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A RANDOMIZED TRIAL OF BILEVEL POSITIVE AIRWAY PRESSURE DEVICE AND HIGH FLOW OXYGEN FOR PERSISTENT DYSPNEA IN

David Hui

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A RANDOMIZED TRIAL OF BILEVEL POSITIVE AIRWAY PRESSURE
DEVICE AND HIGH FLOW OXYGEN FOR PERSISTENT DYSPNEA IN
ADVANCED CANCER PATIENTS

by

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A

THESIS DISSERTATION

Presented to the Faculty of
The University of Texas
Health Science Center at Houston
and
The University of Texas
M. D. Anderson Cancer Center
Graduate School of Biomedical Sciences
in Partial Fulfillment

of the Requirements

for the Degree of

MASTER OF SCIENCE

by

David Hui, BSc, MSc, MD, FRCPC

Houston, Texas

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Abstract

A RANDOMIZED TRIAL OF BILEVEL POSITIVE AIRWAY PRESSURE DEVICE AND HIGH FLOW OXYGEN FOR PERSISTENT DYSPNEA IN ADVANCED CANCER PATIENTS

Publication No. _____ *

David Hui, BSc, MSc, MD, FRCPC

Supervisory Professor: Eduardo Bruera, MD

Background: Dyspnea is a common and distressing symptom among patients with advanced cancer. The role of bilevel positive airway pressure (BIPAP) and Vapotherm in the relief of dyspnea have not been well defined. We aimed to determine and to compare the efficacy of BIPAP and VapoTherm for cancer related dyspnea.

Methods: In this randomized, open-label, crossover study, we randomly assigned advanced cancer patients with persistent dyspnea $\geq 3/10$ to either Vapotherm for 2 hours followed by BiPAP for 2 hours, or BiPAP followed by Vaptherm. A variable washout period was instituted between interventions. The primary end point was change in numeric rating scale before and after each intervention. We planned to enroll 50 patients in total.

Results: Among the 803 patients screened over the last 8 months, 62 (26%) were eligible, and 16 (2%) were enrolled so far. Five patients completed the entire study successfully, 4 discontinued the study prematurely due to prolonged relief of dyspnea, and 7 dropped out for various reasons, including

inability to tolerate BIPAP (N=3), anxiety (N=2), fatigue (N=1) and pain requiring opioids (N=1). The median baseline numeric rating score for dyspnea was 7/10 (interquartile range (IQR) 5-8), and the median baseline Borg score was 4/10 (3-7). Interim analysis revealed that BIPAP was associated with a median change in numeric rating score of -3 (N=10, IQR -6.3 to -1, p=0.007) and modified Borg score of -1 (N=10, IQR -3 to 0.3, p=0.058), while Vapotherm was associated with a median change in numeric rating score of -2 (N=9, IQR -3 to -1, p=0.011) and modified Borg score of -2.5 (N=8, IQR -5.5 to -0.1, p=0.051). Among the 5 individuals who completed the entire study, 2 preferred Vapotherm, 2 favored BIPAP, and 1 liked both. The respiratory rate decreased and the oxygen saturation improved with both interventions. No significant toxicities were observed.

Conclusions: We were successfully able to enroll patients onto this clinic trial. Our preliminary results suggest that BIPAP and Vapotherm are highly efficacious in providing relief for patients with persistent refractory dyspnea. A direct comparison of the two interventions will be done upon study completion. Further research is necessary to confirm our findings.

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Chapter 1. Introduction

A. Background

Dyspnea is a subjective awareness of difficulty breathing, which may be associated with the distressing sensation of suffocation. It is one of the most common and most feared symptoms among cancer patients, occurring in approximately 20-40% of patients at the time of diagnosis of advanced disease (1, 2), and increases up to 50-70% in the last 6 weeks of life (3). Dyspnea has also been shown to be an important prognostic factor for patients with advanced cancer (4, 5).

The pathophysiology of dyspnea is shown in Figure 1 (6). Causes of dyspnea can be classified as cancer-related, treatment-related and psychological factors. Progressive disease may result in parenchymal metastasis, lymphagitic carcinomatosis, airway obstruction, atelectasis, and/or pleural effusion causing difficulty breathing. Complications of cancer, including thromboembolism, pneumonia, sepsis and anemia of chronic disease may also contribute to the sensation of breathlessness. Cancer patients also tend to have poor respiratory reserve because of chronic obstructive pulmonary disease (COPD) and/or prior lung resections, predisposing them to the development of respiratory symptoms. In advanced cancer patients with significant cachexia, dyspnea may also be related to loss of respiratory muscles, an under-

recognized etiology (6). In a small proportion of patients, no identifiable etiologic factors can be found.

Current management of dyspnea involves treatment of any reversible causes and supportive measures to minimize the sensation of dyspnea. Relief of dyspnea can be achieved by a number of pharmacologic and non-pharmacologic measures. Common medications for dyspnea include opioids, bronchodilators, corticosteroids and benzodiazepines. Opioids had proven palliative benefit for dyspnea. In a cross over study with 10 cancer patients, Bruera et al. showed that subcutaneous morphine was more effective at relieving dyspnea compared to placebo 60 minutes after drug administration (7). A systemic review suggested that oral and parenteral, but not nebulized, opioids as effective in managing dyspnea (8). However, the potential benefit with opioids is limited by its toxicity profile, particularly sedation and opioid induced neurotoxicity at higher doses. Even with high doses of opioids and other supportive measures, some patients continue to experience severe dyspnea.

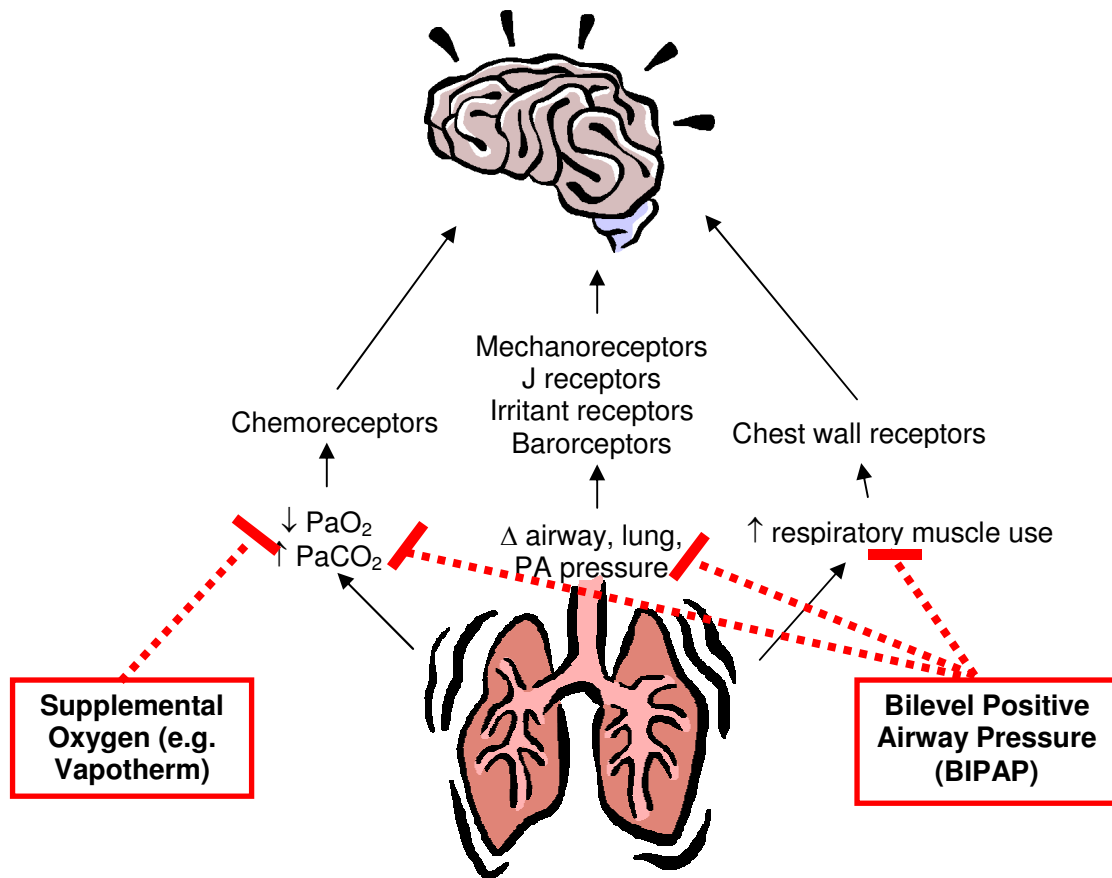


Figure 1. Pathophysiology of Dyspnea and Potential Mechanisms of Action of Supplemental Oxygen and BIPAP. The sensory cortex receives afferent input from mechanoreceptors in airways and chest wall, stretch and irritant receptors in lungs, chemoreceptors in brainstem, and other signals from the motor cortex, generating the sensation of breathlessness. Supplemental oxygen can improve the arterial oxygen level, reducing the level of chemoreceptor activation, and thus the sensation of dyspnea. BIPAP not only improves oxygenation, but also exerts a mechanical effect on the airways and chest wall, which in the process improves ventilation, work of breathing, and potentially dyspnea.

Non-pharmacologic measures such as supplemental oxygen has been shown to be beneficial for patients with hypoxemia, although its role in dyspneic patients who are not hypoxemic remains unresolved (9). A prospective, double-blind crossover trial included 14 advanced cancer patients, and found significant improvements in dyspnea comparing

oxygen to room air by mask (10). However, a larger study with 33 patients did not confirm this benefit (11). The observation that supplemental oxygen therapy only benefits patients with hypoxemia suggests that improved oxygenation is only part of the equation for relief of dyspnea. In recent years, high-flow oxygen delivery devices (VapoTherm) and bilevel positive airway pressure (BIPAP) have become available for treatment of acute or chronic respiratory distress, although their potential for relief of dyspnea in the palliative care population remains to be tested.

VapoTherm is a high flow heat and humidification device that can deliver oxygen of up to 40 L/min via nasal prongs. Studies on VapoTherm have so far focused on patients with acute exacerbations of COPD and congestive heart failure (CHF). A randomized crossover study of VapoTherm by nasal prongs versus supplemental oxygen by non-rebreather mask in 14 COPD patients showed equivalent efficacy in terms of oxygen delivery, but VapoTherm was better tolerated (12). Another study of 5 COPD patients compared high flow versus low flow oxygen via VapoTherm. The high flow oxygen arm was associated with a trend towards decreased dyspnea by both numeric rating scale and Borg scale (13).

BIPAP is a form of non-invasive positive pressure ventilation (NIPPV), and represents another attractive option for relief of dyspnea using pre-set

inspiratory pressure that allows patient to control not only the breathing rate but also the duration of inspiration (14). It is commonly used for treatment of acute respiratory failure, including exacerbations of COPD (15) and CHF (16). Intermittent BIPAP has been studied in the critical care setting for immunocompromised cancer patients who developed pneumonia, and has been demonstrated to reduce the need for intubation, serious complications, and mortality (17).

In the chronic respiratory failure setting, the use of BIPAP has been mostly limited to patients with neuromuscular disorders such as amyotrophic lateral sclerosis (ALS) (18) and Duchenne muscular dystrophy (19) (Table 1). One study included 20 ALS patients randomized to long term BIPAP or best supportive care, and found significant survival and satisfaction in the BIPAP arm (20). A review of 276 patients with chronic respiratory failure from various causes found that BIPAP was associated with improved gas exchange and decreased hospitalization (21).

Table 1. Key Studies of Non-Invasive Positive Pressure Ventilation in Patients with Advanced Respiratory Failure

	Population	Design	NIPPV settings	Intervention period
ACUTE RESPIRATORY FAILURE IN ADVANCED STAGES OF DISEASE				
Benhamou et al. 1992 (22)	Acute on chronic resp. failure (COPD, RLD, bronchiectasis), elderly 76±8 yrs	Prospective N=30	NR	Daily schedule: continuous first 12h, then intermittent days and continuous nights Total: 11.4 days
Freichels et al. 1994 (23)	Acute on chronic resp. failure (cancer, COPD, restrictive). High PaCO ₂	Retrospective case series N=3	NR	Daily schedule: continuous with 1 to 2 hours off mask
Hilbert et al. 2001 (17)	Acute resp. failure (Immunocompromised cancer patients)	Randomized trial on intermittent BIPAP or supp O ₂ N=52 (26)	IPAP: 15±2 cmH ₂ O EPAP: 6±1 cmH ₂ O	Daily schedule: intermittent 45 min up to 3h Total: 6±3 days
Levy et al. 2004 (24)	Acute resp. failure who were DNI	Prospective cohort study N=114	IPAP: 13±3 cmH ₂ O EPAP: 5.3±1 cmH ₂ O	Daily schedule: continuous with intermittent breaks Total: 13.2 ±2.4h
Schettino et al. 2005 (25)	Acute on chronic resp failure (COPD, CHF, advanced cancer) who were DNI	Prospective observational study N=131 (40 cancer)	NR	Daily schedule: continuous. Parameters recorded +2 h, then q12h Total: 2 days
CHRONIC RESPIRATORY FAILURE				
Legar et al. 1994 (21)	Chronic resp. failure (COPD, kyphoscoliosis, muscular dystrophy) on NIPPV	Retrospective case series N=276	NR	Daytime: 1.5±2h Nighttime: 9±2h Total: 6 months
Pinto et al. 1995 (20)	Chronic resp. failure (ALS)	Quasi randomized trial N=20 (10)	NR	NR
Lyll et al. 2001 (26)	Chronic resp. failure (ALS)	Prospective case control N=16	NR	Daytime: as needed Nighttime: continuous Total: 6 months
REVIEW				
Nava et al. 2004 (27)	Review of NIPPV in cancer patients	NA	NA	Gas exchange, pH, RR, dyspnea usually improve in 1-3 hours

Abbreviations: ALS, amyotrophic lateral sclerosis; DNI, do not intubate; EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; NA, not applicable; NIPPV, non-invasive positive pressure ventilation; NR, not reported; RR, respiratory rate

B. Study Rationale

Patients with advanced cancer commonly experience dyspnea. Current treatment options, such as supplemental oxygen, opioids and bronchodilators, provide limited relief of this distressing symptom, with many patients still experiencing persistent dyspnea. One of the limitations of the current method of supplemental oxygen delivery is that it is cumbersome and uncomfortable. The maximum rate delivered via nasal prongs is only 6 L per minute. Patients with higher oxygen requirements have to wear a non-rebreather mask, which can deliver oxygen of up to 15 L per minute (and up to 21 L per minute with the additional oxygen delivery by nasal prongs). However, the mask may create a subjective sensation of suffocation or claustrophobia for patients. These impracticalities, coupled with its limited effectiveness in relief of dyspnea, raises the need for newer modalities of oxygen delivery that can be more successful in managing dyspnea. Vapotherm and BIPAP represent two novel therapeutic options for patients with acute and chronic respiratory failure, although their efficacy in the palliation of dyspnea remains to be tested.

