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Research Article

Effects of Pulmonary Rehabilitation in Patients with Advanced Lung Disease Under Evaluation to Lung Transplantation

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Abstract

Background: Advanced lung disease patients (ADL) present impaired exercise capacity; however, the effects of pulmonary rehabilitation (PR) in these patients are not consensual.

Objectives: To investigate the effects of a PR program on exercise capacity, dyspnea and quality of life in ADL patients on the lung transplant waiting list.

Methods: Prospective study involving participants that completed 36 sessions of PR program that included endurance and muscle strength training. The walking distance in the 6-minute walk test (6MWD), the degree of dyspnea according to the modified Medical Research Council (mMMRC) scale, the BODE index and domains of the Medical Outcomes Study 36-item Short-Form Health questionnaire were evaluated pre and post rehabilitation.

Results: Twenty-nine participants with a mean age of 51.9 ± 9.8 years, 55.2% female were included. Most patients 18 (62.1%) presented COPD, 6 (20.7%) had interstitial lung disease (ILD) and 5 (17.2%) had bronchiectasis. There was a mean increase of 104.7m in the 6MWD (340.2 ± 151.5 m vs. 444.8 ± 111.9 m; $p < 0.001$). The number of patients with higher mMRC score reduced significantly, from 13 (44.7%) to 5 (17.3%; $p = 0.01$) and the proportion of patients in BODE 1-2 increased from 3 (16.7%) to 12 (66.7%; $p = 0.01$). There were clinical and significant improvements in the SF 36 questionnaire in the domains of physical functioning ($p = 0.001$), social role functioning ($p = 0.008$) and emotional role functioning ($p = 0.005$).

Conclusions: PR in patients with advanced lung disease being evaluated for lung transplantation increased exercise capacity, reduces the degree of dyspnea and improved quality of life parameters.

Keywords: *Advanced Lung Disease; Lung Transplantation; Reabilitation; Exercise Tolerance; Six-Minute Walking Test; Quality of Life*

Abbreviations

ADL: Advanced Lung Disease Patients; COPD: Chronic Obstructive Pulmonary Disease; FEV1: Forced Expiratory Volume in the First Second; FVC: Forced Vital Capacity; HR: Heart Rate; HRQoL: General Health Related Quality of Life; ILD: Interstitial Lung Disease; LT: Lung Transplantation; mMRC: modified Medical Research Council; PR: Pulmonary Rehabilitation; RR: Respiratory Rate; SF36 Questionnaire: Medical Outcomes Study 36-item Short-Form Health questionnaire; SpO_2: Peripheral Oxygen Saturation; 1-RM: One Repetition Maximum; 6MWD: 6-Minute Walk Test Distance;6MWT: 6-Minute Walking Test

Highlights

- Pulmonary rehabilitation (PR) increased exercise capacity in advanced lung disease (ALD) patients.
- PR improved heath related quality of life in ALD patients.
- PR reduced dyspnea and improved prognosis of ALD patients.

Background

Advanced lung disease (ALD) is a term used to define chronic, non-malignant pulmonary diseases that affect daily living activities and decrease patient's life expectancy [1]. The term includes different diseases regardless the primary cause of the lung impairment such as chronic obstructive pulmonary disease (COPD), Interstitial lung disease (ILD), cystic fibrosis, pulmonary hypertension and bronchiectasis [1].

Several strategies have been developed aiming to reduce symptoms, improve quality of life and increase survival in patients with ALD and lung transplantation (LT) is the definitive therapeutic option for these patients [2]. Unfortunately, there is usually a long waiting list for lung transplantation which contributes to the progression of the lung disease and to the increase in the risk of mortality [3]. The decreased exercise capacity in ALD is a predictor of mortality before and after lung transplantation, thus pulmonary rehabilitation (PR) in any of these periods is of most importance to reduce additional functional impairment and improve health status and contribute to successful lung transplantation [4].

PR consists in a multidisciplinary intervention that promotes reduction in dyspnea, improvement in the physical capacity and patient's quality of life, presenting a high level of evidence recommendation for treatment of chronic pulmonary diseases [5]. Nevertheless, there is a lack in the literature regarding specific guidelines for pulmonary rehabilitation in patients on waiting list for lung transplantation [6].

A systematic review reported that although there are positive effects of PR in patients with ALD on waiting list for lung transplantation, the majority of the included studies applied different methodologies making it impossible to draw any definitive conclusions about that [7]. Therefore, more studies evaluating the effects of PR in patients on the waiting list for lung transplantation should be performed.

