Effectiveness of High-Flow Nasal Cannula on Pulmonary Rehabilitation in Subjects with Chronic Respiratory Failure

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Research article

Keywords: Chronic respiratory failure, Exercise training, High-flow nasal cannula

Posted Date: August 27th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-55544/v1

Abstract

Backgrounds: There are no clinical data comparing the effect of exercise training using both high fraction of inspired oxygen (F_IO_2) and high flow through a high-flow nasal cannula (HFNC) with that of ordinary supplemental oxygen on exercise capacity in subjects with chronic respiratory failure (CRF) receiving long-term oxygen therapy (LTOT).

Methods: In this randomized study, 32 patients with CRF receiving LTOT were assigned to undergo 4 weeks of exercise training on a cycle ergometer using an HFNC (flow: 50 L/min) with a F_IO_2 of 1.0 (HFNC group; n=16) or ordinary supplemental oxygen via a nasal cannula (flow: 6 L/min) (oxygen group; n=16). Before and after 4 weeks of exercise training, a 6-min walking test, constant-load test, and blood sampling were performed.

Results: Prior to exercise training, the endurance time of the constant-load exercise test using an HFNC was significantly longer than that reported with prescribed oxygen in daily LTOT (p=0.004) or a 6 L/min nasal cannula (p=0.0003). Following 4 weeks of exercise training, change in the 6-min walking distance was significantly greater in the HFNC versus the oxygen group (55.2±69.6 m vs. —0.5±87.3 m, respectively; p=0.04). The plasma levels of adrenaline, noradrenaline, and serum C-reactive protein were significantly decreased only in the HFNC group, after 4 weeks of exercise training.

Conclusions: Despite heterogeneity in the effect among patients, exercise training using both high F_IO_2 and high flow through an HFNC is a potentially superior exercise training modality for CRF patients receiving LTOT.

Clinical Trial Registration — http://www.clinicaltrials.gov. Unique identifier: NCT02804243. Registered 13 June 2016.

Background

Pulmonary rehabilitation reduces dyspnea, increases exercise capacity, and improves quality of life in patients with chronic obstructive pulmonary disease (COPD), interstitial lung disease, bronchiectasis, and pulmonary hypertension [1–4]. High-intensity endurance exercise training (e.g., cycling or walking) is the most commonly applied exercise modality in pulmonary rehabilitation [5–7].

It has been observed that patients with advanced chronic respiratory failure (CRF) receiving long-term oxygen therapy (LTOT) have severe hypoxia during exercise training even if they receive relatively high flow rates of oxygen via a nasal cannula. In addition, the maximal flow rate of oxygen via a nasal cannula during exercise training is approximately 6 L/min. This is due to severe nasal dryness and pain induced by higher flow rates. Low-intensity exercise training has been applied to individuals with CRF who have difficulty in achieving their target intensity because of dyspnea and/or hypoxia. However, it led to insufficient exercise training effects compared with high-intensity exercise training.

Several new options to increase the effects of exercise training have been reported. It has been shown that hyperoxia during exercise training increased the peak work rate [8] or endurance time in the constant-load exercise test [9] in COPD patients. In other studies, exercise training using hyperoxia did not demonstrate a beneficial effect [10–13]. The administration of a high flow heated and humidified gas mixture through high-flow nasal cannula (HFNC) promotes higher and more stable inspiratory oxygen fraction values, decreases anatomical dead space, and generates a positive airway pressure that can improve ventilatory efficiency [14–16]. In addition, it reduces the effort of breathing and enhances patients' comfort and tolerance [16–19]. In a previous study, the duration of the constant-load exercise test in COPD patients receiving LTOT was significantly improved after exercise training consisting of 20 supervised sessions in both the HFNC group and control group, whereas no significant difference between groups was observed in improvement in the duration of the constant-load exercise test [20]. In this study, both groups undergone exercise training at the same fraction of inspired oxygen (F_IO_2). Based on the beneficial effects of an HFNC, we postulated that high intensity exercise training using not only high flow but also high F_IO_2 through an HFNC may lead to an enhancement of exercise capacity in patients with advanced CRF receiving LTOT.

The aim of this randomized, prospective study was to compare the effect of 4 weeks of exercise training using both high F_IO_2 and high flow through an HFNC or supplemental oxygen via a nasal cannula on the exercise capacity (e.g., 6-min walking distance [6MWD]) of CRF patients receiving LTOT.

Methods

Patients

From June 2016 to May 2018, patients with CRF (aged 40–90 years) undergoing LTOT for ≥ 3 months and attending an in-patient rehabilitation program were eligible to participate in the study. Patients with a stable clinical condition (i.e., no exacerbation reported for 3 months prior to the study) and absence of the following exclusion criteria: history of cardiovascular disease (e.g., myocardial infarction or ischemic heart disease, diabetes mellitus under treatment with hypoglycemic agents or insulin, neurological disorders, renal dysfunction (serum creatinine ≥ 1.2 mg/dL), and unable to undergo rehabilitation were enrolled.

In this prospective study, we assessed 42 consecutive patients with CRF receiving LTOT. Prior to enrollment, all patients underwent a 2-week screening period. Of those, seven patients were excluded (two with acute exacerbation, three with history of cardiovascular disease, and two who were unable to undergo rehabilitation), and three patients declined to participate. Thus, the remaining 32 clinically stable CRF patients receiving LTOT were enrolled (Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02804243). This study was approved by the Ethics Committee of the National Hospital Organization Minami-Kyoto Hospital. All patients provided written informed consent prior to their participation.

