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Editorial

Is there a Role for Exercise Training to Improve the Right Ventricle in Pulmonary Arterial Hypertension?

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Exercise training in Pulmonary Arterial Hypertension: changing the paradigm

Pulmonary arterial hypertension (PAH) in a deadly disease characterized by progressive remodeling of the pulmonary arteries, causing a rise in pulmonary vascular resistance (PVR) and overload to the right ventricle (RV) [1]. Initially, the RV adapts by developing concentric hypertrophy and increasing contractility but, if the overload is sustained, it will eventually dilate and progress to failure (RHF) and premature death [2,3]. In addition to support measures (e.g. oxygen therapy, diuretics, oral anticoagulants, and digoxin), current therapeutic targets focus on the molecular pathways underlying the remodeling of pulmonary arteries like prostanoids, endothelin antagonists, phosphodiesterase 5 inhibitors and soluble guanylate stimulator [1]. Despite some progress was obtained in terms pharmacotherapy in the past years, limited functional capacity, poor quality of life and reduced survival still characterize patient outcome [4-6]. Interestingly, although PAH is a disease of the pulmonary vasculature, the prognostic of the patient is closely related to the RV response to the overload. Unfortunately, this response is limited and there are no targeted therapies to support the RV [3].

Exercise training (ExT) is widely known for its preventive and therapeutic proprieties in several chronic diseases [7]. Regarding PAH, past recommendations use to advise restriction of physical activity because of concerns regarding clinical deterioration and adverse outcomes including fatal cardiovascular compromise [8]. This notion was recently challenged by Mereles., *et al.* [9], in a prospective randomized study, providing the first clinical data that supervised ExT was safe and beneficial in severe PAH. In 2009, the European guidelines introduced for the first time a recommendation about exercise, stating that stable patients under optimal therapeutic control should be encourage to be active within symptom limits [10]. The positive effects of ExT in PAH are further strengthened by different meta-analysis, supporting that it improves exercise tolerance, functional capacity, quality of life, peak heart rate and mean pulmonary artery pressure (mPAP) [11,12]. Only a small number of patients showed any training-associated minor adverse events (e.g. episodes of dizziness, presyncope, syncope, palpitations, hypotension or oxygen desaturation), while no major adverse events were reported [11]. However, it should be highlighted that exercise-training programs were supervised in the majority of the studies (or at least in the first weeks), alerting for the need to assess the safety and efficacy of unsupervised training programs. Moreover, in opposition to major chronic diseases, there are no specific guidelines regarding the optimal frequency, intensity, duration, type or progression of exercise to PAH patients. Based on clinical data, it has been suggested that training programs should combine endurance exercise, strength training, and respiratory muscle training [13]. While precise recommendations are lacking, increasing activity of daily living or reducing sedentary time in patients with PAH might be a suitable option to increase the patients' functional status and quality of life.

Exercise training in Pulmonary Arterial Hypertension: impact on right ventricular function and remodeling

The mechanisms underlying these benefits remain largely unknown but it has been postulated that adaptations in respiratory and peripheral muscles may account for the improvements in exercise tolerance, while any improvement in RV function would be a consequence of a decrease in PVR promoted by target drugs to the lungs [6]. However, we have learned from left heart failure (LHF) that exercise training exerts pleiotropic effects, impacting different organs and systems. At the level of the heart, it is known that ExT improves ejection fraction and cardiac remodeling [14,15]. If the same beneficial effects can be obtained for the RV in PAH remains unknown but it seems reasonable to consider that ExT may also influence the RV response. Because of the different embryologic, molecular, structural and functional differences between the left and right heart, results from LHF cannot be directly extrapolated to RHF [2]. Thus, and given the prognostic importance of the RV, it is urgent to understand what is the impact of ExT on RV function and remodeling.

Evidence from clinical studies

In a randomized, prospective clinical trial published last year, Grunig's group showed that 15 weeks of ExT were capable to improve cardiopulmonary hemodynamics assessed by catheterization. Specifically, the training program induced an increase in resting cardiac output and cardiac index, paralleled by a significant reduction in mPAP and PVR [16]. They also showed that cardiac index was improved during exercise in trained patients. Moreover, Strugnell., et al. in a pilot study involving 6 PAH patients submitted to an outpatient exercise-training program, showed an increase in RV ejection fraction and stroke volume during submaximal exercise measured by cardiac MRI despite no change in mean PAP [17]. While these findings point that exercise training may be beneficial for the RV, larger studies are required to confirm these results. There are at least three clinical trials currently ongoing that will assess the impact of exercise training on hemodynamics and cardiac MRI parameters of RV function (United Kingdom: NCT02961023; France: NCT02579954; and Australia: ACTRN12615001041549), but the results are not yet available.

