull, J.H., Backer, V., Hostrup, M. & Ansley, L. (2014b). The impact of exercise-induced bronchoconstriction on athletic performance: A systematic review. *Sports Medicine,* 44, 1749-1761.

Pryor, J.A. & Prasad, S.A. (2008). Physiotherapy techniques. Physiotherapy techniques. *Physiotherapy for respiratory and cardiac problems* (pp. 134-217). Churchill Livingstone, Edinburgh.

Quanjer, P.H., Tammeling, G.J., Cotes, J.E., Pedersen, O.F., Peslin, R. & Yernault, J.C. (1994). Lung volumes and forced ventilatory flows. work group on standardization of respiratory function tests. european community for coal and steel. official position of the european respiratory society. *Revue Des Maladies Respiratoires,* 11 Suppl 3, 5-40.

Ragnarsdottir, M. & Kristinsdottir, E.K. (2006). Breathing movements and breathing patterns among healthy men and women 20-69 years of age. reference values. *Respiration; International Review of Thoracic Diseases,* 73, 48-54.

Ratnovsky, A., Elad, D. & Halpern, P. (2008). Mechanics of respiratory muscles. *Respiratory Physiology & Neurobiology,* 163, 82-89.

Reis, J.F., Alves, F.B., Bruno, P.M., Vleck, V. & Millet, G.P. (2012). Effects of aerobic fitness on oxygen uptake kinetics in heavy intensity swimming. *European Journal of Applied Physiology,* 112, 1689-1697.

Røksund, O.D., Heimdal, J., Clemm, H., Vollsæter, M. & Halvorsen, T. (2016). Exercise inducible laryngeal obstruction: Diagnostics and management. *Paediatric Respiratory Reviews,* 21, 86-94.

Røksund, O.D., Heimdal, J., Olofsson, J., Maat, R.C. & Halvorsen, T. (2015). Larynx during exercise: The unexplored bottleneck of the airways. *European Archives of Oto-Rhino-Laryngology,* 272, 2101-2109.

Roksund, O.D., Maat, R.C., Heimdal, J.H., Olofsson, J., Skadberg, B.T. & Halvorsen, T. (2009). Exercise induced dyspnea in the young. larynx as the bottleneck of the airways. *Respiratory Medicine,* 103, 1911-1918.

Romei, M., Mauro, A.L., D'Angelo, M.G., Turconi, A.C., Bresolin, N., Pedotti, A. & Aliverti, A. (2010). Effects of gender and posture on thoraco-abdominal kinematics during quiet breathing in healthy adults. *Respiratory Physiology & Neurobiology,* 172, 184-191.

Rundell, K.W. & Spiering, B.A. (2003). Inspiratory stridor in elite athletes. *CHEST Journal,* 123, 468-474.

Rundell, K.W., Im, J., Mayers, L.B., Wilber, R.L., Szmedra, L. & Schmitz, H.R. (2001). Self-reported symptoms and exercise-induced asthma in the elite athlete. *Medicine and Science in Sports and Exercise,* 33, 208-213.

Rundell, K.W. & Jenkinson, D.M. (2002). Exercise-induced bronchospasm in the elite athlete. *Sports Medicine (Auckland, N.Z.),* 32, 583-600.

Rundell, K.W. & Sue-Chu, M. (2013). Air quality and exercise-induced bronchoconstriction in elite athletes. *Immunology and Allergy Clinics of North America,* 33, 409-21, ix.

Rupp, N.T., Guill, M.F. & Brudno, D.S. (1992). Unrecognized exercise-induced bronchospasm in adolescent athletes. *American Journal of Diseases of Children,* 146, 941-944.

Rupp, N.T., Brudno, D.S. & Guill, M.F. (1993). The value of screening for risk of exercise-induced asthma in high school athletes. *Annals of Allergy,* 70, 339-342.

Sagar, S.S., Busch, B.K. & Jowett, S. (2010). Success and failure, fear of failure, and coping responses of adolescent academy football players. *Journal of Applied Sport Psychology,* 22, 213-230.

