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Impact of high-flow nasal cannula compared to Venturi mask on exercise tolerance in lung transplant candidates: a crossover randomized clinical trial

Impacto da cânula nasal de alto fluxo em comparação à máscara de Venturi na tolerância ao exercício em candidatos a transplante de pulmão: um ensaio clínico randomizado cruzado

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Abstract

Background: Exercise is important for good health in lung transplant candidates and can be facilitated by oxygen supplementation. **Aim**: To compare the effects of the High-Flow Nasal Cannula (HFNC) and the Venturi mask (VM) on exercise tolerance in lung transplant candidates. **Methods**: This is a randomized crossover clinical trial carried out in the pulmonary rehabilitation program of a public hospital. Lung transplant candidates, over 18 years of age and needing oxygen during exercise were recruited. Two endurance tests on a treadmill were performed in random order with an interval of seven days, one with HFNC and the other with VM (both with FIO2 50%). The variables evaluated herein were endurance time (primary outcome), heart and respiratory rate, oxygen saturation, peripheral lactate, dyspnea, and lower limb fatigue symptoms. **Results**: Twelve participants were included (mean age 42 ± 10 years, 67% male). The time reached in the endurance test with the VM was 580 s (95% Confidence Interval, CI 403 – 756 s) and with the HFNC was 937 s (95% CI 668 – 1205 s); with mean difference of 357 s (95% CI 181 – 533 s) and P=0.001. No significant difference was observed after comparing the responses in other variables between the two conditions. There was no desaturation during any of the tests. **Conclusion**: The HFNC promoted an increase in exercise tolerance when compared to the VM in lung transplant candidates, and both systems were effective in preventing peripheral oxygen desaturation.

Keywords: Oxygen Inhalation Therapy; Nasal Cannula; Exercise Tolerance; Aerobic Exercise; Lung Transplantation.

Resumo

Introdução: O exercício é importante para uma boa saúde em candidatos a transplante de pulmão e pode ser facilitado pela suplementação de oxigênio. **Objetivo**: Comparar os efeitos da Cânula Nasal de Alto Fluxo (CNAF) e da Máscara de Venturi (MV) na tolerância ao exercício em candidatos a transplante de pulmão. **Métodos**: Este é um ensaio clínico randomizado cruzado realizado no programa de reabilitação pulmonar de um hospital público. Foram recrutados candidatos a transplante de pulmão, maiores de 18 anos e com necessidade de oxigênio durante o exercício. Dois testes de resistência em esteira foram realizados em ordem aleatória com intervalo de sete dias, um com a CNAF e outro com a MV (ambos com FIO2 50%). As variáveis avaliadas foram tempo de resistência (*endurance*) (desfecho primário), frequência cardíaca e respiratória, saturação de oxigênio, lactato periférico, dispneia e sintomas de fadiga de membros inferiores. **Resultados**: Doze participantes foram incluídos (idade média de 42 ± 10 anos, 67% do sexo masculino). O tempo alcançado no teste de resistência com a MV foi de 580 s (Intervalo de Confiança de 95%, IC 403 – 756 s) e com a CNAF foi de 937 s (IC 95% 668 – 1205 s); apresentando diferença média de 357 s (IC 95% 181 – 533 s) e P=0,001. Nenhuma diferença significativa foi observada após a comparação das respostas nas demais variáveis entre as duas condições. Não houve dessaturação durante nenhum dos testes. **Conclusão**: A CNAF promoveu um aumento na tolerância ao exercício quando comparada à MV em candidatos a transplante de pulmão, e ambos os sistemas foram eficazes na prevenção da dessaturação periférica de oxigênio.

Palavras-chave: Oxigenoterapia; Cânula Nasal; Tolerância ao Exercício; Exercício Aeróbico; Transplante de Pulmão.

INTRODUCTION

Lung transplantation is the treatment of choice for patients with advanced chronic respiratory failure and threat of short-term mortality[1,2]. Low exercise capacity is one of the reasons for not undergoing this treatment as it increases the chances of intolerance to the surgical procedure and has an increased risks for post-transplant complications[3,4].

