UNIVERSITY OF HULL

Cool facial airflow speeds recovery from exertion induced breathlessness in people with chronic breathlessness

By

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being a Thesis submitted for the Degree of Masters by Research at the University of Hull

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ABSTRACT

Background: Evidence supports facial airflow from a handheld fan to reduce breathlessness in patients with chronic breathlessness. The thesis explored the effectiveness of different airflow speeds on recovery from exertion-induced breathlessness.

Methods: Repeated n=1 randomised controlled trial with moderate-severe chronic breathlessness (mMRC ≥3). The order of four airflow speeds and control (no handheld fan) were randomised for use during the 10 minutes recovery from breathlessness induced by a 1-minute sit-to-stand test (5 tests in total). Outcome measures included Numerical Rating Scale (NRS) breathlessness intensity (every minute), facial skin thermal imaging (0, 3, and 5 minutes), oxygen saturation and heart rate (every 30 seconds) were recorded over 10 minutes. Data were analysed using descriptive statistics, repeated measures ANOVA, with simple contrast analysis.

Results: 10 participants were recruited (n=1 withdrawn due to health concerns, and n=1 excluded due to limited exertion-induced breathlessness post-exercise test). 8 participants (mean age 65± 15yrs, range 34-82yrs; 5 men; 7 COPD, 1 Long Covid) completed assessments. An interaction effect for fan speed over time ($p=0.010$, $\eta_p^2=0.192$) suggests that airflow speed impacted breathlessness recovery from exercise.

Simple contrast analysis of each minute of recovery found a significant difference between fan speed level 2 and control from minutes four to eight, compared with levels 1 and 3 from minutes seven to eight, and level 4 from minutes eight to ten.

A main effect of fan speed ($p=<0.001$, $\eta_p^2=0.758$) and interaction effect of fan speed over time ($p=<0.001$, $\eta_p^2=0.686$) indicate that airflow speed reduced skin facial temperature compared with control. A fan speed of 4.91 m/s had the greatest cooling effect but not the quickest recovery and participants stated they found this speed unpleasant.

Conclusion: Facial airflow from a fan improved exertion-induced breathlessness recovery and reduced facial skin temperature. The proposed optimal airflow speed for breathlessness recovery is ~2.85 m/s.

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LIST OF ABBREVIATIONS

6MWT	6-Minute Walking Test
ACSM	American College of Sports Medicine
BIS	Breathlessness Intervention Service
BPM	Beats per minute
BSS	Breathlessness Support Service
BTF	Breathing Thinking Functional Model
BMI	Body Mass Index
CAT	Chronic obstructive pulmonary disease Assessment Test
CCQ	Clinical COPD Questionnaire
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardio-Pulmonary Exercise Test
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
FANFARE-P	Fan Facial Airflow Recovery from Exercise Patient Trial
FDR	False Discovery Rate
FEV_1	Forced Expiratory Volume in 1 second

FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
HR	Heart Rate
IC	Inspiratory capacity
ICU	Intensive Care Unit
ILD	Interstitial Lung Disease
mmHg	Millimetres of Mercury
mMRC	modified Medical Research Council
NRS	Numerical Rating Scale
PCR	Polymerase Chain Reaction
PIS	Participant Information Sheet
rmANOVA	Repeated Measures Analyses of Variance
SD	Standard Deviation
SGRQ	St George Respiratory Questionnaire
SpO_2	Oxygen Saturation
STS	Sit-to-stand
TLC	Total Lung Capacity

VAS	Visual Analogue Scale

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1.0. INTRODUCTION

1.1. Overview

Click or tap here to enter text.Click or tap here to enter text.Click or tap here to enter text.Click or tap here to enter text.Click or tap here to enter text.Click or tap here to enter text.Click or tap here to enter text.Disabling chronic breathlessness, known medically as dyspnoea, is commonly experienced by patients with life-limiting illnesses, such as chronic obstructive pulmonary disease (COPD) and may persist despite receiving the optimal treatment for the underlying condition (Johnson et al., 2017). Breathlessness is often undertreated (Smallwood et al., 2016), and the impact of living with breathlessness on patients' wellbeing overlooked (Lunn et al., 2019).

The unpleasantness and distress caused by breathlessness may prevent patients from taking part in day-to-day activities and avoid physical activity. This inactivity may result in cardiovascular deconditioning, decreased muscle strength (Laveneziana & Agostoni, 2016), and may perpetuate further episodes and increased severity of breathlessness. Furthermore, inactivity is recognised as a primary risk factor for developing chronic conditions, non-communicable diseases, and obesity (Cunningham et al., 2020). On a global scale, physical inactivity in the general populations was found to be a large contributor to the global chronic health burden, responsible for more than 7% of all-cause and cardiovascular disease deaths (Katzmarzyk et al., 2022). Therefore, increasing a patient's ability to self-manage and improve their breathlessness, and improve exercise tolerance are major goals highlighted to managing chronic lung diseases (O'Donnell et al., 2017).

Exercise-based pulmonary rehabilitation is known to reduce symptoms such as breathlessness in patients with chronic respiratory diseases (Grosbois et al., 2022; McCarthy et al., 2015; Nopp et al., 2022). As well as increasing the quality of life, exercise capacity, and the ability to compensate and control the increasing

inspiratory drive from exertion during physical activity (Gloeckl et al., 2018). However, patients with chronic lung disorders are susceptible to episodes of exertional breathlessness due to the mechanical limitations of their cardiorespiratory system in response to demands placed on the body by exertion-inducing activities (Jolley et al., 2008; O'Donnell et al., 2016). As regular exertion is vital for physical and mental well-being, it is important to provide patients with a toolbox of techniques and interventions which can effectively help them self-manage exertional breathlessness and overcome the fear of exercise. A virtuous cycle of increased physical activity may then prevail.

There is a wide range of techniques and interventions available to help patients manage their breathlessness depending on the underlying causation. Several pharmaceutical options include opioids (Johnson & Currow, 2020), bronchodilators (Calzetta et al., 2017), and inhaled corticosteroids (Parshall et al., 2012). Non-pharmaceutical methods, such as relaxation techniques, mobility aids, neuromuscular electrical stimulation, breathing techniques, inspiratory muscle training, and the handheld fan are identified as being important components for managing breathlessness as part of the Breathing, Thinking, Functioning model (Spathis et al., 2017).

This thesis will focus on the handheld fan and aims to investigate the effects of different airflow speeds from a handheld fan versus control (no handheld fan) on recovery from exertional breathlessness and perceived airflow pleasantness in people with chronic lung conditions.

2.0. LITERATURE REVIEW

2.1. Definitions of Breathlessness

The American Thoracic Society define breathlessness as;

“a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioural responses.” (American Thoracic Society Committee, 1999).

Additional definitions of breathlessness features have been proposed and outlined for clinical application. The widely accepted ‘chronic breathlessness’ term is defined as a breathlessness sensation that persists for more than a month (Wahls, 2012). In addition, ‘acute-on-chronic breathlessness’ describes the acute worsening of chronic breathlessness caused by physical and or emotional exertion which influences the underlying condition (Hutchinson et al., 2019, 2022).

Terms such as ‘refractory breathlessness’ have previously been used to define breathlessness that persists despite optimal treatment (Currow et al., 2014). However, current thinking by Johnson et al., (2017) argues that ‘refractory’ implies ‘complete resistance’, whereas multiple types of pharmaceutical and non-pharmaceutical interventions are succeeding in reducing the effects of breathlessness irrespective of the original condition. Furthermore, patients reported

that ‘refractory’ was not required in the definition of breathlessness and proved unhelpful (Johnson et al., 2017).

Breathlessness assessment and management approaches have developed from single-dimensional breathlessness theories, relating the sensation of breathing effort causing all breathlessness (Altose et al., 1985), to proposing breathlessness as a multi-dimensional symptom influenced by physiological, psychological, and environmental factors (Laviolette & Laveneziana, 2014). By understanding the complex pathophysiology of breathlessness, more effective interventions can be investigated to help patients manage this burdensome symptom.

2.2. Characteristics of Breathlessness

2.2.1. Types of Breathlessness

Breathlessness is categorised into either episodic or continuous breathlessness. The majority of people experiencing breathlessness describe the symptom in episodes or a combination of both episodes and continuous breathlessness states (Reddy et al., 2009). Continuous breathlessness is defined as a breathlessness sensation that persists over 24 hours. The duration is split between short periods (days or weeks) and long periods (months or years) of continuous breathlessness. The cause for breathlessness to expand over 24 hours is a result of numerous factors, including: chest infections and exacerbations of underlying conditions (Simon et al., 2013b). Continuous breathlessness can persist despite optimal treatment of the underlying condition (Simon et al., 2013a).

Episodic breathlessness is defined as breathlessness that is present for a period lasting for seconds to hours, however, the sensation does not exceed 24 hours in length. Simon et al., (2013b) found that patients described the presence of episodic breathlessness as either a trigger response or ‘out of the blue’ with no apparent triggers. Triggers instigating episodic breathlessness fall into either exertion, emotional or environmental categories:

i. Exertion triggers are connected to daily physical activities where body movement occurs regardless of the intensity. Low intensity exertional triggers examples include standing up, dressing, or walking. Whereas exertion can be triggered through higher intensity exercise, such as cycling and jogging. The severity of breathlessness experienced has a strong relationship with the intensity of the exertion undertaken (Simon et al., 2013a).

ii. Emotional triggers for breathlessness are specific to the individuals’ feelings in the moment of a breathlessness breakout. Common emotions associated with breathlessness include anxiety, anger, and pain. However, positive emotions such as excitement and happiness are also a trigger for breathlessness incidents (Simon et al., 2013b).

iii. Environmental triggers are dependable on the climate and air quality. Patients breathlessness can be triggered during both hot and cold temperatures, with the wind being an additional factor. Haines et al., (2020) found in asthma and inducible laryngeal obstruction patients report that air quality (irritants such as dust, perfume, and other chemicals) are also present triggers of breathlessness in the environment.

2.2.2. Descriptors of Breathlessness

Breathlessness, being a subjective symptom, offers a variety of patient descriptors. Grouping patient perceptions of breathlessness may help improve the understanding of patient symptoms and the underlying pathophysiology. Many studies have investigated participants' responses to breathlessness, with specific groups relating to conditions such as COPD, cancer, and healthy volunteers. Wilcock et al., (2002) investigated how patients with COPD, cancer, asthma, interstitial lung disease (ILD) and cardiac failure described their breathlessness using a 15-item questionnaire. The authors aimed to understand the possible discrepancies between how breathlessness impacts patients across medical conditions. Results of the top 3 descriptors across the range of conditions related to ‘I can’t get enough air’, ‘I feel out of breath’, and ‘my chest feels tight’. These results illustrate that breathlessness is not comprised of a single sensory perception. Indeed, three main categories are highlighted to describe the sensations of breathlessness, relating to ‘work or effort’, ‘tightness’, and ‘air hunger’ (Parshall et al., 2012).

The perception of breathlessness through breathing ‘effort or work’ stems from the respiratory muscle afferents to increase neural stimulation of the respiratory drive by the motor and sensory cortex (Jolley & Moxham, 2009). The respiratory drive is affected when the respiratory muscle capacity fails to match the respiratory muscle load (Spinelli et al., 2020). The resultant increase in the respiratory drive can stimulate the patient-reported ‘effort or work’ descriptor of breathlessness.

Tightness in the chest is a descriptor typically used by patients diagnosed with asthma. Chest tightness can be a sensation from both bronchoconstriction and

obstruction in the bronchial airways caused through inflammation (Mims, 2015) and/or mucus hypersecretion (Rubin et al., 2014). However, chest tightness is often associated with mild bronchoconstriction (Antoniu, 2010). The sensation of chest tightness is attributed as a sensory response after vagal afferents signals during increased airways resistance (Lougheed et al., 2006). However, Binks et al., (2012) found no relationship between the tightness sensation and respiratory work.

Air hunger is a distressing sensation described by patients as ‘I am suffocating’ and ‘I need more air’. Predominantly experienced through mechanical ventilation in intensive care units (ICU). It’s stimulated when the respiratory drive increases but the ventilation rate is incapable of matching the ventilation demand. The neural respiratory drive instigates a response to increasing the ventilation rate to recover the oxygen debt. Air hunger is alleviated through pulmonary stretch receptors signalling tidal inflation of the lungs to reduce the respiratory drive (Worsham et al., 2020). Patients on mechanical ventilators have reduced tidal volumes and constant $PaCO_2$ levels, therefore patients can experience involuntary air hunger (Schmidt et al., 2014).

2.3. Prevalence

The prevalence of breathlessness in patient populations is dependent on the underlying disease, the severity of the underlying disease and, in the case of cancer, the stage of the disease. Breathlessness severity also increases with advanced diseases, especially when approaching end-of-life circumstances requiring palliative care (Currow et al., 2008). Understanding and highlighting the prevalence of disease

related breathlessness is important in order that breathlessness receives the attention it deserves (Teunissen et al., 2007). The high prevalence of breathlessness symptoms across multiple disease states, upon hospital admission and in the general population has been reported in numerous studies.

Alkodaymi et al., (2022) conducted a systematic review into the prevalence of COVID-19 symptoms, including breathlessness, from 63 papers with a total sample size of n=257,348. Breathlessness was found to be one of the most common symptoms described by patients. At 3-9 months post-infection, breathlessness was present in 25% of patients and dropped to 21% at 9-12 months post-infection. Breathlessness at >12 months post-infection was recorded in 31% of the population, however, limited studies recorded past the 12 months.

Stevens et al., (2018) conducted a prospective cohort study (n=67,362) examining symptoms upon hospital admission to medical-surgery and obstetric units. The study found breathlessness to be a prevalent symptom, reported by 11% of patients upon admission, while pre-hospital admission breathlessness was present in 16% of cases.

In the general population, breathlessness has been researched as a common symptom experienced regardless of individual physical condition. Data from the national breathlessness survey in Australia reported the prevalence of breathlessness (defined as mMRC $\geq$ 2) as 9.5% (Poulos et al., 2021). Interestingly, 31% of patients with a breathlessness grade of $\geq$ 2 had no respiratory or heart condition, anxiety or depression and no additional risk factors (smoking and obesity), this equates to 5% of those responding to the survey.

Additional factors may impact the prevalence of breathlessness. The review by Ahmadi, (2018) highlighted breathlessness prevalence in the general population is dependent on sex, age, and obesity. Where Ekström et al., (2017) found females were twice as likely (27% vs. 14%) to experience breathlessness (mMRC grade of ≥ 1) compared to males and proposed lower lung volumes in females as a proposed mechanism. Whilst A. K. Smith et al., (2016) identified a 25% prevalence in patients aged 70 and older, with the highest breathlessness prevalence rates having chronic lung disease in the age category. Furthermore, Currow et al., (2017) identified a significant relationship between increasing body mass index (BMI) and the increase of breathlessness prevalence and severity.

Breathlessness is a common symptom across disease states and in the general population. Therefore, it remains crucial for support to be readily available for people experiencing breathlessness to manage their symptom, particularly in individuals with severe breathlessness that impacts quality of life and limits activities of daily living.

2.4. Mechanisms of Breathlessness

The complex nature of breathlessness is expressed through its vast quantity of sensory inputs and breathing mechanics that generate breathlessness in both healthy and patient populations. Understanding the physiological mechanisms of breathlessness at rest and during exertion can enable more effective management techniques for breathlessness.

Breathing mechanics play an important role in the development of breathlessness by communicating through afferent signals from mechanoreceptors in the lungs and chest wall proprioceptors to the central nervous system to regulate the inspiratory neural drive (Mortola, 2019). In healthy individuals, breathlessness is often induced by high altitude exposure (environment), breath-holding, stressful situations inducing panic and anxiety (emotion), and intense exercise (exertional) (Gigliotti, 2010).

During cardiopulmonary exercise testing, minute ventilation can rise from 6 Litres min^{-1} up to 200 Litres min^{-1} (Herdy et al., 2016; Petek et al., 2022). To maintain homeostasis, the increase in ventilatory demand from exercise requires an increase in neural drive to the respiratory muscles (Aliverti, 2016). If the ventilatory demand is too high for the diaphragm alone, accessory respiratory muscles—primarily involved in upper limb movement and postural control—are recruited to assist with ventilation (Durdu et al., 2023). The increase in respiratory muscle effort to meet the ventilatory demand, when perceived by the individual, is commonly used as a descriptor for the sensation of breathlessness in healthy and patient subjects (Grazzini et al., 2005).

- In contrast, patients may experience physiological changes to the lungs which cause mechanical adaptations and impair lung function which induce breathlessness at lower levels of ventilation and, in some cases, at rest. In airway obstructive disease cases, expiratory flow limitations often result in changes to breathing mechanics, ventilatory control, and could develop into exertional breathlessness (Babb, 2013). During exercise, the increased tidal volume and respiration rate can cause a reduction in the expiratory time

(Tantucci, 2013). A reduced expiratory time, often partnered with expiratory flow limitation, may cause insufficient expiration of air, resulting in dynamic hyperinflation of the lungs (Figure 1). The inspiratory muscles are put under excessive load by contracting closer to the total lung capacity and greater tidal pressures (O'Donnell et al., 2020). This additional work of breathing, and potential functional weakness in the inspiratory muscles, may lead to inspiratory muscle fatigue and the sensation of breathlessness. Furthermore, inspiratory muscle fatigue initiates the respiratory muscle metaboreflex instigating the re-distribution of oxygenated blood from the skeletal muscle to the respiratory muscles, decreasing endurance performance (Dempsey et al., 2006; Shiozawa et al., 2022).

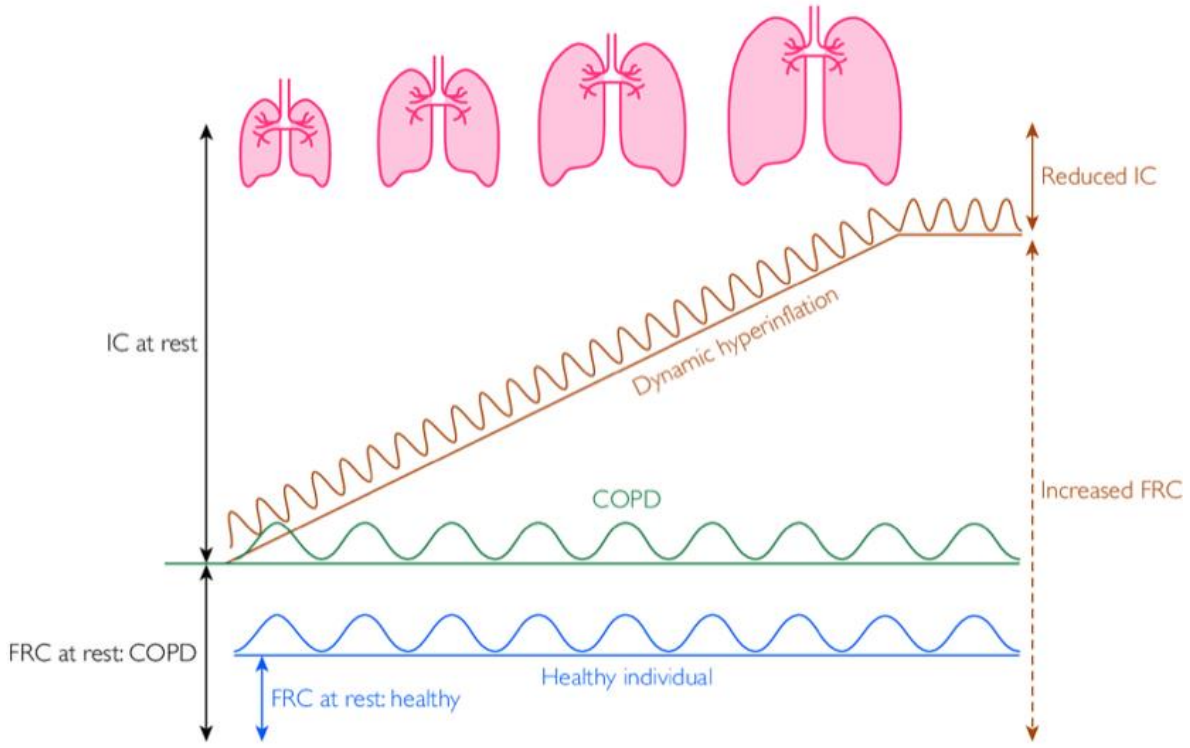


Figure 1. Effects of Dynamic Hyperinflation on Lung Volumes in Individuals With COPD at Rest (Green Line) and During Exertion (Red Line) Taken From

(Usmani et al., 2021). COPD, chronic obstructive pulmonary disease; *FRC*, functional residual capacity; *IC*, inspiratory capacity.

The constant feedback from the sensory receptors involved in respiration dictates the inspiratory neural drive and consequently the sensation of breathlessness. Chemoreceptors are responsible for identifying imbalances in chemical concentrations and generating impulses to alter the inspiratory neural drive and maintain homeostasis (O'Donnell et al., 2020). The location of these receptors can either be central (medulla, brainstem, cerebellum and hypothalamus)(Nattie & Li, 2012) or peripheral (carotid and aortic bodies) (Guyenet & Bayliss, 2015). Peripheral chemoreceptors detect imbalances in pH, O_2 and CO_2 concentrations within the arterial blood and increase ventilation to mediate the chemical concentrations (Buchanan & Richerson, 2009). Whereas central chemoreceptors detect changes in pH levels, O_2 and CO_2 concentrations in the brain and cerebrospinal fluid (Webster & Karan, 2020). An acidic environment of high levels of hydrogen ions caused by high $PaCO_2$ initiates an increase in respiratory drive, in contrast to, alkaline environments of low hydrogen ions with low $PaCO_2$ results in decreasing ventilation rate (Jonkman et al., 2020).

The mechanoreceptors are located throughout the respiratory tract and detect changes in the mechanical status of the lungs and chest walls (Gourine & Spyer, 2009). Producing information with regard to breathing frequency, breathing depth and present irritation triggers (Webster & Karan, 2020). Specific mechanoreceptors within the respiratory tract are slow-adapting stretch receptors that are activated during lung inflation and cause termination of inhalation (Gourine & Spyer, 2009),

and rapid-adapting stretch receptors that determine the rate of inflation over time (Bergren, 2020).

In response to the vast afferent signals, the neural centres responsible for regulating breathing produce efferent impulses to alter the strength of diaphragm contractions (Pozzi et al., 2022) and the activation of the accessory respiratory muscles to meet the ventilatory demands and maintain homeostasis (Aliverti, 2016). The quantity of sensory inputs to regulate breathing at rest and during exercise is extensive and highlighted in Table 1.

Table 1. Possible Sources of Respiratory Sensations (Parshall et al., 2012)**.**

Source Of Sensation	**Adequate Stimulus**
Medullary respiratory corollary discharge	Drives for automatic breathing
Primary motor cortex corollary discharge	Voluntary respiratory drive
Limbic motor corollary discharge	Emotions
Carotid and aortic bodies	Hypercapnia, Hypoxemia, acidosis
Medullary chemoreceptors	Hypercapnia
Slow adapting pulmonary stretch receptors	Lung inflation
Rapid adapting pulmonary stretch receptors	Large lung inflation/deflation, Airway collapse, Irritant substances
Pulmonary c-fibres	Pulmonary vascular congestion
Airway c-fibres	Irritant substances
Upper airway receptors	Cooling of airway mucosa
Muscle spindles in respiratory pump muscle	Muscle change of length during breathing
Tendon organ in respiratory pump muscles	Muscles active force during breathing
Metaboreceptors in respiratory pump muscles	Metabolic activity of respiratory pump
Vascular receptors (heart and lung)	Distention of vascular structures
Trigeminal nerve receptors	Facial skin cooling
Chest wall joint and skin receptors	Tidal breathing motion

Breathlessness can occur when the afferent feedback from the respiratory muscles and regulating sensory inputs don't match the expected response from the efferent signal (Burki & Lee, 2010; O'Donnell et al., 2016). This is known as the theory of mismatch and is detailed below. Multiple differences in the neurophysiological sensations of breathing can be related to the described sensation of breathlessness. Respiratory muscle feedback on contractile strength and frequency relates to the sensation of 'breathing effort', chemical imbalances from ventilatory demand being greater than ventilatory capacity or rapid ventilatory may cause 'air hunger', and pulmonary afferents feedback relating to bronchoconstriction is often described as the sensation of 'tightness in the chest' (Parshall et al., 2012).

2.4.1. Theory of Mismatch

The theory of mismatch suggests breathlessness may be experienced when the feedback generated by the respiratory system is inconsistent with the brain's expected ventilation for any given level of neural respiratory drive (Jolley & Moxham, 2009). Corollary discharge is released by the brainstem to relay information back to the sensory cortex (Gigliotti, 2010). In this process, the corollary discharge sends a copy of the efferent command for the motor activity of the respiratory system (Currow et al., 2013). The command feedback is used to generate a perception of breathing effort in the sensory cortex for the expected ventilation demand.

