Safety of exercise after pulmonary endarterectomy: a systematic review

Alicia Page [1], Kathryn Mares [2] and Ciara McCormack [3,4]

[1]Department of Physiotherapy, Royal Papworth Hospital, Cambridge, UK. [2]School of Health Sciences, University of East Anglia, Norwich, UK. [3]Department of Sport Science and Nutrition, Faculty of Science and Engineering, Maynooth University, Kildare, Ireland. [4]National Pulmonary Hypertension Unit, Mater Misericordiae University Hospital, Dublin, Ireland.

Corresponding author: Ciara McCormack (ciara.a.mccormack@mu.ie)

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Early exercise following PEA for CTEPH appears safe and may enhance recovery. Robust trials, standardised protocols and patient-centred approaches are needed to guide best practice and optimise outcomes. https://bit.ly/4rECN6P

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Abstract

Background Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious complication of pulmonary embolism, leading to high pulmonary arterial pressures. Pulmonary endarterectomy (PEA) surgery is the gold standard treatment for CTEPH, significantly improving patient outcomes. Post-operative cardiac remodelling is an important consideration, highlighting the need to balance early exercise with potential impacts on cardiac recovery. The objective of the present study was to investigate the safety and feasibility of early exercise interventions following PEA surgery for CTEPH, and to review the existing literature on early exercise interventions post-PEA.

Methods A systematic review was conducted using the AMED, CINAHL, Embase and MEDLINE databases. Search terms included "pulmonary endarterectomy", "chronic thromboembolic pulmonary hypertension", "exercise", "exercise training", "mobility" and "rehabilitation". Studies were included if they involved adult patients with CTEPH who underwent PEA and participated in post-operative exercise interventions.

Results The review identified studies with small, heterogeneous patient cohorts engaging in early post-operative exercise following PEA. Interventions included walking, cycling, dumbbell exercises and respiratory training. Safety measures, such as continuous monitoring of oxygen levels and heart rate, were implemented and no adverse events were reported. Improvements in exercise capacity and right heart measurements were observed, suggesting that early exercise is both safe and beneficial.

Conclusion Early exercise interventions following PEA surgery appear safe and feasible, with potential benefits for exercise capacity and cardiac remodelling. Future research should include randomised controlled trials and qualitative studies to confirm these findings and assess impacts on patient quality of life.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of pulmonary embolism characterised by unresolving thromboembolic pulmonary vascular emboli persisting despite medical therapy [1]. This leads to an increase in pulmonary arterial pressure (PAP). CTEPH is associated with progressive right ventricular dysfunction, leading to reduced exercise tolerance and quality of life, and when untreated, can lead to heart failure and death [2]. There are limited studies investigating the epidemiology of CTEPH, with an estimated incidence rate ∼2–6% and a prevalence of 26–38 cases per million [3, 4].

Pulmonary endarterectomy (PEA) is considered to be a curative procedure for patients with CTEPH and remains the gold standard treatment for surgical candidates [5, 6]. However, there is no consensus in the existing literature as to what constitutes operable disease, with different thresholds for surgery internationally [7]. Such variations may result in heterogeneous patient cohorts across countries and could influence post-operative outcomes. Many peri-operative complications in patients undergoing PEA are similar to those observed in general cardiac surgery [8, 9]. However, PEA is also associated with some procedure-specific complications. The most common of these is reperfusion injury, due to high permeability of the pulmonary vasculature which results in oedema accumulating in the airways causing hypoxia [10]. Reperfusion injury typically occurs within 48 h post-surgery and can often be managed with supplemental oxygen; in severe cases, extracorporeal membrane oxygenation may be required [10]. It is essential to recognise these factors, as they significantly influence post-operative recovery and affect patient outcomes, including exercise tolerance and quality of life.

Physiotherapy plays a critical role in the recovery pathway for patients undergoing PEA surgery for CTEPH. Physiotherapists support early mobilisation, which improves later-stage recovery outcomes. Many surgical specialties use enhanced recovery pathways after surgery, which are evidence-based and patient-centred approaches designed to improve outcomes, decrease costs, reduce post-operative complications and shorten hospital length of stay [11]. One crucial component of an enhanced recovery pathway is early mobilisation and exercise, which has been shown in general and thoracic surgery to counteract the adverse physiological consequences of immobility and surgical stress [12]. Exercise training in patients with pulmonary hypertension has been shown to improve exercise capacity and quality of life. Evidence from supervised exercise interventions indicates that such programmes are feasible, safe, and can enhance exercise tolerance, ventilatory efficiency, muscle strength and quality of life, with a low incidence of adverse events when appropriately monitored [13]. However, in patients recovering from PEA, there is currently no published consensus on safe or optimal exercise parameters in the early post-operative period [14].

