Review Article

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Effects of exercise rehabilitation training on patients with pulmonary hypertension

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Abstract

Pulmonary hypertension (PH) comprises a group of pathophysiological syndromes characterized by elevated pulmonary artery pressure and pulmonary vascular resistance, which lead to right ventricular overload, and even right heart failure. PH has a poor prognosis and severely leads to a decline in quality of life. Historically, patients with PH were advised to limit their physical activity. However, an increasing number of studies have reported the safety and efficacy of exercise rehabilitation training in PH. This review briefly examined and summarized the effects of exercise rehabilitation training on PH patients reported in the recent literature. The findings of the reviewed studies indicate that exercise rehabilitation training in PH patients has beneficial effects in terms of exercise capacity and quality of life, vascular and right ventricle remodelling, inflammatory response, muscular function and oxidative stress. However, the underlying mechanisms and appropriate exercise strategies (e.g. the duration and intensity of exercise) still need to be explored. In conclusion, exercise rehabilitation training of the appropriate intensity and frequency can improve the prognosis and quality of life of PH patients. The training should be monitored by professional staff and be provided as an adjunct to pharmacological treatment. Larger clinical trials are required to confirm the safety and efficacy of exercise rehabilitation training in PH.

Keywords

exercise rehabilitation training, pulmonary hypertension, cardiac rehabilitation

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Introduction

Pulmonary hypertension (PH) is a hemodynamic and pathophysiological state defined by a progressive increase in mean pulmonary artery pressure to ≥25 mmHg at rest, as assessed through right heart catheterization. PH was classified into five subgroups according to its pathological, pathophysiological, and therapeutic characteristics at the *Fourth World Symposium on PH* held at Dana Point (California, USA) in 2008 as follows: pulmonary artery hypertension (PAH), PH due to left heart disease, PH due to lung diseases and/or hypoxia, chronic thromboembolic pulmonary hypertension (CTEPH), and PH with unclear and/or multifactorial mechanisms.[1]

PH is a long-term progressive condition, and most patients do not experience any symptoms at the early stage. When the symptoms appear, persistent dyspnoea on exertion is the most frequent symptom. Dyspnoea usually starts insidiously and is often ignored, and this is usually the reason for the delay in the diagnosis of PH. However, at the time of diagnosis, 70% of patients are in New York Heart Association (NYHA) functional class II–III.[2] Currently, PH is irreversible, and it requires lifelong monitoring and treatment. Traditionally, people believed that physical activity had negative effects on patients with PH due to the risk of disease worsening, right ventricular (RV) decompensation and sudden cardiac death.[3] Therefore, PH patients were advised to restrict physical activities, but this led to further deterioration of mobility and exercise tolerance. However,

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in the last few years, an increasing number of reports have indicated that appropriate exercise rehabilitation under strict monitoring could improve the prognosis of patients with PH. A comprehensive literature search was conducted using MeSH terms and keywords such as 'pulmonary hypertension', 'pulmonary arterial hypertension', 'exercise', 'exercise training', 'cardiac rehabilitation', 'exercise rehabilitation training'. No time restriction was introduced to the identified literature. Identified articles about the effects of exercise rehabilitation training on patients with PH were used for the sections on exercise capacity and quality of life, vascular and right ventricle remodelling, inflammatory response, muscular function, and oxidative stress, etc., aiming to promote cardiac rehabilitation among PH patients (Fig. 1 and Table 1). Also, we will demonstrate a link between the inflammatory state and increased reactive oxygen species (ROS) and the pathophysiology of RV dysfunction and vascular remodelling during PH progress.

Effects of exercise rehabilitation training on exercise tolerance and quality of life

The 2009 European Society of Cardiology guidelines for the diagnosis and treatment of PH suggested that PAH patients should be encouraged to be active within the limits of their symptoms.[1] This suggestion was based on a randomized controlled trial (RCT) that observed an improvement in exercise capacity and quality of life in PH patients who participated in an exercise training programme when compared with an untrained control group.[4] Since then, there have been additional uncontrolled clinical experiences about the positive effects of exercise rehabilitation training on patients with PH, including idiopathic pulmonary arterial hypertension (IPAH),[5] congenital heart disease-associated pulmonary arterial hypertension (CHD-APAH),[6] CTEPH,[7] PH after balloon pulmonary angioplasty,[8] connective tissue disease-associated pulmonary arterial hypertension (CTD-APAH),[7] etc. In these studies, the beneficial effects of exercise rehabilitation training were demonstrated mainly through an improvement in peak oxygen uptake (pVO2), 6-minute walking distance (6MWD), haemodynamics, cardiorespiratory function, scores for a quality-of-life questionnaire, exercise capacity in different types of patients with PH.[5–9] The size of these studies ranged from 19 to 183. Due to a growing number of evidence, the 2015 ESC/ERS PH guidelines suggest that stable PAH patients should conduct a closely supervised exercise and respiratory training programme as an add-on therapy (class II, level of evidence B).[10]

