High-Flow Oxygen for Exertional Dyspnea in Cancer Patients

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A. STUDY OBJECTIVES

A.1. Primary Objective. Obtain preliminary estimates of the effect size of oxygen and high flow rate on exertional dyspnea (modified Borg Scale adjusted for work rate and baseline dyspnea). Our *working hypothesis* is that a high flow rate and oxygen will be associated with lower levels of exertional dyspnea than will the control during structured exercise sessions in cancer patients.

A.2. Secondary Objective #1. Determine the completion rate of a randomized controlled trial of exertional dyspnea in cancer patients. Our *working hypothesis* is that at least 80% of patients will participate in the structured exercise sessions until they experience volitional fatigue and complete all dyspnea study assessments.

A.3. Secondary Objective #2. Obtain preliminary estimates of the effects of oxygen and flow rate on physiologic function (respiratory rate and oxygen saturation) and exercise capacity (work rate and exercise duration). Our *working hypothesis* is that oxygen and high flow rate will improve physiologic function and exercise capacity.

B. BACKGROUND AND SIGNIFICANCE

B.1. Dyspnea is defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity."(Parshall *et al.* 2012) It occurs in approximately 10%-70% of cancer patients and is one of the *most feared* symptoms (Solano *et al.* 2006, Tishelman *et al.* 2007). More than 80% of patients with dyspnea have breakthrough episodes, particularly with physical exertion (Reddy *et al.* 2009). Dyspnea is associated with decreased function, quality of life, and survival (Maltoni *et al.* 2005). The *pathophysiological features* of dyspnea are shown in Figure 1. The sensory cortex receives afferent input from various peripheral and central stimuli,

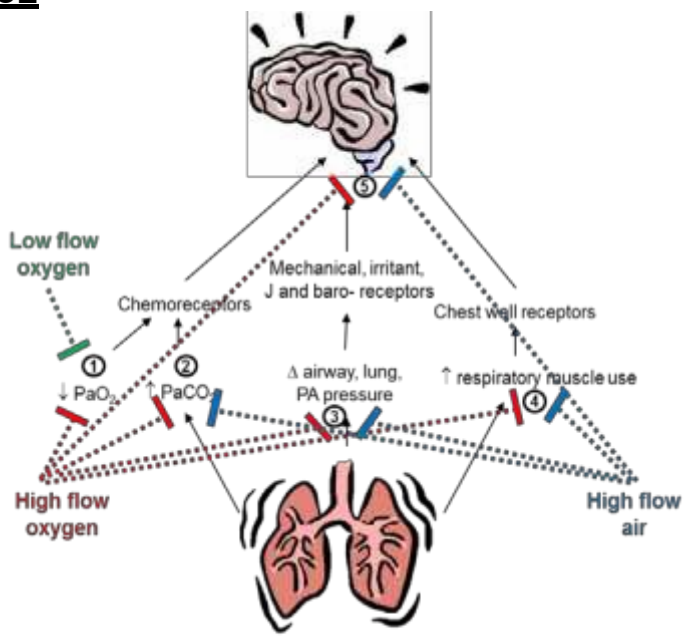

Figure 1. Conceptual Framework for Dyspnea and Potential Mechanisms of Action of High Flow Oxygen. High flow (red) and low flow (green) oxygen are postulated to relieve dyspnea by (1) providing PaO_2 mediated inhibition of dyspnea sensors. Both high flow oxygen (red) and high flow air (blue) may decrease the sensation of shortness of breath by (2) improving ventilation by nasopharyngeal washout, (3) providing positive distending pressure, (4) reducing the work of breathing through improved airway compliance and heated air, and (5) stimulating the trigeminal/glossopharyngeal nerves.

generating the sensation of breathlessness (Mahler 2011, Parshall *et al.* 2012). Parenchymal metastasis, lymphangitic carcinomatosis, airway obstruction, pleural effusion, pneumonia, pulmonary embolism, and atelectasis may cause difficulty breathing in the context of progressive cancer.

The *current management* of dyspnea involves treating any reversible causes and providing supportive measures. Systemic opioids are effective for dyspnea relief (Jennings *et al.* 2002). Low-flow supplemental oxygen (up to 5 L/min) has also been found to be effective, but only in patients with hypoxemia (Bruera *et al.* 1993, Cranston *et al.* 2008). The current method of supplemental oxygen delivery using nasal prongs and non-re-breather masks is limited because these modalities can only deliver limited oxygen flow and are uncomfortable. These impracticalities, coupled with their lack of effectiveness at relieving dyspnea in non-hypoxemic cancer patients, indicate a need for more effective oxygen delivery methods for dyspnea (Ben-Aharon *et al.* 2008, Viola *et al.* 2008). The proposed research is expected to provide new insights into the therapeutic role of HFOx for exertional dyspnea.