During ventilation, afferent signals are produced by the mechanoreceptors of the respiratory system to provide feedback on ventilation demand and capacity (Currow et al., 2013). However, an imbalance occurs when the efferent feedback to

the sensory cortex doesn't match the afferent feedback from the respiratory mechanoreceptors relating to ventilation demand and capacity. This dissociation between the afferent feedback and the efferent command copy feedback determines the intensity of the perception of breathlessness (De Vito, 2021). Minor deviations between the afferent and efferent feedback are minimalised to reduce the awareness of the outgoing motor command, resulting in minimal breathlessness perception. However, large deviations between the feedback causes a conscious awareness of the motor command to the respiratory muscles, generating an intense perception of breathlessness.

2.4.2. Skeletal Muscle

The skeletal muscles of patients with cardio-respiratory diseases can play a role in the development of breathlessness. Patients with conditions such as COPD are prone to lower physical activity levels (Román-Rodríguez & Kocks, 2021) leading to physical deconditioning (Ferreira & Oliveira, 2021).

Patients with COPD may display skeletal muscle composition adaptations whereby the muscle switches from type 1 slow oxidative fibres to primarily type 2 fast (oxidative) glycolytic fibres (Ceco et al., 2017). The shift in muscle fibre types to predominantly fast glycolytic fibres reduce the oxidative capacity of the skeletal muscle (Van Wessel et al., 2010), partnered with reduced oxidative enzyme activity (Maltais et al., 2000), this promotes muscular fatigue. Additional adaptations to the skeletal muscle refer to a smaller cross-sectional area (Gouzi et al., 2013) indicating possible muscle atrophy and limited exercise capacity. The decline in skeletal

muscle oxidative capacity places greater ventilatory demands on the cardio-respiratory system to compensate. The afferent signals from the skeletal muscles increase the inspiratory neural drive and subsequent breathing effort which contribute to the sensation of breathlessness.

There is also the increased risk of muscular fatigue of both the skeletal muscles during exercise and the respiratory muscles following the heightened ventilatory demand. When muscles start to fatigue, the metaboreflex causes a redistribution of blood flow to the fatiguing muscles. Efferent signals increase the activation of the sympathetic nervous system to alter vascular resistance through vasoconstriction and vasodilation of the arterial network (Boushel, 2010). The redirection of blood flow towards the respiratory muscles restricts the skeletal muscles' capacity, resulting in fatigue and decreased exercise performance (Sheel et al., 2018).

Consequently, patients are less willing to undertake physical activity due to the uncomfortable breathlessness experience and muscular fatigue, which promotes the acceleration of their underlying condition and further deconditioning.

2.5. Assessment and Diagnosis

Assessment and diagnosis of breathlessness can be challenging and is often overlooked in a clinical setting, due to the multidimensional structure of breathlessness that consists of the overall breathlessness intensity, sensory qualities, psychological response, impact on physical activity and discomfort. Further, there is a reliance on self-reported measures by patients to assess their own

perceived breathlessness and often nurses and physicians underestimate patient scores of breathlessness sensation (Haugdahl et al., 2015).

Multiple tests and scales are available to assess the severity of breathlessness and its impact on the patient. Elliott-Button et al., (2020) investigated the available techniques used in clinical settings to identify and assess breathlessness in adults with chronic conditions. Severity is assessed individually due to the subjective nature of breathlessness. Therefore, assessment tools rely upon patients scaling their perception of the severity and intensity, using multiple tools such as the Numerical Rating Scale (NRS)(Gift & Narsavage, 1998), Visual Analogue Scale (VAS), modified Borg Scale (Kendrick et al., 2000), and the modified Medical Research Council (mMRC) dyspnoea scale (Bestall et al., 1999).

The impact of breathlessness can be assessed through a variety of questionnaires and tests to examine health, functional capacity, exercise capacity and patient well-being. Reliable and valid questionnaires such as the St George Respiratory Questionnaire (SGRQ)(Nelsen et al., 2017), COPD Assessment Test (CAT)(Gupta et al., 2014), and Clinical COPD Questionnaire (CCQ)(van der Molen et al., 2003) can be applied to specific underlying conditions to assess changes.

Additionally, functional and exercise tests such as the 6-Minute walking test (6MWT), Sit-to-stand test (STS) and Cardio-Pulmonary Exercise Test (CPET) can be performed to display functional and exercise capacity and the breathlessness response to the activity performed. The physical tests can quantify the physical capabilities of the patient to assist in the delivery of management techniques and exercise prescription programmes.

2.6. Disease Associations with Breathlessness

2.6.1. Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is a common term to categorise a group of respiratory diseases characterised by chronic airflow limitation and inflammation (Global Initiative for Chronic Obstructive Lung Disease., 2018). The three main lung diseases are; chronic bronchitis, chronic respiratory failure, and emphysema (Raherison & Girodet, 2009).

Following the Global Burden of Disease study for 2019, it was estimated that COPD cases increased from 114.9 million in 1990 to 213.3 million in 2019 (Safiri et al., 2022). The impact of COPD is also apparent in the global death ranking. The World Health Organisation, (n.d.) stated that COPD is the third leading cause of death 2019 with an annual death toll of 3.23 million. The large scale and prevalence of COPD is attributed to the broad scope of diseases under the umbrella diagnosis.

Chronic bronchitis is defined as a chronic cough and sputum production that persists for ≥3 months of the year, for two consecutive years (Kim & Criner, 2013). Chronic bronchitis is caused through the overproduction of mucus in the airways. Typical catalysts for increased mucus production are associated with noxious inhaled agents, individuals' genetics, and respiratory infections. Removal of the hyperexcreted mucus becomes difficult causing excess build up in the airways and high levels of coughing. The presence of excess mucus results in inflammation of the airways reducing the capacity of the airways for airflow passage (Hogg, 2004)

therefore respiration becomes more difficult increasing the sensation of breathlessness.

Emphysema is defined as the permanent enlargement of the airspaces distal to the terminal bronchioles, supplemented by damage caused to their cell walls (Li et al., 2011). The enlargement in airspaces occurs when the alveolar capillary units are destroyed and supporting tissues of the cell wall are lost (P. L. Shah et al., 2017) causing a largening effect on the alveoli sacs. During inhalation, the alveoli sacs become hyperinflated from the absence of resistance which results in overinflation of the lungs to perform the same respiratory function as prior to the onset of emphysema. The effect of emphysema on lung mechanics causes the airway to collapse during forced expiration resulting in reduced forced expiratory volume in 1 second (FEV_1) and FEV_1 / Forced vital capacity (FVC) ratio (Amariei et al., 2019). Patients experiencing emphysema suffer with discomfort while breathing attributed to the pressure on the thoracic cavity caused through hyperinflation of the lungs. The discomforting nature of emphysema, partnered with the reduced efficiency of breathing (caused by dynamic hyperinflation), creates the sensation of breathlessness in patients. The associated risk factors for emphysema involve smoking, indoor pollutants, environmental irritants, and genetic factors (Suki et al., 2013).

Chronic respiratory failure is defined as the failure of oxygenation and/or carbon dioxide removal within the lung and pulmonary system (Oana & Mukherji, 2014). The body enters a state of hypoxemia when arterial partial pressure of oxygen is below 55 millimetres of mercury (mmHg) (Branson & Faarc, 2018). Hypoxemia is a resultant of a functional failure of the lungs themselves, branded as

a type 1 respiratory failure in the literature. Alternatively, type 2 respiratory failure events happen when the body cannot adequately remove carbon dioxide causing the bodies $PaCO_2$ to increase, the process is known as hypercapnia with PCO_2 levels of > 50mmHg (Lamba et al., 2016). The sources of the functional respiratory failures of the lungs outlined by (Shebl et al., 2022) are displayed in Table 2.

Table 2. Functional Sources of Chronic Respiratory Failures.

Type 1 Respiratory Failure	**Type 2 Respiratory Failure**
Alveolar Hypoventilation	Central nervous system
Low atmospheric pressure	Respiratory muscle dysfunction
Diffusion defects	Chest wall mechanical defects
Ventilation/perfusion mismatch	
Right-to-left shunt	

2.6.2. Asthma

Asthma is a complex condition defined as follows:

“Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.” (Global Initiative for Asthma, 2022).

Common symptoms relating to asthma include shortness of breath, coughing, wheezing and chest tightness (Brigham & West, 2015). While the severity of asthma

is variable depending on the endotype and phenotype classification (Boulet & Boulay, 2014). The two endotypes present within asthma are T-helper type 2-high (eosinophilic) and T-helper type 2-low (non-eosinophilic)(Kuruvilla et al., 2019). The five phenotypes relative to their individual characteristics include Early-onset allergic, Late-onset eosinophilic, Exercise-induced, Obesity-related, and Neutrophilic asthma (Wenzel, 2012).

The pathophysiology of asthma develops through multiple factors like genetics, environmental influences, timing and dose of allergen and the co-exposure with an infection (Murdoch & Lloyd, 2010). The presence of an allergen in the respiratory tract initiates an improper inflammatory response of T-helper cells causing chronic airway inflammation, categorised by the narrowing of the airways (Murdoch & Lloyd, 2010). The increased presence of T-helper cells triggers the immune response, immunoglobin E antibodies, which activate mast cells to cause an influx of inflammatory cells such as eosinophils (Boonpiyathad et al., 2019). This results in bronchoconstriction of the airways, causing a reduction in lung function (Borak & Lefkowitz, 2016) and contributing to the perception of breathlessness (Choi et al., 2018).

The stimuli for bronchoconstriction can be both chemical and physical factors (Cockcroft & Davis, 2006). The chemical trigger for bronchial hyperresponsiveness originates from a multitude of factors.

i. Viral infections of the airways resulting in acute asthma exacerbations (Papadopoulos et al., 2007).
ii. Allergies (e.g. pollen, pets, and dust mites) and toxicants (e.g. diesel particles, air pollution) (Haines et al., 2020; Sokol et al., 2014).

iii. In addition, smoking is a risk factor for bronchial hyperresponsiveness with a significant dose-dependent relationship between bronchial hyperresponsiveness severity and pack-years smoking (Juusela et al., 2013).

Exercise-induced bronchoconstriction is caused by the increased ventilation rate instigated by exercise, causing heat loss and dehydration of the airways (Molis & Molis, 2010). Constriction of the airways smooth muscle increases airway resistance and decreased FEV_1 (Borak & Lefkowitz, 2016) stimulating the sensation of breathlessness. Exercise-induced bronchoconstriction however is not limited to just asthma. Parsons et al., (2011) found that 26% of non-asthmatic adults and 76% of asthmatics were experiencing exercise-related respiratory symptoms otherwise associated with exercise-induced bronchoconstriction (shortness of breath, wheezing, coughing, breathing difficulty, noisy breathing, and chest tightness).

2.6.3. Long Covid

Long COVID, also referred to as post-acute COVID symptom, is the prolonged presence of symptoms following a SARS-CoV-2 infection. The National Institute for Health and Care Excellence, (2020) highlighted three separate definitions covering COVID and long COVID depending on the duration of symptoms experienced by the patient.

i. Acute COVID-19: The patient is displaying symptoms for up to 4 weeks.

ii. Ongoing symptomatic COVID-19: The patient is showing symptoms between 4-12 weeks post-initial infection.

iii. Post-COVID-19 syndrome: The patients' symptoms develop during or after the infection period and are persistent for over 12 weeks without another diagnosis of alternate diseases to justify the symptoms' presence.

The reported prevalence of long COVID has large variability depending on the country and the type of studies. Sudre et al., (2021) analysed (N = 4182) patient reported symptoms following a positive SARS-CoV-2 polymerase chain reaction (PCR) test. The results from the study showed 558 (13.3%) patients reporting symptoms post 28 days from infection, followed by 189 (4.5%) post 8 weeks and 95 (2.3%) post 12 weeks. Totalling 20.1% of patients experiencing either ongoing or long COVID as defined by the National Institute for Health and Care Excellence, 2020) guidelines. However, an even higher prevalence of long COVID has been reported globally through collective meta-analysis by (Chen et al., 2022) indicating 0.43 (95% CI: 0.39-0.46) estimated pooled prevalence of long COVID.

People experiencing long COVID have reported a variety of different symptoms from fatigue to cognitive impairment, and breathlessness (Crook et al., 2021) with studies also showing an overall impairment to the structure and function of vital organs (Dennis et al., 2021). There has been a reported total of 55 long-term effects of long covid, with an estimated 80% of people infected with SARS-CoV-2 experiencing at least one effect of COVID post two weeks of infection (Lopez-Leon et al., 2021). When focusing on breathlessness prevalence in patients, studies have found a prevalence of up to 88% in low-risk individuals with long COVID (Dennis et

al., 2021). In contrast, review studies have found a lower prevalence of breathlessness, 24% of long COVID patients from a sample size of N = 47,910 (Lopez-Leon et al., 2021).

Patients who have been hospitalised by Covid-19 have displayed abnormalities in their lung performance through reduced measures such as; Diffusing Capacity of the Lung for Carbon Monoxide (DLCO), total lung capacity (TLC), FEV_1, FVC and $FEV1_1$/FVC ratio (Mo et al., 2020). This reduced lung function following a SARS-CoV-2 infection in patients could initiate the breathlessness sensation from increased breathing effort perception and the sensation of air hunger. Previous studies identifying a strong association between breathlessness severity and the DLCO % predict outcomes in Covid-19 patients (Shah et al., 2020) and similarly in COPD patients (Elbehairy et al., 2019). Supplementary factors, aside from lung function, could contribute to the worsening of breathlessness such as fatigue resulting in greater perceptions of effort. Patients with underlying conditions, with prior breathing difficulties, are at a heightened risk from the impact of the immune response causing inflammation brought upon by the SARS-CoV-2 infection (Crook et al., 2021).

2.6.4. Cancer

Cancer is a large group of diseases that develop through uncontrollable abnormal cell growth, partnered with the absence of cell death, which spreads around the body (Pérez-Herrero & Fernández-Medarde, 2015). Specific disease categorisation refers to the origin of the cancer growth regardless of where it spreads

to, for example, breast cancer. Treatment of cancer is dependable on the type of cancer, stage of cancer, patient health, and preferences. Common treatments of cancers include chemotherapy, radiotherapy, and surgery.

The prevalence of breathlessness in cancer is specifically high during advanced cancers receiving palliative end-of-life care. Regardless of the origin of cancer, with 90% of lung cancer patients experiencing breathlessness symptoms compared to 50-70% of all cancer patients (Thomas et al., 2011). Similarly, Solano et al., (2006) systematic review found breathlessness was reported in 10-70% of cancer patients (N = 10,029), however, there was no separation into types of cancer within the review.

Breathlessness can occur in cancer patients for numerous reasons, including: direct tumour effect, indirect tumour effect, treatment related, and unrelated to the cancer (Dudgeon et al., 2001). Direct involvement of the cancer can be through airway obstruction due to tumour location (Meriggi, 2018). Tumours can also directly cause breathlessness through phrenic nerve paralysis and superior vena cava syndrome (Jantarakupt & Porock, 2005). Indirect causes of breathlessness from cancer can occur due to anaemia, pneumonia and electrolyte abnormalities (Dudgeon et al., 2001). As well as side-effects of cancer treatments involving surgery, radiation pneumonitis, and pulmonary toxicity from chemotherapy (Strieder et al., 2018). Finally, breathlessness can arise from the psychological aspect of cancer diagnosis and treatment such as anxiety and depression, or comorbid diseases such as COPD and asthma, as mentioned above (Jantarakupt & Porock, 2005).

2.6.5. Lung Disease

Lung disease is a broad term that is used to group all the diseases affecting the airways and lungs combined. The most prevalent lung diseases, such as asthma, COPD and lung cancer have been individually mentioned due to the high prevalence of breathlessness in these populations. However, there are a multitude of additional lung conditions affecting patients which have reported breathlessness that limits their physical capabilities and increases the burden of their disease on their lifestyle. Additional lung conditions associated with breathlessness are described in Table 3.

Table 3. Alternate Lung Conditions Associated With Breathlessness.

Lung Condition	**Description**
Interstitial Lung Disease	Umbrella term encompassing conditions that cause fibrosis of the lungs that restricts the lungs and impairs gas exchange (Aronson et al., 2021).
Idiopathic Pulmonary fibrosis	Thickening and scarring of the tissue surrounding the alveoli, leading to respiratory failure (Richeldi et al., 2017).
Pleural effusion	Excess fluid between the lungs and chest cavity resulting in the diaphragm mechanics being restricted causing reduced lung volume and respiratory function (Skaarup et al., 2020).

Pneumothorax	The accumulation of air within the pleural cavity resulting in pressure increased applied onto the lung, causing the lung to collapse (DeMaio & Semaan, 2021).
Pneumonia	Infection of the lungs causing inflammation of the air sacs (Lim, 2022).
Pulmonary hypertension	Increased pulmonary arterial pressure (≥25mmHg) at rest (Galiè et al., 2015) causing a decrease in cardiac output and gas exchange (Dumitrescu et al., 2017).
Bronchiectasis	Irreversible widening of the smaller regions of the airways leading to increased mucus production, infection, and inflammation of the lungs (Magis-Escurra & Reijers, 2015).

2.6.6. Cardiovascular Disease

Breathlessness is a common symptom seen in cardiovascular disease patients (Barnett et al., 2017) with coronary heart disease and heart failure associated with greater odds of breathlessness occurrence (OR 2.4 [2.04-2.84] and OR 2.74 [2.29-3.28]) respectively (Santos et al., 2016). Through varying cardiovascular diseases, the subsequent events can cause impairment to the function of the lungs or skeletal muscle, chronic inflammation (Kupper et al., 2016), and exercise intolerance (Witte & Clark, 2007).

Patients with a form cardiovascular disease can enter a vicious cycle whereby the underlying disease can cause the avoidance of exercise, therefore, increasing

the disease severity which further increases the breathlessness severity (Aitken et al., 2023). The cardiovascular conditions associated with causing both acute and chronic breathlessness are highlighted in Table 4.

Table 4. Cardiovascular Diseases Causing Acute and Chronic Breathlessness, taken from (Berliner et al., 2016).

Acute Breathlessness	**Chronic Breathlessness**
Myocardial infraction	Arrhythmia
Acute decompensated heart failure	Constrictive pericarditis
Pulmonary edema	Pericardial effusion
High-output failure	Coronary heart disease
Cardiomyopathy	Congestive heart failure
Arrhythmia	Intracardiac shunt
Valvular heart disease	Restrictive cardiomyopathy
Pericardial tamponade	Valvular heart disease

2.6.7. Exertional breathlessness in disease

Exercise is capable of producing the sensation of breathlessness in healthy individuals (Brew et al., 2023). People with chronic lung disorders, are however more susceptible to the sensation of breathlessness as a result of the mechanical limitations arising from the underlying respiratory disease processes and therefore, their response to exercise/exertion may be compromised.

Specifically in COPD, the presence of dynamic hyperinflation at rest increases the end expiratory lung volume (Figure 1) (Usmani et al., 2021), thereby reducing the

inspiratory capacity and inspiratory reserve volume during respiration (Cheyne et al., 2018). Therefore, the expected level of inspiration generated by the neural drive and the resultant inspiratory response creates a neuromechanical dissociation and subsequently increases the sensation of breathlessness (O'Donnell et al., 2017).

The work effort of breathing is also heightened due to dynamic hyperinflation, by placing the inspiratory muscles at a mechanical disadvantage to contract efficiently. The inspiratory muscles are functionally weaker when contracting close to the total lung capacity from increased elastic loading of the chest wall (O'Donnell et al., 2020). This leads to a shortened, rapid, and weaker breathing pattern induced by the shorter contractile length of the inspiratory muscles (Soffler et al., 2017). This response is further heightened during exercise, when tidal volume and breathing frequency are increased.

2.7. Effects of Breathlessness

2.7.1. Physical Activity

The World Health Organisation., (n.d.) define physical activity as 'any bodily movement produced by skeletal muscles that requires energy expenditure'. Guidelines for adults (18-65yrs) regarding physical activity recommend a minimum of 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous intensity aerobic activity per week (Piercy et al., 2018). It is recommended that individuals with chronic conditions such as cancer and COPD are informed to maintain levels physical activity. The 'Exercise is Medicine' through the American College of Sports Medicine (ACSM) (*Rx for Health Series - Exercise Is Medicine*, n.d.) generated the treatment guidelines for patients who experience chronic diseases.

Examples of chronic disease activity guidelines:

i. COPD: Aerobic work building up to 150 minutes per week, starting with small bouts of 5-10 minutes building to 20-60 minutes per day. Strength: 2-3 days per week at 8-12 repetitions per set, 2-4 sets per major muscle group

ii. Cancer: Aerobic work 3-5 times a week, building up to 30-60 minutes per day. Strength training 2-3 days per week doing 6-15 repetitions on major muscle groups

iii. Asthma: Aerobic work 3-5 days per week at 30-40 minutes over the day. Strength training 2-3 days per week at 8-12 reps, 2-4 sets per major muscle group

Patients suffering from chronic breathlessness are prone to decrease their engagement with physical activity (O'Donnell et al., 2020) causing patients to fall short of their recommended physical activity guidelines for their demographics (Bowden et al., 2011). Exercise has been shown to be a stimulus to the sensation of breathlessness in both healthy and patient populations (Grazzini et al., 2005). This may result in the avoidance of exercise by healthy people and patients due to the relationship between exercise and exertion-induced breathlessness (Román-Rodríguez & Kocks, 2021). Breathlessness then becomes a barrier to exercise resulting in the increased risk of developing comorbid diseases (F. W. Booth et al., 2012).

The increased avoidance of physical activity leads to physical deconditioning of the patient, which increases the severity of the underlying condition and symptoms experienced such as breathlessness. Patients with chronic conditions are at an increased risk of developing conditions related to deconditioning. Sarcopenia is

described as the gradual loss of muscle mass, strength, and function (Sepúlveda-Loyola et al., 2020). It is caused by multiple factors, including the decline in neuromuscular junctions, hormone levels, increased inflammatory pathway activation and the process of ageing reducing the ability to replace muscle fibres (Walston, 2012). Similarly, muscle atrophy refers to the wastage and thinning of skeletal muscle which consequently reduces muscle function and strength (Powers et al., 2016). Muscle atrophy occurs when the rate of protein degradation exceeds the rate of protein synthesis (Schiaffino et al., 2013).

A primary treatment to these conditions is the prescription of exercise to increase muscle cell nuclear content (Yin et al., 2021) and induce muscle fibre hypertrophy to combat muscle wastage and regain strength and functionality (Psilander et al., 2019). However, as breathlessness is often a limitation to patients undertaking physical activity, breathlessness management techniques that help delay the onset and hasten recovery from breathlessness could enable patients to have more confidence to participate in physical activity. This would also help combat the underlying disease, reduce comorbid disease, and improve muscular and lung function.

2.8. Breathlessness Management

Current evidence for breathlessness management supports the application of multi-disciplinary services which utilise both pharmacological and non-pharmacological interventions to adequately manage patient symptoms. Breathlessness services such as the Cambridge Breathlessness Intervention Service

(BIS) (S. Booth et al., 2006; Farquhar et al., 2014) and the Breathlessness Support Services (BSS) (Higginson et al., 2014) have demonstrated the effectiveness of a holistic integrated approach encompassing palliative care, respiratory medicine, physiotherapy, and occupational therapy as core components of breathlessness management with treatment constructs depending on the physical, psychological, social, and spiritual needs of the individuals (Brighton et al., 2019). Non-pharmacological interventions are considered a fundamental component to assist patient's self-management of their symptoms both at rest and with activity. A wide array of non-pharmacological interventions are available for the patient to try and these can be divided into three key groups according to the Breathing, Thinking, Functional (BTF) model (Spathis et al., 2017).

2.8.1. Breathing, Thinking, Functional Model

The BTF (Figure 2) is a clinical model used by healthcare professionals to gain a better understanding and improve the application of the most appropriate management techniques according to how the patient responds to chronic breathlessness (Spathis et al., 2017). The model divides the different responses to breathlessness into three key cycles; breathing, thinking and functioning. Each response can generate a vicious cycle to worsen breathlessness if left untreated, therefore by increasing the patient understanding and awareness of their responses to breathlessness appropriate self-management interventions can be introduced to break the cycles and promote patient symptom mastery.

