Effects of High-Flow Nasal Cannula on Exercise Outcomes in Lung Transplant Candidates: A Pilot Study

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ABSTRACT

Introduction: Pulmonary diseases have a significant global prevalence, and lung transplantation is indicated for advanced cases. Rehabilitation is essential for patients on the waiting list and requires ventilatory devices for symptom control during exertion. The high-flow nasal cannula (HFNC) is a promising alternative, but its effects on exercise outcomes are uncertain. **Objectives:** To assess the effects of HFNC on the outcomes of the six-minute walk test (6MWT). **Method:** A randomized crossover clinical trial evaluated ten volunteers listed on the national lung transplant waiting list. Three functional tests were performed: 6MWT, incremental lower limb test with arterial blood gas analysis, and lower limb endurance test with inspiratory capacity measurement. Each test was conducted on different days with different devices: HFNC and conventional oxygen therapy, totaling six test days. The inspired oxygen fraction (FiO_2) was titrated to maintain normoxia between 90% to 96% and was kept constant for both interfaces. **Results:** The 6MWT distance was significantly greater in the HFNC group (mean difference 437.6m ± 40.24m, p=0.001). $PaCO_2$ kinetics were lower in exhaustive exercise with HFNC (mean difference: -3.29mmHg; 95% CI: -4.20 to -2.38mmHg; p<0.001) with less dynamic hyperinflation (mean difference: 0.26L; 95% CI: 0.07 to 0.44L; p=0.007). **Conclusion:** Acute use of HFNC increased the distance covered in the 6MWT with lower physiological stress on blood gas variables and inspiratory capacity, suggesting less dynamic hyperinflation with fewer subjective symptoms.

METHOD

Subjects

Ten volunteers of both sexes, aged 30 to 69 years, listed on the national lung transplant waiting list who presented clinical stability in the last thirty days with diagnoses of COPD, idiopathic or familial pulmonary fibrosis, bronchiectasis, and sarcoidosis under follow-up at the cardiopulmonary rehabilitation outpatient clinic of the Vila Mariana unit of Albert Einstein Israelite Hospital, São Paulo, Brazil, were selected. Exclusion criteria were patients with osteoarticular limitation, neuromuscular disease, anemia (Hb < 11g/dL), hyperglycemia (glucose > 250mg/dL), or other uncontrolled endocrine disease, uncontrolled arrhythmia, left heart failure, and patients diagnosed with pulmonary hypertension.

The study was conducted at a single rehabilitation center following the physiotherapeutic evaluation routine used in the unit. All assessments were performed by the same physiotherapist. At the time of assessments, all patients were undergoing rehabilitation and were at different training times.

The specific material for high-flow therapy used was the MyAirvo™ 2 device. The initial interface was randomly assigned (draw) through conventional oxygen therapy (Venturi mask or adult high concentration non-rebreathing oxygen mask) or through HFNC (Figure 1). The sequence was obtained through the site http://randomization.com which organized the block randomization. Each patient's assessment forms were stored in brown envelopes identified as the initial HFNC group or the initial conventional oxygen therapy group.

The established physical performance tests were conducted on a treadmill, tending to maximum or submaximal efforts. Subjects were evaluated over six days, with each functional test applied on different days to avoid potential fatigue bias.

On the first evaluation day, the 6MWT was conducted to determine walking speed and distance covered in six minutes. During the test, FiO_2 was titrated depending on the patient's need, sufficient to maintain

peripheral oxyhemoglobin saturation (SpO2) between 90% to 96%. For the initial HFNC group, the highest inspiratory flow according to ventilatory demand, tolerance, and patient comfort was applied. These parameters were used on all other test days. On the second evaluation day, a new 6MWT was conducted, but the oxygen therapy instrument used was the opposite of the previous evaluation.

On the third and fourth days, the incremental lower limb test was applied with the same previously titrated FiO_2 and flow. Arterial blood gas samples were collected before and up to two minutes after the tests.

On the fifth and sixth days, the lower limb endurance test was conducted. Inspiratory capacity (IC) measurements before and after the tests were evaluated.

Statistical Analysis

For the pilot study, international recommendations for small-scale study protocols were considered escala[21, 22]. We estimated the difference between the two modalities regarding the distance covered in the 6MWT. To evaluate differences between interfaces, generalized estimating equations models[23] with Gamma distribution and logarithmic link function were adjusted, considering therapeutic modality and the sequence in which they were used as explanatory variables. Mean differences between the measurements estimated by the models were accompanied by 95% confidence intervals. For the modified Borg scale scores, Gamma and Poisson mixture distributions (Tweedie Distribution) with a logarithmic link function were used. Analyses were performed using the SPSS statistical package with a significance level of 5%.

