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Effects of proportional assisted ventilation on exercise performance in idiopathic pulmonary fibrosis patients

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Summary

Background: Patients with idiopathic pulmonary fibrosis (IPF) present an important ventilatory limitation reducing their exercise capacity. Non-invasive ventilatory support has been shown to improve exercise capacity in patients with obstructive diseases; however, its effect on IPF patients remains unknown.

Objective: The present study assessed the effect of ventilatory support using proportional assist ventilation (PAV) on exercise capacity in patients with IPF.

Methods: Ten patients (61.2 ± 9.2 year-old) were submitted to a cardiopulmonary exercise testing, plethysmography and three submaximal exercise tests (60% of maximum load): without ventilatory support, with continuous positive airway pressure (CPAP) and PAV. Submaximal tests were performed randomly and exercise capacity, cardiovascular and ventilatory response as well as breathlessness subjective perception were evaluated. Lactate plasmatic levels were obtained before and after submaximal exercise.

Results: Our data show that patients presented a limited exercise capacity (9.7 ± 3.8 mL O_2/kg/min). Submaximal test was increased in patients with PAV compared with CPAP and without ventilatory support (respectively, 11.1 ± 8.8 min, 5.6 ± 4.7 and 4.5 ± 3.8 min; $p < 0.05$). An improved arterial oxygenation and lower subjective perception to effort was also observed in patients with IPF when exercise was performed with PAV ($p < 0.05$). IPF patients performing

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submaximal exercise with PAV also presented a lower heart rate during exercise, although systolic and diastolic pressures were not different among submaximal tests. Our results suggest that PAV can increase exercise tolerance and decrease dyspnoea and cardiac effort in patients with idiopathic pulmonary fibrosis.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with the histological appearance of usual interstitial pneumonia on surgical lung biopsy.[1] Impaired exercise performance is a characteristic feature of IPF mainly because of the heightened sense of dyspnoea and leg fatigue.[2,3] These symptoms are consequent of reduction in pulmonary volume, increase in lung recoil pressure at a given absolute lung volume,[4] abnormal gas exchange during exercise,[5] cardiac limitations[6] and peripheral skeletal muscle abnormalities.[7]

In an attempt to improve exercise performance and reduce dyspnoea in patients with chronic lung diseases, various forms of non-invasive ventilatory support have been used to assist ventilation during exercise such as: continuous positive airway pressure (CPAP), pressure support ventilation (PSV) and proportional assist ventilation (PAV). All these modalities seems to improve exercise performance in patients with chronic obstructive pulmonary diseases,[8–10] empowering them to make activities that could not be performed without ventilatory support.

Proportional assist ventilation (PAV) is a newer mode of partial ventilatory support that has demonstrated superiority when compared with other modalities. For instance, the PSV and the pressure controlled ventilation (PCV) are limited by pressure and the respiratory cycle is ended by flow and time, respectively, what develops a patient–ventilator asynchrony at rest increasing with effort.[11] In contrast, during PAV, the pressure applied by the ventilator is proportional to the volume and/or flow required allowing a better synchrony between patient's effort and ventilatory support and improvement comfort and dyspnoea.[12,13] This makes PAV ideally suited to assist ventilation during the variable ventilatory demands of exercise, which does not occur with other modalities of ventilatory support.[11,14]

In COPD patients, PAV has been shown to increase exercise tolerance in stable patients,[15,16] to improve exercise tolerance and dyspnoea in hypercapnic COPD patients,[17] and to enable a higher intensity of training in patients with severe COPD, leading to greater improvements in maximum exercise capacity with evidence of true physiological adaptation.[18]

Despite of the effects of PAV in COPD patients, to our knowledge these benefits have never been evaluated in IPF patients. It should be of particular importance to support exercise with PAV in these patients because it could deliver an assisted volume and lending a support to insufflate the lungs with increased elastances[4] and provide ventilatory autonomy, reducing dyspnoea and allowing higher endurance time. Therefore, the aim of the present study was to investigate the effect of PAV on exercise tolerance and breathlessness in IPF patients during submaximal exercise.

Methods

Patients

Thirty-seven patients with documented IPF, identified through clinical records, who attended the Interstitial Lung Diseases Ambulatory Group as outpatients at a Clinical Hospital, over a period of 6 months, were invited to participate in the study. IPF was diagnosed according to American Thoracic Society/European Respiratory Society criteria[1] and all patients had pulmonary biopsy with the usual interstitial pneumonia pattern. Twenty-one patients were excluded mainly due to use of continuous oxygen or cardiac diseases (Fig. 1). Sixteen eligible patients in clinical stability (without exacerbations for at least 3 months) were identified and invited to participate, 4 refused, 12 begun the study and 10 concluded (1 death and 1 gave up) the study. All patients were under corticosteroids as regular treatment and there was no change in medication during the study. Patients had 61.2 ± 9.2 year-old and body mass index (BMI) of 30.6 ± 4.2 kg/m^2 (Table 1).

