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"Recent Advances in Pulmonary  
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## Review

### Corresponding author

Yosuke Izoë, MD

Professor  
Department of Internal Medicine and  
Rehabilitation Science  
Tohoku University Graduate  
School of Medicine, Sendai, Japan  
Tel. 81-22-717-7353  
Fax: 81-22-717-7355  
E-mail: [yosuke.izoe.d4@tohoku.ac.jp](mailto:yosuke.izoe.d4@tohoku.ac.jp)

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# Rehabilitation in Patients Undergoing Lung Transplantation (LTx)

Yosuke Izoë, MD<sup>\*</sup>; Taku Harada, MD, PhD; Masahiro Kohzuki, MD, PhD

*Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Sendai, Japan*

## ABSTRACT

Lung transplantation (LTx) has become an established therapeutic option for treating patients with end-stage pulmonary disease. Before and after LTx, physical ability might be restricted due to certain effects on respiration, circulation, and skeletal muscles. Severe and chronic lung disease is associated with physiological changes. Limb muscle dysfunction, inactivity deconditioning and nutritional depletion can affect exercise capacity and physical functioning in candidates for LTx. At present, evidence-based guidelines for exercise training completed in the before and after LTx phases have not been described. However, the use of exercise training for chronic respiratory failure conditions such as chronic obstructive pulmonary disease (COPD), interstitial lung disease, and cystic fibrosis has been well-documented. This knowledge could be applied to exercise training problems before and after LTx. Pulmonary rehabilitation (PR) has been proven to be effective for the overall improvement of quality of life (QOL) of patients following LTx. PR can improve exercise capacity and QOL, regardless of the type of exercise that is conducted and the disease background of the patient. There are not many large-scale reports on the effects of exercise therapy before and after lung transplantation. Therefore, it is necessary to study the effects of long-term prognosis after LTx.

**KEY WORDS:** Lung transplantation (LTx); Pulmonary rehabilitation (PR); Quality of life (QOL).

## INTRODUCTION

Lung transplantation (LTx) has become an established therapeutic option for treating patients with end-stage pulmonary disease. The first LTx was performed by Hardy at the University of Mississippi, Mississippi, USA in 1963.<sup>1</sup> By 1978, 38 cases of LTx had been performed; however, there were only three survivors over one month after LTx. Cyclosporine has had a major impact on long-term survival after LTx.<sup>2</sup> Cyclosporine was first used for LTx in 1983 at the University of Toronto, Toronto, Canada. Since then, LTx has spread rapidly worldwide.<sup>3</sup> Today, 4,000 cases of LTx are performed annually in Europe and the United States. Furthermore, to date, the number of completed LTx cases has exceeded the cumulative total of 50,000.<sup>4</sup> However, because of difficulties in the acceptance of brain death, the clinical application of LTx was delayed in Japan. The Japanese brain death act for organ transplantation first came into effect in October 1997. The first lung transplants from living donors were successfully performed in Japan in 1998. LTx from a brain-dead cadaver donor (BDCD) was first completed in our country in 2000. A modified Japanese transplantation law has been enforced since July 2010; thereafter, an increase in the number of cadaveric organ transplantations has been achieved. BDCDs were included in 49 transplantation cases in 2016, the largest annual number to date. A total of 332 cadaveric lung transplantation (174 single, 158 bilateral) and, 198 living-donor lobar lung transplantation procedures were performed by the end of 2016. By the end of 2015, 5-year and 10-year survival rates of cadaveric lung transplantations were 72.1% and 58.8%, respectively, which were superior to those noted in the International Registry (53.0% and 31.0%, respectively). Additionally, 5-year and 10-year survival rates of living-donor lobar transplantations were similar to those of cadaveric lung transplantations, at 71.7% and 65.9%,

respectively. However, at present, living-donor lobar transplantations are rarely performed in Europe and the United States. Performing lung transplantations in patients with advanced lung disease is becoming more feasible, especially in those individuals with chronic respiratory failure, cardiovascular risk factors, or muscular and nutritional conditions, all of which are factors that can influence the prognosis of successful lung transplantation. Therefore, pulmonary rehabilitation (PR) is an important process that focuses on avoiding comorbidities and complications.

**REHABILITATION**

Most PR program are fashioned in accordance with the American College of Sports Medicine (ACSM) guidelines, which recommend that patients with chronic diseases participate in aerobic exercise, resistance training, flexibility training, and muscular activities. In general, PR exercise follows the principles of exercise prescription guidelines from the ACMS, which is a methodology based on frequency, intensity, time, and type of activity. Intensity is based on a rated perceived exertion or on 60% to 80% of peak work rate if results from an exercise test are available. The PR program typically must be individualized and the modality and intensity of training tailored for each patient.