A significant factor to consider in patients following PEA surgery is cardiac remodelling and the impact exertion *via* exercise training may have on this process. In most patients following PEA, remodelling occurs, meaning a significant decrease in right ventricle volumes and an improvement in function of the right ventricle [15]. The limited existing literature suggests that the majority of cardiac remodelling occurs within the first month following PEA, followed by a more gradual, sustained remodelling phase of the right side of the heart [16]. Given this evidence, careful consideration is warranted to optimise the timing of early exercise interventions to avoid adversely impacting the post-surgical cardiac remodelling phase.

The British Thoracic Society (BTS) released a clinical statement on pulmonary rehabilitation in 2023, extending the scope of pulmonary rehabilitation to include patients with stable CTEPH [17]. Pulmonary rehabilitation is an exercise and educational programme for people diagnosed with lung conditions who experience breathlessness and reduced exercise tolerance [18]. These BTS recommendations follow the European Respiratory Society (ERS) statement on exercise rehabilitation in patients with severe chronic pulmonary hypertension [19]. In 2019, they stated that exercise was safe and effective in moderate-risk patients with pulmonary arterial hypertension and inoperable CTEPH [19]. While the latest BTS guidelines address stable and inoperable CTEPH patients, new insights may have emerged since 2023, which requires an updated literature review.

This review aims to examine the criteria for initiating early exercise in patients with CTEPH following PEA and to synthesise literature investigating early exercise-based recovery within the first year post-surgery. This review seeks to address the question: which patients diagnosed with CTEPH are appropriate candidates for early-phase exercise interventions following PEA? To answer this, we will examine eligibility criteria for early post-operative exercise participation, the type and intensity of exercise prescribed, and the context in which these interventions are delivered.

Materials and methods

Due to its methodological character, as a literature review, this study did not go through the process of ethical assessment by the Research Ethics Committee. However, as a systematic review it was registered on the PROSPERO International Prospective Register of Systematic Reviews (CRD42024625485) [20] and reported according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 guidelines [21].

Data collection

PICO (population, intervention, comparison and outcome) was used to help construct and build the research question considered. The articles used in this study were selected through AMED (Allied and Complementary Medicine Database), CINAHL, Embase and MEDLINE databases and other sources. The key search terms used were: "pulmonary endarterectomy", "chronic thromboembolic pulmonary hypertension", "exercise", "exercise training", "mobility" and "rehabilitation", and included truncations and variations of each term. Limitations were set for articles in English, but no limit was set on year of publication due to the limited body of existing research. Searches were re-run prior to the final analyses and to check for identification of any further studies.

The population eligibility criteria included adults with CTEPH, who had undergone PEA followed by an exercise intervention post-operatively. Studies including adolescents (<18 years of age) or paediatric patients were excluded. The intervention being reviewed is early post-operative exercise following PEA in patients with CTEPH. Studies were eligible for inclusion if they described what exercise training was completed and when the exercise was initiated following PEA. Articles in which exercise training was initiated >1 year post-operatively were excluded. A control group could include standard care compared to exercise training, but articles were not excluded if there was no control group.

Two researchers independently screened the records against the inclusion criteria. The study design, methodology, participant demographics and baseline characteristics were extracted from the records. In addition to the details of the exercise intervention, eligibility criteria to partake in the exercise intervention, outcome measures assessed, adverse events and any safety measures were extracted from the records. Two researchers were involved in extracting, reviewing and agreeing on the data. This search strategy was peer reviewed prior to data collection using the PRESS (Peer Review of Electronic Search Strategies) checklist [22].

Data analysis

Given the heterogeneity of study designs and outcomes, the data were synthesised narratively with an inductive approach [23]. Tables and figures are used to visually present the evidence, including characteristics of included studies and identified gaps. Any contradictions in the findings were explored through contextual analysis of study populations, settings and methodologies. Two researchers completed the data synthesis to ensure the narrative was robust.

The Joanna Briggs Institution critical appraisal tool has appropriate checklists for all methodologies for the included articles [24]. The ROBINS-I (Risk of Bias in Non-Randomised Studies – of Interventions) assessment tool was also used [25]. Two researchers independently assessed each study and discrepancies were resolved through discussion.

Results

Sample

The database searches yielded a total of 163 published articles when searched with the key terms; 59 duplicates were removed. The remaining 104 articles were screened according to the inclusion and exclusion criteria, and five articles were sought for retrieval. All retrieved articles were obtained for eligibility assessment. Three reports were excluded, including a systematic review and a case report that did not describe any exercise training intervention. The third article was excluded as post-PEA patients were reviewed alongside other CTEPH participants in an exercise programme but it failed to specify when the PEA patients underwent surgery. On review of the trials protocol, it did not appear that this information had been collected as part of the study, justifying exclusion from this review. Citation searches of selected articles also provided one further article that met the inclusion criteria, giving a total of three articles for analysis (figure 1). The characteristic details of the final articles are provided in the supplementary material. No grey or unpublished literature was included in this review.