Thus, the primary aim of the present study was to evaluate the effects of PR on exercise capacity in patients with ALD that were on evaluation for lung transplantation. The secondary aim was to investigate the impact of PR on dyspnea and health related quality of life of the participants.

Methods

Study design, setting and participants

This was a prospective study that included patients with ALD that were referred to the Lung Transplantation Unit of a teaching hospital.

The following inclusion criteria were considered: 1) presents diagnosis of ALD, as previously defined [1]; 2) ≥ 18 years-old; 3) complete the PR program between January 2013 and July 2016. Those with orthopedic problems, cardiac unstable conditions and other decompensated comorbidities were excluded.

This study was approved by the local Ethics committee (ETIC nº 274.673) and was performed according to the Declaration of Helsinki. All participants signed the informed consent form.

Sample size calculation

Sample size calculation was performed according to a mean difference in the six-minute walk distance (6MWD) of 76 meters established after a pilot study with 23 patients. Considering a power of 80% and a 5% level of significance, a sample of 29 patients was estimated.

Main assessments

Lung function

All patients performed the lung function test at baseline using Koko spirometer (Pulmonary Data Service Inc., Louisville, CO, EUA) according to the American Thoracic Society and data was described as absolute and percentage of the predicted values for Brazilian population [8,9]. The variables analyzed were forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and FEV_1 /FVC.

Exercise capacity

Exercise capacity before and after PR was evaluated by 6-minute walking test (6MWT). The test was performed in a 30m corridor following recommendations of European Respiratory Society and American Thoracic Society guidelines [10]. All patients underwent two tests with a minimum interval of 30 minutes between them. Standard phrases of encouragement were given every minute. The following parameters were recorded in the beginning and end of the tests: heart rate (HR), respiratory rate (RR), perception of dyspnea by the modified Borg scale [11] and peripheral oxygen saturation (SpO_2), measured by a portable pulse oximetry (Nonin Medical, Inc., Plymouth, MN, USA). The 6MWD was expressed in absolute and percentage of estimated values for Brazilian population [12].

Modified MRC dyspnea scale

The modified MRC dyspnea scale (mMRC) was used to measure dyspnea sensation at baseline and after PR, categorized into five grades: 0: "I only get breathless with strenuous exercise"; 1: "I get short of breath when hurrying on level ground or walking up a slight hill"; 2: "On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level; 3: I stop for breath after walking about 100 yards or after a few minutes on level ground and 4": I am too breathless to leave the house or I am breathless when dressing" [13].

BODE index

The BODE index is a multidimensional grading system based on 4 different variables: body mass index - BMI (scored from 0 to 1 point); FEV_1 post-bronchodilator expressed as percentage of predicted (scored from 0 to 3 points); dyspnea sensation (MRC scale) (scored from 0 to 3 points) and walked distance in the 6MWT (scored from 0 to 3 points). The final BODE index score ranges from 0 to 10 points: the higher the final score, the worse the patient's condition [14].

Health related quality of life

General health related quality of life (HRQoL) was measured using the internationally validated SF-36. This measure comprises eight domains: vitality, physical functioning, bodily pain, general health perception, physical role functioning, emotional role functioning, social role functioning and mental health. The SF-36 scores range from 0 to 100, with higher scores indicating better HRQoL [15].

Intervention

The PR program encompassed 36 sessions of endurance and strength training three times per week. Endurance training was performed on a treadmill (Inbrasport™, Porto Alegre, Brasil) at 80% of the maximal heart rate achieved in the 6MWT, for 30 minutes three times a week. The initial treadmill speed was 0.8 km/hour which was increased progressively according to the patient's tolerance [16]. Strength training started with initial load of 50% of the maximal load obtained in the one repetition maximum (1-RM) test with progressive increments according to patient's tolerance [17]. The strength training of upper limbs lasted 30 minutes and was performed using Kabat diagonals movement (adduction and abduction of shoulders two minutes each with 2 minutes rest in between) [18]. Patients were instructed to exhale with pursed-lip breathing during the movement. The strength training of lower limbs was performed using additional weights to perform hip and knee flexion and knee extension divided in three sets of 10 repetition each [16].

Patients, if necessary, used supplemental oxygen during the exercise and oxygen saturation was monitored to assure saturation above 90% if necessary.

