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Ambulatory oxygen therapy in lung transplantation candidates with idiopathic pulmonary fibrosis referred for pulmonary rehabilitation

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ABSTRACT

Objective: To determine independent factors related to the use of oxygen and the oxygen flow rate in idiopathic pulmonary fibrosis (IPF) patients placed on a lung transplant waitlist and undergoing pulmonary rehabilitation (PR). **Methods:** This was a retrospective quasi-experimental study presenting functional capacity and health-related quality of life (HRQoL) data from lung transplant candidates with IPF referred for PR and receiving ambulatory oxygen therapy. The patients were divided into three groups on the basis of the oxygen flow rate: 0 L/min (the control group), 1-3 L/min, and 4-5 L/min. Data on functional capacity were collected by means of the six-minute walk test, and data on HRQoL were collected by means of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), being collected before and after 36 sessions of PR including aerobic and strength exercises. **Results:** The six-minute walk distance improved in all three groups (0 L/min: Δ 61 m, $p < 0.001$; 1-3 L/min: Δ 58 m, $p = 0.014$; and 4-5 L/min: Δ 35 m, $p = 0.031$). Regarding HRQoL, SF-36 physical functioning domain scores improved in all three groups, and the groups of patients receiving ambulatory oxygen therapy had improvements in other SF-36 domains, including role-physical (1-3 L/min: $p = 0.016$; 4-5 L/min: $p = 0.040$), general health (4-5 L/min: $p = 0.013$), social functioning (1-3 L/min: $p = 0.044$), and mental health (1-3 L/min: $p = 0.046$). **Conclusions:** The use of ambulatory oxygen therapy during PR in lung transplant candidates with IPF and significant hypoxemia on exertion appears to improve functional capacity and HRQoL.

Keywords: Oxygen; Exercise therapy; Idiopathic pulmonary fibrosis; Rehabilitation; Quality of life.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is an irreversible fibrotic lung disease characterized by progressive fibrosing interstitial pneumonia of unknown cause whose natural history is variable and often unpredictable.[1,2] The pathophysiology of IPF is probably related to repeated microinjury to the pulmonary epithelium that is followed by wound repair processes.[3] This results in a restrictive ventilatory pattern and impaired gas exchange, leading to exertional hypoxemia and functional limitation in many cases.[4] As pulmonary fibrosis advances, exertional breathlessness is triggered by simple daily activities and is the strongest determinant of health-related quality of life (HRQoL) in these patients.[5,6] In addition, oxygen desaturation contributes to exercise intolerance in patients with interstitial lung disease.[7]

In this context, the management of oxygen therapy in patients with IPF is still controversial.[7-9] The 2011 IPF guidelines did not provide guidance on the use of oxygen therapy in patients with exertional hypoxia alone.[2] However, the 2015 British Thoracic Society guidelines state that ambulatory oxygen should not be routinely used in patients who are not hypoxic at rest.[10] Visca et al. evaluated ambulatory oxygen therapy for patients with IPF and obtained significant results regarding important outcomes, such as the six-minute walk distance (6MWD), HRQoL, perception of dyspnea, and ability to walk.[7]

SpO_2 should be taken into consideration because of its association with scores that predict desaturation during the six-minute walk test (6MWT).[8] In a systematic review, Bell et al.[9] investigated the impact of oxygen therapy in patients with IPF and found that it had no beneficial effect on dyspnea, functional capacity, or quality of life. Therefore, there is no robust evidence to recommend the use of ambulatory oxygen therapy in patients with IPF. There is an ongoing clinical trial that is currently in the data collection phase; however, the trial will not quantify the amount of oxygen provided, and it will exclusively compare patients receiving oxygen therapy with those not receiving it.[11] The objective of the present study was to determine independent factors related to the use of ambulatory oxygen therapy and the oxygen flow rate

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in IPF patients placed on a lung transplant waitlist and undergoing pulmonary rehabilitation (PR).

METHODS

Study sample

This was a retrospective quasi-experimental study of IPF patients undergoing PR while on a waiting list for lung transplantation between January of 2018 and March of 2020. The study was carried out in the Department of Pulmonary Rehabilitation of the Santa Casa de Misericórdia de Porto Alegre, located in the city of Porto Alegre, Brazil, and was approved by the local research ethics committee (Protocol no. 04453412.7.0000.5335).

