Effect of 8-week Pulmonary Rehabilitation Program on Dyspnea and Functional Capacity of Patients on Waiting List for Lung Transplantation

INTRODUCTION

Lung transplantation (LTx) is the only therapeutic option for end-stage chronic lung diseases refractory to most medical treatments and is associated with improved quality of life (QoL) and survival [1]. Owing to the limited number of donors, LTx candidates might have to be on the waiting list for a long time [2]. As a consequence, dyspnea and fatigue increase with decreased exercise capacity owing to unpreventable disease progression. Increasing exercise capacity and improving QoL are of utmost importance for a successful LTx in these patients who are scheduled for a complex surgery [1, 3].

In recent years, there is a growing number of publications on pulmonary rehabilitation (PR). Moreover, PR is recommended in patients with chronic obstructive pulmonary disease (COPD), in those with chronic lung diseases with decreased exercise capacity due to dyspnea and fatigue (i.e., interstitial lung diseases, cystic fibrosis, bronchiectasis, and thoracic deformities) and before and after LTx, and in those undergoing lung volume reduction surgery [3-6].

Although many studies showing the benefits of exercise training in patients with end-stage chronic lung diseases have been published, there are a limited number of studies investigating the efficacy and safety of exercise in patients who are on the waiting list for LTx [6-9].

Physical and emotional preparation of a LTx candidate before surgery may reduce the risk for postoperative complications and improve patient-centered outcomes [1, 10, 11]. In addition, such an attempt for well-being may accelerate postoperative healing and increase survival [12]. In particular, exercise training is essential to optimize functional capacity and crossmatch testing before transplantation and to improve QoL and patient outcomes after surgery [13]. Although PR is recommended before and after LTx in many transplantation centers, there are no established clinical...
practice guidelines for PR for LTx candidates and recipients [14, 15]. In daily practice, an effective and a safe exercise program can be implemented depending on the physiological alterations in patients and current exercise training guidelines [15].

In the literature, randomized studies showing the efficacy of the duration of program and number and intensity of sessions under supervision mostly include patients with COPD, and there are a limited number of studies on the content and optimal duration of the program in LTx candidates [11, 16, 17]. PR programs (PRPs) with varying contents and intensities can be applied under direct supervision in the outpatient or inpatient setting or in a combined setting [18-21]. The content and organization of PR programs substantially vary depending on each country and even on each center in a single country [18, 22]. The optimal duration of PR programmes has not been well established yet, and it might range from 6 weeks to 6 months [18]. Although a few guidelines are available, there is no standard content and optimal duration for PRPs [23, 24].

In the present study, we aimed to evaluate the effect of a comprehensive 8-week, outpatient-based PR programme consisting of exercise training twice a week under direct supervision at our center and home-based training thrice a week without supervision on dyspnea and exercise capacity of patients on the waiting list for LTx.

MATERIALS AND METHODS

Between March 2012 and December 2014, medical data of 23 patients who were on the waiting list for LTx, who were referred to the PR unit of Training and Research Hospital, and who completed the 8-week, outpatient-based PR programme twice a week under direct supervision were retrospectively analyzed. All patients received an individual PR programme consisting of physical exercise training, psychological consultation, and nutritional intervention. Exercise capacity was assessed using the 6-minute walking test (6MWT) at baseline and at week 8, whereas the rate of perceived dyspnea was assessed using the Borg scale and Medical Research Council (MRC) dyspnea scale at baseline and at the beginning and end of each session. In all cases, 6MWT was performed under oxygen support.

A written informed consent was obtained from each patient. The study protocol was approved by the local ethic committee of the Istanbul Training and Research Hospital (14.9.2018-1415). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Content of PR Programme

Clinical evaluation and exercise protocol

All patients underwent clinical evaluation by an experienced pulmonologist in the PR unit and received information on their disease and treatment options. In addition, the patients were given psychological support to decrease anxiety for undergoing LTx. 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, as well as psychological support, including effective strategies to overcome chronic conditions. Patients who were in need of medical treatment were consulted to a psychiatrist. In addition, training was provided on the utilization of home oxygen delivery systems, inhaled drugs, and strategies to overcome dyspnea and relaxation exercises.