Sagar, S.S., Lavallee, D. & Spray, C.M. (2007). Why young elite athletes fear failure: Consequences of failure. *Journal of Sports Sciences,* 25, 1171-1184.

Savadatti, R. & Gaude, G.S. (2011). Effect of forward shoulder posture on forced vital capacity-A co-relational study. *Indian Journal of Physiotherapy & Occupational Therapy,* 5, 119-123.

Seys, S., Hox, V., Van Gerven, L., Dilissen, E., Marijsse, G., Peeters, E., Dekimpe, E., Kasran, A., Aertgeerts, S. & Troosters, T. (2015). Damage- associated molecular pattern and innate cytokine release in the airways of competitive swimmers. *Allergy,* 70, 187-194.

Sharp, J.T., Goldberg, N.B., Druz, W.S. & Danon, J. (1975). Relative contributions of rib cage and abdomen to breathing in normal subjects. *Journal of Applied Physiology,* 39, 608-618.

Silvatti, A.P., Sarro, K.J., Cerveri, P., Baroni, G. & Barros, R.M. (2012). A 3D kinematic analysis of breathing patterns in competitive swimmers. *Journal of Sports Sciences,* 30, 1551-1560.

Simon, P.M., Schwartzstein, R.M., Weiss, J.W. & Lahive, K. (1989). Distinguishable sensations of breathlessness induced in normal Volunteers1-3. *Am Rev Respir Dis,* 140, 1021-1027.

Simpson, A.J., Romer, L.M. & Kippelen, P. (2015). Self-reported symptoms after induced and inhibited bronchoconstriction in athletes. *Medicine and Science in Sports and Exercise,* 47, 2005-2013.

Smith, R.J., Kramer, M., Bauman, N.M., Smits, W.L., Bent, J.P. & Ahrens, R.C. (1995). Exercise-induced laryngomalacia. *Annals of Otology, Rhinology & Laryngology,* 104, 537-541.

Smith, M.S. (2006). Physiological profile of senior and junior england international amateur boxers. *Journal of Sports Science & Medicine,* 5, 74-89.

Smoliga, J.M., Mohseni, Z.S., Berwager, J.D. & Hegedus, E.J. (2016). Common causes of dyspnoea in athletes: A practical approach for diagnosis and management. *Breathe,* 12, e22.

Spiering, B.A., Judelson, D.A. & Rundell, K.W. (2004). An evaluation of standardizing target ventilation for eucapnic voluntary hyperventilation using FEV1. *The Journal of Asthma: Official Journal of the Association for the Care of Asthma,* 41, 745-749.

Standring, S. (2015). Larynx. Larynx. *Gray's anatomy: the anatomical basis of clinical practice* (pp. 586). Elsevier Health Sciences.

Takahashi, T., Yamada, S., Tanabe, K., Nakayama, M., Osada, N., Itoh, H. & Murayama, M. (1998). The effects of posture on the ventilatory responses during exercise. *Journal of the Japanese Physical Therapy Association,* 1, 13-17.

Templer, J.W., Von Doersten, P.G., Quigley, P., Scott, G.C. & Davis, W.E. (1991). Laryngeal airway resistance: The relationships of airflow, pressure, and aperture. *Archives of Otolaryngology–Head & Neck Surgery,* 117, 867-870.

Thomas, M. & Bruton, A. (2014). Breathing exercises for asthma. *Breathe,* 10, 312-322.

Thomas, M., McKinley, R.K., Freeman, E. & Foy, C. (2001). Prevalence of dysfunctional breathing in patients treated for asthma in primary care: Cross sectional survey. *BMJ (Clinical Research Ed.),* 322, 1098-1100.

Thomas, M., McKinley, R.K., Freeman, E., Foy, C. & Price, D. (2005). The prevalence of dysfunctional breathing in adults in the community with and without asthma. *Primary Care Respiratory Journal : Journal of the General Practice Airways Group,* 14, 78-82.

Thomas, M., McKinley, R.K., Freeman, E., Foy, C., Prodger, P. & Price, D. (2003). Breathing retraining for dysfunctional breathing in asthma: A randomised controlled trial. *Thorax,* 58, 110-115.

