Ask the Expert

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What is the current status regarding exercise-induced pulmonary hypertension (PH)?

Nothing in the field of PH generates as much discussion or remains so controversial as the question, "What do you think about exercise-induced PH?" The reason is that, clinically, this is a very relevant question in PH. It may arise in a patient who presents with dyspnea with activity. Echocardiography shows essentially normal pulmonary artery systolic pressure (PASP) at rest and pulmonary function tests are also unrevealing. However, the patient describes ongoing and progressive limitations of activity and tells you that the symptoms are only present with exercise. You perform the 6-minute walk distance, which is not normal. This leads to an inquiry regarding whether patients should be evaluated for pulmonary arterial pressure (PAP) response to exercise.

How to define or assess exercise-induced PH is unclear. This subject was the focus of intense discussion at the recent World Symposium in Dana Point. The working definition of pulmonary arterial hypertension (PAH) previously included an exercise component, specifically mean PAP (mPAP) ≥25 mm Hg at rest or 30 mm Hg with exercise with normal left sided filling pressures (pulmonary capillary wedge pressure ≤15 mm Hg) and elevated postvoid residual (>3 Wood units).[1] However, after reviewing available evidence, it was recognized that there was no standardized agreement as to how to define exercise-induced PH.[2] Therefore, the exercise portion of the definition of PAH has been removed.

A systematic review of published data revealed that a significant age-related difference in response to exercise is present.[2,3] While there were only minor differences in PAP at rest, during slight (HR 100-110 bmp) and submaximal (HR 130-135 bpm) exercise, mPAP was significantly higher in older patients (>50 years of age). The upper limit of normal with slight exercise was 29 mm Hg for people <30 years of age, 30 mm Hg for those 30 to 50 years of age, and 45 mm Hg for people >50 years of age. During submaximal exercise, the upper limit of normal was 33 mm Hg for subjects <30 years of age, 36 mm Hg for those between 30-50 years of age, and 47 mm Hg for subjects >50 years of age. Degree of physical training has also been shown to affect PAPs with exercise. Using supine bicycle in 40 healthy patients, 26 who were highly conditioned athletes, the athletes had a higher PASP with exercise than other volunteers (~50 mm Hg vs <30 mm Hg); this difference is due in part to the higher stroke volume among the athletic cohort.[4] In a large series of patients undergoing advanced cardiopulmonary exercise testing for unexplained dyspnea on exertion, the group at Massachusetts General Hospital described distinct patterns of ventilator equivalents and PAP responses to maximal exercise.[5]

Currently, there is no consensus on how to best evaluate for exercise-induced PH. There have been many studies which have used Doppler echocardiography to assess PAP response to exercise. Although readily available and convenient, exercise echocardiogram has several limitations: inability to measure left sided filling pressures (to evaluate for diastolic dysfunction with activity) and cardiac output (high output failure, increase in PASP due to increase in stroke volume), as well as limitations due to poor acoustic window in some patients.

Thus, right heart catheterization with exercise appears necessary for accurate assessment of PAPs in response to activity, of which no agreement exists on the best method. Some clinicians utilize arm exercise with saline bags as weights, most commonly used when femoral access is utilized for right heart catheterization. This approach has limitations due to movement artifacts that could interfere with pressure tracings and difficulty in obtaining sufficient exercise using upper limbs alone. Others have used bicycle with PA catheters placed via internal jugular; this has the potential to produce most reliable results since obtaining PAPs, wedge pressure (immediately upon cessation of activity), and mixed venous and/or cardiac output can be performed. Some investigators use the bicycles in supine position while others use upright ones.

The other unknown factor is if exercise-induced PH should be considered for patients who are at high risk for PAH (family history, setting of associated conditions such as connective tissue disease) with no other explanation for symptoms of dyspnea. Recently, Steen et al published finings in 54 scleroderma patients who underwent exercise echocardiography confirmed by right heart catheterization and determined that exercise studies may be a good method of diagnosing PH early in the high-risk population.[6]

The experts at the Dana Point meeting, based on these data, concluded that further, long-term studies are needed before we can reach any specific conclusions regarding the clinical significance and need for treatment of exercise-induced PH.

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Ask the Expert

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What role does cardiac magnetic resonance imaging (cMRI) have in managing pulmonary arterial hypertension (PAH) patients?

The key determinant of survival in PAH is right ventricular (RV) function. Mortality in PAH is not caused by the elevated pulmonary artery pressures *per se* but by the resultant RV dysfunction and failure. The RV is designed to perform in a low resistance system; ie, the normal pulmonary vasculature. When the RV has to pump the stroke volume against the elevated resistance in PAH, an initial adaptive response occurs in the form of myocardial hypertrophy. Enlargement soon follows in a further compensatory effort of the RV to maintain stroke volume by increasing preload. However, decrease in contractility results in clinical evidence of right heart failure manifested by elevated filling pressures, ascites, and low cardiac output.[1]

The importance of RV functional parameters in determining survival was recognized early from the results of the Primary Pulmonary Hypertension Registry Study.[2] The hemodynamic indices associated with worse outcome were increased right atrial pressure (>12 mm Hg), reduced cardiac index (<2.0 L/min/m^2), and elevated mean pulmonary arterial pressure (>55 mm Hg). The first 2 parameters, which reflect functional capability of the RV, have been validated in other studies over the years as reliable hemodynamic markers with excellent correlation to outcome.

However, as stated in the recent National Heart, Lung and Blood Institute RV Working Group report, the "…knowledge about the role of the right ventricle in health and disease historically has lagged behind that of the left ventricle …. The right ventricle has generally been considered a mere bystander, a victim of pathological processes affecting the cardiovascular system."[1]

This "lag" may be due in part to the difficulty in imaging and quantifying the RV structure and function with Doppler echocardiography. The complex geometry of the RV, its thin-walled structure, as well as its interdependent relationship with the left ventricle (LV) makes the chamber challenging to obtain reliable and reproducible measurements with echocardiography.

As stated, RV function and response to treatment are the most clinically relevant parameters to follow in PAH. Although invasive hemodynamic parameters are considered the "gold standard" for the initial diagnosis and assessing response to treatment, it is not always feasible to obtain repeated invasive measurements to follow response to treatment. Thus, growing interest is emerging in the use of cMRI in PAH, due to its high spatial resolution, accurate assessment of chamber size and function (especially the RV), and the absence of acoustic "window" limitations. Disadvantages to cMRI include lack of widespread availability, higher cost, difficulty in assessing unstable patients or those on CADD pumps, and presence of claustrophobia.

The possible uses of cMRI in PAH are promising and include accurate assessment of RV volume and mass, estimation of hemodynamics utilizing curvature ratio and PA flow velocity area, as well as a marker of remodeling with treatment. In a study of 64 patients, cMRI was compared to other conventional tests as a marker of prognosis. At baseline, predictors of mortality included conventional assessments (functional class, hemodynamics, 6-minute walk distance) and RV and LV end diastolic volume dimensions.[3] At 1-year follow-up, however, only changes in cMRI parameters of RV and LV dimensions indicating progressive RV dilatation remained significant prognostic factors. The recently completed COMPASS-3 trial evaluated, in 100 PAH patients, cMRI at baseline and after 16 weeks of treatment, along with echocardiography and invasive hemodynamics. The forthcoming results will hopefully provide the necessary information on the future use of this imaging modality. cMRI holds promise as a noninvasive tool to assess for evidence of RV response and remodeling with treatment.

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