B.2. High-flow oxygen is an innovative heat and humidification device that can deliver oxygen at a rate of up to 40 L/min via nasal prongs. The device is postulated to relieve dyspnea by maintaining a level of P_aO_2 superior to that of LFOx, which may decrease and inhibit the activation of dyspnea chemoreceptors (Figure 1). The high-flow mechanism, whether delivering oxygen or air, may also improve ventilation (Dewan and Bell 1994), augment end-distending pressure (Locke *et al.* 1993), reduce nasopharyngeal inspiratory resistance (Dysart *et al.* 2009), and stimulate the trigeminal and glossopharyngeal nerves (Figure 1). The inhalation of heated and humidified gas may also decrease bronchoconstriction, improve airway conductance (Fontanari *et al.* 1997), and reduce the metabolic cost of gas conditioning (Dysart *et al.* 2009). *Because of these novel mechanisms, we hypothesize that HFOx and HFAir will relieve dyspnea in patients who are not included in the traditional target population (i.e., patients with hypoxemia), including those with normal oxygen saturation.* This non-hypoxemic population makes up a large proportion of cancer patients with dyspnea (Hui *et al.* 2013b). To our knowledge, to date, no study has specifically evaluated HFOx for dyspnea in non-hypoxemic cancer patients, nor has anyone studied the therapeutic role of HFAir in any patient population.

B.3. High-flow supplemental oxygen improved dyspnea in hypoxemic cancer patients (Hui *et al.* 2013a). We recently conducted the first randomized controlled trial comparing HFOx and bilevel positive airway pressure (two hours each) in advanced cancer patients with refractory dyspnea. Twenty-four of 30 (80%) patients completed the study interventions, suggesting

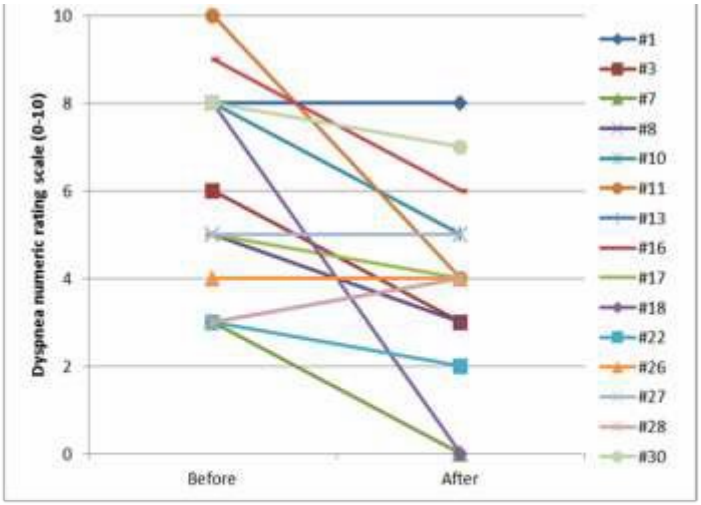

Figure 2. Improvement in Dyspnea Before and after high flow oxygen (N=15)

that a study of these two devices is feasible in this patient population. HFOx (mean change, 1.9; 95% CI, 0.4-3.4; P=0.02) was associated with significant improvements in dyspnea (Figure 2). Remarkably, two patients who completed HFOx reported low dyspnea scores (≤2 of 10) up to 1 hour after discontinuing use of the devices. This observation is of particular interest because the mechanical effect of HFOx on breathing effort may have a long-lasting effect on dyspnea. Overall, 10 of 13 (77%) patients who completed HFOx reported dyspnea improvement, with none experiencing significant adverse effects. Of note, this study was conducted in patients who were predominantly hypoxemic (93%) and did not respond to LFOx. *These data support the feasibility of conducting a clinical trial with HFOx in cancer patients and provide preliminary evidence of its efficacy*. *Importantly, HFOx and HFAir have not been formally tested in non-hypoxemic patients, which is why the proposed trial is particularly novel.*

B.4. Low-flow supplemental oxygen for non-hypoxemic cancer patients (Bruera *et al.* 2003). In a double-blind, randomized trial, we found that LFOx at 5 L/min did not improve dyspnea during a 6-minute walk compared with LFAir at 5 L/min. *The results of this important study highlight the lack of efficacy of LFOx for exertional dyspnea in non-hypoxemic patients and the need to evaluate novel treatment options (i.e., HFOx and HFAir).*

B.5. Study rationale. We expect to advance our understanding of how HFOx can be used to treat exertional dyspnea in non-hypoxemic cancer patients. The effective management of dyspnea may ultimately help *alleviate this devastating symptom*. By elegantly dissecting the high-flow mechanism from the oxygen content and capturing changes in physiologic parameters, we will gain a better understanding of the mechanisms that help alleviate dyspnea and *devise newer, more effective treatments*.

