Effectiveness and safety of exercise training and rehabilitation in chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis

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Contributions: (I) Conception and design: QY An, K Cheng, R Jiang; (II) Administrative support: L Wang, JM Liu; (III) Provision of study materials or patients: QH Zhao, SG Gong, P Yuan, R Zhang; (IV) Collection and assembly of data: QY An, JJ Wang, K Cheng, R Jiang; (V) Data analysis and interpretation: QY An, HT Li, HL Qiu, J He, CJ Luo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Background: Patients with chronic thromboembolic pulmonary hypertension (CTEPH) still have impaired exercise training and quality of life (QoL) despite pulmonary arterial hypertension (PAH)-targeted drugs. Exercise training is considered to improve exercise capacity and QoL in patients with pulmonary hypertension (PH), but this has not been fully studied in CTEPH patients. We conducted the meta-analysis and systematic review to evaluate the effectiveness and safety of exercise training in patients with CTEPH.

Methods: The relevant literature was retrieved for the meta-analysis using the PubMed, EMBASE, and Cochrane Library databases published before December 2020. The primary outcome was a change in six-minute walk distance (6MWD). We also assessed the effect of exercise training on peak oxygen uptake per kilogram (peak VO2/kg), mean pulmonary artery pressure (mPAP) assessed by right heart catheterization (RHC), N-terminal pro-brain-type natriuretic peptide (NT-proBNP), and QoL.

Results: A total of 6 studies with 234 exercise training patients were included. In the pooled analysis, 6MWD significantly improved by 70.14 m (WMD: 58.33 to 81.95, I²=0) after 3-week exercise training. After 12 or 15-week exercise training, 6MWD and peak VO2/kg significantly improved (WMD: 106.22 m, 95% CI: 65.90 to 146.55, I²=87.4%, P<0.0001; 1.84 mL/min/kg, 95% CI: 0.72 to 2.96, P=0.001, respectively). Furthermore, the mPAP decreased by 12.17 mmHg after 12-week exercise training (95% CI: −14.53 to −9.82, P<0.001, I²=99%). The subscales of QoL such as physical function, general health perception, and mental health improved in varying degrees. NT-proBNP did not improve significantly in the pooled analysis. In addition, exercise training was well tolerated without major adverse events occurred during training, and the dropout rate was low.

Discussion: Exercise training may improve exercise capacity, mPAP, and QoL, and was well tolerated among patients with CTEPH. However, more large-scale multicenter studies are needed to confirm the effectiveness and safety of exercise training in patients with CTEPH.

Keywords: Rehabilitation; exercise training; chronic thromboembolic pulmonary hypertension (CTEPH); exercise intolerance; cardiorespiratory fitness

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of pulmonary embolism characterized by unresolved emboli initiating remodelling of pulmonary arteries leading to increase in pulmonary vascular resistance (PVR) (1). According to the 6th World Symposium on pulmonary hypertension (PH) diagnosis and classification criteria (2), CTEPH is classified as WHO group 4. It results in a marked increase in right ventricular remodeling, limited exercise capacity, progressive increase in breathlessness, and eventual right heart failure and death (3,4). The standard of care, pulmonary endarterectomy (PEA), is the most effective therapy for operable CTEPH and can result in near normalization of pulmonary hemodynamics (5,6). Apart from PEA, balloon pulmonary angioplasty (BPA) and/or medical treatment are the recommended options for patients with CTEPH who are ineligible for surgery or who have persistent/recurrent CTEPH after surgery (7-9). Riociguat is the only medical therapy approved for use in patients with CTEPH (10,11). Other pulmonary arterial hypertension (PAH)-targeted therapies [including endothelin receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors (PDE5is), and prostacyclin analogs] are used off label in routine practice (12,13).