Study design

On day 1, arterial blood gases (ABGs) were obtained in the supine position under a prescribed flow of oxygen via a nasal cannula and patients underwent a 6-min walking test (6MWT). On day 2, venous blood samples were obtained in the fasting state in the morning and examined for C-reactive protein (CRP), and plasma catecholamine levels. Pulmonary function tests were performed using the CHESTAC system (Chest M.I. Inc., Tokyo, Japan). In addition, patients underwent an incremental-load exercise test under prescribed oxygen on a cycle ergometer (Aerobike75XL, COMBI, Tokyo, Japan) to assess their maximal exercise capacity. In the following 3 days, the patients underwent (in random order) three constant-load exercise tests with a prescribed flow of oxygen via a nasal cannula, a flow of 6 L/min of oxygen via a nasal cannula, or an HFNC at a flow of 50 L/min with F_IO_2 of 1.0. The HFNC delivered a heated and humidified gas through an Optiflow system (Fisher and Paykel Healthcare, Auckland, New Zealand) using large-bore bi-nasal prongs.

After the constant-load exercise tests, patients completed a 4-week period of exercise training (five sessions per week) using the same workload achieved during the constant-load exercise tests. In the HFNC group, the HFNC was set at maximum F_IO_2 (F_IO_2 of 1.0) and near-maximum inspiratory flow rate (50 L/min) to assess its maximum effects. In the oxygen group, the flow rate of oxygen via a nasal cannula was set at the maximal flow rate (6 L/min).

Venous blood sampling, ABGs, pulmonary function tests and 6MWT on prescribed oxygen were conducted after 4 weeks of exercise training. In the following 3 days, subjects also underwent (in random order) three constant-load exercise tests using the same workload with that of the baseline assessment with prescribed oxygen in daily LTOT, a 6 L/min nasal cannula, or an HFNC at F_IO_2 of 1.0 and 50 L/min.

The primary outcome was change in the 6MWD prior to and following 4 weeks of exercise training. The secondary outcome was change in the duration of constant-load exercise test prior to and after 4 weeks of exercise training.

6MWT

The 6MWT was performed under prescribed oxygen in daily LTOT. According to the guidelines of the American Thoracic Society [21], patients were encouraged using standard methodology every minute of the 6MWT. A pulse oximeter (Anypal Walk, Fukuda Denshi, Tokyo, Japan) with a finger probe was used to measure oxygen saturation by pulse oximetry (SpO_2) and the pulse rate during the 6MWT. In addition, a modified Borg scale [22] was used to quantify the levels of dyspnea perceived by patients at each minute during the 6MWT.

Exercise testing

Both incremental- and constant-load exercise tests were performed with continuous monitoring of SpO_2 and the pulse rate on a cycle ergometer. In addition, continuous transcutaneous carbon dioxide partial pressure ($PtcCO_2$) monitoring was performed using a TOSCA measurement system and TOSCA 500 monitor (Radiometer, Copenhagen, Denmark) [23, 24]. After automated calibration, the TOSCA monitor was attached to the right or left ear lobe. $PtcCO_2$ monitoring was initiated after at least 10 min of equilibration. The incremental-load exercise test was performed according to the appropriate Japanese guidelines [25]. The incremental-load exercise test under prescribed oxygen in daily LTOT was initiated at 5 watts and increased by 5 watts every 2 minutes until the patient's SpO_2 was ≤ 85%, the pulse rate was ≥ 135 beats/min, or the modified Borg scale for dyspnea was ≥ 5. Prior to and following 4 weeks of exercise training, the patients performed three constant-load exercise tests at 80% of the maximum workload achieved with the incremental-load exercise test, with prescribed oxygen in daily LTOT, 6 L/min via a nasal cannula, or an HFNC at F_IO_2 of 1.0 and 50 L/min. The criteria for the termination of the constant-load exercise test were the same as those for the incremental-load exercise test. The SpO_2, pulse rate, and $PtcCO_2$ were measured at 6 min of the constant-load exercise test. All exercise testing was performed in the afternoon.

Exercise training

The patients performed supervised pulse oximeter-monitored continuous exercise training (5 sessions per week) receiving 6 L/min using a nasal cannula or an HFNC at F_IO_2 of 1.0 and 50 L/min. All training sessions were conducted on the same cycle ergometer and supervised by medical staff. Initially, the workload of the exercise training was the same as that of the constant-load exercise test. The criteria for the termination of exercise training sessions were SpO_2 ≤85%, pulse rate ≥135 beats/min, or modified Borg scale for dyspnea ≥5. Whenever the duration of an exercise training session was ≥30 minutes, the workload of the subsequent session was increased by 5 watts.

Randomization

This study was randomized via blinded envelope prior to the initiation of the study.

Power analysis

Based on a previous study [26], differences of 30 meters of change in the 6MWD prior to and following 4 weeks of exercise training between the HFNC group and the oxygen group were decided to be clinically significant, and a standard deviation of 30 meters was expected. The sample size was set to achieve 80% power at a 5% significance level. The calculated sample size in each group was 16 subjects.

Statistical analysis

Data were analyzed using the JMP 9.0 software (SAS Institute, Inc. Cary, NC, USA), and values are expressed as mean ± standard deviation or absolute numbers and percentages. We compared subject characteristics, the results of the 6MWT and constant-load exercise test, and other parameters between the HFNC and oxygen groups. Continuous variables were tested using the unpaired t test or Mann–Whitney U test. Categorical variables were compared using the χ^2 test or Fisher's exact test. To investigate changes in the 6-min walk distance, constant load exercise test, and other parameters prior to and after 4 weeks of exercise training in each group, comparisons of data between those two time points were tested using a paired t test. A $p < 0.05$ denoted statistical significance.

Results

Patient characteristics

Figure 1 shows the study flow chart of this randomized study. In this study, 32 CRF patients receiving LTOT were randomly assigned to undergo 4 weeks of exercise training using an HFNC (n = 16) or a 6 L/min nasal cannula (n = 16). The characteristics of the patients are summarized in Table 1. The cause of CRF was COPD (n = 13), interstitial pulmonary fibrosis (IPF) (n = 15), or bronchiectasis (n = 4).