RESULTS

Participant Characterization Data

The study flowchart is detailed in Figure 2. Ten patients on the national lung transplant list were included. No patients were excluded from the sample. Evaluations were conducted between June 2021 and March 2023. The mean age was 58.7 ± 9 years. 40% were former smokers. 80% of pulmonary diseases were of a restrictive nature. Pulmonary function impairment was classified as moderate to severe (forced vital capacity 47.7% ± 15.1 of predicted, carbon monoxide diffusion 28.9% ± 11.5 of predicted). Patients experienced dyspnea during activities of daily living (ADLs), with a mean score of 5 on the modified Borg scale (Table 1).

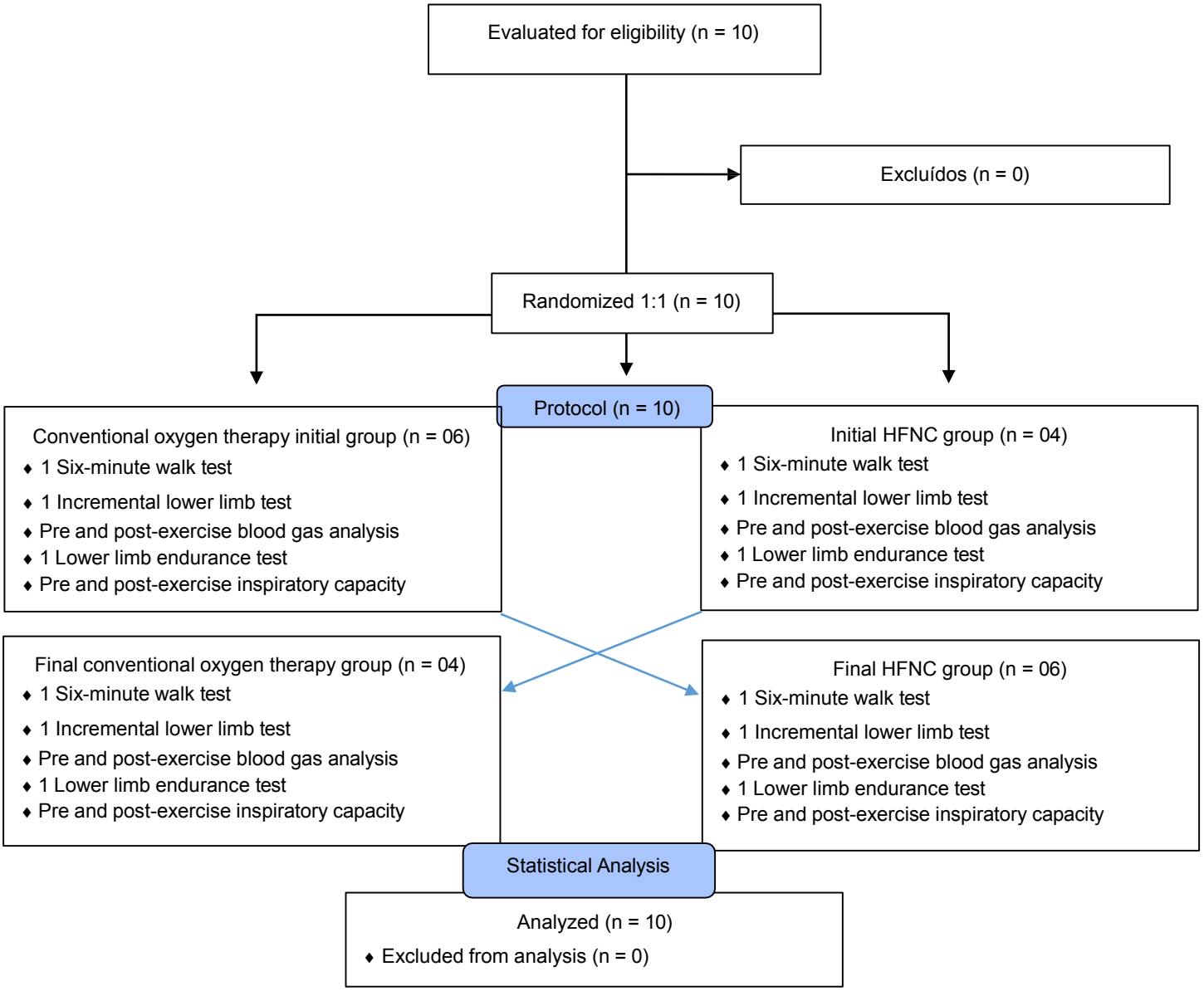

Figure 2. Flowchart of data collection and processes

Table 1. Demographic, clinical, and functional characteristics of patients with pulmonary diseases in cardiopulmonary rehabilitation protocol (n=10)