This contribution will be significant because it represents a *key step in a continuum of research* that is expected to lead to the optimization of HFOx delivery and thus relieve exertional dyspnea in cancer patients and improve their *quality of life*. In the current proposed study, HFOx, HFAir, LFOx, and LFAir will be administered during cardiopulmonary exercise testing. If the preliminary results of this randomized phase II study demonstrate that oxygen or high flow rate affect dyspnea intensity, the next step will be to conduct a larger multi-institutional, randomized controlled trial that is adequately powered to compare HFOx with a control intervention, particularly in the home setting. This would be a logical extension of the proposed study because the use of HFOx has predominantly been limited to the hospital setting. The technology that allows this device to be used at home in an affordable manner is just now becoming available (i.e., Flowrest device). Once the efficacy of HFOx is confirmed, patients will have *much more access* to this therapeutic measure. The proposed study has the

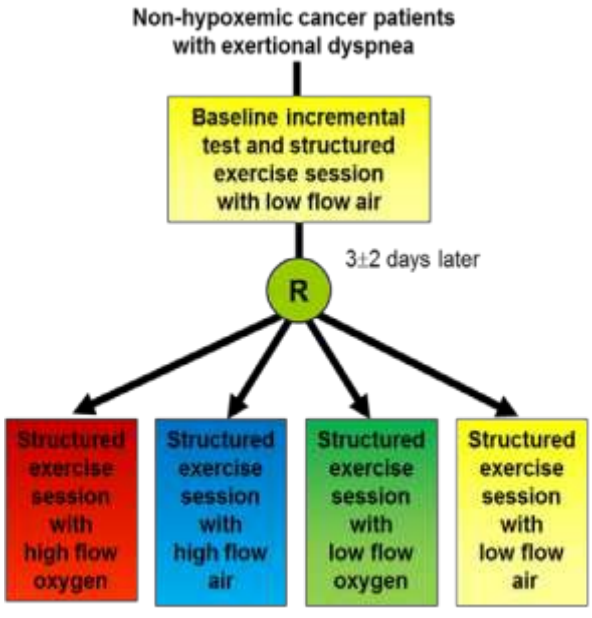

Figure 3. Study Flow Chart.

potential to greatly improve patients' symptom burden, function, and quality of life.

C. RESEARCH DESIGN AND METHODS

C.1. Overall study design (Figure 3). This is a 2x2-factorial, double-blind, randomized, controlled trial of HFOx, HFAir, LFOx, and LFAir in non-hypoxemic cancer patients with dyspnea. We plan to enroll 50 patients in total. Enrolled patients will first complete a baseline structured exercise session with LFAir and return 3±2 days later to be randomly assigned to receive one of the four study interventions during the second structured exercise session. We will use a computer-generated sequence in permuted blocks for randomization, stratified by baseline dyspnea modified Borg Scale and work rate. Even with 2 different flow rates, patients and research staff will be blinded to the gas (i.e., oxygen v. air); thus, this will remain a double-blind study. On the basis of our experience conducting symptom control trials, we believe this study design is feasible and will not be an undue burden for patients. The rationale for the current study design is as follows:

