Exercise-induced Pulmonary Hypertension

Physiological Basis and Methodological Concerns

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Exercise stresses the pulmonary circulation through increases in cardiac output ($\dot{Q}$) and left atrial pressure. Invasive as well as noninvasive studies in healthy volunteers show that the slope of mean pulmonary artery pressure (mPAP)–flow relationships ranges from 0.5 to 3 mm Hg·min·L^{-1}. The upper limit of normal mPAP at exercise thus approximates 30 mm Hg at a $\dot{Q}$ of less than 10 L·min^{-1} or a total pulmonary vascular resistance at exercise of less than 3 Wood units. Left atrial pressure increases at exercise with an average upstream transmission to PAP in a close to one-for-one mm Hg fashion. Multipoint PAP–flow relationships are usually described by a linear approximation, but present with a slight curvilinearity, which is explained by resistive vessel distensibility. When mPAP is expressed as a function of oxygen uptake or workload, plateau patterns may be observed in patients with systolic heart failure who cannot further increase $\dot{Q}$ at the highest levels of exercise. Exercise has to be dynamic to avoid the increase in systemic vascular resistance and abrupt changes in intrathoracic pressure that occur with resistive exercise and can lead to unpredictable effects on the pulmonary circulation. Postexercise measurements are unreliable because of the rapid return of pulmonary vascular pressures and flows to the baseline resting state. Recent studies suggest that exercise-induced increase in PAP to a mean higher than 30 mm Hg may be associated with dyspnea-fatigue symptomatology.

Keywords: pulmonary circulation; pulmonary vascular resistance; pulmonary arterial compliance; cardiac output; exercise capacity

After catheterization of the heart had been introduced as a diagnostic tool by Cournand and his colleagues in the 1940s (1), it was realized that many diseases are associated with elevated pressures in the pulmonary circulation and that this can be a cause of dyspnea and fatigue. The questions asked at that time were about the critical levels of pulmonary artery pressures (PAP) that would be of clinical relevance and whether differences in mechanisms of increased PAP might matter. Wood defined limits of normal based on catheterizations of the heart in 60 healthy subjects at the Brompton hospital, which showed PAP ranging from 8/2 to 28/14 mm Hg, with values never exceeding 30/15, mean 20 mm Hg (2). Consequently, he believed that "serious pulmonary hypertension" usually would be associated with much higher pressures. This view was the basis for defining resting pulmonary hypertension as a mean PAP (mPAP) higher than 25 mm Hg, thus with a safety margin of at least 5 mm Hg above the upper limit of normal (3, 4), still agreed upon at the most recent 2008 expert consensus conference held in Dana Point, California (5). Wood and his contemporaries extrapolated the Poiseuille-Hagen notion of resistance as a ratio between a driving pressure and flow to the pulmonary circulation. Pulmonary vascular resistance (PVR) was defined as the ratio of the difference between mPAP and left atrial pressure (LAP) divided by cardiac output ($\dot{Q}$).

$$\mathrm{PVR} = (\mathrm{mPAP} - \mathrm{LAP})/\dot{Q}$$

The simple use of the PVR equation rewritten as

$$\mathrm{mPAP} = \mathrm{PVR} \times \dot{Q} + \mathrm{LAP}$$

was at the basis of the hemodynamic classification of pulmonary hypertension being caused either by an increased $\dot{Q}$, an increased LAP, or an increased resistance, and identification of associated causal conditions (2). As it was already known that $\dot{Q}$ increases linearly with increased V_{O_2} or workload (6), it was also realized that PAP could remain within limits of normal at rest but briskly increase with exercise in the presence of increased resistance, such as in chronic obstructive lung disease (7) or increased LAP due to left heart failure or mitral stenosis (8).

The early hemodynamic exercise studies in normal subjects showed that LAP remained within normal limits and that mPAP did not increase "a great deal" (3). Accordingly, exercise-induced pulmonary hypertension was defined by an mPAP higher than 30 mm Hg (3, 4). Again, this was understood as a reasonable threshold for pathological values, not strictly an upper limit of normal. Like for the cut-off value of 25 mm Hg at rest, a safety margin was considered, taking into account possible errors of $\pm$2 mm Hg on invasive measurements of vascular pressures with fluid-filled catheters (3). However, participants at the expert consensus conference in Dana Point believed that this cut-off value was not sufficiently supported by the data reported in the literature and therefore decided to omit exercise from any diagnostic criteria for pulmonary hypertension (5).

In the following sections we provide a historical perspective on use of exercise to probe pulmonary vascular disease as well as a summary of recent advancements in invasive and noninvasive measurements that establish the functional significance of PAP responses to exercise.

(*Received in original form November 21, 2012; accepted in final form January 13, 2013*)

Supported by National Institutes of Health grant NIH-K23HL091106 (G.D.L.), Fonds de la Recherche Scientifique Medicale-3.4637.09 (R.N.), Actelion Chair (R.N.), Pfizer Aspire Award (G.D.L.), Marie Curie postdoctoral grant, European Respiratory Society (R.V.).

