


Addressing the changing rehabilitation needs of patients undergoing thoracic surgery

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Abstract

The rehabilitation needs of individuals undergoing thoracic surgery are changing, especially as surgical management is increasingly being offered to patients who are at risk of developing functional limitations during and after hospital discharge. In the past rehabilitative management of these patients was frequently limited to specific respiratory physiotherapy interventions in the immediate postoperative setting with the aim to prevent postoperative pulmonary complications. In the past two decades, this focus has shifted toward pulmonary rehabilitation interventions that aim to improve functional status of individuals, both in the pre- and (longer-term) postoperative period. While there is increased interest in (p)rehabilitation interventions the majority of thoracic surgery patients are however currently on their own with respect to progression of their exercise and physical activity regimens after they have been discharged from hospital. There are also no formal guidelines supporting the referral of these patients to outpatient rehabilitation programs. The current evidence regarding rehabilitation interventions initiated before, during, and after the hospitalization period will be briefly reviewed with special focus on patients undergoing surgery for lung cancer treatment and patients undergoing lung transplantation. More research will be necessary in the coming years to modify or change clinical rehabilitation practice beyond the acute admission phase in patients undergoing thoracic surgery. Tele rehabilitation or web-based activity counseling programs might also be interesting emerging alternatives in the (long-term) postoperative rehabilitative treatment of these patients.

Keywords

Rehabilitation, thoracic surgery, postoperative pulmonary complications, functional limitations, lung cancer, lung transplantation, physical activity, exercise training

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Introduction

Rehabilitation can play an important role in the management of patients undergoing thoracic surgery. In the past rehabilitative management of these patients was frequently limited to specific respiratory physiotherapy interventions in the immediate postoperative setting with the aim to prevent postoperative pulmonary complications.¹ The rehabilitation needs of individuals undergoing thoracic surgery are changing however, especially as surgical management is being offered to older individuals and people with

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Table 1. Published risk factors for developing a postoperative pulmonary complication, categorized into patient factors and procedure factors, further divided into non-modifiable and modifiable.

	Patient Factors	Procedural Factors
Modifiable	<ul style="list-style-type: none"> – Frailty – $\text{VO}_2\text{max} < 15 \text{ ml/min/kg}$ – $\text{BMI} < 18.5$ or $> 40 \text{ kg/m}^2$ – Smoking 	<ul style="list-style-type: none"> – Mechanical ventilation strategy – General vs regional anesthesia – Open abdominal vs laparoscopic surgery
Non-Modifiable	<ul style="list-style-type: none"> – Age – Chronic organ failure – Hypertension – Malignancy 	<ul style="list-style-type: none"> – Duration of procedure – Type of surgery (e.g. thoracic or upper abdominal) – Emergency vs elective surgery

chronic diseases, (multiple) organ failure, and comorbidities. In the past two decades the focus has therefore gradually shifted to pulmonary rehabilitation interventions that aim to improve functional status of individuals, both in the pre- and (longer-term) postoperative period.²⁻⁴

Postoperative pulmonary complications (PPC) such as atelectasis, bronchospasm and pneumonia, remain the most common acute postoperative problem in this population.⁵ While the way in which PPCs are defined varies enormously depending on the scoring system used,⁶ they are typically defined as a “pulmonary abnormality that produces identifiable disease or dysfunction that is clinically significant and adversely affects the clinical course of recovery.”⁷ The development of a PPC can negatively impact on patient outcomes, hospital length of stay and survival. Several physiological changes occur as a result of the systemic inflammatory burden of surgery, as well as effects of anesthesia which can contribute to the development of PPC in patients who are at risk.² These physiological changes include, but are not limited to, reductions in lung volumes, impaired gas exchange, alteration in mucociliary function and diaphragmatic dysfunction.² A number of risk factors, both patient related and procedure related have been identified over the years (see Table 1). Some of these risk factors are modifiable by (p)rehabilitative interventions or adaptations in surgical procedures.

Non-modifiable patient related risk factors include the presence of morbidities such as chronic organ failure, hypertension, or obstructive sleep apnea, as well as the presence of malignancies, and older age.⁸ Modifiable patient related risk factors include functional dependence and physical frailty, sarcopenia, reduced physical fitness as identified by cardiopulmonary exercise testing,⁹ and low ($\text{BMI} < 18.5 \text{ kg/m}^2$) or high ($\text{BMI} > 40 \text{ kg/m}^2$) body mass.¹⁰ Non-modifiable

procedural risk factors mostly relate to the type of surgery performed with thoracic and high abdominal surgery, as well as emergency surgery (in comparison to elective surgery) constituting an elevated risk level.⁸ Modifiable procedural risk factors are primarily related to ventilation and sedation regimens applied during surgery, as well as fluid management approaches.⁸ It is important to mention in this context that the introduction of video-assisted thoracic surgery and “fast track” postoperative management has changed the physiotherapy management in this patient population.² These recent developments will probably make it even more relevant to identify and target treatments to patients who are at highest risk to develop acute complications and/or those who are at risk to remain functionally limited after hospital discharge. A recent systematic review evaluated 11 categories of perioperative care interventions that have been tested in randomized controlled trials with the aim of reducing postoperative pulmonary complications.¹¹ While none of the interventions was supported by high level evidence the protective effects of both goal directed fluid therapy and lung protective intraoperative ventilation are supported by moderate quality evidence. In addition, five other interventions are currently supported by low quality evidence.¹¹ These treatments include enhanced recovery pathways, prophylactic respiratory physiotherapy, prophylactic mucolytics, postoperative CPAP ventilation, and epidural analgesia.¹¹ Incentive spirometry seems not to offer additional benefits beyond standard chest physiotherapy in preventing postoperative pulmonary complications.¹¹

