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Effects of pulmonary rehabilitation on dyspnea and functional capacity on waiting list for lung transplantation: According to obstructive or restrictive pulmonary disease

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Abstract:

BACKGROUND: Pulmonary rehabilitation (PR) has been shown to be effective on exercise capacity and dyspnea in lung transplantation (LTx) candidates. In this study, we aimed to investigate the efficacy of PR and to compare the outcomes in LTx candidates with obstructive and restrictive lung diseases.

METHODS: Between January 2013 and May 2018, medical data of 86 patients who were on the waiting list for LTx were retrospectively analyzed. The patients were divided into two groups based on the diagnosis as obstructive patients (Group 1) and restrictive patients (Group 2). Six-minute walking test (6MWT), the Borg scale, and the modified Medical Research Council dyspnea scores were analyzed.

RESULTS: A total of 65 patients completed the 8-week PR protocol ($n = 42$ in Group 1 and $n = 23$ in Group 2). Irrespective of the initial diagnosis, there was a significant ($P < 0.05$) improvement in the 6MWT distance in both groups without any statistically significant difference between the groups (Group 1, 299 m [42–548] vs. 377 m [84–561], mean increase 78 m, $P < 0.001$; Group 2, 337 m [70–525] vs. 396 m [139–621], mean increase 59 m, $P = 0.002$; Δ, $P = 0.476$). The effect of PR on dyspnea was significantly improved in both groups, whereas there were no differences between groups.

CONCLUSION: PR has a positive effect on exercise capacity and dyspnea in patients with both obstructive and restrictive lung diseases who are on the waiting list for LTx. Our study results suggest that PR is effective in LTx candidates, irrespective of the initial diagnosis.

Keywords:

Chronic obstructive pulmonary disease, exercise training, interstitial lung disease, lung transplantation, pulmonary rehabilitation

Introduction

Lung transplantation (LTx) is the only therapeutic option for end-stage chronic lung diseases refractory to maximal medical treatment and is associated with improved quality of life (QoL) and survival.[1] Due to the limited number of donors, LTx candidates may wait for a long period of

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time on the waiting list.[2] During this time, patients' exercise capacity is gradually reduced due to dyspnea and fatigue related to the progression of disease, especially interstitial lung disease.[3]

Exertional dyspnea and fatigue are the most common disabling symptoms which considerably impair the QoL in patients with advanced obstructive and restrictive lung diseases.[4] In such cases, exercise tolerance decreases due to dyspnea and fatigue.[5] The exercise capacity, which is used in predicting the success rate of LTx, is very limited in LTx candidates with end-stage lung disease.[5]

In recent years, pulmonary rehabilitation (PR) is recommended in many transplantation centers; however, there is no established PR guideline for LTx candidates and recipients.[6] Both LTx and PR date back to the same period in the 1960s and 1970s.[7,8] In literature, the first PR program (PRP) was applied in the 1990s.[9] With the growing number of evidences showing that PR is effective before and after surgery, PR has been mentioned in the related guidelines as a component of LTx.[10]

Review of literature reveals a number of studies suggesting that PR can improve the dyspnea- and fatigue-induced exercise capacity in all LTx candidates with end-stage lung diseases, particularly obstructive lung disease.[4,11] In addition, the physical and emotional preparation of a LTx candidate before surgery may reduce the risk for postoperative complications and improve the patient-centered outcomes.[1,10,12] Such an attempt is also useful for clinicians in identifying eligible candidates and for patients in reducing physical and emotional stress.[13] In clinical practice, PR is recommended as a part of care in this patient population.[11]

The benefits of PR have not been exactly well documented in LTx candidates on the waiting list. To date, a few number of studies are available with heterogeneous sampling and nonstandardized protocols.[1] In a study, Gloeckl *et al*.[10] included patients with chronic obstructive pulmonary disease (COPD); Nishiyama *et al*.[14] included patients with idiopathic pulmonary fibrosis (IPF); while Jastrzebski *et al*.,[12] Florian *et al*.,[1] Kenn *et al*.,[15] Li *et al*.,[16] and Manzetti *et al*.[17] included different diagnoses and number of patients on the waiting list for LTx. Despite these limitations, PR has been shown to be associated with a significant improvement in functional capacity and QoL.[1,12] In addition, many studies demonstrating the benefits of exercise training in patients with end-stage chronic lung diseases and COPD have been published.[11] However, restraining patients from PR before LTx can be deemed as unethical. Therefore, it is unlikely to design a randomized controlled study of PR in LTx candidates.