Procedures

Before the initiation of the PR program patients were fully evaluated by a multidisciplinary team composed of physicians, nurse, psychologist, nutritionist and physiotherapist. Data such as age, sex, body mass index, oxygen saturation, and oxygen supplementation need were recorded. Dyspnea was evaluated using the mMRC and the prognosis of patients with COPD was estimated through the BODE index [13,14].

Thereafter, function test, 6MWT and SF-36 were performed. Patients also completed the one-repetition maximum test to determine the initial load of upper limb and lower limb strength training.

After 36 sessions of PR all patients underwent the same evaluation tests, except function test. All tests were performed by the same investigator and on the same day.

Variables

The following variables were analyzed: six-minute walking distance (6MWD), peripheral oxygen saturation (SpO_2), heart rate (HR), respiratory rate (RR) and dyspnea obtained before and after 6MWT; dyspnea at baseline measured by mMRC and Bode Index (only for COPD patients); and SF-36 domains.

Data analysis

Data was presented as means and standard deviations or medians and interquartile ranges according to their distribution. The comparison of data pre and post PR was performed with the T-test or Wilcoxon Signed Ranks test. The McNemar Bowker test was used to evaluate changes on the mMRC and BODE index. All analyses were performed with the Statistical Package for the Social Science software, version 14.0 (SPSS Inc, Chicago, IL, EUA). An alpha level of 5% was considered.

Results

In the study period 140 patients with ALD were evaluated for lung transplantation and referred for the PR unit. Ninety-six were excluded due to difficulties in attending the sessions on the pre-established dates and 15 did not complete the program due to the attendance in less than 3 sessions per week (n = 4); non-adherence to the program (n = 5); exacerbations (n = 2) hospital admission (n = 1) or death (n = 3). Thus, the final sample comprised 29 patients that completed 36 sessions of PR program (Figure 1).

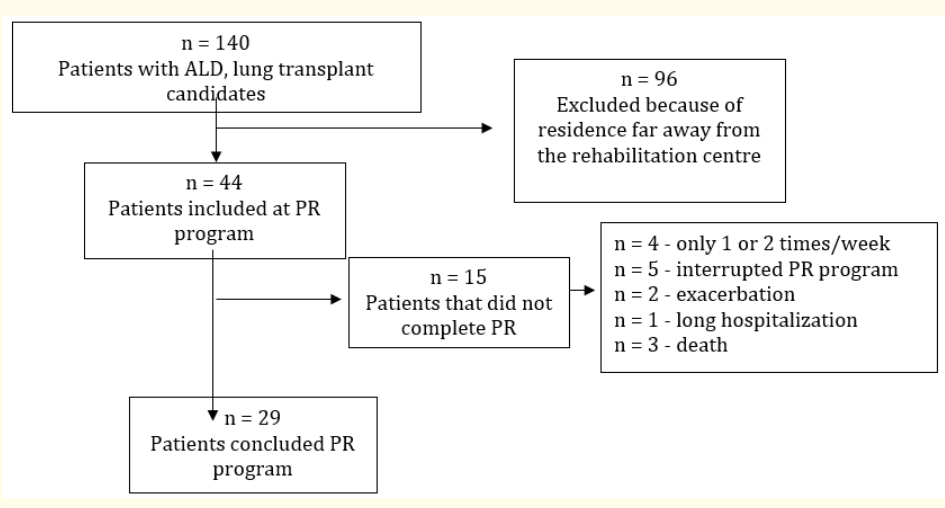

Figure 1: *Flowchart of the participants included in the PR program.*

Demographic data are presented in table 1. Most of the participants had COPD (18/62.1%) and were female (16/55.2%). Eleven patients (11/37.9%) were in home oxygen supplementation (at least 15 hours per day). The BMI was 23.3 ± 6.2 Kg/m^2. Regarding lung function, patients presented reduced values of FVC and FEV1 which was compatible with ALD presentation.

Variables	Participants (n = 29)
Age (years)	51.9 ± 9.8
Gender, female n (%)	16 (55.2)
BMI, Kg/m^2	23.3 ± 6.2
FVC, L	2.1 ± 0.6
FVC, % predicted	57.5 ± 19.0
FEV_1, L	0.9 ± 0.4
FEV_1% predicted	29.6 ± 15.5
FEV_1/FVC	42.5 ± 20.1
COPD, n (%)	18 (62.1)
Interstitial Lung Disease, n (%)	6 (20.7)
Bronchiectasis, n (%)	5 (17.2)
Oxygen supplementation > 15h /day, n (%)	11 (37.9)

Table 1: *Baseline data of the participants of the study.*

Values expressed as mean ± standard deviation and n (%). BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; FVC: Forced Vital Capacity; VEF_1: Forced Expiratory Volume on First Second.