They were properly informed about the study objective and gave their informed consent to participate into the study which was approved by the Ethics Committee of Hospital.

Study protocol

Patients were invited to be present at hospital in five separate days. At the first and second days, patients performed pulmonary function and cardiopulmonary exercise testing on a cycle ergometer. In the 3 subsequent visits, in

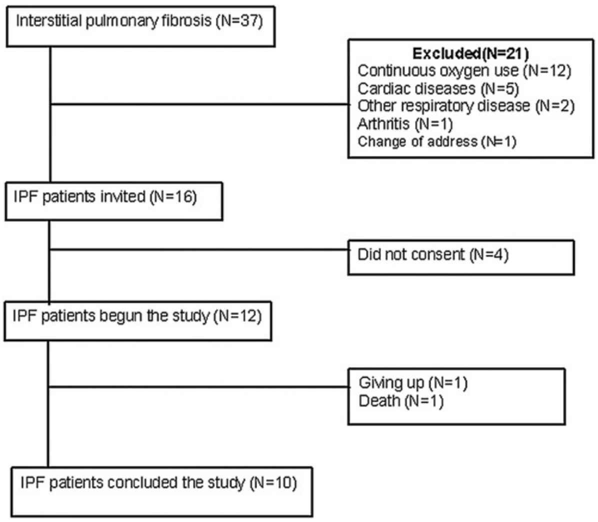

Figure 1 A schematic representation of patient's recruitment.

Table 1 Demographic, anthropometric and functional characteristics of the patients in the study.

Characteristics	Mean (SD)
Anthropometric	
N	10
Sex (M/F)	4/6
Age (yrs)	61.2 (9.2)
Weight (kg)	75.1 (10.5)
Height (cm)	156 (9.0)
BMI (kg/m^2)	30.6 (4.2)
Pulmonary function	
FVC (L)	2.1 (0.7)
(% pred)	79.2 (24.2)
FEV$_1$ (L)	1.8 (0.6)
(% pred)	85.3 (25.8)
FEV$_1$/FVC (%)	85.2 (4.7)
TLC (L)	3.4 (0.9)
(% pred)	77.2 (14.1)
RV (L)	1.3 (0.2)
(% pred)	78.3 (10.7)
DLCO (mL/min/mmHg)	9.1 (2.5)
(% pred)	45.9 (13.2)
Oximetry at rest (SpO$_2$, %)	94.7 (2.0)

Values are presented as mean ± SD, with the exception of sex, which is given as absolute number. M: male; F: female; BMI: body mass index; FVC: forced vital capacity; FEV$_1$: forced expiratory volume in 1 s; TLC: total lung capacity; RV: residual volume; and DLCO: carbon monoxide transfer factor. % pred: % predicted.

non-consecutive days during a week period, patients performed 3 submaximal tests: no support, CPAP and PAV. Tests were performed in a random order, using sealed envelopes. Prior to each exercise test, subjects abstained from food (2 h), caffeinated beverages (4 h) and to any unusual physical effort. All studies were carried out with patients breathing room air. All tests were symptom-limited and during exercise sessions patients cycled at 60 revolutions per minute (ranging from 50 to 70). Exercise tests were stopped if the patients showed oxyhemoglobin desaturation (oxygen saturation <85% — pulse oximetry) (ATS/ACCP, 2003).[19] During the tests, patients were asked their perceived breathlessness and sensation of leg discomfort (Borg, 1982)[20] by pointing to a number or phrase on a 10-point Borg scale set in large type on a sheet in front of them. Before the study, all patients underwent a period during which it was ensured that they were thoroughly acquainted with cycling, the breathing equipment, the facial masks, the ventilator and the Borg scale.