Age (years)	
Mean (SD)	58,7 (9,0)
Diagnosis	
COPD Gold D	2 (20,0%)
Pulmonary fibrosis	1 (10,0%)
Familial pulmonary fibrosis	1 (10,0%)
Idiopathic pulmonary fibrosis	2 (20,0%)
Progressive pulmonary fibrosis	1 (10,0%)
Progressive fibrosing interstitial lung disease	1 (10,0%)
Stage 4 sarcoidosis	2 (20,0%)
Disease Type	
Obstructive	2 (20,0%)
Restrictive	8 (80,0%)
Comorbidities	
COVID-19	4 (40,0%)
Diabetes mellitus	3 (30,0%)
Dyslipidemia	3 (30,0%)
Obesity	3 (30,0%)
Systemic arterial hypertension	6 (60,0%)
Gastroesophageal reflux disease	4 (40,0%)
Depression	3 (30,0%)
Polycythemia	1 (10,0%)
Asthma	1 (10,0%)
Former smoker	4 (40,0%)
Stroke	1 (10,0%)
Spirometry	
Forced expiratory volume in 1 second (FEV1) (% predicted)	
Mean (SD)	43,4 (11,4)
Forced vital capacity (FVC) (% predicted)	
Mean (SD)	47,7 (15,1)
Diffusion capacity for carbon monoxide (DLCO) (% predicted)	
Mean (SD)	28,9 (11,5)
Modified Borg Scale of Perceived Exertion	
Limitation of activities of daily living – Mobility	
Median (Q1; Q3)	5,0 (5,0; 7,0)
Limitation of activities of daily living – Personal hygiene	
Median (Q1; Q3)	5,0 (4,0; 5,0)
Limitation of activities of daily living – Bathing	
Median (Q1; Q3)	5,0 (4,0; 5,0)

SD: standard deviation; Q1: first quartile; Q3: third quartile; n: number of patients

Effects of HFNC on 6MWT

The estimated mean FiO_2 for the tests was 0.58. During the 6MWT, the achieved velocity was significantly higher during exercise with HFNC (mean difference: 0.28 km/h; 95% CI: 0.02 to 0.54 km/h; *p*=0.037), resulting in an increased distance covered (mean distance: 35.25 m; 95% CI: 14.24 to 56.26 m; *p*=0.001), as demonstrated in Table 2.

Table 2. Estimated Means and Confidence Intervals (95% CI) for the 6MWT Outcomes of Patients with Pulmonary Diseases Undergoing Cardiopulmonary Rehabilitation Protocol (n=10)

Measurements	Therapeutic Modality		HFNC – Mask	
	HFNC	Mask	Difference	*p*-value
Achieved Speed (km/h)	4,7 (4,3; 5,3)	4,5 (4,0; 4,9)	0,28 (0,02; 0,54)	**0,037**
O2 Flow Rate (L/min)	36,7 (31,4; 42,9)	14,7 (13,6; 15,8)	22,05 (16,29; 27,81)	**<0,001**
Distance Covered (m)	437,6 (396,3; 483,2)	402,4 (366,4; 441,8)	35,25 (14,24; 56,26)	**0,001**

Values expressed as estimated means and 95% confidence intervals (95% CI)

Effects of HFNC on Blood Gases

Arterial blood gas analyses provide evidence of differences between therapeutic modalities (Table 3) in the mean pH levels before (mean difference: 0.03; 95% CI: 0.02 to 0.04; *p*<0.001) and after the test (mean difference: 0.03; 95% CI: 0.02 to 0.04; *p*<0.001), as well as in $PaCO_2$ levels before (mean difference: -3.32 mmHg; 95% CI: -4.26 to -2.37 mmHg; *p*<0.001) and after the test (mean difference: -3.29 mmHg; 95% CI: -4.20 to -2.38 mmHg; *p*<0.001). There is no evidence of differences between therapeutic modalities for other measures obtained from arterial blood gas analyses (*p*>0.05).