Prehabilitation and rehabilitation in the immediate postoperative period

In recent years there is renewed interest in preoperative rehabilitation to improve the capacity of patients

at risk to withstand anticipated physiological stressors induced by the surgical procedure.² Preoperative interventions typically include elements of patient education, providing assistance in stress and anxiety management, as well as specific rehabilitation strategies including aerobic and resistance training, inspiratory muscle training, as well as (pre-op instructions for) postoperative breathing exercises to prevent atelectasis.² Recent systematic reviews have demonstrated that rehabilitation programs including at least moderate intense aerobic exercise prior to surgery can improve exercise capacity and reduce PPCs and other postoperative complications by about 50%, as well as reducing hospital length of stay in high risk lung cancer surgery populations.^{4,12,13} There is also interest in models such as “surgery school” which combine different interventions including education, early ambulation, breathing exercises, and advice for staying well on discharge.¹⁴ Post operatively it is nowadays routine clinical practice to provide early mobilization and respiratory interventions as part of clinical pathways such as the “Enhanced Recovery After Surgery (ERAS)” program.² Unfortunately, however a majority of patients does not receive any ongoing dedicated rehabilitation care after the immediate postoperative period.² The database of RCTs that have investigated the impact of exercise training both in the immediate postoperative period following thoracic surgery (i.e. lung resection) and following discharge from hospital is at this moment very limited.^{1,2} One RCT evaluated the effectiveness of prophylactic postoperative respiratory physiotherapy for patients undergoing lung resection (n = 42) compared with a control group (n = 34) to prevent postoperative pulmonary complications.¹⁵ The observed incidence of postoperative pulmonary complications across both groups was very low (~4%) with no differences between groups. All patients in this study were on postoperative pathways similar to the enhanced recovery after surgery (ERAS) program used in abdominal surgery, which probably had an impact on the incidence of postoperative complications in this group.^{2,15} Another more recent RCT evaluated the effect of in-hospital physiotherapy treatment on physical recovery and postoperative physical activity levels after lung cancer surgery, compared with an untreated control group.^{16,17} The in-hospital rehabilitative treatment consisted of early mobilization, ambulation, breathing exercises, and thoracic range of motion exercises. While physical fitness for the whole sample was significantly decreased 3 months

postoperatively compared with preoperative values there were no statistically significant differences between the groups regarding physical capacity and physical activity observed. These data indicate a need for more structured and long-term rehabilitation interventions initiated after the immediate postoperative period to improve these outcomes.

Rehabilitation after hospital discharge

These data are also in line with other emerging evidence showing that patients post major surgery continue to present with significant reductions in physical activity, muscle strength and mental well-being in the months after hospital discharge.^{1,18} This is especially true for patients with pre-existing chronic conditions such as COPD and heart failure, patients after solid organ transplantation, and patients undergoing thoracic surgery as part of their malignant chest tumor treatment. It is very likely that these patients could benefit from ongoing rehabilitation support after hospital discharge. Some initial evidence is emerging that these rehabilitation interventions might be effective in this population.¹⁸ The majority of thoracic surgery patients are however currently on their own with respect to progression of exercise and physical activity beyond hospital discharge. There are also no formal guidelines supporting the referral of these patients to outpatient pulmonary rehabilitation programs. Clearly, more research is therefore needed to modify or change clinical rehab practice beyond the acute admission phase in thoracic surgery. Tele rehabilitation or web / app based activity counseling programs might also be interesting alternatives in the long-term postoperative phase. In the following paragraphs evidence in two specific patient groups namely patients after lung transplantation and patients undergoing thoracic surgery as part of their malignant chest tumor treatment will be briefly reviewed in more detail.

Rehabilitation in patients undergoing lung cancer surgery

In addition to its role in the prevention of cancer, accumulating evidence suggests that physical activity in cancer patients and survivors might also contribute to increasing longevity and quality of life.¹⁹ Current guidelines strongly recommend that all cancer survivors should avoid inactivity.²⁰ Physical fitness (i.e. “the maximal ability of a person to perform

activities”) is a well-known predictor of survival in the general population, as well as in chronically diseased populations, and specifically in patients with lung cancer.^{21,22} This suggests an important role for rehabilitative interventions in the comprehensive treatment approach for patients undergoing thoracic surgery for lung cancer. Moreover, different interventions will be needed to adequately address these outcomes. In chronic disease populations, participation in supervised exercise training programs (e.g. as part of an outpatient rehabilitation program) is known to improve physical fitness, but will not necessarily translate into increased participation in daily physical activity. Physical activity coaching interventions on the contrary will increase participation in daily activities but do not necessarily improve physical fitness.²³ In this context it is important to understand that exercise is defined as planned and structured movement intended to improve physical fitness. Exercise is therefore a subcategory of physical activity (i.e. any bodily movement that requires energy expenditure) which needs to be performed at a certain minimal intensity in order to improve the different components of physical fitness (e.g. cardiorespiratory fitness and muscular strength). Other health benefits from regular daily activity can however also be obtained with activities performed at lower intensities (i.e. light or moderate intense physical activities).

Lung cancer is the most commonly diagnosed cancer in men and the third most commonly diagnosed cancer in women,²⁴ with non-small cell lung cancer (NSCLC) being the most prevalent (85% of all lung cancer cases).²⁵ Surgery with or without adjuvant chemotherapy is the recommended treatment in patients with early stage NSCLC (stage I–II). Patients with locally advanced NSCLC (stage III A&B) also often undergo concurrent chemo-radiotherapy. In advanced NSCLC (stage IV), chemotherapy, immunotherapy and/or molecular targeted therapies constitute the first line treatment, mostly followed by a form of maintenance treatment.²⁶ It is challenging to define the optimal treatment choice in patients with NSCLC because of the large heterogeneity in disease stage, pathology, genomic profile, presence of comorbidities and general health status of individual patients. It is clear however that these medical treatments including the surgical procedures will have a potentially large negative effects on both physical fitness and participation in physical activity.^{27,28}

Available research in this area is so far limited. Only one small observational study (n = 28) showed

an impaired (objectively measured) physical activity 6 months after lung resection surgery²⁷ and low levels of physical activity in inoperable patients.²⁹ Lung resection surgery has further been shown to result in reductions in physical fitness that do not fully recover over time.^{27,28} Further, in patients with advanced disease, cancer cachexia associated with muscle wasting is highly prevalent.³⁰ Impairments in physical fitness and muscle wasting combined with high symptom burden are likely associated with avoidance of physical activities. However, an in depth investigation into the specific effects of different treatment regimens on physical activity and physical fitness is currently missing. These data would provide crucial information concerning the needs for rehabilitative interventions. Moreover, it is not known whether in cancer patients and survivors, improving physical fitness or increasing participation in daily physical activities should be the primary treatment target. Priorities might also depend on the disease stages and differences in medical treatments.