Table 1
Characteristics and laboratory data of study participants

	HFNC group (n = 16)	Oxygen group (n = 16)	p value
Age	76.6 ± 5.7	76.0 ± 6.3	0.77
Male	13 (81.3)	11 (73.3)	0.69
BMI	21.9 ± 3.3	22.0 ± 3.7	0.97
Underlying disease			0.23
COPD	6 (37.5)	7 (43.8)	
IPF	9 (56.3)	6 (37.5)	
Bronchiectasis	1 (6.2)	3 (18.7)	
%VC (%)	72.2 ± 15.5	74.8 ± 18.8	0.68
FEV1/FVC (%)	66.7 ± 27.2	61.6 ± 23.2	0.58
$\%DL_{CO}$ (%)	55.4 ± 18.5	60.8 ± 23.7	0.49
Oxygen supply of LTOT during resting (L/min)	1.6 ± 1.3	1.1 ± 0.9	0.17
Oxygen supply of LTOT during exercise (L/min)	3.2 ± 1.8	2.8 ± 1.3	0.54
ABGs			
pH	7.401 ± 0.030	7.410 ± 0.036	0.46
PaO_2 (Torr)	89.6 ± 22.0	82.7 ± 23.5	0.41
$PaCO_2$ (Torr)	43.7 ± 5.2	41.7 ± 7.1	0.41
Comorbidity			
Hypertension	8 (50.0)	11 (68.8)	0.28
Dyslipidemia	9 (56.3)	11 (68.8)	0.47
Diabetes Mellitus	3 (18.8)	3 (18.8)	0.99
Blood (fasting)			
Adrenaline (pg/mL)	20.4 ± 14.7	20.9 ± 16.1	0.92
Noradrenaline (pg/mL)	388.0 ± 228.4	370.7 ± 255.7	0.84
CRP (mg/dL)	0.59 ± 0.58	0.40 ± 0.47	0.32

	HFNC group (n = 16)	Oxygen group (n = 16)	p value
mean ± standard deviation or number (%)			
Abbreviations: HFNC, high-flow nasal cannula; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; VC, vital capacity; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DL_{CO}, diffusion capacity of the lung for carbon monoxide; LTOT, long-term oxygen therapy; ABGs, arterial blood gases; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; CRP, C reactive protein			

There were no significant baseline differences between the two groups (Table 1). Similarly, 6MWD, the maximum workload or time of the incremental-load exercise test, and time of the constant-load exercise test under three conditions did not differ significantly between the two groups (Table 2).

Table 2
Results of the exercise test and 6-minute walking test prior to 4 weeks of exercise training, and the load and duration of exercise training

	HFNC group (n = 16)	Oxygen group (n = 16)	p value
Incremental-load exercise test:			
Maximum workload (watt)	36 ± 10	32 ± 13	0.39
Time (sec)	793 ± 230	724 ± 289	0.47
Constant-load exercise test:			
Time under the prescribed oxygen in daily LTOT (sec)	876 ± 858	950 ± 837	0.82
Time under the 6 L/min nasal cannula (sec)	1065 ± 986	1083 ± 944	0.96
Time under the HFNC (sec)	1473 ± 887	1586 ± 1058	0.75
6-minute walking distance (m)	224.1 ± 109.4	210.1 ± 93.0	0.70
Modified Borg Scale for dyspnea on 6MWT	3.6 ± 2.5	3.6 ± 2.1	0.97
Exercise training:			
Mean workload (watt)	34 ± 11	31 ± 11	0.52
Mean time per session (sec)	1532 ± 282	1218 ± 367	0.01
mean ± standard deviation or number (%)			
Abbreviations: LTOT, long-term oxygen therapy; 6MWT, 6-minute walking test			

Constant-load exercise test under three conditions in all subjects

Figure 2 shows the results of the constant-load exercise test prior to exercise training in all patients. The duration of the constant-load exercise test using an HFNC was significantly longer than that reported with prescribed oxygen in daily LTOT ($p = 0.004$) or a 6 L/min nasal cannula ($p = 0.0003$) (Fig. 2-A). Moreover, there was no significant difference between the two conditions (prescribed oxygen in daily LTOT or a 6 L/min nasal cannula) in the duration of the constant-load exercise test ($p = 0.15$). The modified Borg scale for dyspnea at the termination of the constant-load exercise test under the HFNC tended to be lower compared with that observed under the 6 L/min nasal cannula ($p = 0.07$) (Fig. 2-B).

Six minutes after initiation of the constant-load exercise test, the SpO_2 was significantly higher and the pulse rate was significantly lower with HFNC versus those observed with prescribed oxygen in daily LTOT or 6 L/min nasal cannula (Fig. 3-A, 3-B). There were no significant differences between the three conditions in $PtcCO_2$ six minutes after initiation of the constant-load exercise test (Fig. 3-C).

Exercise training

All patients completed 20 sessions of exercise training. There was no significant difference in the mean workload during exercise training between the groups (HFNC group: 34 ± 11 watt vs. oxygen group: 31 ± 11 watt: $p = 0.52$). The mean duration of the exercise sessions was significantly longer in the HFNC group compared with the oxygen group (1,532 ± 282 sec vs. 1,218 ± 367 sec, respectively; $p = 0.01$) (Table 2). During 4 weeks of exercise training, none of the patients exhibited clinically significant respiratory deterioration, such as rapidly aggravating oxygenation or dyspnea.