Tipton, C.M. & American College of Sports Medicine (2006). *ACSM's Advanced Exercise Physiology,* Lippincott Williams & Wilkins.

Tobin, M.J., Chadha, T.S., Jenouri, G., Birch, S.J., Gazeroglu, H.B. & Sackner, M.A. (1983). Breathing patterns: 2. diseased subjects. *Chest,* 84, 286-294.

Turcotte, H., Langdeau, J.B., Thibault, G. & Boulet, L.P. (2003). Prevalence of respiratory symptoms in an athlete population. *Respiratory Medicine,* 97, 955-963.

Van Diest, I., Verstappen, K., Aubert, A.E., Widjaja, D., Vansteenwegen, D. & Vlemincx, E. (2014). Inhalation/exhalation ratio modulates the effect of slow breathing on heart rate variability and relaxation. *Applied Psychophysiology and Biofeedback,* 39, 171-180.

van Dixhoorn J, Folgering H. (2015). The nijmegen questionnaire and dysfunctional breathing. *ERJ Open Res,* 1, 00001-02015.

van Dixhoorn, J. & Duivenvoorden, H.J. (1985). Efficacy of nijmegen questionnaire in recognition of the hyperventilation syndrome. *Journal of Psychosomatic Research,* 29, 199-206.

van Wijk, Cecile MT Gijsbers, Huisman, H. & Kolk, A.M. (1999). Gender differences in physical symptoms and illness behavior: A health diary study. *Social Science & Medicine,* 49, 1061-1074.

Vellody, V.P., Nassery, M., Druz, W.S. & Sharp, J.T. (1978). Effects of body position change on thoracoabdominal motion. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology,* 45, 581-589.

Verschakelen, J.A. & Demedts, M.G. (1995). Normal thoracoabdominal motions. influence of sex, age, posture, and breath size. *American Journal of Respiratory and Critical Care Medicine,* 151, 399-405.

Vogiatzis, I., Aliverti, A., Golemati, S., Georgiadou, O., LoMauro, A., Kosmas, E., Kastanakis, E. & Roussos, C. (2005). Respiratory kinematics by optoelectronic plethysmography during exercise in men and women. *European Journal of Applied Physiology,* 93, 581-587.

Von Leupoldt, A., Bradley, M.M., Lang, P.J. & Davenport, P.W. (2010). Neural processing of respiratory sensations when breathing becomes more difficult and unpleasant. *Frontiers in Physiology,* 1, 144.

Voutilainen, M., Malmberg, L.P., Vasankari, T. & Haahtela, T. (2013). Exhaled nitric oxide indicates poorly athlete's asthma. *The Clinical Respiratory Journal,* 7, 347-353.

Wahls, S.A. (2012). Causes and evaluation of chronic dyspnea. *American Family Physician,* 86, 173-182.

Walsh, M.L., Takeda, C., Takahashi, A., Ikeda, Y., Endo, M., Miura, A., Kan, A. & Fukuba, Y. (2006). Volitional hyperventilation during ramp exercise to exhaustion. *Applied Physiology, Nutrition, and Metabolism,* 31, 211-217.

Warburton, C. & Jack, S. (2006). Can you diagnose hyperventilation? *Chronic Respiratory Disease,* 3, 113-115.

Weiler, J.M., Bonini, S., Coifman, R., Craig, T., Delgado, L., Capão-Filipe, M., Passali, D., Randolph, C. & Storms, W. (2007). American academy of allergy, asthma & immunology work group report: Exercise-induced asthma. *Journal of Allergy and Clinical Immunology,* 119, 1349.

Weiler, J.M., Hallstrand, T.S., Parsons, J.P., Randolph, C., Silvers, W.S., Storms, W.W. & Bronstone, A. (2014). Improving screening and diagnosis of exercise-induced bronchoconstriction: A call to action. *The Journal of Allergy and Clinical Immunology.in Practice,* 2, 275-80.e7.

Weiss, P. & Rundell, K.W. (2009). Imitators of exercise-induced bronchoconstriction. *Allergy, Asthma & Clinical Immunology,* 5, 7.

