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Symptom Management and Supportive Care

High-Flow Oxygen and High-Flow Air for Dyspnea in Hospitalized Patients with Cancer: A Pilot Crossover Randomized Clinical Trial

David Hui,[a] Farley Hernandez,[a] Diana Urbauer,[b] Saji Thomas,[c] Zhanni Lu,[a] Ahmed Elsayem,[d] Eduardo Bruera[a]

Departments of [a]Palliative Care, Rehabilitation and Integrative Medicine, [b]Biostatistics, [c]Respiratory Care, and [d]Emergency Medicine, MD Anderson Cancer Center, Houston, Texas, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Clinical trial • dyspnea • Hospital equipment • Neoplasms • Oxygen

Abstract

Background. The effect of high-flow oxygen (HFOx) and high-flow air (HFAir) on dyspnea in nonhypoxemic patients is not known. We assessed the effect of HFOx, HFAir, low-flow oxygen (LFOx), and low-flow air (LFAir) on dyspnea.

Subjects, Materials, and Methods. This double-blind, 4×4 crossover clinical trial enrolled hospitalized patients with cancer who were dyspneic at rest and nonhypoxemic (oxygen saturation >90% on room air). Patients were randomized to 10 minutes of HFOx, HFAir, LFOx, and LFAir in different orders. The flow rate was titrated between 20–60 L/minute in the high-flow interventions and 2 L/minute in the low-flow interventions. The primary outcome was dyspnea numeric rating scale (NRS) "now" where 0 = none and 10 = worst.

Results. Seventeen patients (mean age 51 years, 58% female) completed 55 interventions in a random order. The absolute change of dyspnea NRS between 0 and 10 minutes was −1.8 (SD 1.7) for HFOx, −1.8 (2.0) for HFAir, −0.5 (0.8) for LFOx, and − 0.6 (1.2) for LFAir. In mixed model analysis, HFOx provided greater dyspnea relief than LFOx (mean difference [95% confidence interval] −0.80 [−1.45, −0.15]; p = .02) and LFAir (−1.24 [−1.90, −0.57]; p < .001). HFAir also provided significantly greater dyspnea relief than LFOx (−0.95 [−1.61, −0.30]; p = .005) and LFAir (−1.39 [−2.05, −0.73]; p < .001). HFOx was well tolerated. Seven (54%) patients who tried all interventions blindly preferred HFOx and four (31%) preferred HFAir.

Conclusion. We found that HFOx and HFAir provided a rapid and clinically significant reduction of dyspnea at rest in hospitalized nonhypoxemic patients with cancer. Larger studies are needed to confirm these findings (Clinicaltrials.gov: NCT02932332). ***The Oncologist*** 2021;26:e883–e892

Implications for Practice: This double-blind, 4×4 crossover trial examined the effect of oxygen or air delivered at high- or low-flow rates on dyspnea in hospitalized nonhypoxemic patients with cancer. High-flow oxygen and high-flow air were significantly better at reducing dyspnea than low-flow oxygen/air, supporting a role for palliation beyond oxygenation.

Introduction

Dyspnea is a common presenting symptom among hospitalized patients with cancer. It is associated with significant distress, compromised quality of life, and greater mortality. Despite measures to treat any underlying causes, many patients continue to experience chronic refractory dyspnea. Unfortunately, there are no approved treatment options for palliation of dyspnea.

High-flow nasal cannula (HFNC) devices deliver humidified and heated gas at up to 80 L/minute via nasal cannulae and are now commonly used for patients with hypoxemic respiratory failure [1–5]. In addition to enhanced oxygenation, high flow oxygen (HFOx) may alleviate dyspnea by reducing the inspiratory drive and respiratory effort via multiple mechanisms, including decreased nasopharyngeal inspiratory resistance, enhanced nasopharyngeal washout, augmented positive end-expiratory pressure, increased expiratory resistance, stimulation of trigeminal and glossopharyngeal nerves, decreased bronchoconstriction, improved airway conductance, reduced metabolic cost of gas conditioning, and improved oxygenation of locomotor muscles [6–8]. Because many

Correspondence: David Hui, M.D., Department of Palliative Care, Rehabilitation and Integrative Medicine, University of Texas MD Anderson Cancer Center, Unit 1414, 1515 Holcombe Boulevard, Houston, Texas 77030, USA. Telephone: 713-745-7082; e-mail: dhui@mdanderson.org. Received July 15, 2020; accepted for publication October 28, 2020; published Online First on December 16, 2020. http://dx.doi.org/10.1002/onco.13622

mechanisms are more dependent on the flow rate, humidification, and heated gas than gas type, high-flow air (HFAir) may also be beneficial in patients without hypoxemia; however, this concept remains to be tested clinically.

To date, only a handful of clinical trials have examined the effect of HFNC on dyspnea in different patient populations [9–13], and even fewer have specified patient-reported dyspnea as the primary outcome [3, 14–17]. These studies generally found that HFOx improved dyspnea. However, a majority of these studies were conducted in patients with hypoxemia and no studies have specifically examined the effect of HFAir on dyspnea [18, 19]. A better understanding of the impact of HFOx and HFAir on dyspnea may facilitate their use to alleviate dyspnea and improve quality of life. We conducted a crossover clinical trial to assess the effect of HFOx, HFAir, low-flow oxygen (LFOx), and low-flow air (LFAir) on dyspnea in hospitalized patients with cancer without hypoxemia. Our hypothesis was that HFOx and HFAir would improve dyspnea in these patients.

