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Review article

Readdressing the entity of exercise pulmonary arterial hypertension

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ABSTRACT

Exercise pulmonary hypertension (EPH) indicates an abnormally elevated pulmonary artery pressure (PAP) during exercise. The physiological range of PAP during exercise remains poorly defined and, therefore, a universally accepted definition of EPH remains elusive. Nevertheless, previous data concerning the distribution of PAP in normal populations and more recent retrospective clinical data enhanced our ability to define EPH. EPH can impair exercise capacity and cause dyspnea. The underlying pathophysiology of the arterial form of EPH (EPAH) appears to be similar to that seen in resting pulmonary arterial hypertension (PAH), and EPAH individuals are at risk of developing resting PAH. Patients with collagen vascular disease, especially scleroderma, are at risk for EPAH and its presence indicates a relatively poor prognosis. The prevalence of EPAH in scleroderma may be as high as 50%. The utility of pulmonary vasodilator therapy for EPAH is not well defined; however, a sizable subgroup of EPAH patients will achieve an improvement in symptoms.

Contents

1. Introduction

Pulmonary Hypertension (PH) is defined as a mean pulmonary arterial pressure (PAP) of greater than or equal to 25 mmHg at rest [1]. Pulmonary arterial hypertension (PAH), a primary vasculopathic form of PH, carries a high mortality and, if untreated, has an

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average survival of less than 3 years [2]. The clinical significance of PAH is compounded by the fact that it often affects young, otherwise healthy people.

As opposed to PH found at rest, exercise pulmonary hypertension (EPH) indicates a normal pulmonary arterial pressure at rest but an abnormal increase of mean PAP (mPAP) during exercise. Prior to 2008, EPH was defined by an mPAP greater than 30 mm Hg during exercise. The cut-off of 30 mmHg was considered reasonable but was never rigorously validated. In 2008, a special task force at the 4th World Symposium on PH (Dana Point, California) opined that there was inadequate evidence to establish a specific cut-off mPAP value during exercise that had clinical or prognostic significance, and recommended that exercise criteria be eliminated from the definition of PH [3]. Over the ensuing years, the PH community has wrestled with the approach to exercise elevations in mPAP and pulmonary vascular resistance (PVR) in terms of their clinical significance, need for monitoring and therapeutic intervention. In this manuscript, we will review the data concerning mPAP elevations during exercise as well as the approach to exercise PAH (EPAH)- the arterial form of EPH.

2. Normal response of the pulmonary circulation to exercise

Increased oxygen demand during aerobic exercise requires a proportional increase in cardiac output (Q). A several-fold increase of the right ventricular output would require a proportional increase of the PAP if the PVR remained unchanged. Normal subjects are able to accommodate an increase in cardiac output without a proportional increase of the pressure because of the phenomena of vasodilation and vascular recruitment in the pulmonary vasculature. Thus, a relatively low transpulmonary gradient is maintained. This is an essential property of the pulmonary vasculature because, compared to the left ventricle, the right ventricle has less muscle mass and is incapable of handling the high afterloads generated by the systemic circulation. As myocardial work is directly proportional to the transmural pressure, the limited increase in pulmonary arterial pressure aids in conserving myocardial energy.

PAP (mostly systolic) can be estimated echocardiographically [4]; however, echocardiographic estimates are not sufficient for securing the diagnosis of PH. Some echocardiographic methods are tedious and have lower reproducibility (e.g. measuring the ratio of the time to peak pulmonary velocity to ejection time) [5]. It is problematic to obtain reliable pressure measurements by echocardiography during exercise. Furthermore, mPAP and PVR cannot be directly measured by echocardiography. The Chemla equation [6] (mPAP = 0.61*RVSP+2) is sometimes used to derive the mPAP from right ventricular pressure (RVSP), which is relatively easy to estimate based on the peak tricuspid regurgitation velocity by Doppler echocardiography. Ultimately, cardiac catheterization is required for accurate measurements.

Even though early studies suggested that normal individuals demonstrated no significant increase in their PAP with mild supine exercise [7], subsequently it was well documented that PAP invariably increases with submaximal to maximal effort [8–10]. A review of 47 studies totaling more than one thousand right heart catheterizations from healthy individuals found a mean PAP of 14.0 mmHg at rest, 20.8 mmHg with slight exercise and 25.6 mmHg with maximal exercise [10] (Fig. 1).

If we define the upper limit of normal (ULN) as the mean ± 1.96 standard deviations (SD), these data suggest that only 2.5% of the general population will have pulmonary pressure exceeding 20.6 mmHg at rest, 28.5 mmHg with mild exercise and 36.6 mmHg with maximal exercise.

The range of resting mPAP between 20 and 25 mmHg does not meet the definition of PAH, though it is not “normal” by statistical standards (Fig. 1). This safety margin was adopted in order to avoid overdiagnosing patients without evidence that treatment would be beneficial. This gray zone is often referred to as “borderline” PAH. We know that EPAH will progress to resting PAH, at least in some cases (vide infra). That progression will necessarily pass through a (transitional) phase of borderline resting pulmonary hypertension. Therefore, EPAH, borderline PAH and resting PAH may often result from the same pathomechanism.

Highly-trained athletes demonstrate pulmonary hemodynamics that differs from the general population. Aerobic conditioning allows an individual to achieve a high cardiac output by sustaining higher pulmonary pressures, with RVSP measurements exceeding 60 mmHg having been documented [11]. The PVR typically falls below 32 dyn cm^{-5} s (0.4 Wood units) [12] during peak exercise but may reach the limit of recruitment and distention of the pulmonary vasculature. Further increases in the cardiac output would require the PAP to rise. Reaching the PVR adaptation limit is not the only mechanism of pulmonary hypertension in athletes. Compared to untrained individuals, LVEDP as high as 25 mmHg with exercise mmHg has been documented [12,13]. The ability to maintain a high cardiac output requires that the left ventricle accommodate a higher venous return that results in a higher LVED volume and pressure despite the improved left ventricular compliance seen from aerobic conditioning [12,14,15]. Therefore, a high PAP during exercise in highly fit individuals does not imply the presence of a cardiopulmonary disorder.

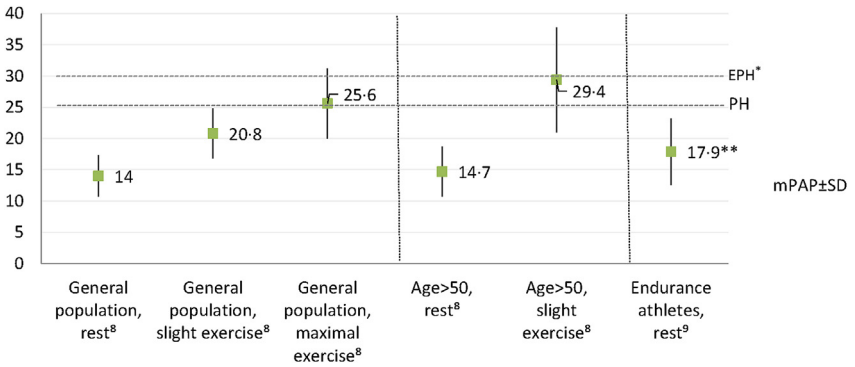

Fig. 1. Mean pulmonary artery pressure at rest and with exercise. *Definition prior to 2008; **mPAP derived from echocardiographic measurement of systolic right ventricular pressure (Chemla formula) [6]; mPAP = mean pulmonary arterial pressure; SD = standard deviation; PH = pulmonary hypertension; EPH = exercise pulmonary hypertension.