Today, CTEPH management is becoming truly multimodal, and advances in PEA, BPA, and PAH-specific drug therapies have significantly improved the prognosis of patients (14,15). However, most patients still suffer exercise intolerance, even after PEA or BPA (9,14-16). Advances in PAH-targeted drug therapies, PEA, and BPA have significantly improved prognosis, and other new treatment regimens have been explored to further improve exercise capacity, quality of life (QoL), and even outcomes (17).

According to the 2019 European Respiratory Society (ERS) statement on exercise training and rehabilitation (18), exercise training has been shown to improve exercise capacity reflected by six-minute walk distance (6MWD) or oxygen consumption at peak exercise (peak VO_{2} and peak VO_{2}/kg), muscular function, quality of life (QoL), right ventricular function and pulmonary haemodynamics in different etiologies of PH patients, including inoperable CTEPH patients (16) or those after BPA (19). Exercise training has also been shown to improve exercise capacity in CTEPH patients after PEA, independent of the PEA therapy (16,20-22). While most studies have focused on patients with PH, including CTEPH, few studies have explored the effect of exercise training on CTEPH patients only.

Therefore, because the benefit of exercise training in CTEPH patients is as yet uncertain, we conducted a meta-analysis and systematic review to evaluate the efficacy and safety of exercise training for patients with CTEPH.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1758) (23).

Methods

Search strategy and study selection

A systematic literature search was conducted in the PubMed, EMBASE, and Cochrane Collaboration databases from their inception to March 2020. We used the terms “exercise training”, “chronic thromboembolic pulmonary hypertension”, and “rehabilitation” to identify studies which evaluated the effects of exercise training on CTEPH. The search was limited to English language articles. Furthermore, we hand-searched the references of the retrieved articles to identify studies not captured by our primary search strategy. We also sent mail to the corresponding authors of articles for available data. This study has been registered at PROSPERO (No. CRD42021236225).

Study selection

The inclusion criteria were: (I) patients diagnosed as CTEPH, and (II) the patients underwent exercise rehabilitation. The diagnosis of CTEPH and their treatment processes were determined according to the guidelines of CTEPH (15,24). The excluded criteria were conference abstracts, animal studies, reviews, or editorials. We included 13 studies that evaluated the effectiveness and safety of exercise training on CTEPH patients.

Data extraction

Two reviewers (R.J. and QY.A.) extracted data performed the literature search, data extraction, and methodological grading independently. The following information was recorded: author, year of publication, demographic and clinical characteristics, study nature, hemodynamics, and exercise intervention outcomes. Disagreements were resolved by consensus.

Outcomes

The primary outcome was a change in 6MWD. The
secondary outcomes included:
(I) Changes of peak VO$_2$ or peak VO$_2$/kg evaluated by cardiopulmonary exercise testing (CPET);
(II) Changes in mean pulmonary artery pressure (mPAP) by right heart catheterization (RHC);
(III) N-terminal pro-brain-type natriuretic peptide (NT-proBNP) changes;
(IV) QoL changes assessed by the SF-36 questionnaire.

Methodological quality
The National Institutes of Health (NIH) quality assessment tool was used for quality assessments of pre-post interventional studies (Table S1) (25). We used the Cochrane Collaboration’s tool to assess the risk of bias of the randomized controlled trials (RCTs) (26). Since less than 10 studies were included in the meta-analysis, publication bias were not assessed.

Data synthesis and statistical analysis
We used random-effects or fixed-effects models to quantitatively synthesize the evidence and to calculate the summary estimates according to $I^2$. Continuous data were analyzed by the weighted mean difference (WMD).

Some studies report continuous variables in the form of quartile intervals or 95% confidence intervals (CI) rather than standard deviations (SD), which need to be converted to SD. The cases were excluded if they could not be transformed into SDs. RevMan 5.4 and Stata version 15 software (Stata Corp., College Station, Texas) were used for statistical analyses.