In patients curatively treated for lung cancer, current evidence suggests impairments in both physical activity and physical fitness.^{27,28,31} It is however not clear whether restoring physical activity or physical fitness (or both) are required to positively impact outcomes such as quality of life, symptoms, cancer recurrence, and survival. Preliminary data from several small randomized controlled pilot studies on the impact of interventions on physical fitness is available while it is completely lacking for interventions targeting physical activity.¹⁸

Rehabilitation for other groups of patients undergoing oncological surgery

While the most compelling evidence is reported in lung cancer patients, where preoperative exercise was shown to be effective in reducing the rate of post-operative complications and length of hospital stay, for other groups of patients undergoing oncological surgery, the evidence is less compelling.³² In analogy with observations from other groups of patients suffering from cancer a marked loss of muscle mass along with worsening cardiorespiratory fitness and HRQoL during neoadjuvant treatment has been observed in esophagogastric cancer patients.^{33,34} While this provides a strong rationale for pre-surgical interventions in this group there are thus far only limited, albeit encouraging, results on the

feasibility and effectiveness of prehabilitation in these patients.^{35–38} Impairments of physical fitness and HRQoL already present before surgery can be further exacerbated by the surgical procedure, adjuvant chemotherapy and persistent malnutrition.³⁹ It has been observed that impairments of cardiorespiratory fitness persist for up to 2 years after surgical treatment,⁴⁰ muscle mass may continue to decline for up to 1 year after treatment,⁴¹ and HRQoL can remain impaired for years.⁴² While this again provides a strong rationale for post-surgery rehabilitation the (promising) evidence in this area is so far limited. In addition to several small observational studies which make it difficult to separate the effects of the rehabilitative interventions from the natural course of recovery after surgery, there are three recent randomized controlled trials available which indicate feasibility, safety and efficacy of (high intensity) exercise training in the postoperative phase in these patients.^{39,43,44}

Rehabilitation in patients undergoing lung transplantation and lung volume reduction surgery

Lung transplantation is an established treatment for patients with end-stage lung disease.⁴⁵ During the last two decades, considerable advances in organ preservation, surgical techniques, immunosuppression and antibiotic therapy have contributed to improvements in postoperative survival.⁴⁶ In response to this there is an increase interest in the need to further improve physical fitness, independent functioning, participation in daily activities and quality of life in these patients.^{47–49}

It has been observed that limitations in exercise capacity and reductions in quality of life often persist in the years following lung transplantation despite of near normal pulmonary function.^{47,48,50–57} Many patients also keep reporting limitations in daily physical functioning after surgery.^{47,48} This highlights the importance of extra-pulmonary factors in contributing to persisting impairments in physical functioning in these patients.⁵⁸ Several of these extra-pulmonary factors can be improved by well-designed rehabilitation interventions. Important aspects that contribute to impairments in physical functioning in candidates for lung transplantation and lung volume reduction surgery include limb muscle dysfunction, inactivity, deconditioning, and nutritional depletion.⁵⁹ Following surgery, extended hospital and intensive care unit length of stay, prolonged sedentary time and

persisting inactivity, as well as immunosuppressant medications and episodes of organ rejection in lung recipients may all affect the lung recipients' recovery in terms of exercise tolerance and quality of life.⁵⁹

Accelerometer data have revealed that candidates for lung transplantation are markedly inactive in daily life.^{60,61} After a further decrease during hospitalization and inactivity comparable to pre-transplant values immediately following hospital discharge,^{62,63} participation in daily activities increases, but remains reduced in comparison with healthy age-matched controls up to 1 year post-transplant (Figure 1).^{63,64} This sedentary behavior is associated with impairments in physical fitness and health related quality of life.^{63,64}

Exercise intolerance and functional disability also often persist following LVRS. Several factors probably contribute to this continued impairment, including baseline skeletal muscle dysfunction, time needed to achieve postoperative improvement in lung function (peak benefit following LVRS at 6–12 months after surgery), inactivity/immobility associated with the perioperative period, and/or time recovering from any complications.⁵⁸ Moreover in contrast with lung transplantation restoration of pulmonary function will not be complete often resulting in persisting ventilatory limitations to exercise and persisting symptoms of exertional dyspnea in these patients. These factors might necessitate adaptations to exercise programs similar to those applied in patients prior to surgery in order to enable offering sufficiently intense training stimuli to the targeted muscle groups.^{58,65} Reducing ventilatory requirements of exercises can be achieved by either reducing the number of muscle groups involved during aerobic or resistance type exercises or by reducing the duration of high intensity exercise bouts by applying interval type exercise.^{58,65}

Increased participation in daily physical activity and exercise after transplantation might be beneficial to improve exercise capacity and to reduce the risk of developing some highly prevalent morbidities after solid organ transplantation, such as osteoporosis, muscle dysfunction, as well as metabolic and cardiovascular abnormalities.⁴⁶ Weight gain after the procedure is a common problem, and metabolic as well as cardiovascular morbidities such as hypertension, diabetes, dyslipidemia, and hyperglycemia rank among the five most common morbidities after lung transplantation.^{46,66} There is some preliminary evidence from small single center studies available showing that either exercise training or participation in regular physical activity may be effective

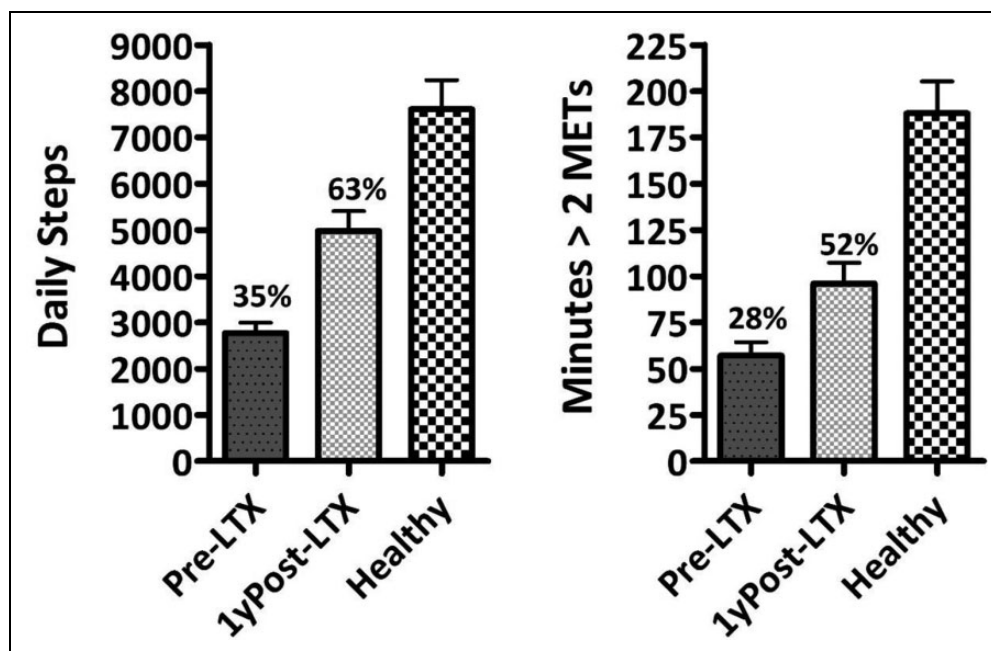


Figure 1. Participation in daily physical activity in patients before (Pre-LTX) and 1 year after (1yPost-LTX) lung transplantation in comparison with healthy, age-matched control subjects (Healthy). Daily step count is illustrated in the left panel and time spent in at least light intense activities requiring more than two metabolic equivalents (METs) is summarized in the right panel. Percentages given above Pre-LTX and 1yPost-LTX columns refer to averages in these groups expressed relative to healthy controls. Graphs constructed with data from previous studies.^{60,64}