Subjects, Materials, and Methods

Patients

Hospitalized patients were recruited from the University of Texas MD Anderson Cancer Center. Inclusion criteria were age 18 years or older, a diagnosis of cancer, an average dyspnea numeric rating scale of ≥4/10 over the past 24 hours, oxygen saturation > 90% on ambient air, able to communicate in English or Spanish, and able to tolerate high-flow nasal cannulae. Exclusion criteria were delirium (i.e., Memorial Delirium Assessment Scale >13), hemodynamic instability, respiratory failure requiring mechanical ventilation or noninvasive ventilation, currently requiring high-flow oxygen for oxygenation and frequent use of rescue opioids >8 times per day or rescue bronchodilators >8 times per day over the last 24 hours. The institutional review board at The University of Texas MD Anderson Cancer Center approved this study (protocol number 2016-0282). All patients provided written informed consent. This study protocol was registered in clinicaltrials.gov (NCT02932332). The cutoff for the dyspnea numeric rating scale was revised to ≥3/10 on April 7, 2017, to facilitate enrollment.

Study Design

This investigator-initiated, double-blind, four-intervention, four-period balanced crossover randomized clinical trial examined the effects of HFOx, HFAir, LFOx, and LFAir in nonhypoxemic patients with cancer with dyspnea. The crossover design was selected to facilitate intraindividual comparison, optimize study power, and assess overall patient preference. Patients received each of the four interventions for 10 minutes. This duration was chosen because the effect of gas exchange was expected to be rapid, because previous dyspnea studies with oxygen delivery used similar durations [20], and because of our desire to minimize attrition. A variable washout period was engineered between study interventions in which we assessed dyspnea every 5 minutes for up to 1 hour until the dyspnea level was within 1 point of the baseline level of dyspnea.

Study Interventions

The Optiflow Respiratory Humidifier (Fisher & Paykel Healthcare, Inc, Irvine, CA) was used to deliver HFOx or HFAir via a nasal cannula. The gas flow rate was titrated by the respiratory therapist, starting at 20 L/minute and increasing every minute by 5–10 L/minute to a maximum of 60 L/minute. Patients were asked to try the highest flow rate possible while remaining comfortable. There were two settings for temperature of gas (34°C or 37°C). The respiratory therapist started at 37°C and lowered the temperature to 34°C if the patient reported discomfort. The fraction of inspired oxygen was standardized at 100% to maximize the difference between the oxygen and air groups. LFOx and LFAir were provided at 2 L/minute using standard nasal cannula.

Randomization and Blinding

A Latin Square design was used to generate the random sequence and ensure that the order of study intervention was balanced. Immediately prior to study treatment initiation, patients were randomized in a 1:1:1:1 ratio to one of four intervention sequences (HFAir-LFAir-HFOx-LFOx, HFOx-HFAir-LFOx-LFAir, LFAir-LFOx-HFAir-HFOx, or LFOx-HFOx-LFAir-HFAir). Allocation was concealed by a secured website that was only accessible to the study respiratory therapist. Only the respiratory therapist was aware of the intervention sequence. The patient, principal investigator, and research staff conducting the study assessments were blinded to the identity of the gas (oxygen vs. air), although flow rate could not be masked. Study team members stepped out of the room during the intervention setup. The gas outlet was concealed with a cloth. HFAir was be delivered by Optiflow in an identical manner to HFOx, except that we used pressurized air instead of oxygen. Maintenance of blinding (oxygen vs. air) was assessed at the end of study.

To minimize cointerventions, patients who required as-needed opioids or bronchodilator anytime during the study for pain or any other reason had to come off study.

Study Assessments and Endpoints

Patient characteristics were obtained at baseline. We assessed dyspnea intensity (primary outcome) "now" using a numeric rating scale from 0 to 10 where 0 = none and 10 = worst. The minimal clinically important difference was 1 point [21]. In addition, we asked patients to rate their level of dyspnea intensity and unpleasantness "now" using the modified dyspnea Borg Scale while patients were at rest [22, 23]. This 0- to 10-point ratio scale has been validated with a higher score indicating worse dyspnea. The use of both the numeric rating scale and the modified Borg scale allowed us to assess the instruments' responsiveness in this preliminary study. Furthermore, the use of these two scales with different anchors and scaling (linear vs. ratio) provided complementary information. Patients completed the scales at enrollment (baseline), at 0, 5, and 10 minutes of each intervention, and every 5 minutes during the washout period.

Adverse effects such as dry eyes, dry nose, nasal moisture, and anxiety were assessed using a 0–10 numeric rating scale, where 0 = none and 10 = worst possible, at 0 and 10 minutes of each intervention.