Table 2 presents the results obtained during the 6MWT pre and after the PR program. Patients increased their distance on the 6MWD by a mean of 104.7 meters ($p < 0.001$). Twenty-four patients (82.7%) reached the minimal clinically significant distance of 50 meters after rehabilitation. The physiological parameters did not significantly change after PR.

Variables	Pre-Rehabilitation	Post- Rehabilitation	Δ (95%CI)	p
6MWD, meters	340.2 ± 151.5	444.8 ± 111.9	104.7 (76.1;133.8)	< 0.001
6MWD, % predicted	59.6 ± 26.4	78.7 ± 21.2	18,8 (13.1; 24.4)	< 0.001
SpO_2 initial	93 (91 - 95)	94 (93 - 96)	1.8 (0.3; 3.2)	0.030
SpO_2 final	80 ± 6	79± 9	-0.5 (-3.8; 2.9)	0.784
RR initial	18 (16 - 22)	18 (16 - 20)	0 (-4; 2)	0.272
RR final	31 (26 - 39)	28 (24 - 38)	0 (-9; 6.5)	0.668
HR initial	89 ± 16	88 ± 12	-0.7 (-6.8; 5.4)	0.810
HR final	122± 19	126 ± 20	3,3 (-2,4; 9)	0.246
Maximal HR (%)	73 ± 11	75 ± 11	2,5 (-1,3; 6,3)	0.191
Dyspnea initial	0.5 (0-2)	0 (0-1)	0 (-2; 0.75)	0.161
Dyspnea final	5 (4-9)	5 (4-7)	0-1 (-3; 0)	0.067

Table 2: *Comparison of variables measured during 6MWT (n = 29).*

Values expressed as mean ± standard deviation or median (interquartile range); Δ mean difference (value post rehabilitation - value pre rehabilitation); 95%CI: 95% Confidence Interval; 6MWD: Distance on the Six-Minute Walking Distance Test; SpO_2: Peripheral Oxygen Saturation; RR: Respiratory Rate; HR: Heart Rate.

The results for dyspnea and BODE index are presented in table 3. There was a significant improvement in dyspnea assessed by mMRC after the rehabilitation program (p = 0.014). Moreover, COPD patients improved their BODE index after pulmonary rehabilitation (p = 0.012).

Variable	Pre-Rehabilitation	Post-Reabilitation	p
mMRC, (n = 29), n (%)			
0 - 1	5 (17.3)	12 (41.4)	
2	6 (20.7)	7 (24.0)	0.014
3	5 (17.3)	5 (17.3)	
4	13 (44.7)	5 (17.3)	
BODE, (n = 18), n (%)			
0 - 4	3 (16.7)	12 (66.7)	0.012
5 - 6	6 (33.3)	2 (11.1)	
7 - 10	9 (50.0)	4 (22.2)	

Table 3: *mMRC and BODE index before and after pulmonary rehabilitation.*

Figure 2 presents the results for quality of life evaluated with the SF-36 questionnaire. There was a significant improvement in the domains physical functioning, bodily pain, emotional and social role functioning, physical role functioning and mental health ($p < 0.05$). The domains emotional and social role functioning increased more than 20 points which is considered a clinically important improvement.