Thus, aerobic exercise is part of the non-pharmacological treatment for lung transplant candidates[5]. However, for safety and greater gains it is necessary that the exercise prescription is individualized and done following appropriate exercise tests[6,7]. An exercise test with constant submaximal workload - endurance test, is the most sensitive to show acute responses to "add-on" interventions, such as non-invasive ventilation and oxygen therapy[8].

Evidence suggests that it is important to supplement oxygen to offer a better clinical condition during the assessment of exercise tolerance[9]. Lung transplant candidates begin to require oxygen therapy as the disease progresses, but guidelines for the use of this therapy do not provide a clear message in this regard[7].

There are several systems of oxygen delivery, such as catheters and masks, each with specific characteristics, such as the conditioning of the inhaled gas, the generated flow capacity and the fraction of inspired oxygen (FiO_2) allowed[10]. The effectiveness for the correction of hypoxemia may be limited by characteristics of these systems[10,11]. An example would be traditional oxygen systems such as the Venturi mask (VM), which are limited in relation to the flow and can generate instability in FiO_2 when there is an increase in peak inspiratory flow, in addition to compromising the ideal conditioning of the gas[11,12].

In recent years, high-flow nasal cannula (HFNC) has emerged as a promising option to release high flows of humidified and heated gas, with a known FiO_2 ranging from 21 to 100%[13]. In addition, HFNC has promoted the elimination of carbon dioxide from the anatomical dead space due to the high flow rates, and the generation of a somewhat low level of positive expiratory pressure, which can recruit alveoli units[10,11,13]. Therefore, the present study aimed to compare the effects of HFNC and VM on exercise tolerance during an endurance test in lung transplant candidates. We hypothesized that the HFNC would lead to better exercise tolerance compared to the VM.

METHODS

This is a randomized crossover clinical trial (registration number: RBR-10gqsbsm; details at: ReBEC[14]). This study design was chosen as it typically requires fewer participants than parallel studies, since each participant acts as his/her own control. The study was approved by the local research ethics committee (CAAE number: 04241018.1.0000.5039), and carried out from December 2018 to September 2019, in the pulmonary rehabilitation program of the Dr. Carlos Alberto Studart Gomes Messejana Hospital (Fortaleza, Ceara, Brazil).

The sample consisted of lung transplant candidates, over 18 years of age, undergoing initial evaluation to participate in a pulmonary rehabilitation program, who were oxygen-dependent, or in need of oxygen supplementation during a symptom-limited incremental exercise test performed before study inclusion. Candidates who did not attend the assessment day, or who did not present an adequate clinical condition on that day were excluded.

In the first meeting with the researcher, subjects were invited to participate and provide signed informed consent. Afterwards, sociodemographic data (age and gender) were recorded from medical records in addition to clinical data: diagnosis, body mass index, distance covered in the six-minute walk test, oxygen prescription, and spirometric results.

Two endurance tests were performed, one with HFNC and the other with VM. The order of the oxygen therapy systems was defined by randomization moments before the first test. The allocation sequence was produced by a researcher and kept by the same researcher in sealed opaque envelopes. The tests were scheduled within an interval of seven days and performed on an ergometric treadmill (Advanced 990, Athletic, Brazil). The application of the oxygen systems and the recording of variables during the endurance tests in all the participants were carried out by a trained researcher, with no blinding of researcher or participants.

In the endurance test, the participants were instructed to walk for as long as possible at a speed equal to the maximum speed and inclination equal to 90% of that achieved in an incremental symptom-limited test[15,16], which was performed on the first assessment day of the pulmonary rehabilitation program. The duration of the endurance test started after a 3-minute warm-up with the same speed achieved in the incremental test, but with no inclination. After this warm-up, inclination was instituted and the participant was instructed to walk until he/she could no longer tolerate it[6,8,15,16]. Each endurance test was divided into three moments for the recording of variables: 1) rest period in the sitting position, after 15 min with the oxygen system; 2) every 3 minutes after starting the test, and; 3) immediately at the end of the test, before starting the recovery period. The endurance time was the primary outcome of this study and corresponded to the period in which the candidate endured the evaluation, excluding the warm-up time[6,8,15,16].