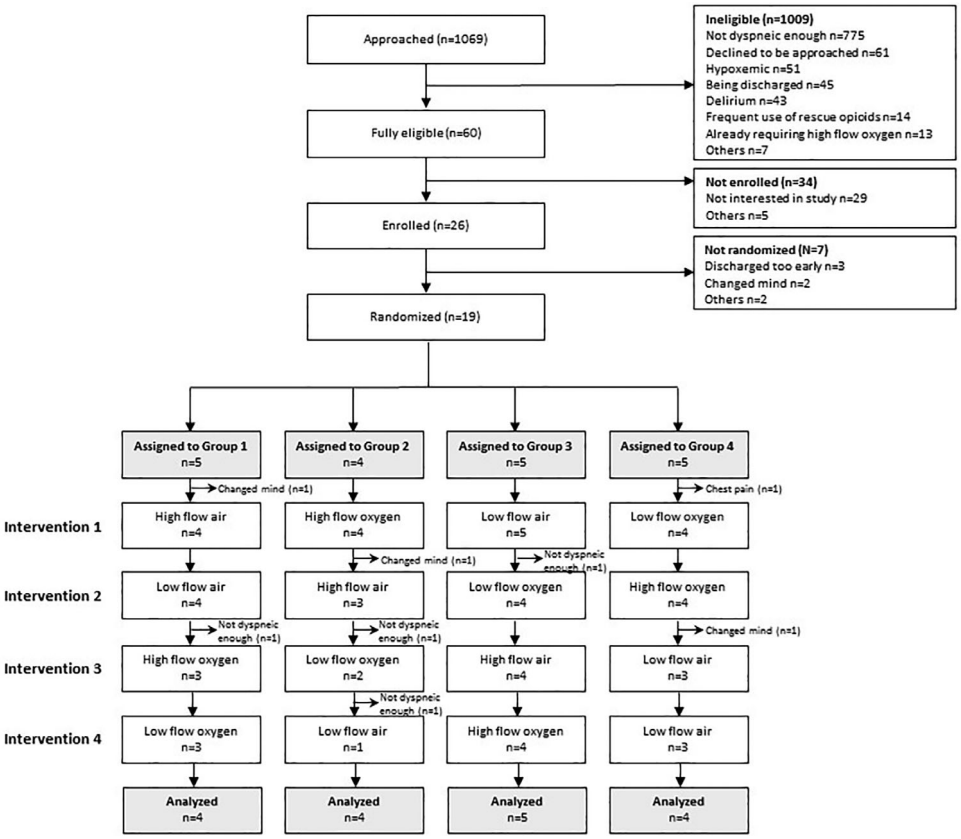

Figure 1. Study flow diagram.

To ensure the identity of treatment was properly masked, the study respiratory therapist documented several variables, including vital signs (heart rate, respiratory rate, and oxygen saturation) at 0 and 10 minutes of each intervention and device settings (oxygen flow and temperature). Blood pressure was examined at the beginning and end of the study.

At the end of the study, patients were asked to guess whether they received oxygen or air for each intervention. They were also asked three questions regarding their overall impression on dyspnea relief ("Which of the following do you prefer the most for relief of your shortness of breath?), discomfort ("Which of the following caused you the most discomfort?"), and final choice (Which of the following would you prefer the most overall for treatment of your shortness of breath, taking all factors into consideration?"). The answers were treatment 1, 2, 3, or 4 or none of the above.

Statistical Analysis

Assuming an 80% completion rate, we estimated that a sample size of 36 patients would provide a 95% confidence interval (CI) between 64% and 92%. Because of funding limitations, this study was terminated after 26 patients.

We summarized the baseline demographics using descriptive statistics. The primary objective of the study was to obtain preliminary estimates of the effect sizes, specifically change from baseline (Minute 0). We fitted a mixed effects linear model to the dyspnea numeric rating scale (NRS) data to account for intrapatient correlation due to the repeated measurements (i.e., change at 5 and 10 minutes). The model had fixed effect terms for treatment, time, and period and a random effect term for intercept. Prior to testing this model, we first tested for a carryover effect by testing the null hypothesis that treatment effect remained the same regardless period of treatment. A p value <.05 would give evidence of a carryover effect. Similar analyses were conducted for the secondary outcomes (modified dyspnea Borg Scale intensity and unpleasantness). The Fisher's exact test was used to compare Global Symptom Evaluation among the four groups. A p value of <.05 was used to define statistical significance.

Results were analyzed using the Statistical Analysis System version 9.4 (SAS Institute Inc., Cary, NC) and Splus 8.2 (TIBCO Software Inc., Palo Alto, CA).

Results

Patient Characteristics

Enrollment occurred between October 18, 2016, and March 30, 2018. Among 1,069 patients approached for this study, 60 were fully eligible and 26 (43%) agreed to enroll (Fig. 1). Nineteen patients were randomized, and 17 (89%) patients completed a total of 55 interventions in a random order.

Table 1 shows the baseline characteristics of patients randomized. The mean age was 51 years (range 29–70),