Welsh, L., Roberts, R.G. & Kemp, J.G. (2004). Fitness and physical activity in children with asthma. *Sports Medicine,* 34, 861-870.

Williams, B., Powell, A., Hoskins, G. & Neville, R. (2008). Exploring and explaining low participation in physical activity among children and young people with asthma: A review. *BMC Family Practice,* 9, 40-2296-9-40.

World Health Organization *Guidelines for safe recreational water environments. Volume 2: Swimming pools and similar environments*. Retrieved from www.who.int/water_sanitation_health/bathing/srwe2full.pdf. Last Accessed: May 10 2017.

Zhu, W., Zeng, N. & Wang, N. Sensitivity, Specificity, Accuracy, Associated Confidence Interval and ROC Analysis with Practical SAS Implementations. Retrieved from http://www.lexjansen.com/nesug/nesug10/hl/hl07.pdf. Last Accessed: May 10 2017.

Appendices

Ethical approvals

University of Kent

School of Sport & Exercise Sciences
Research Ethics and Advisory Group (REAG)
University of Kent at Medway
Chatham Maritime
Kent
ME4 4AG

Ethics Reference:
Prop17_2013_14

Date: 20 December 2013

Dear Dr Irisz Levai ,

Re: Dysfunctional Breathing in Athletes

I am now delighted to confirm that SSES REAG has approved your research study (REF No. Prop17_2013_14) and you are now permitted to recruit participants and commence testing.

If there is the need to amend any aspect of your research, please ensure you inform SSES REAG by completing a request for amendment form and submitting all revised paperwork (participant information sheet, questionnaires, etc.).

If there should happen to be any adverse event during your study, please also ensure SSES REAG is kept informed.

I hope you have a successful study.

With kindest regards,

Steve Meadows

(Chair SSES REAG)

University of Kent

School of Sport & Exercise Sciences
Research Ethics and Advisory Group (REAG)
University of Kent at Medway
Chatham Maritime
Kent
ME4 4AG

Ethics Reference:
Prop82_2013_14

Date: 20 January 2014

Dear Dr Irisz Levai ,

Re: Dysfunctional Breathing in Swimmers

I am now delighted to confirm that SSES REAG has approved your research study (REF No. Prop82_2013_14) and you are now permitted to recruit participants and commence testing.

If there is the need to amend any aspect of your research, please ensure you inform SSES REAG by completing a request for amendment form and submitting all revised paperwork (participant information sheet, questionnaires, etc.).

If there should happen to be any adverse event during your study, please also ensure SSES REAG is kept informed.

I hope you have a successful study.

With kindest regards,

Steve Meadows

(Chair SSES REAG)

Prop 104 - 2014 -15

School of Sport & Exercise Sciences (SSES)

University of Kent

REQUEST FOR AMENDMENT TO RESEARCH ETHICS

School of Sport & Exercise Sciences (SSES)
Research Ethics and Advisory Group (REAG)
University of Kent at Medway
Chatham Maritime
Kent, ME4 4AG

Original Ethics Reference No.:

Prop03_2014_15

Date of request: 01/03/2015

Title of research project: Use of the Nijmegen questionnaire to detect dysfunctional breathing in a recreationally active population

Name of person making request: Dr Irisz Karolina Levai

Details of proposed amendment(s): We would like to amend our protocol as following:

We would like to change the age range of the study from 18-40 to 18-45.

Please attach copies of any new or revised documentation used in the research study. If documentation has been revised please highlight changes.

Reason for amendment:
We would like to investigate dysfunctional breathing in a broader age range.