Results
Characteristics of the participants and study designs
We retrieved 46 studies for further detailed analysis after 144 initial articles were identified by searches, and included 6 studies in our meta-analysis (Figure 1). There was 1 RCT (19) and 5 pre-post intervention studies (16,20-22,27) involving 234 patients treated between 2012 and 2020.

All studies used a supervised exercise training program combined with aerobic exercise (treadmill or bicycle ergometer) and resistance training. All studies were performed in hospital for the first few weeks, with the exercise intensity titrated at 50–70% of the peak exercise capacity, followed by home-based exercise training. The demographics and characteristics of the participants are presented in Table 1.

Quality assessment
The quality assessment of the pre-post interventional studies is detailed in Table S1. Fukui et al.’s study (19) was evaluated by the Cochrane bias risk assessment tool. The study had a low risk of bias in terms of random sequence generation, allocation concealment, blinding, and outcomes assessment, and a high risk of bias for incomplete outcome data and selective reporting.

Six-minute walking distance
The 6MWD was reported in 5 studies involving 150 patients (16,19,21,22,27). In 2 interventional studies (16,22) which evaluated the absolute value of the 6MWD after exercise training, the 6MWD significantly improved by 67.99 m (95% CI: 32.74 to 103.25, $P=0.0002$, $I^2=72\%$) after 12 to 15 weeks of exercise training (Figure 2A). In 3 studies (19,21,27) which evaluated the relative value of the 6MWD, the 6MWD significantly improved by 70.14 m (WMD: 58.33 to 81.95, $I^2=0$) after 3-week exercise training, and this was mirrored by similar changes after 12/15 weeks of exercise training (WMD: 106.22 m, 95% CI: 65.90 to 146.55, $I^2=87.4\%$). Pooled analysis showed that exercise training significantly improved 6MWD results (WMD: 88.16 m, 95% CI: 66.19 to 110.13, $I^2=82.3\%$, $P<0.0001$) (Figure 2B).

Oxygen consumption at peak exercise
The peak VO$_2$/kg was reported in 2 studies involving 52 patients (16,19). There was a significant increase in peak VO$_2$/kg after 12/15 weeks of exercise training, with no heterogeneity (1.84 mL/min/kg, 95% CI: 0.72 to 2.96, $P=0.001$) (Figure 3).

Mean pulmonary arterial pressure
The mPAP was reported in 2 studies involving 101 patients (20). Pooled analysis showed that mPAP decreased after 12-week exercise training (WMD: $-12.17$ mmHg, 95% CI: $-14.53$ to $-9.82$, $P<0.001$, $I^2=99\%$) (Figure 4).

N-terminal pro-brain-type natriuretic peptide
Figure 5 shows the logarithmic scale changes in NT-
proBNP plasma levels. In 2 studies (16,21), NT-proBNP levels decreased by −0.28 ng/L (95% CI: −2.43 to 1.87) after 3 weeks, but increased by 0.44 ng/L (95% CI: −0.12 to 1.01) after 12/15 weeks of exercise training in 3 studies (16,19,22), without statistical significance.

**QoL**

QoL is substantially reduced in patients with CTEPH compared with the healthy population. QoL measures have been shown to correlate with clinical outcomes typically measured in CTEPH (28). Physical burden of the disease, unclear prognosis, high cost of treatment, unemployment and financial uncertainty, social relationships and psychological disorders have also been shown to significantly impact QoL in patients with CTEPH (28,29). In 2 studies (16,19), the subscales for physical function (WMD: 9.97 points, 95% CI: 8.89 to 11.04, P<0.00001, I²=0), general health perception (WMD: 9.88 points, 95% CI: 8.71 to 11.05, P<0.00001, I²=51%), and mental health (WMD: 9.91 points, 95% CI: 8.80 to 11.02, P<0.00001, I²=59%) improved after 15-week exercise training rehabilitation (Table 2). However, role-physical, bodily pain, vitality, and role-emotional did not improve significantly.

