PROTOCOL

The development of a walking test to measure shortness of breath in cardiopulmonary disease

Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC *National Statement on Ethical Conduct in Human Research (2007) – Updated May 2015*, NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2007)* and the *Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95)*.

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STUDY SYNOPSIS

Title:	The development of a walking test to measure shortness of breath in cardiopulmonary disease
Short Title:	Measuring exertional breathlessness with the Dyspnea Challenge
Study sites where project will take place:	The Prince Charles Hospital, Chermside. Griffith University, Gold Coast Campus. Bundaberg Health Promotions, Bundaberg.
Study Objectives:	1. To evaluate breathlessness achieved during the 6MWT a surrogate for the dyspnea challenge test. 2. To determine whether we alter the sensitivity of the dyspnea challenge test by altering the grade of treadmill. 3. To compare the metabolic and dyspnea data between differing cardiopulmonary diseases. 4. To assess the responsiveness of the dyspnea challenge to changes in exertional dyspnea experienced post an acute intervention and exercise rehabilitation programs (Pulmonary and Heart Failure rehabilitation programs).
Study Design:	Prospective, randomised, controlled, single-blind trial
Study Outcome Measures:	Cardiopulmonary function, exertional breathlessness (dyspnea), test sensitivity, test responsiveness and cardiac function.
Study Population:	30 moderate-severe COPD patients (GOLD I-IV) 30 heart failure patients (NYHA I-III) 30 pulmonary hypertension (WHO I-III)
Number of participants:	90
Translation to Changes in Clinical Practice:	The results of this study will contribute to the current body of knowledge relating to measuring exertional breathlessness within patient populations. Results will identify whether the dyspnea challenge can be used to test changes in ED in patient groups and validate the use of the dyspnea challenge to assess ED in these patient populations.
Key Ethical and Safety considerations:	Physical risk, pain or discomfort during activity or other adverse responses associated with the outcome measurements.

i. ***Glossary of Abbreviations, Terms, and Acronyms***

Abbreviation, Term, Acronym	Definition (using lay language)
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise testing
EACPR	European Association for Cardiovascular Prevention and Rehabilitation
DH	Dynamic Hyperinflation
ED	Exertional Breathlessness
EFL	Expiratory Flow Limitation
EELV	End Expiratory Lung Volume
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GU	Griffith University
IC	Inspiratory Capacity
TPCH	The Prince Charles Hospital
HREC	Human Research Ethics Committee
PICF	Patient information and consent form
QoL	Quality of life
GCHPRP	Gold Coast Health Pulmonary Rehabilitation Program
TPCHPRP	The Prince Charles Hospital Pulmonary Rehabilitation Program
6MWT	Six-minute walk test
ADL	Activity of daily living
MDP	Multidimensional Dyspnea Profile
SGRQ	St George Respiratory Questionnaire
NIRS	Near-infrared spectroscopy

- ***Background***

The American Thoracic Society (ATS) defines dyspnea, or breathlessness, as "a subjective experience of unpleasantness and discomfort that is associated with breathing"[1]. Dyspnea occurring during physical activity is known as exertional dyspnea (ED). It is a common symptom of chronic heart and lung disease which inhibits quality of life and impacts the frequency and intensity of physical activity/exercise routines. It is important to note that dyspnea also occurs in health, especially within individuals who are overweight, deconditioned and are aged[2].

As dyspnea is subjective, reported perceptions of this symptom differ in their sensation. Currently, it is recognised that there are three distinct sensations of respiratory discomfort that can be identified using specific descriptors. The feelings are; air hunger, work/effort and tightness. Air hunger refers to an uncomfortable urge to breathe, the kind that is experienced at the end of long breath-hold. Descriptors often used to identify air hunger are "I'm starved for air", "I'm not getting enough air" and are often accompanied by emotional factors such as "frightening" and "like I was going to die". Work/effort sensation is often described as "breathing is difficult", "breathing takes a lot of work", "breathing takes effort". This sensation occurs when there is a self-perceived increase in the effort of breathing. Finally, chest tightness is described as "chest is restricted" or "chest feels tight" and is thought to be unique to asthma sufferers[3].