Vapotherm represents a potentially attractive option for treatment of dyspnea because it can provide heated, humidified high flow oxygen (up to 40 L/min) through nasal prongs. The effect of high flow oxygen on the relief of dyspnea has not been studied in detail, particularly in patients with

persistent dyspnea despite standard oxygen therapy. Postulated mechanisms of how Vapotherm provides relief for dyspnea include (1) the ability to maintain a high level of P_{aO_2} which has a direct effect the perception of dyspnea, (2) stimulation of trigeminal nerve, and (3) the ability to increase positive end expiratory pressure (PEEP).

BIPAP may provide additional benefit to supplemental oxygen therapy (Figure 1). BIPAP not only assists ventilation, but also increases inspiratory flow rate, corrects hypoventilation, resets central respiratory drive, increases exercise capacity, and unloads respiratory muscles (27-29). The last reason is of particular interest for advanced cancer patients who have dyspnea secondary to loss of respiratory muscles. However, the potential benefit of BIPAP needs to be balanced against the discomfort associated with the mask. We believe that some patients would prefer this modality despite the use of facial/nasal mask if it proved to be able to effectively improve dyspnea.

A study investigating the effect of Vapotherm and BIPAP on persistent dyspnea would provide preliminary data regarding the feasibility and efficacy of these non-invasive assist devices for alleviation of breathlessness using a crossover, rather than parallel design. A crossover design is specifically chosen for this study as it allows patients to determine their overall preference after a trial of both interventions.

Findings from this feasibility study, such as adherence, cross over period and outcome measures, could help us to design a larger crossover trial powered to examine differences in efficacy between these two interventions. Our long-term goal is to improve the quality of life and care of patients with advanced cancer who experience the distressing symptom of dyspnea.

C. Hypotheses

We hypothesize that both intermittent BIPAP and Vapotherm are effective in the treatment of persistent dyspnea despite standard supplemental oxygen therapy in advanced cancer patients.

We also postulate that BIPAP is more effective at relieving dyspnea (by numeric rating scale, Borg Scale, global assessment and washout period) than high flow oxygen therapy for patients who can tolerate this treatment, through the added benefits of improving inspiratory flow rate, alveolar recruitment, chest wall expansion.

We further hypothesize that BIPAP can improve ventilation better than Vapotherm.

D. Study Objectives

1. To determine the effects of BIPAP and VapoTherm on the severity of dyspnea compared to baseline as measured by the Numeric rating scale and the Borg scale.
2. To compare the effects of BIPAP and VapoTherm on the severity of dyspnea compared to baseline as measured by the Numeric rating scale and the Borg scale.
3. To determine the effects of BIPAP and VapoTherm on physiologic parameters, including heart rate, respiratory rate, blood pressure and oxygen saturation, and transcutaneous carbon dioxide level.

Chapter 2. Patients and Methods

A. Study Design

This is an open-label, randomized, crossover study involving VapoTherm and BIPAP for patients with cancer-related dyspnea (Figure 2). Eligible patients who agreed to participate were randomized to receive either BIPAP or VapoTherm for 2 hours in the first treatment phase, followed by a variable washout period (up to 1 hour) and then either VapoTherm or BIPAP for 2 hours in the second treatment phase. Because of the nature of study interventions, blinding was not possible.

This study focused on patients with cancer-related dyspnea, which is defined as dyspnea predominately related to the underlying malignancy, with or without other secondary chronic respiratory diseases (e.g. COPD, asthma, idiopathic pulmonary fibrosis). Potential pathologies may include, but not limited to, pulmonary parenchymal metastasis, lymphangitic carcinomatosis, pleural effusion, and significant cachexia with respiratory muscle weakness.

A crossover design was utilized such that each participant had the opportunity to try both VapoTherm and BIPAP. At the end of the study, he/she provided feedback regarding his/her overall preference through a survey directly comparing the two interventions in terms of dyspnea relief

and comfort. This intra-individual comparison would not have been possible with a parallel design.

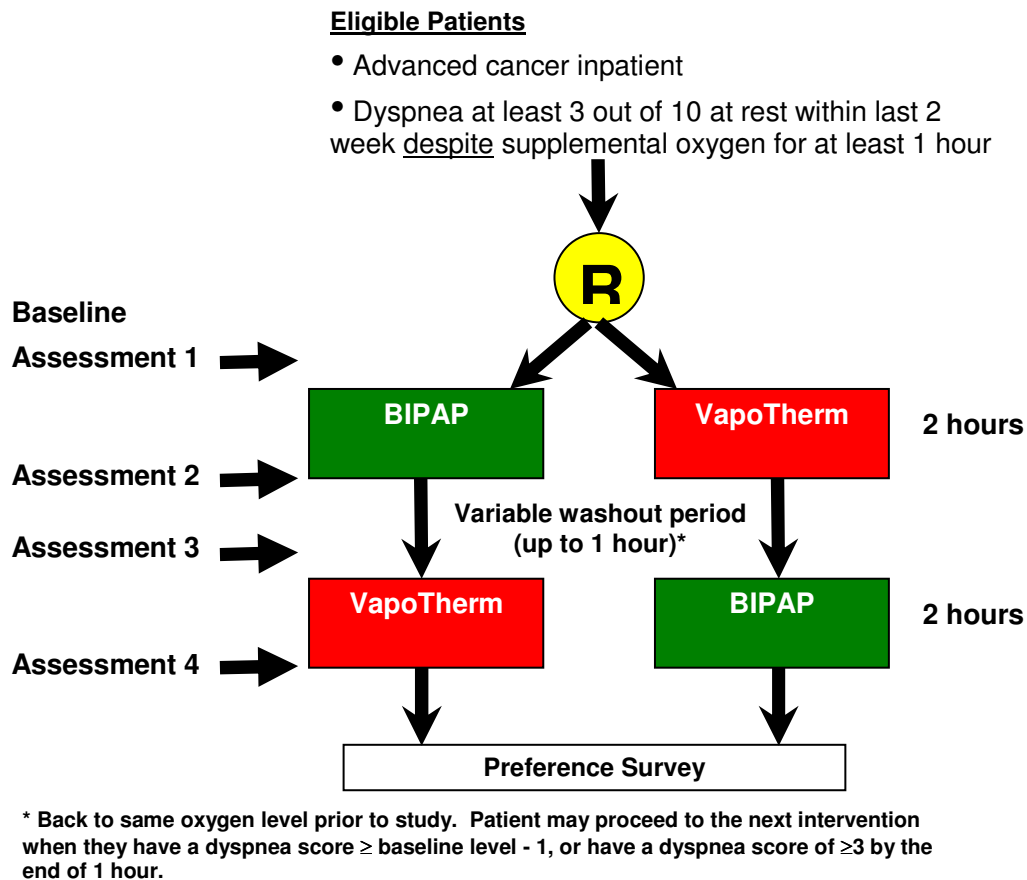


Figure 2. Study Overview. In this open-label, randomized, crossover study, advanced cancer patients with persistent dyspnea were randomized to either BIPAP followed by VapoTherm, or VapoTherm followed by BIPAP. The total study duration was up to 5 hours. Four assessments (before and after each intervention) were conducted during the study period, with a preference survey at the end.

B. Inclusion Criteria

1. History of advanced cancer, defined as locally advanced, recurrent or metastatic disease

2. Patients with persistent dyspnea, defined in this study as dyspnea at rest with an average intensity level ≥ 3 out of a Numeric rating scale from 0 to 10 for at least 2 week and just prior to study initiation, despite supplemental oxygen of up to 21 L/min to keep oxygen saturation $\geq 90\%$
3. Dyspnea is judged clinically to be predominantly due to underlying malignancy, with or without obstructive lung disease
4. Inpatient at M.D. Anderson Cancer Center
5. Patients with cancer treatment related dyspnea are eligible for this study if they meet the eligibility criteria above
6. Able to communicate in English
7. Expected life expectancy >1 week
8. Patients with a diagnosis of pneumonia and/or pulmonary embolism are also eligible for this study if they meet the eligibility criteria above, with dyspnea ≥ 2 weeks prior to the diagnosis of pneumonia

C. Exclusion Criteria

1. Patients who remain hypoxic (i.e. O_2 saturation $<90\%$ despite maximal oxygen delivery (21 L/min) are not included in this study because they are considered to have severe life-threatening respiratory failure and are too unstable for study inclusion.

2. Hemodynamic instability (heart rate >140 beats/minute, systolic blood pressure <80mmHg) within 24 hours of study initiation (as per Clinic Station)
3. Acute respiratory distress requiring intubation
4. Delirium as indicated by a Memorial Delirium Assessment Scale (MDAS) of 13 or higher
5. Glasgow coma scale <8
6. Excessive airway secretions interfering with BIPAP administration
7. History of facial trauma within 1 month of enrollment
8. Upper GI bleed within 2 weeks or esophageal rupture of enrollment
9. Partial or complete small bowel obstruction or severe nausea/vomiting (ESAS nausea >7/10) within 48 hours of enrollment
10. Hemoglobin <8 g/dL at the time of enrollment (blood draw within last 2 weeks)
11. Acute exacerbation of COPD or CHF within 2 weeks of enrollment by history or physical
12. Unwilling to provide informed consent
13. Diagnosis of non-cancer related dyspnea (e.g. COPD, CHF or any chronic respiratory disease) requiring supplemental home oxygen prior to hospitalization.

D. Patient Screening and Recruitment

Newly admitted advanced cancer patients who were potentially dyspneic were identified through multiple sources, including a daily log of inpatients initiated on supplemental oxygen or nebulizer treatments the previous day by respiratory therapy, advanced nurse practitioners from rehabilitation medicine and thoracic medicine, fellows from the palliative care and other collaborators.

Initial screening was conducted using Clinic Station. Based on information from this electronic health record interface, we excluded patients who were discharged, died, hemodynamically unstable, or had a diagnosis of curable cancer, COPD exacerbation, CHF exacerbation, small bowel obstruction, facial trauma or upper GI bleed.

If patients appeared eligible after initial screening, they were approached for study enrollment by our research staff, usually within 24 hours. A two-stage consent process was utilized by first asking patients for their permission to screen them for study eligibility. Patients who met all eligibility criteria were then provided with further information including the informed consent form, and were invited to participate in this study.

E. Study Interventions

Vapotherm: The Vapotherm® 2000i Respiratory Therapy Device was used (Vapotherm, Stevensville, MD, USA). It was approved by the U.S.

Food and Drug Administration (FDA) in 2001 (K042245) to “add moisture to and to warm breathing gases for administration to patients, including neonates/infant, pediatrics, and adults. The environment of use include home, hospital or sub-acute institutional settings”. Patients on the Vapotherm arm received high flow oxygen via nasal prongs. FiO_2 was set at 100% throughout the intervention period. The level of heat (between 35° and 37°) and oxygen flow (between 10 L/min and 40 L/min) were adjusted initially by our study respiratory therapist to minimize dyspnea while keeping the patient comfortable.

BIPAP: The BIPAP Vision® Ventilatory Support System was used (Respironics Inc. Murrysville, Pennsylvania, USA). It was approved by the FDA in 1998 (K982454) for “spontaneously breathing adult patients suffering from acute respiratory failure, acute or chronic respiratory insufficiency, or obstructive sleep apnea in hospitals, or other institutional settings, under the direction of a physician”. Patients assigned to receive BIPAP treatment received non-invasive ventilation delivered through a face or nasal mask. Patients were given a choice of either a ResMed Latex Free Hospital Nasal Mask R611-735/1 (ResMed Ltd, Bella Vista, NSW, Australia) or a ResMed Latex Free Hospital Full Face Mask R143-340/5 (ResMed Ltd, Bella Vista, NSW, Australia). The mask was adjusted and connected to a ventilator set in pressure support mode (S/T). To

minimize discomfort, the system used in this study was leak-tolerant, so that the mask would not need to be airtight.

After securing the mask, the level of support was started at an inspiratory pressure of 8 cm of H₂O and expiratory pressure of 5 cm of H₂O. The pressures were progressively increased and adjusted to maximize alleviation of dyspnea and to minimize discomfort, with a target inspiratory pressure between 8 and 18 cm of H₂O, and target expiratory pressure between 3 and 10 cm of H₂O. The FiO₂ was kept at 100% throughout the intervention period.

F. Intervention Duration

One small randomized study of high flow and low flow oxygen via VapoTherm demonstrated a trend towards improved dyspnea with the high flow arm after 30 minutes of intervention. The minimal time for clinical improvement of dyspnea using BIPAP is not clear from existing literature. However, a number of studies have shown improved oxygenation and physiologic parameters within 1 to 3 hours (Table 1). Thus, we chose a 2 hour period for each intervention, which should give patients enough time to derive some treatment benefits.

G. Study Process

Once the patient signed the informed consent and the patient's attending physician was notified, the study interventions were initiated within 24 hours. A standing order regarding BiPAP, Vapotherm and medication use during the study was placed in the patient's chart to inform clinical staff of this study. Clinical nurses caring for the patient were also given further study information. A randomization list was prepared by our study biostatistician for each stratum in advance.

During the study period (up to 5 hours), our research staff conducted study assessments at 4 time points (Figure 2), and provided close monitoring. Patients who could not tolerate an intervention because of discomfort were offered the opportunity to (1) temporarily halt the intervention and resume when ready, (2) switch to alternative intervention after a variable washout period (if it has not been tried), or (3) discontinue the study. Patients who deteriorated clinically during the study (e.g. severe respiratory distress, oxygen saturation decreased to <90%, decreased mental status, hemodynamic instability) or required breakthrough opioid had to terminate the study prematurely.

At the end of study, patients were offered the opportunity to choose to remain on BIPAP, Vapotherm or return to standard supplemental oxygen therapy. We did not provide any followup or monitoring after completion of study.

H. Washout Period

While the effect of gas exchange is rapid and not expected to carry over significantly, the duration of washout period for patients to return to baseline level of dyspnea after using these interventions has not been defined. Our group has previously conducted a number of crossover trials for dyspnea in advanced cancer patients, comparing parenteral vs. nebulized opioids (30), and air vs. oxygen supplementation (10, 31). The washout periods were relatively short (0-60 minutes) due to the rapid nature of gas exchange. No clinical trials have directly compared both BIPAP and Vapotherm. Among the few crossover trials involving either of these interventions, the washout period varied from 0-10 minutes for BIPAP (32, 33) to 60 minutes for Vapotherm (12). Thus, we felt that a variable wash out period of up to 60 minutes was reasonable for this feasibility study.