Exercise program

All patients received exercise training twice a week under direct supervision at our clinic. Exercise training included treadmill exercises, cycle ergometer exercises, light aerobic exercises, and upper extremity weight bearing. Each session took 60 min and was supervised by a single physiotherapist. The intensity of training was chosen at 60% of the peak heartbeat using 6MWT. During the exercise, oxygen support was delivered through a nasal cannula to maintain an oxygen saturation of ≥88%. Before and after exercise, the blood pressure was measured; moreover, the heart rate was monitored during the exercise. The Borg scale was used before and after each session.

Home-based exercise program

In addition to the supervised exercise program that was administered twice a week in the hospital setting, all patients were instructed to perform a home-based exercise program three 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 conducted, a patient home-based exercise follow-up chart was given to each patient, and chart follow-ups were carried out on a weekly basis by the physiotherapist.

Diet

Each patient received nutritional consultation by the hospital dietician according to body composition evaluation, and nutritional supplements were given, when necessary.
Outcome measurements

6MWT
6MWT was conducted in a 30-m corridor in accordance with the American Thoracic Society (ATS) guidelines. The patients were instructed to walk as fast as they could. Before and after the test, Borg fatigue rating and walking distance were recorded [25, 26].

MRC Dyspnea Scale
The MRC dyspnea scale was used to evaluate perceived dyspnea during daily living activities [27].

Statistical Analysis
Statistical analysis was performed using the Statistical Package for the Social Sciences version 15.0 statistical software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed as means and standard deviations, medians (minimum-maximum), numbers, and frequencies. Normality was assessed using the Shapiro-Wilk test. The Wilcoxon test was used to compare pre- and postexercise results. A p value of <0.05 was considered statistically significant.

RESULTS
Of the 27 LTx candidates who were referred to our unit, 23 completed the 8-week outpatient-based PR programme. Of the 23 patients 57% were males; the mean age of patients was 35±10 (range: 16-48) years. Four patients were operated early, as an appropriate donor was available (Figure 1). The distribution of diagnosis in patients was as follows: bronchiectasis (n=10, 44%), silicosis (n=7, 30%), sarcoidosis (n=2, 9%), idiopathic pulmonary fibrosis (n=1, 4%), COPD (n=1, 4%), and others (n=2, 9%) (Table 1). At the end of the treatment, there was a significant improvement (median: 60 m) in 6MWT scores (360 [70-254] m vs. 300 [139-489] m; p=0.018). In addition, a clinical improvement was observed in Borg (p=0.000) and MRC scores (p=0.008). The median baseline resting and post-exercise Borg scores were 2 (0-4) and 4 (0-10), respectively. The median post-exercise resting Borg score was 0.5 (0-3), and the median post-exercise Borg score was 3 (0.5-8) (p=0.000 for both). There was also a statistically significant difference in the median pre- and post-exercise MRC scores (p=0.008) (Table 2). All patients were under long-term oxygen therapy (LTOT). Only one patient had a history of long-term smoking (patient with COPD), and two patients had a very short duration of smoking; no other patient had used smoked. There were no serious comorbidities affecting the programme because patients who have serious comorbidities before LTx are evaluated in detail and are usually excluded.

Table 1. Baseline demographic characteristics of patients

| Variable | Demographics | Diagnosis |
|----------|--------------|-----------|
| Sex, n (%) | Female 10 | Bronchiectasis 10 |
|          | Male 13 | Silicosis 7 |
|          | Age, year (mean ± SD) 35±10 | Others 6 |
|          | BMI, kg/m², mean (minimum–maximum) 18.8 (13.2–26.2) | Pulmonary Functions, median (range) |
|          | FVC (L) 1.1 (0.7–2) | 6MWT distance (m) 300 (70–524) 360 (139–489) 0.018 |
|          | FEV₁ (L) 0.7 (0.5–1.4) | MRC scores (1–5) 4 (2–5) 4 (2–5) 0.008 |
|          | FVC% 33 (18–47) | Borg scores |
|          | FEV₁% 22 (15–43) | Resting 2 (0–4) 0.5 (0–3) 0.000 |
|          | SD: standard deviation; BMI: body mass index; FVC: forced vital capacity; FEV₁: forced expiratory volume in one second | Postexercise 4 (0–10) 3 (0.5–8) 0.000 |