Individuals with chronic disease, such as chronic obstructive pulmonary disease (COPD)[4, 5], chronic heart failure (CHF)[6, 7] and pulmonary hypertension (PH)[8, 9], all suffer from exertional dyspnea, that which occurs during activity, at levels of exertion in which an age-matched control would not. Regarding the distinct sensations, different chronic diseases can be associated with specific sensations. For example, individuals suffering from COPD often select the sensation of work/effort using descriptors such as "my breathing requires more effort or work." Currently, there is no single physiological correlate that can accurately predict exertional dyspnea. Generally, this is because the overall mechanisms that contribute to dyspnea can vary not only between chronic diseases but also between individuals who have been diagnosed with the same condition[10].

Physiologically, it is accepted that ED originates due to an imbalance between ventilatory demand and ventilatory capacity. Specifically, exertional dyspnea may arise through two neurophysiological pathways; 1) a discriminative process that identifies relevant afferent information on respiratory abnormalities and brings them to consciousness and 2) affective processing that labels the short and long-term sensation as unpleasant or threatening[11-13]. The exact origin of these two pathways within differing cardiopulmonary disease is not yet known, this is in part due to the use of inappropriate protocols, the use of a multitude of measurements within studies that have made data comparison difficult, or through the use of measurements that were not designed to specifically measure exertional dyspnea. It is essential to be able to measure ED within patient populations to 1) individually assess potential mechanisms behind each patient's ED symptoms 2) to be able to test and monitor changes in ED pre vs. post interventions and 3) to be able to identify specific mechanisms within a cardiopulmonary group to tailor interventions or treatments.

While there is no 'gold standard' measure of ED, it is most commonly assessed at rest, either by using questionnaires that ask individuals to rate their ED intensity retrospectively; or by performing field-based exercise tests in which ED is not the primary measure and workload is poorly controlled. These limitations are found in routinely used tests, such as the six-minute

walk test (6MWT), restricting the ability to measure change in ED pre vs. post-intervention. The 6MWT is used routinely in both clinical and research settings to assess an individual's functional capacity as it is inexpensive, reproducible, responsive to standardisation and replicates the everyday activity of daily living (ADL) of walking at a self-paced intensity[14]. The 6MWT has routinely been used to assess ED in clinical research with the use of one of the scales from appendices table 1, often the modified BORG (0-10 scale)[15]. Unfortunately, the 6MWT, although a staple in clinical assessment, has been criticised when used for assessing ED. Firstly, the 6MWT is not designed to measure ED; instead, its primary outcome is six-minute walk distance (6MWD), a measure of functional capacity[16], and secondly as stated by Perrault et al. [17]., not standardising the walking speed limits the evaluation of treatments during repeated tests. This is highlighted in Pepin et al [18] in which the 6MWD did not show a significant change after bronchodilation (Δ in distance 7m, $p>0.005$) despite a significant difference in FEV_1 of 0.18±0.09L pre vs. post-intervention, ($p=<0.001$), whereas a set paced exercise test did with a similar change in FEV_1 of 0.18±0.12L (Δ in distance 144m, $p=0.03$).

To date there appears to be only a small body of research aimed to specifically develop an exercise test with the primary outcome of measuring ED. These studies have focused on developing short, activity-specific protocols which will elicit ED such as 3 minutes of stepping/walking or upper limb routines designed for people with lower-limb limiting factors. Collectively, these tests have similar issues; firstly, the premise of each design is to regulate workload better, but each test relies heavily on the ability of the participants to coordinate their arm/leg speed with an audio player which may not be appropriate for every individual. A protocol utilising a treadmill, where workload may by regulated with better accuracy, may be more suitable. Secondly, ED is measured discretely at the beginning and end of each 3/5-minute bout of exercise. Although a typical method of recording dyspnea in other field tests (6MWT), evidence exists on the benefit of continually measuring dyspnea during exercise; these include; allowing for the spontaneous changes in ED to be collected and a large number of data to be recorded[19]. Continuous methods of collecting ED scores have been used in more recent research[20]. Finally, the tests do not replicate the activity in which people are most symptomatic, namely; climbing stairs or walking uphill [21-24].

Considering the above limitations Morris et al. [25] recently developed a two-minute treadmill dyspnea challenge in which participants walk at a given speed at an individualised gradient. The aim was to evaluate its repeatability and sensitivity using a high (mean rate: mean gradient of 4.0±0.6km/h^{-1}: 10±2%) and a low (rate: mean gradient of 4.0±0.6km/h^{-1}: 6±2%) intensity challenge. The speed was set at 80% of the 6MWT speed and ED was measured continuously using a digital 0-10 scale. They concluded that the dyspnea challenge test is safe, repeatable and sensitive to change in ED. A small sample size is the biggest limitation of this work so far and further study is needed to confirm these findings. The aim of the current research is to continue the development of the dyspnea challenge within COPD patients not only to test its ability to measure ED in a patient population but also to assess the sensitivity of the protocol to changing intensities of exercise. Furthermore, the dyspnea challenge will undergo pre and post intervention testing, both for an acute and longer term interventions, to assess its validity.