Author Contributions: R.N., R.V., B.P.D., Rajeev Saggar, Rajan Saggar, J.-L.V., G.D.L.: analysis and interpretation of data, revision of drafted article, final approval; R.N., R.V., B.P.D., G.D.L.: acquisition of data; R.N.: successive drafts of the article.

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Am J Respir Crit Care Med Vol 187, Iss. 6, pp 576–583, Mar 15, 2013

Originally Published in Press as DOI: 10.1164/rccm.201211-2090CI on January 24, 2013
Internet address: www.atsjournals.org

THE LIMITS OF NORMAL OF THE PULMONARY CIRCULATION AT EXERCISE

The first catheterizations of the right heart in normal humans during exercise were reported in the late 1940s. The results showed a small increase, no change, or sometimes a decrease in mPAP as $\dot{Q}$ was increased with moderate levels of exercise (9, 10). In 1950, Cournand and colleagues observed a sharp increase in mPAP when $\dot{Q}$ was increased to 3.5 times the resting value (11). A similar sharp rise in mPAP at flows above 350% of normal was reported a few years later in isolated perfused lungs (12). However, subsequent studies repeatedly reported a linear increase in mPAP as a function of flow in isolated perfused lungs as well as in intact human beings studied using the unilateral balloon occlusion technique (to double the flow in the contralateral lung) and/or exercise. In his review about pulmonary hemodynamics at exercise published in 1969, Fowler concluded that mPAP–flow relationships are generally best described by a linear approximation until the highest physiologically possible flows, and that previously reported take-off patterns, or disproportionate increase in PAP at the highest flows, were probably explained by a deterioration of the experimental preparation in isolated perfused lung studies and either methodological problems or diastolic dysfunction with an increase in LAP in intact human studies (13).

In 1989, Reeves, Dempsey, and Grover reviewed the published data on invasive pulmonary hemodynamic measurements during exercise in normal subjects (14). They collected 196 measurements in the supine position in 91 subjects (63 men and 28 women from six previous studies) analyzed by V_{O_2} in steps of 50 or 1,000 ml/min as workload was increased. For each step of V_{O_2}, there were no differences in PAP measurements between men and women, so that the data were pooled in the analysis. They also retrieved a total of 104 measurements in 24 subjects (23 men and 1 woman, from four previous studies and unpublished data from Wagner and Moon) who performed incremental upright exercise. This analysis established that supine exercise is associated with a slight decrease in PVR, which is explained by the distensibility of pulmonary resistive vessels in fully recruited lungs in West's zone III. In the upright position, the resting PVR was found to be higher, but the exercise PVR was the same and decreased similarly. This is explained by initial derecruitment caused by a lower $\dot{Q}$ (via decreased venous return). A higher resting PVR accounts for more marked and hyperbolic decrease of PVR at exercise reported in upright subjects (14).

Reeves and colleagues were able to find measurements at rest and at least two levels of exercise in 63 subjects (including 21 women) so that they could calculate linear regressions relating mPAP to $\dot{Q}$ in each of them. On average, each liter per minute of increase in $\dot{Q}$ was accompanied by 1 mm Hg increase in mPAP in young adult men and women. Aging to 60 to 80 years was found to be associated with a more than doubling of the slope of mPAP–$\dot{Q}$ relationships, to an average of 2.5 mm $Hg \cdot min \cdot L^{-1}$.

A more recent review of the literature of invasive pulmonary hemodynamic data in normal subjects conducted by Kovacs and colleagues confirmed these data (15). Invasive measurements of PVR were found in only 13 subjects aged more than 50 years. The review otherwise confirmed an only moderate decrease in PVR at exercise, which was, however, less important or absent in older subjects, and slopes of mPAP–$\dot{Q}$ of approximately 1 mm $Hg \cdot min \cdot L^{-1}$ in subjects of less than 50 years (15).

As noninvasive measurements allow for an easier recruitment of healthy subjects, the problem with defining the limits of normal of the pulmonary circulation during exercise was revisited using a noninvasive Doppler echocardiographic approach. mPAP was estimated from the maximum velocity of tricuspid regurgitation, LAP from the ratio of mitral flow and annulus E/E′ waves, and $\dot{Q}$ was calculated from the left ventricular outflow velocity–time integral (16). In an initial study on 25 healthy subjects aged 35 ± 14 years exercised to a maximum workload of 170 ± 51 W (mean ± SD), the slope of mPAP–$\dot{Q}$ was 1.4 ± 0.6 mm $Hg \cdot min \cdot L^{-1}$, suggesting a normal range (defined as mean − 2 SD to mean + 2 SD) from 0.2 to 2.6 mm $Hg \cdot min \cdot L^{-1}$ (17). This is very similar to previously reported invasive hemodynamic studies (14, 15). The authors repeated the measurements and derived calculations in a population of 56 healthy male and 57 healthy female volunteers aged 19 to 63 years (18). Peak exercise was associated with mPAP of 33 ± 7 mm Hg and $\dot{Q}$ of 18 ± 5 $L \cdot min^{-1}$. The slope of mPAP–$\dot{Q}$ relationships was 1.5 ± 0.5 mm $Hg \cdot min \cdot L^{-1}$, thus defining the limits of normal from 0.5 to 2.5 mm $Hg \cdot min \cdot L^{-1}$. The authors acknowledged that these measurements require the highest levels of skill and training, so that it is not known whether noninvasive stress echocardiography of the pulmonary circulation may be generally applicable. Also, more data are needed on the effects of aging.