Approval granted: (YES) / NO

Reason for approval being denied:

Signed by SSES REAG Chair: S. V. [signature]

Print name: Steve Maddison

Date of approval: 12.03.2015

Study related documents

Date: _____ **Study ID:** NIJM 7

Title of project: Use of the Nijmegen questionnaire to detect dysfunctional breathing in a recreationally active population (Prop03_2014_15)

Name of investigator: Dr Irisz Karolina Levai, Dr John Dickinson

Please initial box

1. I confirm I have read and understand the information sheet dated 01/08/2014 (Version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and if I decide not to participate this will not prejudice my academic performance in any way. ☐
3. I understand that I am free to withdraw at any time without giving any reason. *(If you have any questions, please send an email to ikl3@kent.ac.uk or call 01634 888903).* ☐
4. I understand that my responses will be anonymised before analysis. I give permission for members of the research team to have access to my anonymised responses. ☐
5. I agree to take part in the above research project. ☐

_____ _____ _____

Name of participant Date Signature

General Information

First name(s): _____

Surname: _____

Email: _____@kent.ac.uk

_____@_____

Date: _____ **Study ID:** NIJM 7

University of Kent

General Information

Age: _____ years

Gender: Male ☐ Female ☐

Ethnicity:

1. White British ☐ **2.** White Irish ☐ **3.** Other white ethnic group ☐

4. Pakistani ☐ **5.** Indian ☐ **6.** Bangladesh ☐ **7.** Chinese ☐

8. Any other Asian background ☐

9. White and Black Caribbean ☐ **10.** White and Black African ☐ **11.** White and Asian ☐

12. Black or Black British-Caribbean ☐ **13.** Black or Black British African ☐

14. Any other black background ☐ **15.** Other ethnic group – Arab ☐

17. Prefer not to answer ☐ **18.** Other, please specify: _____

Smoking habits:

Do you smoke? Yes ☐ No ☐

If yes, how many cigarettes do you smoke in a day? 1-5 ☐ 5-10 ☐ More than 10 ☐

Are you an ex-smoker? Yes ☐ No ☐

How many cigarettes did you smoke in a day? 1-5 ☐ 5-10 ☐ More than 10 ☐

How long has it been since you quit? _____

Please tick the relevant box:

☐ **I am happy to be contacted by a member of the research team and being invited to participate in further studies on dysfunctional breathing.**

☐ **I do not wish to participate in further studies.**

Date: _____ **Study ID:** NIJM 7

University of Kent

NIJMEGEN QUESTIONNAIRE (NQ)

Assessment of Breathing Problems

Please score at every complaint, how frequently you experience such a symptom during / straight after exercise (your main sport), by ticking the appropriate box below.

	Never	Rarely	Sometimes	Often	Very often
1. Chest pain	☐	☐	☐	☐	☐
2. Feeling tense (or agitated)	☐	☐	☐	☐	☐
3. Blurred vision	☐	☐	☐	☐	☐
4. Dizziness	☐	☐	☐	☐	☐
5. Confusion, loosing contact with reality	☐	☐	☐	☐	☐
6. Fast or deep breathing	☐	☐	☐	☐	☐
7. Shortness of breath	☐	☐	☐	☐	☐
8. Tightness in the chest	☐	☐	☐	☐	☐
9. Bloated abdominal feelings	☐	☐	☐	☐	☐
10. Tingling of the fingers (pins and needles)	☐	☐	☐	☐	☐
11. Cannot breathe deeply	☐	☐	☐	☐	☐
12. Stiffness in fingers or arms (tension or tightness)	☐	☐	☐	☐	☐
13. Stiffness around the mouth (tension or tightness)	☐	☐	☐	☐	☐
14. Cold hands or feet	☐	☐	☐	☐	☐
15. Thumping of the heart (palpitation)	☐	☐	☐	☐	☐
16. Anxiety (nervousness)	☐	☐	☐	☐	☐

Total: ☐

Version 1 01/08/2014 4

Date: _____ **Study ID:** NIJM 7

SECTION 2. – Sport Information

1. **What is your main sport?** _____

2. **How long have you been taking part in your main sport?** _____

3. **How often do you train for your main sport?**

   Infrequently ☐ 1-2 days a week ☐ 3-4 days a week ☐

   5-6 days a week ☐ 7 days a week ☐

4. **How often do you compete in your main sport?** _____

5. **At what level of competition do you compete?**

   Recreational ☐ Local ☐ County ☐

   National ☐ International ☐

6. **During or after training or competition do you experience any of the following?** Please circle as many as appropriate.