- ***Study Objectives***

  - **Aims**

The overarching aim of the current study is to develop a 2-minute walk treadmill test to evaluate dyspnea. The primary aims are to assess:

i. the relationship between 6MWD and exertional dyspnea scores within a 6MWT when compared against exertional dyspnea scores recorded during the dyspnea challenge.
ii. the sensitivity of the dyspnea challenge to changes in exertional dyspnea via changes to the gradient of the treadmill.
iii. Compare the exertional dyspnea response to the dyspnea challenge in heart failure, pulmonary hypertension and COPD.
iv. To assess the responsiveness of the dyspnea challenge to changes in exertional dyspnea experienced post an acute intervention and exercise rehabilitation programs (Pulmonary and Heart Failure rehabilitation programs).

Secondary aims, of the study, will be:

v. To compare the metabolic cost of the 6MWT and the dyspnea challenge.
vi. To compare the metabolic cost of the dyspnea challenge between cardiopulmonary disease populations.
vii. Establish a minimally important difference (MID) for the dyspnea challenge.

  - **Hypotheses**

It is hypothesised that:

i. Those who walk the furthest will have lower exertional dyspnea scores during the 6MWT.
ii. Exertional dyspnea will increase with an increase in gradient of the dyspnea challenge.
iii. There will be differences between the two tests; there will be no-steady state response in the dyspnea challenge when compared to the 6MWT, a higher peak VO_2 response and a marked difference in oxygen saturation.
iv. The dyspnea challenge is able to detect both acute and longer term changes in exertional dyspnea as a result of interventions.

- ***Methods***

a. Study Design

The research study will be a prospective, randomised, controlled, single-blind trial (Fig. 1). This is a multi-centre study where the outcome measurements will be conducted at The Prince Charles Hospital, Griffith University, Gold Coast Campus, Bundaberg Health Promotions and Central Queensland University, Bundaberg Campus. Ethics approval will be sought before commencement from the Metro North Health HREC B and Griffith University (GU) Human Research Ethics Committees (HREC).