Primary outcome: Change in the 6MWD after 4 weeks of exercise training

Following 4 weeks of exercise training, change in the 6MWD was significantly greater in the HFNC group compared with the oxygen group (55.2 ± 69.6 m vs. -0.5 ± 87.3 m, respectively; $p = 0.04$) (Table 3). Compared with the baseline values, the 6MWD was significantly increased in the HFNC group, but not in the oxygen group (Table 4, Fig. 4). Notably, change in the modified Borg scale for dyspnea at the termination of the 6MWT was not significantly different between the two groups (Table 3).

Table 3

Changes in 6-minute walking test, and constant-load exercise test between the two groups prior to and following 4 weeks of exercise training

	HFNC group (n = 16)	Oxygen group (n = 16)	p value
Δ 6-minute walk distance (m)	55.2 ± 69.6	-0.5 ± 87.3	0.04
Δ Modified Borg Scale for dyspnea on 6MWT	0.0 ± 1.7	0.3 ± 1.5	0.66
Constant-load exercise test:			
Δ Time under the prescribed oxygen in daily LTOT (sec)	430 ± 557	262 ± 581	0.43
Δ Time under the 6 L/min nasal cannula (sec)	732 ± 819	1036 ± 1163	0.43
Δ Time under the HFNC (sec)	828 ± 700	700 ± 840	0.66

mean ± standard deviation or number (%)

Δ, pre-to-post exercise training change

Abbreviations: 6MWT, 6-minute walking test; LTOT, long-term oxygen therapy.

Table 4
Effects of 4 weeks of exercise training on several parameters, 6-minute walking test, and constant-load exercise test in each group

	HFNC group (n = 16)			Oxygen group (n = 16)		
	BL	**4 weeks**	**P value**	**BL**	**4 weeks**	**p value**
6-minute walk distance (m)	224.1 ± 109.4	279.3 ± 103.8	0.006	210.1 ± 93.0	209.6 ± 89.4	0.98
Modified Borg Scale for dyspnea on 6MWT	3.6 ± 2.5	3.6 ± 2.4	0.94	3.6 ± 2.1	3.9 ± 1.8	0.51
Constant-load exercise test:						
Time under the prescribed oxygen in daily LTOT (sec)	876 ± 858	1340 ± 1178	0.01	950 ± 837	1211 ± 963	0.10
Time under the 6 L/min nasal cannula (sec)	1065 ± 986	1835 ± 1171	0.005	1083 ± 944	2119 ± 1102	0.004
Time under the HFNC (sec)	1473 ± 887	2344 ± 1080	0.0007	1586 ± 1058	2285 ± 1061	0.006
%VC (%)	72.2 ± 15.5	71.0 ± 17.0	0.64	74.8 ± 18.8	76.5 ± 18.2	0.12
FEV1/FVC (%)	66.7 ± 27.2	65.2 ± 27.1	0.42	61.6 ± 23.2	62.0 ± 23.0	0.61
$\%DL_{CO}$ (%)	55.4 ± 18.5	57.3 ± 21.4	0.19	60.8 ± 23.7	60.8 ± 23.8	0.20
ABGs						
pH	7.401 ± 0.030	7.385 ± 0.021	0.43	7.410 ± 0.036	7.398 ± 0.039	0.10
PaO_2 (Torr)	89.6 ± 22.0	87.1 ± 22.4	0.72	82.7 ± 23.5	85.3 ± 26.0	0.49
$PaCO_2$ (Torr)	43.7 ± 5.2	44.4 ± 6.2	0.37	41.7 ± 7.1	42.3 ± 7.0	0.53
Blood (fasting)						
Adrenaline (pg/mL)	20.4 ± 14.7	11.6 ± 8.8	0.02	20.9 ± 16.1	18.6 ± 11.0	0.42
Noradrenaline (pg/mL)	388.0 ± 228.4	160.9 ± 95.2	0.005	370.7 ± 255.7	251.8 ± 141.6	0.11
CRP (mg/dL)	0.59 ± 0.58	0.41 ± 0.44	0.04	0.40 ± 0.47	0.56 ± 0.71	0.11

	HFNC group (n = 16)			Oxygen group (n = 16)		
	BL	4 weeks	P value	BL	4 weeks	p value

mean ± standard deviation or number (%)

Abbreviations: 6MWT, 6-minute walking test; LTOT, long-term oxygen therapy; VC, vital capacity; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DL_{CO}, diffusion capacity of the lung for carbon monoxide; ABGs, arterial blood gases; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; CRP, C reactive protein

Secondary outcomes: Change in the duration of the constant-load exercise test after 4 weeks of exercise training

After 4 weeks of exercise training, the durations of the constant-load exercise test under HFNC and 6 L/min nasal cannula in both the HFNC group and oxygen group increased significantly compared with that observed at baseline (Table 4). In contrast, the duration of the constant-load exercise test under prescribed oxygen in daily LTOT in the HFNC group increased significantly compared with that observed at baseline (p = 0.01). However, this increase was not observed in the oxygen group (p = 0.10) (Table 4).

Effects of 4 weeks of exercise training on variables

Regarding changes in the pulmonary function tests, ABGs, the plasma levels of adrenaline, noradrenaline, and serum CRP prior to and following 4 weeks of exercise training, the plasma levels of adrenaline, noradrenaline, and serum CRP were significantly decreased in the HFNC group compared with the respective baseline values. However, these effects were not observed in the oxygen group (Table 4). ABGs and pulmonary function did not worsen after 4 weeks of exercise training using not only 6L/min oxygen but also HFNC (both extremely high F_IO_2 and extremely high flow).

Discussion

The present study was the first randomized, prospective study demonstrating that the use of both high F_IO_2 and high flow through an HFNC significantly prolonged the duration of the constant-load exercise in CRF patients receiving LTOT versus prescribed oxygen in daily LTOT or a 6 L/min nasal cannula. Moreover, this study found that 4 weeks of training using both high F_IO_2 and high flow through an HFNC significantly improved the 6MWD compared with using a 6 L/min nasal cannula. Moreover, only patients using an HFNC exhibited a significant decrease in the plasma levels of adrenaline, noradrenaline, and serum CRP. These results suggest that exercise training using both high F_IO_2 and high flow through an HFNC may be a preferable modality versus a nasal cannula in CRF patients receiving LTOT.