Evidence from pre-clinical studies

Concerning to pre-clinical studies, a summary of the available evidence was recently published by our group [18]. The majority of the studies on the topic used the monocrotaline (MCT) as a model of PHA. Overall, they suggest that ExT can prevent RV systolic [19-27] and diastolic dysfunction [20,22,24] while a minority shows no change (nor beneficial nor deleterious) [25,28,29], and two studies report aggravation [28,30]. Of note, the beneficial effects of ExT on RV function were not always paralleled by a reduction in RV afterload. Those studies reporting enhancement of RV function have in common the use of higher exercise intensities [20,22-25,27], suggesting that the benefit may be intensity-dependent. However, it is not known what is the minimum required dose to promote the exercise-related benefits or what is the maximum deleterious dose to be avoided. Finally, its seems that starting ExT before [19,24,26] or at early disease stages of PAH [20,22,27] may be required for maximal benefits, while beginning in latter stages may limit [22] or even worsen cardiac function [28].

Regarding the RV myocardium, it was shown that ExT prevented fibrosis when initiated before [24] or at the early stages of the disease [22]. Moreover, ExT was shown to prevent metalloproteinase (MMP)-9 activity and promoted an increase of MMP-2 activity, which might have decreased the accumulation of fibrosis [24]. Exercise training was reported to reduce the expression of TNF-alpha/IL-10 and TWEAK, and to modulate downstream regulators of the NF-κB pathway [22,24]. Also, no evidence of tissue inflammatory cell infiltration or cell death was noted following an acute bout of exercise [31], chronic continuous aerobic exercise [21] or high intensity interval training [25]. However, in the more severe form of PAH, ExT seems to result in widespread leucocyte infiltration of the RV [28]. Regarding neurohumoral activation, MCT-trained animals exhibited down-regulation of ET-1 and BNP mRNA in the RV [22]. Apelin is a potent inotropic, anti-apoptotic, anti-inflammatory and pro-angiogenic neurohumoral mediator [32], and its expression was increased in the RV of rats with PAH after high intensity interval training [25]. Finally, training-induced neurohumoral modulation was evident by the prevention of vascular endothelial growth factor (VEGF) mRNA down-regulation [22], which may have contributed to improve cardiac capillary density in MCT-induced PAH [27,28]. Oxidative stress has been implicated in RV maladaptive remodeling and dysfunction [33,34]. By decreasing hydrogen peroxide production (H2O2), ExT training modulated the apoptosis regulator BAX/B-cell lymphoma 2 (Bax/Bcl-2) and caspase-3, thus decreasing apoptotic signaling in RV myocardium of MCT rats [21]. As major sources of reactive oxygen and nitrogen species (RONS), mitochondria themselves, and particularly oxidative phosphorylation complexes, are highly susceptible to oxidative and nitrative damage [35]. ExT performed in early or late PAH happened to prevent protein nitration of mitochondrial complex V and restore its activity [22]. ExT also improved RV myocardial metabolism by preventing the shift from mitochondria-based fatty acid oxidation to glycolysis found in PAH [25]. Similar to the LV, down-regulation of fast alpha–myosin heavy chain together with overexpression of slow beta-isoform is present in the pressure-overloaded RV, but its long-term consequences remain unknown [2]. RV remodeling with ExT was associated with higher expression levels of alpha-MHC isoform [22,24], which is in line with the beneficial effects of exercise training previously reported in LV failure [36,37]. Exercise training, in the form of preconditioning, prevented the MCT-related overexpression of atrogin-1 [24]. When activated, this prominent ubiquitin ligase controls degradation of proteins contributing to cardiac muscle wasting and ventricular dysfunction [38]. Moreover, ExT stimulated the activation of protein kinase B (Akt) [21] that is associated with improved contractile function, cytoprotection, and increased synthesis of normal contractile proteins and metabolic enzymes [39]. RV failure is also associated with abnormalities in calcium handling proteins, including ryanodine receptor (RyR) and Ca2+ ATPase of sarcoplasmic reticulum (SERCA2a). Expression levels of SERCA2a [22], but not RyR [26] were restored in MCT-trained animals, possibly contributing to preserve relaxation rate. In humans and animals with PAH and RV failure, alpha and beta-adrenergic receptors density is decreased, which limits their response to inotropic agents and impairs exertional contractile reserve [40]. Exercise training was shown to suppress the downregulation of alpha-1 adrenergic receptors, to attenuate beta-adrenergic receptors decrease, and to lower muscarinic acetylcholine receptors in the rat model of hypoxia-induced PAH, eventually correcting chronotropic incompetence [41].

Conclusions

Exercise training is a very promising adjunct therapy for stable and well-medicated patients with PAH, but there are no conclusive data regarding the potential favorable benefits on right heart function. The limited available clinical data together with the pre-clinical data suggest that ET may positively impact the RV function and remodeling. Larger clinical trials, specifically assessing cardiac function and remodeling, are necessary to confirm these results.

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