# High-Flow Oxygen for Dyspnea in Hospitalized Cancer Patients

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**Funding source**: This study is supported by the Sabin Family Fellowship Award (P.I. David Hui). The funding for this study starts March 1, 2016.

## A. STUDY OBJECTIVES

**A.1. Primary Objective.** Obtain preliminary estimates of the effect size of high flow oxygen and air on dyspnea. Our working hypothesis is that high flow oxygen/air will be associated with lower levels of dyspnea than low flow oxygen/air in cancer patients.

**A2. Secondary Aim #1.** Determine the completion rate of a randomized controlled trial of dyspnea in cancer patients. Our working hypothesis is that at least 80% of patients will complete the 4 periods of this study.

**A.3. Secondary Aim #2.** Obtain preliminary estimates of the effects of high flow oxygen and air on physiologic function (oxygen saturation, respiratory rate, transcutaneous CO2). Our working hypothesis is that high flow oxygen and air will improve physiologic function.

## 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" [1]. It occurs in approximately 10%-70% of cancer patients and is one of the most feared symptoms [2, 3]. More than 80% of patients with dyspnea have breakthrough episodes, particularly with physical exertion [4]. Dyspnea is associated with decreased function, quality of life, and survival [5]. The pathophysiological features of dyspnea are shown in Figure 1. The sensory cortex receives afferent input from various peripheral and central stimuli, generating the sensation of breathlessness [1, 6]. Parenchymal metastasis, lymphangitic carcinomatosis, airway obstruction, pleural effusion, pneumonia, pulmonary embolism, and atelectasis may cause difficulty breathing in the context of progressive cancer.

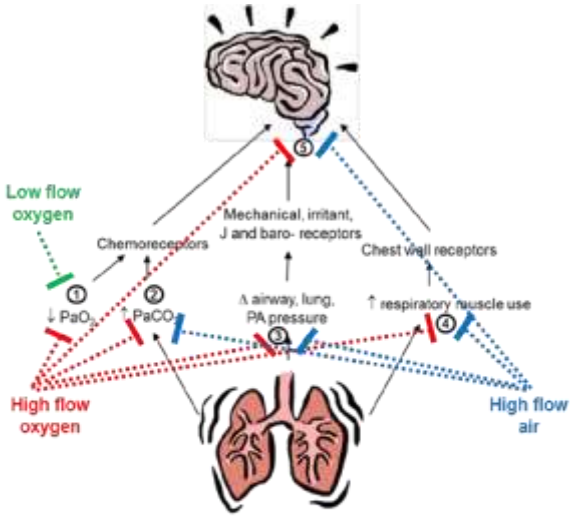


**Figure 1. Conceptual Framework for Dyspnea and Potential Mechanisms of Action of High Flow Oxygen.** High flow (red) and low flow (green) oxygen are postulated to relieve dyspnea by (1) providing $PaO_2$ mediated inhibition of dyspnea sensors. Both high flow oxygen (red) and high flow air (blue) may 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.

The current management of dyspnea involves treating any reversible causes and providing supportive measures. Systemic opioids are effective for dyspnea relief [7]. Low-flow supplemental oxygen (up to 5 L/min) has also been found to be effective, but only in patients with hypoxemia [8, 9]. 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 [10, 11]. The

proposed research is expected to provide new insights into the therapeutic role of HFOx for dyspnea.

**B.2. High-flow oxygen** is an innovative heat and humidification device that can deliver oxygen at a rate of up to 60 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 [12], augment end-distending pressure [13], reduce nasopharyngeal inspiratory resistance [14], and stimulate the trigeminal and glossopharyngeal nerves (Figure 1). The inhalation of heated and humidified gas may also decrease bronchoconstriction, improve airway conductance [15], and reduce the metabolic cost of gas conditioning [14]. 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 [16]. To our knowledge, to date, no published 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 [17].** 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 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.