treatments to reduce the incidence of the metabolic syndrome in transplant recipients.⁶⁷ Increased participation in physical activity and associated health effects can either be achieved by supervised exercise training interventions in the early post-transplant period or by lifestyle physical activity programs, such as for example pedometer-based walking interventions, in the later post-transplant period.⁶⁸

Rehabilitation plays an important role in the preoperative management of patients. Pre-transplant pulmonary rehabilitation can help individuals to maintain or optimize their functional status before surgery.^{69,70} This seems valuable given the observed further reductions in peripheral muscle strength, and slow spontaneous recoveries of exercise capacity and physical activity that are observed in the immediate postoperative phase following hospital discharge (up to 12 months post-transplant) (Figures 2 and 3).^{60,62,63,71}

Exercise prescription in all stages should be individualized, include both aerobic and resistance training, and follow general exercise training principles of specificity, overload and progression.^{72,73} In addition, rehabilitation can provide patients with a comprehensive knowledge base regarding the upcoming surgery, instructions on how to prevent the occurrence of postoperative pulmonary complications, and the impact of

postoperative medications.^{58,70,73} Since impaired exercise capacity is a predictor of thoracic surgery outcomes and survival, rehabilitation might have the potential to improve surgical outcomes.⁵⁸ The potential benefits of pre-transplant rehabilitation are also acknowledged in the latest joint official ATS/ERS statement on pulmonary rehabilitation.⁶⁶ Despite of the high disease and symptom burden in candidates for lung transplantation pre-transplant rehabilitation has consistently been shown to be feasible and capable of improving functional exercise capacity and quality of life if offered appropriately.^{69,74,75} In a cohort of 345 candidates for lung transplantation Li and colleagues found that every 100-m increase in 6-minute walking distance was associated with a 2.6 day decrease in median hospital length of stay.⁷⁶ No formal guidelines exist regarding the optimal content of rehabilitation programs for patients preparing for lung transplantation. In the absence of comparative studies it is therefore advised to follow general recommendations for outpatient pulmonary rehabilitation programs.⁶⁸ Inspiratory muscle training might also be useful in selected patients with pronounced inspiratory muscle weakness.⁶⁸ The specific role of resistance training (possibly combined with nutritional interventions) particularly in frail patients in

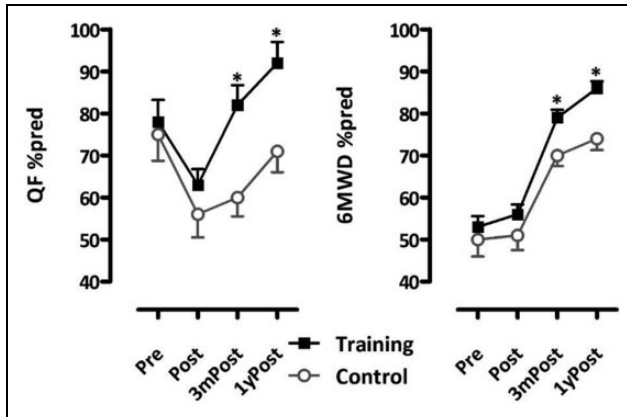


Figure 2. Maximal isometric quadriceps strength (QF, left panel) and 6-minute walking distance (6MWD, right panel) expressed as percentage of normative reference values specific to demographic characteristics of participants (%pred) in a cohort of patients that was longitudinally assessed before (Pre), immediately following hospital discharge after (Post), 3 months (3mPost), and 12 months (1yPost) after lung transplantation. One part of this cohort was randomly allocated to receive a supervised exercise training program during the first 3 months following hospital discharge (Training), the other group (Control) received usual care. Graphs constructed with data from previous study.⁶³

the pre-surgical phase, and the impact of this intervention on post-transplant recovery, has not been sufficiently explored so far and deserves further study.⁵⁹

The importance of early mobilization immediately following surgery is increasingly recognized.^{77,78} It is recommended to begin as early as possible with an emphasis on early mobilization (e.g. upright positioning, passive or active leg cycling, mobilization out of bed, resistance training of legs or neuromuscular electrical stimulation), breathing exercises, secretion clearance, and posture improvement.⁶⁷ Reductions in muscle mass and muscle strength occur early after admission to the ICU and are associated with long-term functional disability,⁷⁹ and increased mortality.⁸⁰ Early active muscle training is therefore an ideal treatment to attenuate this intensive care unit-acquired weakness.⁶⁸ After leaving the ICU a progressively more active treatment approach should be adopted focusing mainly on building sufficient lower extremity strength, balance, and gait to ensure patient safety and minimize the risk of falls prior to hospital discharge.⁶⁸ Preliminary data from retrospective cohort studies suggest that multidisciplinary inpatient rehabilitation might be a viable treatment option for

debilitated patients following heart and/or lung transplantation.^{81,82}

Despite of the documented persistence of physical impairments, increased risks for metabolic as well as cardiovascular morbidities, and the general belief that exercise training has the potential for both short- and long-term benefits in this population, there is a lack of randomized controlled trials on exercise training following hospital discharge for solid organ and lung transplant recipients.^{59,68,83} In a systematic review examining the health benefits and risks associated with exercise following solid organ transplantation only 15 RCTs were identified across kidney, liver, heart, and lung transplant populations.⁸⁴ While acknowledging the potential benefits of (p)rehabilitation in lung transplantation another recent systematic review identified only one RCT among 9 pre-transplant studies and another single RCT among 11 post-transplant studies.⁸⁵