Table 2. Effects of PR programme on dyspnea and exercise capacity

| Variable | Before PR median (minimum–maximum) | After PR median (minimum–maximum) | p |
|----------|------------------------------------|-----------------------------------|---|
| 6MWT     | 300 (70–524)                       | 360 (139–489)                     | 0.018 |
| MRC scores | 4 (2–5)                            | 4 (2–5)                           | 0.008 |
| Borg     | 2 (0–4)                            | 0.5 (0–3)                         | 0.000 |
| Resting  | 4 (0–10)                           | 3 (0.5–8)                         | 0.000 |
| Postexercise | 6MWT: 6-minute walking test; MRC: Medical Research Council |
In the present study, we evaluated the effect of an 8-week outpatient-based PR programme twice a week under direct supervision and home-based training thrice a week without supervision on dyspnea and exercise capacity of patients on the waiting list for LTx. We found a clinical improvement in dyspnea scores and exercise capacity in our study population: the median distance in 6MWT was 300 (70-524) m before the exercise and the median postexercise value increased to 360 m (60 m increase) (p=0.018). We also observed a statistically significant clinical improvement in perceived dyspnea and rating scores after the exercise.

Dyspnea is a common symptom in LTx candidates who have end-stage lung disease [28]. It has been reported that PR is useful in reducing dyspnea [21] and that inspiratory muscle training, in particular, significantly improves the MRC dyspnea score [29]. Although pre- and post-PR median MRC scores were similar in our study, the distribution of scores varied. Thus, there was also a statistically significant difference in the median pre- and postexercise MRC scores (p=0.008).

In the literature, most patients referred to the transplantation centers are patients with COPD (7); however, our study is remarkable as almost all patients are patients without COPD. This can be attributed to the fact that younger patients with a higher life expectancy following transplantation were mostly previously selected for LTx [30]. However, the expected increase in referral of patients with COPD to LTx centers has not been achieved. This situation suggests that pulmonologists in Turkey, particularly working in regional hospitals, do not have enough knowledge about the transplantation or do not show the necessary importance [31].

Although there are no established reference ranges for LTx candidates till date, the increase in 6MWT was higher than the minimal clinically important difference (MCID, 25-33 m) recommended by the American Thoracic Society / European Respiratory Society (ERS) [26]. In the literature, studies showing MCID values for an effective PR programme have mostly involved patients with COPD; however, these values can be used for LTx candidates as both the conditions involve the lungs. Some authors have also advocated that survival rates of these candidates considerably increase following transplantation, as evidenced by an increase in 6MWT scores from those at baseline [1].

Many outpatient-based PR programmes, which are applied for 6-8 weeks twice or thrice a week, for LTx candidates are compliant with the general recommendations of PR. However, the optimal duration of PR programmes has not been established, although a minimum 8-week programme offers more benefits in the long term [32]. In the literature, there are studies showing that an 8-week PR programme twice a week under direct supervision is not effective [33]; however, the British Thoracic Society recommends a 6-week exercise program twice a week under supervision [34]. In our study, despite increased distance in 6MWT after PR programme, the patients experienced less muscle weakness at the end of the test. Current evidence has also suggested that PR programmes may offer greater benefits for patients who are referred in the early stage of the disease [35].

In a study, Florian et al. [1] showed a significant decrease in perceived dyspnea scores (p=0.001) with a mean increase in the distance of 72 m as assessed by 6MWT (p=0.001) in patients undergoing a 36-week PR programme. In our study, we achieved a statistically significant increase in the exercise capacity of patients undergoing a comprehensive, 8-week (total, 16 sessions) PR programme, which was relatively shorter than the aforementioned study and is one of the strengths of our study.

In another study, the effectiveness of a once-weekly supervised PR programme with a standard twice-weekly program was compared; the once-weekly supervision yielded equivalent improvements in the exercise tolerance as the twice-weekly program [36]. However, the health-related QoL outcomes were poorer for once-weekly program in this study. In addition, the aforementioned study did not include transplant candidates. On the basis of the previous findings and our results, we recommend PR programme twice or thrice a week under direct supervision to achieve successful results, as LTx candidates may undergo surgery earlier than expected if an appropriate donor becomes available and because of the possibility of rapid progression of the disease. Similarly, four patients were operated early and excluded from the study as an appropriate donor became available. Of these patients, one attended the PR programme for only for 1 week, whereas the remaining patients were administered the program for approximately 3-4 weeks. Although the duration of PR programme and the number of sessions vary depending on the available means at the facility, PR programme is recommended for LTx candidates, considering its health benefits before and after surgery [5, 6, 12, 14].