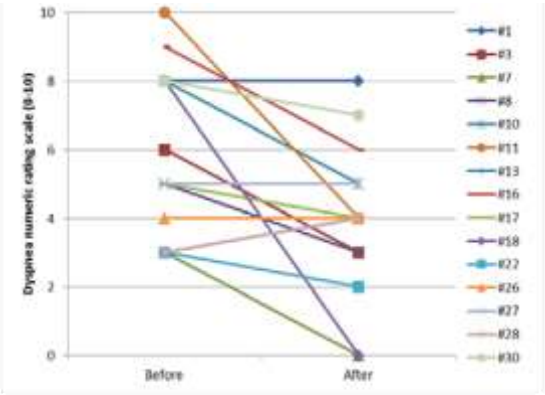


**Figure 2. Improvement in Dyspnea** Before and after high flow oxygen (N=15)

**B.4. Low-flow supplemental oxygen for non-hypoxemic cancer patients [18].** 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 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 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.

## C. RESEARCH DESIGN AND METHODS

**C.1. Study design.** This is a double-blind, 4-intervention, 4-period crossover randomized controlled trial of HFOx, HFAir, LFOx, and LFAir in non-hypoxemic cancer patients (**Figure 3**). We plan to enroll 36 patients in total. The eligibility criteria are listed in **Table 1**. We will use a computer-generated sequence for randomization. Even with 2 different flow rates, patients and research staff will be blinded to the gas (i.e., oxygen v. air) while a separate respiratory therapist will provide the study intervention; thus, this will remain a double-blind study. On the basis of our experience conducting symptom control trials, we believe this study design will not be an undue burden for hospitalized patients (approximately 1-2 hours, including washout).[19] The rationale for the current study design is as follows:

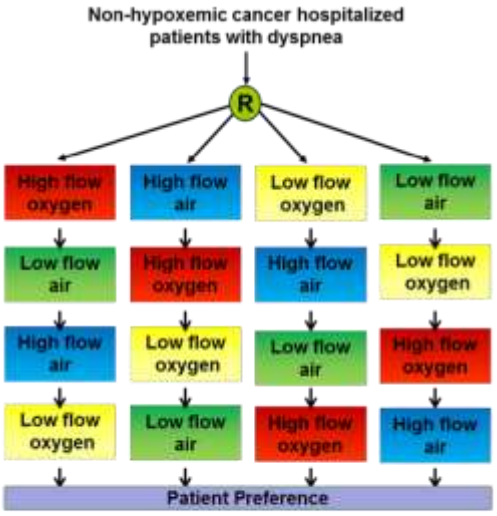


**Figure 3. Study Flow Chart. In this double-blind, 4-intervention, 4-period crossover randomized controlled trial, all patients will try 10 minutes of each intervention, followed by a variable washout period (purple arrow). The sequences above represent one of the 6 Latin Squares that may be used.**

- **Crossover design**—This design allows intra-individual comparison, thus maximizing study power (144 tests in 36 patients) in addition to providing overall preference.[20] We use the Latin square design to minimize the sequences needed.
- **Intervention duration**—We will limit this intervention to only 10 minutes in this proof-of-concept study to minimize study burden and attrition, and to examine the effect of short intervention. We expect the effect of gas exchange to be rapid. Previous dyspnea studies with oxygen delivery have utilized similar durations [8].
- **Variable washout period**—although the washout period is expected to be short (<10 min), it has not been defined. Thus, we will measure dyspnea on the Numeric Rating Scale starting after 10 minutes of each intervention every 5 minutes until patient returns to within 1 point of the baseline level of dyspnea (i.e. immediately prior to starting the first intervention) before we proceed to the next intervention.
- **Inclusion of HFOx, HFAir and LFAir arms**—HFOx has not been tested in non-hypoxemic cancer patients. No published study has examined the therapeutic role of HFAir in any patient population. The efficacy of LFAir has not been studied in the hospitalized population [21].
- **Use of LFAir as control**—LFAir at 2 L/min is a well-accepted control intervention in published studies.