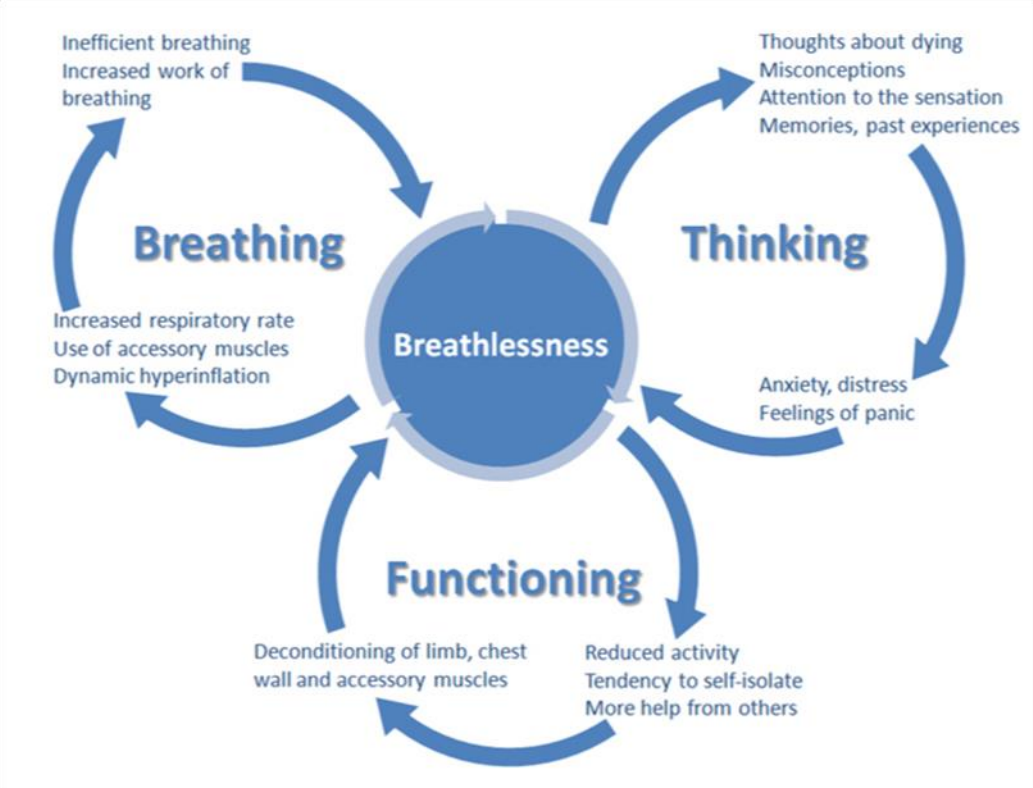


Figure 2. Breathing, Thinking, Functional Clinical Model taken from (Spathis et al., 2017).

2.8.1.1. Breathing

The breathing pattern responds to breathlessness stimuli, as shown in Figure 2, through increasing the inspiratory rate, hyperinflation, and increased activation of accessory muscles to support ventilation efforts to overcome the sensation of breathlessness (Spathis et al., 2017). However, the adverse effects of adaptive breathing can facilitate the sensation of breathlessness through inadequate ventilation resulting from hyperinflation, partnered with the patients' loss of ability to maintain the required ventilation rate for a given situation (Boulding et al., 2016).

This in turn creates a vicious cycle whereby the patients' ventilation response to a breathlessness stimulus generates a greater intensity of breathlessness.

To break the vicious cycle, clinicians can suggest a variety of self-management techniques such as fan therapy, inspiratory muscle training, chest wall vibration, and breathing control (Spathis et al., 2017).

2.8.1.2. Thinking

The thinking component refers to the psychological impact of breathlessness and how patients think and emotionally react to the breathlessness they're experiencing. When feeling breathless, patients are susceptible to negative thoughts, such as distress and even dying (Spathis et al., 2017) which can develop into anxiety and depression and negatively impact their quality of life (Livermore et al., 2008). Additionally, the fear of future episodes of breathlessness or the expectation of breathlessness (Finnegan et al., 2023) often results in patients perceiving a higher severity of breathlessness when undertaking activities (Hanania & O'donnell, 2019) and may result in avoidance of physical activity (Janssens et al., 2011).

The cycle of fear and anxiety surrounding breathlessness contributes to the worsening of breathlessness within the thinking domain, but also activates mechanics in both the breathing and functional domain to worsen breathlessness. Clinicians can use the BTF model to evaluate and prescribe management techniques to combat the psychological aspect of breathlessness. Spathis et al., (2017) outline cognitive behavioural therapy, managing thoughts about

breathlessness, relaxation techniques, mindfulness, and acupuncture as possible non-pharmacological techniques to use in the thinking domain.

2.8.1.3. Functional

The functional reaction to breathlessness may involve a negative cycle of declining physical activity, which in turn compromises social activities, increases self-isolation and may cause further deconditioning (Fiorentino et al., 2020). Indeed, the association between breathlessness and physical activity leads to the avoidance of physical activity to negate the feeling of breathlessness. In addition, the declining ability to perform activities necessitates acceptance of help from others to perform tasks otherwise completed independently (Spathis et al., 2017).

The functioning component of the BTF model is used by clinicians to focus on improving the patient's physical capabilities. A strong body of evidence supports the role of pulmonary rehabilitation. Previous studies have found pulmonary rehabilitation to be effective at reducing the perception and severity of breathlessness (Grosbois et al., 2022; Mccarthy et al., 2015; Nopp et al., 2022). Alternative techniques available to improve and maintain physical activity include pacing, mobility aids, neuromuscular electrical stimulation, and activity promotion (Spathis et al., 2017). By reducing the impact of breathlessness, patients can increase their participation in physical activity and gain more control over their breathlessness symptoms and improve their quality of life. Fan therapy has also been proposed to reduce the burden of breathlessness and improve physical activity levels.

2.8.2. Handheld Fans

The effectiveness of the handheld fan has been investigated through a variety of feasibility randomised controlled trials in both healthy and clinical populations. The research provides a growing platform of evidence regarding the benefits of the handheld fan to relieve breathlessness and hasten recovery from exertion induced breathlessness. In addition, studies of patient preferences and perceptions of the handheld fan help to inform future research and development of the intervention.

2.8.3. Breathlessness at Rest

Patients with advanced conditions and those near end of life, such as terminal lung cancer, often experience breathlessness at rest (Fukushi et al., 2021) or upon minimal movement (S. Booth et al., 2016). The evidence suggests that cool facial airflow from a handheld fan reduces breathlessness in patients at rest. Multiple randomised controlled trials have found a significant difference in breathlessness intensity when applying airflow from the handheld fan to the face compared with the control measure (Galbraith et al., 2010; Kako et al., 2018; Kocatepe et al., 2021; Puspawati et al., 2017) and a significant reduction in NRS breathlessness scores pre- and post-intervention (Wong et al., 2017). When at rest, the benefits of the handheld fan for breathlessness remain present for up to two hours as long as the patient remains completely still (S. Booth et al., 2016).

2.8.3.1. Feasibility of Handheld Fans

Understanding patient perceptions and adherence to the handheld fan intervention can help overcome barriers and increase the uptake of handheld fan usage, as well as inform future trials. Several feasibility studies have assessed patient adherence and the practicality of the handheld fan with positive outcomes (Bausewein et al., 2010; Johnson et al., 2016; Khor et al., 2021; Swan et al., 2019). All studies found that the majority of patients had a positive experience when using the handheld fan, with all patients (n=20) using the handheld fan after 28 days (Swan et al., 2019) and 16 out of 24 using the handheld fan daily (n=9) or occasionally (n=7) after 2-month follow-up (Bausewein et al., 2010). Additionally, Khor et al., (2021) reported that not only did the handheld fan group participants (n=15) intended to use the handheld fan post-study, but all of the participants apart from two in the control group (n=13) expressed their interest in using the handheld fan as a management technique. The positive responses of handheld fan usage correlate with patient qualitative interview data exploring patient experiences with the handheld fan. Patients described the handheld fan as a helpful self-management technique to increase their breathlessness control (Johnson et al., 2016), and hastened their recovery from breathlessness (Swan et al., 2019).

However, the handheld fan did not significantly reduce the patient's average and worst breathlessness scores when used long-term (Bausewein et al., 2010; Johnson et al., 2016; Khor et al., 2021; Swan et al., 2019). This could indicate that the handheld fan is a useful self-management method for overcoming and controlling breathlessness episodes but does not prevent the symptom from occurring overall in daily living.

2.8.3.2. Handheld Fan During Exercise

Patients experiencing chronic persistent breathlessness often refrain from exercise to avoid breathlessness (Lewthwaite et al., 2021). However, the application of airflow during exercise has been reported to increase exercise performance (Long et al., 2021a; Marchetti et al., 2015; Swan et al., 2019). Marchetti et al., (2015) reported that exercise duration at a constant workload (50-75% max) on a cycle ergometer was increased by 34% by the application of airflow from a fan (Marchetti et al., 2015) and other studies have demonstrated an increased 6-minute incremental shuttle walk distance by 55.33m (43.7%) and 21.25m (12.75 to 31.88m) (Swan et al., 2019 and Long et al., 2021) respectively.

Coupled with the positive improvements of fan airflow on exercise performance, fan airflow during exercise also indicates a delay and reduction in breathlessness induced by exercise. Marchetti et al., (2015) measured breathlessness intensity throughout a constant workload exercise test. The results indicated reduced breathlessness at maximal exertion, as well as reduced breathlessness recorded at every time point during the exercise. Similarly, Long et al., (2021) reported reductions in breathlessness intensity induced by the 6-minute walking test by -1.00 (-2.00 to -0.50) unit on the NRS breathlessness rating.

2.8.3.3. Handheld Fan During Recovery from Exercise

Studies that investigate the use of airflow from the handheld fan during recovery from exercise have consistently shown that airflow reduces the time taken

to recover from activity (Long et al., 2021a; Swan et al., 2019). Long et al., (2021) found a significantly shorter recovery time of 10.00 seconds when using the handheld fan during the recovery phase. Similarly, Swan et al., (2019) found that the handheld fan decreased recovery time by 33.5 seconds (-20.4%) when using exercise advice with the handheld fan, and 40.3 seconds (-24.9%) when using the combination of exercise advice, handheld fan, and calming hand (a coping strategy) respectively. The faster recovery from exertional breathlessness is known to be an important benefit of handheld fan use for patients (Johnson et al., 2016; Long et al., 2021a; Swan et al., 2019) and suggests that patients can increase their physical activity levels with handheld fan use and maintain a greater level of control over their self-management of breathlessness.

2.8.3.4. Handheld Fan Properties and Perceptions

Only one published study has explored the physical properties of handheld fans and patient preferences. (T. A. Smith et al., 2022) used a patient-reported rating scale for five different models of handheld fans. Patients scored the different handheld fan models on the pleasantness of airflow, perceived airflow, noisiness, and ease of use. All of the handheld fans had similar visual characteristics with external blades and a small portable body. Patient preferences for handheld fan properties were positively correlated with perceived airflow, pleasantness of airflow and the measured airflow velocity, however, patients showed a negative correlation for the noise of the handheld fan (T. A. Smith et al., 2022). Secondary analysis by Luckett et al., (2017) also highlights the importance of handheld fan specifications

suggesting the need to consider noise, portability, robustness, ease of battery change and offer a variety of airflow speeds to suit patient preference.

Despite the very promising evidence behind fan therapy to relieve and manage breathlessness, patient's perceptions of the handheld fan can be a barrier to handheld fan use and decrease implementation. Prihartadi et al., (2021) highlighted common negative connotations preventing handheld fan usage. Some patients remained sceptical of the handheld fan in regard to its role and credibility as a clinical intervention (Luckett et al., 2017). Patients also described the handheld fan as a 'toy' (Bausewein et al., 2010) and found the handheld fan embarrassing to use out in public (Khor et al., 2021).

Further investigation into understanding patient preferences with respect to handheld fan properties is essential to overcome the challenges patients face when using the handheld fan. By enabling a patient-driven blueprint to develop effective discrete handheld fans, capable of producing an effective airflow speed enables patients to build confidence in actively using the intervention for their breathlessness needs.

2.8.3.5. Handheld Fan Airflow Speeds

There is limited published guidance on the optimal airflow speed for relief of breathlessness from a handheld fan. Smith et al., (2022) investigated patient preferences using an NRS to score the handheld fan properties in relation to perceived airflow, pleasantness of airflow, ease of use and noisiness. The study found a linear relationship between the total score for each handheld fan and airflow

velocity at 30cm, indicating that patients preferred handheld fans capable of producing greater airflow speeds, however, the speeds tested were limited to between 0.4 to 1.9 m/s (Smith et al., 2022).

Similarly, Brew et al., (2023) investigated five different airflow speeds for breathlessness recovery from submaximal exercise in healthy populations. Participants completed six bouts of four-minute exercise tests to induce breathlessness. Over a monitored recovery period participants received one of five different airflow speeds or control (no airflow). The range of airflow was between 0 m/s for control, to the highest of 3.3 m/s. Airflow speeds of 1.7m/s and above significantly improved the speed of recovery against the control, suggesting a dose-dependent relationship between fan airflow speed and breathlessness recovery up to 3.3m/s airflow speed. However, the point at which airflow speed may become uncomfortable was not defined and future studies investigating the preferences for higher airflow speeds, 3.3 m/s and above are required.

2.9. Experimental Rationale

2.9.1. Aims

The aim of this clinical trial was to determine the optimal airflow rate from a handheld fan on recovery from exercise-induced breathlessness in patients with chronic breathlessness. Further, we aimed to determine patient preference on different airflow rates.

2.9.2. Objectives

Primary Objectives

1. Determine whether four airflow speeds delivered from a handheld fan vs. control (no airflow) result in a difference in NRS breathlessness recovery over time.

Secondary Objectives:

1. Determine whether 4 airflow speeds delivered from a handheld fan vs. control (no airflow) result in a difference in oxygen saturation over time.
2. Determine whether 4 airflow speeds delivered from a handheld fan vs. control (no airflow) result in a difference in heart rate over time.
3. Determine whether 4 airflow speeds delivered from a handheld fan vs. control (no airflow) result in a difference in skin facial temperature over time that correlates with NRS breathlessness scoring over time.
4. Determine whether there is a dose-response relationship for airflow speeds in terms of NRS breathlessness grading recovery over time.
5. Determine whether there is a dose-response relationship for airflow speeds in terms of skin facial temperature change over time.
6. Assess patient preferences of airflow speeds, pleasantness of all 4 airflows and handheld fan appearance.
7. Explore and describe a possible learning or fatiguability effect with repeated one-minute sit to stand tests for each participant.

2.9.3. Hypotheses

We will explore multiple hypotheses in this study:

1. The facial airflow delivered from a handheld fan will hasten the recovery from exercise-induced breathlessness in patients with chronic breathlessness (H_1).
2. Facial airflow delivered from a handheld fan will decrease the facial skin temperature post exercise exposure (H_1).

3.0. METHODOLOGY

3.1. Ethics

Institutional permissions were obtained and ethical approval was granted by West of Scotland Research Ethics Committee 4 (REC ref: 21/WS/0102). The trial was registered with International Standard Register Clinical Trial registry (ISRCTN12024425) before the first participant was enrolled. Ethical approval forms are provided in Appendix A.

3.2. Reporting guidelines

The study followed the reporting framework of the Consort checklist guidelines displayed in Appendix D by Schulz et al., (2010).

3.3. Study Design

Fan Facial Airflow Recovery from Exercise Patient Trial (FANFARE–P) was a randomised controlled trial following a prospective, experimental, two-factorial, within subject's design.

3.4. Participants

It was considered that a sample size of 10 participants was sufficient data to answer the research questions. Participants with moderate to severe chronic breathlessness were included. The full inclusion and exclusion criteria were as follows.

3.4.1. Inclusion Criteria

- Chronic breathlessness symptoms as a result of non-malignant lung disease, e.g., asthma, COPD, ILD, and other respiratory diseases.
- modified Medical Research Council (mMRC) dyspnea scale grade of 3 to 4.
- Ability to provide written informed consent or provide witnessed verbal consent.
- Ability to successfully complete the 1 minute STS exercise test and all outcome measures.

3.4.2. Exclusion Criteria

- Unable to provide informed consent either written or witnessed verbal.
- Unable to complete all study measures.
- Unable to complete the exercise test due to musculoskeletal problems.
- Been advised by their clinical care team to avoid physical activity.
- Trigeminal nerve damage.
- Unable to tolerate airflow from the handheld fan.
- Patients using ambulatory oxygen for confirmed exercise-related oxygen desaturation or long-term oxygen therapy.

3.5. Handheld Fan Intervention

The intervention for this study was a commercially available wireless handheld fan, Easy Acc (EasyAcc, Model FNHD-3350BL, China) (Figure 4). Prior to study trials, the fans' ability to maintain the pre-set airflow rate throughout the recovery period was investigated (Figure 3). To ensure fan airflow rate remained consistent throughout the 10-minute recovery phase. The handheld fan remained in a charged state through the USB port connected to the hospital's mains electricity outlet to prevent possible deviations of airflow speed from the pre-determined speeds. The four different fan airflow speeds ± standard deviation (SD) are shown below.

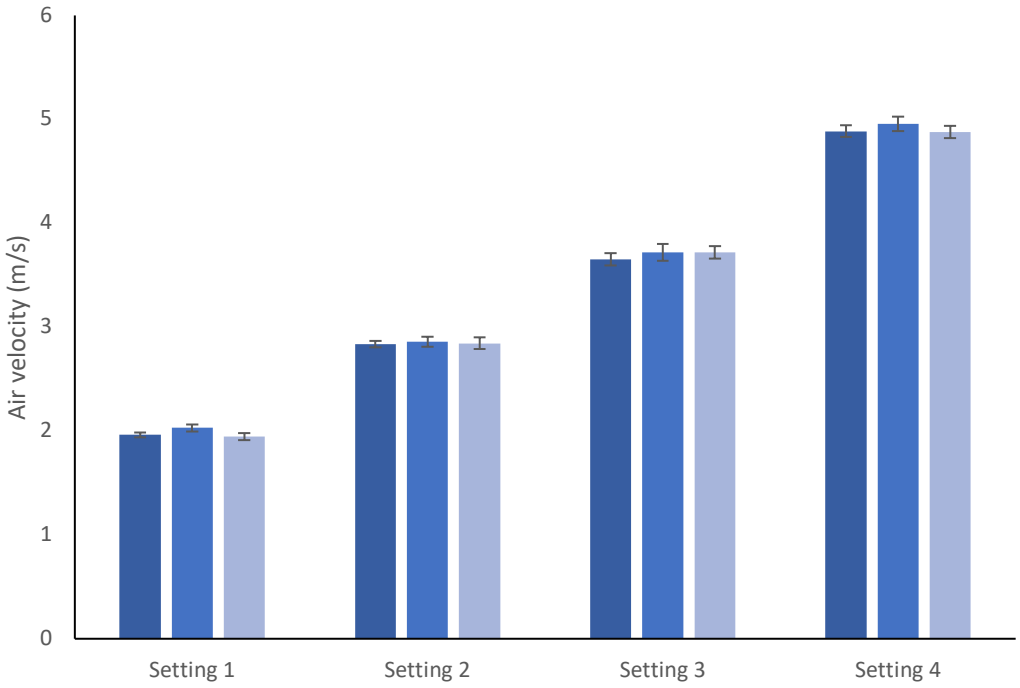


Figure 3. Handheld Fan Performance to Maintain Airflow Velocity Over a 10-Minute Period.

The mean ± SD airflow speed of the four corresponding fan speed levels is as followed: Fan speed level 1 = 1.98 m/s ±0.05. Fan speed level 2 = 2.85 m/s ±0.04. Fan speed level 3 = 3.70 m/s ±0.07. Fan speed level 4 = 4.91 m/s ±0.07.

3.5.1. Comparison

The control intervention for this study consisted of participants recovering from post-exercise breathlessness with no fan intervention. This enabled the comparison between both fan vs. no fan, and each individual fan speeds effectiveness compared to no fan in the analysis.

3.6. Primary Outcome Measures

Breathlessness was scored utilised the Numerical Rating Scale (NRS) with 0 representing no breathlessness at all and 10 representing the worst imaginable breathlessness. Participants were asked how bad their breathlessness was at baseline, maximal exertion and then every minute during the recovery phase.

3.7. Secondary Outcome Measures

Heart rate and oxygen saturation were collectively recorded through a pulse oximeter (Nellcor Puritain Bennett NPB-40, USA). Participants' heart rate (HR) and oxygen saturation (SpO_2) were recorded at baseline, maximal exertion and then at 30-second intervals for the recovery phase.

Facial skin temperature was collected using a FLIR C3 (Teledyne FLIR, United States) thermal imaging camera situated on the tripod to the right-hand side of the participant. The lens was positioned to focus on the lower two branches of the trigeminal nerve region. Skin temperature was recorded at baseline, maximal exertion and then the third and fifth minute of the recovery phase.

3.7.1. Handheld Fan Properties

At the end of the trial, participants were asked about their personal fan airflow preferences and handheld fan aesthetics. Using a 0 to 10 NRS scale, participants were asked to score the pleasantness of each airflow speed. With 0 representing the most pleasant possible, while 10 represented the most unpleasant possible.

Participants were able to re-use the handheld fan to recollect how each airflow speed felt. The second question the participants were asked was, if in a state of breathlessness, which fan speed level would they select. Participants were again free to re-use the handheld fan and confirm their preferred fan speed level. Finally, participants were presented with three different variations of handheld fan designs (Figure 4). Each participant was then asked which handheld fan design was preferable and which they would use daily to combat their breathlessness.

Figure 4. The Three Handheld Fan Types Displayed to Participants. Fan A (external blades), Fan B (Fan U, enclosed blades), Fan C (EasyAcc, enclosed blades).

3.7.2. Patient Field Notes

Following the completion of each trial, a 10-minute additional unmonitored recovery phase provided participants with additional time to recover and prepare for the next trial. During this 10-minutes, small items of discussion regarding the handheld fan experience and participant feedback were noted to describe the trials.

Participants were asked how they felt about each trial with regard to the individual airflow speed, as well as more details about their breathlessness. Participant field notes were categorised into themes relating to the participants' fan airflow speeds experience and regarding the exercise test. The field notes can be found in appendix C and are used to provide supporting descriptors relating to the patients' handheld fan preferences and airflow pleasantness discussions.

3.8. Trial Methods

3.8.1. Recruitment

Participants were identified and invited to participate in the study through a member of their clinical team at an outpatient appointment. Interested participants were given a participant information sheet (PIS) outlining the full details of the study and contact details of the research team for any questions. All participants were given adequate time to consider their participation before being contacted by a member of the research team via phone call to discuss study participation.

Additionally, participants were approached through the research database within the respiratory clinical trials unit. A member of the research team contacted prospective participants, who suffer from breathlessness due to non-malignant lung disease, to discuss their interest and provide details of the study. The prospective participants were provided with a PIS through a member of the clinical trials unit. A member of the research team followed up with the participants to confirm their involvement in the study and arrange a trial date.

3.8.1.1. Informed Consent

Informed consent was provided on the day of the trial. Eligible participants provided either written or witnessed verbal informed consent before taking part in the study.

3.8.1.2. Withdrawal

Participants were withdrawn from the study by the research team if they were judged not fit to continue in the opinion of the research team. For instance, if a patient failed to recover from the 1-minute sit-to-stand exercise test within 15 minutes in terms of breathlessness severity or discomfort. Additionally, participants were also informed of their right to withdraw from the study at any time without a given reason through the informed consent process.

3.8.2. Baseline Assessment

At the start of the trial, participant demographics and baseline assessment measures were obtained. Participant demographics included the participants' age and sex. Baseline assessments included the participants' primary clinical diagnostics group, alongside the participants' mMRC dyspnea grade and resting NRS breathlessness score, heart rate and oxygen saturation.

Due to Covid-19 protocol restrictions at the time of testing, pulmonary function testing was not permitted as the participants' lung function wasn’t a primary outcome measure for the trial and was used as a descriptor of their respective respiratory

condition. Therefore, the participant's most recently recorded pulmonary function was recorded from their medical notes. The pulmonary function measures collected included FEV_1 (L) and the percentage predicted, FVC (L) and the percentage predicted, the FEV_1 to FVC Ratio and the percentage predicted, and gas transfer (DLCO)(mm.min.mmHg) where possible.

3.8.3. Exercise Test

To induce breathlessness, participants completed a 1-minute STS test. Participants started stationary in a standard chair (height 46-48cm) with a flat seat stabilised against a wall. Participants were required to sit with their feet hip-width apart and knees at a 90-degree angle with their hands stationary on the hips without using the hands or arms to assist movement during the test. The participants were then instructed to stand completely straight before returning to a seated position to complete one repetition. The seated position during the 1-minute STS test was defined by touching the chair with their bottom, and not sitting comfortably back into the seat. Participants were challenged to perform as many repetitions as possible that they were comfortable performing over 1 minute to induce breathlessness. At 45 seconds the participants were verbally informed by the researcher "you have 15 seconds remaining". However, if participants felt they had reached a breathlessness state or in discomfort, they were able to stop the exercise test at any moment to initiate the 10-minute recovery phase. Upon completion, the number of completed repetitions and the total exercise time was recorded.

3.8.4. Handheld Fan Recovery

Participants were provided with demonstrations and instructions to hold the handheld fan 10-15cm away from the face. While directing the fan airflow towards the lower two trigeminal nerve branches located at the lower face, nose, and mouth area. Deviations away from the pre-set positioning of the handheld fan due to discomfort was documented as an observation. If a participant was experiencing discomfort during the recovery phase, the fan intervention was stopped, and time was noted.

Upon competition of the exercise test, the fan intervention was applied to start the recovery phase. Participants were continuously monitored for 10-minutes while directing the fan airflow towards the lower two branches of the trigeminal nerve region on the face. The order of fan intervention delivery was randomly allocated prior to the trial by an external randomisation calculator. Throughout the recovery phase, participants were instructed to remain stationary in a comfortable position to limit additional exertion and maintain a consistent position of the thermal imaging camera set-up.

The outcome measures collected during the recovery phase included NRS breathlessness, heart rate, oxygen saturation and facial skin temperature at their respective time points. The trial was then repeated four more times for each four fan speeds and or the control trial. Upon completion of the five trials, participants were asked to score the pleasantness of each fan airflow, their preferred airflow speed for breathlessness recovery and their preferred handheld fan model appearance.