- **Factorial design**—This will allow us to examine the oxygen and high flow effects separately while providing preliminary data about synergism between oxygen and flow.
- **Parallel design**—This design will minimize study burden and attrition compared with a crossover study that requires 5 exercise sessions. We will adjust for inter- individual differences by accounting for both baseline dyspnea score and maximal work rate.
- **Baseline exercise sessions on day 1**—Patients will first complete an incremental exercise test to familiarize themselves with the cycle ergometer and to identify their maximal work rate. They will then complete a structured exercise session with cycle ergometry at a constant work rate of 80% peak with LFAir, which will inform us of their dyspnea response and isotime.
- **Use of LFAir at baseline test**—Neither LFAir nor LFOx has been found to improve dyspnea in non-hypoxemic patients. This will address the placebo effect with nasal cannula use.
- **Inclusion of HFOx and HFAir arms**—To our knowledge, HFOx has not been tested in non-hypoxemic cancer patients. No study has examined the therapeutic role of HFAir in any patient population.
- **Inclusion of LFOx arm**—Although LFOx was found to be ineffective compared with LFAir during the 6-minute walk test, its utility has not been tested with cycle ergometry in cancer patients.
- **Stratification**—To minimize the possibility that baseline dyspnea and exercise performance will affect the outcome, we will stratify patients by this baseline dyspnea modified Borg Scale score at rest (0-3/10 vs. 4-7/10; >7/10 will be excluded) and by their work rate during the first structured exercise session (≤50 W vs. >50 W). The objective of stratified randomization is to ensure a balance of the treatment groups with respect to the various combinations of predictive variables (i.e., the baseline Borg scale and work rate). This will ensure that a similar number of patients from each strata are randomly assigned to each treatment arm but will not require a similar number of patients in each strata. Thus, stratification should not affect the enrollment rate.

C.2. Eligibility criteria. The eligibility criteria are shown in Table 1. The rationale for including patients with obstructive and restrictive lung disease in this study is that the mechanisms of dyspnea relief (e.g., trigeminal nerve stimulation and decreased breathing effort; see Figure 1) are applicable to both types of pulmonary disorder. To ensure homogeneity in the study population and patient safety, we will exclude patients with severe obstructive airway disease (FEV1/FVC <70% post bronchodilator and forced expiratory volume in 1 second <30% predicted).

Table 1. Study Eligibility Criteria

Inclusion Criteria

1. Diagnosis of cancer, with evidence of primary or secondary lung involvement
2. Average dyspnea Borg Scale ≥4 of 10 with severe exertion over the past week
3. Oxygen saturation >90% on ambient air at time of assessment
4. Able to communicate in English or Spanish
5. Karnofsky performance status ≥50%
6. Age ≥18 years
7. Seen at Supportive Care, cardiopulmonary center, thoracic radiation oncology or thoracic medical oncology

Exclusion Criteria

1. Resting dyspnea modified Borg Scale >7 of 10 at enrollment
2. Severe obstructive lung disease (FEV1/FVC <70% post bronchodilator and forced expiratory volume in 1 second <30% predicted)
3. Delirium (i.e., Memorial delirium rating scale >13)
4. History of unstable angina or myocardial infarction in the last week
5. Acute pulmonary embolus or pulmonary infarction in the last week
6. Thrombosis of lower extremities in the last week
7. Acute myocarditis, pericarditis, or endocarditis in the last week
8. Symptomatic aortic stenosis or syncope in the last week
9. Suspected dissecting aneurysm
10. Severe untreated resting arterial hypertension (>200 mmHg systolic, >120 mmHg diastolic) at the time of enrollment
11. Uncontrolled arrhythmias causing symptoms or hemodynamic compromise in the last week
12. Uncontrolled heart failure in the last week
13. Pleural effusion requiring thoracentesis within 1 week of study enrollment or scheduled during the study period
14. Airway obstruction requiring stenting within 1 week of study enrollment or scheduled during the study period
15. Pneumonia requiring antibiotics at the time of study enrollment

C.3. Screening and recruitment. Patients attending our supportive care, thoracic oncology, or cardiopulmonary outpatient clinics will be screened for this study. A two-step consent process will be used. First, verbal consent will be obtained by the study staff before screening potential participants to determine their eligibility. Outpatients may be contacted by phone within 1 week prior to their scheduled clinic visit to inform them of the study so that they can make the necessary arrangements to participate. Eligible patients will be formally enrolled in the study after they have signed the informed consent form indicating their willingness to participate in the trial. Once enrolled, the research staff will work with the patient to identify the 2 ideal study days. We will document the number of patients who are screened, approached, eligible, enrolled, and randomized for the study and the number who complete it. Patients' reasons for

declining to participate will also be captured.

Our clinic has 3 physicians who are supported by a fully staffed interdisciplinary team and who see a mean of 30 patients (8-10 new consults) per day, 5 days per week. One of the physicians is embedded in the thoracic medical oncology clinic and routinely receives referrals for dyspnea.

We will document recruitment and retention rates and reasons that patients dropout. We expect that at least 80% of patients will participate in the structured exercise sessions until they experience volitional fatigue and complete all dyspnea study assessments. Because patients have to make 2 extra visits to MD Anderson for study assessment, we will provide an honorarium of $50 gift card/study day for a total of $100 over 2 study days. We will also provide patients a parking voucher at each study visit as reimbursement for their parking costs (up to 2 vouchers total).