Measurements

Cardiopulmonary exercise testing (CPET)

Cycle ergometer CPET was performed on a digital computer-based exercise system (Sensormedics, Vmax 229, USA) with breath-by-breath analysis of metabolic, ventilatory, and cardiovascular variables while subjects breathing by mouthpiece and wearing noseclips. A standard 1 min incremental cycle exercise protocol was performed. After stabilization and a 3 min period of unloaded pedaling, the rate of power increment was individually selected to provide exercise duration of more than 8 and less than 12 min (ramp protocol), how recommended by previous study.[21] The following data were recorded as moving average of 8 breaths: oxygen uptake (VO$_2$, mL/min STPD), carbon dioxide production (VCO$_2$, mL/min STPD), respiratory exchange ratio (R), minute ventilation (VE, L/min BTPS), ventilatory equivalent for oxygen and carbon dioxide (VE/VO$_2$ and VE/VCO$_2$), end-tidal partial pressures of oxygen and carbon dioxide ($P_{ET}O_2$ and $P_{ET}CO_2$, mmHg), and oxygen pulse (VO$_2$/HR, mL/min/beat). VO$_2$ peak was predicted according to American Heart Association[22] according to gender and age as very weak, weak, regular, good and excellent. VO$_2$ at the anaerobic threshold was established by the gas exchange method inspecting the inflection point of VCO$_2$ with respect to VO$_2$ (modified V-slope) and, secondarily, by the ventilatory method, when VE/VO$_2$ and $P_{ET}O_2$ increased while VE/VCO$_2$ and $P_{ET}CO_2$ remained stable, respectively. VO$_2$ at the respiratory compensation point was defined where VE started to change out of proportion of VCO$_2$, *i.e.*, systematic increase in VE/VCO$_2$ with a consequent decline in $P_{ET}CO_2$.[23] A 12-lead ECG was monitored throughout exercise.

Submaximal exercise test

Before cycling, patients were without ventilatory support for 3 min and another 3 min without ventilatory support or with the modalities PAV or CPAP. Then, patients started cycling 3 min with no load applied. The load was then increased at 60% of maximal load achieved in the incremental test. Peripheral oxygen saturation (SpO$_2$) and heart rate (HR) were continuously monitored by pulse oximetry (Onyx 9500, Nonin, USA), end-tidal carbon dioxide tension (E_TCO_2) and respiratory rate (RR) were monitored continuously at the mask by means of a capnograph (DX-7100, Dixtal, USA), and blood pressure was measured with the cuff technique and recorded each minute and at the end of exercise. Lactate plasmatic levels were obtained before and after submaximal exercise by a lactimeter (Accusport, Boehringer Mannhein GmbH, Germany). Tests were performed at the same time of day to each patient to avoid circadian variation.

Ventilatory settings

Both PAV and CPAP were delivered by ventilator BiPAP (Vision, Respironics, USA) able to compensate for leaks, through a face mask (Respironics, USA) with adequate size for each patient face. All patients were instructed to breathe through the nose in the mask and to keep the mouth closed before exercise tests to prevent leaks. During the exercise, patients breathed spontaneously according to their ventilatory demand. Briefly, adjustment of PAV entails levels for volume-related assist (VA) and flow-related assist (FA) according to the equation of motion.[17]

$$P_{appl} = P_0 + E \times V + R \times V'$$

where P_{appl} is the pressure applied to inflate the respiratory system, P_0 is the elastic recoil pressure at the end of the expiration which is zero if the lung inflation starts from the elastic equilibrium volume of the respiratory system; V and V' are the inspired volume and flow, respectively, E is the total respiratory system elastance and R is total flow resistance. Therefore, E and R should ideally be known to set PAV appropriately. Since measurements of E and R are not routinely performed in patients, they had to be done at the time of the study. We used the ''run-away'' method as described by Younes[24] and co-workers.[17,18] ''Run-away'' phenomenon is the continuation of positive pressure after the end of the patient's inspiratory effort into the neural expiration, the moment in which the amount of pressure delivered by the ventilator exceeds the patient's elastic recoil opposing force, producing a inspiratory flow and a volume after the end of inspiratory muscular effort. Since a display of the ventilator provided continuous recording of flow, volume and airway pressure (P_{aw}), through which occurrence of air leaks was eventually recorded, the ''run-away'' phenomenon was observed on that display. To measure E, FA was set at 1 $cmH_2O\,L^{-1}\,s^{-1}$ whereas VA was set at 2 $cmH_2O\,L^{-1}$, then VA was raised in steps of 2 $cmH_2O\,L^{-1}$ until the ''run-away'' phenomenon occurred. The patients' E was assumed to be the ''run-away'' value minus 2 $cmH_2O\,L^{-1}$. Likewise, R was measured by setting VA and FA at 2 $cmH_2O\,L^{-1}$ and 1 $cmH_2O\,L^{-1}\,s^{-1}$, respectively, then FA was raised in steps of 1 $cmH_2O\,L^{-1}\,s^{-1}$ until the ''run-away'' phenomenon occurred. The values of the FA at the ''run-away'' minus 1 $cmH_2O\,L^{-1}\,s^{-1}$ were assumed to reflect patients' flow resistances. Therefore, individual values of E and R were obtained for each patient before setting PAV. PAV was set at a level corresponding to VA and FA at 60% of the individual values of E and R. An end-expiratory positive airway pressure (EPAP) amounting to 4 cmH_2O was added to PAV. Fig. 2 demonstrates curves of flow (a), volume (b) and airway pressure (c) in PAV modality.[25]