Table 1. Baseline demographics

Variables	Group 1: HFAir-LFAir-HFOx-LFOx (*n* = 5)	Group 2: HFOx-HFAir-LFOx-LFAir (*n* = 4)	Group 3: LFAir-LFOx-HFAir-HFOx (*n* = 5)	Group 4: LFOx-HFOx-LFAir-HFAir (*n* = 5)	Total (*n* = 19)
Age, mean (range), years	55 (35–68)	48 (29–62)	50 (36–59)	51 (34–70)	51 (29–70)
Female sex	2 (40)	3 (75)	3 (60)	3 (60)	11 (57.9)
Married	2 (40)	1 (25)	3 (60)	1 (20)	7 (36.8)
Race					
White	4 (80)	3 (75)	2 (40)	4 (80)	13 (68.4)
Black	1 (20)	1 (25)	2 (40)	0	4 (21.1)
Hispanic	0	0	1 (20)	1 (20)	2 (10.5)
Cancer stage					
II	0	0	0	1 (20)	1 (5.3)
III	0	0	1 (20)	0	1 (5.3)
IV	5 (100)	4 (100)	4 (80)	4 (80)	17 (89.5)
Cancer type					
Breast	0	0	1 (20)	1 (20)	2 (10.5)
Gastrointestinal	3 (60)	1 (25)	1 (20)	2 (40)	7 (36.8)
Genitourinary	0	1 (25)	1 (20)	0	2 (10.5)
Gynecological	0	0	1 (20)	0	1 (5.3)
Hematologic	0	1 (25)	0	1 (20)	2 (10.5)
Thoracic	1 (20)	1 (25)	1 (20)	1 (20)	4 (21.1)
Other	1 (20)	0	0	0	1 (5.3)
Karnofsky Performance Status, mean (SD)	40 (19)	50 (22)	58 (13)	50 (12)	50 (17)
Dyspnea as reason for admission	2 (40)	1 (25)	4 (80)	2 (40)	9 (47.4)
Medications					
Bronchodilators	3 (60)	0	3 (60)	3 (60)	9 (47.4)
Corticosteroids	2 (40)	1 (25)	1 (20)	1 (20)	5 (26.3)
Opioids	4 (80)	3 (75)	5 (100)	3 (60)	15 (78.9)
Supplemental oxygen	3 (60)	1 (25)	3 (60)	2 (40)	9 (47.4)
MIP, mean (SD)	87 (7)	61 (23)	81 (27)	69 (47)	73 (27)
Spirometry, mean (SD)					
FEV1 % predicted	35 (31)	36 (27)	40 (19)	31 (3)	36 (20)
FVC % predicted	34 (29)	37 (27)	46 (14)	29 (1)	37 (20)
FEV1/FVC	75 (7)	72 (11)	67 (12)	91 (16)	76 (14)
Dyspnea NRS, mean (SD)					
At rest	4.8 (1.7)	5.5 (1.9)	4.0 (2.1)	5.2 (0.8)	4.8 (1.7)
With activities	7.8 (2.1)	7.5 (2.4)	7.2 (2.8)	8.6 (1.7)	7.8 (2.1)
Overall	6.5 (1.3)	7.0 (2.0)	5.8 (2.0)	6.2 (1.6)	6.3 (1.7)
MRC Dyspnea score					
1	0	0	1 (20.0)	0	1 (5.6)
2	0	2 (50.0)	1 (20.0)	2 (40.0)	5 (27.8)
3	0	1 (25.0)	2 (40.0)	1 (20.0)	4 (22.2)
4	4 (100.0)	1 (25.0)	1 (20.0)	2 (40.0)	8 (44.4)
Cancer Dyspnea Scale, mean (SD)					
Sense of effort	9.5 (7.2)	10.8 (5.7)	6.8 (3.7)	10.4 (4)	9.3 (5)
Sense of anxiety	4.8 (4)	5.3 (4.7)	4.8 (4.1)	5.2 (4)	5 (3.8)
Sense of discomfort	5.5 (2.1)	4.8 (3.2)	5.4 (4.1)	6.4 (1.7)	5.6 (2.7)
Total score	19.8 (12.7)	20.8 (11.1)	17 (10.8)	22 (7.6)	19.8 (9.8)
MDAS, mean (SD)	2.4 (1.5)	3 (2.7)	3 (1.4)	2.6 (1.7)	2.7 (1.7)
ESAS, mean (SD)					
Pain	6.5 (4)	7.3 (2.5)	5.2 (3.6)	6.8 (4.7)	6.4 (3.5)
Fatigue	6.5 (2.4)	6 (1.8)	6.2 (3.8)	9.3 (1)	6.9 (2.7)

(continued)

Table 1. (continued)

Variables	Group 1: HFAir-LFAir-HFOx-LFOx (*n* = 5)	Group 2: HFOx-HFAir-LFOx-LFAir (*n* = 4)	Group 3: LFAir-LFOx-HFAir-HFOx (*n* = 5)	Group 4: LFOx-HFOx-LFAir-HFAir (*n* = 5)	Total (*n* = 19)
Nausea	0.5 (0.6)	1 (2)	3.6 (4.6)	5.3 (3.8)	2.7 (3.6)
Depression	2 (1.6)	1.5 (1.7)	1.6 (3.1)	6 (3.4)	2.7 (3)
Anxiety	4.5 (3.1)	1 (2)	4 (3.8)	5.5 (3.8)	3.8 (3.4)
Drowsiness	4.3 (3.3)	4 (2.5)	3.4 (4.2)	7.5 (1.9)	4.7 (3.3)
Appetite	3.3 (2.6)	4.5 (2.4)	4.8 (4.4)	6 (2.5)	4.7 (3)
Well-being	7 (2.5)	5.8 (2.1)	4 (2.6)	7.5 (2.1)	5.9 (2.5)
Dyspnea	6.3 (2.2)	7.5 (2.7)	5.8 (1.8)	7 (1.8)	6.6 (2)
Sleep	5.5 (2.5)	6 (2.2)	7.6 (1.7)	8.3 (0.5)	6.9 (2)

Data are presented as *n* (%) unless otherwise specified.
Abbreviations: ESAS, Edmonton symptom assessment system; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HFAir, high-flow air; HFOx, high-flow oxygen; LFAir, low-flow air; LFOx, low-flow oxygen; MDAS, Memorial Delirium Assessment Scale; MIP, maximal inspiratory pressure; MRC, Medical Research Council; NRS, numeric rating scale.