Other variables studied (secondary outcomes) were systemic arterial pressure, heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO_2), peripheral blood lactate (capillary blood sample obtained from the tip of the right hand middle finger; Accutrend® Plus, Roche, Brazil), and perception of dyspnea and lower limb fatigue

scored by the modified Borg scale, with the highest score indicating the worst symptom[17]. To calculate the maximum HR, the following formula was used: HR max = 220 - age.

After carrying out all the endurance tests, the isotime was demarcated which was a specific moment during the test standardized by the research where the variables (physiological responses) were retrospectively evaluated, regardless of the degree of effort[6]. In the present study, the isotime was elected as the shortest endurance time with HFNC or VM achieved among all participants.

The VM (model 28KV, NewMed®, São Paulo, Brazil) was used with a FiO_2 valve equal to 50% and an oxygen flow of 12 L/min with humidification. To calculate the total gas flow released by the entrainment, the formula provided by Woolne and Larkin[18] was used registering 22L/min (ambient oxygen-air mixture). The HFNC (Optiflow™MR850, Fisher & Paykel, New Zealand) was used with a FiO_2 equal to 50% and a total gas flow of 50L/min (ambient oxygen-air mixture), in addition to guaranteed temperature and humidification.

To calculate the sample size, a minimal important difference of 109 s between the time achieved in the endurance tests was considered, assuming an a priori standard deviation of 104 s, according to the work of Cirio et al.[19] in addition to a significance level of 5% and two-tailed test power of 90%, resulting in a sample size of twelve participants.

For the statistical analysis, the Statistical Package for the Social Sciences (SPSS) program version 22.0 (IBM, Armonk, NY, USA) was used, through which descriptive and inferential statistics were performed, with a significance level set at 5% for all tests ($P \leq 0.05$). Continuous data were expressed as mean ± standard deviation or mean (95% confidence interval - CI). Categorical data were presented as absolute and relative frequency. For comparisons, the paired Student's t test or the Wilcoxon test were used, depending on the normality of the data, assessed with the Shapiro-Wilk test.

RESULTS

During the recruitment period, 14 lung transplant candidates were admitted to the pulmonary rehabilitation program. Four of them were already using oxygen continuously and the other ten needed oxygen supplementation only during the incremental test. However, two individuals could not be assessed for this study, one due to a major abdominal aortic aneurysm and one due to respiratory distress on the day of assessment. Thus, 12 subjects concluded the research protocol, presented data for all variables and were used for analysis (Figure 1).

The sociodemographic and clinical characteristics of the 12 lung transplant candidates are shown in Table 1. The sample had a mean age of 42 ± 10 years and there was a predominance of male subjects (8, 67%). Chronic hypersensitivity pneumonia represented the most frequent diagnosis in 4 (33%) subjects, followed by 3 (25%) with bronchiectasis. Spirometric data showed characteristics of restrictive ventilatory disorder in 6 (50%) subjects, obstructive ventilatory disorder in 5 (42%) subjects and 1 (8%) subject showed no ventilatory disorder. The average inclination of the treadmill that represented the imposed load for the endurance tests was 8 ± 1% and the speed was 3 ± 2 km/h. There were no relevant adverse events during the tests.

Table 1. Sociodemographic and clinical characteristics of the sample of lung transplant candidates[a].

Characteristic	Value
Male sex, n (%)	8 (67)
Age, years	42 ± 10
BMI, kg/m^2	22 ± 6
Diagnosis, n (%)	
Chronic hypersensitivity pneumonia	4 (33)
Bronchiectasis	3 (25)
Hermansky-Pudlak syndrome	2 (17)
Alpha-1 antitrypsin deficiency	2 (17)
Lymphangioleiomyomatosis	1 (8)
Distance 6MWT, meters	447 ± 97
Home continuous use of oxygen, n (%)	4 (33)
Endurance test	
Speed, km/h	3 ± 2
Treadmill inclination, %	8 ± 1
Restrictive ventilatory disorder, n (%)	6 (50)
FEV_1, % predicted	55 ± 2
FVC, % predicted	49 ± 4
FEV_1 / FVC, %	111 ± 6
Obstructive ventilatory disorder, n (%)	5 (42)
FEV_1, % predicted	25 ± 6
FVC, % predicted	45 ± 16
FEV_1 / FVC, %	60 ± 17
No ventilatory disorder, n (%)	1 (8)
FEV_1, % predicted	90
FVC, % predicted	103
FEV_1 / FVC, %	73
DLCO, % predicted	37 ± 10