C.4. Randomization. Patient randomization will be performed using the Clinical Trial Conduct website (https://biostatistics.mdanderson.org/ClinicalTrialConduct), which is maintained by the Department of Biostatistics at MD Anderson. The trial statistician will train the respiratory therapists in the use of this website for randomizing patients. We will use a computer-generated sequence in permuted blocks to randomize patients, in a 1:1 ratio, to the two treatment interventions (high flow vs. low flow and oxygen vs. air). To minimize the possibility that baseline dyspnea and exercise performance will affect the outcome, we will stratify patients by baseline dyspnea modified Borg Scale score at rest (0-3/10 vs. 4-7/10) and by work rate during the first structured exercise session (≤50 W vs. >50 W).

C.5. Study interventions. Highly trained respiratory therapists will use the Optiflow Respiratory Humidifier (Fisher & Paykel Healthcare, Inc, Irvine, CA, USA) to deliver HFOx. This device was approved by the U.S. Food and Drug Administration in 2007 (K033710) to add “moisture to, and to warm, the breathing gases for administration to a patient. Gases available for medical use do not contain sufficient moisture and may damage or irritate the respiratory tract, or desiccate secretions of patients whose supraglottic airways have been bypassed. This may be indicated for patients requiring mechanical ventilation, positive pressure breathing assistance, or general medical gases”. HFOx will be delivered via nasal prongs. The flow of oxygen will be maximized (set between 20 and 60 L/min), if tolerated, to minimize dyspnea. The FiO2 will be set at 100%. The level of heat (between 35° and 37°) will be adjusted to keep the patient comfortable. HFAir will also be delivered by Optiflow in an identical manner to HFOx, except that we will use pressurized air instead of oxygen. LFOx and LFAir will be provided at 2 L/min using a nasal cannula identical to that used for high-flow devices. This flow rate is based on the results of a previous large randomized controlled trial of oxygen use in non-hypoxemic patients (Abernethy *et al.* 2010). A respiratory care specialist will be present throughout the study period. We have previously collaborated with the same team of respiratory care specialists on other research projects on high-flow oxygen delivery.

C.6. Blinding procedure. The patients, research staff, and exercise physiologist will be blinded to the assignment of the gas (i.e., oxygen vs. air). Only the respiratory therapist administering the gas will be aware of its identity. Optiflow requires both an air tank and oxygen tank, with a 50-psi outlet. To ensure proper blinding, the respiratory therapist will set up the gas delivery device before the patient and staff enter the room. The gas tanks

and device settings will be covered. The respiratory care specialist will be specifically asked to not to discuss the identity of the study gas. We will assess blinding by asking the patients and study staff about the identity of the gas at the end of study. The flow rate cannot be blinded in this study.

C.7. Exercise ergometry will be conducted by a trained PROSPR exercise physiologist in accordance with the 2003 American Thoracic Society and American College of Chest Physicians guidelines (2003). We chose to use cycle ergometry instead of other modalities (e.g., a 6-minute walk test) to induce exertional dyspnea because a stationary bicycle makes it easier for us to deliver oxygen, monitor the physiologic parameters and work rate, and minimize falls. On the first day, we will administer the baseline questionnaires, including demographics, medication history, performance status, Edmonton Symptom Assessment Scale, dyspnea survey, cancer dyspnea scale, and dyspnea modified Borg scale. We will also measure patients' height, weight, resting ECG, resting blood pressure, and resting heart rate.

Before the start of exercise, research staff will explain the exercise test sequence to the participants, including how to use the dyspnea modified Borg scale. The patient will be asked to pedal at a cadence of approximately 60 rpm during the test. The metabolic cart (Parvo True One, Sandy, UT) will be used to monitor cadence, measure work rate during the exercise test, and control resistance on the cycle ergometer. Patients will begin by pedaling with no resistance for 60 seconds, followed by a warm-up stage of 120 seconds, pedaling at 10 watts (W) of resistance for the first minute and 20 W for the second minute. Their blood pressure and heart rate will be recorded every 2 minutes. Oxygen saturation and electrocardiography results will be monitored every 2 minutes during the exercise sessions. The dyspnea modified Borg Scale will also recorded every minute. Patients will perform cycle ergometry tests at an increment of 10 W/min without oxygen until they experience volitional fatigue. During the 3-minute recovery stage at 10 W, their blood pressure, heart rate, and dyspnea modified Borg scale (rating of perceived dyspnea scale, RPD) will be recorded every minute.