IPF was diagnosed by a multidisciplinary team before PR, on the basis of HRCT and/or surgical lung biopsy findings or the affected lung showing a usual interstitial pneumonia pattern, in accordance with the 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/*Asociación Latinoamericana de Tórax* guidelines.[2] Forty-five patients were included in the study and were divided into three groups on the basis of the oxygen flow rate that was used during PR and that was determined on the basis of DL_{CO} and oxygen saturation: 0 L/min (the control group), 1-3 L/min, and 4-5 L/min. Patients with clinically significant resting hypoxemia (resting SpO_2 ≤ 88%) were prescribed long-term oxygen therapy. The oxygen flow rate was increased as needed during exercise, in order to maintain SpO_2 at > 92%. None of the patients in the control group required oxygen therapy to maintain SpO_2 at > 92%.[12]

Data were retrospectively reviewed from patient medical records, including pre- and post-PR data (when available). Completion of a PR program was defined as participation in at least 36 sessions[12,13] and all post-PR evaluations, including a 6MWT and an HRQoL questionnaire.[14,15]

PR program

The PR program consisted of medical appointments with the PR team every two months and included psychiatric evaluation, nutritional counseling, social assistance, and monthly educational lectures.[12] The physical training component of the program was administered by two physical therapists, with three sessions per week for a total of 36 sessions. During physical training, patients performed a warm-up, followed by muscle strengthening and aerobic exercises. The warm-up consisted of breathing exercises (respiratory cycle) and arm raising. Muscle strengthening was based on arm and leg exercises performed with an initial load of 30% of a one-repetition maximum test, with a set of ten repetitions per exercise. The load was increased by 0.5 kg every seven sessions depending on exercise tolerance.[12] Aerobic exercises were performed on a treadmill at 70% of the speed achieved during the 6MWT, the speed being progressively increased every 6 min for a total of 30 min of exercise. The speed was increased by 0.3 km/h every seven sessions. The modified Borg scale was used for measuring dyspnea and leg fatigue, and the exercises were interrupted if patients reported dyspnea or leg fatigue, as assessed by a modified Borg scale score > 4.

Pulmonary function tests and HRQoL assessment

Pulmonary function tests were performed in accordance with the American Thoracic Society/European Respiratory Society and Brazilian Thoracic Association technical procedures and acceptability and reproducibility criteria.[16-18] All pulmonary function tests were performed in our pulmonary function laboratory, which is certified by the Brazilian Thoracic Association. The same physical therapists administered the pulmonary function tests and the 6MWT, in accordance with the American Thoracic Society recommendations.[14] For the 6MWT, patients were asked to walk down a 30-m corridor (delimited by traffic cones) for 6 min, verbal encouragement being given every minute. Data on HR, blood pressure, and effort perception (as assessed by the modified Borg scale) were obtained before and after the test. Patients were constantly monitored by pulse oximetry so that SpO_2 was maintained at ≥ 88% during the test. When patients presented with an SpO_2 of < 88%, oxygen was provided in an attempt to maintain exertion and encourage patients to tolerate dyspnea. The Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) was used in order to evaluate HRQoL.[15]

Statistical analysis

Data were presented as absolute and relative frequencies, mean ± SD, or median (IQR). The normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Comparisons of proportions were made with the chi-square test for categorical variables. A paired t-test was used in order to compare pre- and post-PR variables in the patients who completed the program. The nonparametric Mann-Whitney and Wilcoxon tests (for unequal variance) were used for between-group comparisons.

For within-group differences, the effect size was calculated in accordance with Cohen,[19] by dividing the difference between the mean values at baseline and at follow-up by the pooled SD of both values. Effect sizes were classified as small (0.2), medium (0.5), or large (0.8).

All statistical analyses were performed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA). A value of $p < 0.05$ was considered significant for all analyses.

RESULTS

A total of 45 patients met the inclusion criteria and were therefore included in the study. Of those, 15 received an oxygen flow rate of 0 L/min, constituting

the control group. Of the remaining 30 patients, 15 received an oxygen flow rate of 1-3 L/min and 15 received an oxygen flow rate of 4-5 L/min. There were no significant differences among the groups regarding most of the baseline characteristics (Table 1). Most (60.5%) of the patients were male (n = 26), and the mean age was 60 ± 10 years. There were significant differences among the groups regarding lung function outcomes such as the FEV_1/FVC ratio (p < 0.001) and DL_{CO} (p = 0.003), with worse parameters in patients with greater need for oxygen.

Table 2 shows the results of the 6MWT. The 6MWD improved in all three groups (0 L/min: Δ 61 m, p < 0.001; 1-3 L/min: Δ 58 m, p = 0.014; and 4-5 L/min: Δ 35 m, p = 0.031). The control group had an improvement in dyspnea sensation (p = 0.002) and leg fatigue (p = 0.004). Additionally, HR values were significantly different in the 4-5 L/min group (p = 0.014).

With regard to HRQoL, SF-36 physical functioning domain scores improved in all three groups (0 L/min: p = 0.018; 1-3 L/min: p = 0.021; and 4-5 L/min: p = 0.024). As can be seen in Table 3, the groups of patients who received ambulatory oxygen therapy had improvements in other SF-36 domains, including role-physical (1-3 L/min: p = 0.016; 4-5 L/min: p = 0.040), general health (4-5 L/min: p = 0.013), social functioning (1-3 L/min: p = 0.044), and mental health (1-3 L/min: p = 0.046).