n: Absolute frequency; BMI: Body Mass Index; 6MWT: 6-Minute Walk Test; FEV_1: Forced Expiratory Volume in the First Second; FVC: Forced Vital Capacity; DLCO: Lung Diffusing Capacity for Carbon Monoxide. [a]Data expressed as absolute (relative) frequency, or mean ± standard deviation.

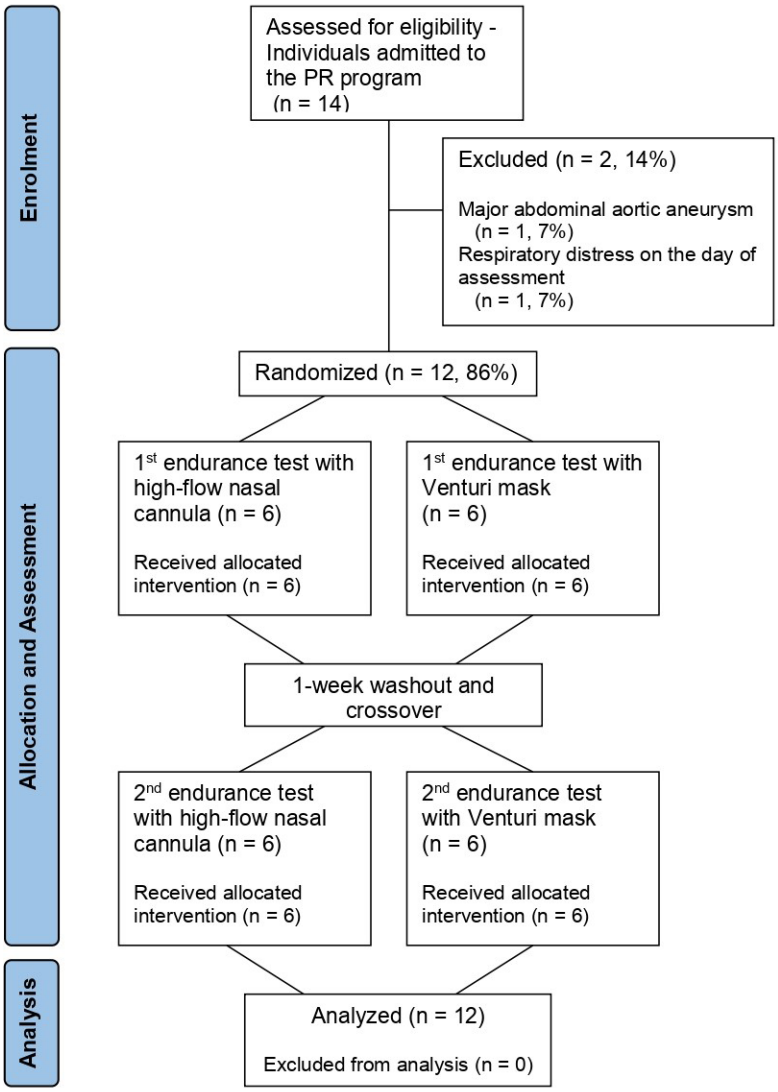

Figure 1. Flow diagram of the study. PR: pulmonary rehabilitation.

The endurance time reached a mean of 580 s (95% CI 403 – 756 s) with VM, and of 937 s (95% CI 668 – 1205 s) with HFNC. The mean difference between these groups (HFNC minus VM) was 357 s (95% CI 181 – 533 s); P = 0.001. In an individual analysis of the 12 candidates, it was observed that in 10 (83%) there was a gain in endurance time with the HFNC, however, in 2 (17%) who had a diagnosis of bronchiectasis, there was no difference in the result achieved (Figure 2). The interruption of the tests in eleven candidates was due to the symptom of dyspnea and none of them reached the maximum heart rate calculated for their age (results not shown).