The American Thoracic Society/European Respiratory Society statement on field walking tests determined an increase of ≥ 30 meters in the 6MWD (with a variability of 25 to 33 meters) as clinically relevant [27]. In the present study, 4 weeks of exercise training using an HFNC improved the 6MWD by 55 meters. Although the sample size in this study was small, the results can be considered significant and definitive.

Several factors for improving the duration of exercise using an HFNC have been considered. Firstly, the F_IO_2 values induced via an HFNC are more stable and much higher than those of standard oxygen delivery systems [28]. Use of an HFNC can achieve a F_IO_2 of 1.0, whereas the F_IO_2 associated with a 6 L/min nasal cannula was estimated to be approximately 0.4. Additionally, an HFNC generates a high flow rate that can exceed the subject's peak inspiratory flow rate, thus reducing entrainment of room air and dilution of the administered oxygen [29, 30]. Secondly, continuous flushing of the upper airway via an HFNC reduces dead space [31]. This effect may enhance alveolar ventilation if tidal volume is the same, and should increase the oxygen concentration of upper airway at the end of expiration. Thirdly, the high flow rates of an HFNC generate a positive nasopharyngeal pressure which linearly correlates with the administered flow rate in healthy volunteers and patients with stable COPD, IPF, and postcardiac surgery [29, 32–36]. When the mouth of the patients is open, the HFNC produces low positive nasopharyngeal pressure [35] and this condition is frequent during exercise. This low-level positive nasopharyngeal pressure generated using an HFNC may reduce the effort of breathing through enhancing oxygenation by positive end-expiratory pressure (PEEP), providing a low-level inspiratory assistance, and reducing a preload as a counter-PEEP effect. We assume that the use of an HFNC enabled patients to perform prolonged exercise training through the aforementioned mechanisms, resulting in a significant improvement in the 6MWD.

In the present study, our patients had advanced CRF. Thus, their exercise capacity was presumed to be low. To exert the maximal effect of exercise training on exercise capacity, we assessed the maximal effects of an HFNC on long-term exercise training using both maximum F_IO_2 and near-maximum inspiratory flow rate. The present study showed that 4 weeks of training using an HFNC significantly increased the 6MWD. However, it is unclear whether high flow rate or 100% FiO_2 are responsible for the beneficial effects on exercise capacity. Future studies comparing the effect of long-term exercise training using supplemental oxygen or HFNC with the equivalent F_IO_2 on the exercise capacity are warranted.

In this study, the HFNC group was used a F_IO_2 of 1.0 during exercise training. Prolonged hyperoxia has been implicated in organ toxicity processes, such as acute lung injury [37–39]. Systemically, hyperoxia induces peripheral vasoconstriction [40] and, increases production of reactive oxygen species [41]. Recently, arterial hyperoxia is associated with poor hospital outcome in various subsets of critically ill patients [42–44]. On the other hand, there are few studies on the effects of high concentration oxygen administration during exercise training. It has been demonstrated that 100% oxygen administration during 8 weeks of aerobic high-intensity interval training increased peak oxygen uptake and peak workload to a considerable extent in severe COPD patients [45]. In our study, the HFNC group showed no deterioration in PaO_2 values, pulmonary function tests including diffusion capacity of the lung for carbon monoxide, and the modified Borg Scale for dyspnea on 6MWT (Table 4). These results indicate that 4 weeks of exercise training using an HFNC at F_IO_2 of 1.0 might not induce hyperoxic lung injury. Indeed, the possibility of a much longer period of training using an HFNC with high F_IO_2 inducing hyperoxic lung injury is undeniable.

In addition, the use of a high F_IO_2 during exercise for CRF patients may cause CO_2 retention. In the present study, the partial pressure of arterial carbon dioxide values in the HFNC group were not significantly changed prior to and after 4 weeks of exercise training (Table 3). In addition, there were no significant differences between the three conditions (i.e., prescribed oxygen in daily LTOT vs. 6 L/min via a nasal cannula vs. HFNC at F_IO_2 of 1.0 and 50 L/min) in $PtcCO_2$ 6 min after initiation of the constant-load exercise test (Fig. 3-C). Based on these results, we assume that the risk of CO_2 retention caused by exercise training using an HFNC at FIO_2 of 1.0 is low.

In this study, the plasma levels of adrenaline, noradrenaline, and serum CRP were examined to investigate the effects of exercise training on systemic inflammation and sympathetic activity. The results showed that the HFNC group had a significant reduction in the plasma levels of adrenaline, noradrenaline, and serum CRP after 4 weeks of exercise training compared with the baseline values. It is likely that exercise training reduces the level of CRP by decreasing the production of cytokines in adipose tissue, skeletal muscles, endothelial and blood mononuclear cells, improving endothelial function and insulin sensitivity, and inducing an antioxidant effect [46]. Previous studies reported that the observed enhancement of antioxidant pathways and suppression of pro-oxidant mechanisms in the rostral ventrolateral medulla of rabbits with chronic heart failure contribute to the normalization of sympathetic nerve activity after exercise training [47]. It has been demonstrated that exercise training decreased the level of CRP in the serum [48, 49] and sympathetic activity [50] in patients with COPD. Prolonged exercise training using an HFNC may lead to a decrease in the plasma levels of adrenaline, noradrenaline, and serum CRP.