3.9. Data Analysis

Data analysis for this thesis was conducted through JASP Team (2022). JASP (Version 0.16.3)[Computer software]. Since this is a randomized crossover two-factorial design with replication on all factors, repeated measures analyses of variance (rmANOVA) will be used for analysing the different hypotheses. Results will be displayed both in text and graphically through line graphs using mean and 95% confidence interval (CI).

Participant demographics, baseline assessment and lung function were analysed using descriptive statistics. Continuous variables were summarised using mean ± standard deviations.

Objectives 1 to 4: The effect of airflow and time on NRS breathlessness, facial skin temperature, heart rate and oxygen saturation were explored using a repeated measures ANOVA (rmANOVA) per outcome measure. Each rmANOVA analysed the main effect for fan speed, in addition to, the interaction effect for fan speed over time. Following the rmANOVA, a simple contrast analysis was conducted for comparison of each fan speed against the control measure and results corrected using the false discovery rate (FDR). All rmANOVA included assumption test of sphericity and the greenhouse-giesser correction was used where appropriate.

Objective 5 and 6: A polynomial contrast analysis was performed to explore the dose-response relationship between fan airflow speed and breathlessness and temperature response.

Objective 7: Handheld fan speed preference and preferred aesthetics were summarised using descriptive statistics (means ± standard deviations) and

graphically plotted using raincloud plots. Handheld fan speed pleasantness was analysed using rnANOVA with a greenhouse-giesser correction. Results were displayed using line graphs.

Objective 8: The learning effect and fatigability of the sit-to-stand test was explored using a rmANOVA and simple contrast analysis, with each exercise performance score compared to the first recorded sit-to-stand test.

4.0. RESULTS

4.1. Participant Characteristics

Fifteen patients were provided with a PIS following initial interest expressed to their hospital clinician. Five patients declined to participate, reasons for declining were: i) not feeling able to perform the study measures (n=3), ii) illness (n=1), and iii) time constraints (n=1).

Ten participants were randomised and nine completed the study (Figure 5). One was withdrawn during the trial due to low oxygen saturation (SpO_2) during the first STS test (SpO_2 <80%). One participant was excluded from data analysis as the participant achieved a significantly lower exertional NRS breathlessness score post-STS test (NRS 2 out of 10) in comparison to fellow participants suggesting the participant was reserved during the initial exercise test or initially misinterpreted the NRS scoring system. Indeed, the group mean NRS breathlessness baseline measure was 1.5±1.0 and post-exercise 6.5±1.9. Analysis of the excluded

participant's STS performance and effect on breathlessness outcomes are displayed in appendix B.

4.1.1. Participant Demographics

Ten participants enrolled on the study (6 male; mean ± SD age 67 ± 14 yrs, height 169 ± 10cm, body mass 93 ± 25 kg). Primary medical conditions causing breathlessness were COPD (n=7), COPD with asthma (n=2) and Long covid (n=1). Results from spirometry show moderate-to-severe airway obstruction: FEV_1 54± 23% predicted, FVC 81 ± 19% predicted and FEV_1/FVC 0.51 ± 0.18 (Table 5).

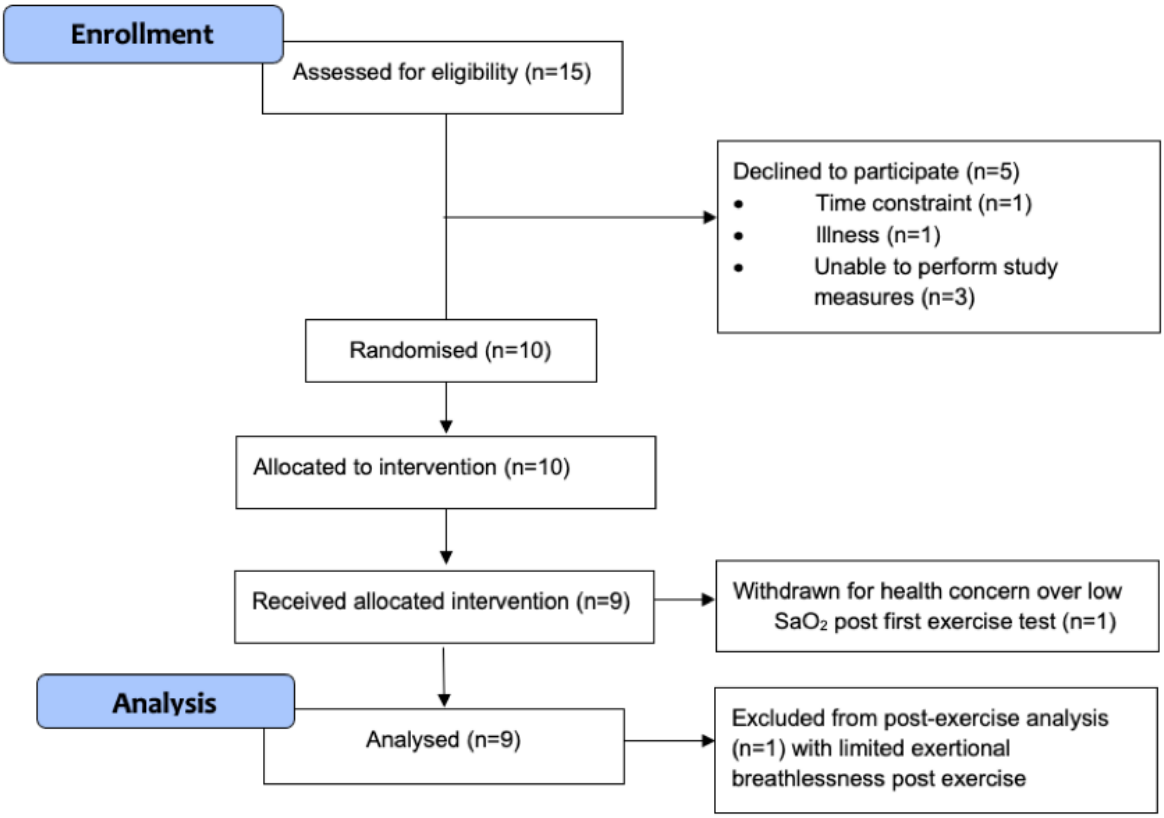


Figure 5. Consort Flow Diagram for Study Recruitment (Schulz et al., 2010).

Table 5. Participant Characteristics.

	Mean	Std. Deviation
Age (years)	67.00	13.87
Sex (Male / Female)	6 / 4	
Height (cm)	169.11	9.90
Body Mass (kg)	92.80	25.41
RESTING Heart Rate (Bpm)	75.60	8.44
RESTING Oxygen Saturation (%)	94.50	3.06
Resting NRS Breathlessness	1.50	0.97
mMRC Grade	3.60	0.52
FEV_1 (L)	1.53	0.74
FEV_1 (% Predicted)	53.88	22.58
FVC (L)	2.88	0.64

FVC (% Predicted)	80.72	18.86
FEV_1/FVC (L)	0.51	0.18
FEV_1/FVC (% Predicted)	65.89	21.96

NRS numerical rating scale, *mMRC* modified medical research council, *FEV_1* forced expiratory volume in one second and *FVC* forced vital capacity.

4.2. Breathlessness Recovery

The sit-to-stand test induced a mean NRS breathlessness score of 6.85±1.73 displayed in Figure 6. A statistically significant interaction effect was noted for fan speed over time ($F(40,280)=1.661$, $p=0.010$, $\eta_p^2=0.192$). Simple contrast analysis at each minute of recovery highlighted a significant difference between fan speed level 2 and control, from minute four to minute eight of recovery (Figure 6). In comparison, a statistically significant difference was found from minutes seven to eight for fan speel level 1 and fan speed level 3. Fan speed level 4 starting showed differences from control from minute eight to minute 10.

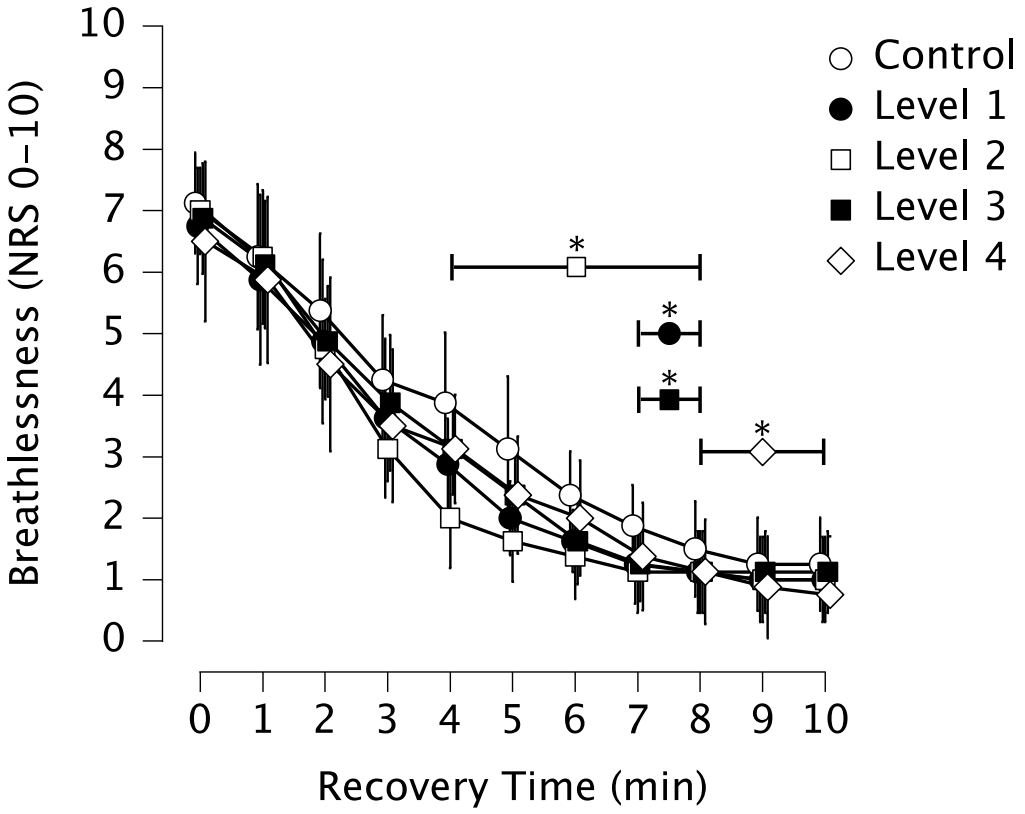


Figure 6. Mean (95% ci) breathlessness recovery over 10-minutes following a one-minute sit-to-stand test in patients (n=8) with chronic breathlessness, using fan therapy at different airflow speeds and a control (no airflow). Asterisks (*) indicate statistically significant differences ($p<0.05$) to control, connecting bars display the minute spread of the statistical significance.

A dose-response relationship between airflow speed and breathlessness recovery was analysed using a polynomial contrast analysis. The analysis found no statistical significance across fan airflow speeds and breathlessness over 10-minutes of recovery ($T(28)=-1.540$, $p=0.135$, FDR, $p=0.27$).

To further visualise the effect of fan airflow on breathlessness recovery, the area under the curve was analysed. The results found no statistically significant difference for the main effect of fan speed ($F(4,28)=1.797$, $p=0.158$, $\eta_p^2=.204$). However, simple contrast analysis of the area under the curve found a statistically significant difference before false discovery rate corrections between fan speed level 2 and the control ($T(28)=-2.517$, $p=0.018$, FDR, $p=0.072$) (Figure 7). Additionally, no statistical significance was found for fan speed level 1 ($T(28)=-1.944$, $p=0.062$, FDR, $p=0.097$), Fan speed level 3 ($T(28)=-1.496$, $p=0.146$, FDR $p=0.097$), and fan speed level 4 ($T(28)=-1.862$, $p=0.073$, FDR, $p=0.146$).

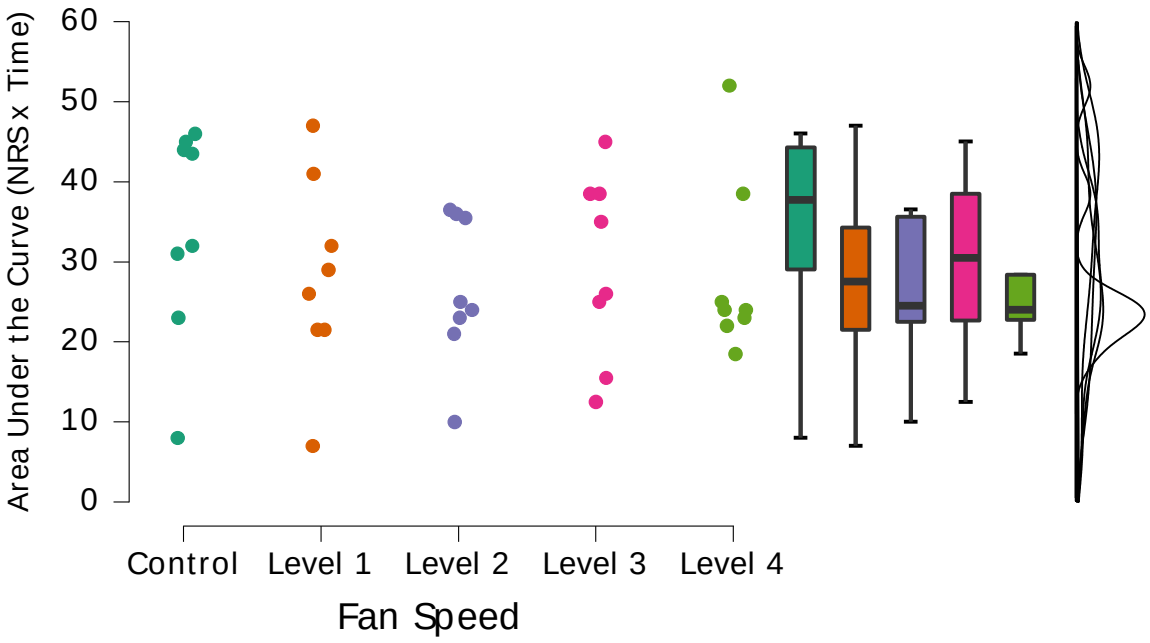


Figure 7. Raincloud plot displaying the area under the curve for breathlessness recovery to baseline in patients (n=8) with chronic breathlessness

following a one-minute sit-to-stand exercise test, while utilising fan therapy of four different airflow speeds vs. Control (no airflow).

4.3. Facial Skin Temperature

Facial skin temperature response to airflow found consistent cooling of the face compared to the control (no fan). The rmANOVA found a statistically significant interaction effect of fan speed over time ($F(8,48)=13.113$, $p=<0.001$, $\eta_p^2=0.686$) and a significant main effect of fan speed ($F(4,24)=18.827$, $p=<0.001$, $\eta_p^2=0.758$). Simple contrast analysis identified a significant difference between all four fan speeds to compared to the control ($p<0.001$, FDR, $p<0.001$) (Figure 8). Further, polynomial contrast analysis found a statistically significant linear relationship ($T(24)=-7.961$, $p=<0.05$, FDR, $p<0.05$), suggesting a dose-response relationship between fan airflow speed and facial skin temperature over time. A representative thermal image of a participant following five minutes of airflow therapy is presented in Figure 9.

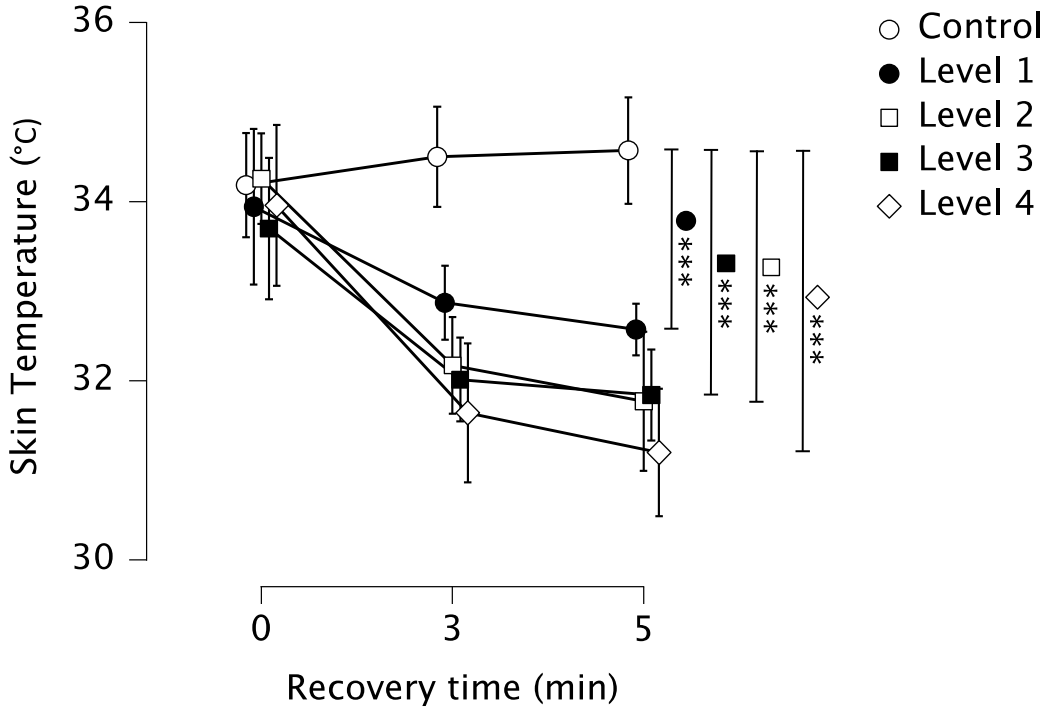


Figure 8. Mean (95% CI) facial skin temperature over five-minutes following a one-minute sit-to-stand exercise test while using fan therapy of four different airflow speeds and control (no airflow). Asterisks (***) indicate statistically significant differences ($p<0.001$) to control.

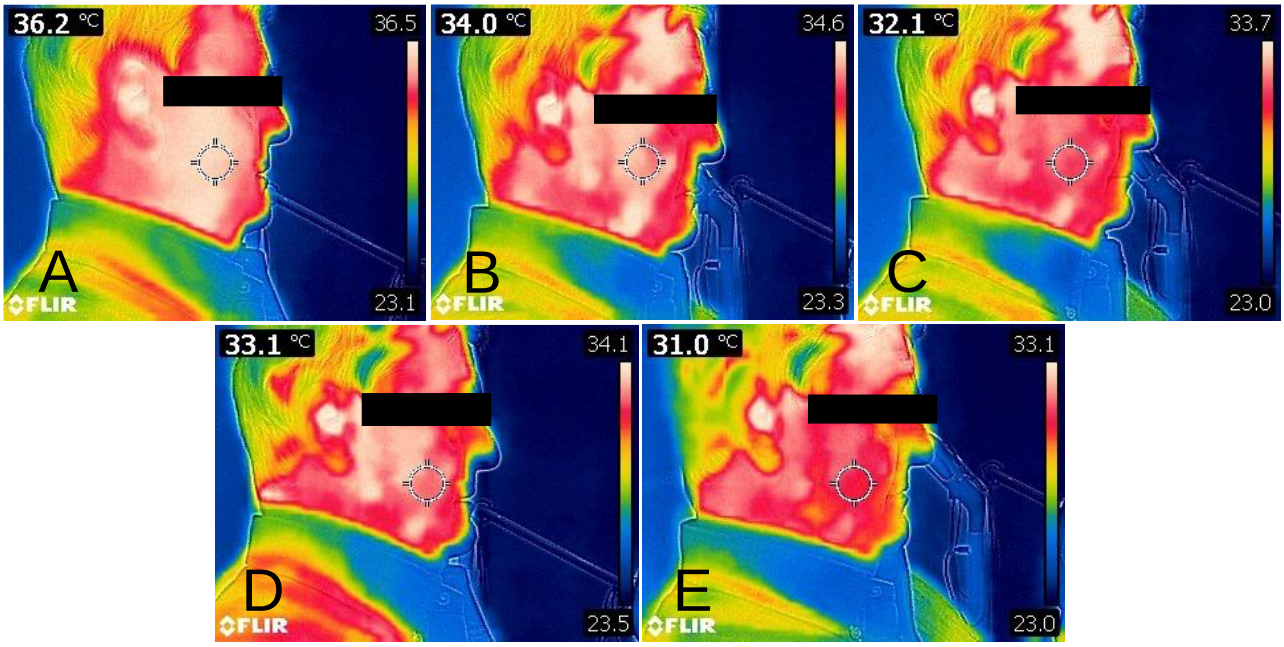


Figure 9. Thermal images showing facial skin temperature five minutes post-exercise while using fan therapy of four different airflow speeds vs control (no fan). The temperature recorded from the trigeminal nerve region is displayed in the top left of each image. The colour palette's warm colours (white, red) represent the hottest parts of the image, cold colours (green, blue, dark blue) represent the coolest parts. Control (A), Fan speed level 1 (B), Fan speed level 2 (C), Fan speed level 3 (D), Fan speed level 4 (E).

4.4. Heart Rate

Heart rate recovery over 10-minute recovery found no main effect of fan speed ($F(4,24)=1.693$, $p=0.184$, $\eta_p^2=0.220$) and no interaction effect of fan speed over time ($F(80,480)=1.060$, $p=0.350$, $\eta_p^2=0.150$)(Figure 10).

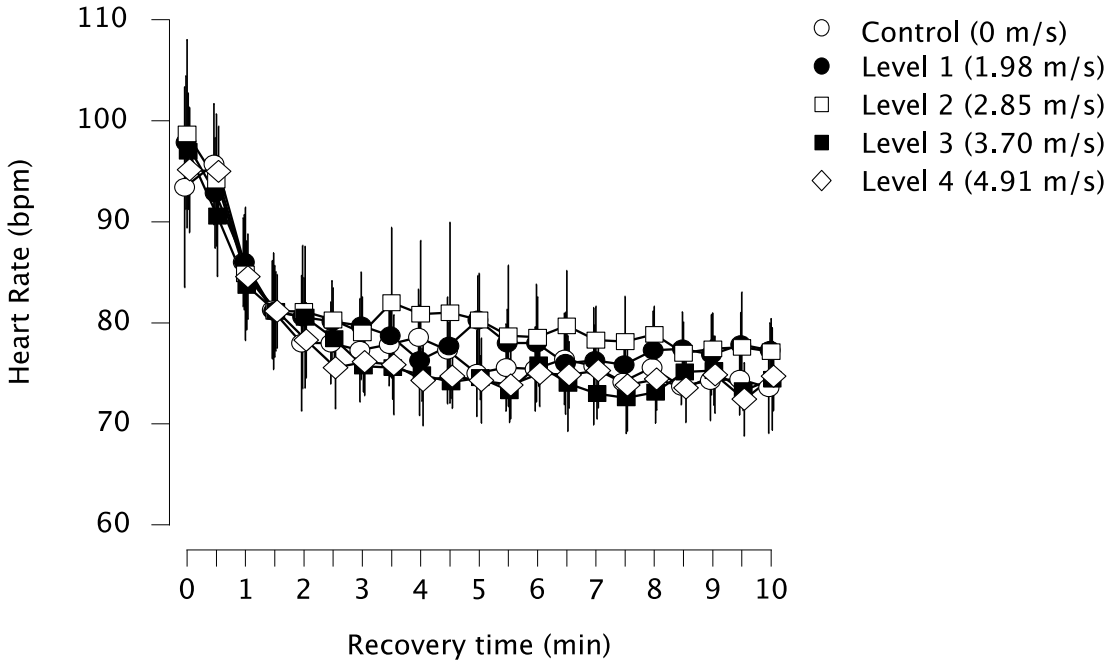


Figure 10. Mean (95% CI) heart rate recovery for 10-minutes post one-minute sit-to-stand exercise test while using fan therapy of four fan airflow speeds vs control (no airflow).

4.5. Oxygen Saturation

No main effect of fan speed ($F(1.69,10.19)=0.440$, $p=0.625$, $\eta_p^2=0.068$) and no interaction effect of fan speed over time ($F(80,480)=0.991$, $p=0.504$, $\eta_p^2=0.142$) was noted for oxygen saturation following the sit-to-stand tests (Figure 11).