The behavior of physiological variables, lower limb fatigue symptom and dyspnea during the endurance tests can be seen in Table 2. For any oxygen system the comparison of variables between the averages at rest and post-test was statistically significant, except for SpO_2 in both groups, and lactate in the VM group. There was no desaturation in any of the groups. Comparing the differences between the means of the two systems (HFNC minus VM), the results did not show statistical significance for any of the variables.

The value of physiological variables and symptoms of dyspnea and lower limb fatigue recorded at isotime, determined as the third minute during the tests, as well as the mean difference (95% CI) between groups (HFNC minus VM) are shown in Table 3. The 95% CI analysis showed that there was no statistical difference for any of the variables.

In the analysis of the variables recorded at rest and at isotime, comparing the mean RR in the tests with the two oxygen systems (HFNC and VM), a statistical difference was observed between the means at rest and isotime of the test with VM (Figure 3).

DISCUSSION

The present study evaluated, for the first time, the effects of HFNC as oxygen support in candidates for lung transplantation in relation to oxygen therapy by VM, during the performance of an endurance test on a treadmill.

Table 2. Physiological variables with HFNC and VM in endurance tests in the lung transplant candidates[a].

Variable	HFNC			VM			Mean difference between groups (95% CI)
	Rest	Post-test	Mean difference (95% CI)	Rest	Post-test	Mean difference (95% CI)	
Borg dyspnea	0.3 ± 0.5	5 ± 2*	5 (3 - 6)	0.1 ± 0.3	5 ± 2*	5 (4 - 7)	-1 (-2 – 1)
Borg fatigue lower limbs	0 ± 0	4 ± 3*	4 (2 - 6)	0.1 ± 0.3	4 ± 3*	4 (2 - 5)	0 (-1 – 1)
RR, bpm	22 ± 5	37 ± 10*	15 (10 -20)	22 ± 5	36 ± 7*	14 (9 -18)	1 (-4 – 7)
SpO_2, %	98 ± 2	96 ± 2	-2 (-4 - 0)	98 ± 2	95 ± 3	-3 (-5 - 0)	-1 (-1 – 3)
HR, bpm	89 ± 21	138 ± 20*	49 (31 – 66)	88 ± 17	133 ± 17*	45 (32 – 58)	3 (-4 – 11)
SBP, mmHg	114 ± 10	155 ± 24*	41 (29 – 52)	116 ± 9	153 ± 27*	37 (23 – 51)	4 (-8 – 16)
DBP, mmHg	73 ± 9	88 ± 9*	15 (10 – 20)	74 ± 9	86 ± 25*	12 (-1 – 24)	3 (-9 – 16)
Lactate, mmol/L	2.7 ± 1	4.6 ± 1.8*	2 (1 – 3)	3.2 ± 1.4	3.8 ± 1.4	0.6 (0 – 1)	1 (0 – 3)

HFNC: High-flow nasal cannula; VM: Venturi Mask; RR: respiratory rate; SpO_2: Peripheral oxygen saturation; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure. [a]Data expressed as mean ± SD or mean (95% confidence interval - CI). *P<0.05 *vs.* rest.

Table 3. Physiological variables measured with HFNC and VM at isotime in the lung transplant candidates[a].

Variable	Isotime HFNC	Isotime VM	Mean difference (HFNC minus VM)
Borg dyspnea	2 ± 1	2 ± 2	-0.3 (-1.0 – 0.4)
Borg fatigue lower limbs	1 ± 1	1 ± 1	-0.4 (-2 – 1)
RR, bpm	26 ± 7	29 ± 6	-3 (-7 – 2)
SpO_2, %	98 ± 1	98 ± 2	-0,3 (-1 – 2)
HR, bpm	113 ± 33	117 ± 17	-3 (-16 – 9)
SBP, mmHg	128 ± 19	133 ± 20	-6 (-23 – 11)
DBP, mmHg	79 ± 10	79 ± 11	0 (-8 – 8)

HFNC: High-flow nasal cannula; VM: Venturi Mask; RR: respiratory rate; SpO_2: Peripheral oxygen saturation; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure. [a]Data expressed as mean ± SD or mean (95% confidence interval - CI).