Considering the physiological alterations before LTx and exercise training guidelines, an effective and safe program can be applied.[18] In literature, there is a limited number of studies investigating the efficacy of PR according to the diagnosis (i.e., chronic obstructive lung disease and restrictive lung disease).[19] We believe that establishing the efficacy of PR according to the diagnosis would pave the way for tailoring individual programs and for developing specific PR techniques for each patient.

In the present study, we hypothesized that the presence of end-stage lung disease-related factors would affect the PR response and that individualized programs would increase the efficacy of PR in LTx candidates. Therefore, we aimed to investigate the efficacy of PR and to compare the outcomes in LTx candidates with similar physiopathological characteristics.

Methods

Study design and study population

Between January 2013 and May 2018, medical data of 86 patients who were on the waiting list for LTx at the transplantation centers located in Istanbul province and who were referred to the PR unit of Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital were retrospectively analyzed. The patients were divided into two groups based on the diagnosis as obstructive patients (Group 1, n = 42) and restrictive patients (Group 2, n = 23). Six-minute walking test (6MWT), the Borg scale, and the modified Medical Research Council (mMRC) dyspnea scores of the patients were recorded at baseline and at the end of 8-week PRP.

Content of pulmonary rehabilitation program

The PRP involved muscle strengthening exercises, aerobic training, clinical evaluation, psychiatric evaluation, nutritional counseling, social assistance, and educational lectures. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics committee approval was received for this study from the local Ethics Committee of the Ministry of Health, Istanbul Training and Research Hospital (approval date: 14/9/2018, document number 1415).

Clinical evaluation and exercise protocol

All patients underwent clinical evaluation by an experienced pulmonologist in the PR unit and received an education on their disease and treatment options. The patients were also given psychological support to decrease anxiety for LTx surgery. All patients received education on daily practice encouraging healthy behaviors such as regular physical activity, healthy

diet, reasonable drug use, compliance to treatment, and disease self-management and psychological support including effective strategies to overcome chronic conditions. The patients who were in need of medical treatment were referred to a psychiatrist. In addition, training on the utilization of home oxygen delivery systems and inhaled drugs and strategies to overcome dyspnea and relaxation exercises were imparted.

Exercise program

All patients underwent exercise program twice a week under supervision for 8 weeks. In addition, they were asked to perform a home-based exercise program which was scheduled as 3 days/week and to fill out the exercise follow-up form. During the exercise program, all patients received continuous oxygen therapy in accordance with the medical prescription and were monitored with pulse oximetry. The oxygen flow rate was set to maintain an oxygen saturation of >88%.

Aerobic training

The exercise intensity was predetermined to be 50%–70% of the maximum heart rate. The exercise intensity was gradually increased based on the severity of dyspnea perception and fatigue ratio. The aerobic exercise program consisted of treadmill walking, cycle ergometer, and arm ergometer training. Group exercises were performed in sets of 15 min each with three exercise modalities. During the exercises, oxygen saturation, heart rate, and the Borg scores were recorded.

Strengthening/resistance training

The resistance targets were set at loads equivalent to 20%–40% of a one-repetition maximum maneuver and performed between 8 and 12 repetitions for one to two sets per session. Dumbbell and free weight bags were used in supervised exercise sessions. The training focused on exercise for biceps, triceps, quadriceps, hamstring, and hip muscles.

Home-based exercise program

In addition to the supervised exercise program which was administered for 2 days at the hospital, the patients were asked to perform a home-based exercise program for 3 days a week. The program included breathing exercises (local expansion exercises, diaphragmatic breathing, and pursed lip breathing), free walking, and upper- and lower-extremity strengthening exercises with TheraBand®. To ensure that the home-based exercise program was performed, a patient home-based exercise follow-up chart was given to each patient and chart follow-ups on a weekly basis were carried out by the physiotherapist.