In summary there are indications from a limited number of small, single center studies that outpatient rehabilitation involving supervised exercise training might be beneficial for patients to improve clinically relevant outcomes both in the pre- and post-transplant phase.⁶⁸ This is however only supported by low quality evidence and none of the existing RCTs measured effects of exercise training on crucial long-term outcomes such as sustained improvements in QOL and participation in daily activity, survival, incidence of metabolic and cardiovascular morbidities and cost-effectiveness.^{59,86} Sufficiently powered, high quality, multicenter RCTs are needed to address these important issues.⁶⁸ Cohort studies in this patient group offer limited information because of the considerable spontaneous improvements across outcomes that is typically observed in the immediate post-transplant phase.⁶⁸

Home-based training with remote monitoring via tele-health platforms might be a useful alternative to fully supervised outpatient rehabilitation programs in the long-term follow up of these patients.⁸⁷ During home-based telerehabilitation programs patients undergo supervised rehabilitation often using video-conferencing and sometimes using telemonitoring of physiological signals like oxyhaemoglobin saturation and pulse rate. Promising initial results have been obtained applying these techniques.^{88,89} Recent studies investigating different platforms for web-based telerehabilitation, have reported that online pulmonary rehabilitation had similar benefits to center-based pulmonary rehabilitation program in people with

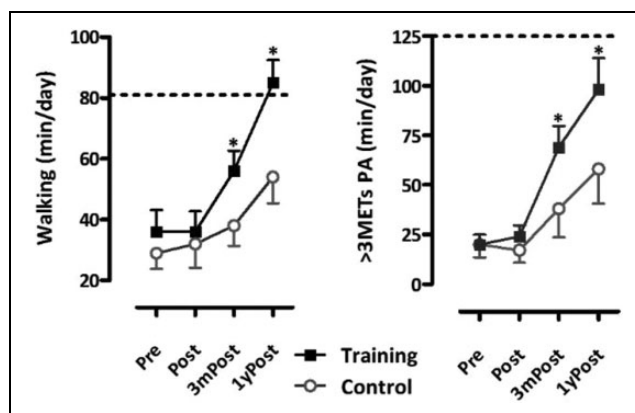


Figure 3. Daily time spent walking (Walking, left panel) and daily time spent in moderate intense activities requiring at least three metabolic equivalents (>3METs PA, right panel) in a cohort of patients that was longitudinally assessed before (Pre), immediately following hospital discharge after (Post), 3 months (3mPost), and 12 months (1yPost) after lung transplantation. One part of this cohort was randomly allocated to receive a supervised exercise training program during the first 3 months following hospital discharge (Training), the other group (Control) received usual care. Dashed lines represent average values observed in healthy, age-matched control subjects. Graphs constructed with data from previous studies.^{60,63,64}

COPD.^{90,91} While initial results of these studies seem promising, cost-effectiveness and acceptance rates on a larger scale still remain to be established.⁹² Center-based telerehabilitation approaches can be especially attractive in situations when large distances have to be covered by patients to attend supervised outpatient programs.⁶⁸ A Canadian model using videoconferencing to support local health professionals at remote sites to deliver effective exercise training has shown promising results.⁹³

The effects of pedometer-based activity coaching programs might be another interesting alternative to supervised exercise interventions since exercise intolerance and physical inactivity can persist for several years following successful surgery. Literature on effective interventions to increase physical activity are scarce in this population. One ongoing project (ClinicalTrials.gov Identifier: NCT04122768) aims to test the effectiveness of a tele coaching program to enhance physical activity and to analyze the association between physical activity and long-term health benefits in this population at risk. The program is based on an activity coaching application that has previously been successfully applied in patients with chronic obstructive pulmonary disease.^{94,95}

Rehabilitation for patients with chronic thromboembolic pulmonary hypertension undergoing pulmonary endarterectomy

Despite of severe symptoms and limitations in exercise capacity, until recently physical activity including exercise training has often been discouraged in patients with pulmonary artery hypertension, particularly in those with more advanced disease due to safety concerns.⁹⁶ In the meantime, however, exercise training has been shown to be safe and efficacious in these patients,⁹⁷ and international guidelines recommend its use in experienced centers for patients who are clinically stable and on optimal pharmacological treatment.⁹⁶ It has further been observed that after successful pulmonary endarterectomy surgery, patients can still have limited exercise capacity,⁹⁸ especially if pulmonary hemodynamics do not completely normalize.⁹⁹ Only two uncontrolled studies have so far explored the effects of postoperative exercise training in these patients.^{100,101} Despite some promising initial results more rigorous studies including randomized controlled trials will be needed in the coming years to determine the efficacy of exercise training in patients after pulmonary endarterectomy.

Conclusions and research needs

There is an urgent need to develop evidence-based clinical pathways to offer support to patients undergoing thoracic surgery starting from the time of diagnosis until their re-integration in the community setting.¹⁸ To achieve this, there is a need to continue to better understand the risk profile of those patients who are likely to remain functionally impaired after hospital discharge. There is also an urgent need to determine optimal exercise training parameters and modalities across the continuum of rehabilitation care for patients undergoing major thoracic surgery. Clinical practice should continue to evolve and progress from interventions that are prophylactic and precautionary to treatments that specifically target perioperative recovery by applying preoperative education, postoperative pulmonary complication (PPC) prevention, and treatments targeting musculoskeletal and functional impairments in the long-term postoperative period.² Based on low quality evidence it can be concluded that rehabilitation programs including supervised exercise training can be effective in improving limb muscle dysfunction, exercise

capacity, and quality of life both pre- and post-lung transplantation and in patients undergoing thoracic surgery as part of their lung cancer treatment.^{18,88} Appropriate training parameters in terms of duration, frequency, and intensity seem necessary to achieve improvements in limb muscle function and exercise capacity.⁶⁸ In the absence of comparative studies and sufficient evidence it seems reasonable to follow general recommendations for exercise training interventions during outpatient pulmonary rehabilitation programs. The short- and long-term effects of exercise and physical activity interventions on functional status, participation in daily physical activities and quality of life should be further explored. Remotely monitored (tele-health) home-based exercise programs, or pedometer-based activity coaching interventions might be interesting alternatives to supervised outpatient rehabilitation interventions in the long-term postoperative phase and therefore warrant further exploration.