Before and after LTx, physical ability might be restricted due to certain effects on respiration, circulation, and skeletal muscles. Severe and chronic lung disease is associated with physiological changes. Limb muscle dysfunction, inactivity deconditioning and nutritional depletion can affect exercise capacity and physical functioning in candidates for LTx.<sup>5</sup> After LTx, extended intensive care unit (ICU) and hospital stays, prolonged sedentary time and persisting inactivity, the use of immunosuppressant medications and episodes of organ rejection might affect lung recipients' recovery in terms of their exercise tolerance and quality of life (QOL).

LTx recipients often experience persistent impairments in exercise capacity and skeletal muscle function despite a vast improvement in lung function after transplantation. Rehabilitation might be beneficial in improving exercise capacity in lung transplant recipients. At present, evidence-based guidelines for exercise training completed in the before and after LTx phases have not been described. However, the use of exercise training for chronic respiratory failure conditions such as chronic obstructive pulmonary disease (COPD), interstitial lung disease, and cystic fibrosis has been well-documented. This knowledge could be applied to exercise training problems before and after LTx.<sup>6</sup> A systematic review has reported an examination of the evidence for rehabilitation on functional outcomes in lung transplant recipients.<sup>7</sup> There are also reports that exercise training has improved exercise capacity in lung transplant recipients (Table 1).<sup>8-10,12-14</sup> There were a variety of study designs, including one controlled trial and five prospective cohort studies. Outcome measures included spirometry six-minute walk test (6MWT),<sup>10,14</sup> quadriceps and handgrips force (QF and HGF),<sup>9,10</sup> health-related QOL,<sup>14</sup> maximal oxygen consumption (VO<sub>2max</sub>), and VO<sub>2peak</sub>.<sup>8,9,12</sup> peak power output,<sup>8</sup> endurance time,<sup>13</sup> and additional measures of hemodynamic responses<sup>12</sup> to exercise and mitochondrial bioenergetics.<sup>13</sup> Six studies<sup>8-10,12-14</sup> included aerobic exercise, and two studies included both aerobic and resistance exercise. In these studies, exercise tolerance was improved. In addition, the presence of osteoporosis accompanying long-term oral administration of steroid drugs helps to uncover the effectiveness of resistance exercises in randomized controlled trials (RCTs).<sup>15</sup>

**Rehabilitation before LTx**

Rehabilitation is important in the preoperative management of patients.<sup>17</sup> Before LTx rehabilitation can help individuals to maintain or optimize their functional status before undergoing surgery.<sup>18</sup> The importance of pretransplant rehabilitation has been shown in the latest joint American Thoracic Society/Euro-

**Table 1:** Summary of Studies.

| Author                             | Study design       | Sample size | Interventions                                 | Outcome measures                                | Findings   |
|------------------------------------|--------------------|-------------|---|---|--|
| Ross et al <sup>12</sup>           | Prospective cohort | 8           | Aerobic exercise                              | VO <sub>2max</sub> , hemodynamic responses      | Increased VO <sub>2max</sub>                                     |
| Stiebellehner L et al <sup>8</sup> | Prospective cohort | 9           | Aerobic exercise                              | VO <sub>2max</sub> , W <sub>peak</sub>          | Significant Increase in VO <sub>2max</sub> and W <sub>peak</sub> |
| Guerrero et al <sup>13</sup>       | Controlled trial   | 12          | Aerobic exercise                              | Mitochondrial respiration                       | Significant Increase in Bioenergetics at cellular level          |
| Maury G et al <sup>10</sup>        | Prospective cohort | 36          | Aerobic and resistance exercise               | 6MWD, QF, HGF, FEV <sub>1</sub>                 | Significant Increase in 6MWD, QF, HGF                            |
| Munro et al <sup>14</sup>          | Prospective cohort | 36          | Aerobic and resistance exercise and education | 6MWD, FEV <sub>1</sub> , FVC, SF36              | Significant Increase in 6MWD, FEV <sub>1</sub> , and FVC         |
| Vivodtzev et al <sup>9</sup>       | Prospective cohort | 12          | Aerobic exercise                              | VO <sub>2max</sub> , T <sub>end</sub> , VE, QF, | VO <sub>2max</sub>   |

6MWD: Six-minute walk distance; FEV<sub>1</sub>: Forced expiratory volume in one second; FVC: Forced vital capacity; HGF: Handgrip force; QF: Quadriceps force; RCT: Randomized controlled trial; SF36: Short-form 36 questionnaire; VO<sub>2max</sub>: Maximal oxygen consumption ; w, workload.