The articles included in this review were published between 2013 and 2020, and published across two countries: Germany (n=1) and Italy (n=2). Of these articles, two are prospective cohort studies and one is a retrospective data analysis. The key findings are discussed in the following subsections.

Participants included in early post-operative exercise

The two prospective studies have no set criteria for inclusion in exercise post-operatively. Baseline characteristics are presented in table 1. Nagel *et al.* [26] provided a variety of baseline characteristics, allowing for comprehension of the population. Conversely, Polastri *et al.* [27] did not provide right heart catheterisation (RHC) baseline measurements, making it difficult to understand the included sample population and challenging to compare to other studies.

The retrospective study completed by La Rovere *et al.* [28] excluded patients with post-operative complications limiting their completion of a 6-min walk test (6MWT); however, the study does not elaborate on what the complications were. In this study patients were divided into two groups retrospectively according to the post-surgery haemodynamic response. Group 1 had to meet at least one of the following criteria: mean PAP (mPAP) ⩽25 mmHg, ⩾50% reduction in mPAP or ⩾70% reduction in pulmonary vascular resistance from pre-operative evaluation. Group 2 included all other patients who did

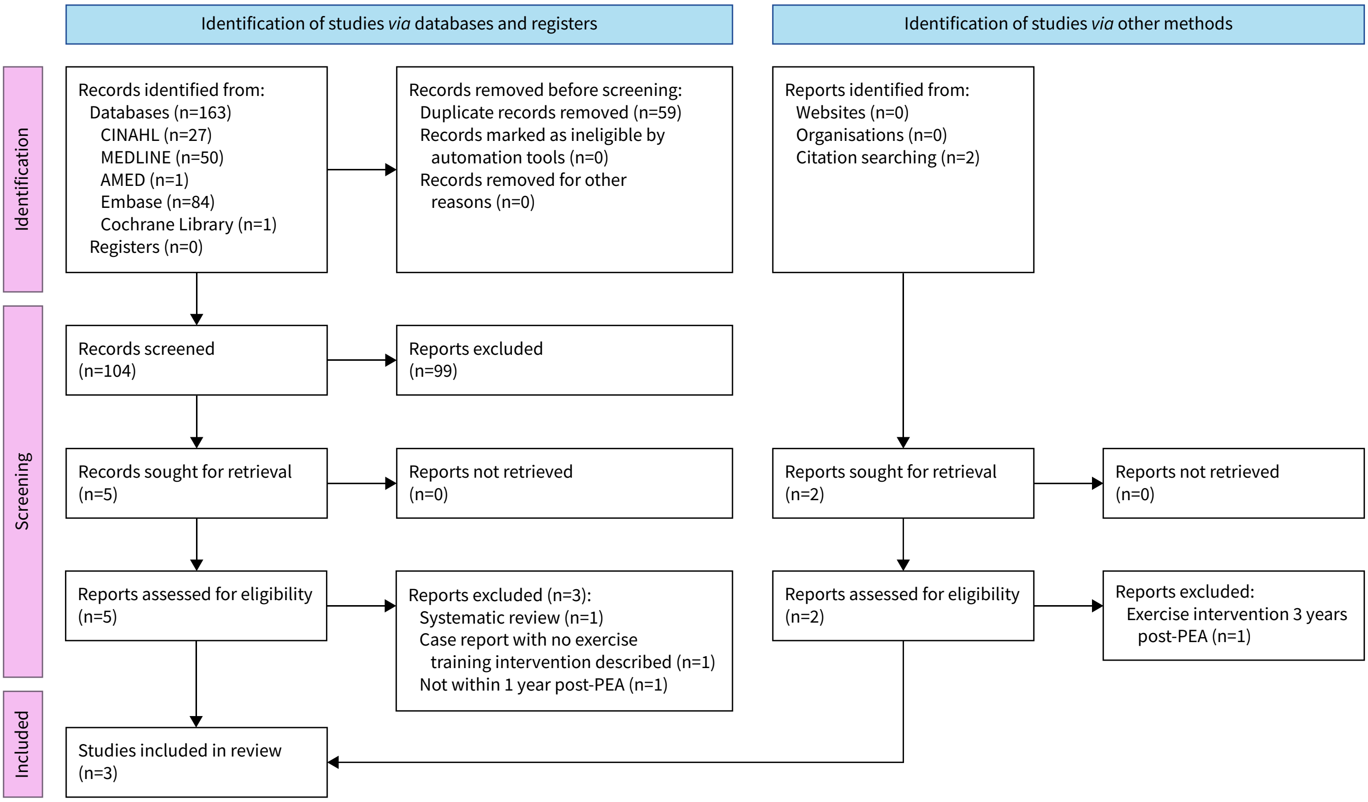

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowchart. PEA: pulmonary endarterectomy.

not meet any of these criteria. The article does not provide any justification for the selected parameters. Although the 6MWT was used as eligibility criteria for the study, baseline patient data for the 6MWT pre-operatively were not provided.