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References

1. Granger CL. Physiotherapy management of lung cancer. *J Physiother* 2016; 62: 60–67.
2. Denehy L, Granger CL, El-Ansary D, et al. Advances in cardiorespiratory physiotherapy and their clinical impact. *Expert Rev Respir Med* 2018; 12: 203–215.
3. Rodrigues A, Munoz Castro G, Jacome C, et al. Current developments and future directions in respiratory physiotherapy. *Eur Respir Rev* 2020; 29: 200264.
4. Steffens D, Beckenkamp PR, Hancock M, et al. Preoperative exercise halves the postoperative complication rate in patients with lung cancer: a systematic review of the effect of exercise on complications, length of stay and quality of life in patients with cancer. *Br J Sports Med* 2018; 52: 344.
5. Serpa Neto A, Hemmes SN, Barbas CS, et al. Incidence of mortality and morbidity related to postoperative lung injury in patients who have undergone abdominal or thoracic surgery: a systematic review and meta-analysis. *Lancet Respir Med* 2014; 2: 1007–1015.
6. Agostini P, Cieslik H, Rathinam S, et al. Postoperative pulmonary complications following thoracic surgery: are there any modifiable risk factors? *Thorax* 2010; 65: 815–818.
7. O'Donohue WJ, Jr. Postoperative pulmonary complications. When are preventive and therapeutic measures necessary? *Postgrad Med* 1992; 91: 167–170.
8. Miskovic A and Lumb AB. Postoperative pulmonary complications. *Br J Anaesth* 2017; 118: 317–334.
9. Benzo R, Kelley GA, Recchi L, et al. Complications of lung resection and exercise capacity: a meta-analysis. *Respir Med* 2007; 101: 1790–1797.
10. Ramachandran SK, Nafiu OO, Ghaferi A, et al. Independent predictors and outcomes of unanticipated early postoperative tracheal intubation after nonemergent, noncardiac surgery. *Anesthesiology* 2011; 115: 44–53.
11. Odor PM, Bampoe S, Gilhooly D, et al. Perioperative interventions for prevention of postoperative pulmonary complications: systematic review and meta-analysis. *BMJ* 2020; 368: m540.
12. Cavalheri V and Granger C. Preoperative exercise training for patients with non-small cell lung cancer. *Cochrane Database Syst Rev* 2017; 6: CD012020.
13. Kamarajah SK, Bundred J, Weblin J, et al. Critical appraisal on the impact of preoperative rehabilitation and outcomes after major abdominal and cardiothoracic surgery: a systematic review and meta-analysis. *Surgery* 2020; 167: 540–549.
14. Moore JA, Conway DH, Thomas N, et al. Impact of a peri-operative quality improvement programme on postoperative pulmonary complications. *Anaesthesia* 2017; 72: 317–327.
15. Reeve JC, Nicol K, Stiller K, et al. Does physiotherapy reduce the incidence of postoperative pulmonary complications following pulmonary resection via open thoracotomy? A preliminary randomised single-blind clinical trial. *Eur J Cardiothorac Surg* 2010; 37: 1158–1166.
16. Jonsson M, Ahlsson A, Hurtig-Wennlof A, et al. In-hospital physiotherapy and physical recovery 3 months after lung cancer surgery: a randomized controlled trial. *Integr Cancer Ther* 2019; 18: 15347354 19876346.
17. Jonsson M, Hurtig-Wennlof A, Ahlsson A, et al. In-hospital physiotherapy improves physical activity level after lung cancer surgery: a randomized controlled trial. *Physiotherapy* 2019; 105: 434–441.
18. Cavalheri V, Burtin C, Formico VR, et al. Exercise training undertaken by people within 12 months of

- lung resection for non-small cell lung cancer. *Cochrane Database Syst Rev* 2019; 6: CD009955.
19. Wang Y, Song H, Yin Y, et al. Cancer survivors could get survival benefits from postdiagnosis physical activity: a meta-analysis. *Evid Based Complement Alternat Med* 2019; 2019: 1940903.
 20. Patel AV, Friedenreich CM, Moore SC, et al. American College of Sports Medicine roundtable report on physical activity, sedentary behavior, and cancer prevention and control. *Med Sci Sports Exerc* 2019; 51: 2391–2402.
 21. Brunelli A, Pompili C, Salati M, et al. Preoperative maximum oxygen consumption is associated with prognosis after pulmonary resection in stage I non-small cell lung cancer. *Ann Thorac Surg* 2014; 98: 238–242.
 22. Burtin C, Bezuidenhout J, Sanders KJC, et al. Hand-grip weakness, low fat-free mass, and overall survival in non-small cell lung cancer treated with curative-intent radiotherapy. *J Cachexia Sarcopenia Muscle* 2020; 11: 424–431.
 23. Troosters T, Blondeel A, Rodrigues FM, et al. Strategies to increase physical activity in chronic respiratory diseases. *Clin Chest Med* 2019; 40: 397–404.
 24. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
 25. Sher T, Dy GK and Adjei AA. Small cell lung cancer. *Mayo Clin Proc* 2008; 83: 355–367.
 26. Hirsch FR, Scagliotti GV, Mulshine JL, et al. Lung cancer: current therapies and new targeted treatments. *Lancet* 2017; 389: 299–311.
 27. Granger CL, McDonald CF, Irving L, et al. Low physical activity levels and functional decline in individuals with lung cancer. *Lung Cancer* 2014; 83: 292–299.
 28. Win T, Groves AM, Ritchie AJ, et al. The effect of lung resection on pulmonary function and exercise capacity in lung cancer patients. *Respir Care* 2007; 52: 720–726.
 29. Edbrooke L, Granger CL, Clark RA, et al. Physical activity levels are low in inoperable lung cancer: exploratory analyses from a randomised controlled trial. *J Clin Med* 2019; 8: 1288.
 30. Vagnildhaug OM, Balstad TR, Almberg SS, et al. A cross-sectional study examining the prevalence of cachexia and areas of unmet need in patients with cancer. *Support Care Cancer* 2018; 26: 1871–1880.
 31. Burtin C, Franssen FME, Vanfleteren L, et al. Lower-limb muscle function is a determinant of exercise tolerance after lung resection surgery in patients with lung cancer. *Respirology* 2017; 22: 1185–1189.
 32. Steffens D, Delbaere K, Young J, et al. Evidence on technology-driven preoperative exercise interventions: are we there yet? *Br J Anaesth* 2020; 125: 646–649.
 33. Guinan EM, Doyle SL, Bennett AE, et al. Sarcopenia during neoadjuvant therapy for oesophageal cancer: characterising the impact on muscle strength and physical performance. *Support Care Cancer* 2018; 26: 1569–1576.
 34. van Meerten E, van der Gaast A, Looman CW, et al. Quality of life during neoadjuvant treatment and after surgery for resectable esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 2008; 71: 160–166.
 35. Inoue J, Ono R, Makiura D, et al. Prevention of postoperative pulmonary complications through intensive preoperative respiratory rehabilitation in patients with esophageal cancer. *Dis Esophagus* 2013; 26: 68–74.
 36. Minnella EM, Awasthi R, Loiselle SE, et al. Effect of exercise and nutrition prehabilitation on functional capacity in esophagogastric cancer surgery: a randomized clinical trial. *JAMA Surg* 2018; 153: 1081–1089.
 37. Piraux E, Caty G, Reychler G, et al. Feasibility and preliminary effectiveness of a tele-prehabilitation program in esophagogastric cancer patients. *J Clin Med* 2020; 9: 2176.
 38. Yamana I, Takeno S, Hashimoto T, et al. Randomized controlled study to evaluate the efficacy of a preoperative respiratory rehabilitation program to prevent postoperative pulmonary complications after esophagectomy. *Dig Surg* 2015; 32: 331–337.
 39. Simonsen C, Thorsen-Streit S, Sundberg A, et al. Effects of high-intensity exercise training on physical fitness, quality of life and treatment outcomes after oesophagectomy for cancer of the gastro-oesophageal junction: PRESET pilot study. *BJS Open* 2020; 4: 855–864.
 40. von Döbeln GA, Nilsson M, Adell G, et al. Pulmonary function and cardiac stress test after multimodality treatment of esophageal cancer. *Pract Radiat Oncol* 2016; 6: e53–e59.
 41. Elliott JA, Doyle SL, Murphy CF, et al. Sarcopenia: prevalence, and impact on operative and oncologic outcomes in the multimodal management of locally advanced esophageal cancer. *Ann Surg* 2017; 266: 822–830.
 42. Schandl A, Lagergren J, Johar A, et al. Health-related quality of life 10 years after oesophageal cancer surgery. *Eur J Cancer* 2016; 69: 43–50.