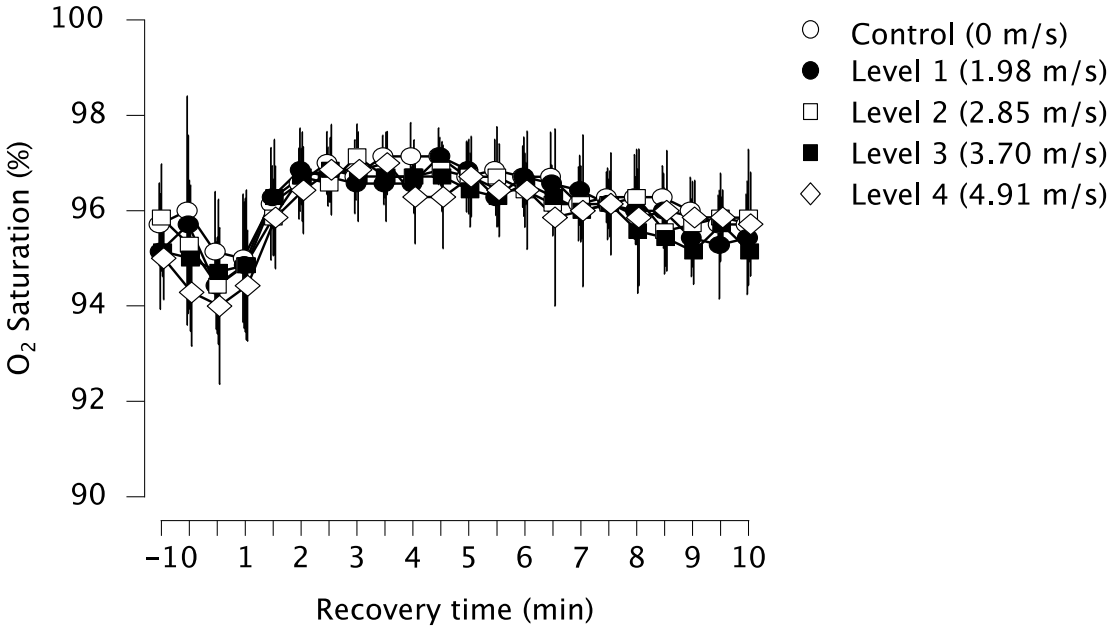


Figure 11.

Mean (95% CI) oxygen saturation response to exercise and recovery over 10-minutes post one-minute sit-to-stand test while using fan therapy of four different airflow speeds and control (no airflow).

4.6. Fan Airflow Preference and Pleasantness

Fan speed level two had the most pleasant NRS score, mean ± SD, 2.1 ± 1.6. In contrast, fan speed level 4 displayed the most unpleasant score (NRS score was 6.2 ± 4.2) (Figure 12). Further polynomial contrast analysis into the pleasantness ratings found a significant linear correlation between fan airflow speed and unpleasantness score ($T(24)=2.701$, $p=0.012$, FDR $p=0.036$), suggesting the pleasantness decreases with increasing airflow speed. Fan speed level 2 was preferred most often (n=5), followed by fan speed level 3 (n=2). Both fan speed

levels 1 and 4 were the most preferential by only one participant. Finally, participants were asked about their preferences regarding fan appearance (Figure 4). Fan B (internal blades) was preferred by 7 participants, Fan C (EasyAcc) by 2 participants, and no participants preferred Fan A (external foam blades).

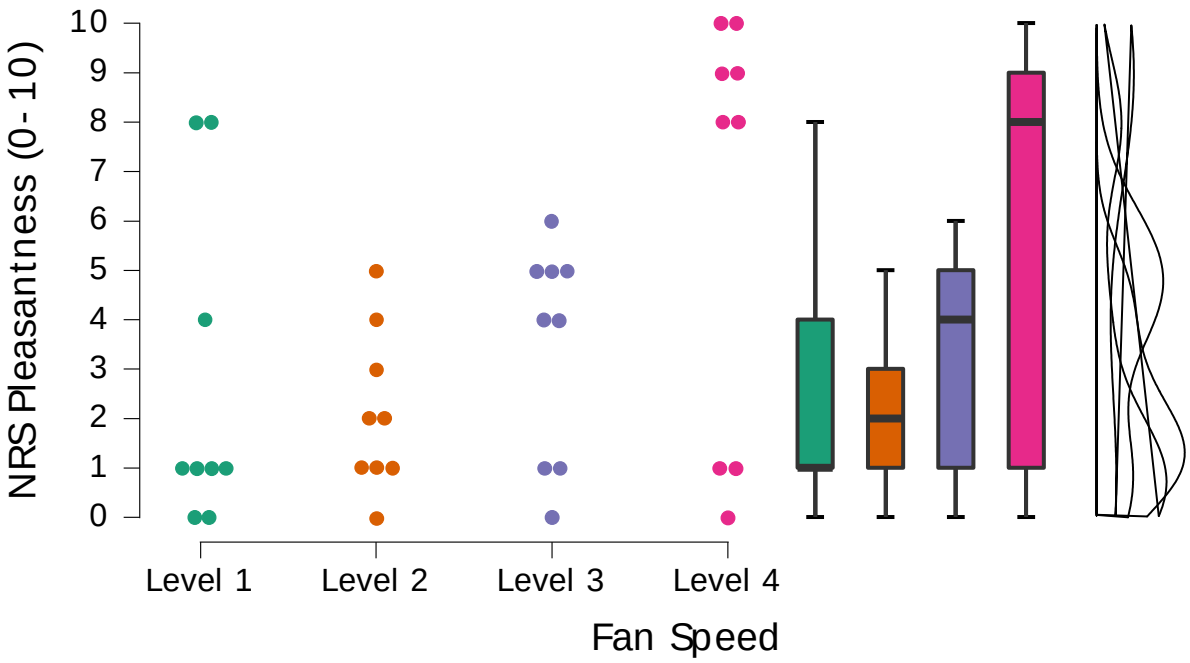


Figure 12. Raincloud plot of fan airflow pleasantness ratings (0 rating representing most pleasant possible, 10 rating representing the most unpleasant possible) from patients (n=9) with chronic breathlessness after using fan therapy for exercise-induced breathlessness recovery.

4.7. Exercise Test Performance

The learning effect and possible fatigability of the sit-to-stand exercise test were analysed using a rmANOVA. The sit-to-stand exercise test violated the

assumptions of sphericity, therefore the Greenhouse-Geisser correction was implemented. The analysis found no statistical significance between the five efforts ($F(4,32)=2.155$, $p=0.168$) (Figure 13).

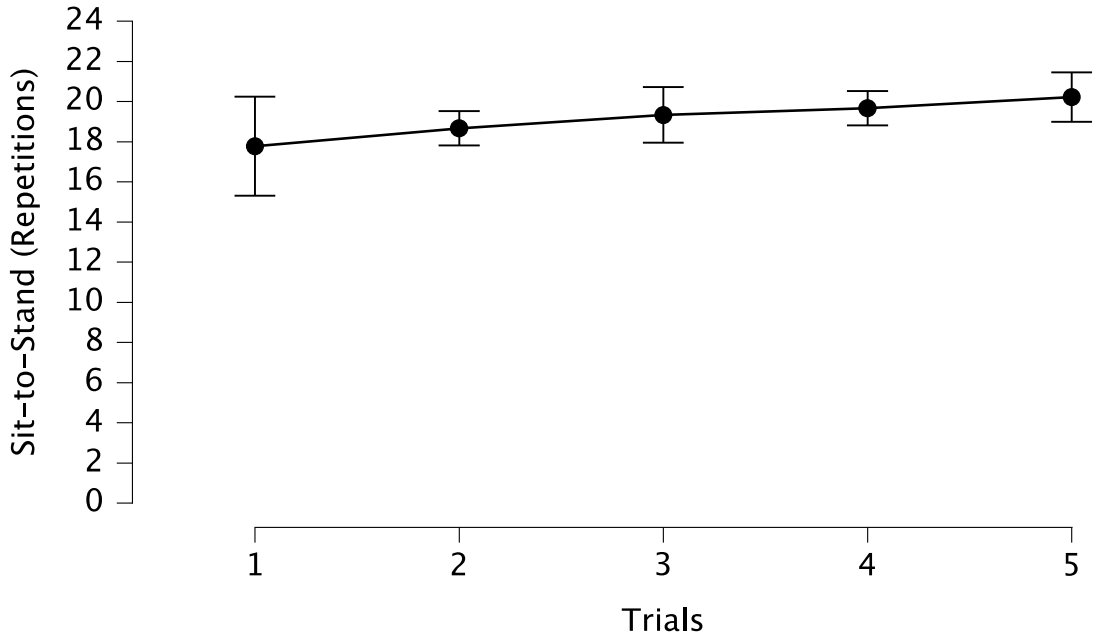


Figure 13. Mean (95% CI) number of repetitions during the five bouts of the sit-to-stand exercise test from the participants (n=9).

5.0. DISCUSSION

5.1. Main Findings

The study aimed to investigate the effect of different airflow speeds from a handheld fan on exercise-induced breathlessness recovery in patients with chronic breathlessness. The study identified that a handheld fan was effective in reducing recovery time from exercise-induced breathlessness when compared to no handheld

fan. Whilst the fan airflow speed of 2.85m/s produced the optimal speed of recovery time from exercise-induced breathlessness and was rated the most preferable airflow speed by the participants. These results suggest that breathlessness management and clinical trials using a handheld fan should focus on airflow speeds of ~2.85m/s to optimise recovery from exertional breathlessness.

5.2. Comparisons with Previous Literature

The study is the first study to identify an optimal fan airflow speed to improve exercise-induced breathlessness recovery in patients with chronic breathlessness. When comparing participant demographics, the age range recruited in studies investigating fan therapy on breathlessness focused on a mean age range between 62 to 72 years (Johnson et al., 2016; Long et al., 2021b; Marchetti et al., 2015; Swan et al., 2019) compared to the mean age of 67±14 years within the study. Furthermore, the majority of participants recruited in the study were male (60%), which is comparative to Swan et al., (2019). However, other literature had either equal male to female populations (Johnson et al., 2016), or predominantly female participants (Long et al., 2021b; Marchetti et al., 2015).

Our results complement investigations into a single fan airflow speed, where reductions in breathlessness recovery from the 6-minute walking test in COPD (Long et al., 2021a), and incremental shuttle walk test in patients with chronic breathlessness patients (Swan et al., 2019) have been reported. However, no verified airflow speeds were defined in either study. Previous efforts to quantify the effects of ‘high’ and ‘low’ airflow speeds on breathlessness recovery in clinical

populations were unable to differentiate between airflow speeds due to the limited sample size inherited by the study design (Johnson et al., 2016). Our findings support a recent report in healthy subjects, where Brew et al., (2023) found airflow speeds between 1.7 m/s and 3.3 m/s increased the speed of recovery from exercise-induced breathlessness.

Breathlessness recovery appeared hastened despite no observable physiological benefits in heart rate or oxygen saturation recovery compared with no handheld fan. These findings are consistent with the previous literature displaying no significant differences between groups in patient populations with COPD (Long et al., 2021a; O'Driscoll et al., 2011). Similarly, Brew et al., (2023) found no effect of the handheld fan on either heart rate or oxygen saturation when applying four different airflow speeds. The handheld fan has also been found not to modify oxygen saturation and heart rate when applied at rest in cancer patients (Kako et al., 2018).

The patients in this study preferred an airflow speed of 2.85 m/s. These findings support the most preferable airflow speed reported in healthy participants of 2.5 m/s (Brew et al., 2023). In patients with COPD, previous studies on handheld fan airflow preference showed the highest airflow of 1.92 m/s at 30cm away from the face was preferred by patients with chronic breathlessness (T. A. Smith et al., 2022). However, the study only investigated airflow speeds between 0.44 m/s to 1.92 m/s, with a significant linear correlation between airflow and pleasantness reported. In contrast, a linear correlation was not apparent in the current study with our results appearing to indicate a ceiling effect of airflow speed on pleasantness whereby airflow may become detrimental after 3.70 m/s. Anecdotal observations during this research suggest beyond fan speed level 2 (2.85 m/s), some patients reported

feeling uncomfortable with higher airflow speeds and at fan speed level 4 (4.91 m/s) the airflow was described as “suffocating” by one patient, as well as causing a premature stoppage of the handheld fan application during one trial.

The majority of patients (7 out of 9) preferred the aesthetic design of fan B with a small compact build with internal blades. This handheld fan coincides with Luckett et al., (2017) specifications of the handheld fan being highly portable, whereby patients could carry the handheld fan with little disruption. Despite the overwhelming preference for fan B, the compromise of this build is in the limited airflow speed available. Smith et al., (2022) demonstrated the large variance of handheld fan properties from blade size, rotational speed, weight, and noisiness which formulate fan performance, whilst simultaneously impacting patient preference. Given the wide variety of commercial handheld fans available to patients, understanding the physical properties the patients value most can allow handheld fan development which doesn’t compromise on the proposed optimal airflow speed to maximise patient recovery and adherence.

Previous literature has used a multitude of exercise tests to induce or assess a breathlessness response. Common exercise protocols include the 6MWT (Johnson et al., 2016; Long et al., 2021b), incremental shuttle walk test (Swan et al., 2019) and CPET (Marchetti et al., 2015).

The 1-minute STS test used here is a valid and reliable test which can be utilised to elicit a physiological response comparable to the 6MWT (Crook et al., 2017), while maintaining good test-retest reliability (Wang et al., 2022). It is acknowledged that the STS has relatively low ecological validity compared with the

6MWT, as patients wouldn’t experience multiple repetitive bouts of this movement in a short period of time compared to 6 minutes of walking. However, this alternative exercise testing method was successful in eliciting an exertional breathlessness response (NRS score immediately post-exercise was 6.85±1.73) (Figure 6). The STS was also selected for pragmatic reasons: i) minimal burden to be placed on the patient, as repeated bouts can be conducted at a single visit, ii) minimal resource requirement (space and equipment) and, iii) the number of repetitions and mean breathlessness was similar across trials (Appendix E).

5.3. Mechanisms

The proposed mechanism underpinning fan therapy is that the stimulation of the trigeminal nerve through the cooling effect of the fan's airflow. Our findings displayed a linear relationship between increasing airflow speed and decreased facial skin temperature at 5 minutes post-exercise. This aligns with previous literature, whereby significant reductions in facial skin temperature were noted with increasing airflow speeds in a dose-response manner post-exercise (Brew et al., 2023) and when comparing fan-to-face and leg at rest in cancer patients (Kako et al., 2018). The cooling of the face, partnered with the lower breathlessness scores reported here would support the diving response theory relating to the cooling stimulation of the trigeminal nerve region (Galbraith et al., 2010). Meanwhile, evidence has also proposed that cooling of the face reduced the central ventilatory chemoreflex response to hypercapnia in healthy individuals, plus reduced breathing frequency in individuals with malignant and non-malignant disease (Aucoin et al., 2023).

Whilst a linear relationship was identified for airflow speed and facial cooling, the linear relationship was not present for airflow speed and breathlessness. Therefore, increasing the airflow speed beyond a certain point may no longer be beneficial for recovery from exercise-induced breathlessness. We postulate that a ceiling effect may have been reached where increasing airflow no longer improves the recovery from breathlessness. In the context of the mechanism, there is a possibility that the maximal activation of the lower 2/3rds of the trigeminal nerve has been achieved. One commentary/alternate theory proposed by Marchetti et al., (2015) suggested that the application of fan airflow alters the patients' perception of their breathlessness and initiates changes to their breathing patterns to reduce dynamic hyperinflation. Meanwhile, Johnson et al., (2015) suggested that facial airflow may alter the brain's activity and subsequent changes in breathlessness perceptions. It is of note that the patient's preferred fan airflow speed corresponds with that of the most favourable breathlessness recovery response.

5.4. Strengths and Limitations

The main strength of the study was the randomised controlled crossover design, which eliminated the allocation bias of the intervention and allowed for sufficient statistical analysis comparisons between the fan airflow speeds and control. The within participant cross-over design does maintain certain limitations through the extensive analysis following the cross-over of 5 different intervention arms, which reduces the power of the study. Although, protocols to minimise the

cross-over effect of the intervention were through randomisation of the intervention delivery. Despite the extensive analysis, the study retained a power of 80% following post-hoc power analysis calculation.

A wash-out period of 10 minutes was incorporated to eliminate possible carryover effects of the handheld fan and allow the participant a rest in-between exercise tests and recovery periods. Previous studies have identified 10 minutes to be an insufficient period between fan-to-face and fan-to-leg at rest (Galbraith et al., 2010). However, S. Booth et al., (2016) found the carryover of fan benefits to persist while stationary and minimal exertion eliminated the carryover.

To our knowledge, this is the first trial which has tested the handheld fan airflow speed reliability and consistency ready for patient application during the trial. The airflow speed tests simulated the distance and duration of the handheld fan utilised in the study to ensure there were no deviations from the desired speed differentials for the trials.

The study encountered a number of limitations worthy of note. Firstly, there was the absence of blinding to the participants and researcher. Blinding of the intervention was not feasible due to the nature of the handheld fan with its physical presence and airflow sensation. Therefore, the lack of blinding throughout inherits a risk of reporting bias from the researcher and the participant.

It is also acknowledged there was no familiarisation visit for the one-minute sit-to-stand exercise test, with only a short demonstration taking place before the trial. This inherits the possible learning effects of the exercise test over the five efforts. However, randomisation of the intervention delivery was intended to minimise

the learning effect and possible adaptation in exercise performance. Additionally, due to the subjects involved in the study, it was designed to be a low-time burden and incur minimal discomfort to the patient. The inclusion of a familiarisation test would increase the risk of patients fatiguing and consequently increase the length of the trial visit.

Furthermore, the NRS breathlessness and alternate scales, such as the BORG, modified Borg, and VAS, used to quantify breathlessness experienced in a patient are all subjective and individual to a patient. Therefore, the subjectivity of this method inherits error when comparing between participants as everyone's perceptions are relative to their own experiences, similar to pain. However, the NRS scale has been used in comparable studies investigating chronic breathlessness (Johnson et al., 2016; Long et al., 2021b; Swan et al., 2019). In addition, the NRS scale has been found to show good test-retest reliability (Janssens et al., 2019).

Additionally, it is accepted that a solely COPD diagnostic subgroup would increase the homogeneity of the study population. However, the study is focused on relief of exertional breathlessness, a symptom in people with chronic breathlessness that occurs, irrespective of the optimal treatment for their underlying lung disease or condition (Johnson et al., 2017). Indeed, the potential mechanisms underpinning the fan are not directed at altering or improving the pathophysiology of the disease and, instead, target the relief of breathlessness through olfactory and trigeminal nerve stimulation which modulates and decreases neuro-respiratory drive (Aucoin et al., 2023). Post-hoc sensitivity analysis on COPD patients only found no materialistic difference in the statistical outcome or interpretation of the results regarding fan

airflow speeds and NRS breathlessness recovery compared with the original analysis.

Due to the exploratory nature of the study, no sample size calculation was conducted. It was estimated a sample size of 10 should provide sufficient data to answer the research question and inform future sample sizes. A post-hoc power analysis was conducted through G*power (Faul et al., 2007) to analyse the power of the study, the results indicated a power of 80% was maintain from n=9 participants.

The post-analysis resulted in a sample size of 8 participants for the primary outcome. The removal of one participant after the trial visit violates the protocol design. However, the elimination of these results highlights the necessary input of a familiarisation visit to both the exercise test and NRS scoring system. The data excluded from the analysis are displayed in Appendix B alongside a detailed justification for their exclusion and the results from the analysis should these data have been retained.

5.5. Future Research

The findings of this study complement previous literature describing the effective use of a handheld fan for breathlessness recovery. For the first time, we identified a possible optimal airflow speed for breathlessness recovery in patients with breathlessness which requires additional trials to confirm our findings. Future research with the proposed optimal airflow speed of 2.85m/s should focus on how this airflow speed can improve breathlessness during daily life. Further, these findings may inform the development of a handheld fan capable of supplying the

optimal airflow speed while conforming to patients' views on handheld fan aesthetics. The development of a new handheld fan for clinical application would require re-testing for exercise-induced breathlessness recovery and effectiveness for daily activity.

In addition to airflow speed advancements, further research is required to understand the mechanisms surrounding breathlessness, specifically for patient populations. Further understanding of breathlessness mechanisms could provide information to advance the understanding of the mechanisms surrounding fan therapy, and how to maximise a handheld fan to optimise breathlessness recovery.

The final direction for future research is to investigate the effects of airflow presence against a cooling effect. Understanding the individual effects of the airflow presence and the cooling effects of the trigeminal nerve receptors could help unpick the mechanisms for relieving breathlessness.

6.0. CONCLUSIONS

Fan therapy is a portable, cost-effective management technique widely available to patients to improve their recovery from exercise-induced breathlessness. Our data suggest that a fan airflow speed of 2.85m/s provided the greatest reduction in breathlessness recovery time. For the first time, we identified a possible detrimental effect of higher airflow speeds on breathlessness recovery. The findings

provide clinical direction for handheld fan prescription for the alleviation of exertional breathlessness and provide guidance for handheld fan design for future clinical trials.

7.0. REFERENCES

Ahmadi, Z. (2018). The burden of chronic breathlessness across the population. *Current Opinion in Supportive & Palliative Care*, *12*(3), 214–218. https://doi.org/10.1097/SPC.0000000000000364

Aitken, C. R., Stewart, G. M., Walsh, J. R., Palmer, T., Adams, L., Sabapathy, S., & Morris, N. R. (2023). Exertional dyspnea responses to the Dyspnea Challenge in heart failure: Comparison to chronic obstructive pulmonary disease. *Heart & Lung*, *58*, 108–115. https://doi.org/10.1016/j.hrtlng.2022.11.010

Aliverti, A. (2016). The respiratory muscles during exercise. *Breathe*, *12*(2), 165. https://doi.org/10.1183/20734735.008116

Alkodaymi, M. S., Omrani, O. A., Fawzy, N. A., Shaar, B. A., Almamlouk, R., Riaz, M., Obeidat, M., Obeidat, Y., Gerberi, D., Taha, R. M., Kashour, Z., Kashour, T., Berbari, E. F., Alkattan, K., & Tleyjeh, I. M. (2022). Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis. *Clinical Microbiology and Infection : The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases*, *28*(5), 657–666. https://doi.org/10.1016/j.cmi.2022.01.014

Altose, M., Cherniack, N., & Fishman, A. P. (1985). Respiratory sensations and dyspnea. *Journal of Applied Physiology (Bethesda, Md. : 1985)*, *58*(4), 1051–1054. https://doi.org/10.1152/JAPPL.1985.58.4.1051

Amariei, D. E., Dodia, N., Deepak, J., Hines, S. E., Galvin, J. R., Atamas, S. P., & Todd, N. W. (2019). Combined Pulmonary Fibrosis and Emphysema: Pulmonary Function Testing and a Pathophysiology Perspective. *Medicina*, *55*(9). https://doi.org/10.3390/MEDICINA55090580

American Thoracic Society committee. (1999). Dyspnea. *American Journal of Respiratory and Critical Care Medicine*, *159*(1), 321–340. https://doi.org/10.1164/ajrccm.159.1.ats898

Antoniu, S. A. (2010). Descriptors of dyspnea in obstructive lung diseases. *Multidisciplinary Respiratory Medicine*, *5*(3), 216. https://doi.org/10.1186/2049-6958-5-3-216

Aronson, K. I., Swigris, J. J., Bajwah, S., Bianchi, P., Corte, T. J., Danoff, S. K., Lee, J. S., Lindell, K. O., Maher, T., Martinez, F. J., Meek, P. M., Raghu, G., Rouland, G., Rudell, R., Russell, A. M., Ryerson, C. J., Safford, M. M., Sheth, J. S., Suzuki, A., & Wijsenbeek, M. S. (2021). Patient-centered Outcomes Research in Interstitial Lung Disease: An Official American Thoracic Society Research Statement. *Https://Doi.Org/10.1164/Rccm.202105-1193ST*, *204*(2), E3–E23. https://doi.org/10.1164/RCCM.202105-1193ST

Aucoin, R., Lewthwaite, H., Ekström, M., von Leupoldt, A., & Jensen, D. (2023). Impact of trigeminal and/or olfactory nerve stimulation on measures of

inspiratory neural drive: Implications for breathlessness. *Respiratory Physiology & Neurobiology*, *311*, 104035. https://doi.org/10.1016/J.RESP.2023.104035

Babb, T. G. (2013). Exercise Ventilatory Limitation: The Role Of Expiratory Flow Limitation. *Exercise and Sport Sciences Reviews*, *41*(1), 11. https://doi.org/10.1097/JES.0B013E318267C0D2

Barnett, L. A., Prior, J. A., Kadam, U. T., & Jordan, K. P. (2017). Chest pain and shortness of breath in cardiovascular disease: a prospective cohort study in UK primary care. *BMJ Open*, *7*(5), e015857. https://doi.org/10.1136/bmjopen-2017-015857

Bausewein, C., Booth, S., Gysels, M., Kühnbach, R., & Higginson, I. J. (2010). Effectiveness of a hand-held fan for breathlessness: a randomised phase II trial. *BMC Palliative Care*, *9*. https://doi.org/10.1186/1472-684X-9-22

Bergren, D. R. (2020). Modeling rapidly adapting pulmonary stretch receptor activity to step-wise and constant pressure inflation of the lungs. *Respiratory Physiology & Neurobiology*, *276*, 103410. https://doi.org/10.1016/j.resp.2020.103410

Berliner, D., Schneider, N., Welte, T., & Bauersachs, J. (2016). The Differential Diagnosis of Dyspnea. *Deutsches Ärzteblatt International*. https://doi.org/10.3238/arztebl.2016.0834

Bestall, J. C., Paul, E. A., Garrod, R., Garnham, R., Jones, P. W., & Wedzicha, J. A. (1999). Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax*, *54*(7), 581–586. https://doi.org/10.1136/THX.54.7.581