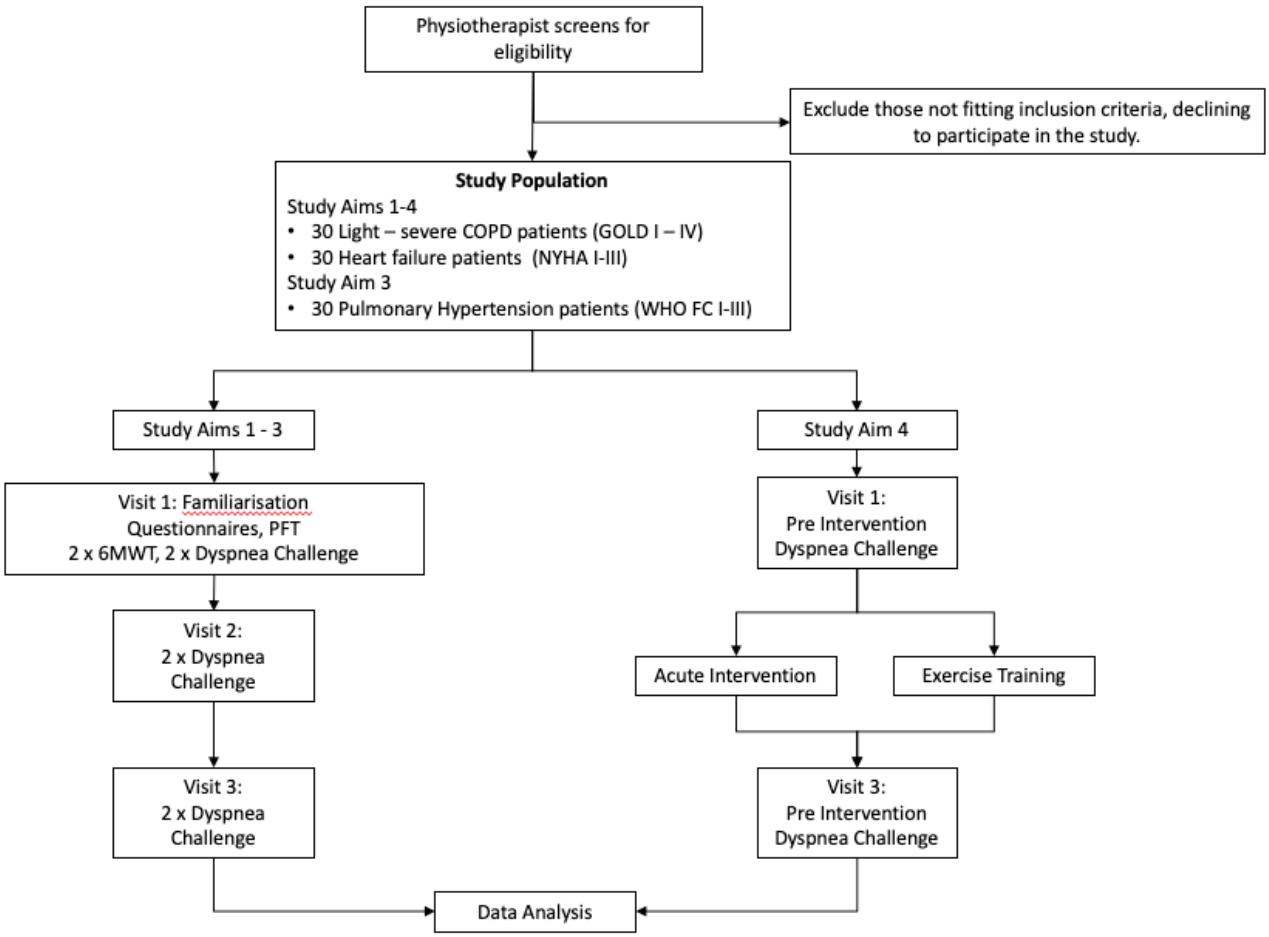

Figure. 1: Study schematic

b. Study Setting

The study will be undertaken at the TPCH, GU Gold Coast Campus, Bundaberg Health Promotions and Central Queensland University Bundaberg Campus. Participants will be recruited from the Gold Coast University Hospital, The Prince Charles Hospital and Bundaberg Health Promotions. Data collection will take place at: Griffith University Gold Coast Campus (GO2, 2.41 or G40 4.16), the Prince Charles Hospital rehabilitation gymnasium, Bundaberg Health Promotions gymnasium or Central Queensland University Bundaberg campus (building 1, Physiotherapy gymnasium). The principle researchers at the Prince Charles Hospital are: Mr Craig Aitken (Exercise Science), Professor Norman Morris (Physiotherapist), Ms Tanya Palmer (Physiotherapist) and Dr James Walsh (Physiotherapist). At Bundaberg Health Promotions: Ms Tanya Palmer (Physiotherapist), Dr Martin Strahan (Medical Doctor). At Central Queensland University: Ms Tanya Palmer. At Griffith University: Professor Norman Morris, Dr Surendran Sabapathy (Exercise Physiology), Mr Craig Aitken, Dr Glenn Stewart (Exercise Science). At the Gold Coast University Hospital: Dr Sivakumaran (Medical Doctor Respiratory Medicine) and Ms Menaka Louis (Physiotherapist).

c. Study Population

Thirty individuals with COPD, thirty with heart failure and thirty with pulmonary hypertension will be recruited into the study if they meet the following criteria:

- A known diagnosis COPD, heart failure or pulmonary hypertension.
- Completed the Gold Coast Health pulmonary or cardiac rehabilitation Program.
- Completed the Prince Charles Hospital pulmonary or cardiac rehabilitation Program.
- Completed the Bundaberg Health Promotions cardiac or pulmonary rehabilitation program.
- Are clinically stable and are on firm, optimised respiratory or cardiac therapy for six weeks before enrolment.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD) categories I-IV.
- New York Heart Association (NYHA) for Heart Failure categories I-III.
- World Health Organisation (WHO) for Pulmonary Hypertension categories I-III.
- Aged ≥ 18 years old.