We introduced a variable washout period between the two interventions to determine the optimal duration required for patients to return to baseline dyspnea level, which was defined as greater than or equal to the dyspnea level on Numeric rating scale just prior to starting study minus 1. For instance, if a patient had dyspnea rating of 5/10 prior to study, then any score of 4 or above was considered to be back to baseline. During the washout period, patients were given the same level of supplemental

oxygen just prior to study initiation. For patients whose dyspnea had not returned to \geq baseline -1 level at the end of 1 hour, they were able to proceed to the next intervention only if dyspnea $\geq 3/10$. However, if their dyspnea level remained $< 3/10$ at the end of 1 hour, they would not be eligible to proceed to the next intervention.

Patients were asked about their level of dyspnea on a numeric rating scale every 10 minutes after they have completed the first intervention for up to 1 hour. This allowed us to determine the time for dyspnea to develop, and whether there is any significant difference between VapoTherm and BIPAP. To minimize bias in this measurement, patients were only told that a waiting period of up to 1 hour was required to start the next intervention, but not the requirement that they need to return to baseline to proceed.

I. Medication Use

Medications such as opioids, steroids and bronchodilators could have an effect on dyspnea, and could affect the findings of this study if given around the study period. While it would be ideal to minimize these co-interventions by ensuring that patients are on stable doses of medications before starting the study, inpatients have frequent medication changes during the hospitalization making it difficult to control this factor.

To minimize the effect of opioids, steroids and bronchodilators on the measurement of dyspnea during the study, patients who were receiving scheduled and/or breakthrough doses of these medications for any indications would need to wait for a short duration prior to initiating study interventions, defined in this study as at least 1 hour for opioids and steroids, and 30 minutes for bronchodilators prior to study initiation as pre-study dose. Patients receiving continuous opioid infusion by patient controlled analgesia pump were able to enroll onto the study if they have not required breakthrough doses for at least 1 hour.

During the study period (up to 5 hours), patients who required any breakthrough opioids (parenteral, oral, inhaled), breakthrough steroids (parenteral, oral or inhaled) or scheduled/breakthrough bronchodilators were considered as dropouts, and the study interventions were discontinued. Patients could continue to receive scheduled doses of opioids and steroids during the study period.

J. Study Outcome Measures

This study included 4 main assessments—before and after each of the two interventions (Figure 2 and Table 2). All study assessment forms can be found in Appendix A.

Table 2. Study Outcome Measures

Assessment Items	First assessment	Second assessment	Third assessment	Fourth assessment
Demographic variables/Baseline	x			
Medication history	x			
MDAS	x			
ECOG performance status	x			
Physical including weight	x			
Cancer Dyspnoea Scale	x			
Numeric Rating Scale	x	x	x	x
Modified Borg scale	x	x	x	x
Adverse events	x	x	x	x
Vitals	xx	xx	xx	xx
Continuous TcCO ₂ monitoring	xx	xx	xx	xx
Continuous oximetry monitoring	xx	xx	xx	xx
Respiratory settings	x	x	x	x
Duration of intervention		x	x	x
Global symptom evaluation		x		x
Preference survey				x
Study satisfaction questions				x

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MDAS, Memorial Delirium Assessment Scale; TcCO₂ transcutaneous carbon dioxide

x = one measurement, xx = heart rate, respiratory rate, TcCO₂, and O₂ saturation were recorded every 30 minutes during each intervention by using the trend function

1. Baseline Patient Characteristics

Baseline demographics were collected from the patient and/or health records just prior to initiation of first intervention, and included the following:

- Demographics (date of birth, gender, race)
- Cancer diagnosis (date of diagnosis, cancer type, treatments received)
- Comorbidities (chronic pulmonary or cardiac conditions such as COPD, CHF, bronchiectasis)
- Medications
- Previous BIPAP/Vapotherm use (number of times, most recent use)

- Primary etiology of dyspnea
- Dyspnea measures (see below for details)
- To better characterize the dyspnea at baseline, we also used the Cancer Dyspnoea Scale, a validated 12 item questionnaire specifically designed to assess the quality of dyspnea in cancer patients (34). Each item has a score between 1 and 5, with a total score of up to 60, along with sub-scores for sense of effort, anxiety, and discomfort (Appendix A).
- ECOG performance status at the time of study initiation. This is a validated numeric rating scale with a score from 0 to 4 related to patient's functional status (35), where 0=Fully active, able to carry on all pre-disease performance without restriction; 1=Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2=Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3=Capable of only limited self care, confined to bed or chair more than 50% of waking hours; 4=Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
- Memorial Delirium Assessment Scale (MDAS) is a 10 item questionnaire validated in cancer patients for assessment of delirium (36). It can be administered by a physician, a nurse or a research

coordinator, assigning a score between 0 and 30. A score of >13 is suggestive of delirium

- Focused physical examination of the cardiorespiratory system, and included the vitals (heart rate, respiratory rate, blood pressure, oxygen saturation) as per standard clinical practice

2. Dyspnea Measures

Dyspnea is a subjective sensation experienced by patients. The numeric rating scale (0=no dyspnea and 10=worst dyspnea) (37-39) and modified Borg scale (37-40) are two of the most commonly used scales to assess the severity of dyspnea. As there is no established gold standard for measurement of dyspnea, we used both scales in this study.

The numeric rating scale is a 0 to 10 categorical scale validated for rating severity of dyspnea, with 0 denoting no dyspnea, and 10 representing worst dyspnea (37-39). Patients were asked their level of dyspnea at the moment of assessment.

The modified Borg scale represents another 0 to 10 categorical scale for rating the severity of dyspnea. The Borg scale was initially developed to determine the sensation of exertion with exercise. Overtime, it has been modified and validated for the assessment of dyspnea. Although the range for both numeric rating scale and modified Borg scale is between 0

and 10, the two scales have different anchors and assess dyspnea differently. The modified Borg scale has more descriptors throughout its range, and is designed as a ratio scale in which a rating of 2 represents half the degree of dyspnea as 4, which is in turn half as severe as 8 (37-40).

Both dyspnea assessments were performed immediately prior to initiation of first intervention (assessment 1), immediately before completion of first intervention (assessment 2), immediately before the second intervention (assessment 3) and immediately before completion of second intervention (assessment 4) (Figure 2).

3. Toxicities

While we did not expect significant side effects from Vapotherm or BIPAP, it was important to document any common or severe adverse effects. These included dry eyes, dry mouth, mask discomfort, feeling of suffocation, stomach bloating, anxiety, trouble eating, trouble drinking, trouble speaking and trouble sleeping. Since many of these side effects were not captured in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, we developed a specific patient reported outcome form for this study in which patients were asked to rate their side effects from 0 (none) to 10 (worst).

4. Physiologic Measures

At each of the four assessments, we determined the vital signs (heart rate (HR), respiratory rate (RR), blood pressure (BP), and oxygen saturation (O_2 sat). O_2 saturation was monitored using the Alaris® SpO₂ module-8200 series oximeter (Alaris Medical Systems, Cardinal Health-Alaris Products, San Diego, CA, USA). Tissue PCO₂ level was monitored using the Sentec Digital Monitoring System TCO₂M® Transcutaneous Monitor, Novamatrix Model #860 (Novamatrix Medical Systems Inc., Wallingford, CT, USA) placed on the skin over the face heated between 37°C and 45°C (41-43). Blood gases were not performed to minimize patient discomfort.

5. Device Settings

The BIPAP and Vapotherm settings were documented by respiratory therapy. BIPAP settings included mode, breath type, inspiratory oxygen (F_iO_2), respiratory rate, inspiratory pressure (IPAP), expiratory pressure (EPAP), and average tidal volume (V_T). Vapotherm settings included FiO_2 , oxygen flow and temperature.

6. Global Symptom Evaluation and Patient Preference

At the end of each intervention, patients were asked to provide a global assessment of the device on their breathing (worse, about the same, or better). If their answer was better, they were asked to rate how much

better their symptoms were (almost the same, hardly any better at all, a little better, somewhat better, moderately better, a good deal better, a great deal better, a very great deal better). If their answer was worse, they were asked to rate how much worse their symptoms were (almost the same, hardly worse at all, a little worse, somewhat worse, moderately worse, a good deal worse, a great deal worse, a very great deal worse). The global symptom evaluation can help provide an anchor for determining the minimal clinical important difference for the numeric rating scale and modified Borg scale. A second independent part of this tool given out at the end of the study asked patients regarding their satisfaction with the study. This tool has been used by various symptom researchers (44, 45).

A preference survey was given to patients at the end of the study who tried both BIPAP and Vapotherm. Subjects were asked to directly compare the two devices regarding dyspnea relief, comfort, overall choice. Given that no clinical trials have examined both BIPAP and Vapotherm, this survey was specifically designed for this study.

K. Statistical Analyses

Our primary outcome was to determine estimates of the magnitude of changes in dyspnea scores before and after each intervention, which would be compared using a crossover design. We planned to enroll 50

patients overall, with 25 patients receiving BIPAP first then Vapotherm second, and with 25 patients receiving Vapotherm first then BIPAP second). This would allow us to declare as statistically significant a difference in mean change scores of 0.6 standard deviations between treatment groups, assuming a two-sided significance level of 0.05 and 80% power. Patients were expected to return to their approximate baseline score between treatments.

For the purpose of this thesis, the interim data for 16 patients enrolled so far were analyzed. Descriptive statistics (e.g. means, medians, standard deviations) were used to describe the preliminary findings regarding dyspnea scores, adverse effects, vitals and overall preference, and to minimize repeated comparisons. The paired Student's t-test was used to compare continuous variables (e.g. vitals) before and after each intervention, and the paired Wilcoxon test was used for non-parametric variables (e.g. numeric rating scale, modified Borg scale and adverse effects). Upon completion of accrual (i.e. 50 subjects), we would be able to conduct a more detail statistical analysis to directly compare the findings between Vapotherm and BIPAP. The Statistical Package for the Social Sciences (SPSS version 16.0, SPSS Inc., Chicago, Illinois) software was used for statistical analysis.

Given the preliminary nature of this analysis, we combined all results related to BIPAP use from both treatment arms, and also all results related to Vapotherm use from both treatment arms. In the final analysis, the results would be analyzed in a crossover fashion if there was no significant period effect.

Chapter 3. Study Process

While study design is the most critical part of the research process, the success of a clinical trial depends on many other factors, including coordination of study process, commitment and training of research staff, meticulous data management, satisfactorily addressing the regulatory aspects of this study, and appropriate resource allocation. This chapter aims to highlight some of the operational aspects of this clinical trial.

A. Study Protocol and Institutional Approval

The study protocol writing process took approximately 4 months between October and February 2009, with input from Dr. Bruera, Dr. Hui, Dr. Price from Critical Care, Dr. Faiz for Pulmonary Medicine, Clarence Finch and Laura Withers from Respiratory Therapy, and Dr. Palmer from Biostatistics. After multiple revisions, it was submitted and eventually approved by the Clinical Research Committee at M.D. Anderson Cancer Center on April 8, 2009. This was subsequently approved by the institutional review board on July 24, 2009. A copy of the study consent is provided in the Appendix B. The study was formally activated on August 11, 2009. This clinical trial was registered at ClinicalTrials.gov (registration number NCT00934128).

B. Standard Operating Procedure

A 12-page standard operating procedure was created shortly before study activation. This study manual outlined each of the steps involved in this study, and defined the specific role for research physician, coordinator and respiratory therapist (Appendix C). This important document helped to provide orientation to research staff members, to standardize the study procedures and to improve communication between team members.

C. Research Team

The research team consisted of a research coordinator, two respiratory therapists and a research fellow (Dr. Hui). Dr. Bruera oversaw the operation of this study, along with the research nurse manager and head of respiratory therapy.

During the month before and the month after study activation (July to September 2009), we focused on ensuring all research staff were comfortable with the study process, optimizing the study forms, and identifying potentially eligible patients. Multiple training sessions were provided to help familiarize each research team member with his/her role and to improve overall coordination. Training consisted of didactic lectures with Powerpoint presentations as well as practical mock sessions. All members were provided with a copy of the standard operating procedure. Moreover, Dr. Hui provided one-on-one training for our research

coordinator on a daily basis for two months to optimize the patient enrollment process.

The research team met regularly during research meetings (once every 1-2 weeks) to discuss issues related to the screening and recruitment process, study assessments, data monitoring and trouble shooting. Minutes were kept and sent out to team members with action list items to ensure accountability.

D. Patient Accrual and Trouble Shooting

One of the major challenges of this study related to patient accrual. Before study activation, Dr. Hui presented at the Critical Care departmental meeting, palliative care departmental meeting, and respiratory therapy team meetings to promote this study.

We initially relied predominantly on clinical respiratory therapists to provide us with names of patients who may be dyspneic. However, we soon realized that this referral process had limited success, likely due to the fact that clinical respiratory therapists are generally unfamiliar with clinical trials. The palliative care team referred patients regularly, although those patients were generally too ill for enrollment. In October 2009, we started receiving an automated list of patients who were newly started on oxygen therapy or nebulizer treatments throughout the hospital. We also

engaged the advanced nurse practitioners from Thoracic Medicine and Rehabilitation Team, who started to make regular referrals.

To improve accountability and participation, we sent out e-mails once to twice a week to referring sources to update them regarding any progress in recruitment, and to encourage further referrals. Since October 2009, this study has been able to consistently enroll patients.

E. Data Management

We created a tracking Excel database to facilitate daily screening of potentially eligible patients. This tracking database consisted of patient medical record numbers, date of referral, source of referral, patient location, reasons for ineligibility or refusals (if applicable). It provided an up-to-date summary of patient recruitment.

An Access database was created by our departmental data analyst to record information captured in this study. Data were entered in this database within 1 week of patient enrollment, and periodically checked for accuracy and completeness.

F. Study Funding and Budget

Clinical research can be expensive. The hiring of research staff, use of equipment and study supplies can be costly, depending on nature of the

study. A budget was created for this clinical trial (Appendix). This budget included only the cost of equipment and supplies. The cost of hiring research personnel was not included as it was covered by our departmental funds.

Chapter 4. Preliminary Results

A. Patient Accrual and Enrollment

Over 800 patients were screened during the past 8 months. As shown in Figure 3, a large proportion of the referrals were from the oxygen/nebulizer log, which was generated automatically every day. Referrals from thoracic medicine were most likely to be enrolled.