TABLE 1 Baseline characteristics of included studies

First author [ref.], year	Sample size (n)	Age (years)	Gender (% male)	Body measures	Baseline RHC measures	Baseline walk distance	Time exercise commenced from surgery
Nagel [26], (2020)	45	57±12.44	78	BMI 26.52±5.13 kg·m^{-2}	RAP 10.48±6.20 mmHg mPAP 45.10±11.66 mmHg	6MWT 371.95±97.95 m	3.26±0.89 weeks
Polastri [27], (2013)	26	53 (19–77)	58	BMI 23.8 (20.4–41.2) kg·m^{-2}	Not available	Distance walked 0 m	From intensive care stay
La Rovere [28], (2018)	110 Group 1: 84	Group 1: 60.4±13.8	Group 1: 40	Group 1: BSA 1.8±0.2 m^2	Group 1: RAP 5.6±3.4 mmHg mPAP 43.0±12.8 mmHg	Not available	Group 1: 16.0±8.7 days
	Group 2: 26	Group 2: 57.9±13.1	Group 2: 42	Group 2: BSA 1.8±0.2 m^2	Group 2: RAP 5.8±4.2 mmHg mPAP 41.8±13.2 mmHg		Group 2: 16.7±11.5 days

Data are presented as mean±SD or median (range), unless otherwise stated. RHC: right heart catheterisation; BMI: body mass index; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; 6MWT: 6-min walk test; BSA: body surface area

All included articles provided a time frame for the start of post-operative exercise. Polastri *et al.* [27] was the only study that did not provide a specific time frame, stating that exercise rehabilitation started in the intensive care unit (ICU) immediately following surgery. Although this provides an insight into the early commencement of rehabilitation, it is not specific as to whether this is pre- or post-extubation, affecting the type of exercise rehabilitation that can be completed. La Rovere *et al.* [28] presented the time frame for both groups in days, with group 2 starting exercise slightly later than group 1. These articles demonstrate a diverse sample of patients that can be included in post-operative exercise following PEA.

The type and intensity of exercise prescribed

All included studies followed comparable exercise prescription, consisting of incremental exercises through walking, cycling and light resistance training through dumbbell exercises. Additionally, each study incorporated respiratory training during the acute post-operative period. Nagel *et al.*'s [26] intervention consisted of daily interval cycle ergometer training, walking, dumbbell training of single muscle groups using low weights (0.5–1 kg) and respiratory training. This study did not describe the respiratory training involved. During the 3 weeks of inpatient rehabilitation, patients completed a minimum of 1.5 h of exercise per day, delivered in intervals. Notably, the exercise programme was implemented only 5 days per week. This is likely due to staffing provision at the hospital, but no explanation is provided. Following the inpatient period, patients continued a home-based exercise programme for 19 weeks, supported by an individualised training manual and the provision of a cycle ergometer for home use. At home, the exercise expectation was a minimum of 15 min per day, 5 days per week. There is no explanation of how patients were supported by clinicians to complete the home exercise programme.

La Rovere *et al.* [28] set out a similar exercise intervention. Incremental exercise training was performed on a static bike, plus abdominal, upper and lower limb muscle activities including lifting progressively increasing light weights (0.30–0.50 kg) and shoulder arm circling. However, more intensity exercise details were provided, with incremental training increased until participants could perform 30 min continuous cycling at 50–70% of the maximal load calculated based on the admission 6MWT. Similar to Nagel *et al.* [26], La Rovere *et al.* [28] set up a 3-week structured inpatient rehabilitation programme which consisted of daily sessions but did not outline a specific exercise time duration. Although a 3-week exercise rehabilitation programme was described, the length of stay at the centre was slightly longer for those in group 2 (group 1: 24.9±9.5 days *versus* group 2: 27.0±6.8 days).

Polastri *et al.* [27] also included both respiratory training and exercise rehabilitation through strengthening exercises, walking and the use of a cycle ergometer. Respiratory training in this study included manual and device-assisted rehabilitation to remove excessive pulmonary secretions and prevent pulmonary complications. Post-operative rehabilitation was performed twice daily Monday to Friday, and once on Saturday by physiotherapists, but exercise time duration was not provided, in contrast to Nagel *et al.* [26]. Unlike the other studies, Polastri *et al.* [27] did not have a set time frame for the exercise programme but reported that the median length of stay was 9.5 days on the ward (range 3–20 days), providing a more acute post-operative account of exercise post-PEA.