Table 2. Absolute change in dyspnea scores between 0 and 10 minutes

Dyspnea scores	HFOx Mean (SD)	HFAir Mean (SD)	LFOx Mean (SD)	LFAir Mean (SD)
Dyspnea Numeric Rating Scale				
Minute 0	4.2 (1.7)	4.1 (2.1)	3.6 (2.1)	3.8 (1.5)
Minute 5	3.4 (1.7)	3.1 (1.7)	3.7 (2.2)	3.8 (1.8)
Minute 10	2.6 (1.8)	2.8 (2.0)	3.3 (2.0)	3.1 (2.1)
Change from 0 to 5 minutes (95% CI)	−0.7 (−1.7 to 0.3)	−1.4 (−2.5 to −0.2)	−0.4 (−1.1 to 0.3)	−0.1 (−0.6 to 0.4)
Change from 0 to 10 minutes (95% CI)	−1.8 (−2.8 to −0.7)	−1.8 (−3.0 to −0.5)	−0.5 (−1.0 to 0.1)	−0.6 (−1.3 to 0.2)
Modified Borg Scale Intensity				
Minute 0	3.4 (1.6)	2.7 (1.2)	2.8 (1.7)	2.7 (1.9)
Minute 5	2.4 (1.5)	2.3 (1.3)	2.6 (1.4)	2.5 (1.9)
Minute 10	1.7 (1.3)	2.1 (1.4)	2.3 (1.5)	2.7 (1.8)
Change from 0 to 5 minutes (95% CI)	−1.0 (−1.9 to −0.2)	−0.6 (−1.4 to 0.1)	−0.4 (−1.2 to 0.4)	−0.4 (−0.7 to −0.0)
Change from 0 to 10 minutes (95% CI)	−1.8 (−2.8 to −0.7)	−0.7 (−1.6 to 0.2)	−0.5 (−1.2 to 0.2)	−0.1 (−0.4 to 0.2)
Modified Borg Scale Unpleasantness				
Minute 0	3.8 (1.9)	2.7 (1.6)	3.2 (1.9)	3.4 (2.7)
Minute 5	2.2 (1.6)	2.8 (2.7)	2.9 (1.6)	2.8 (2.0)
Minute 10	1.9 (1.4)	2.4 (2.0)	2.5 (2.1)	2.8 (2.1)
Change from 0 to 5 minutes (95% CI)	−1.4 (−2.7 to −0.0)	−0.3 (−1.0 to 0.5)	−0.2 (−0.9 to 0.5)	−0.6 (−1.4 to 0.2)
Change from 0 to 10 minutes (95% CI)	−1.8 (−3.3 to −0.4)	−0.5 (−1.6 to 0.5)	−0.7 (−1.6 to 0.2)	−0.6 (−1.5 to 0.2)

Abbreviations: CI, confidence interval; HFAir, high-flow air; HFOx, high-flow oxygen; LFAir, low-flow air; LFOx, low-flow oxygen.

11 (58%) were female, and 13 (68%) were white. Seventeen (90%) had metastatic cancer.

The mean dyspnea at baseline was 6.3 (SD 1.7) and the median Medical Research Council dyspnea score was 3. A majority were on opioids (*n* = 15, 79%) and almost half were on supplemental oxygen (*n* = 9, 47%) despite being nonhypoxemic.

In regard to device setting, the mean flow rate was 36.3 (SD 14.3) L/minute for HFOx and 35.9 (SD 12.9) L/minute for HFAir. The mean temperate was 35.2°C (SD 2.3°C) and 34.9°C (SD 2.7°C), respectively.

Change in Dyspnea Scores

Table 2 shows the average absolute change in dyspnea scores between 0 and 10 minutes. Specifically, the change in dyspnea NRS was −1.8 [−2.8, −0.7] for HFOx, −1.8 [−3.0, −0.5] for HFAir, −0.5 [−1.0, 0.1] for LFOx, and − 0.6 [−1.3, 0.2] for LFAir.

In mixed model analysis adjusting for study period and time, HFOx provided greater dyspnea relief than LFOx (difference [95% CI] −0.80 [−1.45, −0.15], $p = .02$) and LFAir (−1.24 [−1.90, −0.57], $p < .001$). HFAir also provided significantly greater dyspnea relief than LFOx (−0.95 [−1.61, −0.30],

Table 3. Mixed model analysis of change in dyspnea scores between 0 and 10 minutes

Variables	Estimate[a]	95% CI	*p* value
Dyspnea numeric rating scale			
Intervention			<.001
HFOx	−1.34	−1.90 to −0.79	<.001
HFAir	−1.50	−2.06 to −0.93	<.001
LFOx	−0.54	−1.13 to 0.04	.07
LFAir	−0.11	−0.68 to 0.46	.71
HFOx vs. HFAir	0.15	−0.49 to 0.80	.64
HFOx vs. LFOx	−0.80	−1.45 to −0.15	.02
HFOx vs. LFAir	−1.24	−1.90 to −0.57	<.001
HFAir vs. LFOx	−0.95	−1.61 to −0.30	.005
HFAir vs. LFAir	−1.39	−2.05 to −0.73	<.001
LFOx vs. LFAir	−0.44	−1.11 to 0.24	.20
Time effect			.03
5 minutes	−0.62	−1.09 to −0.15	.01
10 minutes	−1.13	−1.58 to −0.67	<.001
10 minutes vs. 5 minutes	−0.51	−0.96 to −0.05	.03
Period effect			<.001
1	−1.72	−2.24 to −1.20	<.001
2	−0.54	−1.11 to 0.02	.06
3	−1.25	−1.83 to −0.67	<.001
4	0.02	−0.59 to 0.63	.94
1 vs. 2	−1.18	−1.80 to −0.55	<.001
1 vs. 3	−0.47	−1.10 to 0.17	.15
1 vs. 4	−1.74	−2.41 to −1.07	<.001
2 vs. 3	0.71	0.05 to 1.37	.03
2 vs. 4	−0.57	−1.26 to 0.13	.11
3 vs. 4	−1.28	−1.97 to −0.58	.001
Modified Borg Scale Intensity			
Intervention			<.001
HFOx	−1.47	−1.98 to −0.96	<.001
HFAir	−0.62	−1.14 to −0.1	.020
LFOx	−0.50	−1.03 to 0.03	.07
LFAir	−0.04	−0.57 to 0.48	.87
HFOx vs. HFAir	−0.85	−1.40 to −0.31	.003
HFOx vs. LFOx	−0.97	−1.53 to −0.42	.001
HFOx vs. LFAir	−1.43	−1.99 to −0.87	<.001
HFAir vs. LFOx	−0.12	−0.67 to 0.43	.67
HFAir vs. LFAir	−0.57	−1.13 to −0.02	.04
LFOx vs. LFAir	−0.45	−1.02 to 0.12	.12
Time effect			.33
Period effect			.006
Modified Borg Scale Unpleasantness			
Intervention			.001
HFOx	−1.57	−2.28 to −0.86	<.001
HFAir	−0.20	−0.92 to 0.53	.59
LFOx	−0.31	−1.05 to 0.44	.42
LFAir	−0.56	−1.29 to 0.18	.14