Exclusion Criteria:

- Musculoskeletal disorders that prevent walking on the treadmill.
- Significant co-morbidities that would exclude exertional exercise or any contraindications to exercise as defined by the American College of Sports Medicine.
- Oxygen therapy that would exclude the wearing of portable metabolic cart.
- Chest wall binder Part C of study only - Extensive cardiac history and/or untreated high blood pressure.

d. Recruitment and Consent

- Individuals with COPD, heart failure and pulmonary hypertension will be recruited from the Gold Coast University Hospital, The Prince Charles Hospital and Bundaberg Health Promotions cardiac or pulmonary rehabilitation program.
- Those recruited from the Gold Coast University Hospital site will complete data collection at the Griffith University Gold Coast campus exercise science laboratories. Those recruited from The Prince Charles Hospital site will complete the study on-site in the physiotherapy gym. Those recruited from the Bundaberg Health Promotions rehabilitation program will undertake data collection at either the on-site gymnasium facility or Central Queensland University, Bundaberg campus physiotherapy laboratories.
- Any individual deemed appropriate for the study will be approached by the treating physiotherapist to be made aware of the study. If interested, a researcher will explain the study in more detail. Interested individuals will then be screened against the inclusion criteria. Those who meet the eligibility criteria and are interested in participating in the research will be provided with the participant information sheet, which includes the contact information of the research team, by the treating clinician.
- If the potential participant wishes to participate, one of the study investigators will discuss the study with the potential participant via the informed consent process.
- Once all information has been given a participant will be given a cooling-off period of 48 hours to consider participation if required. Participants will also be assured of withdrawal rights even after informed consent has been obtained.
- The consent process will be respectful and acknowledge the cultural and linguistic diversity of the participants, as well as various levels of understanding and literacy issues. Provisions will be put in place including the use of an interpreter service for participants

whose primary language is other than English. We will also adapt our explanations and provide support with conveying the content of the participant information and consent form to cater for various levels of understanding and literacy issues.

a. Participant confidentiality

Information will be stored during the research project in paper copy format (i.e. medical records, investigation reports, research paperwork) in a regulatory binder and electronic format (i.e. excel spreadsheet on hard drive). Only site staff (i.e. principal and co-investigators) will have direct access to medical records and study-specific related documentation. This information will be stored in locked cabinets in a secure location at TPCH, Central Queensland University or GU all of which require 24-hour key card access. Information will be stored in electronic format on computers with site-specific security precautions, i.e. password-protected database on a password-protected computer in a secure office within TPCH, Central Queensland University and GU.

Once the relevant data has been extracted and linked, the electronic data will have all identifiable information removed so that the data file that is to be analysed and stored will be non-identifiable. A copy of the non-identifiable data file will be provided to other members of the research team at GU, TPCH, Bundaberg Health Promotions and Central Queensland University so that they can assist with the data analysis, which will be securely deleted once the analysis and reporting phase of the research study is completed. The study information will be kept for a minimum of 5 years post completion of the study as per the NHMRC guidelines.

Results obtained from the study will be presented to all participants in a written report. All data will be represented as group averages, and no participant will be able to be identified. Participants will also be able to access any published documents resulting from the project.

b. Participant safety

There is a potential risk of participants experiencing an adverse event or reaction with the outcome measurements and exercise tests during the study. These may include angina, presyncope or syncope, dysrhythmias, physical pain or discomfort, and musculoskeletal injury. This risk is inherent with undertaking any exertional activities including the outcome measures such as the six-minute walk test and the dyspnea challenge. However, these risks will be mitigated by ensuring a comprehensive assessment and screening of participants and close monitoring during the outcome measurements. We will only use participants who have been medically cleared to complete a rehabilitation program and have been deemed safe to exercise by their medical team. We will also adhere to the standard precautions and contraindications for exercise testing in COPD, heart failure and pulmonary hypertension patients as per the ERS and ATS guidelines[26, 27]. All investigators have completed basic life support and first aid training in addition, there will be at least one investigator trained in the use of oxygen and defibrillation present or near-by. The settings for data collection (Prince Charles Physiotherapy gymnasium and Griffith University G40 Laboratories 1.16, Central Queensland University, building 1 Physiotherapy and Bundaberg Health Promotion rehabilitation gymnasium) are equipped with medical oxygen and an automated defibrillator. The supervisors of the project are highly experienced in supervising exercise tests in chronic disease.