Nonetheless, there are some limitations to this study. First, our sample size was small, and the number of the patients decreased throughout the study. Therefore, we were unable to compare the efficacy of short-term and long-term PR programme in our study. Second, we were unable to evaluate emotional aspects and health-related QoL in our study. QoL was also evaluated using the Short Form-36 and completed at baseline for each patient; however, it was not included in the analysis owing to missing data at the end of intervention. We recommend further comprehensive, large-scale, long-term studies to confirm our findings.

The benefits of PR programme have not been well-documented in patients who are on the waiting list for LTx. To date, a few number of studies are available with heterogeneous sampling and nonstandardized protocols [1, 12, 19, 37]. Our study is also consistent with these previous studies with similar limitations.

In conclusion, our study results suggest that an 8-week outpatient-based PR programme consisting of training twice a week under supervision is effective to decrease perceived dyspnea and fatigue and to improve exercise capacity in patients who are on the waiting list for LTx. However, it should be noted that PR programme encompasses the whole period until surgery, and patients should be educated that adherence/compliance to the program would improve the results. Finally, further large-scale, multicenter studies are...
needed to establish the optimal duration and content of a PR programme in LTx candidates.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethic committee of the Istanbul Training and Research Hospital (Date: 14.9.2018; No: 1415).

Informed Consent: A written informed consent was obtained from all patients who participated in this study.