Pulmonary function tests

Lung volumes and forced vital spirometry (forced vital capacity (FVC)) were measured with a body plethysmograph (Collins GS II, EUA). The predicted values of pulmonary volumes of Goldman and Becklake (1959),[26] and the spirometry predicted values of Knudson et al. (1983)[27] were used. The carbon monoxide transfer factor (DL_{CO}) was made by single-breath testing technique and the predicted values of Gaensler and Smith (1973)[28] were used. All the tests were performed according to American Thoracic Society/European Respiratory Society.[29–31]

Statistical analysis

The parametric distribution of data was evaluated using Kolmogorov—Smirnov test. Comparison between variables was made using one-way analysis of variance (ANOVA) followed by Holm—Sidak (parametric) or Tukey (non-parametric) post-hoc tests. Sigma Stat version 3.01 software package (San Jose, USA) was used for statistical analysis, with the level of significance set at $p < 0.05$.

Results

Ventilatory settings

The E and R values were 12.8 ± 1.0 $cmH_2O\,L^{-1}$ and 3.4 ± 0.5 $cmH_2O\,L^{-1}\,s^{-1}$, respectively. PAV parameters were 7.7 ± 0.6 $cmH_2O\,L^{-1}$ and 2.0 ± 0.3 $cmH_2O\,L^{-1}\,s^{-1}$ of VA and FA, respectively.

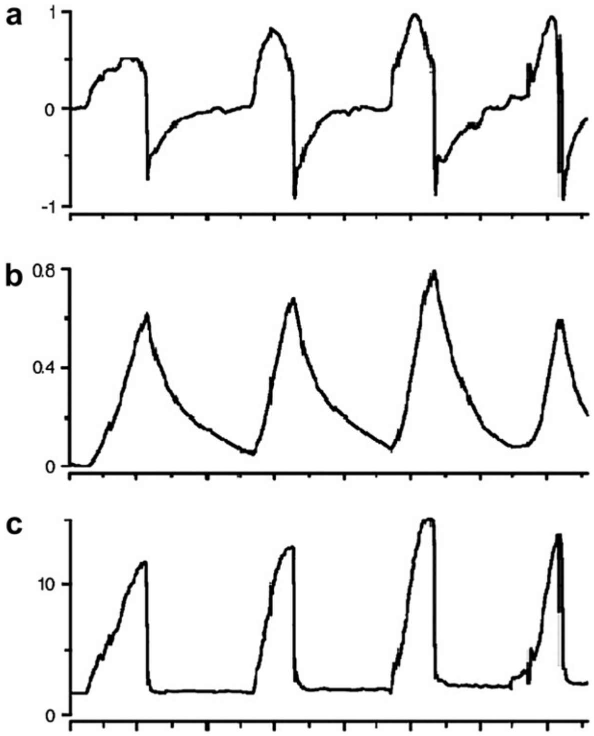

Figure 2 Curves of flow (a), volume (b) and airway pressure (c) in PAV modality. Values are presented in ''y'' axis (a) flow in $L\,s^{-1}$; (b) volume in L; (c) pressure in cmH_2O. ''X'' axis is represented by time in seconds.

Demographic, anthropometric and functional characteristics

Data are presented in Table 1. Ten patients were studied being 4 with less than 60 years old and 5 were overweight ($BMI > 30\ kg/m^2$). Total lung capacity (TLC) was higher than 80% predicted in 4 patients, between 60 and 80% predicted in 5 patients, and between 40 and 60% predicted in 1 patient. Seven patients presented IC/TLC <50% predicted and DL_{CO} was <40% predicted in 3 patients. All patients presented pulse oximetry at rest over than 90%.

Maximal capacity of exercise

Maximal exercise capacity (W_{peak}) was severely impaired in studied IPF patients and mean W_{peak} obtained was 42 ± 14.9W. Maximal aerobic capacity average was 9.79 ± 3.85 mL O_2/kg/min and four patients reached VO_2max (plateau); the physiological responses to the incremental test in different levels of effort are summarized in Table 2. Nine patients presented a very weak aerobic capacity (6W/3M) and one patient (1M) a weak aerobic capacity. In 7 patients, O_2 pulse was lower than 5 mL O_2/beat/min and only 1 patient presented O_2 pulse higher than 10 mL O_2/beat/min. Five patients reported exercise limitation due to leg fatigue and in 5, exercise was interrupted due to oxygen desaturation (<85%).