DISCUSSION

In the present study we found that the use of ambulatory oxygen during a PR program is associated with improved HRQoL in lung transplant candidates with IPF. Functional capacity and the 6MWD were found to have improved in all three groups, a finding that suggests that oxygen therapy alone does not affect these outcomes. Similar findings regarding the 6MWD have been reported in studies involving PR. Dowman et al.[20] reported that PR probably improves the 6MWD by 40.07 m in patients with interstitial lung disease. In the present study, the 6MWD improved by approximately 37.25 m in patients with IPF.

With regard to the baseline characteristics of the patients investigated in the present study, DL_{CO} was lower in those who received ambulatory oxygen therapy than in those who did not (the control group). Pulmonary interstitial compromise may be associated with a greater need for oxygen during exercise. In a previous study, multivariate analysis showed that resting SpO_2 and DL_{CO} ≤ 40% were predictive of desaturation during the 6MWT.[8] Thus, our findings are important in that, despite lower DL_{CO} in the groups of patients receiving ambulatory oxygen therapy, the 6MWD increased by 58 m in those who received an oxygen flow rate of 1-3 L/min and by 35 m in those who received an oxygen flow rate of 4-5 L/min, with greater exercise tolerance. The fact that patients in all three groups presented with desaturation after the 6MWT might be due to low DL_{CO} at baseline. An increase in the 6MWD is important because a reduced 6MWD is strongly and independently associated with increased mortality in patients with IPF. In addition, the 6MWD is a better predictor of 6-month mortality than is FVC.[21,22]

The findings of the present study are consistent with the literature. Visca et al.[7] investigated IPF patients receiving oxygen therapy through cylinders for use at home for 15 days and found positive results regarding the 6MWD, the sensation of breathlessness, and the ability to walk.[7] Bell et al.[9] reported that oxygen therapy during exercise had no beneficial effect on functional capacity. It is of note that, in our study, the group of patients who received the highest oxygen flow rates had submaximal HR values, showing better exercise tolerance. This finding is consistent with those of Dowman et al.,[23] whose study involved the use of

Table 1. Baseline characteristics of the study participants.[a]

Variable	Total sample	Oxygen flow rate			p
		0 L/min	1-3 L/min	4-5 L/min	
	(N = 45)	(n = 15)	(n = 15)	(n = 15)	
Male sex	26 (60.5)	7 (50.0)	7 (50.0)	12 (80.0)	0.099
Age, years	60 ± 10	56 ± 913	65 ± 4	62 ± 7	0.387
BMI, kg/m^2	26.8 ± 4.71	26.4 ± 5.69	28.6 ± 4.78	26.6 ± 3.67	0.726
FEV_1, % predicted	55 ± 15	53 ± 17	52 ± 10	57 ± 16	0.700
FVC, % predicted	50 ± 14	48 ± 14	46 ± 7	54 ± 17	0.547
FEV_1/FVC ratio	0.97 ± 0.13	1.09 ± 0.08	0.95 ± 0.09	0.85 ± 0.07	< 0.001
DL_{CO}, % predicted	36 ± 13	50 ± 12	34 ± 7	27 ± 4	0.003
PASP, mmHg	44.2 ± 14.7	44.3 ± 11.6	42.8 ± 17.1	45.6 ± 14.6	0.821
6MWD, m	407 ± 97	422 ± 82	415 ± 118	387 ± 92	0.498
Hypertension	12 (26.7)	5 (33.3)	2 (13.3)	5 (33.3)	1.000
Diabetes mellitus	5 (11.1)	2 (13.3)	1 (6.7)	2 (13.3)	1.000
Osteopenia	2 (5.0)	-	-	2 (13.3)	0.108
Former smoker	18 (40.0)	6 (40.0)	2 (13.3)	10 (66.7)	0.140
Smoking, years	20 [9-31]	13 [8-21]	5 [1-5]	30 [18-38]	0.060

[a]Data presented as n (%), mean ± SD, or median [IQR]. PASP: pulmonary artery systolic pressure; and 6MWD: six-minute walk distance.