Table 3. Estimated Means and 95% Confidence Intervals (95% CI) for Measurements Obtained from Arterial Blood Gas Analyses Conducted Before and After the Incremental Lower Limb Exercise Test in Patients with Pulmonary Diseases Undergoing Cardiopulmonary Rehabilitation Protocol (n=10)

Measurements	Therapeutic Modality		HFNC – Mask	
	HFNC	Mask	Difference	*p*-value
Arterial pH				
Pre-Test	7,4 (7,4; 7,5)	7,4 (7,4; 7,4)	0,03 (0,02; 0,04)	**<0,001**
Post-Test	7,4 (7,4; 7,4)	7,4 (7,4; 7,4)	0,03 (0,02; 0,04)	**<0,001**
Arterial Partial Pressure of Carbon Dioxide (mmHg)				
Pre-Test	37,5 (35,0; 40,2)	40,8 (38,2; 43,6)	-3,32 (-4,26; -2,37)	**<0,001**
Post-Test	37,2 (34,2; 40,4)	40,5 (37,4; 43,7)	-3,29 (-4,20; -2,38)	**<0,001**
Arterial Partial Pressure of Oxygen (mmHg)				
Pre-Test	184,3 (138,4; 245,5)	179,2 (147,2; 218,2)	5,11 (-30,20; 40,42)	0,777
Post-Test	176,9 (138,2; 226,5)	172,0 (153,5; 192,7)	4,90 (-29,03; 38,84)	0,777
Arterial Base Excess (mEq/L)				
Pre-Test	2,4 (1,1; 3,6)	2,1 (1,0; 3,2)	0,24 (-0,09; 0,57)	0,154
Post-Test	-0,3 (-1,9; 1,3)	-0,5 (-2,2; 1,2)	0,24 (-0,09; 0,57)	0,154
Arterial Bicarbonate (mEq/L)				
Pre-Test	26,3 (24,7; 28,1)	26,8 (25,3; 28,3)	-0,48 (-1,08; 0,12)	0,118
Post-Test	24,0 (22,4; 25,8)	24,5 (22,8; 26,3)	-0,44 (-1,00; 0,12)	0,126
Arterial Oxygen Saturation (%)				
Pre-Test	98,5 (97,7; 99,2)	98,8 (98,4; 99,2)	-0,36 (-1,11; 0,38)	0,343
Post-Test	98,4 (97,8; 99,1)	98,8 (98,6; 99,0)	-0,36 (-1,10; 0,38)	0,343
Arterial Lactate (mmol/L)				
Pre-Test	11,6 (9,6; 14,0)	11,4 (8,7; 15,0)	0,15 (-1,95; 2,26)	0,886
Post-Test	28,6 (19,5; 42,0)	28,3 (19,6; 40,7)	0,38 (-4,90; 5,66)	0,887

Values expressed as estimated means and 95% confidence intervals (95% CI); *p*-values corrected using the sequential Bonferroni method

Effects of HFNC on Dynamic Hyperinflation and Exercise-Induced Dyspnea

There is evidence of differences between therapeutic modalities (Table 4) in the mean IC at baseline (mean difference: 0.32 L; 95% CI: 0.07 to 0.57 L; *p*=0.013) and at the end of the endurance test (mean difference: 0.26 L; 95% CI: 0.07 to 0.44 L; *p*=0.007), as well as in the scores of the modified Borg Scale of Perceived Exertion at rest (mean difference: -0.23; 95% CI: -0.43 to -0.03; *p*=0.025), after maximal exercise with HFNC (mean difference: -1.55; 95% CI: -2.87 to -0.23; *p*=0.021), and during recovery (mean difference: -0.46; 95% CI: -0.81 to -0.10; *p*=0.011).

Table 4. Estimated Means and 95% Confidence Intervals (95% CI) for Inspiratory Capacity Measures and Scores on the Modified Borg Scale of Perceived Exertion During the Lower Limb Endurance Test in Patients with Pulmonary Diseases Undergoing Cardiopulmonary Rehabilitation Protocol (n=10)

Measurements	Therapeutic Modality		HFNC – Mask	
	HFNC	Mask	Diferença	HFNC
Inspiratory Capacity (L)				
Initial	2,0 (1,6; 2,6)	1,7 (1,3; 2,2)	0,32 (0,07; 0,57)	**0,013**
Final	1,6 (1,3; 2,0)	1,4 (1,1; 1,8)	0,26 (0,07; 0,44)	**0,007**
Modified Borg Scale of Perceived Exertion				
Rest	0 (0,6; 1,5)	1 (0,7; 1,8)	-0,23 (-0,43; -0,03)	**0,025**
Maximum	6 (5,0; 7,7)	8 (6,3; 9,6)	-1,55 (-2,87; -0,23)	**0,021**
Recovery	1 (1,3; 2,6)	2 (1,7; 3,1)	-0,46 (-0,81; -0,10)	**0,011**

Values expressed as estimated means and 95% confidence intervals (95% CI); *p*-values corrected using the sequential Bonferroni method