**Muscle strength**

With regard to the muscle power, the quadriceps force increased by 3.4±3.8 kilogram force after 12-week exercise training in Takeshi Inagaki’s study (22) (P<0.05). In Shigefumi Fukui’s study (19), quadriceps force, but not forearm, significantly increased after 12-week exercise training in the cardiac rehabilitation group (26.4±8.1 vs. 29.1±8.1 kg, P<0.01).
<table>
<thead>
<tr>
<th>Author, year (ref.#)</th>
<th>No. of patients</th>
<th>Exercise training intervention</th>
<th>Duration</th>
<th>Primary endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ekkehard Grünig 2012, (27)</td>
<td>n=45; female: 16; age: 61±15 years</td>
<td>Rehabilitation clinic for first 3 weeks: interval bicycle ergometer, walking, respiratory training (low workloads, 5 days/week, a minimum of 1.5 h/day), single muscle groups (low weights) Training at home for 12 weeks: bicycle ergometer (≥30 min/day at 5 days a week) Psychological support and mental training</td>
<td>3 weeks; 15 weeks</td>
<td>6MWD; CPET; peak VO$_2$; WHO-FC; QoL; oxygen pulse; workload</td>
<td>6MWD↑; QoL↑; peak VO$_2$↑; peak VO$_2$/kg↑; workload↑; HRmax↑; HRrest↑; WHO-FC (−)</td>
</tr>
<tr>
<td>Christian Nagel 2012, (16)</td>
<td>n=35; female: 16; age: 61±15 years</td>
<td>Protocol same as Ekkehard Grünig 2012, (27)</td>
<td>3 weeks; 15 weeks</td>
<td>6MWD; QoL; CPET; NT-proBNP; WHO-FC; workload; BDI; parameters of gas exchange; sPAP; blood pressure; HR</td>
<td>6MWD↑; QoL↑; peak VO$_2$↑; peak VO$_2$/kg↑; HR max↑; workload↑; Borg Scale↑; NT-proBNP↑; WHO-FC (−); HR max↑</td>
</tr>
<tr>
<td>Takeshi Inagaki 2014, (22)</td>
<td>n=8; age: 64±12 years</td>
<td>In-hospital class and a home-based program for 12 weeks, 40–60 min/week Lower-and-upper limb strength training Endurance training (walking, a cycle ergometer at 60% of the target heart rate) Respiratory exercises Education</td>
<td>12 weeks</td>
<td>6MWD; echocardiography; BNP; dyspnoea severity; pulmonary function; exercise capacity; physical activity; peripheral muscle force</td>
<td>6MWD↑; TDI scores↑; QoL↑; Ex↑; SGRQ scores↑; MRC scores (−); BDI scores (−); HRR (−); WHO-FC (−)</td>
</tr>
<tr>
<td>Shigefumi Fukui 2016, (19)</td>
<td>n=17; female: 10; age: 70±7 years</td>
<td>Hospital training for 1 week: Bicycle ergometer, walking, low-intensity resistance exercise in lower limbs Outpatient training for 11 weeks: Walking, 30–60 min/time, 4–5 times/week; low-intensity resistance exercise in lower limbs, 3 days/week Educational courses, including lifestyle guidance, counselling, psychological support</td>
<td>12 weeks</td>
<td>6MWD; peak VO$_2$; QoL; quadriceps strength; CPET; WHO-FC; exercise load; QoL</td>
<td>6MWD↑; peak VO$_2$↑; oxygen pulse↑; QoL↑; WHO-FC↑</td>
</tr>
</tbody>
</table>

Table 1 (continued)
Table 1 (continued)

