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Mini-review

Aerobic exercise-related attenuation of arterial pulmonary hypertension: A right arrow targets the disease?

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ABSTRACT

Characterized by progressive elevation of mean pulmonary artery pressure and pulmonary vascular resistance, pulmonary arterial hypertension (PAH) is an important health problem that contributes to right heart failure. Pulmonary arterial remodeling and constriction are two prominent features of PAH. It is a traditional view that increasing pulmonary blood flow and pressure, aerobic exercise does more harm than good to the pulmonary vasculature in PAH. However, recent studies have documented a potential benefit of low-intensity aerobic exercise for PAH patients. Here the current mini-review outlines the evidence and challenges for this additional tool in our armamentarium to combat this ominous disease.

Contents

Pulmonary arterial hypertension (PAH) is a serious clinical condition characterized by a mean pulmonary artery pressure (mPAP) >25 mm Hg at rest, an expiratory pulmonary artery wedge pressure (PAWP) >15 mm Hg, and a pulmonary vascular resistance (PVR) >3 Wood units [1]. PAH is usually classified into idiopathic pulmonary arterial hypertension (IPAH) and PAH associated with rheumatic diseases, congenital heart diseases, systemic-to-pulmonary shunts, portal hypertension and human immunodeficiency virus (HIV) infection [1]. The main pathophysiological characteristic of PAH is an anomalous pulmonary vasoconstriction in response to endothelial injury, due to an altered balance between endogenous vasoconstrictors/mitogens, such as endothelin (ET) isoform 1 and thromboxane A_2; and vasodilatory/antimitotic substances such as prostacyclin (prostaglandin I_2, PGI_2) and nitric oxide (NO) (reviewed in [2,3]). The abnormal pulmonary vasoconstriction is due to a reduced production of PGI_2 [4], reduced bioavailability of NO [5], and increased expression of ET-1 receptors in the lungs [6]. In addition, alterations in the mitochondria, inflammation, dysregulation of growth factors and abnormal angiogenesis lead the pulmonary microcirculation to a proliferative state and to resistance to apoptosis [7]. These abnormalities may be acquired, genetically mediated as a result of mutations in the bone morphogenetic protein receptor-2 or activin-like kinase-1, or epigenetically inherited (as a result of the epigenetic silencing of genes such as superoxide dismutase-2) [7]. As endothelial dysfunction persists, the small pulmonary arteries undergo

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vascular remodeling, resulting in large structural changes of the heart, a limitation in exercise capacity and, ultimately, right ventricular failure [8].

1. Exercise training in PAH

Despite the availability of several treatment options, the long-term prognosis for patients with PAH remains unsatisfactory [9]. Since many physicians fear that exercise could put further strain on a heart decompensated or prone to right ventricular heart failure, exercise training is generally not recognized as part of the treatment in PAH. Exercise training is also generally considered contraindicated in PAH treatment due to the possible occurrence of low cardiac output (CO), arrhythmias, pulmonary venous congestion, and hypoxemia [10]. More recently, however, interest in exercise training as an adjunct therapy to the long-term medical management of PAH has grown [11].

So far, several randomized clinical studies published between January 1980 and August 2016, have evaluated the effect of closely supervised and monitored low-level exercise training programs on systolic pulmonary arterial pressure (PAPs), measured by Doppler ultrasound [12–19]. One study evaluated the mean pulmonary blood volume and peak flow velocity in the main pulmonary artery by magnetic resonance imaging (MRI) [20]. All these studies are small, enrolling a minimum of 20 up to a maximum of 183 patients in either a control or an exercise training group. In addition, patients had either idiopathic or secondary forms of PAH due to congenital heart diseases, left heart disease, chronic thromboembolic disease, connective tissue and lung diseases. Patients were subjected to a hospital-based exercise training program 7 days a week for a variable duration of 6 to 18 weeks. The exercise training program consisted of combined aerobic exercise at a bicycle ergometer (30-s cycles at a lower workload and 60-s cycles at 20 to 35 W), resistance exercise (30 min a day of training with 500 to 1000 g dumbbells), and respiratory training (body perception, yoga, and respiratory muscle strengthening exercises). After hospital discharge, patients continued to exercise at home for 5 days a week, for 15 to 30 min for 12 weeks. Only 2 studies, and from the same research group, showed a reduction of the PAPs at 3 weeks after exercise training for up to 15 weeks [14,15]. The remaining studies showed no significant difference of PAPs between the control and the exercise group. In one study the exercise group experienced an increased mean pulmonary blood volume and a reduced peak flow velocity in the pulmonary artery at MRI [20]. A clear limitation of all these studies is that they have analyzed only PAPs as the endpoint to evaluate the effects of exercise training on PAH. A recent meta-analysis [21], looking at low intensity aerobic exercise such as walking, cycling, and light weight lifting, and including inspiratory muscle training for 6–18 weeks, found that closely supervised and monitored low-level exercise training programs are associated with improvement of various alternative non-invasive parameters of cardiac function and exercise capacity. Improvements documented in the exercise training group included increased peak oxygen consumption (peak VO_2) by 1.1–2.1 mL/kg/min, decreased heart rate at rest and during exercise, increased six minute walk distance (6MWD) by 17–96 m, improvement in functional class by at least one class, and better quality of life. Such improvements were greater than those observed in any clinical trial with medical therapy for PAH, and even more dramatic when one considers that most of the patients were already in combination therapy [21].