After at least a 2-hour rest period, patients will perform a structured exercise session, with an initial warm up period of ≤3 minutes followed by constant work rate cycle ergometry at 80% of the peak work rate and using LFAir, until they experience volitional fatigue. The work rate during this test will be used for stratification.

During the second session, 3±2 days later, patients will be asked to repeat the structured exercise with one of the four study interventions. The study assessments conducted on the first day will be repeated. We will use the constant work rate test for the comparison because it has been found to be more responsive for dyspnea than have incremental tests (Teunissen et al. 2007). A gas exchange analysis will not be conducted because the high flow and oxygen content can interfere with measurements of VO2 (ml/kg/min), VO2 (L), VCO2 (L), VE (L), PetO2 (mm Hg), and PetCO2 (mm Hg), making accurate assessments infeasible. After consulting with our pulmonary collaborator and exercise physiology team (PROSPR), we have decided to measure the work rate and use this as a factor for stratification.

Although we do not expect patients to experience desaturation during exercise based on our previous studies, if we find significant hypoxemia during testing with LFAir or HFAir (and even LFOx and HFOx) arms, patients will not be able to continue with this study and will be considered as dropouts. The termination point is defined by (1)

participant volitional fatigue, (2) abnormal hemodynamic responses to increasing workload, (3) inability to maintain bike cadence, (4) arrhythmias detected on the ECG including changes suggesting ischemia, (5) loss of any monitoring signals, or (6) hypoxemia [O2 saturation <88%] while exercising. Patients will be monitored throughout structured exercise testing, and will have access to urgent medical care if needed. Because this study is designed to induce dyspnea with exercise and some participants had to stop the exercise testing due to leg cramps before they became dyspneic, we will ask study participants not to continue with the rest of the study if their maximum level of dyspnea Borg scale intensity is less than 4/10 by the end of the first incremental test (in keeping with inclusion criteria #2). We will enroll a total of 50 patients who completed all 3 exercise tests and had dyspnea of at least 4/10 at the end of the first incremental test.

C.8. Study assessments. See Table 2 for a detailed description of the study assessments. The dyspnea Borg scale (intensity) will be the primary endpoint because it has been used in multiple other cycle ergometry-based studies (Mahler *et al.* 2005, Mahler *et al.* 2007, Mahler *et al.* 2009, Travers *et al.* 2008). This is a 0 to 10 categorical scale for rating the severity of dyspnea by the patient, and is the primary outcome measure in this study. It is a ratio scale with descriptive anchors throughout the range in which a rating of 8 signifies breathlessness twice as severe as 4, which in turn is twice as severe as 2 (Laboratories 2002). We will be measuring it at baseline and then every minute during the structured exercise tests. This scale has been used extensively in pulmonary research and has good reliability and validity for assessing dyspnea (Dorman *et al.* 2007, Kendrick *et al.* 2000, Mancini and Body 1999). The minimal clinically important difference is 1.0 in patients with chronic obstructive pulmonary disease (Ries 2005). This scale can be administered quickly, and was found to be easy to use by patients (Kendrick *et al.* 2000). In a study that compared the dyspnea modified Borg Scale, numeric rating scale and visual analog scale, the modified Borg scale was preferred by participants and was recommended as the best tool to quantify dyspnea intensity (Hareendran *et al.* 2012). Furthermore, its use is recommended by the American Thoracic Society and American College of Chest Physicians for Cardiopulmonary Exercise Testing (ATS/ACCP 2003). The modified dyspnea Borg scale is also routinely used by our PROSPR group that conducts the cycle ergometry testing. We will also assess the degree of unpleasantness associated with dyspnea using a separate modified Borg scale as well.

Table 2. Summary of Study Assessments

Assessment (estimated time to complete)	Warm up	First structured test		Second structured test	
		Before	During	Before	During
Baseline demographics (15-20 min)[1]	✓				
Medication history (5 min)[2]	✓	✓	✓	✓	✓
Karnofsky performance status (1 min)[3]		✓		✓	
Edmonton Symptom Assessment Scale (5 min)[4]	✓				
Dyspnea survey (5 min)[5]	✓				
Cancer Dyspnea Scale (5 min)[6]		✓		✓	
Baseline Dyspnea Index (5 min)[7]	✓				
Modified Dyspnea Borg scale – intensity and unpleasantness (<1 min)[8]		✓	✓	✓	✓
Vital signs, electrocardiogram (3 min)[9]		✓	✓	✓	✓
Exercise test variables[10]	✓		✓		✓
Oxygen device settings[11]			✓		✓
Adverse effects (5 min)[12]		✓	✓	✓	✓
Blinding, global impression, satisfaction (<3 min)[13]					**End**