Outcome measurements

- 6MWT – The test was conducted in a 30-m corridor according to the American Thoracic Society (ATS) guidelines. Before and after the test, oxygen saturation, heart rate, Borg rating, and walking distance were recorded[11]
- mMRC-Dyspnea Scale – Perceived dyspnea during the activities of daily living was evaluated using the mMRC scale.[11]

Statistical analysis

Statistical analysis was performed using the SPSS version 15 statistical software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean and standard deviation, median (minimum–maximum), number (n), and frequency (%). The Shapiro–Wilk test was used to test the normality of the distribution of all variables. The Wilcoxon signed-rank test was used to compare the pre- and post-exercise results of the groups, whereas the Mann–Whitney U-test was used for group-wise comparisons. The Chi-square test was used to analyze categorical variables. $P < 0.05$ was considered statistically significant.

Results

Of all the patients, 65 completed ($n = 42$ in Group 1 and $n = 23$ in Group 2) the 8-week PR protocol. Twenty-one (24.4%) patients were unable to complete the program for several reasons. Of the completers, 55% and 87% were male and 64.6% and 35.4% were female in Group 1 and Group 2, respectively. The mean age was 37.59 years in Group 1 and 41.21 years in Group 2, indicating no significant difference. The study's flowchart is depicted in Figure 1. The number of male patients ($P = 0.009$) and the mean body mass index ($P = 0.014$) were statistically significantly higher in Group 2 than Group 1. However, the mean pulmonary artery systolic pressure was higher in Group 1 (41.28 mmHg) than Group 2, although not statistically significant.

The most common diagnoses in Group 1 included bronchiectasis in 25 patients (59.5%, $P < 0.001$), COPD in 13 patients (31%), and cystic fibrosis in four

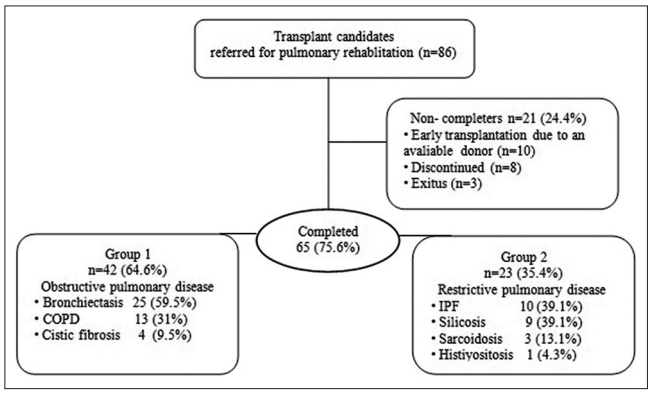

Figure 1: Study's flowchart. COPD: Chronic obstructive lung disease, IPF: Idiopathic pulmonary fibrosis, PLCH: Pulmonary Langerhans cell histiocytosis

patients (9.5%). The most common diagnoses in Group 2 included IPF in ten patients (39.1%), silicosis in nine patients (39.1%), sarcoidosis in three patients (13.1%), and histiocytosis in one patient (4.3%). Table 1 summarizes the demographic and clinical characteristics of both patient groups.

Pulmonary rehabilitation program effects

Functional exercise capacity

The distance from the 6MWT was compared with that of the reference values.[11] No statistically significant differences were found in the increased 6MWT distance values (Δ, $P = 0.476$) between Group 1 (77.41 m, $P < 0.001$) and Group 2 (59.34 m, $P = 0.002$) [Table 2]. Irrespective of the initial diagnosis, there was a significant ($P < 0.05$) improvement in the 6MWT distance in both groups without any statistically significant difference between the groups (Group 1, 299 m [42–548] vs. 377 m [84–561], mean increase 78 m, $P < 0.001$; Group 2, 337 m [70–525] vs.