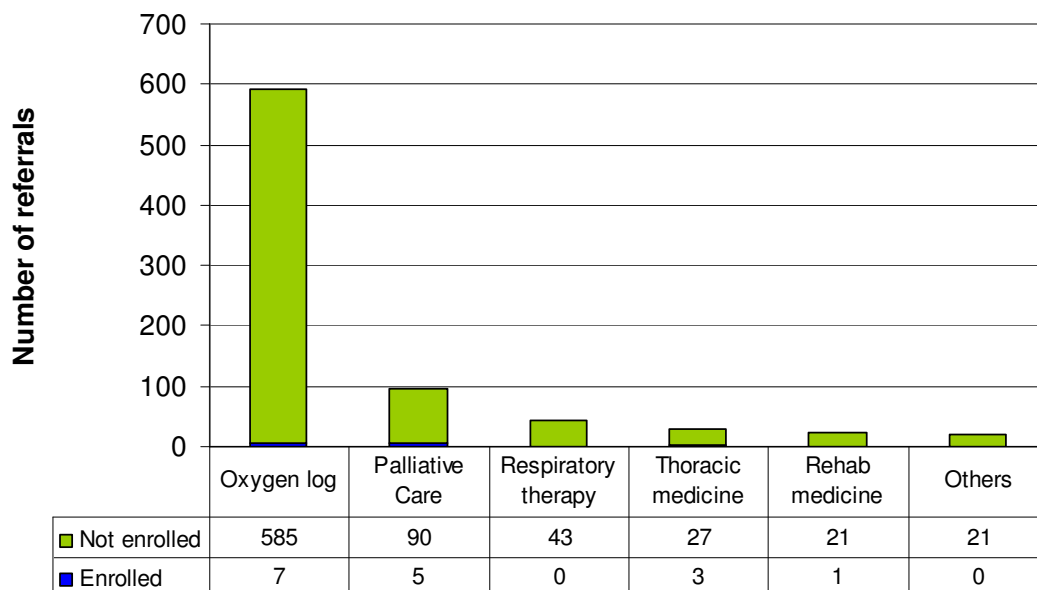


Figure 3. Referral Sources

The study flow chart is shown in Figure 4. Approximately 30% were discharged or died before we completed screening, reflecting the rapid pace of hospital discharge. Among the 549 patients who completed screening, almost 90% were ineligible, with a diagnosis of curable cancer, not dyspneic enough, contraindications to BIPAP, delirium and non-cancer

dyspnea being the major reasons. Among the 62 eligible patients who completed screening, 16 (26%) enrolled onto the study.

Only 5 of 16 patients were able to complete both BIPAP and Vapotherm. As shown in Figure 3, 4 patients did not proceed to the second intervention after the full 1 hour washout period because they experienced prolonged relief of dyspnea and never returned to baseline (3 after BIPAP and 1 after Vapotherm). Two patients who completed BIPAP as the first intervention dropout out during the washout period because of fatigue and pain requiring opioid use. Three patients who tried BIPAP as the second intervention had to discontinue prematurely because they were unable to tolerate BIPAP (claustrophobia, positive pressure, and nausea after 45 minutes of BIPAP). Two other patients had difficulty tolerating both devices due to high levels of anxiety.

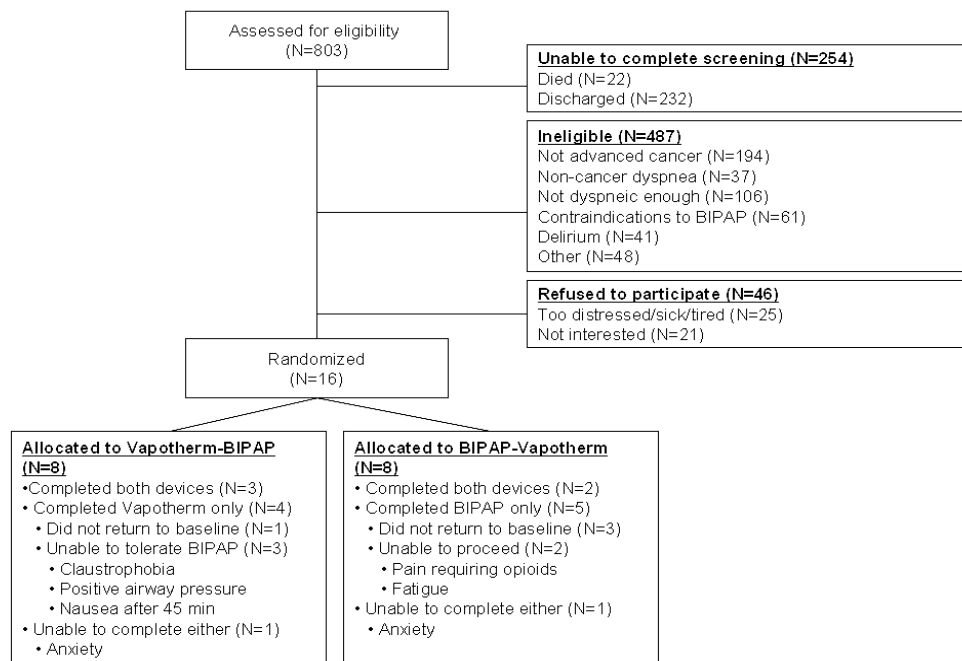


Figure 4. CONSORT Diagram

B. Baseline Characteristics

The baseline characteristics for the 16 patients enrolled onto this study so far are shown in Table 3. Almost half of them had lung cancer, and a majority had metastatic disease. Reasons for dyspnea included involvement of the lung parenchyma, pleural effusion, cachexia and lymphagitic carcinomatosis. Pneumonia and pulmonary embolism were also present in a small proportion of patients. Importantly, a substantial number of these patients were already on supplemental oxygen, bronchodilators, opioids and steroids.

Table 3. Patient Characteristics

Clinical characteristics	N (%)*
Age, median (range)	62.5 (29-79)
Female sex	9 (56%)
Race	
Caucasian	14 (87%)
African American	2 (13%)
Cancer type	
Lung	7 (44%)
Breast	4 (25%)
Gastrointestinal	2 (13%)
Others	3 (18%)
Cancer stage	
Metastatic	12 (75%)
Locally advanced	4 (25%)
Co-morbidities	
COPD	4 (25%)
Asthma	0
CHF	0
Bronchiectasis	0
Performance Status	
3	13 (81%)
4	3 (19%)
Reasons for dyspnea**	
Lung parenchymal involvement	12 (75%)
Pleural effusion	6 (38%)
Cachexia/muscle weakness	6 (38%)
Lymphangitic carcinomatosis	2 (13%)
Pneumonia	3 (19%)
Pulmonary embolism	1 (6%)
Baseline medications	
Supplemental oxygen	16 (100%)
Bronchodilators	16 (100%)
Opioids	15 (94%)
Steroids	8 (50%)
Previous experience with BIPAP/Vapotherm	
BIPAP	1 (6%)
Vapotherm	0

C. Dyspnea Scores

At baseline, the median dyspnea numeric rating scale was 7/10 (interquartile range 5-8), and the median modified Borg scale was 4/10 (3-7). Using the Cancer Dyspnea Scale, our cohort reported a sense of effort subscale score of 11/20 (standard deviation (SD) 5), anxiety subscale

score of 7/16 (SD 5), discomfort subscale score of 6/12 (SD 3), and a total dyspnea score of 23/48 (SD 8).

The changes in dyspnea score by numeric rating scale and modified Borg scale are shown in Figure 5. Overall, BIPAP was associated with a median change in numeric rating score of -3 (N=10, interquartile range -6.3 to -1, $p=0.007$) and modified Borg score of -1 (N=10, interquartile range -3 to 0.3, $p=0.058$), while Vapotherm was associated with a median change in numeric rating score of -2 (N=9, interquartile range -3 to -1, $p=0.011$) and modified Borg score of -2.5 (N=8, interquartile range -5.5 to -0.1, $p=0.051$).

Global assessment of dyspnea was consistent with the overall reduction of dyspnea scores, and confirmed that patient found the interventions helpful for their shortness of breath. As shown in Figure 6, 10 of 11 patients who successfully completed BIPAP reported that it improved their dyspnea, with 4 of them experiencing at least a good deal of relief. Seven of 9 patients found Vapotherm to be useful in improving their dyspnea.

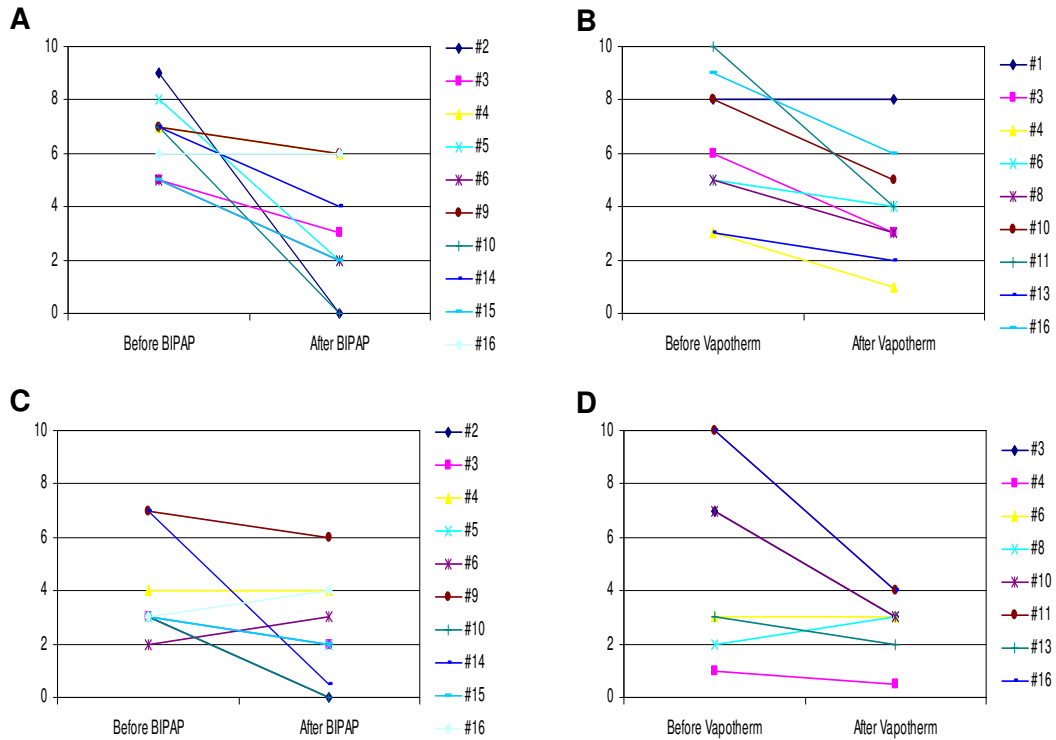


Figure 5. Changes in Dyspnea Scores. The numeric rating scale was plotted for each patient before and after (A) BIPAP and (B) Vapotherm. The Borg scale was also plotted for each patient before and after (C) BIPAP and (D) Vapotherm.

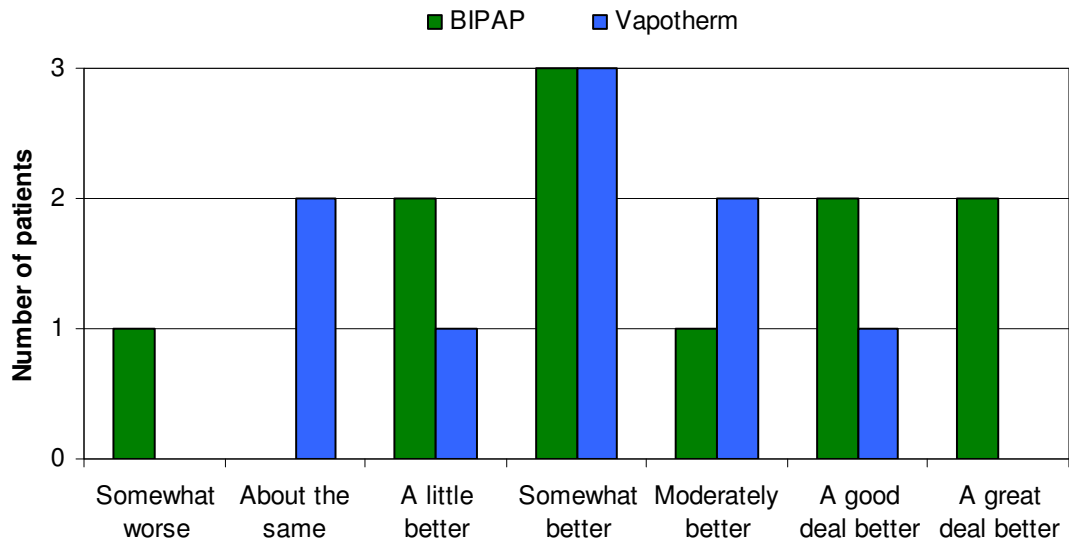


Figure 6. Global Assessment of Dyspnea after BIPAP and Vapotherm

D. Physiologic Measures

The physiologic changes before and after study interventions are shown in Table 4. After BIPAP, patients generally had a lower heart rate, respiratory rate and oxygen saturation. However, the transcutaneous carbon dioxide level did not change significantly. Vapotherm was associated with improved oxygenation and decreased respiratory rate.

Table 4. Physiologic Measures

Average values	BIPAP				Vapotherm			
	Before (SD)	After (SD)	Change (SD)	P-value	Before (SD)	After (SD)	Change (SD)	P-value
Heart rate (beats per minute)	97 (15)	96 (8)	-6 (5)	0.01	107 (17)	105 (14)	-3 (7)	0.45
Respiratory rate (per minute)	26 (5)	22 (5)	-4 (2)	0.002	26 (10)	22 (9)	-4 (10)	0.32
Systolic blood pressure (mmHg)	128 (20)	128 (14)	-9 (12)	0.11	143 (12)	142 (22)	-2 (22)	0.86
Diastolic blood pressure (mmHg)	74 (10)	75 (17)	0 (10)	0.94	84 (5)	85 (9)	+1 (9)	0.77
Oxygen saturation (%)	94 (6)	100 (1)	+8 (5)	0.006	92 (4)	97 (1)	+5 (3)	0.01
Transcutaneous carbon dioxide level	35 (7)	38 (9)	+2 (3)	0.13	36 (4)	33 (5)	-2 (2)	0.04

Abbreviation: SD, standard deviation

E. Adverse Effects

As shown in Table 5, patients on BIPAP reported some difficulties drinking and talking as well as the mask being uncomfortable, which was balanced by less discomfort with nasal prong use. Remarkably, patients reported a lesser sensation of suffocation on BIPAP. The main adverse effect for Vapotherm was moisture in the nose.

