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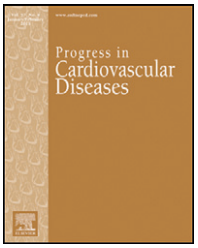

The Effect of Exercise Training on the Pulmonary Arterial System in Patients With Pulmonary Hypertension

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ABSTRACT

Given the unique and clinically ominous pathology associated with pulmonary arterial (PA) hypertension (PH) and its implications for the eventual deterioration of right ventricular function, exercise training (ET) was historically not recommended. More recently, a body of literature demonstrating the safety and efficacy of ET in PH has emerged. The primary focus of this review is to provide a synopsis of current evidence assessing the effects of ET on the PA system in patients with PH. The current body of evidence is relatively small and it is not clear if ET improves PA function or vessel characteristics. Nevertheless, studies have consistently found ET leads to numerous clinically relevant benefits including increased: 1) aerobic capacity, 2) muscle strength, 3) exercise tolerance, and 4) quality of life. Thus, ET, given its clinical benefits, is likely to enjoy increased utilization in patients with PH.

Introduction

The benefits of exercise training (ET) in virtually all humans, including those diagnosed with a clinically stable chronic disease are numerous.[1–4] The potential value of ET for those patients diagnosed with a chronic disease lies in the fact that functional capacity is oftentimes significantly compromised. The underlying concept behind ET is that it plays a role in reversing some of the pathophysiologic processes associated with chronic disease and improves clinical trajectory (i.e., functional capacity, quality of life, and prognosis). Perhaps the chronic disease population where the benefits of ET, and its clinical acceptance, are most well established is in patients diagnosed with heart failure (HF).[3–5] Patients diagnosed with pulmonary arterial (PA) hypertension (PH) comprise another chronic disease population where the deficits in exercise capacity and prognostic outlook are comparable if not worse than those seen in patients with HF.[6–8] PH is a chronic disease precipitated by one of several pathologic mechanisms, including idiopathic, genetic, congenital, and associated connective tissue diseases such as scleroderma.[9] A commonly accepted criterion for the diagnosis of PH is a mean resting PA pressure (PAP), measured by right heart catheterization, of 25 mmHg or more with a concomitant pulmonary capillary wedge pressure of 15 mmHg or less.[9,10]

Because of the significant pathologic consequences associated with PH and its implications for deteriorating right

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Abbreviations and Acronyms
CO = cardiac output
ET = exercise training
HF = heart failure
NO = nitric oxide
PA = pulmonary artery/arterial
PAH = pulmonary arterial hypertension
PAP = pulmonary artery pressure
PH = pulmonary hypertension
PVR = pulmonary vascular resistance
RV = right ventricular
WHO = World Health Organization

ventricular (RV) function as well as the perceived potential for a precipitous and possibly life threatening drop in c ardiac output during periods of physical exertion, ET was historically not recommended for these patients. More recently, however, a promising body of literature demonstrating the safety and efficacy of ET in patients with PH has emerged. The initial positive findings have increased enthusiasm and interest in this area, resulting in an acceleration of scientific inquiry. A key issue that has not been thoroughly addressed to this point is the impact of ET on the PA system itself, which directly ties to lifestyle intervention and its potential to lower PAP in patients with PH. This is a highly relevant question for this field of research: Does ET, through an improvement in PA vasorelaxation and/or architecture, elicit a significant reduction in PAP; a reduction that could potentially contribute to altering the clinical trajectory of patients with PH in a favorable manner?

This review addresses several areas briefly and one area substantially in patients with PH: 1) Summarize the impact PH has on the physiologic response to aerobic ET; 2) Provide a detailed synopsis of the current body of literature assessing the effect of ET on the PA system and subsequently PAP; 3) Highlight the currently available evidence demonstrating other areas of clinical benefit as well as safety of ET; 4) Highlight indications and contraindications for ET, as well as discuss basic principles of ET prescription; and 5) Discuss directions for future research in this field.

Alteration of physiologic and structural status of the PA system and resultant response to ET in PH

Under normal physiologic conditions, the PA system is able to significantly distend and recruit a greater proportion of the vascular network during aerobic ET, accommodating the multifold increase in cardiac output (≈3–4-fold or greater at maximal exercise).[11] PAP is mathematically defined as the product of cardiac output and pulmonary vascular resistance (PVR), plus pulmonary venous pressure. During low-intensity aerobic exercise, there is no substantial rise in PAP, given the concomitant decrease in PVR. At higher intensities of exercise, there is an increase in PAP, which lags behind the rise in cardiac output secondary to the drop in PVR.[12,13] The increase in PAP with exercise is greater with aging while the influence of exercise on PVR appears to be age-independent.[12,13]

The primary pathology associated with PH is a variable compromise in vessel wall characteristics, favoring increased stiffness, and vasodilatory dysfunction[11,14,15], resulting in a significant rise in PAP and PVR at rest and during exercise (Fig. 1). This creates a number of consequences that directly impact the capacity to perform aerobic exercise: 1) Increased ventilation–perfusion mismatch, which, if severe enough, decreases arterial oxygen saturation; 2) Decreased pulmonary venous return leading to a decrease in left-sided cardiac output (CO); and 3) Possible leftward shift in the ventricular septum; decreasing left ventricular filling capacity and further compounding the reduction in cardiac output.[16,17] As PH disease severity progresses, RV dysfunction/deterioration progresses, which further contributes to a decline in cardiac output.[18] Given the fact that the degree of augmentation in cardiac output during exercise is a primary determinant of aerobic capacity[1], the oftentimes significant reduction in this key exercise variable in patients with PH is inevitable. Moreover, given the relationship between cardiopulmonary physiology and aerobic exercise, the degree of limitation in exercise capacity reflects PH disease severity.[11,16,18,19]

Aerobic exercise performance is significantly influenced by factors other than elevated pulmonary pressure and diminished left-sided CO in patients with PH. Specifically, both respiratory and skeletal muscle dysfunction/weakness appears to play an important role in the degree to which aerobic capacity is diminished in patients with PH.[20–23] The fact that respiratory and skeletal muscle dysfunction/weakness appears to contribute to a diminished aerobic capacity in patients with PH also indicates there are several potential therapeutic targets, either in isolation or synergistically, that may also improve clinical status.

Synopsys of human and animal ET protocols in PH[24–34]

Table 1 lists seven human and four animal studies that have assessed the effect of ET, primarily aerobic in nature, on PA function; primarily assessed by systolic PAP. There was also some assessment of vessel wall characteristics and the impact of ET in an animal model. The cause of PH in the human trials included idiopathic, congenital heart disease, connective tissue disease, and thromboembolic PH. In the animal studies, PH was either induced by monocrotaline or hypoxia.

Doppler echocardiography was the primary measurement technique for systolic PAP in the human trials. Magnetic resonance imaging assessed pulmonary blood flow in one human trial. Right heart catheterization was used to assess PAP in two animal studies. Other assessment techniques in animal studies were: 1) Digital imaging of sectioned PA rings, 2) Isometric force production of sectioned pulmonary artery rings, and 3) Western blot analysis.

All but one[33] human trial incorporated the same ET protocol, combining aerobic, respiratory and resistance ET. Details of the predominantly used ET protocol are as follows: For the first three weeks, subjects underwent a hospital-based ET program 7 days a week. The protocol was supervised by physical therapists and physicians. ET consisted of the following: 1) **Aerobic ET:** Interval cycle ergometry; 30 s at a lower workload and 60 s initially at 20 to 35 W. This intensity