In addition to exercise training, both Nagel *et al.* [26] and La Rovere *et al.* [28] included mental health training to improve participant's perception of their individual physical abilities and limitations. Further psychological support was also offered to all participants. Education and nutrition programmes were also included in the programme setup. Although these wraparound factors were not included in the review's aims and objectives, it is important to acknowledge the additional support provided by these two programmes and how they might have affected the uptake of exercise or engagement with the programme.

The context of the exercise setting

Both Nagel *et al.* [26] and La Rovere *et al.* [28] involved transfer from the hospital where the PEA had been undertaken to a rehabilitation centre for the exercise intervention, whereas in Polastri *et al.* [27] exercise intervention took place at the operating hospital, with exercise rehabilitation starting on the ICU and continued on the cardiac ward.

It is well documented in German practice that 3–4 weeks of inpatient treatment at rehabilitation centres is offered and specialised for certain medical indications, *e.g.* cardiac and orthopaedic [29]. They also provide comprehensive preventive programmes for high-risk groups, with the goal to prevent or delay early retirements and severe disabilities.

NAGEL *et al.* [26] also included a 19-week home exercise programme following the 3-week inpatient exercise rehabilitation [26]. There was little detail provided on how exercise progression was managed or progressed during this outpatient period.

Safety factors

Across all studies, patients were continuously monitored *via* oxygen saturation (S_{pO_2}) and heart rate monitoring during exercise sessions, with oxygen supplementation and heart rate responses adjusted as needed to ensure safety. In the retrospective review by LA ROVERE *et al.* [28], all patients received anticoagulation therapy, targeting an International Normalised Ratio between 2.5 and 3.5. Notably, no adverse events were reported in any of the studies.

Safety measures varied, with NAGEL *et al.* [26] lacking detailed comments on how outpatient training was monitored. However, during the in-hospital and subsequent home-based exercise training phases, right heart size decreased further, with mean right ventricular area reduced to 18.8±5.3 cm^2 (mean change 3.1±5.4 cm^2, −10.9%; p=0.004). Furthermore, patients showed a significant improvement in 6MWT distance from pre-PEA to 3 weeks after PEA by 74±81 m (25±29%; p<0.0001). 6MWT distance increased by 55±54 m from 3 to 6 weeks after PEA and by 65±64 m from 3 to 22 weeks after PEA (15.6% and 18.2%, respectively), with each result statistically significant at p<0.0001. NAGEL *et al.* [26] therefore concluded it was safe and reasonable to start the rehabilitation programme at an early point in time following PEA to enhance clinical improvements and prevent them from worsening or reaching a plateau. Similarly, LA ROVERE *et al.* [28] found right heart measurements showed significant improvements post-exercise, indicating enhanced clinical outcomes.

Critical appraisal

The risk of bias is presented in figure 2. Across the included studies, the greatest potential source of bias was related to outcome measurement. For example, POLASTRI *et al.* [27] reported no RHC data to contextualise the effects of exercise. Furthermore, they presented baseline walking distance values of 0 m for all participants, which were then used as the comparator for post-rehabilitation results. This raises concerns about the accuracy of baseline assessment and the validity of subsequent improvements. Similarly, NAGEL *et al.* [26] reported baseline RHC values but provided no immediate post-PEA measurements. This omission makes it difficult to disentangle the relative contributions of surgery and exercise training to the observed outcomes.

The LA ROVERE *et al.* [28] study, like many retrospective designs, was limited by missing data, which increases the risk of selection bias [28]. Selection bias occurs when the study sample does not adequately represent the target population, leading to results that may not be generalisable [30]. This limitation may detract from otherwise important findings, such as the observation that improvements in exercise capacity