No significant life-threatening adverse events were documented. Four of 16 patients died within 1 month of study completion. The deaths were not attributed to this study, but reflected the poor prognosis of our patient population.

Table 5. Patient Reported Adverse Effects Before and After BIPAP/Vapotherm

Median	BIPAP				Vapotherm			
	Before (IQR)	After (IQR)	Change (IQR)	P-value	Before (IQR)	After (IQR)	Change (IQR)	P-value
Dry eyes	2 (0-3.8)	1.5 (0, 4.5)	0 (0, 0)	1.0	1 (0, 3)	0 (0, 3)	-1 (-3, 0)	0.07
Eye irritation	0 (0-1.8)	0 (0, 3)	0 (-0.75, 0)	0.58	0 (0, 5)	0 (0, 0)	0 (-3.5, 0)	0.10
Moist nose	2 (0.5, 2.8)	0 (0, 2)	0 (-1.75, 0)	0.75	2 (0, 5)	4.5 (2.5, 6.3)	+1.5 (-0.3, 3.3)	0.13
Nasal prongs uncomfortable	4.5 (0.5, 5.8)	0 (0, 0)	-2.5 (-3.8, -1.2)	0.007	0 (0, 3)	2 (0, 2.5)	0 (-0.3, 1.8)	0.50
Mask painful	0 (0, 0)	0.5 (0, 3)	+1.5 (0.8, 2.3)	0.07	-	-	-	-
Suffocating	3 (0, 4.8)	0 (0, 0.8)	-2.5 (-3.8, 0)	0.03	0 (0, 7)	0.5 (0, 1.8)	0 (-0.3, 0.3)	0.71
Bloating	0.5 (0, 2.8)	0 (0, 1.8)	0 (-1, 0)	0.59	3 (1, 6)	1 (0, 2.3)	-1 (-1.8, 0)	0.04
Feel anxious	1.5 (0, 2.0)	0 (0, 2.8)	0 (-0.8, 0)	0.71	5 (0, 6)	0 (0, 1)	-2 (-4.3, 0)	0.07
Trouble eating	4 (0.5, 6)	3.5 (0.5, 6.5)	-2 (-2.8, 2)	0.76	3 (0, 6)	1 (0, 5.5)	0 (-0.3, 0.3)	1.0
Trouble drinking	2 (0, 3)	3.5 (0, 7)	0.5 (-1.8, 4.5)	0.44	0 (0, 4)	0 (0, 0.5)	0 (0, 0)	0.66
Trouble talking	1.5 (0, 4.3)	6.5 (2.8, 7.8)	+2 (0, 7)	0.07	5 (0, 6)	1 (0, 2.8)	0 (-1.8, 0.5)	0.50
Trouble sleeping	2.5 (0.3, 5.8)	3.5 (1.3, 5)	0 (-1, 2.3)	0.67	7 (5, 8)	0 (0, 1.3)	-4.5 (-7.3, -1.5)	0.03

Abbreviations: IQR, interquartile range; “-“, not applicable

F. Washout Period

The duration of washout period was an important outcome, as it is a measure of the duration of therapeutic effect after discontinuation of the first intervention. Three of 6 patients who completed BIPAP and 1 of 7 who completed Vapotherm as the first intervention experienced significant relief of dyspnea (i.e. $\leq 2/10$) even after they returned to supplemental

oxygen for 1 hour, and were not eligible to proceed to the next phase of the study.

Table 6. Washout Period Dyspnea Scores and Outcome

Patient #	First treatment	Baseline dyspnea	Washout Period Numeric Rating Scores							Tried 2 nd treatment
			0 min	10 min	20 min	30 min	40 min	50 min	60 min	
4	BIPAP	7	6	2	1	2	2	2	3	Yes
5	BIPAP	8	2	3	1	1	2	2	2	No
6	BIPAP	5	2	5						Yes
9	BIPAP	7	6	3	4	3				No*
14	BIPAP	7	4	0	0	0	0	1	1	No
15	BIPAP	5	2	2	2	2	2	2	2	No
1	Vapotherm	8	8	-	7					Yes
3	Vapotherm	6	3	3	5					Yes
8	Vapotherm	5	3	3	4					Yes
10	Vapotherm	8	5	7						Yes
11	Vapotherm	10	4	2	1	1	4	2	2	No
13	Vapotherm	3	2	3						Yes
16	Vapotherm	9	6	7	7	6	7	6	6	Yes

*This patient dropped out of study early during the washout period due to fatigue.

G. Patient Preference and Satisfaction

In addition to dyspnea scores and global assessments, patients who tried both interventions were asked at the end of the study to directly compare Vapotherm and BIPAP, and provide us with their overall preference.

Among the 5 individuals who completed the entire study, 2 patients preferred Vapotherm for relief of dyspnea, 2 patients preferred BIPAP, and one liked both. However, 4 of 5 patients reported BIPAP as causing more discomfort than Vapotherm. Taking all factors into consideration, 2 patients preferred Vapotherm, 2 patients preferred BIPAP, and 1 preferred both.

A satisfaction survey was completed by 10 patients who completed a substantial part of this study. All 10 patients agreed that this was “worthwhile” and that they would “do this study again” and “recommend this study to others”. Seven of 10 patients agreed that this study “improved his/her quality of life”.

Chapter 5. Discussion

We presented the preliminary results of an open label randomized Phase II clinical trial comparing BIPAP and Vapotherm for the relief of persistent dyspnea among inpatients with advanced cancer. After screening over 800 patients, we found 62 (8%) eligible individuals, and enrolled 16 out of a planned total of 50 patients. Despite challenges with recruitment and attrition, our results supported that both devices provide significant relief for dyspnea and decrease the work of breathing. Further efforts to complete this study are warranted.

A. Recruitment and Retention

This study had several unique challenges, making it difficult to recruit patients. First, our study population involved advanced cancer patients with persistent dyspnea, who represent a population with extremely poor prognosis and low performance status. In fact, many of these patients were delirious, in acute distress, or too weak/tired to participate in our study. Second, our study focused on recruiting patients with persistent rather than episodic dyspnea because we believed that BIPAP and Vapotherm are best suited for this purpose. This significantly limits the number of eligible subjects as persistent dyspnea is not as common (46). Third, only hospitalized patients were included in this study. These patients were generally admitted for acute illness or complications, with rapid changes in their health status. This, coupled with the busy hospital

course with multiple investigations and/or procedures, and the unpredictable discharge planning, made it difficult to find a window of opportunity for patients to participate in the study. Finally, patients were generally less inclined to enroll onto supportive care studies than cancer treatment trials (47). Thus, successful recruitment required screening of large number of patients, regular monitoring, impeccable coordination, cohesive teamwork and a flexible schedule. It was encouraging that we were able to enroll 16 patients between October 2009 and March 2010, representing approximately one third of the accrual target. Putting this in perspective, a review of the 6 randomized clinical trials included in a recent metaanalysis examining the effect of oxygen for dyspnea showed the median sample size to be 24 (range 7-51) (3).

Despite the relatively short duration of this study, attrition represented another major challenge. Only 5 of 16 subjects were able to complete the entire study. Four subjects did not proceed to the second phase because their dyspnea score were too low after the first intervention. Five subjects had some difficulty tolerating BIPAP due to anxiety, claustrophobia, positive airway pressure and nausea. Our finding is consistent with literature which showed that 10-30% of patients have BIPAP intolerance (48, 49). Interestingly, 2 of these patients had difficulty tolerating Vapotherm as well. Thus, BIPAP and Vapotherm may not be appropriate

for all patients, particularly those who are frail and in distress. Better patient selection and longer washout period are necessary for future trials.

B. Improvement in Dyspnea

The numeric rating scale and modified Borg scale indicated some improvement with both BIPAP and Vapotherm. Due to the small sample size, we did not compare the change in dyspnea scores between the two interventions. However, the numeric rating scale appeared to favor BIPAP, while the modified Borg scale showed greater improvement with Vapotherm. This discrepancy may be due to random variation, the different sensitivity of the scales, and/or how patients interpreted these tools. A larger sample size with formal statistical testing is necessary.

A difference of 21 mm on a 100 mm visual analog scale was found to be clinically significant in a study of heart failure patients (50). However, there is no established minimal clinical important difference for both numeric rating scale and modified Borg scale (37). Thus, we included a global symptom assessment at the end of each intervention. Consistent with the dyspnea scores, a majority of the patients reported the devices to be useful in relieving their dyspnea. This benefit, if confirmed, is highly encouraging given that a majority of our patients were already on maximal supportive measures with supplemental oxygen, steroids, opioids and bronchodilators. As hypothesized, BIPAP and Vapotherm may exert their

therapeutic effects on dyspnea through multiple mechanisms rather than just improved oxygenation alone.

We were somewhat surprised by the prolonged washout period, as other studies demonstrated that patients become dyspneic shortly after discontinuation of supplemental oxygen (10, 31). Three patients who tried BIPAP and one on Vapotherm reported significant and long lasting improvement after discontinuation of the respective interventions. We initially hypothesized that BIPAP is better than Vapotherm for relief of dyspnea, given that it not only improves oxygenation, but also ventilation, muscle fatigue and alveolar recruitment. Upon completion of accrual, we would be testing this specific hypothesis.

C. Toxicities

Safety is an important outcome for this study. Patients who were able to tolerate the devices reported minimal toxicities. While the BIPAP mask was associated with some discomfort, patients also found the nasal prongs to be somewhat uncomfortable. Although BIPAP may result in the sensation of suffocation in some patients, our patients reported a reduction in this symptom while on BIPAP, consistent with its beneficial effort on dyspnea.

D. Improvement in Physiologic Measures

Our preliminary examination of physiologic measures demonstrated that the oxygen saturation improved while the respiratory rate decreased by approximately 4/minute with both interventions, consistent with a decreased work of breathing. Interestingly, tissue carbon dioxide level did not drop significantly with BIPAP. However, it is important to point out that a majority of the patients enrolled so far had hypoxemic respiratory failure rather than hypercapneic respiratory failure. As shown by the transcutaneous carbon dioxide level, these patients were in a hyperventilation state at baseline, and thus BIPAP had limited impact on this parameter.

E. Limitations

This study has several limitations. First, the primary outcome measure of dyspnea was a subjective numeric rating scale. Rather than a direct benefit from the study interventions, the positive finding could simply be the result of placebo and/or trial effect, such as positive interaction with study staff. To assess dyspnea from different angles, we incorporated two different dyspnea scales, global assessment, washout period assessment and a number of objective secondary endpoints such as vital signs. Second, ascertainment bias was particularly important as blinding was not possible for this study. Third, we only examined the study interventions for 2 hours each and in hospitalized patients only. The longer term benefit in outpatients is unclear. Further studies are necessary to examine these

options. Finally, it is important to recognize the interim results reported here were based on 16 patients only, and our conclusions could change with a larger sample size.

F. Conclusions

Based on the preliminary analysis of 16 patients, we found that BIPAP and Vapotherm provided excellent dyspnea relief for advanced cancer patients who had persistent dyspnea despite standard therapeutic options. The use of these devices was associated with minimal toxicities and positive physiologic changes. We were also able to demonstrate the feasibility of enrolling very sick patients onto this study. Our next step would be to complete this clinical trial, which would allow us to directly compare the efficacy of these two modalities. If the findings remained positive, larger, more definitive research studies examining these interventions for longer periods are warranted.

Appendix
A. Study Forms

Patient Demographics and Baseline Characteristics for Dyspnea Study
Assessment #1 Only

Age: _____	Gender: _____	Date of Birth: _____
Ethnicity: <div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> White <input type="checkbox"/> Asian <input type="checkbox"/> Black </div> <div> <input type="checkbox"/> Hispanic <input type="checkbox"/> Other _____ </div> </div>		
Cancer Diagnosis: Date of diagnosis: _____ Cancer histology: _____ Cancer stage: _____ Cancer treatments received (include systemic therapy and radiation): _____ _____		
Medical Co-morbidities: <div style="display: flex; justify-content: space-between;"> <div> COPD Asthma CHF Bronchiectasis Others </div> <div> <input type="checkbox"/> Yes <input type="checkbox"/> Yes <input type="checkbox"/> Yes <input type="checkbox"/> Yes </div> <div> <input type="checkbox"/> No <input type="checkbox"/> No <input type="checkbox"/> No <input type="checkbox"/> No </div> </div> _____		
Reason for dyspnea: _____		
<div style="display: flex;"> <div style="flex: 1;"> <u>Current Medications:</u> Bronchodilators (e.g. Salbutamol): Steroids (e.g. prednisone): Opioids (e.g. morphine): Others </div> <div style="flex: 2; padding-left: 10px;"> Please list name, dosage, frequency and route _____ _____ _____ _____ _____ _____ _____ </div> </div>		

Research Staff Signature:

Previous BIPAP/CPAP/Vapotherm			
<input type="checkbox"/>	BIPAP	If yes,	How many times in the past? _____ When was the last time? _____ What was reason? _____
<input type="checkbox"/>	CPAP	If yes,	How many times in the past? _____ When was the last time? _____ What was reason? _____
<input type="checkbox"/>	Vapotherm	If yes,	How many times in the past? _____ When was the last time? _____ What was reason? _____
Current ECOG Performance Status:			
<input type="checkbox"/>	1	<input type="checkbox"/>	3
<input type="checkbox"/>	2	<input type="checkbox"/>	4
Physical Examination Findings:			
Weight (kg)		_____	
Heart rate (beats/minute)		_____	
Respiratory rate (/minute)		_____	
Blood pressure		_____	
(systolic/diastolic)		_____	
Temperature (°F)		_____	
Oxygen saturation (%)		_____	
Supplemental oxygen (L/min)		_____	
Respiratory examination		_____	
Cardiac examination		_____	

Research Staff Signature:

Numeric Rating Scale for Screening Purposes (2 Step Consent)

Please circle the number to indicate the average level of your **shortness of breath over the last 2 weeks**.

No shortness
of breath

Worst
possible
shortness
of breath

0 1 2 3 4 5 6 7 8 9 10

Please circle the number to indicate the level of your **shortness of breath NOW**.