Table 2 The physiological responses to the incremental exercise test in different levels of effort.

Exercise peak	Mean (SD)
Load (W)	42 (14.9)
VO_2 (mL/kg/min)	9.7 (3.8)
VO_2 (% pred)	38.9 (20.5)
HR (% pred)	87.5 (12.5)
VO_2/HR (mL O_2/beat/min)	5.7 (3.7)
VE/MVV	0.4 (0.1)
Dyspnoea (score)	7.6 (2.5)
RCP	
Load (W)	36.5 (17.3)
VO_2 (mL/kg/min)	8.8 (2.3)
HR (% peak)	97 (4)
VO_2/HR (mL O_2/beat/min)	5.1 (2.3)
VE (L/min)	36 (8.7)
AT	
Load (W)	17.5 (11.2)
VO_2 (mL/kg/min)	6.4 (1.5)
HR (% peak)	88 (5)
VO_2/HR (mL O_2/beat/min)	4.1 (1.6)
VE (L/min)	26.3 (8.3)

Values are presented as mean ± SD. AT: anaerobic threshold; RCP: respiratory compensation point; VO_2: oxygen consumption; HR: heart rate; VE: minute ventilation; MVV: maximal voluntary ventilation; and VO_2/HR: O_2 pulse.

Submaximal exercise test

PAV and CPAP were well tolerated by all patients. Air leaks, monitored by means of the display of the ventilator, did not occur. ''*Run-away*'' phenomenon did not occur during the trials with PAV. CPAP did not improved endurance time compared with non-ventilatory support (5.6 ± 4.7 min *vs.* 4.5 ± 3.8 min, respectively). Submaximal exercise with PAV support improved the endurance time (11.1 ± 8.8 min; $p < 0.05$) compared with tests performed without ventilatory support exercise or CPAP (Fig. 3A).

Reported breathlessness by IPF patients before and during submaximal exercise tests was also evaluated (Fig. 3B). Before exercise, patients presented similar breathlessness perception (no breathlessness) at rest ($p > 0.05$). Patients' breathlessness perception increased as soon as they started to pedal with no applied load when they were not receiving ventilatory support or with CPAP while the perception remained unchanged with PAV (0.5 ± 0.0; 0.5 ± 0.0, 0.0 ± 0.0 respectively, $p < 0.05$). PAV resulted in reduction in effort perception at the first minute of loaded exercise in comparison without ventilatory support exercise or with CPAP (0.0 ± 0.0, 1.0 ± 0.0; 0.5 ± 0.0, respectively; $p < 0.05$). This reduced breathlessness perception remained until the fifth minute (4 ± 2; 4 ± 2 and 3 ± 2, respectively; $p < 0.05$).

Respiratory and cardiac parameters during the exercise

The profile of respiratory and cardiac parameters during the 3 submaximal exercise sessions (without ventilatory support and with CPAP or PAV) is represented in Figs. 4 and 5. At rest, patients presented similar SpO_2 at rest ($p > 0.05$). Before submaximal exercise test begins (0W), patients already presented an increase in SpO_2 with PAV when compared with exercise performed without ventilatory support or with CPAP (respectively, $96 \pm 1\%$, $95 \pm 2\%$ and $95 \pm 2\%$; $p < 0.05$) (Fig. 4A). During all exercise, oxygen desaturation was reduced with IPF patients under PAV support when compared with CPAP or without ventilatory support and, at the end of exercise, SpO_2 of patients exercising with PAV remained at higher levels (respectively, $92 \pm 3\%$, $89 \pm 5\%$ and $88 \pm 5\%$; $p < 0.05$) (Fig. 4A).