This study had several limitations. Firstly, the underlying disease in the patients of this study was heterogeneous, so both high F_IO_2 and high flow through an HFNC may have different effects on their underlying disease. In addition, their respiratory failure was severe (thus receiving LTOT). Therefore, it may be difficult to generalize the results of the present study to other patient populations such as those with COPD alone, mild respiratory failure, etc. Secondly, the sample size of this study was small. However, the differences observed in the improvement of the 6MWD after exercise training between the HFNC and oxygen groups were sufficiently large to be considered significant. Thirdly, the oxygen group did not demonstrate a significant improvement in the 6MWD after 4 weeks of exercise training. Respiratory failure in our patients was severe; thus, we assumed that they may be at a high risk of adverse events, such as severe hypoxia and arrythmia during exercise training. Therefore, we set strict criteria for the termination of the exercise training (ie. $SpO_2 \leq 85\%$, pulse rate ≥ 135 beats/min) to prevent the occurrence of adverse events during the test. Although there were no adverse events observed during exercise training in the present study, it is possible that the oxygen group had a shorter exercise training duration owing to more frequent stoppage of the training in response to desaturation or tachycardia. Therefore, significant improvement in the 6MWD after 4 weeks of exercise training may not be observed in the oxygen group.

Conclusion

We demonstrated that 4 weeks of exercise training using both high F_IO_2 and high flow through an HFNC significantly improved the 6MWD, and decreased systemic inflammation and sympathetic activity. Future research involving large sample sizes or homogenous populations (e.g., patients with COPD alone) is warranted. However, based on the present findings, exercise training using both high F_IO_2 and high flow through an HFNC is safe and may become an effective modality in CRF patients receiving LTOT.

Abbreviations

ABGs: arterial blood gases; COPD: chronic obstructive pulmonary disease; CRF: chronic respiratory failure; CRP: C-reactive protein; F_IO_2: fraction of inspired oxygen; HFNC: high-flow nasal cannula; IPF: interstitial pulmonary fibrosis; LTOT: long-term oxygen therapy; PEEP: positive end-expiratory pressure; $PtcCO_2$: transcutaneous carbon dioxide partial pressure; 6MWD: 6-min walking distance; 6MWT: 6-min walking test; SpO_2: oxygen saturation by pulse oximetry.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the National Hospital Organization Minami-Kyoto Hospital. All patients provided written informed consent prior to their participation.

Consent to publish

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

Drs. Yuichi Chihara, Tomomasa Tsuboi, Kensuke Sumi, and Atsuo Sato have no conflicts of interest to disclose.

Funding

This study was supported by Fukuda Foundation for Medical Technology. This financial support was used to purchase SpO_2 monitors and TOSCA sensors.

Author Contributions

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Data analysis and interpretation, and drafting the article: Y. C, T. T.

Critical revision of the article: Y. C, T. T, K. S, A. S

Final approval of the article: Y. C, T. T, K. S, A. S

Acknowledgments

The authors thank Drs. Masayoshi Minakuchi, Susumu Oguri, Hiromasa Tachibana, Shigeki Sakai, and Satoko Tabata for valuable comments and suggestions with regard to this manuscript.

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Figures

Figure 1.

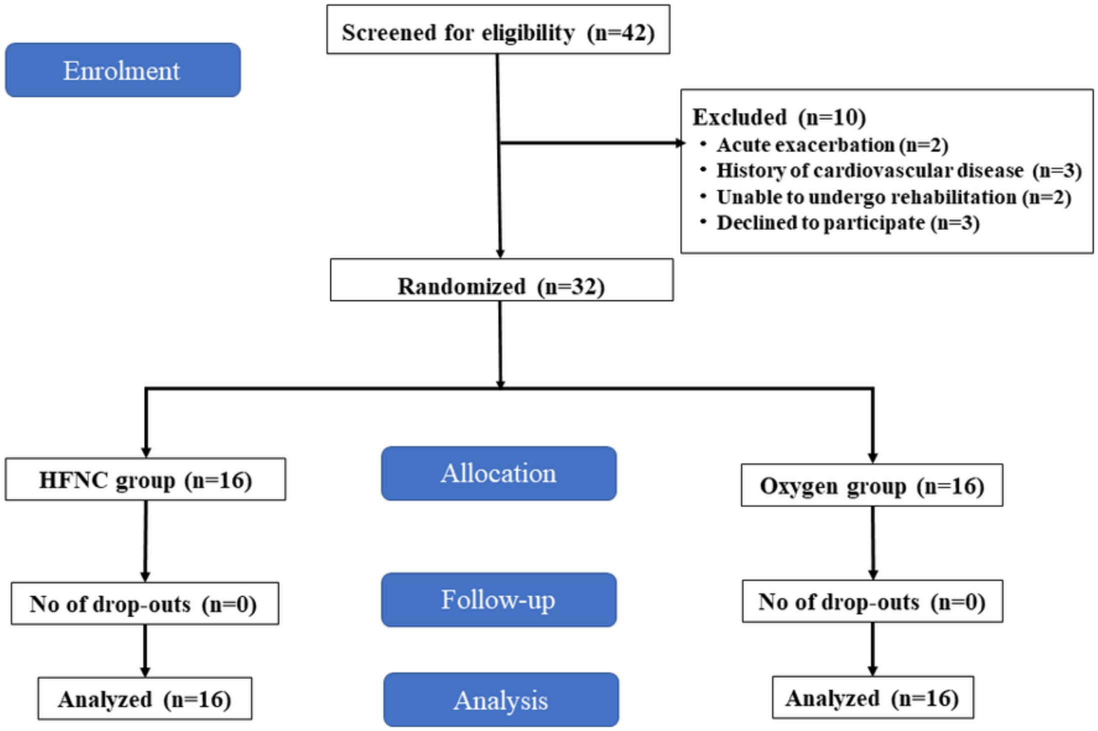

Figure 1

Flow chart of trial design. Abbreviations: HFNC, high-flow nasal cannula; FIO2, a fraction of inspired oxygen

Figure 2.