No shortness
of breath

Worst
possible
shortness
of breath

0 1 2 3 4 5 6 7 8 9 10

Research Staff Only

Patient agreed to be screened:

☐ Yes

☐ No

If patient disagreed, please
indicate reason(s):

After screening, patient is eligible:

☐ Yes

☐ No

If not eligible, please
indicate reason(s):

Research Staff Signature:

Numeric Rating Scale for Study Assessments

Assessment #1, #2, #3, #4 (please circle)

Please circle the number to indicate the level of your **shortness of breath NOW**.

No shortness
of breath

Worst
possible
shortness
of breath
10

0 1 2 3 4 5 6 7 8 9

Research Staff Signature:

Modified Borg Scale for Study Assessments

Assessment #1, #2, #3, #4 (please circle)

Please circle the number that best describes **the sensation of your shortness of breath NOW** (e.g. extremely weak sensation, extremely strong sensation).

0	Nothing at all
0.5	Extremely weak (just noticeable)
1	Very weak
2	Weak (light)
3	Moderate
4	Somewhat strong
5	Strong (heavy)
6	
7	Very strong
8	
9	
10	Extremely strong (almost maximal)
*	Maximal

Research Staff Signature:

Cancer Dyspnoea Scale
Assessment #1 only

The Cancer Dyspnoea Scale

We would like to ask you about your breathlessness or difficulty in breathing. Please answer each question by circling only the numbers that best describes the breathing difficulty that you felt *during the past few days*. Base your response on your first impression.

	Not at all	A little	Somewhat	Considerably	Very much
1 Can you inhale easily?	1	2	3	4	5
2 Can you exhale easily?	1	2	3	4	5
3 Can you breathe slowly?	1	2	3	4	5
4 Do you feel short of breath?	1	2	3	4	5
5 Do you feel breathing difficulty accompanied by palpitations and sweating?	1	2	3	4	5
6 Do you feel as if you are panting?	1	2	3	4	5
7 Do you feel such breathing difficulty that you don't know what to do about it?	1	2	3	4	5
8 Do you feel your breath is shallow?	1	2	3	4	5
9 Do you feel your breathing may stop?	1	2	3	4	5
10 Do you feel your airway has become narrower?	1	2	3	4	5
11 Do you feel as if you are drowning?	1	2	3	4	5
12 Do you feel as if something is stuck in your airway?	1	2	3	4	5

Calculation method

- Add the scores for each factor together.
 Factor 1 = (items 4 + 6 + 8 + 10 + 12) – 5 = sense of effort
 Factor 2 = (items 5 + 7 + 9 + 11) – 4 = sense of anxiety
 Factor 3 = 15 – (items 1 + 2 + 3) = sense of discomfort
- Add the total scores for each factor together = total dyspnoea

*Subtractions are to make adjustments for 0 as a state of absence of dyspnoea.

Research Staff Signature: _____

Global Symptom Evaluation
Assessments #2 only

After starting your new treatment, how are your symptoms?

- ☐ Worse
- ☐ About the same
- ☐ Better

If you answered better, are your symptom?

- ☐ Almost the same, hardly any better at all
- ☐ A little better
- ☐ Somewhat better
- ☐ Moderately better
- ☐ A good deal better
- ☐ A great deal better
- ☐ A very great deal better

If you answered worse, how much worse are your symptom?

- ☐ Almost the same, hardly any worse at all
- ☐ A little worse
- ☐ Somewhat worse
- ☐ Moderately worse
- ☐ A good deal worse
- ☐ A great deal worse
- ☐ A very great deal worse

Research Staff Signature:

Global Symptom Evaluation and Study Satisfaction

After starting your new treatment, how are your symptoms?

- ☐ Worse
☐ About the same
☐ Better

If you answered better, are your symptom?

- ☐ Almost the same, hardly any better at all
☐ A little better
☐ Somewhat better
☐ Moderately better
☐ A good deal better
☐ A great deal better
☐ A very great deal better

If you answered worse, how much worse are your symptom?

- ☐ Almost the same, hardly any worse at all
☐ A little worse
☐ Somewhat worse
☐ Moderately worse
☐ A good deal worse
☐ A great deal worse
☐ A very great deal worse

Participating in a clinical trial / research study is a personal choice and an individual experience. We would like to get your feedback on how well we did in meeting your needs.

Directions: Please answer each question by circling Y (for yes), N (for no), or U (for uncertain).

Was it worthwhile for you to participate in this research study? Y N U

If you had to do it over, would you participate in this research study again? Y N U

Would you recommend participating in this research study to others? Y N U

Did your quality of life get better by participating in this research study? Y N U

Did your quality of life get worse by participating in this research study? Y N U

If there was **one thing** that could have been done to improve your experience in this research study, what would it be?

Research Staff Signature:

Patient Preference Survey

Assessment #4 only

1. How would you consider your breathing while on BIPAP as compared to before the study? (Choose one)

Much worse
Worse
Same
Better
Much better

2. How would you consider your breathing while on VapoTherm as compared to before the study? (Choose one)

Much worse
Worse
Same
Better
Much better

3. How would you consider your breathing comparing BIPAP to VapoTherm? (Choose one)

BIPAP is much better
BIPAP is better
Same
VapoTherm is better
VapoTherm is much better

4. Which of the following would you prefer the most for relief of your shortness of breath? (Choose one)

BIPAP
VapoTherm
Both
None of above

5. Which of the following causes you the most discomfort? (Choose one)

BIPAP
VapoTherm
Both
None of above

6. Which of the following would you prefer the most overall, taking all factors into consideration? (Choose one)

BIPAP
VapoTherm
Both
None of above

7. If you have tried both nasal and facial mask while on BIPAP, which one do you prefer more? (Choose one)

Facial mask
Nasal mask
Both
None of above

Research Staff Signature: _____

Washout Period Data Collection and Decision Making Sheet

During washout period only

Baseline dyspnea score (assessment #1) _____/10

Cutoff score for starting 2nd intervention (if baseline dyspnea score = 3, then the cutoff score = 3; otherwise, subtract 1 from the baseline dyspnea score to get cutoff score) _____/10

Please indicate patients' level of dyspnea during the washout period:

Time (24:00)	Interval	Dyspnea score	Instruction
	10 minute	_____/10	Proceed to 2 nd intervention if \geq cutoff; otherwise, wait 10 minutes and repeat assessment
	20 minute	_____/10	Proceed to 2 nd intervention if \geq cutoff; otherwise, wait 10 minutes and repeat assessment
	30 minute	_____/10	Proceed to 2 nd intervention if \geq cutoff; otherwise, wait 10 minutes and repeat assessment
	40 minute	_____/10	Proceed to 2 nd intervention if \geq cutoff; otherwise, wait 10 minutes and repeat assessment
	50 minute	_____/10	Proceed to 2 nd intervention if \geq cutoff; otherwise, wait 10 minutes and repeat assessment
	60 minute	_____/10	Proceed to 2 nd intervention if \geq cutoff OR if score $\geq 3/10$; otherwise, terminate study

Research Staff Signature: _____

Patient Reported Adverse Effect Form
Assessment #1, #2, #3, #4 (please circle)

Please indicate if you experience any of the following **now**:

	Not at all										Worst possible
	0	1	2	3	4	5	6	7	8	9	10
I have dry eyes	0	1	2	3	4	5	6	7	8	9	10
I have eye irritation	0	1	2	3	4	5	6	7	8	9	10
Moisture in my nose	0	1	2	3	4	5	6	7	8	9	10
The nasal prong is uncomfortable	0	1	2	3	4	5	6	7	8	9	10
The mask is painful	0	1	2	3	4	5	6	7	8	9	10
I feel I am suffocating	0	1	2	3	4	5	6	7	8	9	10
My stomach is bloated	0	1	2	3	4	5	6	7	8	9	10
I feel anxious	0	1	2	3	4	5	6	7	8	9	10
I have trouble eating	0	1	2	3	4	5	6	7	8	9	10
I have trouble drinking	0	1	2	3	4	5	6	7	8	9	10
I have trouble talking	0	1	2	3	4	5	6	7	8	9	10
I have trouble sleeping	0	1	2	3	4	5	6	7	8	9	10
Others Please specify: _____	0	1	2	3	4	5	6	7	8	9	10
Others Please specify: _____	0	1	2	3	4	5	6	7	8	9	10

Research Staff Signature: _____

Dropout

Assessment #2, #3, #4 (please circle)

Dropout (only if patient unable to complete study)

Time of study dropout

Phase of study dropout

- ☐ Before starting intervention 1
- ☐ During intervention 1
- ☐ During washout period
- ☐ During intervention 2
- ☐ After intervention 2

Reason(s) for dropout

Research Staff Signature: _____

Data Collection for Respiratory Settings

	Assessment #1	Assessment #2 30/60/90/120min	Assessment #3	Assessment #4 30/60/90/120min
Start time				
End time				
Device (Bipap, Vapotherm or Suppl. O ₂)				
Interface (facial mask, nasal mask, nasal prongs)				
FiO ₂ (%) Reading				
IPAP (mmHg) Reading				
EPAP (mmHg) Reading				
O ₂ flow (Vapotherm or Supplemental O ₂) Reading				
TcCO ₂ (mmHg) Q30min				
SpO ₂ (%) Q30min				
RR (minute)				
HR (minute)				
BP (systolic/ diastolic)				
Temp (°F)				
Comments				

Research Staff Signature: _____

B. Study Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

An Exploratory Trial of Bilevel Positive Airway Pressure Device
and High Flow Oxygen for Persistent Dyspnea in Advanced
Cancer Patients
2009-0164

Study Chair: Eduardo Bruera

1

.

Participant's Name

Medical Record Number

You are being asked to take part in this clinical research study at The University of Texas M. D. Anderson Cancer Center ("M. D. Anderson"). This consent form explains why this research study is being done and what your role will be if you choose to take part. This form also describes the possible risks connected with being in this study. After reviewing this information with the person responsible for your enrollment, you should know enough to be able to make an informed decision on whether you want to take part in the study.

You are being asked to take part in this study because you have advanced cancer and are experiencing shortness of breath.

DESCRIPTION OF RESEARCH

2. PURPOSE OF STUDY

The goal of this clinical research study is to learn if specialized breathing devices reduce the sensation of shortness of breath in patients with advanced cancer who are experiencing shortness of breath. Researchers want to learn if these devices can help to control shortness of breath.

The 2 devices being tested and compared are called BiPAP (bilevel positive airway pressure) and Vapotherm.

3. DESCRIPTION OF STUDY

Study Devices

The **BiPAP device** is designed to help people get more air in and out of their lungs without using as much effort as regular breathing. The air is given through a mask, and the amount of air can be set to different levels.

The **Vapotherm device** is also designed to deliver air in and out of the lungs. The air is warmed, filtered for bacteria, and then delivered through the nose using a tube under the nostrils.

Screening Tests

Signing this consent form does not mean that you will be able to take part in this study. You will have "screening tests" to help the doctor decide if you are eligible to take part in this study. The following tests and procedures will be performed:

You will have a physical exam, including measurement of your weight and vital signs (heart rate, breathing rate, blood pressure, and temperature).

The level of oxygen in your blood will be measured using a soft clamp placed on your finger.

You will be asked about your breathing, and you will rate how hard it is to breathe.

You will complete 3 questionnaires. Two (2) of them have questions about the breathing symptoms, and the third questionnaire has questions about any confusion you may be experiencing. This should take a total of less than 15 minutes.

From your medical record, the study staff will collect information about your age, sex, race, cancer type, any drugs you are taking, and possible causes of shortness of breath.

The research staff will discuss the screening test results with you. If the screening tests show that you are not eligible to take part in the study, you will not be enrolled. Other treatment options will be discussed with you.

Study Groups

If you are found to be eligible to take part in this study, you will be randomly assigned (as in the flip of a coin) to 1 of 2 groups.

Group 1 will receive air through BiPAP for up to 2 hours and then air through Vapotherm for up to 2 hours.

Group 2 will receive air through Vapotherm for up to 2 hours and then air through BiPAP for up to 2 hours.

The study staff will help you use the devices.

If you have trouble with one of the devices, you can be switched to the other device before the 2-hour period is over.

After using the first device, you will wait for up to 60 minutes before switching over to the other device. This waiting period will occur no matter if you used the first device for the full 2 hours or not.

During the waiting period, you will return to the same air delivery device and oxygen level that you were using just before you started the study. The study staff will also be checking to see if you are still eligible to use the second device.

Study Tests

During the study period, your vital signs and level of air breathed out will be recorded using a measuring device on your chest.

Before and after using the devices, you will rate how hard it is to catch your breath.

After using the second device, you will fill out a questionnaire that has questions about which device you prefer. This should take less than 5 minutes.

Length of Study

You will be on this study for up to 5 hours. You will be taken off study and the device will be stopped if intolerable side effects occur while using a study device.

Use of Other Drugs

During the 4-5 hour study period, you will not be allowed to take certain drugs for standard care that may affect the study tests. These drugs include certain pain-killer drugs (such as morphine and hydromorphone), steroids (such as prednisone and dexamethasone), and inhaled drugs (such as ipratropium and salbutamol).

Any doses of inhaled drugs (regularly scheduled doses and "as needed" doses) and any "as needed" doses of pain-killer drugs and steroids that fall within the 4-5 hour study period will be put on hold and will be given to you right after the study is complete.

You may, however, choose to take these drugs, either because your shortness of breath is not controlled, or because these drugs are needed to treat other problems (such as pain). If you and your doctor decide that you should take these drugs during the study period, you will be taken off study so you can receive these drugs. The reason for stopping your study participation is that these drugs may affect how you rate your shortness of breath.

This is an investigational study. The BIPAP and Vapotherm devices are commercially available and FDA approved for delivering oxygen when medically needed, including in patients with advanced cancer. The investigational part of this study is to collect information from asking patients to rate how well the study devices may affect shortness of breath.

There will be no cost to you for using the breathing devices during the study.

Up to 50 patients will be enrolled in this study. All will be enrolled at M. D. Anderson.

4. RISKS, SIDE EFFECTS, AND DISCOMFORTS TO PARTICIPANTS

While on this study, you are at risk for side effects. You should discuss these with the study doctor. The known side effects are listed in this form, but they will vary from person to person. In most cases, the side effects will go away shortly after the device is stopped but in some cases the side effects may last longer.

"Likely" side effects occur in more than 20% of patients, "common" side effects occur in 3-20% of patients, and "rare" side effects occur in fewer than 3% of patients.

BiPAP Side Effects

The BiPAP face mask may likely cause discomfort.

BiPAP may commonly cause stomach bloating and/or drying of the eyes.

BiPAP may rarely cause pink eye.

Vapotherm Side Effects

Vapotherm may likely cause uncomfortable moisture in the nose.