**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.

**Table 1. Study Eligibility Criteria**

**Inclusion Criteria**

1. Diagnosis of cancer
2. Patients seen by palliative care, thoracic oncology, pulmonary medicine, or emergency care at MD Anderson Cancer Center
3. Dyspnea Numeric Rating Scale at rest ≥3 of 10 (average over last 24 hour)
4. Non-hypoxemic (i.e. oxygen saturation >90% on ambient air)
5. Able to communicate in English or Spanish
6. Age ≥18 years
7. Able to tolerate high-flow oxygen/air

**Exclusion Criteria**

1. Memorial Delirium Rating Scale >13
2. Hemodynamic instability
3. Respiratory failure requiring mechanical ventilation or non-invasive ventilation
4. Frequent use of rescue opioids >8x/day or rescue bronchodilators >8x/day over last 24 hours
5. Currently requiring high flow oxygen for oxygenation

**C.3. Recruitment.** Patients seen by the supportive care team, thoracic oncology, pulmonary medicine, or emergency care will be screened for this study. The supportive care inpatient consultation team sees 80 patients (10-20 new consults) per day. 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. Before signing any consent document, a respiratory care therapist will allow patients a trial of high-flow oxygen/air to ensure tolerance of high flow. 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 ideal time to conduct the study. We will document the number of patients who are screened, approached, eligible, enrolled, and randomized for the study and the number who complete it. When patients complete study procedures, they will be compensated with a $25 gift card as a show of appreciation for their time and participation. Patients' reasons for declining to participate will also be captured.

**C.4. Randomization.** Randomization will be performed immediately before the patient is ready to start study procedures by our study respiratory therapist 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 1:1:1:1 ratio, to the four treatment sequences from a Latin square. Each sequence has a specific order of high flow oxygen, low flow oxygen, high flow air, and low flow air.

**C.5. Study interventions.** Respiratory therapists will use a high flow oxygen device 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 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. This flow rate is based on the results of a previous large randomized controlled trial of oxygen use in non-hypoxemic patients [21]. 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.** The patients and research staff will be blinded to the assignment of the gas (i.e., oxygen vs. air). The gas will be delivered via gas outlets inside the patient's room, located behind the bed. Only the respiratory therapist administering the gas will be aware of its identity. To ensure proper blinding, the research staff will step out of the room while the respiratory therapist sets up the gas delivery device. The gas supply will be covered with a piece of cloth to ensure proper concealment. 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. Study outcomes.** See Table 2 for a detailed description of the study assessments. We will also collect data on patient demographics and study feasibility outcomes (rates of enrollment and attrition). The study interventions will be provided to patients while at rest, and dyspnea ratings will only be assessed when patients are at rest.

**C.8. Co-interventions.** We expect that co-interventions will be minimal because of the short study period. We will document any regularly scheduled, bronchodilators or opioids given 1 hour before or during the study period. However, if patients required as need opioids (for pain or any other reasons) or bronchodilators during the study period, they will need to come off study and will need to be replaced.

**C.9. 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.10. Data Safety Monitoring Board (DSMB).** The MD Anderson DSMB will be providing monitoring for patient safety and data quality assurance purposes.

**C.11. Dropouts.** Patients will come off study if (1) they decide for any reason to stop; (2) they did not achieve within 1 point of the baseline level of dyspnea after 1 hour during the washout period, (3) they require as need opioids (for pain or any other reasons) or bronchodilators during the study period. These individuals will need to be replaced.

**C.12. Stopping rule.** This is a short study and we expect limited attrition. We will stop the study at patient request or if patients required as need opioids (for pain or any other reasons) or bronchodilators during the study period.

**Table 2. Summary of Study Assessments**

| | Baseline | Intervention | Washout period | End of study |
|---|---|---|---|---|
| Demographics and baseline data[1] | ✓ | - | - | - |
| Dyspnea numeric rating scale (<1 min)[2] | ✓ | 0, 5, 10 min | q5min | - |
| Dyspnea Borg scale – intensity and unpleasantness (<1 min)[3] | ✓ | 0, 5, 10 min | q5min | - |
| Physiologic variables (5 min)[4] | ✓ | 0, 10 min | - | - |
| Blood pressure | ✓ | - | - | ✓ |
| Adverse effects (<1 min)[5] | - | 0, 10 min | - | - |
| Length of washout (5+ min)[6] | - | - | ✓ | - |
| Device settings[7] | ✓ | ✓ | - | - |
| Blinding, preference (<1 min)[8] | - | - | - | ✓ |

[1] We will collect birthdate, sex, race, cancer diagnosis, co-morbidities, dyspnea cause and baseline, Karnofsky Performance status, the frequency of use of scheduled and as-needed opioids, steroids, and bronchodilators in the 24 hours before and during the study. Validated questionnaires that will be assessed at baseline include the Edmonton Symptom Assessment Scale (measures 10 symptoms [pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and well-being] using numeric rating scales [22]) and the Cancer Dyspnea Scale (12-item questionnaire to assess the quality of dyspnea in cancer patients during the previous few days [23]. Each item has a score between 1 and 5, for a maximum of 60). 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, 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 [24].