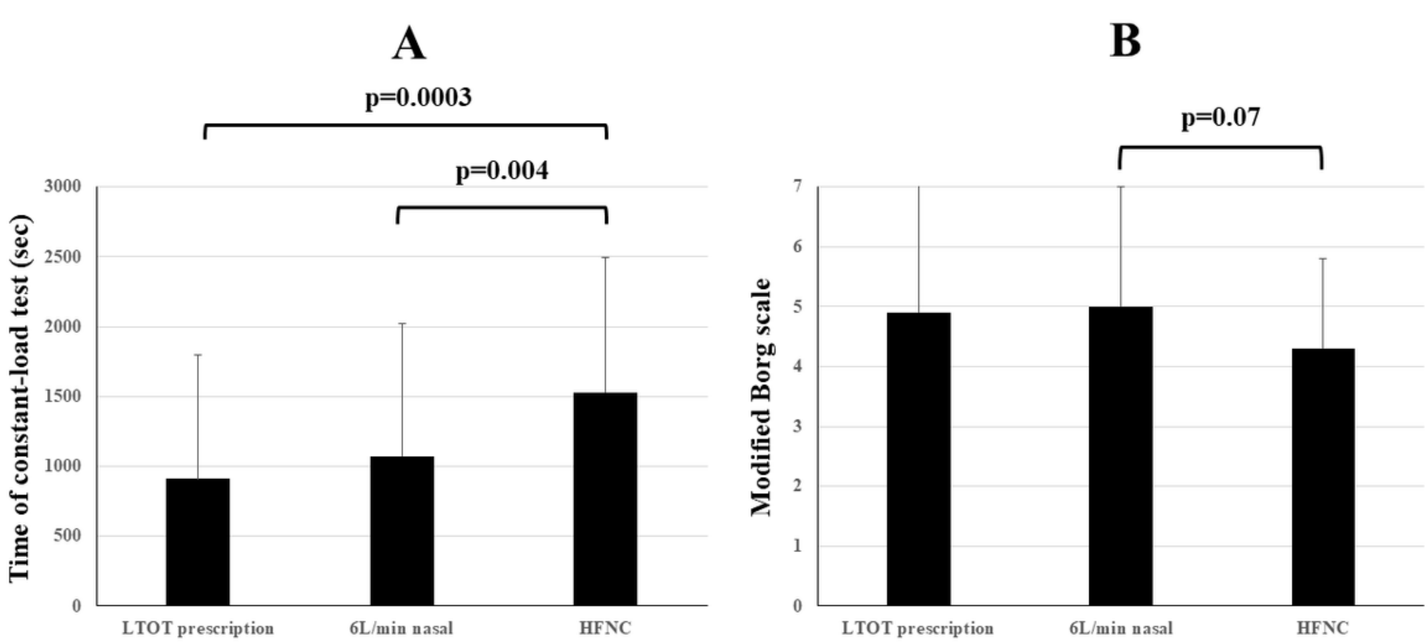

Figure 2

Time (A) and modified Borg scale (B) during the constant-load exercise test prior to 4 weeks of exercise training. The time of the constant-load exercise test using an HFNC was significantly longer than that reported with prescribed oxygen or a 6 L/min nasal cannula (A). The modified Borg scale for dyspnea at the termination of the constant-load exercise test under the HFNC tended to be lower compared with that observed under the 6 L/min nasal cannula (B). Data are presented as mean values ±standard deviation. Abbreviations: LTOT, long-term oxygen therapy; HFNC, high-flow nasal cannula