(continued)

Table 3. (continued)

Variables	Estimate[a]	95% CI	*p* value
HFOx vs. HFAir	−1.37	−2.08 to −0.66	<.001
HFOx vs. LFOx	−1.26	−1.98 to −0.55	.001
HFOx vs. LFAir	−1.01	−1.75 to −0.28	.008
HFAir vs. LFOx	0.11	−0.61 to 0.82	.77
HFAir vs. LFAir	0.36	−0.37 to 1.09	.33
LFOx vs. LFAir	0.25	−0.50 to 1.00	.50
Time effect			.22
Period effect			.04

[a]Estimated change based on linear mixed model: Change in dyspnea between 0 and 10 minutes = Treatment + Time + Period.
Abbreviations: CI, confidence interval; HFAir, high-flow air; HFOx, high-flow oxygen; LFAir, low-flow air; LFOx, low-flow oxygen.

Table 4. Changes in vital signs over time

Vital signs	HFOx Mean (SD)	HFAir Mean (SD)	LFOx Mean (SD)	LFAir Mean (SD)
Heart rate, bpm				
Minute 0	88.9 (16.9)	89.4 (17.0)	89.8 (17.9)	91.0 (12.8)
Minute 5	86.9 (16.9)	89.2 (18.9)	91.9 (16.9)	92.9 (15.2)
Minute 10	86.1 (14.9)	89.1 (17.1)	88.8 (17.6)	90.0 (13.2)
Change from 0 to 5 minutes (95% CI)	−2.4 (−4.6 to −0.3)	−0.1 (−2.3 to 2.1)	1.3 (−2.8 to 5.3)	0.8 (−2.1 to 3.7)
Change from 0 to 10 minutes (95% CI)	−2.8 (−5.2 to −0.4)	−0.4 (−2.7 to 2.0)	−0.8 (−2.9 to 1.2)	−1.0 (−2.7 to 0.7)
Respiration rate, bpm				
Minute 0	18.0 (2.6)	18.1 (2.5)	18.6 (3.0)	18.5 (3.3)
Minute 5	17.6 (2.4)	18.0 (2.6)	18.0 (3.0)	18.2 (2.9)
Minute 10	17.3 (2.4)	18.3 (2.9)	17.5 (2.5)	18.8 (3.1)
Change from 0 to 5 minutes (95% CI)	−0.4 (−1.1 to 0.2)	−0.2 (−1.1 to 0.8)	−0.5 (−1.3 to 0.3)	−0.3 (−1.2 to 0.6)
Change from 0 to 10 minutes (95% CI)	−0.7 (−1.2 to −0.1)	0.1 (−0.7 to 1.0)	−1.1 (−1.9 to −0.3)	0.3 (−0.5 to 1.1)
Blood oxygen saturation level, %				
Minute 0	97.2 (2.2)	96.3 (1.7)	95.5 (2.4)	94.9 (1.7)
Minute 5	99.6 (0.8)	96.5 (1.6)	98.0 (1.5)	95.2 (2.3)
Minute 10	99.7 (0.6)	96.1 (2.1)	98.2 (1.6)	95.1 (2.1)
Change from 0 to 5 minutes (95% CI)	2.3 (0.9 to 3.7)	0.2 (−0.3 to 0.7)	2.5 (1.3 to 3.7)	0.3 (−0.3 to 1.0)
Change from 0 to 10 minutes (95% CI)	2.5 (1.2 to 3.8)	−0.1 (−0.9 to 0.6)	2.6 (1.2 to 4.1)	0.2 (−0.6 to 0.9)
Transcutaneous carbon dioxide level, mmHg				
Minute 0	33.8 (3.2)	34.1 (3.1)	34.1 (2.9)	34.4 (3.2)
Minute 5	32.9 (4.0)	33.3 (3.4)	34.5 (3.1)	34.9 (3.3)
Minute 10	33.7 (3.5)	32.9 (3.9)	34.3 (3.1)	34.7 (3.3)
Change from 0 to 5 minutes (95% CI)	−0.5 (−2.2 to 1.1)	−0.6 (−1.2 to 0.0)	0.4 (−0.2 to 1.0)	0.4 (−0.1 to 0.9)
Change from 0 to 10 minutes (95% CI)	−0.1 (−1.4 to 1.1)	−1.1 (−2.4 to 0.1)	0.3 (−0.2 to 0.8)	0.3 (−0.3 to 0.9)

Abbreviations: CI, confidence interval; HFAir, high-flow air; HFOx, high-flow oxygen; LFAir, low-flow air; LFOx, low-flow oxygen.

p = .005) and LFAir (−1.39 [−2.05, −0.73], p < .001; Table 3). No difference was found between HFOx and HFAir or between LFOx and LFAir. There was a significant period effect with the greatest magnitude of change in the first period (Table 3). No significant carryover effect was detected. Borg scale intensity and unpleasantness showed similar changes (Table 3).