   Coughing | Excess Mucus Production | Chest Tightness

   Wheezing | Difficulty in Breathing (Dyspnoea) | **NONE** of above

   Other_____

7. **During training or competition what environmental conditions seem to make your breathing worse?** Please circle as many as appropriate.

   Cold Climate | Dry Air | High Pollen Content

   High Pollution | Altitude | **NONE** of above

   Other_____

Date: _____ **Study ID:** NIJM 7

University of Kent

SECTION 3. – Respiratory Health

		Yes	No
1.	**Have you ever suffered from asthma?**	☐	☐
2.	Did you use asthma medication in the past?	☐	☐
3.	**Are you currently diagnosed asthmatic?**	☐	☐
4.	Are you currently using medication for your asthma?	☐	☐
5.	**Do you suffer from exercise-induced asthma (EIA)?**	☐	☐
6.	Are you currently using medication for your exercise-induced asthma (EIA)?	☐	☐
7.	**Have you ever had a Eucapnic Voluntary Hyperventilation Challenge (EVH) test?**	☐	☐

If yes, the test was a. Positive ☐ b. Negative ☐ c. Don't know/Can't remember ☐

If you have answered **YES** to either or both of **Questions 4** and **6** please complete table below.

Reliever (Blue inhaler)	**Preventer** (Brown, red or orange inhaler)		**Combination** (Purple inhaler)	**Other**
I do not know the name of the inhaler(s), but I am using: Please tick the appropriate box(es)				Montelukast
Blue inhaler: ☐	Brown, red or orange inhaler: ☐		Purple inhaler: ☐	Zafirlukast
I do know the name of the inhaler(s): Please circle as many as appropriate				Pranlukast
Airomir®	Asmabec®	Serevent®	Fostair®	
Asmasal®	Beclazone®	Atimos®	Seretide®	
Salamol®	Becodisks®	Foradil®	Symbicort®	
Salbulin®	Clenil Modulite®	Oxis®		
Salbutamol®	Pulvinal Beclomethasone®	Intal®		
Pulvinal®	Qvar®	Tilade®		
Ventolin®	Easyhaler Budenoside®			
Bricanyl®	Novolizer Budenoside®			
	Pulmicort®			
	Alvesco®			
	Flixotide®			
	Asmanex Twisthaler®			
If your medication is not on the list, please give more details:				

Date: _____ **Study ID:** NIJM 7

If you have answered **YES** to **Question 2** **(Did you use asthma medication in the past?)** please complete table below.

Reliever (Blue inhaler)	**Preventer** (Brown, red or orange inhaler)		**Combination** (Purple inhaler)	**Other**
I do not know the name of the inhaler(s), but I am using: Please tick the appropriate box(es)				Montelukast
Blue inhaler: ☐	Brown, red or orange inhaler: ☐		Purple inhaler: ☐	Zafirlukast
I do know the name of the inhaler(s): Please circle as many as appropriate				Pranlukast
Airomir®	Asmabec®	Serevent®	Fostair®	
Asmasal®	Beclazone®	Atimos®	Seretide®	
Salamol®	Becodisks®	Foradil®	Symbicort®	
Salbulin®	Clenil Modulite®	Oxis®		
Salbutamol®	Pulvinal Beclomethasone®	Intal®		
Pulvinal®	Qvar®	Tilade®		
Ventolin®	Easyhaler Budenoside®			
Bricanyl®	Novolizer Budenoside®			
	Pulmicort®			
	Alvesco®			
	Flixotide®			
	Asmanex Twisthaler®			
If your medication is not on the list, please give more details:				

THANK YOU VERY MUCH FOR YOUR PARTICIPATION

IN THIS SURVEY!

Study ID: Date:

University of Kent

Health Questionnaire

SECTION 1. – General Health

PART 1.