Peer-review: None

Author contributions: Concept - L.K.; Design - L.K., E.P.; Materials - L.K., E.P.; A.B., N.D.B.; Data Collection and/or Processing - L.K., E.P., A.B., N.D.B.; Analysis and/or Interpretation - L.K., E.P.; Literature Search - L.K.; Writing Manuscript - L.K.; Critical Reviews - E.P., N.D.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Florian, J, Rubin A, Mattiello R, et al. Impact of pulmonary rehabilitation on quality of life and functional capacity in patients on waiting lists for lung transplantation. J Bras Pneumol 2013;39:349-56. [CrossRef]
2. Hook JL, Lederer DJ. Selecting lung transplant candidates: where do current guidelines fall short? Expert Rev Respir Med 2012;6:51-61. [CrossRef]
3. Rochester CL. Pulmonary rehabilitation for patients who undergo lung-volume-reduction surgery or lung transplantation. Respir Care 2008;53:1196-202.
4. Foster S, Thomas HM 3rd. Pulmonary rehabilitation in lung disease other than chronic obstructive pulmonary disease. Am Rev Respir Dis 1990;141:601-4. [CrossRef]
5. Pehlvani E, Balci A, Kilic L, et al. Preoperative Pulmonary Rehabilitation for Lung Transplant: Effects on Pulmonary Function, Exercise Capacity, and Quality of Life; First Results in Turkey. Exp Clin Transplant 2018;16:455-60.
6. Ries AL, Bauldoff GS, Carlin BW, et al. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. Chest 2007;131:4-42. [CrossRef]
7. Nici L, Donner C, Wouters E, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 2006;173:1390-413. [CrossRef]
8. Wijkstra PJ, Wempe JB. New tools in pulmonary rehabilitation. Eur Respir J 2011;38:1468-74. [CrossRef]
9. Mathur S, Hornblower E, Levy RD. Exercise training before and after lung transplantation. Phys Sportsmed 2009;37:78-87. [CrossRef]
10. Langer D. Rehabilitation in patients before and after lung transplantation. Respir Physiol Neurobiol 2011;177:189-98. [CrossRef]
11. Glocenk R, Halle M, Kenn K. Interval versus continuous training in lung transplant candidates: a randomized trial. J Heart Lung Transplant 2012;31:934-41. [CrossRef]
12. Li M, Mathur S, Chowdhury NA, et al. Pulmonary rehabilitation in lung transplant candidates. J Heart Lung Transplant 2013;32:626-32. [CrossRef]
13. Rochester CL, Fairburn C, Crouch RH. Pulmonary rehabilitation for respiratory disorders other than chronic obstructive pulmonary disease. Clin Chest Med 2014;35:369-89. [CrossRef]
14. Trojetto T, Elliott RJ, Rashid S, et al. Availability, characteristics, and barriers of rehabilitation programs in organ transplant populations across Canada. Clin Transplant 2011;25:E571-8. [CrossRef]
15. Wickerson L, Rozenberg D, Janaudis-Ferreira T, et al. Physical rehabilitation for lung transplant candidates and recipients: An evidence-informed clinical approach. World J Transplant 2016;6:517-31. [CrossRef]
16. Puente-Maestu L, Sánz ML, Sánz P, et al. Comparison of effects of supervised versus self-monitored training programmes in patients with chronic obstructive pulmonary disease. Eur Respir J 2000;15:517-25. [CrossRef]
17. O’Neill B, McKevitt A, Rafferty S, et al. A comparison of twice-versus once-weekly supervision during pulmonary rehabilitation in chronic obstructive pulmonary disease. Arch Phys Med Rehabil 2007;88:167-72. [CrossRef]
18. Spruit MA, Pitta F, Garvey C, et al. Differences in content and organisational aspects of pulmonary rehabilitation programmes. Eur Respir J 2014;43:1326-37. [CrossRef]
19. Kenn K, Gloeckl R, Soennichsen A, et al. Predictors of success for pulmonary rehabilitation in patients awaiting lung transplantation. Transplantation 2015;99:1072-7. [CrossRef]
20. Vivodtzev I, Pison C, Guerrero K, et al. Benefits of home-based endurance training in lung transplant recipients. Respir Physiol Neurobiol 2011;177:189-98. [CrossRef]
21. Jastrzebski D, Gawlik R, Koziełski J, et al. Dyspnea and quality of life in patients with pulmonary fibrosis after six weeks of respiratory rehabilitation. J Physiol Pharmacol 2006;57:139-48.
22. Johnston CL, Maxwell LJ, Allison JA. Pulmonary rehabilitation in Australia: a national survey. Physiotherapy 2011;97:284-90. [CrossRef]
23. International guidelines for the selection of lung transplant candidates. The American Society for Transplant Physicians (ASTP)/American Thoracic Society(ATS)/European Respiratory Society(ERS)/International Society for Heart and Lung Transplantation(ISHLT). Am J Respir Crit Care Med 1998;158:315-9. [CrossRef]
24. Orenes JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006;25:745-55. [CrossRef]
25. Brooks D, Solway S, Gibbons WJ. ATS statement on six-minute walk test. Am J Respir Crit Care Med 2003;167:1287. [CrossRef]
26. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014;44:1428-46. [CrossRef]
27. Fletcher CM, Elmes PC, Fairbairn AS, et al. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. Br Med J 1959;2:257-66. [CrossRef]
28. Antoniú SA. Descriptors of dyspnea in obstructive lung diseases. Multidiscip Respir Med 2010;5:216-9. [CrossRef]
29. Pehlvani E, Mutluay F, Balci A, et al. The effects of inspiratory muscle training on exercise capacity, dyspnea and respiratory functions in lung transplantation candidates: a randomized controlled trial. Clin Rehabil 2018;32:1328-39. [CrossRef]
30. Büyükkale S, Bakan ND, Isgörücü Ö, et al. Late-breaking abstract: First 24 lung transplantations: Single center results from Turkey. Eur Respir J 2014;44:P2450.
31. Dabak G, Dalar L, Taşçı E, et al. Lung transplantation in Turkey: lessons from surgeons and pulmonologists. Turk J Med Sci 2016;46:1434-42. [CrossRef]
32. Beauchamp MK, Evans R, Janaudis-Ferreira T, et al. Systematic review of supervised exercise programs after pulmonary rehabilitation in individuals with COPD. Chest 2013;144:1124-33. [CrossRef]
33. Ringbaek TJ, Broendum E, Hemmingsen L, et al. Rehabilitation of patients with chronic obstructive pulmonary disease. Exer-
Exercise twice a week is not sufficient! Respir Med 2000;94:150-4. [CrossRef]

34. British Thoracic Society Standards of Care Subcommittee on Pulmonary Rehabilitation. Pulmonary rehabilitation. Thorax 2001;56:827-34. [CrossRef]

35. Holland AE, Hill CJ, Glaspole I, et al. Predictors of benefit following pulmonary rehabilitation for interstitial lung disease. Respir Med 2012;106:429-35. [CrossRef]

36. Liddell F, Webber J. Pulmonary rehabilitation for chronic obstructive pulmonary disease: a pilot study evaluating a once-weekly versus twice-weekly supervised programme. Physiotherapy 2010;96:68-74. [CrossRef]

37. Jastrzebski D, Ochman M, Ziora D, et al. Pulmonary rehabilitation in patients referred for lung transplantation. Adv Exp Med Biol 2013;755:19-25. [CrossRef]