pean Respiratory Society (ATS/ERS) official statement on pulmonary rehabilitation.<sup>20</sup> Rehabilitation can provide patients with a comprehensive knowledge base regarding the upcoming surgery, potential complications, and the impact of post-operative medications.<sup>18</sup> The ideal content of education and exercise training before LTx has been proposed by Rochester et al (Tables 2 and 3).<sup>16</sup> Patients in the phase before LTx are intervened with respiratory rehabilitation for each pulmonary disease. Before LTx, while patients were waiting for surgery, rehabilitation was found improve exercise tolerance and activity of daily living (ADL), without any significant change in respiratory function.<sup>11</sup> Patients with severe pulmonary disease are typically unable to perform aerobic exercise. Such patients are encouraged to acquire ADL. Additionally, performing exercise using lower muscular strength is tolerated well by this patient population, while performing upper limb training using an upper limb ergometer might lead to difficulty breathing. This is because upper limb exercise can be difficult to synchronize with the breathing. Exercise therapy should include warm-up and cool-down period of about 5 to 10 minutes, as well as stretching and joint range of motion training.<sup>6</sup>

**Rehabilitation after LTx**

The importance of acute phase rehabilitation performed in the ICU has been recognized.<sup>20,21</sup> Early post-operative rehabilitation is very important. Decrease of muscle mass and muscle strength occur early after admission to the ICU, and are associated with

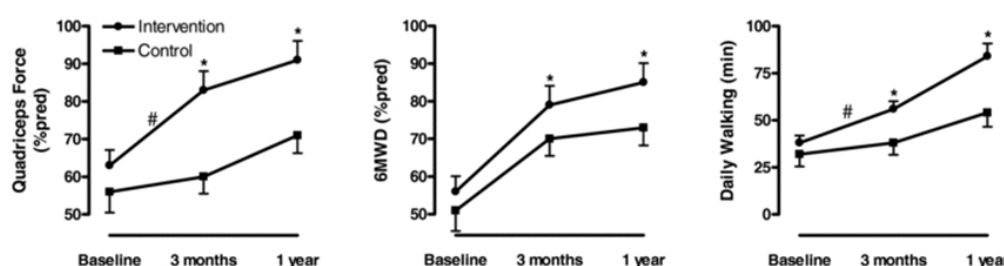
long-term functional disability, and increased mortality.<sup>22</sup> Thus, early active muscle training prevents ICU-acquired weaknesses from increasing. Active lower limb resistance training has previously been proved to be an effective and feasible treatment option for severely disabled patients.<sup>23</sup> When patients are discharged from the ICU, a more active rehabilitation approach should be sought mainly with respect to building sufficient lower extremity strength, balance and gait to ensure patient safety and to minimize the risk of falls prior to hospital discharge. The suggested content of rehabilitation during hospitalization after LTx is summarized in Table 4.<sup>16</sup> At one year after transplantation, exercise tolerance typically improves. However exercise tolerance is remarkable ever in the first three months (Figure 1).<sup>16</sup> After LTx, ventilator disability improves. However, exercise capacity has been found to be lower than the predicted value as compared with one year after LTx.<sup>16</sup> In general, exercise limitations after LTx not only decrease respiration and circulation but also decrease the utilization rate of oxygen supply and its uptake in muscles.<sup>27</sup> After transplantation, it is important for exercise therapy at home to give guidance about continuing exercise (Table 5).<sup>29</sup> Following transplantation, it should be noted that osteoporosis can be caused because of a decrease in bone density due to lack of physical activity. Therefore, these patients are at a higher risk for fractures. For preventing osteoporosis, administration of bisphosphonate and resistance exercise are considered useful. Balance training is also effective for reducing the risk of falls and fractures. However, patients at a high risk of falling should

| <b>Table 2:</b> Elements of Educational Content of Rehabilitation before LTx. <sup>16</sup> |
|---|
| Educational topics before transplantation   |
| Familiarization with the surgical procedure   |
| Preparation for the perioperative period  |
| - Secretion management  |
| - Controlled coughing techniques  |
| - Chest tubes   |
| - Wound and pain management   |
| - Importance of early mobilization  |
| Disease-specific educational topics   |
| - Anatomic and physiologic basis of symptoms  |
| - Importance and proper use of supplemental oxygen therapy                                  |
| - Management of daily activities: pacing energy conservation and when to stop exercise      |

| <b>Table 3:</b> Elements of Exercise Training during Rehabilitation before LTx. <sup>16</sup>   |
|---|
| - Begin with initial evaluation that examines hemodynamic stability, oxygen requirements, bone health, body mass index, medical comorbidities, respiratory mechanics, and overall functional capacity |
| - Complete patient assessment using psychological, health related and generic (e.g., SF-36) QOL measures, shortness-of-breath questionnaires, manual muscle testing, and 6MWD.                        |
| - PR should consist of exercise training, including progressive aerobic exercise and upper/lower extremity strengthening under close supervision and continuous monitoring.                           |
| - Exercise should begin at low intensity and be progressed gradually to the highest capacity tolerated by the individual, maintaining adequate oxygenation during activity.                           |
| - Place strong emphasis on patient/caregiver education, as well as psychological, dietary and occupational therapy support.   |
| - Frequent reassessments are necessary because of the progression of the underlying lung disease; close communication with patients' health care providers outside PR is essential.                   |