<table>
<thead>
<tr>
<th>Author, year (ref.#)</th>
<th>No. of patients</th>
<th>Exercise training intervention</th>
<th>Duration</th>
<th>Primary endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maria Teresa La Rovere 2019, (20)</td>
<td>n=84; female: 40; age: 60.4±13.8 years</td>
<td>Structured program for 3 weeks: Incremental exercise training for 30 min at 50–70% of the maximal load based on 6MWD</td>
<td>3 months</td>
<td>6MWD; hemodynamics; pulmonary function; arterial blood gases</td>
<td>6MWD↑; RAP↓; PAP↓; TPG↓; PVR↓; TPR↑; PaO₂↑; FVC (-); FEV1 (-); FEV1/FVC (-)</td>
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<td></td>
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<td>Muscle activities of abdomen and limbs, lifting progressively light weights (0.30–0.50 kg); shoulder and full arm circling</td>
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<td></td>
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<td>Nutritional programs and psychosocial counselling</td>
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<td></td>
<td></td>
<td>Education</td>
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<tr>
<td>Christian Nagel 2020, (21)</td>
<td>n=45; female: 22; age: 57.6±12.4 years</td>
<td>Protocol same as Ekkehard Grünig 2012, (27)</td>
<td>3 weeks; 19 weeks</td>
<td>WHO-FC; 6MWD; echocardiography; QoL; CPET; NT-proBNP</td>
<td>6MWD↑; QoL↑; peak VO₂↑; peak VO₂/kg↑; workload↑; NT-proBNP↓; RA area↓; RV area↓; sPAP↓; TAPSE↑; left ventricular eccentricity index↓; EqCO₂↓; BDI↓; HR↓; peak HR↓; O₂ at AT↑</td>
</tr>
</tbody>
</table>

BNP, brain natriuretic peptide; BDI, dyspnoea index; CPET, cardiopulmonary exercise testing; Ex, amount of exercise; EqCO₂, respiratory equivalent for CO₂; FVC, forced vital capacity; FEV1, forced expiratory volume at 1 second; HR, heart rate; VO₂, oxygen uptake; oxygen pulse; VO₂/heart rate; MRC, Medical Research Council dyspnoea grade; WHO-FC, WHO functional class; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; sPAP, systolic pulmonary arterial pressure; SGRQ, St. George’s Respiratory Questionnaire; TDI, transition dyspnoea index; TPG, transpulmonary gradient; TPR, transpulmonary; TAPSE, tricuspid annular plane systolic excursion; 6MWD, six-minute walk distance.
Safety of exercise training

In this study, exercise training was well tolerated, and the dropout rate was 3.8%. About 3.5–5.6% of the patients who underwent training experienced syncope or palpitations. Furthermore, no major adverse events, such as symptom progression, right heart failure, or death, occurred during exercise training (Table 3).

Discussion

The results of meta-analysis suggest that patients with CTEPH can gain significant improved exercise capacity, cardiorespiratory fitness, and QoL after exercise training.
Furthermore, exercise training was well tolerated with a low dropout rate.

Our study has important clinical implications. Because of the fear that exercise would worsen cardiac function, exercise rehabilitation was once discouraged in PAH patients. Recently, supervised exercise training rehabilitation has been recommended for PH patients with evidence of exercise rehabilitation (Class I, A) (30). The 2019 ERS exercise training and rehabilitation statement acknowledges the strong evidence of the benefits of exercise training in PH (18). Exercise training has shown beneficial effects as an add-on to PAH-specific drug therapies among patients with CTEPH (16).

**Effect of exercise training on exercise capacity and QoL**

6MWD, as the primary endpoint, has been demonstrated to be significantly increased in many studies (12,31-33). In this meta-analysis, exercise tolerance, measured by the 6MWD and peak VO$_2$, significantly improved after exercise training.

From the summarized ERS statement on the QoL in many studies (18), bodily pain and general health perception generally have no significant differences. Our study indicated that physical functioning, general health perception, and mental health significantly improved in patients with CTEPH. Exercise training combined with PAH-specific drug therapies has shown beneficial effects among CTEPH patients (16). Current guidelines recommend PEA as the preferred treatment for patients with operable CTEPH (12,32). Additionally, BPA is an alternative therapy choice for inoperable patients (34,35). A systematic review confirmed that BPA or PEA can improve exercise capacity (36).