Table 2. Exercise performance and dyspnea before and after pulmonary rehabilitation in the study participants (N = 45), by oxygen flow rate.[a]

Variable	Before PR	After PR	p
0 L/min			
6MWD, m	422 ± 82	483 ± 78	< 0.001
HR, bpm	125 ± 21	126 ± 15	0.987
SpO_2, %	80 ± 6	82 ± 6	0.586
Dyspnea, modified Borg scale score	4 ± 2	3 ± 1	0.002
Leg fatigue, modified Borg scale score	3 ± 3	1 ± 1	0.004
1-3 L/min			
6MWD, m	415 ± 118	473 ± 80	0.014
HR, bpm	121 ± 18	121 ± 19	10.000
SpO_2, %	80 ± 12	84 ± 5	0.264
Dyspnea, modified Borg scale score	4 ± 3	3 ± 1	0.267
Leg fatigue, modified Borg scale score	2 ± 2	2 ± 3	0.695
4-5 L/min			
6MWD, m	386 ± 92	421 ± 99	0.031
HR, bpm	123 ± 22	139 ± 20	0.014
SpO_2, %	81 ± 8	79 ± 7	0.368
Dyspnea, modified Borg scale score	4 ± 3	4 ± 2	0.578
Leg fatigue, modified Borg scale score	2 ± 2	2 ± 1	0.325

[a]Data presented as mean ± SD. PR: pulmonary rehabilitation; and 6MWD: six-minute walk distance.

Table 3. Health-related quality of life before and after pulmonary rehabilitation in the study participants (N = 45), by oxygen flow rate.[a]

Variable	Before PR	After PR	p
0 L/min			
Physical functioning	30 [16.2-40]	37.5 [30-68.7]	0.018
Role-physical	25 [0-68.7]	12.5 [0-93.7]	0.762
Bodily pain	52 [71-51]	62.5 [43.5-96]	0.476
General health	44.5 [31.7-69.5]	47 [17.5-75.7]	0.724
Vitality	47.5 [40-62.5]	55 [41.2-68.7]	0.373
Social functioning	75 [62.5-96.7]	75 [53.2-87.3]	0.765
Role-emotional	66 [8.2-66.9]	83.3 [33-100]	0.291
Mental health	72 [52-87]	76 [69-92]	0.306
1-3 L/min			
Physical functioning	35 [20-45]	52.5 [33.7-72.5]	0.021
Role-physical	12.5 [0-50]	62.5 [0-81.2]	0.016
Bodily pain	67 [58.5-90]	64 [50.7-85.5]	0.541
General health	54.5 [35.7-77]	52 [37-65.7]	0.929
Vitality	75 [47.5-76.2]	70 [55-85]	0.092
Social functioning	62.7 [21.8-78.2]	81.2 [50-100]	0.044
Role-emotional	16.5 [0-100]	66.6 [33-100]	0.109
Mental health	84 [67-92]	84 [75-92]	0.046
4-5 L/min			
Physical functioning	12.5 [6.25-32.5]	25 [10-40]	0.024
Role-physical	0 [0-0]	25 [0-50]	0.040
Bodily pain	71 [52-100]	60 [41-71]	0.407
General health	45 [30-60]	65 [42-77]	0.013
Vitality	55 [25-80]	70 [25-90]	0.261
Social functioning	62.5 [50-100]	75 [62.5-87.5]	0.683
Role-emotional	0 [0-33]	33.3 [0-33.3]	0.171
Mental health	80 [56-88]	72 [56-84]	0.423

[a]Data presented as median [IQR]. PR: pulmonary rehabilitation.

supplemental oxygen vs. compressed air during a test performed on a cycle ergometer, with patients showing better exercise tolerance, improved saturation, and improved dyspnea.

Regarding HRQoL, SF-36 physical functioning domain scores improved in all three groups in the present study. This improvement is related to improved functional capacity as assessed by the 6MWT. However, the groups of patients receiving ambulatory oxygen therapy also had improvements in other SF-36 domains, including social functioning (in those who received an oxygen flow rate of 1-3 L/min), mental health (in those who received an oxygen flow rate of 1-3 L/min), and general health (in those who received an oxygen flow rate of 4-5 L/min). It is of note that, despite worse initial lung function, the group of patients receiving higher oxygen flow rates had improvements in physical aspects of HRQoL and in perceived general health. PR itself has been reported to have positive effects on HRQoL.[20] In a study of patients with interstitial lung disease, long-term oxygen therapy was found to improve HRQoL, with improvements in five SF-36 domains.[9] However, the results of the aforementioned study[9] were not reproduced in a study by Sharp et al.[24] Neither study investigated the use of oxygen therapy during exercise.[9,24]

Our study has limitations. Because of the single-center quasi-experimental design and the small sample size, the study is prone to the effects of confounding factors and to type II errors. In addition, we found significant differences among the groups regarding baseline lung function and DL_{CO}, which could have influenced our results.

Improving quality of life is clinically significant because physical activity improves functional capacity and has an impact on the decline in lung function. The results of the present study show that the combined use of ambulatory oxygen therapy and PR in lung transplant candidates with IPF and significant exertional hypoxemia increases functional capacity and HRQoL.

AUTHOR CONTRIBUTIONS

AM, RDMP, SA, and GW: conceptualization; methodology; investigation; data curation; and drafting of the manuscript. GMH, EC, JF, and SCM: investigation; data curation; drafting of the manuscript; and reviewing and editing of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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