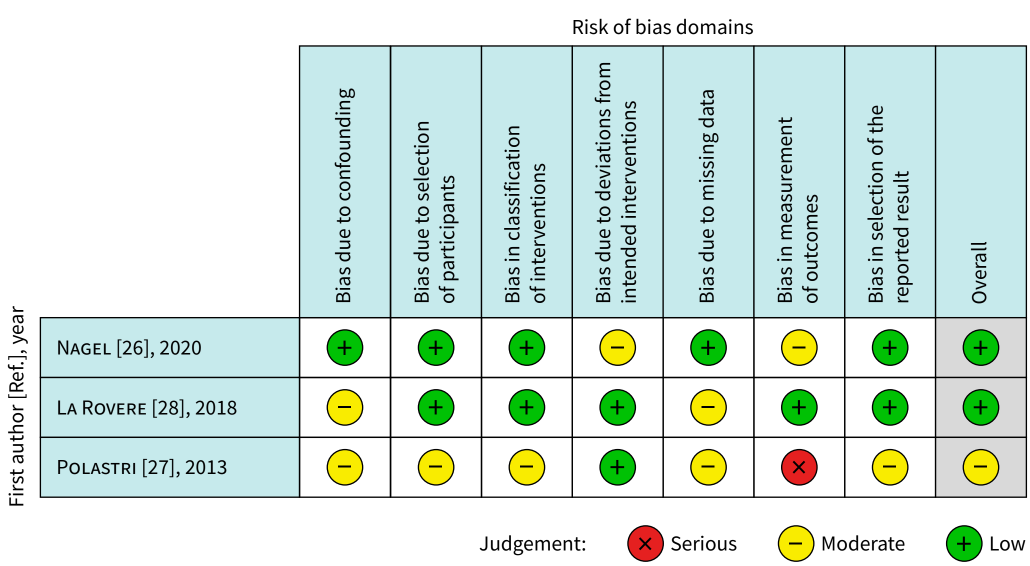

FIGURE 2 Overview of the review authors' judgements about each risk of bias item for all included studies.

appeared independent of post-operative haemodynamic change. Retrospective designs also make it more difficult to control for confounding variables [31]. Nonetheless, this study included the largest sample size (n=110) of all those reviewed, providing valuable insights into real-world clinical practice [28].

The Polastri *et al*. [27] study also demonstrates a risk of selection bias, as participant inclusion was dependent on *ad hoc* informed consent. In addition, this prospective study was limited by a very small sample size, a single-site design and the absence of a control group. Finally, La Rovere *et al*. [28] did not report baseline values for the 6MWT, despite discussing its role in participant inclusion. The absence of this information raises further concerns about selection bias and outcome validity.

Despite these methodological limitations, all studies provided valuable preliminary data and contribute to the emerging evidence base for early post-operative exercise interventions in CTEPH. Collectively, they highlight both the feasibility and potential benefits of such approaches, while underscoring the need for larger, controlled and methodologically robust trials.

Discussion

Overview of findings

This systematic review examined the evidence regarding early exercise interventions for patients with CTEPH following PEA. Overall, the findings indicate that post-operative exercise can be performed safely in this patient population following PEA. Importantly, structured exercise training appears to preserve and even enhance exercise capacity for up to 3 months after surgery, irrespective of the degree of haemodynamic improvement achieved post-surgery.

The included studies were interventional, observational or retrospective in design, each contributing unique insights despite methodological limitations. Collectively, the evidence suggests that early mobilisation and structured exercise are feasible and well tolerated following PEA. In the following sections, these findings will be considered in relation to existing literature, focusing on four key areas: participant characteristics; exercise type and intensity; contextual and safety considerations; and implications for clinical practice.

Participants in early post-operative exercise

A key consideration when interpreting the findings is the variability in the clinical definition of CTEPH. The diagnostic threshold for mPAP was lowered from ⩾25 to ⩾20 mmHg in 2019 [32]. As this review included studies published before and after the change, heterogeneity in the study populations is possible. Although this shift is unlikely to alter the overall conclusions of the review, it raises the question of whether patients diagnosed under the new 2019 criteria may have greater exercise capacity due to earlier disease detection. Earlier diagnosis may allow for less deconditioned patients to undergo surgery, potentially influencing the safety, timing and outcomes of post-operative rehabilitation.

Another consideration is the variation in S_{pO_2} targets across countries. In the Nagel *et al.* [26] and Polastri *et al.* [27] studies, supplemental oxygen was administered when S_{pO_2} dropped to <90% [26, 27]. This aligns with American College of Cardiology Foundation/American Heart Association recommendations that oxygen levels should aim to maintain at >90% [33]. However, some peri-operative protocols have accepted thresholds as low as 85% [34]. This variability complicates interpretation of safety and tolerance across international cohorts, and highlights the need for standardised S_{pO_2} reporting in future studies.

Type and intensity of exercise

Baseline pre-operative assessments such as the 6MWT and RHC were commonly used to guide training intensity. La Rovere *et al.* [28] utilised 6MWT results, whereas Nagel *et al*. [26] included RHC data at baseline but not immediately post-PEA, with the next measurement taken at 22 weeks. The absence of early post-operative haemodynamic data limits differentiation between surgical and exercise training effects.

The studies included in this review incorporated strengthening exercises, including upper limb resistance training, alongside aerobic activities such as walking and cycling. These exercise components are broadly consistent with those reported in exercise programmes for pulmonary hypertension populations [19, 35, 36], suggesting potential alignment between post-PEA rehabilitation and established pulmonary hypertension exercise approaches. All interventions followed an incremental structure and included respiratory training during the acute post-operative period.