After exercise training, patients with CTEPH after PEA had improved exercise tolerance for up to 3 months (20-22).
We included patients with PEA, BPA, or inoperable CTEPH. Although our meta-analysis showed that exercise training improved exercise capacity, we could not perform a subgroup analysis due to the limited number of included studies.

In previous studies, exercise training has been reported to improve exercise capacity and different aspects of QoL among different WHO groups of PH patients. In this study, we focused on the effect of exercise training on CTEPH patients. By pooled analysis, exercise training improved QoL to different degrees in patients with CTEPH.

**Effect of exercise training on hemodynamics and cardiac function**

The focus of most exercise training studies in the field of PH are the changes in exercise capacity. Only 1 RCT study aimed to evaluate the changes of invasive hemodynamics during rest and exercise as secondary endpoints. Altogether, the study revealed a significant improved cardiac index, mPAP and PVR at rest among PAH or inoperable CTEPH patients after exercise training rehabilitation. So far, few exercise training studies have focused on the hemodynamics of CTEPH patients. Recently, a systematic review and meta-analysis evaluated the effectiveness and safety of exercise training in CTEPH after PEA. PEA surgery can improve hemodynamics (mPAP, transpulmonary resistance, cardiac output, cardiac index, PVR, systematic vascular resistance and pulmonary capillary wedge pressure) and right ventricular ejection fraction (RVEF) immediately. Three months of exercise training after PEA increased the RVEF by 3.53% (95% CI: 6.31–11.94, P<0.00001, I²=0) independently of PEA surgery. However, 3-month exercise training did not influence the hemodynamic parameters mentioned above.

In our study, the mPAP measured by RHC significantly decreased after 12-week exercise training. It is inferred that exercise training may improve pulmonary circulation, but more multicenter studies are needed to confirm this among patients with CTEPH.

This study also found that exercise training did not improve the logarithmic scale of NT-proBNP plasma levels. In the future, we need more studies to confirm the efficacy of exercise training on biomarkers.

**Muscle strength**

In this systematic review, only two studies evaluated the effects of exercise on muscle strength. Most current literature and evidence focus on the evaluation of exercise capacity, QoL, hemodynamics and echocardiography. Limited clinical trials of PAH focused on the effects of exercise training on skeletal and respiratory muscle function. Leg fatigue and dyspnoea during exercise are the main indications of skeletal muscle dysfunction in PAH patients. The underlying cause of peripheral muscle weakness is not completely clear, but may involve atrophy, capillary rarefaction, fibre type switch or sarcomeric dysfunction. Quadriceps muscle training has been shown to be effective in improving quadriceps muscle strength and endurance capacity in PAH patients. Inspiratory muscle strength largely depends on diaphragm muscle function, which can be explained by a reduction in force generating capacity of the diaphragm muscle fibres. Respiratory muscle dysfunction is common and

| Table 2 Changes in the quality of life of patients with CTEPH after exercise training |
|---------------------------------|--------|--------|
| Variable                        | WMD (95% CI) | P value |
| Physical functioning            |        |        |
| Shigefumi Fukui 2016 (19)       | 9.97 (8.89, 11.04) | <0.0001 |
| Ekkehard Grüning 2012 (27)      |        |        |
| Role-physical                   |        |        |
| Shigefumi Fukui 2016 (19)       | 0.03 (-1.50, 1.56) | 0.97   |
| Ekkehard Grüning 2012 (27)      |        |        |
| Bodily pain                     |        |        |
| Shigefumi Fukui 2016 (19)       | 0.01 (-0.96, 0.97) | 0.99   |
| Ekkehard Grüning 2012 (27)      |        |        |
| General health perception       |        |        |
| Shigefumi Fukui 2016 (19)       | 9.88 (8.71, 11.05) | <0.0001 |
| Ekkehard Grüning 2012 (27)      |        |        |
| Vitality                        |        |        |
| Shigefumi Fukui 2016 (19)       | 0.07 (-1.04, 1.17) | 0.91   |
| Ekkehard Grüning 2012 (27)      |        |        |
| Role-emotional                  |        |        |
| Shigefumi Fukui 2016 (19)       | 0.01 (-0.93, 0.95) | 0.98   |
| Ekkehard Grüning 2012 (27)      |        |        |
| Mental health                   |        |        |
| Shigefumi Fukui 2016 (19)       | 9.91 (8.80, 11.02) | <0.0001 |
| Ekkehard Grüning 2012 (27)      |        |        |