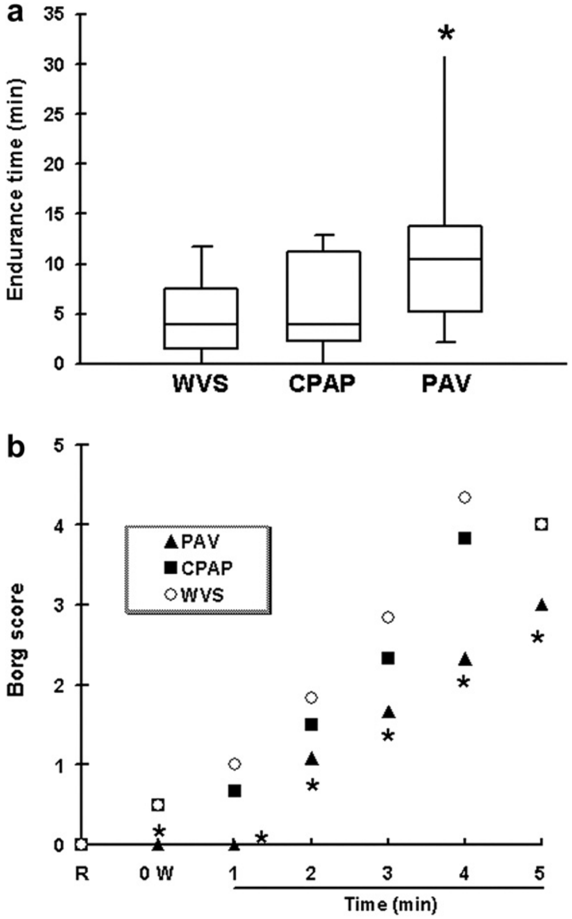

Figure 3 (A). Endurance time during submaximal exercise without ventilatory support and with CPAP or PAV modalities in IPF patients. Values are presented as median and interquartiles values of endurance times in three conditions; *$p < 0.05$ when compared with without ventilatory support (WVS) and CPAP. (B). Breathlessness perception by IPF patients before and during submaximal exercise tests with PAV, CPAP or without ventilatory support. Values are presented as mean ± SD of effort subjective perception (Borg Score) before, at each minute of the submaximal exercise. R = at rest; 0W = pedaling with no load; *$p < 0.05$ when compared with the values getting without ventilatory support and CPAP.

Patients' exhaled end-tidal carbon dioxide tension (E_TCO_2) at rest was at similar levels in all submaximal exercise sessions (Fig. 4B). As soon as patients begun to exercise with no load was applied (0W), IPF patients already presented an increase

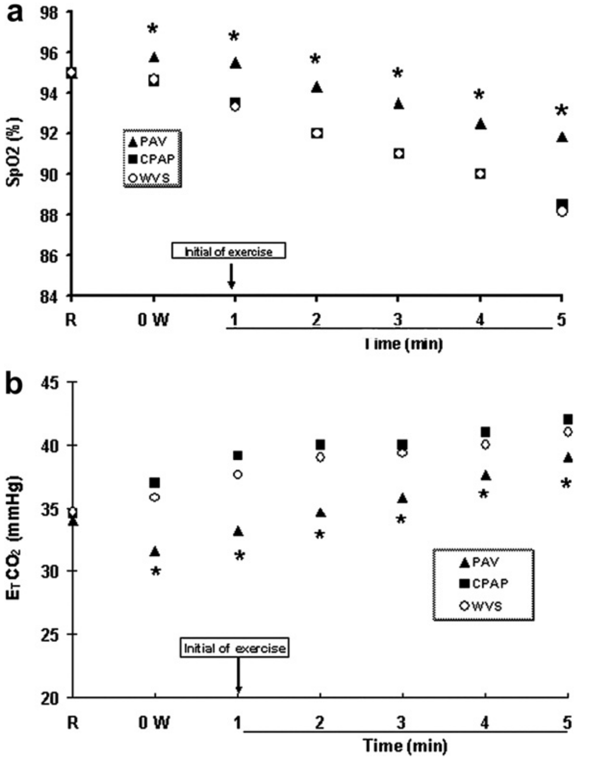

Figure 4 (A—B) Profile of respiratory parameters during the submaximal exercise without ventilatory support and with CPAP or PAV. Values are presented as mean ± SD of oxygen peripheric saturation (SpO_2; A) and of exhaled end-tidal carbon dioxide tension (E_TCO_2; B), before, at each minute of the submaximal exercise. R = at rest; 0W = pedaling with no load; *$p < 0.05$ when compared with the values getting without ventilatory support and CPAP.

in the E_TCO_2 levels when exercise was performed without ventilatory support and with CPAP while E_TCO_2 remained unchanged when patients performing exercise with PAV ($p < 0.05$). The increase in E_TCO_2 levels was lower when patients exercised with PAV compared when patients without ventilatory support or with CPAP and, at the fifth minute exercise test, E_TCO_2 was at lower levels in patients performing exercise with PAV (respectively, 39 ± 5 mmHg, 41 ± 8 mmHg and 42 ± 4 mmHg) ($p < 0.05$) (Fig. 4B).

The respiratory rate (RR) was similar between patients while exercising without ventilatory support, with CPAP or PAV before the exercise begins, at each minute of exercise until the fifth minute.