Table 5. Adverse events

Adverse events[a]	Change from baseline	HFOx	HFAir	LFOx	LFAir
Dry nose	Improved	7 (53.8)	7 (58.3)	5 (38.5)	6 (46.2)
	Same	0 (0.0)	1 (8.3)	1 (7.7)	1 (7.7)
	Worsened	4 (30.8)	2 (16.7)	7 (53.8)	2 (15.4)
Moisture in nose	Improved	4 (30.8)	5 (41.7)	4 (30.8)	4 (30.8)
	Same	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)
	Worsened	6 (46.2)	7 (58.3)	5 (38.5)	2 (15.4)
Nasal prong uncomfortable	Improved	2 (15.4)	2 (16.7)	1 (7.7)	2 (15.4)
	Same	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Worsened	5 (38.5)	5 (41.7)	5 (38.5)	3 (23.1)
Anxiety	Improved	4 (30.8)	4 (33.3)	5 (38.5)	4 (30.8)
	Same	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Worsened	3 (23.1)	4 (33.3)	1 (7.7)	4 (30.8)
Feeling of suffocation	Improved	1 (7.7)	2 (16.7)	1 (7.7)	2 (15.4)
	Same	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Worsened	2 (15.4)	4 (33.3)	0 (0.0)	2 (15.4)
Trouble talking	Improved	4 (30.8)	4 (33.3)	3 (23.1)	4 (30.8)
	Same	1 (7.7)	1 (8.3)	1 (7.7)	0 (0.0)
	Worsened	2 (15.4)	3 (25.0)	2 (15.4)	4 (30.8)
Dry eyes	Improved	4 (30.8)	3 (25.0)	3 (23.1)	2 (15.4)
	Same	1 (7.7)	3 (25.0)	2 (15.4)	4 (30.8)
	Worsened	2 (15.4)	1 (8.3)	1 (7.7)	1 (7.7)
Eye irritation	Improved	3 (23.1)	3 (25.0)	4 (30.8)	2 (15.4)
	Same	2 (15.4)	4 (33.3)	2 (15.4)	2 (15.4)
	Worsened	2 (15.4)	0 (0.0)	0 (0.0)	2 (15.4)

Data are presented as *n* (%).
[a]Adverse effects related to supplemental oxygen use were assessed using a numeric rating scale from 0 (not at all) to 10 (worst possible) before and after the study intervention.
Abbreviations: CI, confidence interval; HFAir, high-flow air; HFOx, high-flow oxygen; LFAir, low-flow air; LFOx, low-flow oxygen.

Change in Vital Signs and Adverse Effects

As shown in Table 4, heart rate, respiratory rate, and transcutaneous carbon dioxide level did not differ significantly. HFOx and LFOx both had an increase in O_2 saturation at 5 minutes, which remained at 10 minutes. All four interventions were well tolerated with no significant adverse effects (Table 5)

Overall Preferences

Figure 2 shows the overall preference at the end of study. Seven (54%), four (31%), one (8%), and one (8%) patients preferred HFOx, HFAir, LFOx, and LFAir, respectively.

Discussion

In this double-blind crossover trial of hospitalized patients with cancer, HFOx was associated with rapid relief of dyspnea at rest. We also found that, for the first time, HFAir offered a similar magnitude of benefit to HFOx in nonhypoxemic patients with dyspnea. Both interventions were well tolerated. Our findings support a potential therapeutic role for high flow rate as a palliative therapy. Larger confirmatory trials examining longer duration of use are warranted.

Dyspnea studies are challenging to conduct, particularly in the acute cancer care setting. This study's focus on patients with cancer with dyspnea at rest essentially limits our trial participants to those with significant symptom burden, a poor performance status, and a short life expectancy. Many of these patients had delirium or other acute complications and were not eligible for the study. Some patients who were eligible were unable to participate because they were too distressed, tired, or busy. In the inpatient unit, patients often had multiple clinical visits, investigations, and treatments, making it difficult to run the study without interruptions. Moreover, a high baseline intensity of dyspnea was a predictor of attrition [24]. We incorporated several strategies to address these challenges, including the use of a crossover design to maximize study power and limiting treatment duration to only 10 minutes each.

Consistent with our hypothesis, HFOx was associated with a statistically significant improvement in dyspnea within 5–10 minutes of use as compared with LFOx and LFAir. Given that the minimal clinical important difference was 1 point [21], this magnitude of effect was considered clinically significant. This finding was consistent with previous studies by our group and others conducted in the palliative care, emergency, and critical care settings [3, 9–16]. Encouragingly, a majority of patients blindly selected HFOx as a treatment of choice at the end of study.

To our knowledge, this is the first randomized trial to document that HFAir was associated with a statistical and clinically significant improvement in dyspnea. Indeed, HFAir