Adverse events during the study will be determined as outlined by the National Health and Medical Research Council (NHMRC, 2016) definition, i.e. “Any untoward medical occurrence

in a patient or clinical trial participant administered a medicinal product, and that does not necessarily have a causal relationship with this treatment" (26). The participant will also be monitored for any adverse reactions as per the NHMRC (2016) definition, i.e. "Any untoward and unintended response to an investigational medicinal product related to any dose administered" (26). In addition, serious adverse events or adverse reactions will be defined as "Any adverse event/adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity" (NHMRC, 2016) (26). The adverse event log document will be used to keep a detailed record of such incidences, with appropriate action taken as required. All serious adverse events will be reported to all associated HRECs within 24 hours.

c. Participant withdrawal from the study

Participants will be advised that they may withdraw from the study at any time without any implications for their care or relationship with the. The participant will be requested to notify us, if possible, prior to withdrawing from the study and to complete the 'Participant Withdrawal of Consent Form' as part of the PICF. Participants will also be withdrawn from the study if they have a significant adverse event or change in their medical status and it is deemed unsafe for them to continue with the investigation. At the time of withdrawal, it will be ascertained from the participant whether they will allow the continued collection and use of their information by the researchers. If they do not permit this, their data will be securely disposed or deleted from the data file.

d. Study Procedure

Participants may be required to complete all three parts of this study, there are a total of nine visits over the three parts. Visits 1-3 will address question one and investigate the ability of the 6MWT and its outcome measure of six-minute walk distance (6MWD) to act as a surrogate measure of exertional dyspnea (ED). The secondary outcomes are to non-invasively monitor cardio-pulmonary factors to compare the metabolic costs of both tests and compare this across disease population. Visits 4-6 will address question two and consider the sensitivity of the dyspnea challenge in heart and lung disease groups by asking individuals to perform the dyspnea challenge at differing gradients ranging from 3 to 8%. Visits 7-9 will address question four and secondary aim seven to assess the responsiveness of the dyspnea challenge in heart and lung disease groups by asking individuals to perform the dyspnea challenge pre and post an intervention that has proven to increase or decrease dyspnea. There will be an acute challenge using a chest wall binder that will be applied only to COPD participants which is known to increase dyspnea and then a longer term intervention being that of Pulmonary and Heart Failure Rehabilitation which is known to improve dyspnea in the COPD and HF populations. Participants will complete two dyspnea challenges pre and post the exercise rehabilitation programs which will be completed outside of this study. Participants included in the acute challenge part of the study will complete the dyspnea challenge in random order on two separate visits with and without a chest wall binder fitted.

Part A:

Visit 1 – Familiarisation will be split into three parts; 1) participant information/consent and health assessment, 2) pulmonary function testing (PFT) and 3) exercise testing. 1) Participants will enter the laboratory and the full extent of the study, both part A, B and C, will be explained with the aid of the information sheet. If the participant is happy to proceed, voluntary consent will be obtained followed by the completion of a health screening assessment and the St George Respiratory questionnaire (SRGQ) for COPD participants or Kansas City Cardiomyopathy Questionnaire for heart failure participants, the medical research council (mMRC) questionnaire, Dyspnoea-12 questionnaire, and a hospital anxiety and depression (HADS) questionnaire to summarise the impact of disease and dyspnea on their overall health status. 2) PFT – resting blood pressure and forced spirometry (Medikro Spirostar 2000, Medikro Oy, Kuopio, Finland) will be measured according to standard protocols[28]. 3) familiarisation testing will be performed for both a six-minute walk test (6MWT) and the 2-minute dyspnea challenge (DC). Each subject will be informed of the safety precautions, including criteria for safely terminating an exercise test (per the American College of Sports Medicine Guidelines for Exercise Testing and Prescription, 2009).

The 6MWT will be performed using a standardised protocol [29]. Participants will walk along a long, flat, straight, temperature-controlled corridor on a course measuring 30 metres. The turnaround points will be marked by black tape along the floor. Each participant will be asked to walk as far as possible with only standardised encouragement given. Pulmonary gas exchange (Metamax, Cortex BXB, Lepzig, Germany), cardiac output (PhysioFlow, Manatec Biomedical, Paris, France), and muscular tissue oxygen saturation of the gastrocnemius (PortaMon Artinis Medical Systems, Einsteinweg, The Netherlands) will be monitored continuously throughout the protocol. After each minute, the severity of dyspnoea, (modified 0-10 Borg Scale), heart rate and forehead oxygen tissue saturation (RAD-5v Masimo Corp, Irvine, CA, USA) will be recorded. At the end of the test, sensory and affective measures of ED will be assessed using a Multidimensional Dyspnea Profile (MDP)[30].