In another prospective clinical RCT, 87 patients with PAH and inoperable CTEPH on stable PH-targeted medication were assigned to a training group and a control group (84% World Health Organization (WHO) functional class III/IV). The training protocol included interval cycle ergometer training at low workloads (10–60 w), walking, dumbbell training of single muscle groups at low weights (500–1000 g) and respiratory training for at least 1.5 h per day. After 15 weeks, the results showed that the pVO_2/kg was markedly

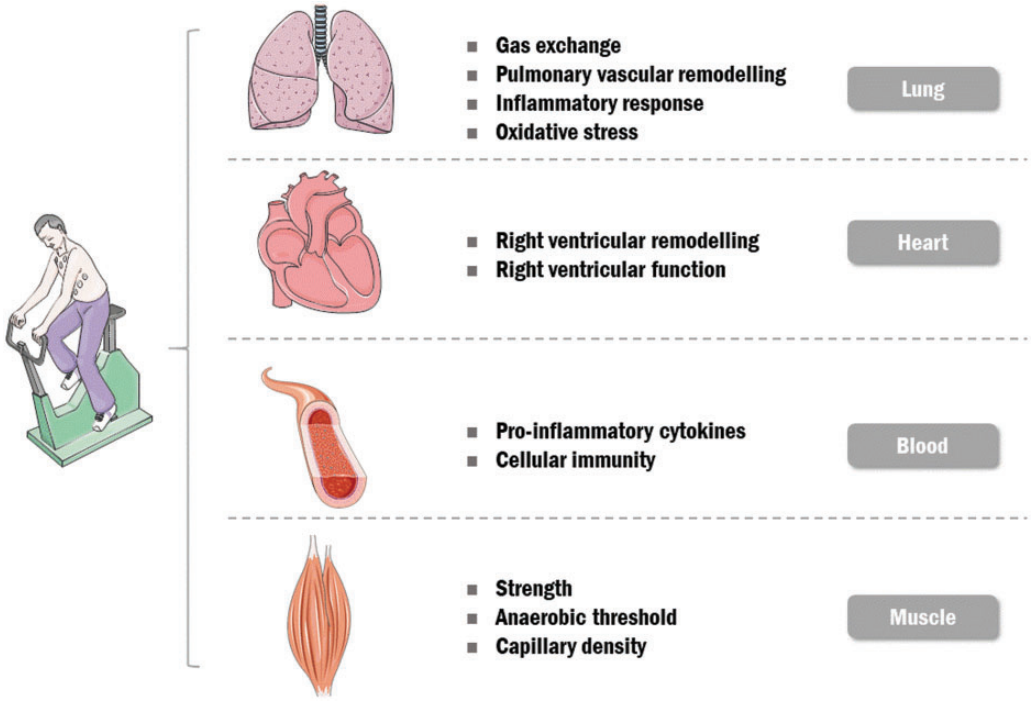

Fig. 1. Main system-based improvements in pulmonary hypertension with exercise training. The benefits of exercise training involve lung, heart, circulating blood and peripheral muscle, which are main systems associated with pathological changes in PH as well.

Table 1. Major improvements of exercise training in pulmonary hypertension.