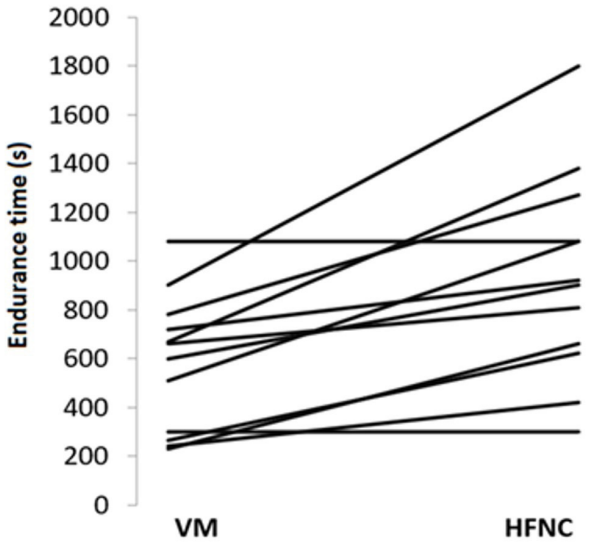

Figure 2. Comparison of individual endurance time (in seconds, s) between VM and HFNC in the lung transplant candidates. VM: Venturi Mask; HFNC: High-flow nasal cannula.

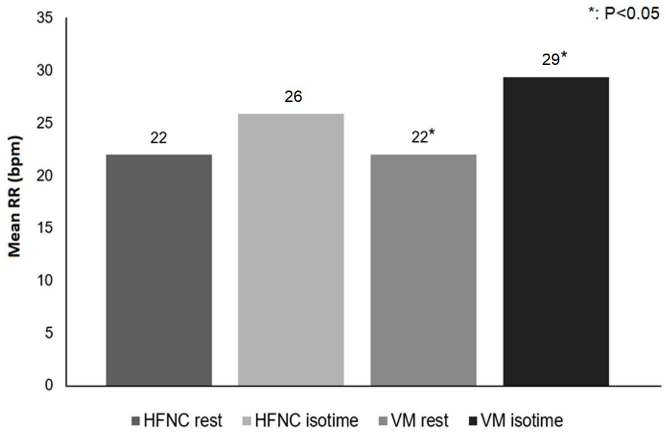

Figure 3. Respiratory rates at rest and at isotime with HFNC and VM in the lung transplant candidates. HFNC: High-flow nasal cannula; VM: Venturi Mask; RR: respiratory rate; bpm: breaths per minute.

HFNC superiority was observed with a mean difference in endurance time between the two oxygen systems of 357 s (95% CI 181 – 533 s).

Studies in patients with COPD have shown gains lower than those found in the present study. In the study by O'Donnell et al.[20], the authors found a mean difference of 105 s in exercise tolerance during a cycle ergometer test after using bronchodilator. Based on other studies, another research group reported a gain between 100-200 s after aerobic training in patients with COPD[21]. Casaburi[22] proposed that a minimum variation of 105 s (1.75 min) should be considered as clinically significant for endurance tests. Another review suggested a value of 85 s (1.25 min), after reviewing clinical trials involving patients

with COPD[23]. The current study has found a higher value than those reported by these other studies.

In a similar study, but evaluating patients with COPD only, the authors concluded that a high-flow oxygen system, when compared to a low-flow one, was responsible for greater performance in cycle ergometer exercise time, in addition to a better level of oxygenation[24]. Cirio et al.[19] showed a similar result in patients with clinically stable severe COPD who performed the endurance test on a cycle ergometer, with HFNC versus VM. These studies in patients with COPD used oxygenation systems like the ones used in the present study. Unfortunately, the different study population compromises a direct comparison with the present study. However, HFNC seems to be beneficial, regardless of the study population. In disagreement with our findings and those reported by Chatila et al.[24], Cirio et al.[19], and Prieur et al.[25], observed that HFNC does not improve exercise tolerance in COPD patients recovering from acute exacerbation, possibly due to the reduction in SpO_2 that occurred and the increase in dynamic hyperinflation and inspiratory muscle dysfunction[26], as a result of a recent disease exacerbation.