Vapotherm may rarely cause the feeling of breathing difficulty (like you are choking or suffocating but are actually not).

Other Risks

Questionnaires may contain questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable. If you have concerns after completing the questionnaire, you are encouraged to contact your doctor or the study chair.

This study may involve unpredictable risks to the participants.

5. POTENTIAL BENEFITS

The breathing devices may help to control the shortness of breath during the 4-5 hour study period. Future patients may benefit from what is learned in this study. There may be no benefits for you in this study.

6. ALTERNATE PROCEDURES OR TREATMENTS

You may choose not to take part in this study. You may choose to receive drugs for shortness of breath. The drugs may include, for example, opioids (pain-relievers) or bronchodilators (airway-wideners). You may use either BiPAP or Vapotherm without taking part in this study.

You may choose to receive other investigational therapy, if available. You may choose not to have treatment for shortness of breath at all. In all cases, you will receive appropriate medical care.

I understand that the following statements about this study are true:

7. M. D. Anderson may benefit financially from my participation and/or from what is learned in this study.
8. I may ask the study chair any questions I have about this study, including questions about the costs. I may contact the study chair, Dr. Eduardo Bruera, at 713-792-6085. I may also contact the Chair of M.

D. Anderson's IRB at 713-792-2933 with any questions that have to do with this study or my rights as a study participant.

9. My participation in this research study is strictly voluntary. I may refuse to take part in this study without any penalty or loss of benefits to which I am otherwise entitled. I may also withdraw from participation in this study at any time without any penalty or loss of benefits. I should first discuss leaving the study with my doctor. If I withdraw from this study, I may still be treated at M. D. Anderson.
10. I understand that the study may be changed or stopped at any time by the study chair, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP) (a regulatory agency that oversees research in humans), or the IRB of M. D. Anderson.
11. I will be informed of any new findings that might affect my willingness to continue taking part in the study.
12. M. D. Anderson will take appropriate steps to keep my personal health information private. However, there is no guarantee of absolute privacy. Federal agencies (such as the FDA and the OHRP), and the IRB of M. D. Anderson might review my record to collect data or to check that the research is being done safely and correctly. In some situations, the FDA could be required to reveal the names of participants.
13. If I suffer injury as a direct result of taking part in this study, M. D. Anderson will provide medical care. However, this medical care will be billed to my insurance provider or me in the ordinary manner. I understand that I will not be reimbursed for expenses or compensated financially by M. D. Anderson for this injury. I may also contact the Chair of M. D. Anderson's IRB at 713-792-2933 with questions about study-related injuries.
14. Certain tests, procedures, and/or medications that I may receive as part of this study may be without cost to me because they are for research purposes only. However, my insurance provider or I may be financially responsible for the cost of supportive care and treatment of any complications resulting from the research tests, procedures, and/or medications, including hospitalization, nausea, vomiting, low blood cell counts, and dehydration. Standard medical care that I receive under this research study will be billed to my insurance provider and/or me in the ordinary manner. I should learn before taking part in this study which parts of the research-related care will be provided without charge, which costs my insurance provider will

pay for, and which costs will be my responsibility. I may ask to speak with a financial counselor about the costs of this study.

15. I understand that there are no plans to compensate me for any patents or discoveries that may result from my participation in this research. I will receive no compensation for taking part in this study.

Authorization for Use and Disclosure of Protected Health Information:

- A. During the course of this study, the research team at M. D. Anderson will be collecting information about you. This information may include your medical history, study schedule, and the results of any of your tests, therapies, and/or procedures. The purpose of collecting and sharing this information is to learn about how the study procedures may affect the disease and any study-related side effects. Your doctor and the research team may share your study information with the parties named in Section E below.
- B. If you refuse to provide your authorization to disclose your protected health information, you will not be able to participate in this research study.
- C. Your protected health information will be protected according to state and federal law. However, there is no guarantee that your information will remain confidential, and it may be re-disclosed at some point.
- D. All identifying information such as your name and address will be kept private. This information may be kept at M. D. Anderson forever. You will be assigned a code number so that your name will not be used. The research team at M. D. Anderson will be able to link the code number to your name. In some instances, in order to ensure the scientific value of the study, the parties named in Section E below will be able to view your study record but will not be permitted to copy any identifying information contained in your record.
- E. Your information may be shared with the following parties:
 - The FDA
 - The OHRP
 - The IRB of M. D. Anderson
 - Officials of M. D. Anderson
 - Clinical study monitors who verify the accuracy of the information
 - Individuals with medical backgrounds who determine the effect that the study procedures may have on the disease

Individuals who put all the study information together in report form

- F. You have the right to see and reproduce your records related to the research study, and ask for corrections, for as long as this information is held by the study chair and/or M. D. Anderson. However, in some studies, in order to ensure the scientific value of the study, participants are not able to view or reproduce their study records until the research has been completed with all participants in the study. If possible for this study, your doctor will be able to discuss your clinical test results with you.
- G. There is no expiration date for the use of your protected health information. You may withdraw your authorization to share your protected health information at any time in writing. Instructions on how to do this can be found in the M. D. Anderson Notice of Privacy Practices (NPP). You may contact the IRB Staff at 713-792-2933 with questions about how to find the NPP. If you withdraw your authorization, you will be removed from the study and the study chair and staff will no longer use or disclose your protected health information in connection with this study, unless the study chair or staff needs to use or disclose some of your research-related protected health information to preserve the scientific value of the study. The parties listed in Section E above may use any study data that were collected before you canceled your authorization.

CONSENT/PERMISSION/AUTHORIZATION FOR TREATMENT

Having read and understood the above and having had the chance to ask questions about this study, think about the study, and talk with others as needed, I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I have been given a signed copy of this consent document.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF PARTICIPANT

DATE

I was present during the explanation of the research to be performed under Protocol **2009-0164**.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF WITNESS TO THE VERBAL CONSENT

PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR)

DATE

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF PERSON RESPONSIBLE & RELATIONSHIP

DATE

I have discussed this clinical research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF STUDY CHAIR OR PERSON OBTAINING
CONSENT

DATE

Translator

I have translated the above informed consent as written (without additions or subtractions)

into _____ and assisted the people obtaining/providing

(Name of Language)

consent by translating all questions and responses during the consent process for this participant.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

NAME OF TRANSLATOR

SIGNATURE OF TRANSLATOR DATE

- ☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line.)

Standard Operating Procedure for
Vapotherm and Intermittent BiPap for Respiratory
Support in Patients with Advanced Neoplasm Trial
[VIBRANT Study]

Protocol 2009-0164

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PRINCIPAL INVESTIGATOR: DR. EDUARDO BRUERA

Research Team Contacts

	Research RN	Research RT	Research MD
First	Cheryl Scott Pg: 606-3536 Ph: 745-1948	Laura Withers Pg: 404-1049 Ph: 745-7400	David Hui Pg: 606-3376 Ph: 745-7082
Second	Rachael Lane Pg: 606-2296 Ph: 563-1859	Quan Nguyen Pg: 606-5894 Ph: 563-6715	Sriram Yennu Pg: 404-6350 Ph: 792-3938
Third	Brenda Coldman Pg: 563-1685 Ph: 404-4509	Clarence Finch Pg: 404-9418 Ph: 745-5475	Eduardo Bruera Pg: 606-3633 Ph: 792-6084
Fourth	David Hui Pg: 606-3376 Ph: 745-7082		

Clinical RT Contacts (Pre-screen)

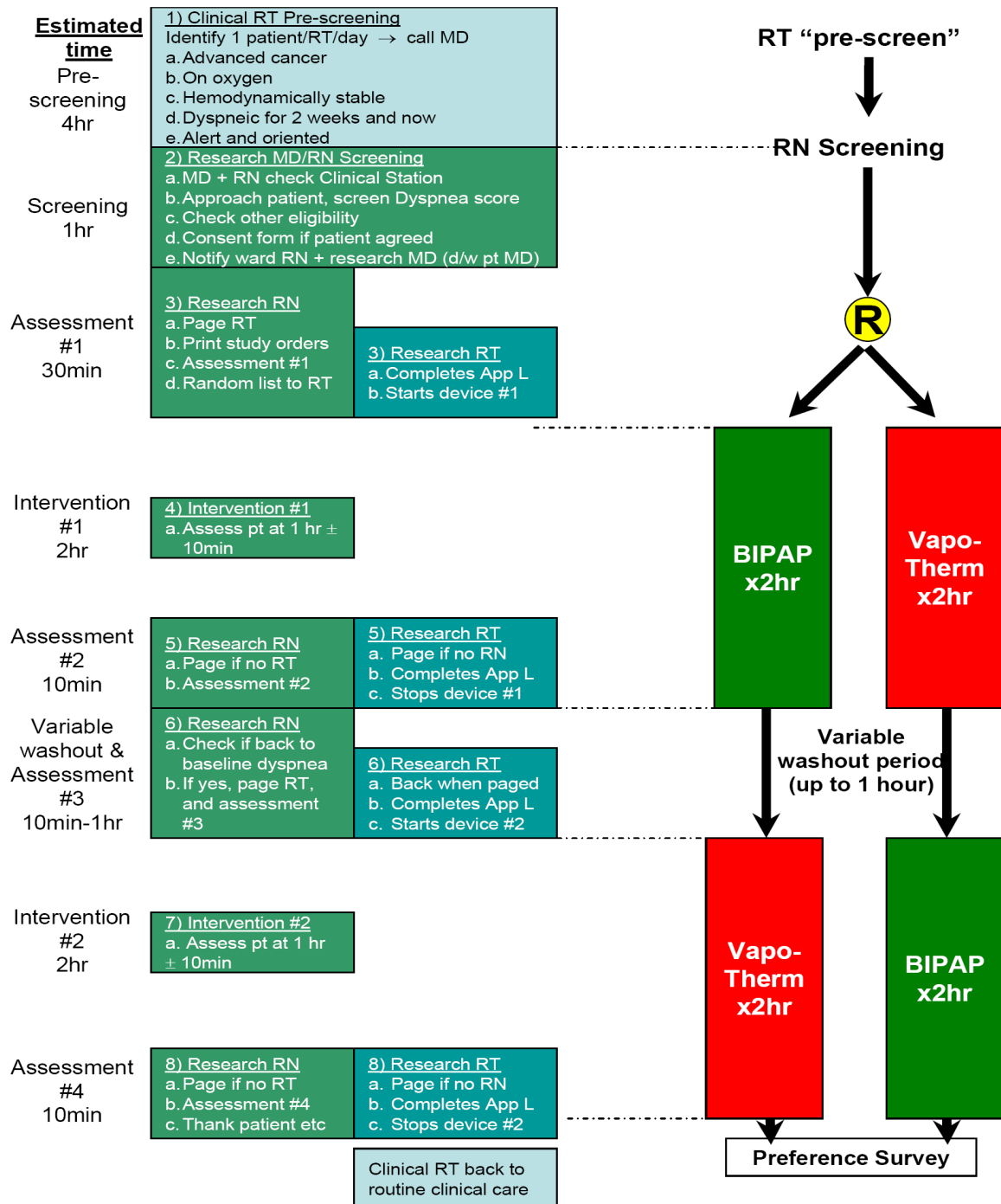
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Study Collaborators

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General Information and Study Flowchart

- Study runs Monday to Friday, 8am-5pm
- Study interventions need to be initiated at or before noon
- Any questions during this study should be directed to **Dr. David Hui (606-3376, dhui@mdanderson.org)**



Eligibility Criteria

Inclusion criteria:

- 1) Diagnosis of advanced cancer, defined as locally advanced, recurrent or metastatic disease
- 2) Patients with persistent dyspnea, defined in this study as dyspnea at rest with an average intensity level ≥ 3 out of a numeric rating scale from 0 to 10 for at least 2 week and just prior to study initiation, despite supplemental oxygen of up to 21 L/min to keep oxygen saturation $\geq 90\%$
- 3) Dyspnea is judged clinically to be predominantly due to underlying malignancy, with or without obstructive lung disease
- 4) Inpatient at M.D. Anderson Cancer Center
- 5) On stable doses of opioids, steroids and bronchodilators, defined as no significant change ($\pm 20\%$) in the total daily dose over the last 48 hours
- 6) Able to communicate in English
- 7) Expected life expectancy > 1 week
- 8) Patients with a diagnosis of pneumonia are also eligible for this study if they meet the eligibility criteria above, with dyspnea ≥ 2 weeks prior to the diagnosis of pneumonia.

Exclusion criteria:

- 1) Patients who remain hypoxic (i.e. O_2 saturation $< 90\%$ despite maximal oxygen delivery (21 L/min) are not included in this study because they are considered to have severe life-threatening respiratory failure and are too unstable for study inclusion.
- 2) Hemodynamic instability (HR > 140 , SBP < 80) within 24 hours of study initiation as per clinic station
- 3) Acute respiratory distress requiring intubation
- 4) Delirium as indicated by a Memorial Delirium Assessment Scale (MDAS) of 13 or higher
- 5) Glasgow coma scale < 8
- 6) Excessive airway secretions interfering with BIPAP administration
- 7) History of facial trauma within 1 month of enrollment
- 8) Upper GI bleed within 2 weeks or esophageal rupture of enrollment
- 9) Partial or complete small bowel obstruction or severe nausea/vomiting (ESAS nausea $> 7/10$) within 48 hours of enrollment
- 10) Hemoglobin < 8 g/dL at the time of enrollment (blood draw within last 2 weeks)
- 11) Acute exacerbation of COPD or CHF within 2 weeks of enrollment by history or physical
- 12) Pulmonary embolus within 1 week of enrollment by history or physical
- 13) Unwilling to provide informed consent
- 14) Age 18 or under
- 15) Diagnosis of non-cancer related dyspnea (e.g. COPD, CHF or any chronic respiratory disease) requiring supplemental home oxygen prior to hospitalization.

1) Pre-screening (Clinical RT/Research MD)

- a) Clinical RTs (names and contact) in AM shift identifies potentially eligible inpatients for dyspnea study:
 - i) Advanced cancer (metastatic or locally advanced)
 - ii) On supplemental oxygen and sat >90%
 - iii) Hemodynamically stable
 - iv) Likely able to tolerate BIPAP and Vapotherm
 - v) Alert and oriented
 - vi) “Do you have shortness of breath? If yes, for how long roughly?” If the answer is for 2 weeks or longer, patients are potentially eligible for study
- b) If patient met above criteria, please discuss the following with the patient:
 - i) “We have a clinical trial to see if we can help improve your shortness of breath. You get to try two different types of breathing machines for about 2 hours each. I think it may be of interest to you. Would you like to learn more about this study?”
 - ii) If yes, this patient is potentially eligible
- c) Try to identify at least **one** potentially eligible patient per day per RT.
- d) Clinical RTs page research MD on or before 10am, regardless of whether you have a patient or not
 - i) If potentially eligible patient, provide the MRN, name and location for any potentially eligible patients. This will be captured on a screening log
 - ii) If no patients, please let research MD know as well
- e) If research MD has not received any pages by 10am, will page the research RTs to find out what happened.
- f) If research MD not answering within 10 minutes, please page research MD again. If still no answer within 5 minutes, page second research MD.