43. Chang YL, Tsai YF, Hsu CL, et al. The effectiveness of a nurse-led exercise and health education informatics program on exercise capacity and quality of life among cancer survivors after esophagectomy: a randomized controlled trial. *Int J Nurs Stud* 2020; 101: 103418.
44. O'Neill LM, Guinan E, Doyle SL, et al. The RESTORE randomized controlled trial: impact of a multidisciplinary rehabilitative program on cardiorespiratory fitness in esophagogastric cancer survivorship. *Ann Surg* 2018; 268: 747–755.
45. Arcasoy SM and Kotloff RM. Lung transplantation. *New Engl J Med* 1999; 340: 1081–1091.
46. Chambers DC, Cherikh WS, Goldfarb SB, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-fifth adult lung and heart-lung transplant report—2018; focus theme: multiorgan transplantation. *J Heart Lung Transplant* 2018; 37: 1169–1183.
47. Myaskovsky L, Dew MA, McNulty ML, et al. Trajectories of change in quality of life in 12-month survivors of lung or heart transplant. *Am J Transplant* 2006; 6: 1939–1947.
48. Smeritschnig B, Jaksch P, Kocher A, et al. Quality of life after lung transplantation: a cross-sectional study. *J Heart Lung Transplant* 2005; 24: 474–480.
49. Gerbase MW, Soccacal PM, Spiliopoulos A, et al. Long-term health-related quality of life and walking capacity of lung recipients with and without bronchiolitis obliterans syndrome. *J Heart Lung Transplant* 2008; 27: 898–904.
50. Ambrosino N, Bruschi C, Callegari G, et al. Time course of exercise capacity, skeletal and respiratory muscle performance after heart-lung transplantation. *Eur Respir J* 1996; 9: 1508–1514.
51. Krieger AC, Szidon P and Kesten S. Skeletal muscle dysfunction in lung transplantation. *J Heart Lung Transplant* 2000; 19: 392–400.
52. Lands LC, Smountas AA, Mesiano G, et al. Maximal exercise capacity and peripheral skeletal muscle function following lung transplantation. *J Heart Lung Transplant* 1999; 18: 113–120.
53. Pantoja JG, Andrade FH, Stokic DS, et al. Respiratory and limb muscle function in lung allograft recipients. *Am J Respir Crit Care Med* 1999; 160: 1205–1211.
54. Schwaiblmair M, Reichensperner H, Muller C, et al. Cardiopulmonary exercise testing before and after lung and heart-lung transplantation. *Am J Respir Crit Care Med* 1999; 159: 1277–1283.
55. Studer SM, Levy RD, McNeil K, et al. Lung transplant outcomes: a review of survival, graft function, physiology, health-related quality of life and cost-effectiveness. *Eur Respir J* 2004; 24: 674–685.
56. Wang XN, Williams TJ, McKenna MJ, et al. Skeletal muscle oxidative capacity, fiber type, and metabolites after lung transplantation. *Am J Respir Crit Care Med* 1999; 160: 57–63.
57. Bartels MN, Armstrong HF, Gerardo RE, et al. Evaluation of pulmonary function and exercise performance by cardiopulmonary exercise testing before and after lung transplantation. *Chest* 2011; 140: 1604–1611.
58. Rochester CL. Pulmonary rehabilitation for patients who undergo lung-volume-reduction surgery or lung transplantation. *Respir Care* 2008; 53: 1196–1202.
59. Mathur S, Janaudis-Ferreira T, Wickerson L, et al. Meeting report: consensus recommendations for a research agenda in exercise in solid organ transplantation. *Am J Transplant* 2014; 14: 2235–2245.
60. Langer D, Iranzo MA, Burtin C, et al. Determinants of physical activity in daily life in candidates for lung transplantation. *Respir Med* 2012; 106: 747–754.
61. Wickerson L, Mathur S, Helm D, et al. Physical activity profile of lung transplant candidates with interstitial lung disease. *J Cardiopulm Rehabil Prev* 2013; 33: 106–112.
62. Wickerson L, Mathur S, Singer LG, et al. Physical activity levels early after lung transplantation. *Phys Ther* 2015; 95: 517–525.
63. Langer D, Burtin C, Schepers L, et al. Exercise training after lung transplantation improves participation in daily activity: a randomized controlled trial. *Am J Transplant* 2012; 12: 1584–1592.
64. Langer D, Gosselink R, Pitta F, et al. Physical activity in daily life 1 year after lung transplantation. *J Heart Lung Transplant* 2009; 28: 572–578.
65. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013; 188: e13–e64.
66. Forli L, Bollerslev J, Simonsen S, et al. Disturbed energy metabolism after lung and heart transplantation. *Clin Transplant* 2011; 25: E136–E143.
67. Li CX, Xu JM, Qin W, et al. Meta-analysis of the effects of exercise training on markers of metabolic syndrome in solid organ transplant recipients. *Prog Transplant* 2018; 28: 278–287.
68. Langer D. Lung transplantation. In: Donner CF, Ambrosino N and Goldstein R (eds) *Pulmonary rehabilitation*. 2nd ed. Boca Raton, FL: CRC Press, 2020; 42: 409–419.
69. Hoffman M, Chaves G, Ribeiro-Samora GA, et al. Effects of pulmonary rehabilitation in lung transplant