| Table 4: Elements of Rehabilitation during Hospitalization after LTx. <sup>16</sup>  |
|--|
| - Begin approximately 24 h post-operatively, with an emphasis on early mobilization (e.g., bed cycle, neuromuscular electrical stimulation), breathing exercise, secretion clearance, and posture improvement.                                   |
| - Early in-patient post-operative rehabilitation should include breathing retraining, reassessing supplemental oxygen requirements, balancing activities, building upper and lower extremity range of motion, and managing any neuropathic pain. |
| - Because of incisional pain and the denervated cough reflex of the donor lung, patients require direction and encouragement to cough.   |
| - At a later stage, begin with transfers from bed to chair and start ambulation using a specialized walker, with careful management of chest tubes and pain.   |
| - Exercise progression should gradually incorporate lower limb resistance training.  |
| - Lifting and upper limb range of motion precautions and limitations persist up to 6 weeks post-operatively dependent on the type of surgical approach.  |
| - Ensure that lower extremity strength, balance, and gait are sufficient to ensure patient safety and minimize the risk of falls before hospital discharge.  |
| - Necessary medical and adaptive equipment should be provided at discharge.  |

Figure 1: Progression of Quadriceps Force, Six-Minute Walking Distance (6MWD) and Daily Walking Time during the Intervention Period (Baseline to 3 Months Post-operation), and During the Follow-up Period (3 months to 1 year post operation).<sup>24</sup>



\*significant difference between the groups; #significant difference in slopes between the groups.

Table 5: Example Exercise Therapy Regimens Performed at Home after LTx.<sup>29</sup>

|                  | Recommended  | Comment   |
|------------------|--|---|
| Frequency • time | Four to five times per week<br>30 minutes per time   | Continuous exercise   |
| Intensity        | Set the target heart rate in 6-minute walking distance or cardiopulmonary exercise testing | <ul style="list-style-type: none"> <li>Regularly evaluate and adjust exercise prescription</li> <li>one year after LTx, exercise tolerability improves</li> <li>Decrease of muscle condition and muscle atrophy cause limitation of exercise</li> </ul> |
| Type             | Treadmill exercise, bicycle ergometer, upper limb ergometer                                | Increase anaerobic metabolism threshold   |

be watched over during training. Importantly, it is also key to continue exercise while enjoying it.

**QOL IN PATIENTS WITH LUNG TRANSPLANTATION (LTx)**

Pulmonary rehabilitation has been proven to be effective for the overall improvement of QOL of patients following LTx. The improvement of QOL is dependent on the incidence of post-operative complications, including infections and rejections, which can lead to increased physical restrictions in addition to symptoms of depression and anxiety.<sup>29,31</sup> After LTx, pulmonary function is generally improved; however, patients may continue to have significant limitations as the result of general deconditioning, poor strength, and other peripheral factors, with physiological changes associated with post-transplantation medications

compounding this effect.<sup>32</sup> Traditionally, outcome measurements after LTx have been primarily based on survival and pulmonary function recovery. However, in recent years, increasing attention has been given to assessment of survival and recovery, with particular importance given to patients' self-evaluations of health-related quality of life (HRQOL) after the transplant procedure.<sup>34,35</sup> HRQOL has been reported by several investigators to improve significantly within the first few years after LTx.<sup>35,36</sup> Beyond two years after LTx-the frame in which any major clinical complications to occur may begin to develop and threaten the patients recovered autonomy-HRQOL declines again. Furthermore, many investigators have shown that exercise capacity continues to be impaired after LTx despite the removal of limitations.<sup>37,38</sup> Peripheral factors limiting exercise capacity are almost universally seen and are attributed to multiple factors, including

the myotoxic effects of immunosuppressants and deconditioning.<sup>39</sup>

#### A PROBLEM TO BE SOLVED

There are not many large-scale reports on the effects of exercise therapy before and after lung transplantation. PR can improve exercise capacity and QOL, regardless of the type of exercise that is conducted and the disease background of the patient. Comprehensive respiratory rehabilitation in combination with exercise therapy and education has also been shown to improve exercise tolerability and HRQOL.<sup>14</sup> However, it has been reported that after LTx, the rate of return to work is low. It has already been reported that depression can result in a decrease in QOL.<sup>41</sup> In future, it is necessary to consider the effects of psychotherapy, psychological support, and behavioral therapy for depression on patients after LTx. It is reported that it is necessary to evaluate QOL by increasing the number of cases and continuing examine appropriate evaluation methods.<sup>40</sup> This has been shown to increase the effectiveness of exercise therapy for LTx. Therefore, it is necessary to study the effects of long-term prognosis after LTx.

#### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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