2) Screening (Research MD/RN, estimate ~1 hour)

- a) Research MD will review patient data (starting with the most likely candidate) on Clinic Station to determine eligibility. If patient not eligible on paper, research RN will inform patients.
- b) If likely eligible, research MD will inform research RN do further pre-screening on Clinic Station before going up to unit to approach patient to
 - i) Discuss study protocol briefly, and ask for permission to screen
 - ii) Ask him/her about dyspnea rating **over the last 2 weeks** on numeric rating scale (has to be $\geq 3/10$)
 - iii) Ask him/her about dyspnea rating **now** on numeric rating scale (has to be $\geq 3/10$)
 - iv) Document the above in Appendix B
- c) Research RN will complete rest of eligibility screening
 - i) If eligible, explain study in detail, provide consent form and ask if patient agrees to participate. If yes, go to Section 2.c.iv. If no, go to Section 2.c.i
 - ii) If not eligible or patient refused to participate, thank the patient and inform RT patient not enrolled
 - iii) Document the above in Appendix B
 - iv) Ensure patient signed consent form
- d) Determine if study can be started **today**
 - i) Research RN will check with patient first
 - ii) Research RN will notify the unit RN most responsible for the patient's care at the time that patient has agreed to participate in this 5 hour study, and discuss the following:
 - (1) Whether there are any tests/procedures (if yes, whether they can be rescheduled until after the study?)
 - (2) Patients who are already on scheduled opioids or steroids may continue to receive them as per clinical care
 - (3) Patients who require any **breakthrough opioids** (parenteral, oral, inhaled), **breakthrough** steroids (parenteral, oral or inhaled) or **scheduled/breakthrough** bronchodilators will be asked to hold the medications if possible. Otherwise, they will need to come off study
 - iii) If patient okay and available, notify research MD so he will notify attending physician of the study and obtain approval.
 - iv) Once all parties have agreed to proceed (patient, attending MD, unit RN, research RN/MD), then proceed to Section 3
 - v) If not, determine if alternative time/day would work for him/her (note that study should be started at or before noon). If patient cannot be on study today, ask if he/she would be okay doing it tomorrow (start at Section 2.b.iii again)
- e) If multiple patients eligible on the same day, start study on one patient first, and then return to the other patient the next day (start at Section 2.b.i).

3) Assessment #1 – Baseline before intervention #1 (Research RN and Research RT, estimate 30 minutes)

- a) Page research RT
- b) At the time when patient is ready to start the interventions, research RN will print the study order form and include in chart.
- c) Research RN will work with patient and family to complete the assessment #1 study forms, and perform vitals assessments and focused respiratory and cardiac examination
 - i) Appendix A - Patient Demographics and Baseline Characteristics
 - ii) Appendix C - Numeric Rating Scale for Study Assessments
 - iii) Appendix D - Modified Borg Scale for Study Assessments
 - iv) Appendix E - Cancer Dyspnoea Scale
 - v) Appendix J - Patient Reported Adverse Effect Form
- d) Research RN will provide research RT with randomization code to decide which intervention would be started first.
- e) Research RT will perform the following
 - i) Get equipments organized
 - ii) Explain to patient how the interventions work
 - iii) Answer any questions and provide reassurance
 - iv) Complete assessment #1 Appendix L- Data Collection for Respiratory Settings
 - v) Set recording trend (30, 60, 90 and 120min) for vitals assessment (HR, RR, BP), TCO₂ and oximetry reading
 - vi) Once patient and research RN all ready, start intervention #1 using the following parameters

Vapotherm:

Device: Vapotherm® 2000i Respiratory Therapy Device

FiO₂: set at 100%

Heat: between 35° and 37°

Oxygen flow: titrate between 10 L/min and 40 L/min to achieve the highest oxygen flow to minimize dyspnea while keeping the patient comfortable

BIPAP:

Device: The BIPAP Vision® Ventilatory Support System

Mask: choice of nasal or face mask

Mode: pressure support mode (S/T)

FiO₂: set at 100%

IPAP and EPAP: started at an inspiratory pressure of 8 cm of H₂O and expiratory pressure of 5 cm of H₂O. Titrate to minimize dyspnea and discomfort. Target inspiratory pressure between 8 and 18 cm of H₂O, and target expiratory pressure between 3 and 10 cm of H₂O

4) Intervention #1 (Research RN and Research RT, estimate 2 hours)

- a) Once patient on stable respiratory setting, research RT will leave and plan to return approximately 10 minutes before termination of intervention #1. During this time, research RT will be available by pager.
- b) Research RN may also leave after completion of assessment #1 after notifying unit nurses to keep an eye on patient and to page her/RT if needed.
- c) Research RN will return after 1 hour of intervention (± 10 minutes) to see how the patient is doing. If patient in distress, notify RT. Otherwise, leave and return approximately 10 minutes before termination of intervention #1.
- d) Anytime during the study, patients who could not tolerate an intervention because of discomfort will be offered the opportunity to
 - i) Temporarily halt the intervention (back to supplemental O₂) and resume when ready. Research RT will be paged ASAP, complete appendix L.
 - ii) Switch to alternative intervention after a variable washout period (if only tried first intervention – go to section 4. Research RN will complete Appendix K and research RT will complete Appendix L).
OR
 - iii) Discontinue the study and go back to supplemental O₂. Research RT will be paged ASAP. Research RN will complete Appendix K and research RT will complete Appendix L.
- e) If patients require any **breakthrough opioids** (parenteral, oral, inhaled), **breakthrough** steroids (parenteral, oral or inhaled) or **scheduled/breakthrough** bronchodilators, they will need to come off study. Research RN and research RT will be paged by unit RN, fill out Appendix K and L, respectively.

5) Assessment #2 (Research RN and Research RT, estimate 10 minutes)

- a) Both research RN and research RT will return approximately 10 minutes before conclusion of intervention #1. If one or the other not available, page each other ASAP (or their backups).
- b) During the next 5-10 minutes, research RN will work with patient and family to complete the assessment #2 study forms before research RT stops intervention #1.
 - i) Appendix C - Numeric Rating Scale for Study Assessments
 - ii) Appendix D - Modified Borg Scale for Study Assessments
 - iii) Appendix F - Global Symptom Evaluation
 - iv) Appendix J - Patient Reported Adverse Effect Form
 - v) Appendix K - Data Collection for Assessments
- c) Research RT will complete assessment #2 Appendix L - Data Collection for Respiratory Settings
- d) Upon completion of all assessments, research RT will stop intervention #1 and put patient back on baseline intervention (same as prior to study).
- e) Go to washout period (Section 6).

6) Washout period and assessment #3 (Research RN and Research RT, estimate 10 minutes to 1 hour)

- a) Research RT may leave if patient stable, but will be paged back if and when patient ready to start intervention #2.
- b) Research RN will check if patient returns to close to baseline level of dyspnea using Appendix I every 10 minutes (e.g. if patient's baseline dyspnea is 5, then he/she has to be at least 4 or above to start next intervention).
- c) Once patient is ready for next intervention, research RN will page research RT back ASAP.
- d) In the meantime, research RN will complete assessment #3 with patient
 - i) Appendix C - Numeric Rating Scale for Study Assessments
 - ii) Appendix D - Modified Borg Scale for Study Assessments
 - iii) Appendix J - Patient Reported Adverse Effect Form
- e) Research RT will perform the following:
 - i) Get equipments organized
 - ii) Explain to patient how the interventions work
 - iii) Answer any questions and provide reassurance
 - iv) Complete assessment #3 Appendix L- Data Collection for Respiratory Settings
 - v) Set recording trend (30, 60, 90 and 120min) for vitals assessment (HR, RR, BP), TCO₂ and oximetry reading
 - vi) Once patient and research RN all ready, start intervention #2 using the following parameters

Vapotherm:

Device: Vapotherm® 2000i Respiratory Therapy Device

FiO₂: set at 100%

Heat: between 35° and 37°

Oxygen flow: titrate between 10 L/min and 40 L/min to achieve the highest oxygen flow to minimize dyspnea while keeping the patient comfortable

BIPAP:

Device: The BIPAP Vision® Ventilatory Support System

Mask: choice of nasal or face mask

Mode: pressure support mode (S/T)

FiO₂: set at 100%

IPAP and EPAP: started at an inspiratory pressure of 8 cm of H₂O and expiratory pressure of 5 cm of H₂O. Titrate to minimize dyspnea and discomfort. Target inspiratory pressure between 8 and 18 cm of H₂O, and target expiratory pressure between 3 and 10 cm of H₂O

7) Intervention #2 (Research RN and Research RT, estimate 2 hours)

- a) Once patient on stable respiratory setting, research RT will leave and plan to return approximately 15 minutes before termination of intervention #2. During this time, research RT will be available by pager.
- b) Research RN may also leave after completion of assessment #2, and notify unit nurses to keep an eye on patient, then page her/RT if needed.
- c) Research RN will return after 1 hour of intervention (± 10 minutes) to see how the patient is doing. If patient in distress, notify RT. Otherwise, leave and return approximately 15 minutes before termination of intervention #2.
- d) Anytime during the study, patients who could not tolerate an intervention because of discomfort will be offered the opportunity to
 - i) Temporarily halt the intervention (back to supplemental O₂) and resume when ready. Research RT will be paged ASAP, complete appendix L.
 - ii) Discontinue the study and go back to supplemental O₂. Research RT will be paged ASAP. Research RN will complete Appendix K and research RT will complete Appendix L.
- e) If patients require any **breakthrough opioids** (parenteral, oral, inhaled), **breakthrough** steroids (parenteral, oral or inhaled) or **scheduled/breakthrough** bronchodilators, they will need to come off study. Research RN and Research RT will be paged, fill out Appendix K and L, respectively.

8) Assessment #4 (Research RN and Research RT, estimate 15 minutes)

- a) Both research RN and research RT will return approximately 15 minutes before conclusion of intervention #2. If one or the other not available, page each other ASAP (or their backups).
- b) During the next 10 minutes, research RN will work with patient and family to complete the assessment #4 study forms before research RT stops intervention #2.
 - i) Appendix C - Numeric Rating Scale for Study Assessments
 - ii) Appendix D - Modified Borg Scale for Study Assessments
 - iii) Appendix G - Global Symptom Evaluation and Study Evaluation
 - iv) Appendix H - Patient Preference Survey (**done after patient back on supplemental oxygen**)
 - v) Appendix J - Patient Reported Adverse Effect Form
- c) Research RT will complete assessment #4 Appendix L - Data Collection for Respiratory Settings
- d) Upon completion of all assessments, research RT will stop intervention #2 and put patient back on baseline intervention (same as prior to study).
- e) Study completed. Research RN and research RT sign over the clinical RT. No further followup. Resume all medications as per prior to study.
- f) Thank patient, unit RN and clinical RT
- g) Patient has the opportunity to return to baseline oxygen delivery, or use BiPAP or Vapotherm if agreed by with attending team

D. Study Budget

BUDGET

	Year 1	Year 2	Year 3
A. Personnel (Indicate percent effort, salary, and names of personnel)			
Respiratory therapists	\$0 (dept)		
Research RN	\$0 (dept)		
Data coordinator	\$0 (dept)		
Fringe Benefits Total			
Category Total	\$0		
B. Permanent Equipment (Itemize)			
Sentec Digital Monitoring System	\$9,700.00		
Category Total	\$9,700.00		
C. Supplies (Group into major categories)			
CPAP Mask (50 units)	\$1550.00		
CPAP tubing (50 units)	\$485.00		
O2 filter (50 units)	\$101.00		
Vaportherm Filter & Setup (50 units)	\$6,745.00		
Sentec Digital Monitoring System supplies (50 units)	\$3180.00		
Category Total	\$12655.00		
D. Travel (DoD. Travel (Domestic only)			
Category Total	\$0		
E. Miscellaneous (List specific amounts for each item)			
Category Total	\$0		
F. SUBCONTRACTS (CATEGORIZE ON CONTINUATION PAGE)			
Category Total			
Total Direct Costs	\$21761.00		
G. Indirect Costs: ____% (Excluding permanent equipment)	\$0		
Total Indirect Costs			
TOTAL ANNUAL COSTS	\$21761.00		
H. Total Amount Requested (Sum of all years including indirect costs; transfer this amount to the budget section of the on-line form)			

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Vita

Dr. David Hui was born in Luton, England on July 10, 1975, the son of Rupert Hui and Ella Hui. He completed his Bachelor of Science degree in Biochemistry and Molecular Biology at the University of British Columbia, Vancouver, Canada in 1997. He was then awarded a postgraduate scholarship from the Natural Sciences and Engineering Research Council to train under Dr. Victor Ling in the same department, and completed his Master of Science thesis on the molecular mechanisms of multi-drug resistance in cancer in 1999.

Dr. Hui entered medical school at the University of British Columbia in 1999, followed by internal medicine residency at the University of Alberta between 2003 and 2006, Edmonton, and medical oncology fellowship at the British Columbia Cancer Agency between 2006 and 2008. He is currently board certified in internal medicine and medical oncology in Canada and the United States.

Dr. Hui is completing a 2 year clinical research fellowship in Supportive and Palliative Oncology under the mentorship of Dr. Eduardo Bruera at the University of Texas M.D. Anderson Cancer Center, funded by the Royal College of Physicians and Surgeons of Canada Clinical Investigator Program. During this time, he has also enrolled onto the Patient Based Biological Research program at M.D. Anderson Cancer Center, working towards another Master degree in Patient Based Biological Research through the University of Texas at Houston Graduate School of Biological Sciences.

His research interests include symptom management clinical trials and integration of palliative care into oncology. He has authored and/or co-authored approximately 40 peer reviewed papers, with his work appearing in various journals such as the *Journal of American Medical Association*, the *Journal of Clinical Oncology* and *Cancer*. In addition to multiple book chapters, he is the author of a popular internal medicine textbook, *Approach to Internal Medicine*, and the co-editor of a medication handbook, *Drugs & Drugs*. He is the recipient of multiple clinical, research, teaching and leadership awards, and has been invited to present at various national and international meetings.