Binks, A. P., Moosavi, S. H., Banzett, R. B., & Schwartzstein, R. M. (2012). "Tightness" Sensation of Asthma Does Not Arise from the Work of Breathing. *Https://Doi.Org/10.1164/Ajrccm.165.1.2105061*, *165*(1), 78–82. https://doi.org/10.1164/AJRCCM.165.1.2105061

Boonpiyathad, T., Sözener, Z. C., Satitsuksanoa, P., & Akdis, C. A. (2019). Immunologic mechanisms in asthma. *Seminars in Immunology*, *46*, 101333. https://doi.org/10.1016/J.SMIM.2019.101333

Booth, F. W., Roberts, C. K., & Laye, M. J. (2012). Lack of exercise is a major cause of chronic diseases. *Comprehensive Physiology*, *2*(2), 1143. https://doi.org/10.1002/CPHY.C110025

Booth, S., Farquhar, M., Gysels, M., Bausewein, C., & Higginson, I. J. (2006). The impact of a breathlessness intervention service (BIS) on the lives of patients with intractable dyspnea: A qualitative phase 1 study. *Palliative & Supportive Care*, *4*(3), 287–293. https://doi.org/10.1017/S1478951506060366

Booth, S., Galbraith, S., Ryan, R., Parker, R. A., & Johnson, M. (2016). The importance of the feasibility study: Lessons from a study of the hand-held fan used to relieve dyspnea in people who are breathless at rest. *Palliative Medicine*, *30*(5), 504–509. https://doi.org/10.1177/0269216315607180/FORMAT/EPUB

Borak, J., & Lefkowitz, R. Y. (2016). Bronchial hyperresponsiveness. *Occupational Medicine*, *66*(2), 95–105. https://doi.org/10.1093/OCCMED/KQV158

Boulding, R., Stacey, R., Niven, R., & Fowler, S. J. (2016). Dysfunctional breathing: a review of the literature and proposal for classification. *European Respiratory Review*, *25*(141), 287. https://doi.org/10.1183/16000617.0088-2015

Boulet, L. P., & Boulay, M. È. (2014). Asthma-related comorbidities. *Http://Dx.Doi.Org/10.1586/Ers.11.34*, *5*(3), 377–393. https://doi.org/10.1586/ERS.11.34

Boushel, R. (2010). Muscle metaboreflex control of the circulation during exercise. *Acta Physiologica*, *199*(4), 367–383. https://doi.org/10.1111/J.1748-1716.2010.02133.X

Bowden, J. A., To, T. H. M., Abernethy, A. P., & Currow, D. C. (2011). Predictors of chronic breathlessness: A large population study. *BMC Public Health*, *11*(1), 1–10. https://doi.org/10.1186/1471-2458-11-33/TABLES/5

Branson, R. D., & Faarc, R. (2018). Oxygen Therapy in COPD. *Respiratory Care*, *63*(6), 734–748. https://doi.org/10.4187/RESPCARE.06312

Brew, A., O'Beirne, S., Johnson, M. J., Ramsenthaler, C., Watson, P. J., Rubini, P. A., Fagan, M. J., Swan, F., & Simpson, A. (2023). Airflow rates and breathlessness recovery from submaximal exercise in healthy adults: prospective, randomised, cross-over study. *BMJ Supportive & Palliative Care*, spcare-2023-004309. https://doi.org/10.1136/spcare-2023-004309

Brigham, E. P., & West, N. E. (2015). Diagnosis of asthma: Diagnostic testing. *International Forum of Allergy and Rhinology*, *5*, S27–S30. https://doi.org/10.1002/ALR.21597

Brighton, L. J., Miller, S., Farquhar, M., Booth, S., Yi, D., Gao, W., Bajwah, S., Man, W. D.-C., Higginson, I. J., & Maddocks, M. (2019). Holistic services for people with advanced disease and chronic breathlessness: a systematic review and meta-analysis. *Thorax*, *74*(3), 270–281. https://doi.org/10.1136/thoraxjnl-2018-211589

Buchanan, G. F., & Richerson, G. B. (2009). Role of chemoreceptors in mediating dyspnea. *Respiratory Physiology & Neurobiology*, *167*(1), 9. https://doi.org/10.1016/J.RESP.2008.12.002

Burki, N. K., & Lee, L. Y. (2010). Mechanisms of Dyspnea. *Chest*, *138*(5), 1196. https://doi.org/10.1378/CHEST.10-0534

Calzetta, L., Ora, J., Cavalli, F., Rogliani, P., O'Donnell, D. E., & Cazzola, M. (2017). Impact of LABA/LAMA combination on exercise endurance and lung hyperinflation in COPD: A pair-wise and network meta-analysis. *Respiratory Medicine*, *129*, 189–198. https://doi.org/10.1016/j.rmed.2017.06.020

Ceco, E., Weinberg, S. E., Chandel, N. S., & Sznajder, J. I. (2017). Metabolism and Skeletal Muscle Homeostasis in Lung Disease. *American Journal of Respiratory Cell and Molecular Biology*, *57*(1), 28–34. https://doi.org/10.1165/rcmb.2016-0355TR

Chen, C., Haupert, S. R., Zimmermann, L., Shi, X., Fritsche, L. G., & Mukherjee, B. (2022). Global Prevalence of Post-Coronavirus Disease 2019 (COVID-19) Condition or Long COVID: A Meta-Analysis and Systematic Review. *The Journal of Infectious Diseases*, *226*(9), 1593–1607. https://doi.org/10.1093/INFDIS/JIAC136

Cheyne, W. S., Gelinas, J. C., & Eves, N. D. (2018). Hemodynamic effects of incremental lung hyperinflation. *American Journal of Physiology-Heart and Circulatory Physiology*, *315*(3), H474–H481. https://doi.org/10.1152/ajpheart.00229.2018

Choi, Y. J., Suh, D. I., Sohn, M. H., & Koh, Y. Y. (2018). Dyspnea Perception During Induced Bronchoconstriction Is Complicated by the Inhaled Methacholine in Children With Clinical Asthma. *Allergy, Asthma & Immunology Research*, *10*(2), 131. https://doi.org/10.4168/AAIR.2018.10.2.131

Chronic obstructive pulmonary disease (COPD). (n.d.). Retrieved October 20, 2022, from https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)

Cockcroft, D. W., & Davis, B. E. (2006). Mechanisms of airway hyperresponsiveness. *The Journal of Allergy and Clinical Immunology*, *118*(3), 551–559. https://doi.org/10.1016/J.JACI.2006.07.012

Crook, H., Raza, S., Nowell, J., Young, M., & Edison, P. (2021). Long covid—mechanisms, risk factors, and management. *BMJ*, *374*. https://doi.org/10.1136/BMJ.N1648

Cunningham, C., O' Sullivan, R., Caserotti, P., & Tully, M. A. (2020). Consequences of physical inactivity in older adults: A systematic review of reviews and meta-analyses. *Scandinavian Journal of Medicine & Science in Sports*, *30*(5), 816–827. https://doi.org/10.1111/SMS.13616

Currow, D. C., Abernethy, A. P., & Ko, D. N. (2014). Chest clinic The active identification and management of chronic refractory breathlessness is a human right. *Thorax*, *69*, 393–394. https://doi.org/10.1136/thoraxjnl-2013-204701

Currow, D. C., Dal Grande, E., Sidhu, C., Ekström, M., & Johnson, M. J. (2017). The independent association of overweight and obesity with breathlessness in adults: a cross-sectional, population-based study. *European Respiratory Journal*, *50*(3), 1700558. https://doi.org/10.1183/13993003.00558-2017

Currow, D. C., Higginson, I. J., & Johnson, M. J. (2013). Breathlessness – current and emerging mechanisms, measurement and management: A discussion from an European Association of Palliative Care workshop. *Palliative Medicine*, *27*(10), 932–938. https://doi.org/10.1177/0269216313493819

Currow, D., Ward, A., Clark, K., Burns, C., & Abernethy, A. (2008). Caregivers for people with end-stage lung disease: Characteristics and unmet needs in the whole population. *International Journal of Chronic Obstructive Pulmonary Disease*, *Volume 3*, 753–762. https://doi.org/10.2147/COPD.S3890

De Vito, E. L. (2021). Possible Role of Corollary Discharge in Lack of Dyspnea in Patients With COVID-19 Disease. *Frontiers in Physiology*, *12*, 719166. https://doi.org/10.3389/fphys.2021.719166

DeMaio, A., & Semaan, R. (2021). Management of Pneumothorax. *Clinics in Chest Medicine*, *42*(4), 729–738. https://doi.org/10.1016/J.CCM.2021.08.008

Dempsey, J. A., Romer, L., Rodman, J., Miller, J., & Smith, C. (2006). Consequences of exercise-induced respiratory muscle work. *Respiratory*

Physiology & Neurobiology, *151*(2–3), 242–250. https://doi.org/10.1016/J.RESP.2005.12.015

Dennis, A., Wamil, M., Alberts, J., Oben, J., Cuthbertson, D. J., Wootton, D., Crooks, M., Gabbay, M., Brady, M., Hishmeh, L., Attree, E., Heightman, M., Banerjee, R., & Banerjee, A. (2021). Original research: Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open*, *11*(3), 48391. https://doi.org/10.1136/BMJOPEN-2020-048391

Dudgeon, D. J., Kristjanson, L., Sloan, J. A., Lertzman, M., & Clement, K. (2001). Dyspnea in Cancer Patients. *Journal of Pain and Symptom Management*, *21*(2), 95–102. https://doi.org/10.1016/S0885-3924(00)00258-X

Dumitrescu, D., Sitbon, O., Weatherald, J., & Howard, L. S. (2017). Exertional dyspnoea in pulmonary arterial hypertension. *European Respiratory Review*, *26*(145). https://doi.org/10.1183/16000617.0039-2017

Durdu, H., Demir, R., Zeren, M., Basturk, P., Arabaci, H. O., Sinan, U. Y., & Kucukoglu, M. S. (2023). Evaluation of primary and accessory respiratory muscles and their influence on exercise capacity and dyspnea in pulmonary arterial hypertension. *Heart & Lung*, *57*, 173–179. https://doi.org/10.1016/j.hrtlng.2022.09.015

Ekström, M., Schiöler, L., Grønseth, R., & Johannessen, A. (2017). Absolute values of lung function explain the sex difference in breathlessness in the general population. *Jesús Martinez-Moratalla Rovira*, *5*(8), 1602047. https://doi.org/10.1183/13993003.02047-2016

Elbehairy, A. F., O'Donnell, C. D., Elhameed, A. A., Vincent, S. G., Milne, K. M., James, M. D., Webb, K. A., Neder, J. A., & O'Donnell, D. E. (2019). Low resting diffusion capacity, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *Journal of Applied Physiology*, *127*(4), 1107–1116. https://doi.org/10.1152/JAPPLPHYSIOL.00341.2019/ASSET/IMAGES/LARGE/ZDG0091931570003.JPEG

Elliott-Button, H. L., Johnson, M. J., Nwulu, U., & Clark, J. (2020). Identification and Assessment of Breathlessness in Clinical Practice: A Systematic Review and Narrative Synthesis. *Journal of Pain and Symptom Management*, *59*(3), 724-733.e19. https://doi.org/10.1016/J.JPAINSYMMAN.2019.10.014

Farquhar, M. C., Prevost, A. T., McCrone, P., Brafman-Price, B., Bentley, A., Higginson, I. J., Todd, C., & Booth, S. (2014). Is a specialist breathlessness service more effective and cost-effective for patients with advanced cancer and their carers than standard care? Findings of a mixed-method randomised controlled trial. *BMC Medicine*, *12*(1). https://doi.org/10.1186/S12916-014-0194-2

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175–191. https://doi.org/10.3758/BF03193146/METRICS

Ferreira, E. V. M., & Oliveira, R. K. F. (2021). Mechanisms of exercise intolerance after COVID-19: new perspectives beyond physical deconditioning. *Jornal*

Brasileiro de Pneumologia, *47*(5). https://doi.org/10.36416/1806-3756/E20210406

Finnegan, S. L., Dearlove, D. J., Morris, P., Freeman, D., Sergeant, M., Taylor, S., & Pattinson, K. T. S. (2023). Breathlessness in a virtual world: An experimental paradigm testing how discrepancy between VR visual gradients and pedal resistance during stationary cycling affects breathlessness perception. *PLOS ONE*, *18*(4), e0270721. https://doi.org/10.1371/journal.pone.0270721

Fiorentino, G., Esquinas, A. M., & Annunziata, A. (2020). Exercise and Chronic Obstructive Pulmonary Disease (COPD). *Advances in Experimental Medicine and Biology*, *1228*, 355–368. https://doi.org/10.1007/978-981-15-1792-1_24/COVER

Fukushi, I., Pokorski, M., & Okada, Y. (2021). Mechanisms underlying the sensation of dyspnea. *Respiratory Investigation*, *59*(1), 66–80. https://doi.org/10.1016/J.RESINV.2020.10.007

Galbraith, S., Fagan, P., Perkins, P., Lynch, A., & Booth, S. (2010). Does the Use of a Handheld Fan Improve Chronic Dyspnea? A Randomized, Controlled, Crossover Trial. *Journal of Pain and Symptom Management*, *39*(5), 831–838. https://doi.org/10.1016/J.JPAINSYMMAN.2009.09.024

Galiè, N., Humbert, M., Vachiery, J. L., Gibbs, S., Lang, I., Torbicki, A., Simonneau, G., Peacock, A., Noordegraaf, A. V., Beghetti, M., Ghofrani, A., Sanchez, M. A. G., Hansmann, G., Klepetko, W., Lancellotti, P., Matucci, M., McDonagh, T., Pierard, L. A., Trindade, P. T., … Hoeper, M. (2015). 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *European*

Respiratory Journal, *46*(4), 903–975. https://doi.org/10.1183/13993003.01032-2015

Gift, A. G., & Narsavage, G. (1998). Validity of the numeric rating scale as a measure of dyspnea. *American Journal of Critical Care : An Official Publication, American Association of Critical-Care Nurses*, *7*(3), 200–204. https://doi.org/10.4037/ajcc1998.7.3.200

Gigliotti, F. (2010). Mechanisms of dyspnea in healthy subjects. *Multidisciplinary Respiratory Medicine*, *5*(3), 195. https://doi.org/10.1186/2049-6958-5-3-195

Global Initiative for Asthma. (2022). *Global Strategy for Asthma Management and Prevention*. Https://Ginasthma.Org.

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (2018 REPORT). (2018). www.goldcopd.org

Gloeckl, R., Schneeberger, T., Jarosch, I., & Kenn, K. (2018). Pulmonary Rehabilitation and Exercise Training in Chronic Obstructive Pulmonary Disease. *Deutsches Ärzteblatt International*. https://doi.org/10.3238/arztebl.2018.0117

Gourine, A. V., & Spyer, K. M. (2009). Autonomic Nervous System: Central Respiratory Control. In *Encyclopedia of Neuroscience* (pp. 883–890). Elsevier. https://doi.org/10.1016/B978-008045046-9.00652-5

Gouzi, F., Préfaut, C., Abdellaoui, A., Roudier, E., De Rigal, P., Molinari, N., Laoudj-Chenivesse, D., Mercier, J., Birot, O., & Hayot, M. (2013). Blunted muscle

angiogenic training-response in COPD patients versus sedentary controls. *European Respiratory Journal*, *41*(4), 806–814. https://doi.org/10.1183/09031936.00053512

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*(11), 1403–1412. https://doi.org/10.1016/j.rmed.2005.03.005

Grosbois, J.-M., Gephine, S., Kyheng, M., Henguelle, J., Le Rouzic, O., Saey, D., Maltais, F., & Chenivesse, C. (2022). Physical and affective components of dyspnoea are improved by pulmonary rehabilitation in COPD. *BMJ Open Respiratory Research*, *9*(1), e001160. https://doi.org/10.1136/bmjresp-2021-001160

Gupta, N., Pinto, L. M., Morogan, A., & Bourbeau, J. (2014). The COPD assessment test: a systematic review. *The European Respiratory Journal*, *44*(4), 873–884. https://doi.org/10.1183/09031936.00025214

Guyenet, P. G., & Bayliss, D. A. (2015). Neural control of breathing and CO2 homeostasis. *Neuron*, *87*(5), 946. https://doi.org/10.1016/J.NEURON.2015.08.001

Haines, J., Chua, S. H. K., Smith, J., Slinger, C., Simpson, A. J., & Fowler, S. J. (2020). Triggers of breathlessness in inducible laryngeal obstruction and asthma. *Clinical & Experimental Allergy*, *50*(11), 1230–1237. https://doi.org/10.1111/CEA.13715

Hanania, N. A., & O'donnell, D. E. (2019). Activity-related dyspnea in chronic obstructive pulmonary disease: physical and psychological consequences, unmet needs, and future directions. *International Journal of Chronic Obstructive Pulmonary Disease*, *14*, 1127. https://doi.org/10.2147/COPD.S188141

Haugdahl, H. S., Storli, S. L., Meland, B., Dybwik, K., Romild, U., & Klepstad, P. (2015). Underestimation of patient breathlessness by nurses and physicians during a spontaneous breathing trial. *American Journal of Respiratory and Critical Care Medicine*, *192*(12), 1440–1448. https://doi.org/10.1164/RCCM.201503-0419OC/SUPPL_FILE/DISCLOSURES.PDF

Herdy, A. H., Ritt, L. E. F., Stein, R., de Araújo, C. G. S., Milani, M., Meneghelo, R. S., Ferraz, A. S., Hossri, C., de Almeida, A. E. M., da Silva, M. M. F., & Serra, S. M. (2016). Cardiopulmonary Exercise Test: Background, Applicability and Interpretation. *Arquivos Brasileiros de Cardiologia*, *107*(5), 467. https://doi.org/10.5935/ABC.20160171

Higginson, I. J., Bausewein, C., Reilly, C. C., Gao, W., Gysels, M., Dzingina, M., McCrone, P., Booth, S., Jolley, C. J., & Moxham, J. (2014). An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *The Lancet Respiratory Medicine*, *2*(12), 979–987. https://doi.org/10.1016/S2213-2600(14)70226-7

Hogg, J. C. (2004). Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *The Lancet*, *364*(9435), 709–721. https://doi.org/10.1016/S0140-6736(04)16900-6

Hutchinson, A., Allgar, V., Cohen, J., Currow, D. C., Griffin, S., Hart, S., Hird, K., Hodge, A., Mason, S., Northgraves, M., Reeve, J., Swan, F., & Johnson, M. J. (2022). Mixed-methods feasibility cluster randomised controlled trial of a paramedic-administered breathlessness management intervention for acute-on-chronic breathlessness (BREATHE): study findings. *ERJ Open Research*, *8*(4). https://doi.org/10.1183/23120541.00257-2022

Hutchinson, A., Johnson, M. J., & Currow, D. (2019). Acute-on-Chronic Breathlessness: Recognition and Response. *Journal of Pain and Symptom Management*, *57*(5), e4–e5. https://doi.org/10.1016/j.jpainsymman.2019.01.012

Janssens, T., De Peuter, S., Stans, L., Verleden, G., Troosters, T., Decramer, M., & Van den Bergh, O. (2011). Dyspnea Perception in COPD. *Chest*, *140*(3), 618–625. https://doi.org/10.1378/chest.10-3257

Janssens, T., Geidl, W., Carl, J., Pfeiffer, K., Lehbert, N., Wittmann, M., Schultz, K., & Von Leupoldt, A. (2019). Reliability and validity of dyspnea numeric rating scales as a patient-reported outcome in pulmonary rehabilitation of COPD. *Physiotherapists*, OA3810. https://doi.org/10.1183/13993003.congress-2019.OA3810

Jantarakupt, P., & Porock, D. (2005). Dyspnea management in lung cancer: applying the evidence from chronic obstructive pulmonary disease. *Oncology Nursing Forum*, *32*(4), 785–797. https://doi.org/10.1188/05.ONF.785-797

Johnson, M. J., Booth, S., Currow, D. C., Lam, L. T., & Phillips, J. L. (2016). A Mixed-Methods, Randomized, Controlled Feasibility Trial to Inform the Design of a Phase III Trial to Test the Effect of the Handheld Fan on Physical Activity and

Carer Anxiety in Patients With Refractory Breathlessness. *Journal of Pain and Symptom Management*, *51*(5), 807–815. https://doi.org/10.1016/J.JPAINSYMMAN.2015.11.026

Johnson, M. J., & Currow, D. C. (2020). Opioids for breathlessness: a narrative review. *BMJ Supportive & Palliative Care*, *10*(3), 287–295. https://doi.org/10.1136/bmjspcare-2020-002314

Johnson, M. J., Simpson, M. I. G., Currow, D. C., Millman, R. E., Hart, S. P., & Green, G. (2015). Magnetoencephalography to investigate central perception of exercise-induced breathlessness in people with chronic lung disease: a feasibility pilot. *BMJ Open*, *5*(6). https://doi.org/10.1136/BMJOPEN-2014-007535

Johnson, M. J., Yorke, J., Hansen-Flaschen, J., Lansing, R., Ekström, M., Similowski, T., & Currow, D. C. (2017). Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. *European Respiratory Journal*, *49*(5), 1602277. https://doi.org/10.1183/13993003.02277-2016

Jolley, C. J., Luo, Y.-M., Steier, J., Reilly, C., Seymour, J., Lunt, A., Ward, K., Rafferty, G. F., Polkey, M. I., & Moxham, J. (2008). Neural respiratory drive in healthy subjects and in COPD. *European Respiratory Journal*, *33*(2), 289–297. https://doi.org/10.1183/09031936.00093408

Jolley, C. J., & Moxham, J. (2009). A physiological model of patient-reported breathlessness during daily activities in COPD. *European Respiratory Review : An Official Journal of the European Respiratory Society*, *18*(112), 66–79. https://doi.org/10.1183/09059180.00000809

Jonkman, A. H., De Vries, H. J., & Heunks, L. M. A. (2020). Physiology of the Respiratory Drive in ICU Patients: Implications for Diagnosis and Treatment. *Critical Care*, *24*(1). https://doi.org/10.1186/S13054-020-2776-Z

Juusela, M., Pallasaho, P., Rönmark, E., Sarna, S., Sovijärvi, A., & Lundbäck, B. (2013). Dose-dependent association of smoking and bronchial hyperresponsiveness. *European Respiratory Journal*, *42*(6), 1503–1512. https://doi.org/10.1183/09031936.00073712

Kako, J., Morita, T., Yamaguchi, T., Kobayashi, M., Sekimoto, A., Kinoshita, H., Ogawa, A., Zenda, S., Uchitomi, Y., Inoguchi, H., & Matsushima, E. (2018). Fan Therapy Is Effective in Relieving Dyspnea in Patients With Terminally Ill Cancer: A Parallel-Arm, Randomized Controlled Trial. *Journal of Pain and Symptom Management*, *56*(4), 493–500. https://doi.org/10.1016/j.jpainsymman.2018.07.001

Katzmarzyk, P. T., Friedenreich, C., Shiroma, E. J., & Lee, I.-M. (2022). Physical inactivity and non-communicable disease burden in low-income, middle-income and high-income countries. *British Journal of Sports Medicine*, *56*(2), 101–106. https://doi.org/10.1136/bjsports-2020-103640

Kendrick, K. R., Baxi, S. C., & Smith, R. M. (2000). Usefulness of the modified 0-10 Borg scale in assessing the degree of dyspnea in patients with COPD and asthma. *Journal of Emergency Nursing*, *26*(3), 216–222. https://doi.org/10.1067/men.2000.107012

Khor, Y. H., Saravanan, K., Holland, A. E., Lee, J. Y. T., Ryerson, C. J., McDonald, C. F., & Goh, N. S. L. (2021). A mixed-methods pilot study of handheld fan for

breathlessness in interstitial lung disease. *Scientific Reports*, *11*(1), 6874. https://doi.org/10.1038/S41598-021-86326-8

Kim, V., & Criner, G. J. (2013). Chronic Bronchitis and Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine*, *187*(3), 228. https://doi.org/10.1164/RCCM.201210-1843CI

Kocatepe, V., Can, G., & Oruç, Ö. (2021). Lung Cancer-Related Dyspnea: The Effects of a Handheld Fan on Management of Symptoms. *Clinical Journal of Oncology Nursing*, *25*(6), 655–661. https://doi.org/10.1188/21.CJON.655-661

Kupper, N., Bonhof, C., Westerhuis, B., Widdershoven, J., & Denollet, J. (2016). Determinants of Dyspnea in Chronic Heart Failure. *Journal of Cardiac Failure*, *22*(3), 201–209. https://doi.org/10.1016/j.cardfail.2015.09.016

Kuruvilla, M. E., Lee, F. E. H., & Lee, G. B. (2019). Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease. *Clinical Reviews in Allergy & Immunology*, *56*(2), 219. https://doi.org/10.1007/S12016-018-8712-1

Lamba, T. S., Sharara, R. S., Singh, A. C., & Balaan, M. (2016). Pathophysiology and classification of respiratory failure. *Critical Care Nursing Quarterly*, *39*(2), 85–93. https://doi.org/10.1097/CNQ.0000000000000102

Laveneziana, P., & Agostoni, P. (2016). Exertional dyspnoea in cardiorespiratory disorders: the clinical use of cardiopulmonary exercise testing. *European Respiratory Review : An Official Journal of the European Respiratory Society*, *25*(141), 227–229. https://doi.org/10.1183/16000617.0044-2016