Polastri *et al.* [27] did not report as to whether patients walked or exercised outside scheduled physiotherapy sessions. Ambulatory activity was assessed only during physiotherapist reviews, limiting measurement accuracy and progression based on staffing availability. The authors noted that pedometers could have improved monitoring, and recent studies suggest wearable devices may offer a valid, scalable alternative for exercise testing in pulmonary hypertension populations [37]. Incorporating digital health tools into future post-PEA exercise research could improve adherence monitoring, particularly in centres serving geographically dispersed patients, in line with emerging evidence from pulmonary hypertension populations [35].

Exercise intensity may also have been conservative. La Rovere *et al*. [28] adapted a protocol designed for individuals with COPD, while Nagel *et al*. [26] used a pulmonary hypertension protocol [26, 28]. Although both approaches were safe and feasible, they may not fully reflect the improved haemodynamic status of post-PEA patients. More individualised, progressive approaches may be required to optimise outcomes as surgical recovery advances.

Context of the exercise setting

Rehabilitation settings differed across studies, with most interventions delivered in rehabilitation centres rather than acute hospitals. This limits transferability to health systems such as the UK NHS, where dedicated inpatient rehabilitation post-PEA is not routinely available [38].

Although Nagel *et al*. [26] used home-based programmes, this approach contrasts with BTS recommendations, which favour direct supervision by specialists for CTEPH rehabilitation and discourage remote monitoring [19]. However, growing evidence from pulmonary hypertension populations supports the safety and feasibility of hybrid or remotely supervised exercise models [35, 39, 40]. A recent systematic review and meta-analysis demonstrated that home-based exercise interventions, delivered alone or within hybrid programmes, achieved improvements in exercise capacity, cardiorespiratory outcomes and quality of life comparable to centre-based rehabilitation, with no severe adverse events reported [36]. High adherence rates further support the acceptability of home-based exercise, although limited use of self-monitoring tools may constrain comprehensive safety assessment. These findings suggest that digitally supported home-based rehabilitation may represent a viable alternative where access to specialist centres is limited, provided appropriate monitoring strategies are incorporated.

Timing of exercise initiation also varied. Polastri *et al*. [27] commenced mobilisation in intensive care, while Nagel *et al*. [26] reported an average delay of 3.26 weeks. There is no agreed definition of "early" rehabilitation after PEA or indeed other surgeries. However, enhanced recovery after surgery pathways, combined with exercise prehabilitation, promotes early mobilisation and prioritises physical activity across the peri-operative period [12, 41]. Applying this framework to PEA may support earlier engagement in rehabilitation and position prehabilitation as an integral component of post-operative recovery.

Walking outcome measures varied. The 6MWT was most commonly used [26, 28], while the incremental shuttle walk test (ISWT), which maximises exercise capacity through external pacing, has also been utilised in some studies [42]. The 6MWT is routinely performed with patients with CTEPH prior to PEA, and it has been shown that heart rate response is of clinical relevance in this patient group [43]. In contrast, the ISWT is more widely used within pulmonary rehabilitation programmes [44]. With the introduction of new BTS guidelines recommending pulmonary rehabilitation prior to PEA [17], it is likely that patients will encounter a mix of outcome measures across their pre- and post-operative care pathways. This heterogeneity poses challenges for interpreting change over time and for synthesising evidence, highlighting the need for greater consistency in outcome selection to enable meaningful comparisons and facilitate future meta-analyses.

All included studies also highlighted the need for qualitative research to better understand whether the observed and sustained improvements in exercise capacity following PEA translate into meaningful gains in quality of life. It is well documented that patients with CTEPH generally have a reduced quality of life, and prospective studies in pulmonary hypertension populations demonstrate that exercise training can improve quality of life [45, 46]. Nagel *et al*. [26] reported that supervised exercise training helped patients to recognise their improved physical abilities post-PEA. However, the potential role of psychosocial support, such as clinical psychology input, was not explored and may be relevant for optimising recovery.

Safety considerations

Despite the absence of a control group, Nagel *et al*. [26] provided valuable insights into the safety and tolerability of early exercise training following PEA. Notably, exercise limitation persisted in some patients despite normalised haemodynamics, with 24% of the cohort demonstrating residual CTEPH at 22 weeks post-operatively. Although this subgroup was not analysed separately, exercise training was well tolerated across the cohort. These findings suggest that exercise capacity is not determined by haemodynamics alone, and may also reflect symptom burden, deconditioning and patient perceptions of exercise.