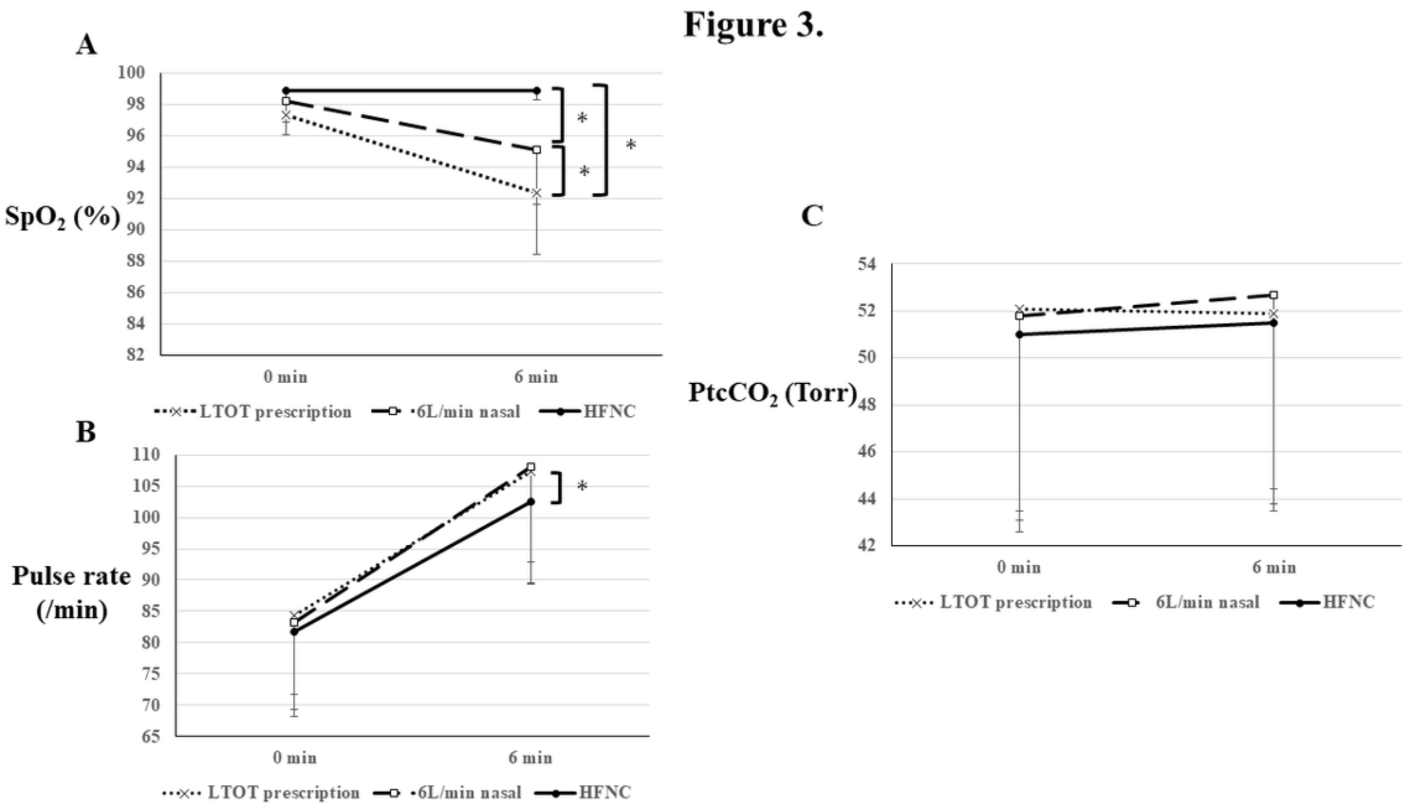

Figure 3

Changes in SpO2 (A), pulse rate (B), and PtcCO2 (C) at 0 and 6 min of the constant-load exercise test prior to 4 weeks of exercise training. A single asterisk indicates p <0.05 between the two conditions. Abbreviations: LTOT, long-term oxygen therapy; HFNC, high-flow nasal cannula; SpO2, percutaneous oxygen saturation; PtcCO2, transcutaneous carbon dioxide partial

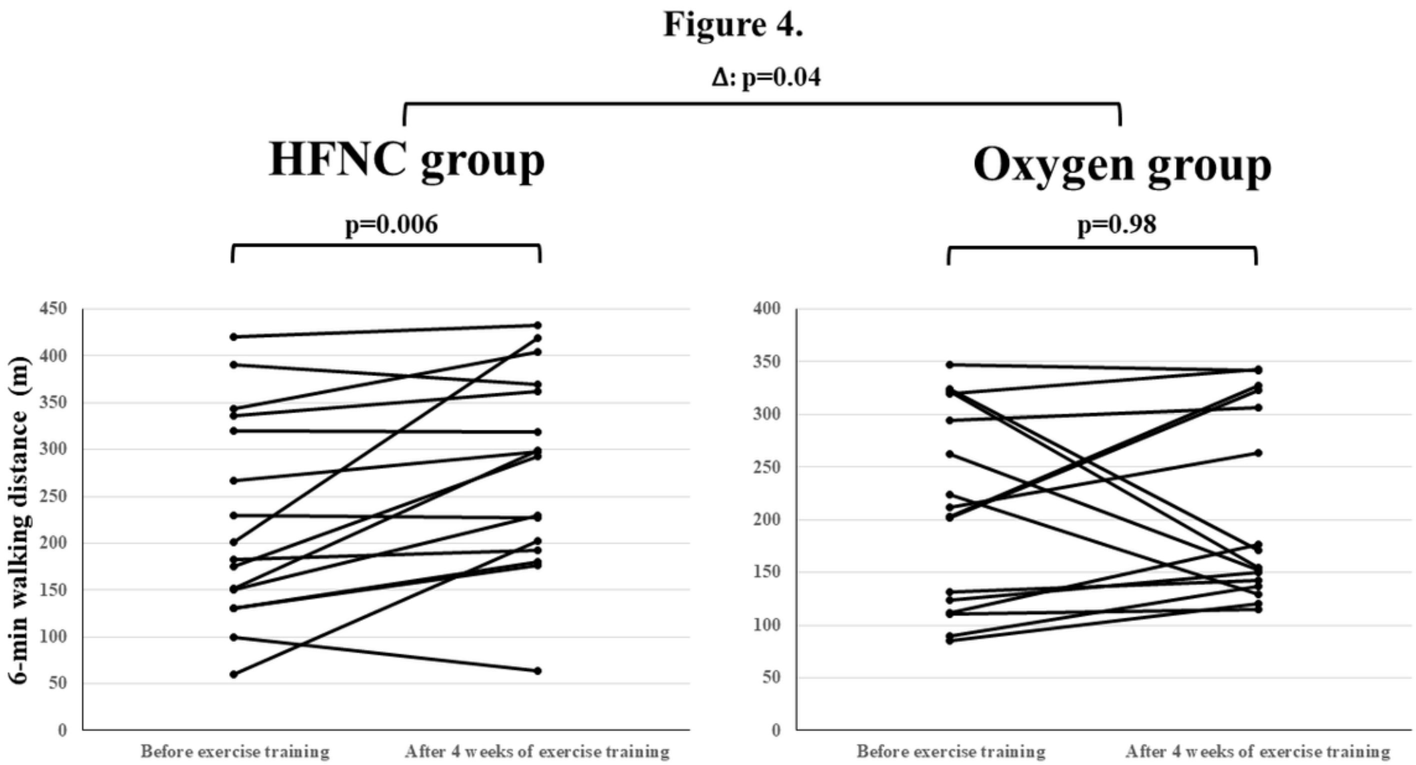

Figure 4

Change in the 6-minute walking distance in the HFNC and oxygen groups after 4 weeks of exercise training. Abbreviations: HFNC, high-flow nasal cannula

Supplementary Files

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- StudyProtocol.docx
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