- candidates: a systematic review. *BMJ Open* 2017; 7: e013445.
70. Rochester CL, Fairburn C and Crouch RH. Pulmonary rehabilitation for respiratory disorders other than chronic obstructive pulmonary disease. *Clin Chest Med* 2014; 35: 369–389.
71. Maury G, Langer D, Verleden G, et al. Skeletal muscle force and functional exercise tolerance before and after lung transplantation: a cohort study. *Am J Transplant* 2008; 8: 1275–1281.
72. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011; 43: 1334–1359.
73. 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: 517–531.
74. Glöckl R, Halle M and Kenn K. Interval versus continuous training in lung transplant candidates: a randomized trial. *J Heart Lung Transplant* 2012; 31: 934–941.
75. Manzetti JD, Hoffman LA, Sereika SM, et al. Exercise, education, and quality of life in lung transplant candidates. *J Heart Lung Transplant* 1994; 13: 297–305.
76. Li M, Mathur S, Chowdhury NA, et al. Pulmonary rehabilitation in lung transplant candidates. *J Heart Lung Transplant* 2013; 32: 626–632.
77. Burtin C, Clerckx B, Robbeets C, et al. Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med* 2009; 37: 2499–2505.
78. Needham DM, Chandolu S and Zanni J. Interruption of sedation for early rehabilitation improves outcomes in ventilated, critically ill adults. *Aust J Physiother* 2009; 55: 210.
79. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; 364: 1293–1304.
80. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA* 2002; 288: 2859–2867.
81. Janaudis-Ferreira T, Cheung B, Uy K, et al. Changes in functional outcomes after an inpatient rehabilitation program for solid organ transplant recipients. *Transplantation* 2014; 98: 841.
82. Shiner CT, Woodbridge G, Skalicky DA, et al. Multidisciplinary inpatient rehabilitation following heart and/or lung transplantation—examining cohort characteristics and clinical outcomes. *PM R* 2019; 11: 849–857.
83. Wickerson L, Mathur S and Brooks D. Exercise training after lung transplantation: a systematic review. *J Heart Lung Transplant* 2010; 29: 497–503.
84. Didsbury M, McGee RG, Tong A, et al. Exercise training in solid organ transplant recipients: a systematic review and meta-analysis. *Transplantation* 2013; 95: 679–687.
85. Hume E, Ward L, Wilkinson M, et al. Exercise training for lung transplant candidates and recipients: a systematic review. *Eur Respir Rev* 2020; 29: 200053.
86. Hume E, Ward L, Wilkinson M, et al. Exercise training for lung transplant candidates and recipients: a systematic review. *European Respiratory Review* December 2020; 29(158): 200053.
87. Vivodtzev I, Pison C, Guerrero K, et al. Benefits of home-based endurance training in lung transplant recipients. *Respir Physiol Neurobiol* 2011; 177: 189–198.
88. Hansen H, Bieler T, Beyer N, et al. Supervised pulmonary tele-rehabilitation versus pulmonary rehabilitation in severe COPD: a randomised multicentre trial. *Thorax* 2020; 75: 413–421.
89. Tsai LL, McNamara RJ, Moddel C, et al. Home-based telerehabilitation via real-time videoconferencing improves endurance exercise capacity in patients with COPD: the randomized controlled TeleR Study. *Respirology* 2017; 22: 699–707.
90. Bourne S, DeVos R, North M, et al. Online versus face-to-face pulmonary rehabilitation for patients with chronic obstructive pulmonary disease: randomised controlled trial. *BMJ Open* 2017; 7: e014580.
91. Chaplin E, Hewitt S, Apps L, et al. Interactive web-based pulmonary rehabilitation programme: a randomised controlled feasibility trial. *BMJ Open* 2017; 7: e013682.
92. Cox NS, McDonald CF, Alison JA, et al. Telerehabilitation versus traditional centre-based pulmonary rehabilitation for people with chronic respiratory disease: protocol for a randomised controlled trial. *BMC Pulm Med* 2018; 18: 71.
93. Stickland M, Jourdain T, Wong EY, et al. Using Telehealth technology to deliver pulmonary rehabilitation in chronic obstructive pulmonary disease patients. *Can Respir J* 2011; 18: 216–220.
94. Demeyer H, Louvaris Z, Frei A, et al. Physical activity is increased by a 12-week semiautomated telecoaching programme in patients with COPD: a multicentre randomised controlled trial. *Thorax* 2017; 72: 415–423.
95. Loeckx M, Rabinovich RA, Demeyer H, et al. Smartphone-based physical activity telecoaching in chronic obstructive pulmonary disease: mixed-methods

- study on patient experiences and lessons for implementation. *JMIR mHealth uHealth* 2018; 6: e200.
96. Grunig E, Eichstaedt C, Barbera JA, et al. ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. *Eur Respir J* 2019; 53: 1800332.
 97. Glöckl R, Schneeberger T, Boeselt T, et al. Exercise training in patients with pulmonary hypertension: a systematic review and meta-analysis. *Pneumologie* 2019; 73: 677–685.
 98. Fukui S, Ogo T, Goto Y, et al. Exercise intolerance and ventilatory inefficiency improve early after balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. *Int J Cardiol* 2015; 180: 66–68.
 99. Reesink HJ, van der Plas MN, Verhey NE, et al. Six-minute walk distance as parameter of functional outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *J Thorac Cardiovasc Surg* 2007; 133: 510–516.
 100. La Rovere MT, Pinna GD, Pin M, et al. Exercise training after pulmonary endarterectomy for patients with chronic thromboembolic pulmonary hypertension. *Respiration* 2019; 97: 234–241.
 101. Nagel C, Nasereddin M, Benjamin N, et al. Supervised exercise training in patients with chronic thromboembolic pulmonary hypertension as early follow-up treatment after pulmonary endarterectomy: a prospective cohort study. *Respiration* 2020; 99: 577–588.