Exercise tolerance and quality of life
- 6MWD↑[6–8,12,14]
- Quality of life score↑[6–8]
- Heart rate at rest↓[7]
- pVO2↑[6–8]
- Oxygen saturation↑[7]
- Maximal workload ↑[7]
- 1-, 2- and 3-year survival rate↑[7]

Vascular and right ventricular remodelling

Tissue level:
- Intramyocardial capillaries↑[17]
- RV extracellular matrix↓[18–20]
- RV systolic pressure↑[18,19]
- Pulmonary artery thickness↓[22,26]
- Pulmonary artery resistance↓[20]
- Cardiac hypertrophy[18,23–25]

Molecule level:
- P-GSK-3β/GSK-3β↓[22]
- Pulmonary eNOS↑[18]
- SERCA2a↓[19]
- Neurohumoral activation↓[19]

Inflammatory response
- Th17 lymphocytes↓[30]
- IL-1β↓[30]
- IL-6β↓[30]
- Apelin↑[18]

Muscle function

Functional level:
- Anaerobic threshold of the quadriceps↑[5,36]
- Strength of quadriceps↑[5]
- Strength of respiratory muscle↑[37]

Tissue and molecule level:
- Capillary/muscle fibre↑[36]
- Oxidative enzyme activity↑[5]
- Type-I (slow) muscle fibres↑[5,36]
- Type-IIx fibres↓[36]

Oxidative stress
- Pulmonary physiological angiogenesis↑[41]
- H_2O_2 concentration in lung↑[41]
- Activity of glutathione peroxidase↑[41]
- H_2O_2 concentration in RV↓[24,42]
- Lipid peroxidation in RV↓[42]

Note: Existing literature about the effects of exercise rehabilitation training on patients with PH mainly focused on exercise capacity and quality of life, vascular and right ventricle remodelling, inflammatory response, muscular function and oxidative stress, which are involved in the pathological process in PH.
6MWD: 6-minute walking distance; eNOS: endogenous nitric oxide synthase; GSK-3β: glycogen synthesis kinase; H_2O_2: hydrogen peroxide; PH: pulmonary hypertension; pVO_2: peak oxygen uptake; RV: right ventricular.

increased in the training group, with an increase of $3.1 \pm 2.7\,mL{\cdot}min^{-1}{\cdot}kg^{-1}$ (24.3% mean increase relative to the baseline), while the control group showed a reduction of $0.2 \pm 2.3\,mL{\cdot}min^{-1}{\cdot}kg^{-1}$ (0.9% mean increase relative to the baseline) ($P < 0.01$). The cardiac index at rest and during exercise, mean pulmonary artery pressure, pulmonary vascular resistance (PVR), 6MWD, quality of life scores and exercise tolerance in the training group were also markedly improved compared with the control group.[9] Thus, the findings indicated that exercise rehabilitation training may act as a valid adjuvant therapy in patients with inoperable CTEPH.

Improvement in 6MWD has been used as a parameter to assess the prognosis of PH in clinical trials. This is based on the findings of a meta-analysis which reported that improvement in 6MWD of >41.8 m is associated with lower odds of a clinical event at 12 weeks.[11] Another meta-analysis observed up to 53 m improvement in 6MWD at 15 weeks with a combination of aerobic (treadmill or cycle ergometer) and resistance training, which was greater than that reported with PH-specific pharmacotherapies (35.61 m).[12,13] Further, exercise rehabilitation training was found to improve prognosis and increase survival rate in PH patients with different levels of disease severity. Another clinical trial found that the improvement in 6MWD of WHO functional class IV patients was more profound than that in WHO functional class II/III patients after exercise rehabilitation training.[14]

In some types of PH with an inadequate response to PH-targeted medication, such as CTD-APAH, CHD-APAH and inoperable CTEPH, exercise rehabilitation training could also significantly improve 6MWD, pVO2 and quality of life.[6–8] This was demonstrated in a prospective study that assessed the short- and long-term efficacy of exercise training as an add-on to disease-targeted pharmacotherapy in CTD-APAH patients. Twenty-one PAH patients with a confirmed rheumatologic diagnosis showed a significant improvement in 6MWD (by 67 ± 52 m after 3 weeks [$P < 0.001$] and by 71 ± 35 m after 15 weeks [$P = 0.003$]), quality of life score ($P < 0.05$), heart rate at rest, pVO2, oxygen saturation, maximal workload and the 1-, 2- and 3-year survival rate (100%, 100%, and 73%, respectively)

after 15 weeks training.[7] In contrast, some studies have shown that there is no significant improvement in the above indicators of PH patients after exercise rehabilitation training; these findings could be related to the use of a small sample, inconsistent criteria for patient selection or low exercise intensity or frequency due to the lack of supervision outside the hospital.[15]