The DC will be performed be on a treadmill in a temperature-controlled laboratory. Participants will walk on a treadmill for 2-minutes at a speed of 3km/h^{-1} and a gradient of 4%. Perrault *et al*., [17] found that 93% of patients suffering from moderate-severe COPD managed to complete a 3-minute walk test at 1.5km/h on a flat surface and that only 84% managed to complete the test at 2.5km/h. The gradient selected was chosen as previous research in 8 participants with mild COPD managed to achieve a 2-minute challenge at between 4-6% gradient[25]. Electrocardiogram (ECG), Heart rate (HR) and oxygen saturation (SpO_2) will be monitored continuously using a portable saturation monitor (RAD-5v Masimo Corp, Irvine, CA, USA). Ratings of ED will be participant self-reported every 10 seconds using a 0-10 Numerical Rating Scale (NRS) on a PC-based system with a computer monitor mounted in front of the treadmill. Pulmonary gas exchange (Metamax, Cortex BXB, Lepzig, Germany), cardiac output ($\dot{Q}$) (PhysioFlow, Manatec Biomedical, Paris, France) and muscle tissue oxygen saturation (MtO_2) (PortaMon Artinis Medical Systems, Einsteinweg, The Netherlands) will be monitored continuously. At the end of the test, sensory and affective measures of ED will be assessed using the MDP[30].

Visit 2 and 3 – During these two visits, participants will perform 2x6MWT and 2xDC. These tests will be performed in a randomised order with 30 minutes of rest in between. 1x6MWT and 1xDC will be performed as above with the same equipment and measures assessed. The other two tests they will be performed without the pulmonary gas exchange measures being assessed. This is to negate the impact of the face mask on self-perceived ratings of exertional dyspnea. During these two tests, ECG, $\dot{Q}$, MtO_2, HR, SpO_2, and blood pressure will be monitored as above. At the end of each test the MDP will be performed.

Part B:

Visit 4-6 – During these visits' participants will perform 6xDC at various gradients of between 3-8% at a speed of 1.5km/h as above. These will be performed in a randomised order. During each test ECG, $\dot{Q}$ (PhysioFlow, Manatec Biomedical, Paris, France), HR and SpO_2 (RAD-5v Masimo Corp, Irvine, CA, USA) will be monitored continuously throughout the test. Ratings of ED will be participant self-reported every 10 seconds using a 0-10 Numerical Rating Scale (NRS) on a PC-based system with a computer monitor mounted in-front of the treadmill. At the end of each test, as per previous tests, the MDP will be completed to assess the sensory and affective components of ED.

Part C:

Visit 7 and 8 (COPD Participants Only) – Will be completed prior to commencing Pulmonary or Heart Failure Rehabilitation programs (chronic intervention, Figure 1) and the wearing of chest wall binders will only be completed by COPD participants (acute intervention, Figure 1). During these visits participants will be asked to complete 2x DCs per visit. Each test will be completed wearing a forehead oximeter to measure heart rate, rhythm and arterial oxygen saturation. Two of the four DC tests participants will wear a chest wall binder. These four tests will be performed in a random order. At the end of each test participants will be asked to complete the MDP.

Visit 9 – Will be completed after the completion of Pulmonary or Heart Failure Rehabilitation programs by participants. During this visit participants will be asked to complete 2xDC. Each test will be completed wearing a forehead oximeter to measure heart rate, rhythm and arterial oxygen saturation. At the end of each test participants will be asked to complete the MDP and TDI questionnaires.

e. Outcome Measures

1. Primary outcome measure:
   a. Dyspnea (ED) –
      - Modified Borg 0-10 Scale - A common measure taken during field-based testing. This will be measured using a 0-10 scale and does not involve any invasive procedures. This 0-10 scale has been used previously within COPD patients during the dyspnea challenge[25].
      - *Multidimensional Dyspnea Profile (MDP)*: The MDP contains 11 items which participants rate on a continuous scale (0-10) and a forced-choice question for five sensory qualities [31]. The profile is split into three subsections; Sensory Dimension (SQ), Breathing Discomfort (A1) and Emotional Response (A2)[30]. This has been previously validated within clinical settings[32].
      - *Dyspnea*-12: A 12 descriptor item questionnaire that provides an overall score for breathlessness severity that matches the participants breathing 'these days'. It incorporates seven physical items and five affective items. Frequently used at baseline and during follow-up assessments[33].
      - *Baseline and Transition Dyspnoea Index (BDI/TDI):* The BDI/TDI measures the severity of breathlessness at the beginning of an intervention (BDI) then again at the end of the intervention (TDI). The questionnaire is comprised of three subsections; Functional Impairment, Magnitude of Task and Magnitude of Effort. This has been previously validated within clinical settings[34].
   b. Functional capacity
      - *Six-minute walk distance (6MWD):* the maximum distance walked in six minutes during the six-minute walk test (6MWT). The 6MWT is used routinely in clinical settings due to its simplicity and relatively short execution time. This will be conducted at either the Prince Charles Hospital or Griffith University by a physiotherapy clinician or exercise scientist.
2. Secondary outcome measures:
   c. Exercise capacity
      - *Cardiopulmonary factors* – Metabolic data will be collected during one 6MWT and one Dyspnea Challenge. All tests will be completed under supervision by an exercise scientist, medical professional and/or qualified physiotherapist.
   d. Central Hemodynamic responses
      - *Physio Flow:* during both the 6MWT and dyspnea challenge Q, HR and SV will be recorded continuously at rest, exercise and in recovery by the Physio Flow device at a frequency of 5s. Six electrodes will be placed on all subjects, two on the eft carotid (Z1 and Z2), two in the breast area (EKG1 and EKG2) and two in the chest area (Z3 and Z4 – EKG3). The validity of the Physio Flow in a COPD population has been shown previously [35]