Laviolette, L., & Laveneziana, P. (2014). Dyspnoea: a multidimensional and multidisciplinary approach. *European Respiratory Journal*, *43*(6), 1750–1762. https://doi.org/10.1183/09031936.00092613

Lewthwaite, H., Li, P. Z., O'Donnell, D. E., & Jensen, D. (2021). Multidimensional breathlessness response to exercise: Impact of COPD and healthy ageing. *Respiratory Physiology & Neurobiology*, *287*, 103619. https://doi.org/10.1016/J.RESP.2021.103619

Li, Y., Swensen, S. J., Karabekmez, L. G., Marks, R. S., Stoddard, S. M., Jiang, R., Worra, J. B., Zhang, F., Midthun, D. E., De Andrade, M., Song, Y., & Yang, P. (2011). Effect of emphysema on lung cancer risk in smokers: A computed tomography-based assessment. *Cancer Prevention Research*, *4*(1), 43–50. https://doi.org/10.1158/1940-6207.CAPR-10-0151/35748/AM/EFFECT-OF-EMPHYSEMA-ON-LUNG-CANCER-RISK-IN-SMOKERS

Lim, W. S. (2022). Pneumonia—Overview. In *Encyclopedia of Respiratory Medicine* (pp. 185–197). Elsevier. https://doi.org/10.1016/B978-0-12-801238-3.11636-8

Livermore, N., Butler, J. E., Sharpe, L., McBain, R. A., Gandevia, S. C., & McKenzie, D. K. (2008). Panic Attacks and Perception of Inspiratory Resistive Loads in Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine*, *178*(1), 7–12. https://doi.org/10.1164/rccm.200711-1700OC

Long, A., Cartwright, M., & Reilly, C. C. (2021a). Impact of fan therapy during exercise on breathlessness and recovery time in patients with COPD: a pilot

randomised controlled crossover trial. *ERJ Open Research*, *7*(4). https://doi.org/10.1183/23120541.00211-2021

Long, A., Cartwright, M., & Reilly, C. C. (2021b). Impact of fan therapy during exercise on breathlessness and recovery time in patients with COPD: a pilot randomised controlled crossover trial. *ERJ Open Research*, *7*(4), 211–2021. https://doi.org/10.1183/23120541.00211-2021

Lopez-Leon, S., Wegman-Ostrosky, T., Perelman, C., Sepulveda, R., Rebolledo, P. A., Cuapio, A., & Villapol, S. (2021). More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Scientific Reports*, *11*(1), 16144. https://doi.org/10.1038/S41598-021-95565-8

Lougheed, M. D., Fisher, T., & O'Donnell, D. E. (2006). Dynamic Hyperinflation During Bronchoconstriction in Asthma. *Chest*, *130*(4), 1072–1081. https://doi.org/10.1378/chest.130.4.1072

Luckett, T., Phillips, J., Johnson, M. J., Farquhar, M., Swan, F., Assen, T., Bhattarai, P., & Booth, S. (2017). Contributions of a hand-held fan to self-management of chronic breathlessness. *European Respiratory Journal*, *50*(2), 1700262. https://doi.org/10.1183/13993003.00262-2017

Lunn, S., Dharmagunawardena, R., Lander, M., & Sweeney, J. (2019). It's hard to talk about breathlessness: a unique insight from respiratory trainees. *Clinical Medicine*, *19*(4), 344–347. https://doi.org/10.7861/CLINMEDICINE.19-4-344

Magis-Escurra, C., & Reijers, M. H. (2015). Bronchiectasis. *BMJ Clinical Evidence*, *2015*. /pmc/articles/PMC4356176/

Maltais, F., LeBlanc, P., Whittom, F., Simard, C., Marquis, K., Bélanger, M., Breton, M. J., & Jobin, J. (2000). Oxidative enzyme activities of the vastus lateralis muscle and the functional status in patients with COPD. *Thorax*, *55*(10), 848. https://doi.org/10.1136/THORAX.55.10.848

Marchetti, N., Lammi, M. R., Travaline, J. M., Ciccolella, D., Civic, B., & Criner, G. J. (2015). Air Current Applied to the Face Improves Exercise Performance in Patients with COPD. *Lung*, *193*(5), 725–731. https://doi.org/10.1007/S00408-015-9780-0/TABLES/3

Mccarthy, B., Casey, D., Devane, D., Murphy, K., Murphy, E., & Lacasse, Y. (2015). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*, *2015*(2). https://doi.org/10.1002/14651858.CD003793.PUB3/MEDIA/CDSR/CD003793/IMAGE_N/NCD003793-CMP-004-08.PNG

Meriggi, F. (2018). Dyspnea in Cancer Patients: A Well-Known and Neglected Symptom. *Reviews on Recent Clinical Trials*, *13*(2), 84–88. https://doi.org/10.2174/1574887113666180326112116

Mims, J. W. (2015). Asthma: Definitions and pathophysiology. *International Forum of Allergy and Rhinology*, *5*, S2–S6. https://doi.org/10.1002/ALR.21609

Mo, X., Jian, W., Su, Z., Chen, M., Peng, H., Peng, P., Lei, C., Chen, R., Zhong, N., & Li, S. (2020). Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *European Respiratory Journal*, *55*(6). https://doi.org/10.1183/13993003.01217-2020

Molis, M. A., & Molis, W. E. (2010). Exercise-Induced Bronchospasm. *Sports Health*, *2*(4), 311. https://doi.org/10.1177/1941738110373735

Mortola, J. P. (2019). How to breathe? Respiratory mechanics and breathing pattern. *Respiratory Physiology & Neurobiology*, *261*, 48–54. https://doi.org/10.1016/J.RESP.2018.12.005

Murdoch, J. R., & Lloyd, C. M. (2010). Chronic inflammation and asthma. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, *690*(1–2), 24–39. https://doi.org/10.1016/j.mrfmmm.2009.09.005

National Institute for Health and Care Excellence. (2020). COVID-19 rapid guideline: managing the long-term effects of COVID-19. *COVID-19 Rapid Guideline: Managing the Long-Term Effects of COVID-19*. https://www.ncbi.nlm.nih.gov/books/NBK567261/

Nattie, E., & Li, A. (2012). Central Chemoreceptors: Locations and Functions. *Comprehensive Physiology*, *2*(1), 221. https://doi.org/10.1002/CPHY.C100083

Nelsen, L. M., Kimel, M., Murray, L. T., Ortega, H., Cockle, S. M., Yancey, S. W., Brusselle, G., Albers, F. C., & Jones, P. W. (2017). Qualitative evaluation of the St George's Respiratory Questionnaire in patients with severe asthma. *Respiratory Medicine*, *126*, 32–38. https://doi.org/10.1016/J.RMED.2017.02.021

Nopp, S., Moik, F., Klok, F. A., Gattinger, D., Petrovic, M., Vonbank, K., Koczulla, A. R., Ay, C., & Zwick, R. H. (2022). Outpatient Pulmonary Rehabilitation in Patients with Long COVID Improves Exercise Capacity, Functional Status,

Dyspnea, Fatigue, and Quality of Life. *Respiration*, *101*(6), 593. https://doi.org/10.1159/000522118

Oana, S., & Mukherji, J. (2014). *Acute and chronic respiratory failure* (pp. 273–288). https://doi.org/10.1016/B978-0-7020-4086-3.00019-9

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*. https://doi.org/10.3389/fphys.2017.00082

O'Donnell, D. E., Elbehairy, A. F., Faisal, A., Webb, K. A., Neder, J. A., & Mahler, D. A. (2016). Exertional dyspnoea in COPD: the clinical utility of cardiopulmonary exercise testing. *European Respiratory Review*, *25*(141), 333–347. https://doi.org/10.1183/16000617.0054-2016

O'Donnell, D. E., Milne, K. M., James, M. D., de Torres, J. P., & Neder, J. A. (2020). Dyspnea in COPD: New Mechanistic Insights and Management Implications. *Advances in Therapy*, *37*(1), 41. https://doi.org/10.1007/S12325-019-01128-9

O'Driscoll, B. R., Neill, J., Pulakal, S., & Turkington, P. M. (2011). A crossover study of short burst oxygen therapy (SBOT) for the relief of exercise-induced breathlessness in severe COPD. *BMC Pulmonary Medicine*, *11*. https://doi.org/10.1186/1471-2466-11-23

Papadopoulos, N. G., Xepapadaki, P., Mallia, P., Brusselle, G., Watelet, J. B., Xatzipsalti, M., Foteinos, G., Van Drunen, C. M., Fokkens, W. J., D'Ambrosio, C., Bonini, S., Bossios, A., Lötval, J., Van Cauwenberge, P., Holgate, S. T.,

Canonica, G. W., Szczeklik, A., Rohde, G., Kimpen, J., … Johnston, S. L. (2007). Mechanisms of virus-induced asthma exacerbations: state-of-the-art. A GA2LEN and InterAirways document. *Allergy*, *62*(5), 457. https://doi.org/10.1111/J.1398-9995.2007.01341.X

Parshall, M. B., Schwartzstein, R. M., Adams, L., Banzett, R. B., Manning, H. L., Bourbeau, J., Calverley, P. M., Gift, A. G., Harver, A., Lareau, S. C., Mahler, D. A., Meek, P. M., & O'Donnell, D. E. (2012). An Official American Thoracic Society Statement: Update on the Mechanisms, Assessment, and Management of Dyspnea. *American Journal of Respiratory and Critical Care Medicine*, *185*(4), 435. https://doi.org/10.1164/RCCM.201111-2042ST

Parsons, J. P., Craig, T. J., Stoloff, S. W., Hayden, M. Lou, 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 and Asthma Proceedings*, *32*(6), 431–437. https://doi.org/10.2500/AAP.2011.32.3501

Pérez-Herrero, E., & Fernández-Medarde, A. (2015). Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. *European Journal of Pharmaceutics and Biopharmaceutics*, *93*, 52–79. https://doi.org/10.1016/J.EJPB.2015.03.018

Petek, B. J., Tso, J. V, Churchill, T. W., Guseh, J. S., Loomer, G., DiCarli, M., Lewis, G. D., Weiner, R. B., Kim, J. H., Wasfy, M. M., & Baggish, A. L. (2022). Normative cardiopulmonary exercise data for endurance athletes: the Cardiopulmonary Health and Endurance Exercise Registry (CHEER). *European*

Journal of Preventive Cardiology, *29*(3), 536–544. https://doi.org/10.1093/eurjpc/zwab150

Physical activity. (n.d.). Retrieved October 14, 2022, from https://www.who.int/news-room/fact-sheets/detail/physical-activity

Piercy, K. L., Troiano, R. P., Ballard, R. M., Carlson, S. A., Fulton, J. E., Galuska, D. A., George, S. M., & Olson, R. D. (2018). The Physical Activity Guidelines for Americans. *JAMA*, *320*(19), 2020. https://doi.org/10.1001/JAMA.2018.14854

Poulos, L. M., Ampon, R. D., Currow, D. C., Marks, G. B., Toelle, B. G., & Reddel, H. K. (2021). Prevalence and burden of breathlessness in Australian adults: The National Breathlessness Survey—a cross-sectional web-based population survey. *Respirology*, *26*(8), 768–775. https://doi.org/10.1111/resp.14070

Powers, S. K., Lynch, G. S., Murphy, K. T., Reid, M. B., & Zijdewind, I. (2016). Disease-Induced Skeletal Muscle Atrophy and Fatigue. *Medicine and Science in Sports and Exercise*, *48*(11), 2307. https://doi.org/10.1249/MSS.0000000000000975

Pozzi, M., Rezoagli, E., Bronco, A., Rabboni, F., Grasselli, G., Foti, G., & Bellani, G. (2022). Accessory and Expiratory Muscles Activation During Spontaneous Breathing Trial: A Physiological Study by Surface Electromyography. *Frontiers in Medicine*, *9*, 814219. https://doi.org/10.3389/FMED.2022.814219/FULL

Prihartadi, A. S., Impelliziere Licastro, G., Pearson, M., Johnson, M. J., Luckett, T., & Swan, F. (2021). Non-medical devices for chronic breathlessness: use, barriers

and facilitators for patients, carers and clinicians - a scoping review. *BMJ Supportive & Palliative Care*. https://doi.org/10.1136/BMJSPCARE-2021-002962

Psilander, N., Eftestøl, E., Cumming, K. T., Juvkam, I., Ekblom, M. M., Sunding, K., Wernbom, M., Holmberg, H. C., Ekblom, B., Bruusgaard, J. C., Raastad, T., & Gundersen, K. (2019). Effects of training, detraining, and retraining on strength, hypertrophy, and myonuclear number in human skeletal muscle. *Journal of Applied Physiology*, *126*(6), 1636–1645. https://doi.org/10.1152/JAPPLPHYSIOL.00917.2018/ASSET/IMAGES/LARGE/ZDG0061930230007.JPEG

Puspawati, N. L., Sitorus, R., & Herawati, T. (2017). Hand-held fan airflow stimulation relieves dyspnea in lung cancer patients. *Asia-Pacific Journal of Oncology Nursing*, *4*(2), 162–167. https://doi.org/10.4103/APJON.APJON_14_17

Raherison, C., & Girodet, P. O. (2009). Epidemiology of COPD. *European Respiratory Review*, *18*(114), 213–221. https://doi.org/10.1183/09059180.00003609

Reddy, S. K., Parsons, H. A., Elsayem, A., Palmer, J. L., & Bruera, E. (2009). Characteristics and Correlates of Dyspnea in Patients with Advanced Cancer. *Https://Home.Liebertpub.Com/Jpm*, *12*(1), 29–36. https://doi.org/10.1089/JPM.2008.0158

Richeldi, L., Collard, H. R., & Jones, M. G. (2017). Idiopathic pulmonary fibrosis. *The Lancet*, *389*(10082), 1941–1952. https://doi.org/10.1016/S0140-6736(17)30866-8

Román-Rodríguez, M., & Kocks, J. W. H. (2021). Targeting exertional breathlessness to improve physical activity: the role of primary care. *Npj Primary Care Respiratory Medicine 2021 31:1*, *31*(1), 1–7. https://doi.org/10.1038/s41533-021-00254-8

Rubin, B. K., Priftis, K. N., Schmidt, H. J., & Henke, M. O. (2014). Secretory Hyperresponsiveness and Pulmonary Mucus Hypersecretion. *Chest*, *146*(2), 496–507. https://doi.org/10.1378/CHEST.13-2609

Rx for Health Series - Exercise is Medicine. (n.d.). Retrieved June 6, 2023, from https://www.exerciseismedicine.org/eim-in-action/health-care/resources/rx-for-health-series/

Safiri, S., Carson-Chahhoud, K., Noori, M., Nejadghaderi, S. A., Sullman, M. J. M., Ahmadian Heris, J., Ansarin, K., Mansournia, M. A., Collins, G. S., Kolahi, A. A., & Kaufman, J. S. (2022). Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. *BMJ*, *378*. https://doi.org/10.1136/BMJ-2021-069679

Santos, M., Kitzman, D. W., Matsushita, K., Loehr, L., Sueta, C. A., & Shah, A. M. (2016). Prognostic Importance of Dyspnea for Cardiovascular Outcomes and Mortality in Persons without Prevalent Cardiopulmonary Disease: The Atherosclerosis Risk in Communities Study. *PLoS ONE*, *11*(10). https://doi.org/10.1371/JOURNAL.PONE.0165111

Schiaffino, S., Dyar, K. A., Ciciliot, S., Blaauw, B., & Sandri, M. (2013). Mechanisms regulating skeletal muscle growth and atrophy. *FEBS Journal*, *280*(17), 4294–4314. https://doi.org/10.1111/febs.12253

Schmidt, M., Banzett, R. B., Raux, M., Morélot-Panzini, C., Dangers, L., Similowski, T., & Demoule, A. (2014). Unrecognized suffering in the ICU: addressing dyspnea in mechanically ventilated patients. *Intensive Care Medicine*, *40*(1), 1–10. https://doi.org/10.1007/s00134-013-3117-3

Schulz, K. F., Altman, D. G., & Moher, D. (2010). CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *The BMJ*, *340*(7748), 698–702. https://doi.org/10.1136/BMJ.C332

Sepúlveda-Loyola, W., Osadnik, C., Phu, S., Morita, A. A., Duque, G., & Probst, V. S. (2020). Diagnosis, prevalence, and clinical impact of sarcopenia in COPD: a systematic review and meta-analysis. *Journal of Cachexia, Sarcopenia and Muscle*, *11*(5), 1164. https://doi.org/10.1002/JCSM.12600

Shah, A. S., Wong, A. W., Hague, C. J., Murphy, D. T., Johnston, J. C., Ryerson, C. J., & Carlsten, C. (2020). A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations. *Thorax*, *76*(4), 402–404. https://doi.org/10.1136/THORAXJNL-2020-216308

Shah, P. L., Herth, F. J., van Geffen, W. H., Deslee, G., & Slebos, D. J. (2017). Lung volume reduction for emphysema. *The Lancet Respiratory Medicine*, *5*(2), 147–156. https://doi.org/10.1016/S2213-2600(16)30221-1

Shebl, E., Mirabile, V. S., Sankari, A., & Burns, B. (2022). *Respiratory Failure*. https://www.ncbi.nlm.nih.gov/books/NBK526127/

Sheel, A. W., Boushel, R., & Dempsey, J. A. (2018). Competition for blood flow distribution between respiratory and locomotor muscles: implications for muscle fatigue. *Journal of Applied Physiology (Bethesda, Md. : 1985)*, *125*(3), 820–831. https://doi.org/10.1152/JAPPLPHYSIOL.00189.2018

Shiozawa, K., Kashima, H., Mizuno, S., Ishida, K., & Katayama, K. (2022). Blood pressure and coeliac artery blood flow responses during increased inspiratory muscle work in healthy males. *Experimental Physiology*, *107*(9), 1094–1104. https://doi.org/10.1113/EP090504

Simon, S. T., Higginson, I. J., Benalia, H., Gysels, M., Murtagh, F. E. M., Spicer, J., & Bausewein, C. (2013a). Episodes of breathlessness: types and patterns - a qualitative study exploring experiences of patients with advanced diseases. *Palliative Medicine*, *27*(6), 524–532. https://doi.org/10.1177/0269216313480255

Simon, S. T., Higginson, I. J., Benalia, H., Gysels, M., Murtagh, F. E. M., Spicer, J., & Bausewein, C. (2013b). Episodic and Continuous Breathlessness: A New Categorization of Breathlessness. *Journal of Pain and Symptom Management*, *45*(6), 1019–1029. https://doi.org/10.1016/J.JPAINSYMMAN.2012.06.008

Skaarup, S. H., Lonni, S., Quadri, F., Valsecchi, A., Ceruti, P., & Marchetti, G. (2020). Ultrasound Evaluation of Hemidiaphragm Function following Thoracentesis: A Study on Mechanisms of Dyspnea Related to Pleural Effusion. *Journal of Bronchology and Interventional Pulmonology*, *27*(3), 172–178. https://doi.org/10.1097/LBR.0000000000000627

Smallwood, N., Currow, D., Booth, S., Spathis, A., Irving, L., & Philip, J. (2016). Physicians' attitudes to dyspnoea management in advanced chronic obstructive pulmonary disease (COPD). *European Respiratory Journal*, *48*(suppl 60), PA3748. https://doi.org/10.1183/13993003.CONGRESS-2016.PA3748

Smith, A. K., Currow, D. C., Abernethy, A. P., Johnson, M. J., Miao, Y., Boscardin, ‡ W John, & Ritchie, C. S. (2016). Prevalence and Outcomes of Breathlessness in Older Adults: A National Population Study. *J Am Geriatr Soc*, *64*, 2035–2041. https://doi.org/10.1111/jgs.14313

Smith, T. A., Cho, J. G., Roberts, M. M., Swami, V., & Wheatley, J. R. (2022). Hand-held fans: Physical Properties and Perceptions of Patients with COPD. *Journal of Pain and Symptom Management*, *63*(1), e9–e16. https://doi.org/10.1016/J.JPAINSYMMAN.2021.07.006

Soffler, M. I., Hayes, M. M., & Schwartzstein, R. M. (2017). Respiratory Sensations in Dynamic Hyperinflation: Physiological and Clinical Applications. *Respiratory Care*, *62*(9), 1212–1223. https://doi.org/10.4187/respcare.05198

Sokol, K., Sur, S., & Ameredes, B. T. (2014). Inhaled Environmental Allergens and Toxicants as Determinants of the Asthma Phenotype. *Advances in Experimental Medicine and Biology*, *795*, 43. https://doi.org/10.1007/978-1-4614-8603-9_4

Solano, J. P., Gomes, B., & Higginson, I. J. (2006). A Comparison of Symptom Prevalence in Far Advanced Cancer, AIDS, Heart Disease, Chronic Obstructive Pulmonary Disease and Renal Disease. *Journal of Pain and Symptom Management*, *31*(1), 58–69. https://doi.org/10.1016/J.JPAINSYMMAN.2005.06.007

Spathis, A., Booth, S., Moffat, C., Hurst, R., Ryan, R., Chin, C., & Burkin, J. (2017). The Breathing, Thinking, Functioning clinical model: a proposal to facilitate evidence-based breathlessness management in chronic respiratory disease. *Npj Primary Care Respiratory Medicine*, *27*(1), 27. https://doi.org/10.1038/s41533-017-0024-z

Spinelli, E., Mauri, T., Beitler, J. R., Pesenti, A., & Brodie, D. (2020). Respiratory drive in the acute respiratory distress syndrome: pathophysiology, monitoring, and therapeutic interventions. *Intensive Care Medicine*, *46*(4), 606. https://doi.org/10.1007/S00134-020-05942-6

Stevens, J. P., Dechen, T., Schwartzstein, R., O'Donnell, C., Baker, K., Howell, M. D., & Banzett, R. B. (2018). Prevalence of Dyspnea Among Hospitalized Patients at the Time of Admission. *Journal of Pain and Symptom Management*, *56*(1), 15-22.e2. https://doi.org/10.1016/J.JPAINSYMMAN.2018.02.013

Strieder, M., Pecherstorfer, M., & Kreye, G. (2018). Symptomatic treatment of dyspnea in advanced cancer patients: A narrative review of the current literature. *Wiener Medizinische Wochenschrift*, *168*(13–14), 333–343. https://doi.org/10.1007/S10354-017-0600-4/FIGURES/2

Sudre, C. H., Murray, B., Varsavsky, T., Graham, M. S., Penfold, R. S., Bowyer, R. C., Pujol, J. C., Klaser, K., Antonelli, M., Canas, L. S., Molteni, E., Modat, M., Jorge Cardoso, M., May, A., Ganesh, S., Davies, R., Nguyen, L. H., Drew, D. A., Astley, C. M., … Steves, C. J. (2021). Attributes and predictors of long COVID. *Nature Medicine*, *27*(4), 626. https://doi.org/10.1038/S41591-021-01292-Y

Suki, B., Sato, S., Parameswaran, H., Szabari, M. V., Takahashi, A., & Bartolák-Suki, E. (2013). Emphysema and Mechanical Stress-Induced Lung Remodeling. *Physiology*, *28*(6), 404. https://doi.org/10.1152/PHYSIOL.00041.2013

Swan, F., English, A., Allgar, V., Hart, S. P., & Johnson, M. J. (2019). The Hand-Held Fan and the Calming Hand for People With Chronic Breathlessness: A Feasibility Trial. *Journal of Pain and Symptom Management*, *57*, 1051-1061.e1. https://doi.org/10.1016/j.jpainsymman.2019.02.017

Tantucci, C. (2013). Expiratory Flow Limitation Definition, Mechanisms, Methods, and Significance. *Pulmonary Medicine*, *2013*, 1–6. https://doi.org/10.1155/2013/749860

Teunissen, S. C. C. M., Wesker, W., Kruitwagen, C., de Haes, H. C. J. M., Voest, E. E., & de Graeff, A. (2007). Symptom prevalence in patients with incurable cancer: a systematic review. *Journal of Pain and Symptom Management*, *34*(1), 94–104. https://doi.org/10.1016/J.JPAINSYMMAN.2006.10.015

Thomas, S., Bausewein, C., Higginson, I., & Booth, S. (2011). Breathlessness in cancer patients – Implications, management and challenges. *European Journal of Oncology Nursing*, *15*(5), 459–469. https://doi.org/10.1016/J.EJON.2010.11.013

Usmani, O. S., Dhand, R., Lavorini, F., & Price, D. (2021). Why We Should Target Small Airways Disease in Our Management of Chronic Obstructive Pulmonary Disease. *Mayo Clinic Proceedings*, *96*(9), 2448–2463. https://doi.org/10.1016/J.MAYOCP.2021.03.016

van der Molen, T., Willemse, B. W. M., Schokker, S., ten Hacken, N. H. T., Postma, D. S., & Juniper, E. F. (2003). Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health and Quality of Life Outcomes*, *1*, 13. https://doi.org/10.1186/1477-7525-1-13

Van Wessel, T., De Haan, A., Van Der Laarse, W. J., & Jaspers, R. T. (2010). The muscle fiber type–fiber size paradox: hypertrophy or oxidative metabolism? *European Journal of Applied Physiology*, *110*(4), 665. https://doi.org/10.1007/S00421-010-1545-0

Wahls, S. A. (2012). Causes and evaluation of chronic dyspnea. *American Family Physician*, *86*(2), 173–180. https://pubmed.ncbi.nlm.nih.gov/22962929/

Walston, J. D. (2012). Sarcopenia in older adults. *Current Opinion in Rheumatology*, *24*(6), 623–627. https://doi.org/10.1097/BOR.0b013e328358d59b

Webster, L. R., & Karan, S. (2020). The Physiology and Maintenance of Respiration: A Narrative Review. *Pain and Therapy*, *9*(2), 467–486. https://doi.org/10.1007/s40122-020-00203-2

Wenzel, S. E. (2012). Asthma phenotypes: the evolution from clinical to molecular approaches. *Nature Medicine*, *18*(5), 716–725. https://doi.org/10.1038/nm.2678

Wilcock, A., Crosby, V., Hughes, A., Fielding, K., Corcoran, R., & Tattersfield, A. E. (2002). Descriptors of breathlessness in patients with cancer and other cardiorespiratory diseases. *Journal of Pain and Symptom Management*, *23*(3), 182–189. https://doi.org/10.1016/S0885-3924(01)00417-1

Witte, K. K., & Clark, A. L. (2007). Why does chronic heart failure cause breathlessness and fatigue? *Progress in Cardiovascular Diseases*, *49*(5), 366–384. https://doi.org/10.1016/j.pcad.2006.10.003

Wong, S. L., Leong, S. M., Chan, C. M., Kan, S. P., & Cheng, H. W. B. (2017). The Effect of Using an Electric Fan on Dyspnea in Chinese Patients With Terminal Cancer. *The American Journal of Hospice & Palliative Care*, *34*(1), 42–46. https://doi.org/10.1177/1049909115615127

Worsham, C. M., Banzett, R. B., & Schwartzstein, R. M. (2020). Air Hunger and Psychological Trauma in Ventilated Patients with COVID-19. An Urgent Problem. *Annals of the American Thoracic Society*, *17*(8), 926–927. https://doi.org/10.1513/AnnalsATS.202004-322VP

Yin, L., Li, N., Jia, W., Wang, N., Liang, M., Yang, X., & Du, G. (2021). Skeletal muscle atrophy: From mechanisms to treatments. *Pharmacological Research*, *172*, 105807. https://doi.org/10.1016/J.PHRS.2021.105807

8.0. APPENDIX

8.1. Appendix A

Ethical approval by Research Ethics Committee.