CTEPH, chronic thromboembolic pulmonary hypertension.

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may contribute to exercise limitation. Recently, a pilot RCT revealed inspiratory muscle training improved inspiratory muscle strength and functional exercise capacity in PAH and CTEPH (44). In future, larger multicentre studies should focus on the integrating programming of low-intensity endurance, strength, and breathing training programs in various forms of PH, including CTEPH.

Safety of exercise training

In our systematic review, about 3.5–5.6% of the CTEPH patients experienced syncope or palpitations during exercise training. No major adverse events occurred among participants. However, consistent with the safety and efficacy of exercise training in various forms of PH, exercise training was an effective but not a completely harmless add-on therapy, and should be closely monitored (18,27).

Limitations

First, there are limited studies which have evaluated the efficacy and safety of exercise training in patients with CTEPH. The sample size of the included studies was small, and most studies were not RCTs. Although several RCTs have evaluated the efficacy of exercise training in patients with PAH and CTEPH, data associated with CTEPH were not available. Second, most included studies were short-term studies, and did not evaluate prognosis endpoints. Therefore, we were unable to assess the continuous impact of exercise training on these clinical endpoints. Third, most studies were single-center studies, and future multicenter RCTs are needed to better characterize the long-term benefits in CTEPH patients in the real world. Finally, selection bias cannot be completely excluded for all meta-analyses.

Conclusions

The findings of the present meta-analysis suggest that exercise training may improve exercise capacity, including 6MWD and peak VO2/kg. Exercise training also improves mPAP and QoL. However, more large-scale multicenter studies are needed to confirm the effectiveness and safety of exercise training in patients with CTEPH.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-1758

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1758). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study has been registered at PROSPERO (No. CRD42021236225).

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Table 3: Exercise training-related adverse events

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Adverse events</th>
</tr>
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<tbody>
<tr>
<td>Christian Nagel 2012, (16)</td>
<td>35</td>
<td>Syncope in 1 patient; herpes zoster infection in 1 patient</td>
</tr>
<tr>
<td>Shigefumi Fukui 2016, (19)</td>
<td>17</td>
<td>None</td>
</tr>
<tr>
<td>Maria Teresa La Rovere 2019, (20)</td>
<td>84</td>
<td>None</td>
</tr>
<tr>
<td>Ekkehard Grüning 2012, (27)</td>
<td>45</td>
<td>Syncope in 1 patient; episodes of supraventricular tachycardia in 2 patients</td>
</tr>
</tbody>
</table>
formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

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and Functional Exercise Capacity in Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension: A Pilot Randomised Controlled Study. Heart Lung Circ 2021;30:388-95.

## Supplementary

**Table S1** The National Institutes of Health (NIH) quality assessment tool for before-after (pre-post) study with no control group

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<td>1. Was the study question or objective clearly stated?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Were eligibility/selection criteria for the study population prespecified and clearly described?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4. Were all eligible participants that met the prespecified entry criteria enrolled?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5. Was the sample size sufficiently large to provide confidence in the findings?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6. Was the test/service/intervention clearly described and delivered consistently across the study population?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>8. Were the people assessing the outcomes blinded to the participants’ exposures/interventions?</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Quality Rating</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
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</tbody>
</table>