e. Impact of disease

- *St. George Respiratory Questionnaire (SGRQ)*: is a reliable and valid measure of quality of life within a COPD population. It is a 50-item questionnaire that has two parts. Part 1 assesses the frequency and severity of symptoms with a 1,3 or 12month recall period. Part 2 refers to the activities that cause or are limited by breathlessness. These will be performed at both sites during the study.
- *Kansas City Cardiomyopathy Questionnaire (KCCQ-12*): has validity and sensitivity to capture the impact of heart failure on patients' lives and is strongly associated with clinical events over time. It has a 2-week recall period on symptoms associated with heart failure. Includes 7 domains; symptom frequency, symptom burden, symptom stability, physical limitations, social limitations, quality of life and self efficacy.

f. Skeletal muscle oxidative capacity

- *Near-infrared spectroscopy (NIRS):* is a non-invasive and fairly inexpensive method for measuring skeletal muscle blood flow and oxidative metabolism [36]. Measurements on the vastus lateralis muscle will be performed as previously described [37]. This will be conducted at the exercise testing laboratory in GO2 building at Griffith University's Gold Coast campus.

f. Data Analysis

As subjects act as their own controls, a repeated measures Analysis of Variance statistic will be used for quantitative (physiological) data. All tests will be of a 2-within factor design: time and experimental condition. Dyspnea scores will be measured in the same way. Any non-normal distributed data, highlighted by variance ratio tests, will have a non-parametric Kruskal-Wallis test being applied. Post-hoc analysis will be conducted on any statistically significant data identified post study. Questionnaire data will be analyzed using a Wilcoxon signed rank test. For other comparisons, descriptive statistics alone will be used. Data may be further explored using appropriate parametric or non-parametric correlation statistics. All statistical tests will be done with SPSS software with a significance threshold of $P<0.05$.

g. Translation to Changes in Clinical Practice

The primary aims for this study are to assess whether 6MWD is an adequate surrogate measure of exertional dyspnea and to assess the ability of the dyspnea challenge to monitor changes in dyspnea scores during increasing resistance of exercise. Clinically, exertional dyspnea is measured using poorly controlled or inadequate tests. Providing a test, that can be used clinically, that will induce exertional dyspnea and monitor changes in this symptom, allow for the individualised mechanisms and treatments to be effectively examined. Information gathered from such a test will allow for the creation of individualised symptom management strategies. With a resulting improvement in dyspnea symptoms and an increase in physical activity. Furthermore, this study answers the call for a challenge to be created in which allows for extended physiological factors to be measured allows for a comprehensive physiological characterisation for those who may have close to normal pulmonary function scores.

It is intended that the results from this study will be published in a peer reviewed journal. Results will also be disseminated locally within the relevant departments; The Prince Charles Hospital, Bundaberg Health Promotions, Central Queensland University and Griffith University. It is

proposed that the results will be presented at a respiratory or cardiac conference, although the conference has not been decided upon.

h. Timeline

An updated timeline for the study is provided (Fig. 2) to outline timeframes for ethics submission and approval, participant recruitment, intervention period, outcome measurements, data analysis and write up.

i. Funding

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	Nov 2022	Dec 2022	Jan 2023	Feb 2023	Mar 2023	Apr 2023	May 2023	Jun 2023	Jul 2023	Aug 2023	Sep 2023	Oct 2023	Nov 2023	Dec 2023	Jan 2024	Feb 2024
Ethics submission and approval																
Participant recruitment and baseline measurements																
Data analysis and write-up																

Fig. 2: Study timeline

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