		Yes	No
1.	In the last 4 weeks have you suffered from or been treated for chest infection?	☐	☐
2.	In the last 2 weeks have you suffered from or been treated for any other illnesses?	☐	☐
3.	Have you consumed any caffeine within the past 4 hours?	☐	☐
4.	Do you currently smoke? If yes, how many cigarettes per day? _____	☐	☐
5.	Are you pregnant or have you had a baby in the last 6 months?	☐	☐
6.	Do you have any injury or condition that limits your mobility? If yes, please explain: _____	☐	☐
7.	Are you currently taking any medications? If yes, please provide details: _____	☐	☐
8.	Have you to your knowledge had any adverse/allergic reaction to any medication? If yes, please provide details: _____	☐	☐

PART 2.

		Yes	No
1.	Has your doctor ever said that you have a heart condition OR high blood pressure?	☐	☐
2.	Have you ever experienced wheeze/cough or felt pain in your chest at rest or when you do physical activity?	☐	☐
3.	Do you lose balance because of dizziness OR have you lost consciousness in the last 12 months? Please answer NO if your dizziness was associated with over-breathing (including during vigorous exercise).	☐	☐
4.	Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?	☐	☐
5.	Are you currently taking prescribed medications for a chronic medical condition?	☐	☐
6.	Do you have a bone or joint problem that limits your physical activity? (e.g. knee, ankle, shoulder, elbow or other)	☐	☐
7.	Has your doctor ever said that you should only do medically supervised physical activity or is there any other condition why you shouldn't participate in physical activity?	☐	☐

If you answered **YES** to one or more of the questions above, please go to **SECTION 2** on Page 2.

Study ID: Date:

SECTION 2. – Chronic Medical Conditions

	Yes	No
1. **Do you have cancer of any kind?**		
a. Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head and neck?	☐	☐
b. Are you currently receiving cancer therapy (such as chemotherapy or radiotherapy)?	☐	☐
2. **Do you have Heart Disease or Cardiovascular Disease?** *This includes coronary Artery Disease, High Blood Pressure, Heart Failure, Diagnosed Abnormality of Heart Rhythm.*	**Yes**	**No**
a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments.)	☐	☐
b. Do you have an irregular heartbeat that requires medical management? (e.g. atrial fibrillation, premature ventricular contraction)	☐	☐
c. Do you have chronic heart failure?	☐	☐
d. Do you have a resting blood pressure equal to or greater than 140/90 mmHg with or without medication? (Answer YES if you do not know your resting blood pressure.)	☐	☐
e. Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?	☐	☐
3. **Have you had a Stroke?** *This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event.*	**Yes**	**No**
a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments.)	☐	☐
b. Do you have any impairment of walking or mobility?	☐	☐
c. Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?	☐	☐

Study ID: Date:

4. **Do you have any Metabolic Conditions?** **Yes** **No**

This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes.

a. Is your blood sugar often above 13.0 mmol/L? (Answer YES if you are not sure.) ☐ ☐

b. Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys and the sensation in your toes and feet? ☐ ☐

Yes **No**

5. **Do you have other Metabolic Conditions** such as thyroid disorders, pregnancy-related diabetes, chronic kidney disease or liver problems? ☐ ☐

6. **Do you have a Respiratory Disease?**

This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure. **Yes** **No**

a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments.) ☐ ☐

b. Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy? ☐ ☐

c. Has your doctor ever said you have high blood pressure in the blood vessels of your lungs. ☐ ☐

d. If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week) or have you used your rescue medication more than twice in the last week? ☐ ☐

If asthmatic, please go to Page 6.

7. **Do you have any Mental Health Problems or Learning Difficulties?**

This includes Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome etc. **Yes** **No**

Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments.) ☐ ☐

Study ID: Date:

	Yes	No
8. **Do you have Arthritis, Osteoporosis or Back Problems?**		
a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments.)	☐	☐
b. Do you have joint problems causing pain, a recent fracture or facture caused by osteoporosis or cancer, displaced vertebra (e.g. spondyolisthesis) and/or spondylosis/pars defect (a crack in the bony ring on the back of the spinal column)?	☐	☐
c. Have you had steroid injections or taken tablets regularly for more than 3 months?	☐	☐
9. **Do you have any other medical condition not listed above or do you live with two chronic conditions?**	**Yes**	**No**
a. Have you experienced blackout, fainted or lost consciousness as a result of a head injury within the last 12 months?	☐	☐
b. Do you have a medical condition that is not listed, such as epilepsy, neurological conditions, kidney problems etc.?	☐	☐
c. Do you currently live with two chronic conditions?	☐	☐
10. **Are there any other relevant conditions/injuries/illnesses that you are aware that you have which have not been covered in this questionnaire?**	**Yes**	**No**
	☐	☐