The occurrence of benefits from aerobic exercise is also supported by preclinical studies. Indeed, data from several animal studies showed favorable effects of exercise (conducted for 3–5 weeks, 30–60 min per session, at 50–60% of maximum aerobic capacity), on mPAP, measured by right heart catheterization [22–26]. In all these studies, PAH was induced by exposure of rats to hypoxia or monocrotaline. In one study, conducted on adult rats with single-dose monocrotaline-induced PAH [22,27], the exercise training resulted in reduced wall thickness of small pulmonary arteries, decreased pressure overload and hypertrophy of the right ventricle. In a second study conducted on adult rats with hypoxia-induced PAH [24], the exercise training improved endothelium-dependent vasodilation, resulting in a reduction of mPAP and PVR. In a third study using the same model of hypoxia-induced PAH [25], the exercise group had a significantly lower rise in resting mPAP compared with a sedentary control group. A fourth study [26] used a model of PAH induced by monocrotaline at two doses, a lower dose to induce stable PAH and a higher dose to induce progressive PAH. Increase in CO and reduction of PVR were significantly more accentuated in the exercise group compared with the sedentary group. In this issue of *Vascular Pharmacology* [22], using a monocrotaline-induced model of PAH in adult rats, Colombo et al. have focused on the mechanisms that explain the effects of exercise on PH, providing experimental evidence that aerobic exercise training promotes a significant increase in hydrogen peroxide (H_2O_2)/vascular endothelial growth factor (VEGF)/Akt signaling in the pulmonary bed, which is operating for the development of physiological angiogenesis in the pulmonary vascular bed (Fig. 1). This response was associated with improvement of right ventricular function, as assessed by echocardiography [22].

2. Research avenues

During aerobic exercise training, the pulmonary circulation is able to accommodate the increased CO through relaxation and recruitment of new vessels [28]. During low-intensity aerobic exercise training, mPAP remains constant because of the concomitant reduction of PVR. Conversely, during high-intensity exercise training, there is an increase in mPAP mainly due to increased CO [28]. In PAH, however, these physiological adaptations seem to be non-operational because of impaired NO-mediated vasodilation. Although clinical evidence in support for a positive role of exercise training in PAH is growing, mechanisms explaining the effects on the functional characteristics of the pulmonary circulation in PAH are still unclear. Colombo and co-authors [22] have here focused on the role of H_2O_2-induced angiogenesis as a possible mechanism explaining the increased pulmonary vascular reserve during exercise. The authors showed the increase of H_2O_2 in PAH-trained animals. Aerobic exercise training also increased the expression of VEGF, which was positively correlated with Akt phosphorylation. Others have shown that exercise training reduces levels of monocytes and macrophages, as well as the expression of inflammatory genes such as tumor necrosis factor (TNF)-alpha and interleukin (IL)-6 in the pulmonary circulation, resulting in decreased reactive oxygen species (ROS) production and physiological angiogenesis [29,30]. Despite the study by Colombo et al., preclinical and clinical studies analyzing the rationale for benefits of exercise training in PAH are still lacking, and a deeper understanding on how aerobic exercise training may improve pulmonary vasodilation and reduce mPAP in patients with PAH would be worthwhile.

The 2009 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines on PAH [31] suggested that patients may undertake supervised exercise rehabilitation at centers experienced in both PAH patient care and rehabilitation. However, the 2015 ESC/ERS guidelines [32] highlighted some current gaps in the knowledge about the optimal method of exercise rehabilitation and the intensity and duration of the training. In addition, they acknowledged the lack of understanding of mechanisms for the improvement of symptoms and functional capacity by exercise, as well as the effects of exercise on prognosis, Therefore, there is no clear recommendation can be deduce from current guidelines.

3. Summary and conclusions

In this 2016 Olympic year, we are fascinated by the grace of physically trained athletes; more currently, in everyday's life, we ourselves directly experience the benefits of exercise. Preclinical studies and clinical trials now support the concept that one new prescription for