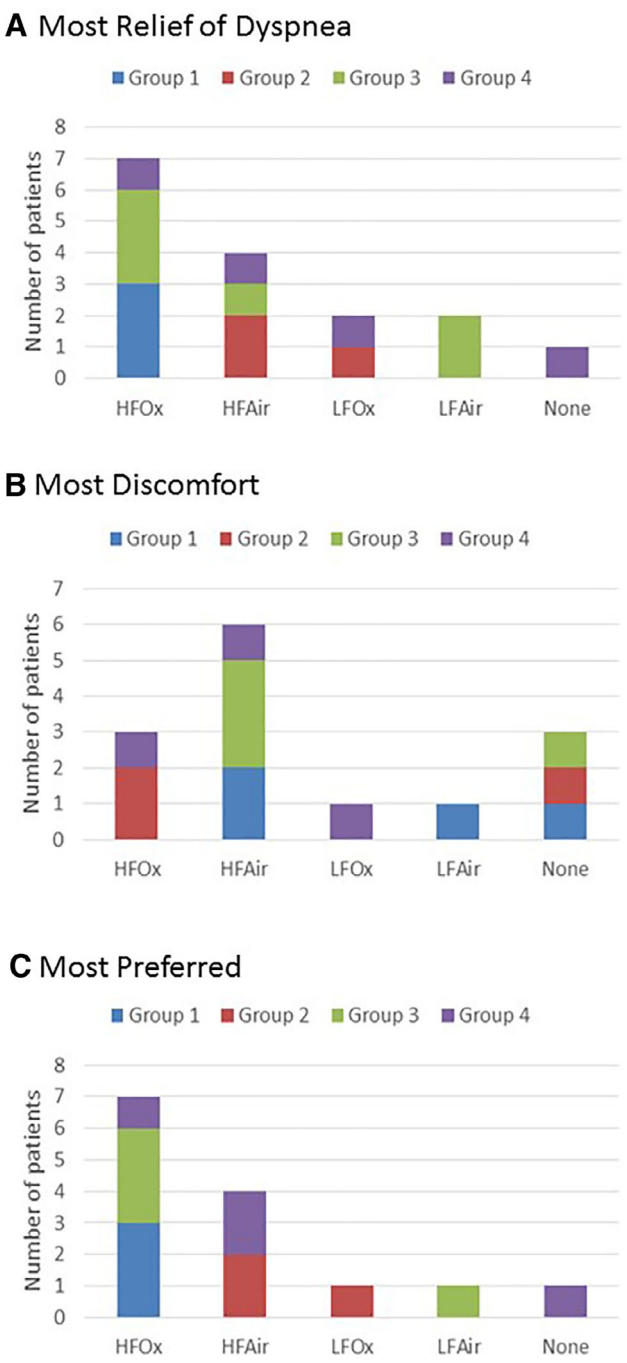

Figure 2. Patient preferences.
Abbreviations: HFAir, high-flow air; HFOx, high-flow oxygen; LFAir, low-flow air; LFOx, low-flow oxygen.

was identical to HFOx except for delivery for gas type. The similar magnitude of benefit between HFOx and HFAir suggests that high-flow, heated, humidified gas may contribute to relief of dyspnea in nonhypoxemic patients with cancer.

Our study suggests that HFAir may represent a novel intervention for nonhypoxemic patients; larger studies are needed to confirm our findings in patients with cancer and other populations. Without the requirement for oxygen, high-flow nasal cannula devices could be used in the community setting where many patients with dyspnea are normoxemic. Overall, HFOx and HFAir were well tolerated. Although some patients reported that high flow was less comfortable than low flow, a majority preferred high-flow delivery after taking dyspnea relief into consideration.

Previous studies found that supplemental oxygen was helpful for dyspnea relief among patients with hypoxemia but not those without hypoxemia [25]. This was consistent with our observation that there was no significant difference in dyspnea scores between HFOx and HFAir and between LFOx and LFAir, despite attainment of higher oxygen saturation in the oxygen groups. Prior to enrollment, almost half of our patients were on supplementary oxygen despite being normoxemic, suggesting room for further education on the use of supplemental oxygen.

We observed a significant period effect with a greatest difference observed in the first period that was independent of the intervention effect. One potential reason is that patients might have a greater expectation with the first intervention. Another explanation may be related to the study design. Specifically, patients were able to proceed to the next intervention as soon as their dyspnea was ± 1 point of their baseline level of dyspnea. This meant patients often started at a lower level of dyspnea for the second, third, and fourth interventions. Future studies may consider having patients return to at least their baseline level of dyspnea before starting the next intervention.

This study has several limitations. It was conducted in a single tertiary care cancer center, and the findings may not be generalizable to other patient populations. The sample size was small, and we were not able to enroll the target number of patients within the funding period. Moreover, not all patients were able to complete the four interventions. Given that flow rate could not be masked, we could not exclude that "placebo effect" may contribute the dyspnea relief in the high-flow groups. Of note, a recent meta-analysis suggested airflow therapy with fan or medical air improved dyspnea [26]. We also only tested the interventions for a short time to minimize study burden. Despite these limitations, the magnitude of effect was large and the comparisons were statistically significant. This study was not adequately powered to detect a carryover effect; moreover, the variable washout period was designed to ensure patients had similar dyspnea scores at time 0. We also examined multiple secondary outcomes, which should be considered for hypothesis-generation purposes only.

Conclusion

This pilot crossover study provided preliminary data to support the mechanistic basis for high-flow, heated, humidified air and oxygen to alleviate dyspnea at rest. Given that many patients suffering from dyspnea are nonhypoxemic, the beneficial effects observed in this population may, upon further research, open up a new indication for the use of high-flow nasal cannula in the acute care and community settings beyond oxygenation.

Acknowledgments

We thank all the patients who participated in this study. We are grateful to Dr. Kenneth Hess, a biostatistician who

was instrumental to the study design and died before this study was completed. This study was supported by the Andrew Sabin Family Fellowship Award. D.U. was supported in part by a National Institutes of Health Cancer Center Support Grant (P30CA016672). D.H. was supported in part by grants from the National Cancer Institute (1R01CA214960-01A1; 1R01CA225701-01A1) and the National Institute of Nursing Research (1R21NR016736-01). The funding organizations had no role in the design or conduct of the study; in collection, management, analysis, or interpretation of the data; or in preparation, review, or approval of the manuscript.

Author Contributions

Conception/design: David Hui, Eduardo Bruera
Provision of study material or patients: David Hui, Ahmed Elsayem, Eduardo Bruera
Collection and/or assembly of data: David Hui, Farley Hernandez, Saji Thomas, Zhanni Lu
Data analysis and interpretation: David Hui, Diana Urbauer
Manuscript writing: David Hui, Diana Urbauer, Eduardo Bruera
Final approval of manuscript: David Hui, Farley Hernandez, Diana Urbauer, Saji Thomas, Zhanni Lu, Ahmed Elsayem, Eduardo Bruera

Disclosures

The authors indicated no financial relationships.

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