If yes, please provide details:

_____

Date: _____ Study ID: DB_____

University of Kent

EVH - PROVOCATION CHALLENGE

Fractioned exhaled Nitric Oxide (FeNO) **Average FeNo:**

Test 1 (ppb)	
Test 2 (ppb)	

Baseline Spirometry

Spirometry	FEV_1 (litres)	FVC (litres)	PEF (l/min)	FEV_1/FVC%
1st Flow Loop				
2nd Flow Loop				
3rd Flow Loop				
Best				
% Predicted				

**Predicted value must be 80% or above*

Best Baseline FEV_1 _____ **must be within 5% of second best FEV_1*

10% of Best Baseline FEV_1 _____

Target Minute Ventilation (Best FEV_1x30) _____

EVH Challenge

Time	Total volume of air expired (litres)	Expected	Correction
1 min			
2 min			
3 min			
4 min			
5 min			
6 min			

Post EVH Spirometry

Post EVH	Effort 1			Comments	Effort 2			Comments	Best FEV_1 (at minute)
	FEV_1	FVC	PEF		FEV_1	FVC	PEF		
3 mins (9 mins)									
5 mins (11 mins)									
7 mins (13 mins)									
10 mins (16 mins)									
15 mins (21 mins)									

POST BRONCHODILATOR

Bronchodilator _____ **Dose** _____

	Effort 1			Effort 2			Effort 3		
	FEV_1	FVC	PEF	FEV_1	FVC	PEF	FEV_1	FVC	PEF
% Predicted									

COMMENTS:

Study ID: Date:

University of Kent

$VO_{2\ max}$ test – Visit ____

Stage	(time)	Workload	Borg 10	RPE	HR	RER
0.	0 – 2 mins	0W	_____	_____	_____	_____
1.	2 – 5 mins	0W	_____	_____	_____	_____
2.	5 – 6 mins	25W	_____	_____	_____	_____
3.	6 – 7 mins	50W	_____	_____	_____	_____
4.	7 – 8 mins	75W	_____	_____	_____	_____
5.	8 – 9 mins	100W	_____	_____	_____	_____
6.	9 – 10 mins	125W	_____	_____	_____	_____
7.	10 – 11 mins	150W	_____	_____	_____	_____
8.	11 – 12 mins	175W	_____	_____	_____	_____
9.	12 – 13 mins	200W	_____	_____	_____	_____
10.	13 – 14 mins	225W	_____	_____	_____	_____
11.	14 – 15 mins	250W	_____	_____	_____	_____
12.	15 – 16 mins	275W	_____	_____	_____	_____
13.	16 – 17 mins	300W	_____	_____	_____	_____
14.	17 – 18 mins	325W	_____	_____	_____	_____
15.	18 – 19 mins	350W	_____	_____	_____	_____

Study ID: Date:

University of Kent

Visit _____ Condition: _____

70% of maximal power: _____

Stage	(time)	Workload	Borg 10	RPE	PAIN	HR	RER
0.	0 – 2 min	0W	_____	_____	_____	_____	_____
1.	2 – 5 min	0W	_____	_____	_____	_____	_____
2.	5 – 6 min		_____	_____	_____	_____	_____
3.	6 – 7 min		_____	_____	_____	_____	_____
4.	7 – 8 min		_____	_____	_____	_____	_____
5.	8 – 9 min		_____	_____	_____	_____	_____
6.	9 – 10 min		_____	_____	_____	_____	_____
7.	10 – 11 min		_____	_____	_____	_____	_____
8.	11 – 12 min		_____	_____	_____	_____	_____
9.	12 – 13 min		_____	_____	_____	_____	_____
10.	13 - 14 min		_____	_____	_____	_____	_____
11.	14 – 15 min		_____	_____	_____	_____	_____