Cardiac responses to exercise were also evaluated at each minute during submaximal exercise. IPF patients presented a similar double product and heart rate before exercise and with no load applied in all submaximal exercise sessions ($p > 0.05$) (Fig. 5A and B). At first and second minutes of exercise with PAV, patients presented lower values of double product and heart rate when compared with exercise performed without ventilatory support or with CPAP. After that, cardiac responses were similar among all submaximal exercise sessions until the end of exercise.

Lactate levels at the end of exercise sessions were evaluated to establish if the effort levels were similar during submaximal exercises. It can be observed that, after exercise, patients without ventilatory support, with CPAP or PAV presented similar levels of lactate (respectively, 3.6 ± 0.9 mmol/L, 3.3 ± 0.6 mmol/L and 3.6 ± 1.0 mmol/L; $p > 0.05$). Without ventilatory support or with CPAP, eight patients stopped the exercise due to dyspnoea and oxygen peripheric saturation <85% while in patients with PAV most patients (60%) interrupted exercise due to leg fatigue (6 patients).

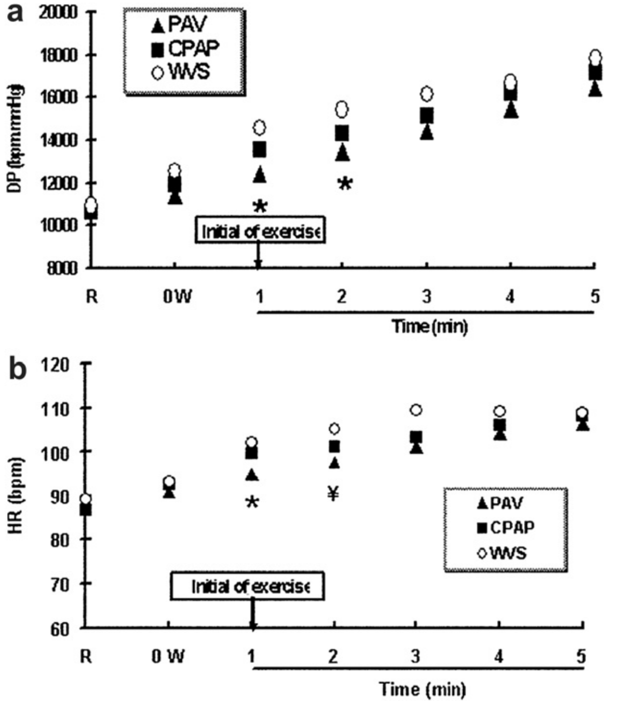

Figure 5 (A—B) Profile of cardiac parameters during the submaximal exercise without ventilatory support and with CPAP or PAV. Values are presented as mean ± SD of double product (DP; A) and heart rate (HR; B) before, at each minute of the submaximal exercise. R = at rest; 0W = pedaling with no load; *$p < 0.05$ and $^{¥}p = 0.05$.when compared with the values getting without ventilatory support and CPAP.

Discussion

This is the first study demonstrating the effects of PAV during exercise in IPF patients. Our findings show that PAV was well tolerated and improved exercise performance and arterial oxygen and reduced perceived exertion in IPF patients. Nevertheless, our results suggest that PAV decreases cardiac effort due to exercise in these patients. Several studies have been performed in an attempt to improve exercise performance in IPF patients including O_2 therapy,[2,32] inhalation of morphine[33] or anesthetic aerosols,[34] inhalation of nitric oxide,[35] however, none of them demonstrated effectiveness. Hence, our study proposes feasible benefits that these patients could get with this ventilatory support during submaximal exercise.

We cannot compare our results with other in this population, however, the present results extend the observation of use of PAV during exercise in COPD patients.[15—18] These authors found that PAV support during cycle exercise increases endurance time in COPD patients. In the present study, we observed that PAV doubled submaximal exercise capacity in patients with IPF reinforcing the benefits of PAV such as reducing dyspnoea, breathlessness perception and hypoxemia. However, decreased cardiac effort during exercise has never been previously observed.

Exercise limitation is a very common symptom reported by patients with IPF and is attributed to a reduction in gas exchange, ventilatory capacity, dyspnoea, cardiac limitation and peripheral muscle weakness.[1,3,4,6,7,21,39] During exercise, 20–30% of the exercise-induced widening of the alveolar–arterial O_2 gradient may be caused by some impairment of oxygen diffusion and the arterial O_2 pressure (PaO_2) and arterial O_2 saturation (SaO_2) fall increasing the ventilatory demand and the workload of the inspiratory muscles.[1] PAV is a ventilatory modality that offers partial support to patients based on their elastance and resistance and there is evidences suggesting that it can unload inspiratory muscles and improve respiratory efficiency.[24] Thus, reduction in dyspnoea observed in our study may be explained due to unloading the inspiratory muscles and/or reducing E_TCO_2 (improved respiratory efficiency), capability to match spontaneous changes in patients' ventilatory demands and pattern (comfort) that has also been reported in COPD patients.