WoSRES

NHS Greater Glasgow and Clyde

Dr Flavia Swan
Research fellow
University of Hull
Wolfson Palliative Care Research Centre
Hull York Medical School
University of Hull, Hull
HU6 7RX

West of Scotland REC 4
Research Ethics
Clinical Research and Development
Dykebar Hospital
Grahamston Road
Paisley
PA2 7DE

Date 14 October 2021
Direct line 0141 314 0214
E-mail WoSREC4@ggc.scot.nhs.uk

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

Dear Dr Swan

Study title:	**FAN Facial Airflow Recovery from Exercise - Patient Trial (FANFARE-P)**
REC reference:	**21/WS/0102**
IRAS project ID:	**300915**

Thank you for your letter of 01 October 2021, responding to the Research Ethics Committee's (REC) request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a Sub-Committee of the REC. A list of the Sub-Committee members is attached.

Confirmation of ethical opinion

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

Good practice principles and responsibilities

The UK Policy Framework for Health and Social Care Research sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of research transparency:

1. registering research studies
2. reporting results
3. informing participants
4. sharing study data and tissue

Conditions of the favourable opinion

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

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

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

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

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

Registration of Clinical Trials

All research should be registered in a publicly accessible database and we expect all researchers, research sponsors and others to meet this fundamental best practice standard.

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant. For this purpose, 'clinical trials' are defined as the first four project categories in IRAS project filter question 2. Failure to register a clinical trial is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/

If you have not already included registration details in your IRAS application form, you should notify the REC of the registration details as soon as possible.

Further guidance on registration is available at: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/transparency-responsibilities/

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter.

Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/

N.B. If your study is related to COVID-19 we will aim to publish your research summary within 3 days rather than three months.

During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you haven't already done so, please register your study on a public registry as soon as possible and provide the REC with the registration detail, which will be posted alongside other information relating to your project. We

are also asking sponsors not to request deferral of publication of research summary for any projects relating to COVID-19. In addition, to facilitate finding and extracting studies related to COVID-19 from public databases, please enter the WHO official acronym for the coronavirus disease (COVID-19) in the full title of your study. Approved COVID-19 studies can be found at: https://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/

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

After ethical review: Reporting requirements

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

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report
- Reporting results

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites taking part in the study, subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management permission (in Scotland) being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

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

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [FANFARE P clinical trials insurance]		19 July 2021
GP/consultant information sheets or letters [FANFARE P GP letter]	1.0	25 June 2021
IRAS Application Form [IRAS_Form_29072021]		29 July 2021
Letter from sponsor [FANFARE P sponsor letter]		23 July 2021
Participant consent form [FANFARE P Consent form]	1.1	23 September 2021
Participant information sheet (PIS) [FANFARE P Patient Information Sheet]	1.1	23 September 2021
Research protocol or project proposal [FANFARE P Trial Protocol]	1.0	25 June 2021
Response to Request for Further Information [Fanfare P REC cover letter]		01 October 2021
Summary CV for Chief Investigator (CI) [FANFARE P Chief Investigator cv]		02 July 2021

Statement of compliance

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

User Feedback

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

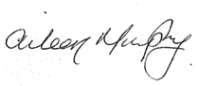
HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS project ID: 300915 Please quote this number on all correspondence

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

Yours sincerely

p.p. 

Dr Ken James
Chair

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to: Katie Skilton, University of Hull

West of Scotland REC 4

Attendance at Sub-Committee of the REC meeting

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Wendy Cohen	Speech & Language Therapist	Yes	(Alternate Vice Chair)
Dr Sean MacBride-Stewart	Medicines Management Resources Lead for Pharmacy Services	Yes	
Dr Christine Milligan	Retired - Pharmaceutical Industry	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Aileen Murphy	REC Assistant

Approval of ethics amendment by Research Ethics Committee.

Amendment Tool v1.6 06 December 2021	For office use QC: No

Section 1: Project information

Short project title*:	FANFARE-P Trial
IRAS project ID* (or REC reference if no IRAS project ID is available):	300915
Sponsor amendment reference number*:	Amendment_01 - Substantial
Sponsor amendment date* (enter as DD/MM/YY):	14 February 2022
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	The main changes are; 1. We are changing to ONE handheld fan that will be used to deliver FOUR different airflow sppeds to the participants in the study. The change reflects that we have had technical and reliablity problems with the modified fan models stated in the ethics application. We have therefore changed to a different handheld fan model which has not been modified by engineering and has passed PAT testing 2. We are requesting a 6 month extension on the recruitment period from 28.02.2022 to 30.08.2022 as we will not be starting recruitment until ethical approval is received for the change of fan model used in the study. The change of fan means that participants will perform five sit to stand tests , one less than previously stated. 3. We are requesting that Thomas Burrell, MSc Student researcher is added to the research team members as his details were missed out on the ethics application and he will be helping with collecting the data from participants under the supervision of the research team.

Project type (select):	**Specific study**			
	Research tissue bank			
	Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	**Yes**		No	
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	**NHS/HSC REC**			
	Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a **modified amendment** (i.e. a substantial amendment previously given an unfavourable opinion)?	Yes		**No**	
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	Yes	No	No	No
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	Yes		**No**	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	Yes		**No**	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	Yes		**No**	
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	Yes		**No**	
Did the study involve adults lacking capacity OR does the amendment introduce this?:	Yes		**No**	
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this?:	Yes		**No**	
Did the study involve prisoners or young offenders who are in custody or supervised by the probation service OR does the amendment introduce this?:	Yes		**No**	
Did the study involve children OR does the amendment introduce this?:	Yes		**No**	
Did the study involve NHS/HSC organisations prior to this amendment?:	**Yes**		No	
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	Yes		**No**	
	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	**Yes**	No	No	No
Which nations had participating NHS/HSC organisations prior to this amendment?	**Yes**	No	No	No
Which nations will have participating NHS/HSC organisations after this amendment?	**Yes**	No	No	No
Was this a "single site, self sponsored" study in England or Wales prior to this amendment?	Yes		**No**	

Section 2: Summary of change(s)

Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the Amendment Tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, click the "Add another change" box.

Change 1					
Area of change (select)*:	Study Design				
Specific change (select - only available when area of change is selected first)*:	Other significant change to study design that can be implemented within existing resource in place at participating organisations - Please specify in the free text below				
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	Change from the 2 handheld fan models specified in the ethics application to 1 handheld fan model that is a different design and delivers 4 airflow speeds. The cost of the new fan is covered by the funding for the study and will be loaned to the participating organisation.				
Applicability:		England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:		**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):		**All**		Some	
				Remove all changes below	

Change 2					
Area of change (select)*:	Participant Procedures				
Specific change (select - only available when area of change is selected first)*:	Participant procedures - significant change that can be implemented within existing resource at participating organisations - Please specify in the free text below				
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	The new handheld fan delivers 4 airflow speeds therefore the participant will be performing 5 sit to stand tests in total rather than 6 (4 with airflow delivered after and 1 with no airflow, control). The change of handheld fan also means that we will change the airflow preference questions so we will ask participants about the 4 airflow speeds from the new handheld fan and which of 3 different fan models they like the most. This minor change can be implemented as the research team members are conducting the precedures and data collection from the participants at the participating organisation				
Applicability:		England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:		**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):		**All**		Some	
				Remove all changes below	

Change 3					
Area of change (select)*:	Study Design				
Specific change (select - only available when area of change is selected first)*:	Extension to study duration that will not have any additional resource implications for participating organisations - Please specify in the free text below				
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	6 month extension on the recruitment period from 28.02.22 to 30.08.22. This change can implemented as the research team members are responsible for all of the participant data collection at the participating organisation.				
Applicability:		England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:		**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):		**All**		Some	
				Remove all changes below	

Change 4	
Area of change (select)*:	Researchers
Specific change (select - only available when area of change is selected first)*:	Other - Please specify in the free text below
Further information (free text - note that this field will adapt to the amount of text entered):	Request to add Thomas Burrell, MSc student at University of Hull to the research team members as his name was omitted from the IRAS ethics application

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	

Add another change

Section 3: Declaration(s) and lock for submission

Declaration by the Sponsor or authorised delegate

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

*Name [first name and surname]**:	Katie Skilton
*Email address**:	researchgovernance@hull.ac.uk

Lock for submission

Please note: This button will only become available when all mandatory (*) fields have been completed. When the button is available, clicking it will generate a locked PDF copy of the completed amendment tool which must be included in the amendment submission. Please ensure that the amendment tool is completed correctly before locking it for submission.

Lock for submission

After locking the tool, proceed to submit the amendment online. The "Submission Guidance" tab provides further information about the next steps for the amendment.

Section 4: Review bodies for the amendment

Please note: This section is for **information only**. Details in this section will complete automatically based on the options selected in Sections 1 and 2.

	Review bodies																	
	UK wide:						England and Wales:				Scotland:				Northern Ireland:			
	REC	Competent Authority MHRA - Medicines	Competent Authority MHRA - Devices	ARSAC	Radiation Assurance	UKSW Governance	REC (MCA)	CAG	HMPPS	HRA and HCRW Approval	REC (AWIA)	PBPP	SPS (RAEC)	National coordinating function	HSC REC	HSC Data Guardians	Prisons	National coordinating function	Category:
Change 1:	Y					Y				Y									C
Change 2:	Y					Y				Y									C
Change 3:	N					(Y)				(Y)									C
Change 4:	N					Y				Y									A
Overall reviews for the amendment:																			
Full review:	Y					Y				Y									
Notification only:	N					N				N									
Overall amendment type:	Substantial																		
Overall Category:	A																		

Ethical approval by Hull York Medical School ethics committee.

Hull York Medical School

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30 June 2021

Dr Flavia Swan
Research Fellow
Hull York Medical School

Dear Flavia

21 37 – Fan Facial Airflow Recovery from Exercise: FANFARE Trial Protocol

Thank you for submitting your application to the HYMS Ethics Committee. The application has been reviewed on behalf of HYMS Ethics Committee with respect to the documents received on 25th June 2021.

I am pleased to inform you that I do not have any HYMS specific ethical concerns and am happy to confirm HYMS Ethics approval.

On behalf of the Ethics Committee, we wish you success with this study.

Kind regards

Yours sincerely

Professor Thozhukat Sathyapalan
Chair
HYMS Ethics Committee

Approval of ethics amendment by Hull York Medical School ethics committee.

Hull York Medical School

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8th February 2022

Dr Flavia Swan
Research Fellow in Cancer Rehabilitation
Hull York Medical School

Dear Flavia,

21 37 - Fan Facial Airflow Recovery from Exercise Patient Trial (FANFARE-P)

Thank you for submitting your amended application to the HYMS Ethics Committee. The amendments have been reviewed on behalf of HYMS Ethics Committee with respect to the documents received on 3rd February 2022.

I am pleased to inform you that I do not have any HYMS specific ethical concerns and am happy to confirm HYMS Ethics approval.

On behalf of the Ethics Committee, we wish you success with this study.

Kind regards

Yours sincerely

Professor Thozhukat Sathyapalan
Chair
HYMS Ethics Committee

NHS
Hull University Teaching Hospitals
NHS Trust

HULL YORK MEDICAL SCHOOL

PARTICIPANT INFORMED CONSENT FORM

Fan Facial Airflow Recovery from Exercise (FANFARE)

IRAS Study Number: 300915 **Name of Researchers:** Flavia swan, Miriam Johnson

Please initial the boxes

1. I confirm that I have read and understood the information sheet dated 28.02.22, version 1.2, 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 that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of any of my medical notes and data collected during this study may be looked at by responsible individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data. ☐
4. I agree that anonymised research data gathered from the study can be used for up to five years by authorised researchers from the University of Hull working on similar studies. ☐
5. I agree that a thermal image of the cheek area of my face can be recorded and an anonymous picture (eyes blocked out) can be used in presentations or publications arising from this project ☐
6. I agree that anonymised research data gathered from the study can be used in presentations or publications arising from this project ☐
7. I agree to my GP/hospital consultant being informed of my participation in the study. ☐
8. I agree to take part in the above study ☐

Name of participant	**Date**	**Signature**
_____	_____	_____

Name of verbal consent witness	**Date**	**Signature**
_____	_____	_____

Name of person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	**Date**	**Signature**
_____	_____	_____

When completed, 1 for patient; 1 for researcher file; 1 (original) to be kept in patient notes

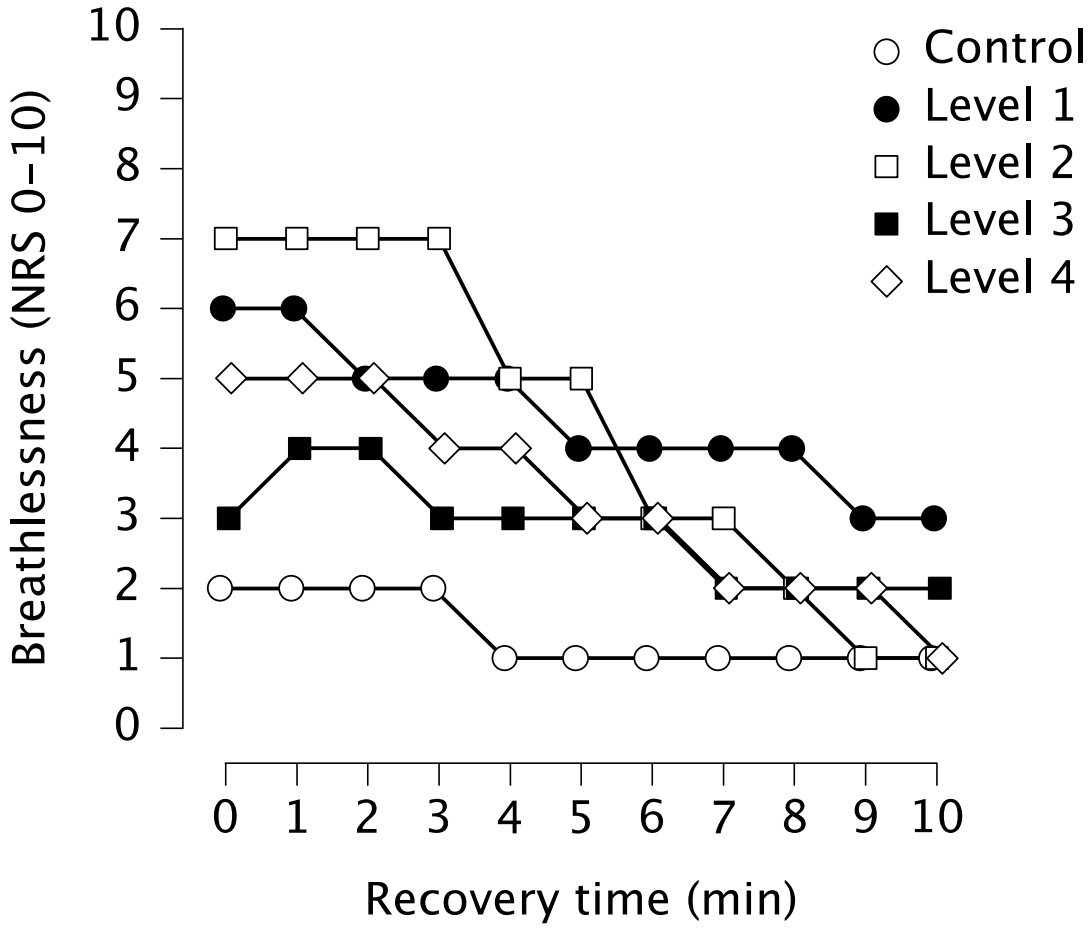
8.2. Appendix B

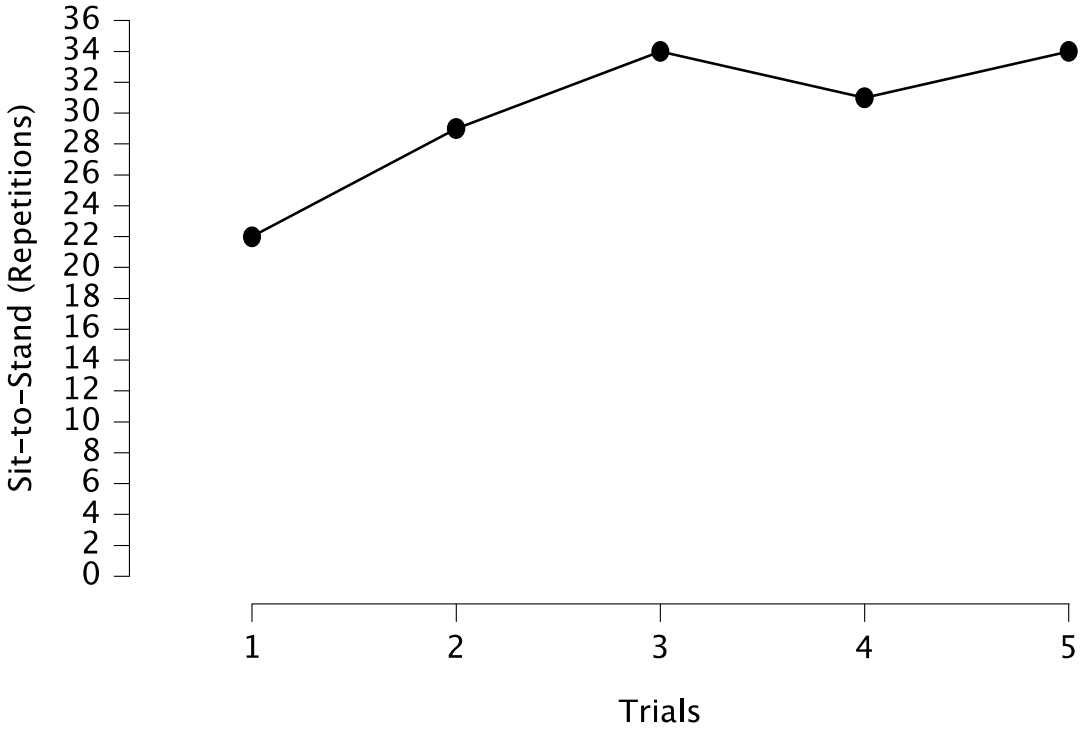
Sensitivity analysis and justification for removal of n=1 participants

n=1 participant was excluded post-analysis due to limited exertional breathlessness displayed following the 1-minute sit-to-stand tests. The first figure depicts the NRS breathlessness score outcomes of the trials following an intervention order of control, level 3, level 1, level 4, and level 2.

The second figure displays the participants' performance during the 5 sit-to-stand tests. It is anticipated the participant was reserved in their efforts during the initial sit-to-stand efforts causing low exertion-induced breathlessness. The participants’ results indicate a 31.82% increase from the first (22 repetitions) and second (29 repetitions) efforts. As well as a 54.55% increase from the first effort to the maximal effort (34 repetitions).

The table displays the statistical analysis outcome when including all participants (n=9). Following the rmANOVA for breathlessness recovery, a change in the interaction effect for fan speed over time ($F(40,320)=1.243$, $p=0.158$, $\eta p2=0.134$) occurred.


Breathlessness (NRS 0–10)
0
1
2
3
4
5
6
7
8
9
10
Control
Level 1
Level 2
Level 3
Level 4
0 1 2 3 4 5 6 7 8 9 10
Recovery time (min)


Sit-to-Stand (Repetitions)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
1 2 3 4 5
Trials

Within Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
Fan Speed	6.053	4	1.513	0.248	0.909	0.003	0.030
Residuals	195.184	32	6.099				
Time	1768.642	10	176.864	45.877	< .001	0.733	0.852
Residuals	308.412	80	3.855				
Fan Speed ✻ Time	18.125	40	0.453	1.243	0.158	0.008	0.134
Residuals	116.638	320	0.364				

Note. **Type III Sum of Squares**

8.3. Appendix C

Patient field notes summarised into themes relating to the handheld fan and exercise test.

Comment Section	Subsection	Emergent themes	Summarised Comments
Fan	Control	Recovery with no fan was perceived to be the worst recovery. Patients labelled control experience as uncomfortable.	• Worst perceived recovery • Dislike • Uncomfortable • Heavier breathing
	Level 1	Presence of low airflow speed was beneficial, however, limited in effectiveness as patients felt the airflow speed was unsatisfactory for their recovery needs.	• Presence of airflow helped • Not enough airflow • High intensity breathlessness wouldn’t be helped by lvl 1
	Level 2	Patients preferred this airflow speed, allowing for a perceived faster recovery compared to the rest.	• Max 10 minutes of airflow due to the cooling effect • Wasn't an uncomfortable airflow • Patient perceived a faster recovery • Effortless breathing
	Level 3	Mixed themes from level 3, patients found the airflow comfortable. However, higher speed meant patients were fighting against the airflow resulting in different breathing techniques being applied.	• "comfortable" • fighting against the airflow (mouth breathing)

	Level 4	Difficult airflow speed to manage. Patients struggled and felt suffocated during level 4, with 1 early stoppage. High airflow speed was causing adverse symptoms. Potential positives were the perception of widening of airways to assist the intake of air.	• "Hard to breathe" • “Uncomfortable” (n=2) • “forcing you into a deeper breath and holding it” • Either didn’t find it uncomfortable/liked airflow speed n=2 • Cold airflow caused headaches and a runny nose • Fighting against airflow • Perception of “widening of airways”
	Experience	Breathing techniques followed pulmonary rehab methods using the nose inhale then mouth exhale. Higher airflow speeds caused adaptations in technique to exhale through nose to combat the larger airflow force to the mouth region.	• Control / Level 1 / Level 2 followed inhalation through nose and exhale through mouth (n=3). • Level 3 followed inhale through mouth, exhale through nose. • Level 4 followed ‘inhalation through nose and exhale through nose’ OR ‘Inhalation through mouth and exhale through nose’
Exercise test	Exercise test appeared limited by patients’ muscle or joint capacity rather than breathlessness symptom. Breathlessness only became apparent towards the later stages or upon completion.		• No breathlessness present during the exercise test (n=2) • Patient felt breathless towards the end of STS test (n=2) • Limited exercise test performance due to muscular fatigue, hip and or knee restriction (n=2)

8.4. Appendix D

Consort checklist used for reporting the study.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

CONSORT 2010 checklist *Page 1*

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

8.5. Appendix E

Table shows the comparison between STS repetitions and corresponding maximal exertional breathlessness in participants (n=9).

	STS Test Performance (repetitions per minute)		**NRS Breathlessness Score (0-10)**		
STS Trial	Mean	± SD	Mean	± SD	Minimum / Maximum
1st	17.778	3.632	5.667	2.000	2 / 9
2nd	18.667	5.745	6.556	2.297	3 / 10
3rd	19.333	7.036	7.000	1.732	4 / 10
4th	19.667	6.265	6.889	1.764	4 / 10
5th	20.222	6.906	6.889	1.691	4 / 10