Extensive exercise may increase pulmonary artery pressure and some patients may suffer from exercise-induced hypoxaemia, arrhythmia, right heart failure, left main coronary artery compression and sudden death.[3] However, we found a high degree of tolerance to training with low drop-out rates and exercise-associated adverse events in patients with PH.[13] Among 183 patients with PH who underwent exercise rehabilitation training, adverse events appeared in 13.6% of the patients. Presyncope occurred immediately after the end of the bicycle ergometer training in one patient and was therefore most probably related to the intensity of the exercise. Two patients were diagnosed with episodes of supraventricular tachycardia that occurred during the exercise training and self-limiting. The other adverse events were not directly related with the exercise itself, for example, pulmonary infection. Most of these adverse events were observed within the training process in the first 3 weeks, and no adverse events have been reported in other clinical trials with a small sample size.[14] To sum up, exercise rehabilitation training was not absolutely safe for all PH patients. It is therefore important to ensure that the exercise intensity and frequency are set under the supervision of professional personnel, especially in the initial stage of training.

Effects of exercise rehabilitation training on vascular and right ventricular remodelling

Structural remodelling in the small peripheral pulmonary arteries is a common characteristic in all forms of PH. Hyperplasia and hypertrophy of smooth muscular cells lead to a progressive increase in vascular resistance, and this in turn leads to an increase in RV afterload, which results in RV remodelling, and consequently, right heart failure.[16] In order to clarify the effects of exercise rehabilitation training on RV function and remodelling, two different dosages of monocrotaline (MCT) were used to establish stable PH and progressive PH in rats. The results showed that the rats with stable PH could fully tolerate exercise rehabilitation training and that their exercise tolerance was markedly improved. This was associated with a significant increase in the capillary density of RV myocardial tissue.[17] Consistently, in MCT-induced mild PAH rats, exercise training was found to attenuate RV fibrosis and improve RV systolic pressure, thus improving RV function.[18,19] Another study also showed that voluntary running could delay PVR increases, RV adverse remodelling and subsequently the heart failure onset in PAH rats induced by MCT.[20]

The processes of vascular and RV remodelling involve a multitude of cellular and molecular elements. Glycogen synthesis kinase (GSK-3β) is a protein that is inactivated by phosphorylation, and it has been found to be involved in cardiac hypertrophy and angiogenesis.[21] Rafael et al.[22] analysed whether exercise rehabilitation training could modulate the expression of GSK-3β to favourably influence RV remodelling in MCT-induced PH. They assigned MCT-induced PH rats to the following groups: sedentary control (SC), sedentary MCT (SM), trained control (TC) and trained MCT (TM). RV end-systolic pressure was decreased by 45% in the TM group compared with the SM group ($P < 0.05$). Furthermore, the SM group displayed structural disorganization of cardiomyocytes, but this was less evident in the TM group. The TM group showed a significant increase (86%) in the total volume of intramyocardial capillaries and a reduction (46%) in pulmonary artery thickness compared with the SM group ($P < 0.05$). The p-GSK-3β/GSK-3β ratio of cardiac homogenates was increased by 1.4-fold in the SM group compared with the SC group. However, in the TM group, the ratio was significantly decreased by 37% compared to the SM group ($P < 0.05$). The results above indicate that exercise rehabilitation training resulted in positive changes in RV and pulmonary artery remodelling, which is associated with the level of GSK-3β. Another study showed that chronic exercise could enhance the pulmonary endogenous nitric oxide (NO) synthase expression in PAH rats, which may increase NO production and NO-dependent vasodilatation.[18] Also, improvements in SERCA2a, a marker of cardiac remodelling, and neurohumoral activation, including reduced endothelin-1, brain natriuretic peptide and vascular endothelial growth factor, were caused by exercise interventions in MCT-induced PAH.[19]

However, there is controversy about the effect of exercise rehabilitation on cardiac hypertrophy. It has been found that high-intensity interval training in PAH rats could attenuate RV hypertrophy and dysfunction.[18] Despite that, other studies have shown that this parameter was not affected by varying exercise intensities either.[23–25] Thus, the effects of this intervention on cardiac hypertrophy may need further investigation.