In the current study, the effect on endurance time cannot be explained by the capacity of HFNC to offer a more stable FIO_2 than VM, since in none of the situations the candidates presented hypoxemia induced by the tests, with no statistical significance in the comparison of the difference in the average SpO_2 between rest and post-test. The study assumes that the gain in endurance time can be explained by changes caused in alveolar ventilation and minute volume derived from the reduction of dead space in the upper airways and elimination of carbon dioxide due to the characteristic of HFNC releasing high flows[27]. For Delorme et al.[28], there is a change proportional to high flow values, which in the present study was 50L/min. One group of authors also considered that there may be a decrease in the work of breathing, demonstrated by means of an esophageal catheter, when using HFNC during sleep in patients with COPD[29].

The effect on endurance time can also be attributed to the benefits of potential positive expiratory pressure generated by the flow in the candidates' airways. The work by Parke and McGuinness[30], measured the pressure in the airways caused by the high-flow system in cardiac patients and concluded that there is an expiratory pressure that produces a beneficial clinical effect. In a systematic review there is a report, in an animal model, that the flow can generate positive pressure, resulting in increased intra-alveolar volume[13].

In two candidates from our sample diagnosed with bronchiectasis, the endurance time was the same regardless of the oxygen delivery system. To identify predictors of exercise tolerance in patients with bronchiectasis, the literature suggests that spirometry alone is not capable of predicting exercise capacity, also citing skeletal muscle dysfunction as a potential contributor[31]. The present investigation did not assess skeletal muscle function; therefore, it was not possible to attribute the finding to the condition of the peripheral muscles. In another study, a patient with interstitial lung disease also showed no change in the endurance time when inhaling oxygen through a nasal cannula with a reservoir in relation to the conventional system, and this was explained by the way the patient breathed during the test, losing the expected effect with the reservoir cannula[32].

There was no statistically significant difference between the mean differences (HFNC minus VM) in secondary outcomes, despite a longer endurance time when using the HFNC. This might have happened due to the sample calculation being performed for the endurance time, and not for the secondary outcomes.

Regarding the measurement of lactate at rest during the test with VM, a higher value was observed in relation to that found with HFNC. Values above 2.6 mmol/L are classified as slightly altered, and above 3.6 mmol/L as moderately elevated[33]. Glycolytic metabolism leads to reduced exercise capacity for those on a pre-transplant list[34]. Engelen et al.[35] suggested that early lactic acidosis has a negative influence on exercise fitness and that patients with COPD and reduced carbon monoxide diffusion are more prone to low muscle oxidative capacity. Thus, it is questionable whether the closer-to-normal lactate values at rest in the use of HFNC contributed positively to the 62% increase in endurance time, which seems to be of clinical importance.

In the isotime analysis, we observed that there was no statistical difference between the groups for any of the variables. These results are different from those presented by Gloeckl et al.[36], who found better SpO_2 values in the isotime with a nasal cannula coupled with a reservoir, compared to the conventional nasal catheter. A possible explanation for their findings is that the FIO_2 delivered by a nasal catheter gets lower with an increase in minute volume during exercise. The RR was higher at isotime compared to the measurements at rest, only in the test with a VM. The study assumes that lower RR with HFNC at isotime may indicate less respiratory effort, a factor possibly related to the observed increase in endurance time with this device.

Limitations of this study include not blinding the choice of oxygen therapy system to assessors, therapist or participants, patients with heterogeneous diseases, and a small sample size, which may limit the external validity of the findings. The performance of the endurance test on a treadmill can also be seen as a limitation, as most previous studies opted for performing the test on a cycle ergometer. Additionally, performing muscle strength tests could have helped explain the results.

CONCLUSION

The results of this study lead to the conclusion that HFNC determined a mean gain of 357 s (95% CI 181 – 533 s)

during an endurance test on a treadmill in lung transplant candidates when compared to a conventional system (i.e. VM). Both systems were effective in preventing peripheral oxygen desaturation. Further research is needed to better explain these findings, with a larger sample, blinded design, and a more detailed assessment of physiological responses, to corroborate the findings of the present research and expand the clinical applicability of the interventions in patients with advanced lung diseases in rehabilitation programs.

FUNDING

None.

CONFLICT OF INTEREST

None.

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