[1] Medical record number, birthdate, sex, race, cancer diagnosis, co-morbidities, dyspnea cause, spirometry, and baseline electrocardiogram. Bedside spirometry will be performed at baseline using the MicroLoop spirometer (Micro Direct, Inc., Lewiston, ME) according to published guidelines (Miller et al. 2005). This device was approved by the American Thoracic Society and US FDA. Various spirometry parameters will be documented, including vital capacity, forced expiratory volume in 1 second, forced vital capacity, forced expiratory volume//forced vital capacity, peak inspiratory flow, and peak expiratory flow. We will also assess maximal inspiratory pressure using the NS 120-TRR NIF Monitor (Instrumentation Industries Inc., Bethel Park, PA) according the American Thoracic Society Guideline.(2002)

[2] The frequency of use of scheduled and as-needed opioids, steroids, and bronchodilators in the 4 hours before and during the study.

[3] An 11-point scale that rates patients' functional status between 0% (death) and 100% (completely asymptomatic) (Schag *et al.* 1984).

[4] Validated questionnaire that measures 10 symptoms (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and well-being) using numeric rating scales (Bruera *et al.* 1991). ESAS will be reported as part of patient characteristics because it provides useful information on a patients' symptom expression/burden at baseline. These variables could potentially be predictors of symptom response.

[5] Characterization of patients' level dyspnea, number of exacerbation episodes, triggers, episode duration, and activity level

[6] Validated 12-item questionnaire to assess the quality of dyspnea in cancer patients during the previous few days (Tanaka *et al.* 2000). Each item has a score between 1 and 5, for a maximum of 60.

[7] The Baseline dyspnea index (BDI) is a validated scale used to assess dyspnea under 3 domains: 1) functional impairment, which examines the impact that dyspnea has on the ability to carry out daily activities; 2) magnitude of task, which examines the type of task that results in dyspnea; and 3) magnitude of effort, which establishes the level of effort that leads to dyspnea. BDI ranges from 0 (very severe impairment) to 4 (noimpairment) for each domain, with a total score of 0 to 12.(Mahler *et al.* 1984, Mahler and Wells 1988, Witek and Mahler 2003)

[8] The Modified Dyspnea Borg Scale-Intensity is the primary outcome measure, a 0 (no dyspnea) to 10 (worst dyspnea) ratio scale validated for rating dyspnea severity (Dorman *et al.* 2007,

Powers and Bennett 1999); this will be measured every minute during exercise testing. Modified Dyspnea Borg Scale-Unpleasantness is one of the secondary outcomes.

[9] Heart rate, respiratory rate and blood pressure will be measured at baseline and every 2 minutes during the exercise sessions. Continuous oxygen saturation and electrocardiogram monitoring will be provided during the exercise sessions, and documented every 2 minutes during testing. During the cool down period, these will be measured every 1 minute

[10] Work rate (Watts) is calculated as follows: resistance of the flywheel x distance/revolution (m/revolution) x pedaling rate (revolution/min) x time (minute). One Watt is equivalent to 6 $kg \cdot m \cdot min^{-1}$. It will be measured continuously during exercise testing. We will also document symptoms (e.g. fatigue and leg discomfort) q2min during exercise testing, as well as reasons for stopping (e.g., breathlessness, fatigue, and leg discomfort) and the duration of exercise.

[11] Device settings include FiO_2, oxygen flow, and temperature.

[12] Adverse effects related to supplemental oxygen use, such as dry eyes, dry nose, nasal moisture, and anxiety, will be assessed using a numeric rating scale from 0 (not at all) to 10 (worst possible) before and after the intervention.

[13] We will assess blinding (oxygen v. air) and global impression (better/no change/worse) of patients and research staff.

C.9. Exertional dyspnea clinical trials (Hui *et al.* 2014). Our department has an invested interest in developing novel therapeutics for exertional dyspnea in cancer patients. We have just completed a double-blind, randomized controlled trial to determine the effect of subcutaneous fentanyl on exertional dyspnea. After a baseline 6- minute walk test, patients were given fentanyl or a placebo and then asked to repeat the test. We enrolled 20 non-hypoxemic cancer patients in 5 months, with 100% completion. We also currently have 2 active double-blind, randomized controlled trials with fentanyl pectin nasal spray (expected to complete accrual by Feb 2015) and fentanyl buccal tablet. Because these opioid trials can only enroll patients who are opioid tolerant there should be many eligible patients for the proposed study.