Exercise rehabilitation training could prevent vascular remodelling in chronic hypoxia. Weissmann et al.[26] established a hypoxia-induced PH model in mice. The results showed that a combination of training plus sildenafil had a more significant inhibitory effect on increase in small pulmonary vessel muscularization than treatment with sildenafil only. Thus, exercise rehabilitation training seems to be a promising adjunct to pharmacotherapy. Consistently, in MCT-induced PAH model in rats, exercising training attenuated pulmonary arterial wall thickness in both small-diameter and middle-diameter vessels.[18]

In contrast, in the rat model of progressive PH, exercise rehabilitation training worsened survival and accelerated pulmonary vascular remodelling; additionally, it induced widespread leukocyte infiltration into the RV. During the training process, the increase in pulmonary artery pressure

and right cardiac afterload resulted in a temporary increase in RV wall stress. In the case of a poorly adapted RV, exercise rehabilitation training aggravated RV inflammation rather than alleviating it, and accelerated the progression to right heart failure.[17] Thus, evidence suggests that there is a possibility of accelerating RV dysfunction and worsening the patient's clinical condition if exercise is performed once the disease is advanced. Careful studies in humans are required to assess whether this pre-clinical experience is true in humans also as only animal studies are available regarding this part now.

Effects of exercise rehabilitation training on inflammatory response

Complicated changes involved with cytokines (interleukins and tumour necrosis factor), cellular immunity (T lymphocytes, natural killer cells, macrophages) indicate that PH is, in part, an inflammatory disease.[27] Pro-inflammatory cytokine levels are linked to death in PH.[28] One study showed that suppression of the inflammatory response after acute pulmonary embolism limited RV damage and prevented right heart failure.[29] Thus, understanding the association between inflammation and PH may help to identify future therapeutic targets. In one study, before exercise rehabilitation training, patients with IPAH showed increased levels of Th2 lymphocytes, regulatory T lymphocytes, IL-6 and TNF-α, while the levels of Th1/Th17 lymphocytes and IL-4 were reduced. In IPAH patients rather than healthy participants, exercise induced an immediate relative decrease in Th17 lymphocytes and a sustained reduction of IL-1-β and IL-6.[30] The results demonstrate that exercise seems to elicit an immune-modulating effect in PAH patients.

Massive RV inflammation has been observed in various parts of the RV myocardium in rats with progressive PH.[17] In the case of progressive PH, RV wall stress is probably higher during exercise due to elevated PVR. Short periods of mechanical stretch (10 min) could trigger myocardial overexpression of pro-inflammatory cytokines (such as TNF-α and IL-6), followed by leukocyte infiltration.[31] Therefore, excessive RV wall stress could stimulate RV inflammatory response in progressive PH. However, in the case of stable PH, RV inflammation remained unchanged. Also, in MCT-induced mild PAH rats, high-intensity interval training was found to increase anti-inflammatory mediator apelin level in RV.[18] The findings of the study indicate that RV inflammation in PH may be of pathophysiological significance.

Effects of exercise rehabilitation training on muscle function

In the past, cardiopulmonary dysfunction was considered to be the main limiting factor in PH; however, researchers have now identified muscle dysfunction as a potential cause of severe clinical manifestations in patients with PH. Muscle dysfunction causes dyspnoea, fatigue, and impaired motor ability, which are the main clinical manifestations of PH.[32] Prolonged exercise restriction and decreased cardiac output lead to reduced oxygen supply to the muscle and cause morphological changes in the muscle, such as muscle atrophy, muscle fibre type conversion and reduced aerobic metabolism.[33] Furthermore, MCT-induced PAH in rat showed marked loss of gastrocnemius weight and body weight, accompanied with increases in IL-1β and CRP locally and systematically.[34] Another study showed that high circulating markers of inflammation were associated with peripheral muscle fatigue in hospitalised geriatric patients.[35]

De Man et al.[5] first reported the effects of exercise rehabilitation training on limb muscle function and morphology in IPAH. In their study, 19 clinically stable IPAH patients (NYHA functional class II–III) participated in a 12-week out-of-hospital exercise rehabilitation training programme, including cycling and quadriceps training. After the programme was completed, the patients' comprehensive endurance capacity was found to have significantly improved. The anaerobic threshold of the quadriceps was increased by 34% ($P = 0.001$), and strength was increased by 13% ($P = 0.005$). It is likely that the improvement in endurance capacity induced by exercise rehabilitation training was associated with changes in the quadriceps. Quadriceps biopsy results for these patients showed increased capillarisation and oxidative enzyme activity, especially of the type-I (slow) muscle fibres. However, there were no signs of muscle hypertrophy or conversion of muscle fibre types; this indicated that there were no morphological changes in the muscle tissue. This finding is probably related to the short duration and low intensity of training.