Table 1: Baseline demographic characteristics of patients

Variable	Group 1 (obstructive) (*n*=42)	Group 2 (restrictive) (*n*=23)	*P**
Demographics			
Sex (male/female), *n* (%)**	23/19 (55/45)	20/3 (87/13)	0.009
Age (year)	37.59 (14-68)	41.21 (24-62)	0.320
BMI (kg/m^2)	19.96 (12.70-32.40)	23.52 (13.20-33.70)	0.014
Diagnosis, *n* (%)**			
Bronchiectasis	25 (59.5)		<0.001
COPD	13 (31)		
Cystic fibrosis	4 (9.5)		
IPF		10 (43.5)	
Silicosis		9 (39.1)	
Sarcoidosis		3 (13.1)	
Histiocytosis		1 (4.3)	
6MWT			
6MWD (m)	299 (42-548)	337 (70-525)	0.269
Borg, resting	2 (0-4)	1 (0-3)	0.044
Borg, postexercise	4 (0-10)	4 (0-10)	0.355
mMRC	3 (1-5)	3 (0-5)	0.240
Pulmonary functions			
FVC, L	1.28 (0.60-2.47)	1.51 (0.70-2.94)	0.062
FVC, percentage of predicted	34.64 (19.2-58.35)	38.91 (18-72.90)	0.185
FEV_1, L	0.77 (0.39-1.48)	1.12 (0.56-2.01)	0.002
FEV_1, percentage of predicted	25.36 (12.5-50.00)	35.33 (16.00-63.60)	0.006
PASP (mmHg)	41.28 (25.00-83.00)	38.04 (25.00-75.00)	0.082

Data are expressed in median (minimum–maximum) or percentage. *The Mann–Whitney U-test, **The Chi-square test. $P<0.05$ was considered statistically significant. BMI: Body mass index, IPF: Idiopathic pulmonary fibrosis, COPD: Chronic obstructive pulmonary disease, 6MWT: 6-min walking test, 6MWD: 6-min walking distance, mMRC: Modified Medical Research Council Council, FVC: Forced vital capacity; FEV_1: Forced expiratory volume in 1 s, PASP: Pulmonary artery systolic pressure

Table 2: Dyspnea, fatigue, and exercise capacities before and after pulmonary rehabilitation

Variable	Group 1 (obstructive) (*n*=42)				Group 2 (restrictive) (*n*=23)				Difference (*P*)
6MWT	Before PR Median (minimum-maximum)	After PR Median (minimum-maximum)	In-group (Δ) median (minimum-maximum)	*P*	Before PR Median (minimum-maximum)	After PR Median (minimum-maximum)	In-group (Δ) median (minimum-maximum)	*P*	
6MWD (m)	299 (42-548)	377 (84-561)	77.41 (−35-262)	<0.001	337 (70-525)	396 (139-621)	59.34 (−83-231)	0.002	0.476
Borg 1*	2 (0-4)	1 (0-5)	1 (0-4)	0.005	1 (0-3)	1 (0-3)	1 (0-3)	0.036	0.689
Borg 2**	4 (0-10)	3 (0-9)	1 (0-6)	0.003	4 (0-10)	3 (1-7)	1 (0-7)	0.011	0.901
mMRC (0-5)	3 (1-5)	3 (0-5)	1 (0-3)	<0.001	3 (0-5)	3 (0-5)	0 (0-2)	0.046	0.447

*Borg, resting. **Borg, postexercise. PR: Pulmonary rehabilitation, 6MWD: 6-min walking distance, mMRC: Modified Medical Research Council, 6MWT: 6-min walking test

396 m [139–621], mean increase 59 m, $P = 0.002$). Despite the low mean 6MWT distance at baseline, the mean increase in the distance after PRP was significant in Group 1.

Dyspnea

Although a statistically significant decrease was achieved in the mMRC dyspnea score of both groups (Group 1, $P < 0.001$; Group 2, $P = 0.046$), there was no statistically significant difference between the groups ($P = 0.447$) [Table 2]. The effect of PRP on dyspnea was statistically significantly improved in Group 1 (Borg, resting: $P = 0.005$, postexercise: $P = 0.003$, and mMRC: $P < 0.001$) and Group 2 (Borg, resting: $P = 0.036$, postexercise: $P = 0.011$, and mMRC: $P < 0.001$). The dyspnea scores and exercise capacities of both groups before and after PRP are shown in Table 2.