C.10. Co-interventions. We will ask patients to use their usual inhaled medications on the day of the test as appropriate.

C.11. Training of research staff. An orientation will be held with all research staff involved in this study to introduce them to the study design and standardize the provision of each intervention. Particular attention will be paid to ensuring that research staff provide patients with proper instructions so they understand the study assessments. We will also have several mock-ups for practicing the study procedures.

C.12. Data Safety Monitoring Board (DSMB). The MD Anderson DSMB will be providing monitoring for patient safety and data quality assurance purposes.

D. STATISTICAL ANALYSIS

D.1. Sample size justification. Using 10 patients per arm (assuming 20% attrition, 50 total), we will have 86% power to detect a 1-standard deviation (SD) main effect and 86% power to detect a 2-SD interaction effect (assessed as the difference between the joint effect and an additive effect) with an alpha of 5%. These are large effects, but the main objective is to obtain preliminary estimates of effect sizes. We have expressed the treatment effects as multiples of the standard deviation because we do not have valid preliminary estimates of the within-group standard deviations on which to base these calculations.

D.2. Analysis plan. For the primary analysis, we will use a general linear model, with a Borg dyspnea score at isotime as the outcome variable and including the following

parameters as covariates: flow rate, oxygen, flow rate-oxygen interaction, work rate, and baseline dyspnea at rest, prior to the first exercise test. Isotime is defined as the time of the last set of measurements before completion of the baseline constant work rate test. Because of HFOx, VO2 max cannot be accurately measured. Instead, we will calculate the work rate (in watts), defined as the resistance of the flywheel x distance/revolution (m/revolution) x pedaling rate (revolution/min) x time (minute).

Because dyspnea is also repeatedly measured over time, secondary analyses will include a mixed-effects linear model on the longitudinal dyspnea scores, using the same 5 model parameters. For all analyses, we will use data graphs and residual analyses to verify assumptions, with data transformations as necessary. If more than 10% of patients are missing data, we will use multiple imputation in our analyses. Recognizing that dyspnea in cancer patients may have multiple etiologies, we will document its potential causes and perform subgroup analyses to determine whether a particular patient group benefits more from the study interventions. These analyses will be considered exploratory and hypothesis-generating. If y is the endpoint, x1 is the flow rate (1 for high and 0 for low), and x2 is oxygen (1 for oxygen and 0 for ambient air), we will fit the following linear model: y = a + b1*x1 + b2*x2 + b3*x1*x2, with some additional terms. The effect of the flow rate (i.e., the adjusted mean difference between high and low flow) can be calculated as b1 for ambient air and b1 + b3 for oxygen. Similarly, the effect of oxygen can be calculated as b2 for low flow and b2 + b3 for high flow. Approximate 95% confidence intervals for these effect estimates can be computed given the estimated covariance matrix of the model parameters.

We will estimate the proportion of patients who complete the study; this analysis will include an appropriate 95% confidence interval.

To estimate the effects of oxygen and flow rate on physiologic function (respiratory rate and oxygen saturation) and exercise capacity (work rate and exercise duration), we will use mixed-effects linear models because most of these are measured repeatedly over time. Given the limited number of patients, the results will be considered exploratory. Adverse events will be assessed using a numeric rating scale from 0 to 10 before and after intervention. Differences in these scores for each type of adverse event will be analyzed using general linear models, as described above for the primary endpoint.

E. DATA CONFIDENTIALITY PROCEDURES

Health information will be protected and we will maintain the confidentiality of the data obtained from the patient's chart.

Collection of identifiers: We will collect and securely store patients' identifiers (including name and medical record number). Each patient will be assigned a study number that will be the only identifier to figure in the analytical file and personal data will not be disclosed in any form. The key linking these numbers will be retained in a securely locked file by the investigator.

Data Storage: Protection of electronic and paper records will be guaranteed. All electronic records will be stored on password-protected institution computers behind the institution firewall. Any paper records will be classified and stored in locked files inside a locked office.

Training of personnel: Only MDACC personnel trained in maintaining confidentiality, the principal investigators and co-investigators, will have access to study records.

Data sharing: Study data will not be shared with any individuals or entities without an IRB-approved protocol. The data will be kept by the principal investigator in a locked file cabinet and password protected computers.

Final disposition of study records: PHI may be maintained indefinitely, aggregated in the future, and used for future IRB-approved research studies.

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