In a recent study on the effect of exercise rehabilitation training on changes in the muscle tissue of PH patients, five IPAH patients were assessed before and after a 12-week rehabilitation programme, including strength and endurance training of the arm and quadriceps. After the programme, both the surface area of type-I muscle fibres and the capillary/muscle fibre ratio were increased; additionally, the number of type-II x muscle fibres was significantly reduced. The decrease in the proportion of type-II x fibres might have resulted in an increase in the anaerobic threshold of muscle, therefore improving exercise capacity.[36]

Increased dyspnoea and reduced exercise capacity in PH can be partly ascribed to impaired respiratory muscle function. A prospective research was designed to assess the impact of exercise and respiratory training on respiratory muscle strength in PAH patients. Respiratory muscle function was assessed based on twitch mouth pressure (TwPmo) during non-volitional supramaximal magnetic phrenic nerve stimulation. The results showed that there was a significant improvement in TwPmo. Thus, exercise rehabilitation training combined with respiratory function training could be an effective adjuvant treatment for severe PH.[37] However, whether exercise rehabilitation training could also improve respiratory muscle function in the absence of respiratory training also needs to be investigated.

Effects of exercise rehabilitation training on oxidative stress

Oxidative stress, which is defined as an imbalance between ROS and antioxidant molecules, has been reported to be associated with the inflammation and vascular remodelling of PH.[38] Pulmonary artery smooth muscle cells directly produce multiple inflammatory mediators in response to oxidative stress in vitro, which may be part of a cascade that leads to the vascular and perivascular changes in PH.[39] ROS act as mediators of angiogenesis. In the presence of an effective antioxidant defence system, a low concentration of ROS could promote angiogenesis. However, if the production of ROS was out of control, it could attract a large number of macrophages and thus strengthened oxidative stress and thereby promoted pathological angiogenesis.[40] The main ROS involved in intracellular signalling during angiogenesis is hydrogen peroxide (H_2O_2). A study found that aerobic exercise could positively regulate the H_2O_2/VEGF/p-Akt signalling pathway to promote pulmonary physiological angiogenesis, thereby improving RV function. In the study, rats with MCT-induced PAH were divided into the SM, TM, SC and TC groups. The results showed an increase in lung H_2O_2 concentrations in the TM group. The activity of glutathione peroxidase in the TM group was 49% higher than that in the TC group ($P < 0.05$); this could mean that aerobic exercise increases the activity of peroxidase and maintains the H_2O_2 balance.[41] Thus, exercise rehabilitation training may promote physiological angiogenesis signalling through the regulation of oxidative stress in PH, which may be involved in the development of collateral routes for pulmonary blood flow.

Another animal experiment found that the levels of inducible NO synthase and nitrotyrosine in PAH rats that performed aerobic exercise were considerably high, which indicates that oxidative stress was enhanced in these rats. However, the activity of antioxidant molecules was not examined.[18,25] Contrary to the above conclusions, aerobic exercise had a positive effect on oxidative stress in an experimental model of Cor pulmonale, by decreasing H_2O_2 concentrations and lipid peroxidation in RV.[24,42] Therefore, the modulatory role of aerobic exercise on oxidative stress in PH needs further investigation.

Conclusion

The mechanisms via which exercise rehabilitation training affects PH are not completely clear, and large clinical trials are needed to confirm its safety and effectiveness. Furthermore, in future studies, it would be interesting to investigate the effects of different types of training, for example, isometric strength training, which has recently been found to be significantly different from endurance training in the context of physiological adaptations.[43]

The existing literature seems to indicate that exercise rehabilitation training of the appropriate intensity and frequency can improve the prognosis and quality of life of PH patients. Despite the finding, exercise rehabilitation training in PH is still limited by gaps in knowledge about the optimal method of rehabilitation and the intensity and duration of the training. And there should be studies systematically comparing training modalities and intensities among different PH subgroups. Nonetheless, the findings together indicate that the training should be regulated under the supervision of professional staff, and should be provided as an adjunct to pharmaceutical treatment. Cardiac rehabilitation has become an integral part of the comprehensive treatment for coronary heart disease but is still being explored in the context of PH.

Authors' contribution

XJ Zhang collected, examined and summarized relevant literature and DY Xu modified the manuscript.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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