Discussion

In the present study, we evaluated the effect of an 8-week PRP on dyspnea and exercise capacity in LTx candidates with end-stage obstructive or restrictive lung diseases. We found that PRP yielded a clinical improvement in these patients, irrespective of the initial diagnosis. More interestingly, although the mean baseline 6MWT distance was worse in the obstructive patients (299 m) than the restrictive patients (337 m), a higher increase was found after PRP in the obstructive patients (77.4 m vs. 59.3 m). This situation may be due to a ceiling effect of the 6MWT due to the physical limitation of the possible extent of fast walking.[20] Although the median increase in neither group was statistically significant ($P = 0.476$), the increase in the 6MWT distance was higher than the minimal clinically important difference (25–33 m) as recommended by the ATS/European Respiratory Society.[21] In the entire study population, the median increase in the 6MWT distance after exercise was statistically significant (68.37 m) ($P < 0.05$). In a study, Florian *et al*.[1] reported a 72-m increase in the 6MWT distance in patients undergoing 32-session PRP ($P = 0.001$). In the aforementioned study, patients with interstitial lung disease were also included, as in our study; however, the underlying diseases were not considered in the final analysis. In another study, Kaymaz *et al*.[22] applied an 8-week PRP to patients with interstitial lung disease ($n = 10$) and found a 60-m increase in the median 6MWT distance, which is consistent with our findings related to the patients with interstitial lung disease, despite a higher number of sample size in our study ($n = 42$). Similarly, Holland *et al*.[23] reported a 57-m increase with an 8-week PRP and Nishiyama *et al*.[14] reported a 46.3-m increase with a 10-week PRP.

In our study, we also observed a statistically significant ($P < 0.05$) clinical improvement in the perceived dyspnea scores in both groups (Group 1, Borg, resting: $P = 0.005$, postexercise: $P = 0.003$, and mMRC: $P < 0.001$ vs. Group 2, Borg, resting: $P = 0.036$, postexercise: $P = 0.011$, and mMRC: $P < 0.001$). On the other hand, some authors have advocated that 8-week PRP twice a week under supervision is not effective.[24] However, the British Thoracic Society recommends a 6-week exercise program twice a week under supervision.[25] In our study, the distance in 6MWT increased after PRP and less fatigue at the end of the test in both groups.

Because restrictive lung disease is associated with rapid desaturation during exercise,[26] a lower intensity and long-term exercise program appears to be more effective in this patient population. However, it should be kept in mind that such group of diseases may rapidly progress.[27] Unfortunately, there is no randomized study available on the content and optimal duration of the program in LTx candidates; therefore, we use empirical data based on our clinical observations. According to previous study findings, we consider that a longer duration for PRP is needed to optimize the exercise capacity of patients with restrictive lung disease than those with obstructive lung disease.[27] Although several lung volume-lowering techniques have been developed to maintain the exercise capacity and QoL in COPD patients who have been waiting for LTx for a long period of time, there is no option, but the early referral to PRP for patients with restrictive lung disease. Current evidences have not recommended an optimal duration of PRP for patients with restrictive lung disease; however, early referral seems to be associated with favorable results.[23]

The majority of the referral patients to the LTx centers are COPD patients. Interestingly, 75% of our patients were diagnosed other than COPD (i.e., bronchiectasis in 44% and silicosis in 30%). This can be attributed to the fact that younger patients with a higher life expectancy following transplantation were mostly selected for LTx previously.[28] However, the lack of expected increase in the survival over time indicates that more efforts should be paid to refer COPD patients to the transplantation centers and that pulmonologists in Turkey, particularly working in regional hospitals, have limited knowledge and familiarity on transplantation or may overlook this issue.[29]

In literature, a few number of studies are available on LTx candidates investigating the efficacy of PRP with heterogeneous sampling and small sample sizes. In our study, we classified the patients into groups according to their physiopathological characteristics and attempted to contribute to the existing data from a different perspective. Nonetheless, small sample size and patient classification according to the underlying physiopathological mechanism alone can be deemed as the main limitations of this study. In addition, we were

only able to evaluate the first 8-week outcomes of PRP in which the sample size was the highest. Finally, we were unable to evaluate emotional aspects and health-related QoL in our study.

Conclusion

Irrespective of the initial diagnosis, PR had a positive effect on exercise capacity and dyspnea in patients with both obstructive and restrictive lung diseases who were on the waiting list for LTx. We believe that the present study is important in that it provides PRP responses of patients with similar physiopathological characteristics, which would pave way for tailoring individual programs.

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Conflicts of interest
There are no conflicts of interest.

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