[2] Dyspnea intensity assessed by Numeric Rating Scale is the primary measure. It is a 0 (no dyspnea) to 10 (worst dyspnea) categorical scale validated for rating the severity of dyspnea[25-27].

[3] The intensity of and unpleasantness associated with dyspnea will be assessed using the Borg scale, a validated ratio scale that ranges from 0 (no dyspnea) to 10 (worst dyspnea).[25,27]

[4] Heart rate, respiratory rate, oxygen saturation, and transcutaneous $CO_2$ level will be measured.

[5] 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).

[6] Dyspnea intensity will be assessed using the NRS scale every 5 minutes until patients return to baseline. The duration of washout is a useful secondary outcome.

[7] $FiO_2$, flow rate, and temperature.

[8] We will assess blinding (oxygen v. air) of patients and research staff after each treatment. At the end of the study, patients will be asked which of the 4 interventions they prefer

## D. STATISTICAL CONSIDERATIONS

### D.1. Analysis plan.

**Design:** We propose a 4-period, 4-intervention balanced Latin-square cross-over (Williams) design with 4 sequences and 36 patients (i.e., 9 replicates per sequence). The primary outcome is the Dyspnea Numeric Rating Scale (0-10). Each intervention is 10-minutes long with NRS assessments at 0, 5 and 10 minutes. Washout periods between interventions will continue until NRS assessment returns to within one unit of baseline.

**Primary analysis:** We will fit a mixed effects linear model to the Dyspnea Numeric Rating Scale data to account for the repeated measurements (i.e. 0, 5 and 10 minutes) which yield period, sequence, and carryover effects and to model the various inter-patient and intra-patient sources of variation. Appropriate data visualization and residual analyses will also be performed. The primary objective of the study is to obtain preliminary estimates of the effect sizes (In a mixed model, the slope of change will provide an estimate of effect size. We will also determine the mean change in NRS over 10 minutes for each study intervention).

**Secondary analysis #1:** We will estimate the completion rate as the proportion of patients starting treatment that complete all four interventions.

**Additional secondary analyses:** Using mixed effects linear models we will obtain preliminary estimates of the study effects for physiologic function (oxygen saturation, respiratory rate, transcutaneous $CO_2$). We will also assess washout period duration in a similar fashion. Finally, we will tabulate patient intervention preferences obtained at the end of the study.

**D.2. Sample size justification.** We will enroll 36 patients over 2 years. Although due to the complexity of the statistical models we cannot accurately estimate the precision of our effect estimates, based on our experience with mixed effects models, 36 patients with 12 repeated measurements (3 times for each of 4 interventions) will provide adequate precision. If the completion rate is 80% then with 36 patients, a 95% confidence interval on this estimate would extend from 64% to 92%.

## E. DATA CONFIDENTIALITY PROCEDURES

Study data will be collected and managed using REDCap (Research Electronic Data Capture) tools hosted at MD Anderson or hardcopy surveys. Participants will have the option to complete surveys electronically or hardcopy. Data entry of any hardcopy survey will be completed using REDCap software. REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. In the case of multi-center studies REDCap uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions. REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson Cancer Center's Department of Research Information Systems & Technology Services.

REDCap has undergone a Governance Risk & Compliance Assessment (05/14/14) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and UTMDACC Institutional Policy #ADM0335. Those having access to the data file include the study PI and research team personnel. Users are authenticated against MDACC's Active Directory system. All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis. Following publication study data will be archived in REDCap.

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 protected to the best of our ability. 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 investigator, collaborators, and research staff will have access to study records.

Data sharing: Study data will not be shared with outside individuals or entities without IRB approval. 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 kept forever in an MD Anderson database, combined with other patients' information in the future, and used for future research studies.

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