Safety is further supported by evidence from non-surgical CTEPH and pulmonary arterial hypertension populations. A large European multicentre randomised controlled trial (RCT) demonstrated that standardised exercise training, delivered as an adjunct to medical therapy, was feasible and safe, with improvements in exercise tolerance and quality of life [47]. Similarly, a recent 2025 systematic review by BEIS *et al*. [13] concluded that exercise training is effective and safe in pulmonary hypertension, improving functional capacity and cardiorespiratory fitness. Taken together, these findings support the plausibility of exercise safety following PEA, particularly given that pulmonary pressures are reduced post-operatively and continue to decline for up to 18 months [45]. They also reinforce the need for a formal RCT to evaluate early post-operative exercise rehabilitation following PEA.

POLASTRI *et al*. [27] reported a median baseline daily walking distance of 0 m, although the timing of this measurement was unclear and may reflect assessment during intensive care rather than pre-operative status. The absence of RHC data limits interpretation regarding exercise safety in the context of cardiac remodelling [27]. Nonetheless, the absence of reported adverse events provides reassurance that early mobilisation and exercise were generally well tolerated in this cohort.

None of the studies described the use of sternal precautions following PEA. This omission is notable, as PEA typically requires a median sternotomy, after which standard sternal precautions are often advised to protect sternal healing. Traditionally, patients are advised to avoid pushing, pulling or lifting with the upper limbs for up to 12 weeks post-operatively [48]. However, clinical practice is increasingly variable, with some centres adopting movement-based approaches that encourage load bearing within safe ranges [49], while others do not apply formal precautions [50]. This variability highlights an important gap in reporting, and raises questions regarding how differing precautionary protocols may have influenced exercise prescription, adherence, functional recovery and patient confidence across studies.

Limitations

This systematic review has several limitations. Namely, the limited number of eligible studies identified (n=3), combined with small and heterogeneous patient populations, substantially limits the strength of the conclusions that can be drawn. In addition, most included studies were single centre in design, restricting generalisability and limiting statistical power. Heterogeneity across studies, including variation in study design, exercise prescription, outcome measures and post-operative protocols, further constrains comparability. As such, the findings of this review should be interpreted as exploratory and hypothesis-generating rather than definitive.

The small evidence base specifically addressing exercise following PEA reflects the broader scarcity of research in this area. These limitations are partially attributable to the specialised nature of both the intervention and the population studied. PEA is a highly specialised procedure, conducted in a small number of centres across Europe, which poses challenges for recruiting large, diverse cohorts. Additionally, it is important to consider the evolving definition of CTEPH during the study inclusion period, as this may have introduced variability in study populations, making direct comparisons between studies more complex.

Recommendations

Future research should prioritise well-designed prospective studies, including RCTs where feasible, to evaluate exercise training as an adjunct intervention for patients with CTEPH in the early post-operative period following PEA surgery. However, given the internal validity of exercise-based RCTs is often compromised by contamination bias, whereby control participants sensitised during recruitment voluntarily increase their physical activity after becoming aware of exercise-related health benefits. This behavioural response reduces contrast between study arms and attenuates the observed treatment effect. Such challenges are particularly relevant in rehabilitation research, where withholding activity may be impractical or unethical. Alternative trial designs, such as Zelen's design involving post-randomisation consent for the intervention group only [51], may offer a pragmatic solution and warrant consideration in future studies evaluating early rehabilitation following PEA.

Longer term follow-up studies are also warranted to better characterise the safety of exercise training in relation to haemodynamic recovery and cardiac remodelling, and to confirm the absence of adverse effects over time. In parallel, future trials should be informed by the broader evidence base in pulmonary hypertension and non-surgical CTEPH populations, while accounting for the unique physiological and clinical considerations associated with post-operative recovery following PEA.

In addition to quantitative trials, incorporating qualitative methods would provide valuable insights into patients lived experiences, perceived benefits and barriers to exercise participation. Such perspectives could inform the development of more personalised and acceptable rehabilitation programmes.

Finally, greater consensus is needed regarding post-operative clinical parameters, particularly target S_{pO_2} thresholds following PEA. Standardised reporting of minimum S_{pO_2} threshold targets within study protocols would enhance comparability across international studies and contribute to the development of more consistent, evidence-informed rehabilitation guidelines.

Conclusion

This review indicates that exercise training may be safe and feasible in the early recovery period following PEA for patients with CTEPH. Exercise could potentially serve as a valuable adjunct to surgical intervention, with the potential to enhance functional outcomes beyond haemodynamic improvements alone.

However, careful consideration must be given to the rehabilitation setting, staff expertise and clinical context when applying these findings more broadly. Key gaps remain, particularly the lack of large-scale RCTs, lack of consensus on post-operative care standards and limited exploration of patient perspectives. Addressing these gaps will be critical to strengthen the evidence base, guide clinical best practice and optimise post-operative rehabilitation for this complex patient population.

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