PAV was associated with significantly lower E_TCO_2 levels than cycling during without ventilatory support or with CPAP (Fig. 4B). As reduced E_TCO_2 levels were not associated with changes in respiratory rate, we can suppose that this occurred due to an improvement in the tidal volume caused by a better respiratory efficiency. The use of E_TCO_2 assessment may be criticized, however, we used this parameter only for monitoring purposes.

It has been claimed that the major advantage of PAV compared to conventional modes of partial ventilatory support is represented by its capability to match spontaneous changes in patients' ventilatory demands and pattern. This should be particularly attractive during exercise where the breathing pattern changes rapidly to meet the metabolic requirements.[14–16] Interestingly, one of the most common benefits observed in COPD patients using PAV is the reduction in dyspnoea and improvement in the ventilatory capacity.[15–18] In our study, PAV also resulted in reduction in effort perception during all exercise time in IPF patients (Fig. 3B).

A PAV reduced hypoxemia in IPF patients was also previously described in COPD patients.[16,17] Interestingly, hypoxemia was the main cause of exercise interruption in 80% of IPF patients without ventilatory support or with CPAP, however, this occurred only in 40% in our patients with PAV support (Fig. 4A). A 4% decrease in peripheral oxygen saturation observed during exercise in our patients reveals a worst prognosis[19,36] and may suggest that studied population presented moderate to severe disease stage.

In the present study, it was observed a decrease in the cardiac effort (double product and heart rate) in patients using PAV support. Although we cannot explain this fact, it is possible that this reduction was consequent of a reduction in the inspiratory effort.[37] The benefits of PAV during exercise in the cardiac effort were evaluated only by three studies in COPD patients, however, no difference was observed in those patients.[15,16,18]

Study limitation

A 60% of VA and FA settings were used to avoid ''run-way'' during exercise[15–18] however, the level of support offered may be lower than patients' demand. The adherence of patient to a non-invasive ventilatory support depends on his comfort assuring a higher acceptance.[13] In the present study, none of the patient reported discomfort during PAV support and we believe that this may also influence the observed benefits. The subjects and an investigator supervising the exercise tests were not told which mode of ventilation was used. However, subjects would have perceived pressure difference during PAV compared with CPAP or when exercising without ventilatory support. Investigators would have heard the ventilator noise during PAV. Therefore, true blinding of subjects and investigators was not possible. Some authors use *sham* ventilation, however, previous reports in the literature have shown that patients presented lower exercise performance using such circuits.[17] In addition, other investigators consider that sham ventilation significantly increases the risk of producing a type 1 error.[18]

Application of CPAP in the present study was not set according to the literature. This lack of tailoring could explain why CPAP was not as efficient as PAV in improving endurance time and dyspnoea. In contrast, PAV was tailored to the respiratory mechanics of individual patients. Therefore, in these circumstances, the difference between PAV and CPAP might well reflect differences in individual settings rather than differences between ventilatory modes. Hence the conclusion that PAV is superior to CPAP to improve exercise tolerance is not warranted on the basis of our data. However, our results show that performing exercise with PAV is better than exercising without ventilatory support. The present study evaluated a reduced number of patients ($n = 10$) which can limit the detection of small variation in the studied variables and might be presented as preliminary findings. However, the amount of patients in the present study was higher than in the previous studies evaluating the effect of PAV in COPD patients.[15–18]

Clinical implications

Our results indicating an increase in endurance time with PAV may be promising, as this mode might allow the training stimulus to be increased above that possible in the absence of mechanical support. Thus, our findings reinforce those previously observed in COPD patients suggesting that PAV delivered by portable ventilators can proportionate a better comfort to patients with ventilatory limitation suggesting its usefulness during exercise in pulmonary rehabilitation programmes to improve cardiopulmonary conditioning.[38,39]

In conclusion, proportional assist ventilation delivered by a face mask was able to improve exercise tolerance and reduce dyspnoea in IPF patients. Potential advantages and disadvantages of proportional assist ventilation compared to other modes of partial ventilatory assistances need further physiological studies. Additional information is also needed to elucidate the appropriate application of proportional assist ventilation in respiratory rehabilitation programmes.

Conflict of interest

The authors have no conflict of interest.

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