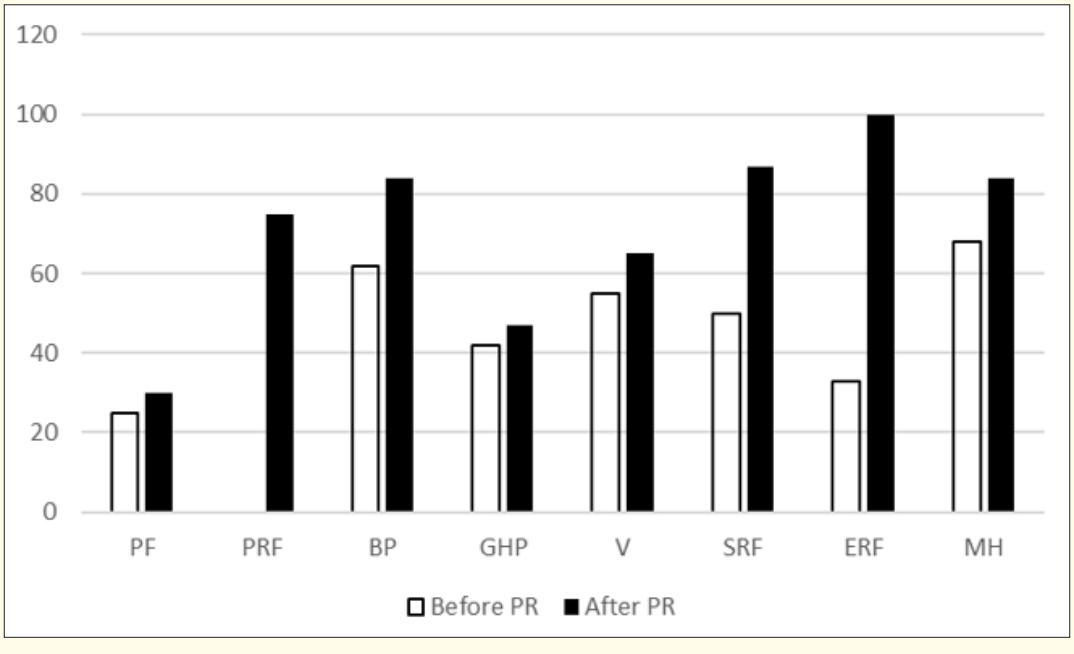

Figure 2: *Comparison of SF-36 domains before and after Pulmonary Rehabilitation.*
PF: Physical Functioning; PRF: Physical Role Functioning; BP: Bodily Pain; GHP: General Health Perceptions; V: Vitality; SRF: Social Role Functioning; ERF: Emotional Role Functioning; MH: Mental Health. Student t test and Wilcoxon.

Discussion

The main result of this study was that PR program improved exercise capacity in patients with ALD, as measured by the 6MWD test. Secondarily, there was also an improvement in the quality of life measured by the SF-36 questionnaire, and a significant decrease in dyspnea after PR. Moreover, patients also presented an improvement in the prognosis according to the BODE index.

Patients with ALD and lung transplant candidates usually present impaired exercise capacity [4]. In the present study there was a significant increase in the 6MWD test after PR. Florian., *et al.* evaluated the effects of PR in patients with lung diseases and candidates for lung transplantation and showed a significant increase in the 6MWD test after 12 weeks of rehabilitation (mean increase of 72 meters) [19]. The higher mean increase of 6MWD in the present study can be justified by the bigger proportion of COPD patients (62,1%) that usually reach a better 6MWD after PR when compared to patients with other lung diseases [20].

Other studies have also found an increase in the 6MWD after PR. Jastrzebski., *et al.* have shown that patients on the waiting list for lung transplantation significantly increased their 6MWD after 12 weeks of Nordic walking program [21]. Kenn., *et al.* retrospectively evaluated the effects of 5 weeks of PR in 811 lung transplant candidates and showed an average increase of 55.9 meters. The differences in the 6MWD test in the last two studies were smaller than the improvement presented in the present study. This difference could be explained to the duration of the PR program, since longer programs tends to provide better benefits [22].

A recent study including 345 patients suggested that PR performed before lung transplantation can preserve exercise capacity and decrease the length of hospitalization after the transplant. An increase of 100 meters in the 6MWD was associated with a decrease of 2.6 days of hospitalization (n = 207 patients, interquartile range: 0.9 - 4.3 days; p = 0.003) with a decrease in the number of postoperative major complications [23]. These data and the results of the present manuscript point out to the importance of PR in these group of patients since greater distance in the 6MWD are associated with less risk of death on the pre-transplant period and contribute to better outcomes after surgery [4].

Responsiveness is the capacity of a measure to detect meaningful change over time. Relatively few studies have been explicitly designed to assess the responsiveness of 6MWD but a large number of randomised trials provide insights into how responsive 6MWD is to treatment effects: COPD, the minimal important difference was 48 m (95% CI 32 - 65m), ILD was 39 m (95% CI 15 - 62m) and bronchiectasis was 41 m (95% CI 19 - 63m) [24]. In our study, the majority of patients achieved the improvement in the 6MWD test above the minimal important difference.

Considering dyspnea measured by Borg scale during 6MWT, it wasn´t observed significant improvement after PR, which suggests that even after increasing 6MWD the discomfort felt by the patients remained the same. This finding suggests that an improved exercise tolerance (i.e. increasing the 6MWD) can be achieved even with the same perception of dyspnea. However, other authors have found a reduction in the Borg score after PR in patients listed for lung transplantation [19].

Dyspnea is the most prevalent symptom in patients with ALD [1]. In this study there was a decrease on the proportion of patients with high degrees of dyspnea according to the mMRC scale: 13 (44.7%) *versus* 5 (17.3%). Also, the proportion of patients with the lowest degree (0 - 1; p = 0.014) changed from 5 (17.3%) to 12 (41.4%) after PR. Jastrezebski., *et al.* evaluated dyspnea using the mMRC scale in 31 patients with interstitial lung disease before and after 6 weeks of pulmonary rehabilitation and did not find significant difference in this variable (p < 0.06) [25]. The length of the PR program could explain the better results obtained in the present study for this variable [4,6].

The BODE index predicts prognosis related to mortality and hospitalization in patients with COPD. High BODE index indicates worse prognosis [14]. In the present study there was a significant improvement in the BODE index after PR in patients with ALD. The number of patients with BODE index 7 - 10 reduced from 9 (50%) to 4 (22.2%) and the number of patients with BODE 0-4 increased from 3 (16.7%) to 12 (66.7%) suggesting that there was an improvement in the prognosis after the 36 sessions. Cote., *et al.* evaluated the BODE index in 116 patients with COPD that performed PR compared to a control group of 130 COPD patients without rehabilitation. Patients in the intervention group had a reduction in the BODE index which remained stable in the following two years with a reduced mortality and hospitalization rates when compared to the control group (p < 0.001) [26].

The improvement in exercise capacity after RP does not automatically translate into improvement in the patient's quality of life. This is because the improvement in quality of life is also influenced by psychosocial, cultural and genetic factors [27]. In the present study, however, besides the increase in exercise capacity there was an improvement in the quality of life after PR on the following SF36 domains: physical functioning, bodily pain and mental health. There was also a clinically significant improvement in the domains physical role functioning (36 points; $p = 0.001$), social role functioning (21 points; $p = 0.008$) and emotional role functioning (30 points; $p = 0.005$). There wasn't any significant difference in the domains general health perceptions or vitality.

Jastreszebski., *et al.* evaluated the quality of life of 31 patients with interstitial lung disease after 6 weeks of PR and found significant improvement in the SF-36 questionnaire in the following domains: physical role functioning, physical functioning, vitality, social role functioning and mental health ($p < 0.05$) [25]. Florian., *et al.* showed similar effects of PR on quality of life in 58 patients with advanced lung disease on the waiting list for lung transplantation using the SF-36 [19]. Although both studies have found improvement in quality of life, only the last study showed an improvement in functional capacity domain above 20 points, which is the minimal clinically significant difference [28]. This result could be explained, at least in part, by the fact that in the study of Jastreszebski., *et al.* patients performed only Nordic walking instead of a multidisciplinary rehabilitation program where, apart from exercise training, patients receive also nutritional, psychological and educational support [5,29].

The present study presents some limitations that should be pointed out. Firstly, although it has been used in other studies to evaluate the effects of PR in quality of life in patients with chronic lung diseases, the SF-36 is not a disease-specific quality of life questionnaire [19,22,30]. However, patients with different diagnosis were include in the study it became difficult to select a specific questionnaire for the assessment of the quality life. Secondly, there was a disproportional number of COPD patients as compared to the number of patients with restrictive diseases. Nevertheless, it was not possible to control for the etiology of ALD, since this sample represented the clinical practice in the ALD outpatient clinics. Other authors have also encountered this type of heterogeneity [22].

Conclusions

In the conclusion, PR program increased exercise capacity, ameliorated dyspnea index and improved quality of life patients with ALD before lung transplantation. Moreover, patients with COPD had also their prognosis improved. Further studies are needed in order to reproduce these results in other ALD patients and to verify long term outcomes of PR including the period after lung transplantation.

Declarations

Ethics Approval and Consent to Participate

This study was approved by Committee Ethics of Universidade Federal de Minas Gerais under reference number: 274.673 and in the Trial registration: Clinical Trials Registry: RBR-2jfwqx, http://www.ensaiosclinicos.gov.br/rg/RBR-2jfwqx/.

Consent for Publication

Not applicable. The manuscript don´t contains any individual person's data in any form (including individual details, images or videos).

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Competing Interests

The authors declare that they have no competing interests.

Author´s Contributions and Consent for Publication

All authors were involved in the design of this study. EVM, DSE, RAC and VMA were involved in the selection and management of patients. EVM, DSE, RAC, VMA, DSRV and MH were involved with analysis and discussion of results. All authors contributed to the manuscript from the outset and read and approved the final draft and if approved, agree to make public the content of the article, being responsible by its content.

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