Even though mPAP–$\dot{Q}$ plots can be described by a linear adjustment, inspection of a sufficient number of mPAP–$\dot{Q}$ coordinates discloses a slight curvilinearity (19). This is explained by the distensibility of pulmonary resistive vessels and adds to the effects of vascular recruitment to decrease PVR at exercise (14). *In vitro* measurements of pulmonary vascular distensibility (α) reveal (on average) a 2% change in diameter per mm Hg of mean pressure, and this value is remarkably constant over a wide range of animal species (19, 20). The same α of 2%/mm Hg explains essentially all of the natural curvilinearity of multipoint mPAP–$\dot{Q}$ relationships, so that the relationships between mPAP, $\dot{Q}$, and LAP can be described by the equation:

$$mPAP = \frac{\left[(1 + \alpha LAP)^5 + 5\alpha R_0 \dot{Q}\right]^{\frac{1}{5}} - 1}{\alpha},$$

where R_0 is total pulmonary vascular resistance. This equation is more complicated than the traditional PVR equation, and an α of 2%/mm Hg pressure may not seem substantial. We therefore modeled the effects of increasing α from 0.1 to 10% on the relationships between mPAP and $\dot{Q}$ at LAP maintained constant, as compared with the same relationships predicted by the "linear" model. The results are illustrated in Figure 1. It is apparent that a normal value of 2% markedly decreases mPAP at high levels of $\dot{Q}$ and that a decrease in α from 2 to 0.1% greatly increases mPAP at exercise.

A recalculation of α from multipoint mPAP–$\dot{Q}$ relationships measured in a small number of young adult volunteers in normoxia and in hypobaric hypoxia revealed a value of 2%/mm Hg, which tended to decrease in hypoxia (19). The same calculation of α on the basis of exercise stress echocardiographic measurements in 113 normal volunteers in normoxia revealed an α of 1.3 ± 1.0%/mm Hg. In this study, maximum workload and $\dot{Q}$ were higher in men than in women ($P < 0.05$), but mPAP–$\dot{Q}$ relationships were not different. However, women had a higher α (1.6 ± 1.3 vs. 1.1 ± 0.6%/mm Hg; $P < 0.05$). In addition, the average mPAP–$\dot{Q}$ slope was higher and α lower in subjects older than 50 years, even though the study did not include very old subjects (18).

A rigorous reevaluation of the upper limits of normal from the noninvasive measurements reported by Argiento and colleagues (17) indicates the upper limits of normal of mPAP at exercise of 34 mm Hg at a $\dot{Q}$ less than 10 L/min, 45 mm Hg at a $\dot{Q}$ greater than 10 and less than 20 L/min, and 52 mm Hg at a $\dot{Q}$ greater than 20 and less than 30 L/min (Figure 2). These values are in agreement with those previously reported in invasive

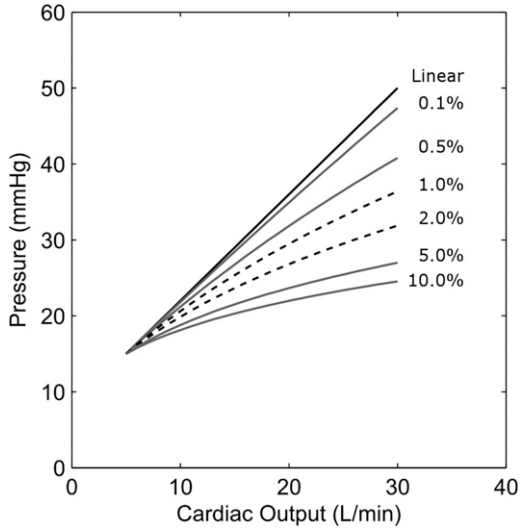

Figure 1. Modeled mean pulmonary artery pressure–flow relationships at progressively increased pulmonary vascular distensibility expressed as % increase in diameter per mm Hg pressure (or α). α is normally less than 2%/mm Hg. A slight increase in vascular distensibility may result in marked decrease in pulmonary artery pressures at exercise.

studies. Because of the uncertainty about the accuracy and precision of echocardiographic measurements of the pulmonary circulation at exercise (16), we analyzed multipoint mPAP–$\dot{Q}$ relationships measured at right heart catheterization of 24 normal subjects (15 men and 9 women, aged 54 ± 16 yr) referred to the Massachusetts General Hospital for unexplained dyspnea. These subjects qualified as healthy, as their exercise capacity was normal and no cardiac, pulmonary, or systemic disease accounting for dyspnea could be found. Twenty of them have been reported previously as normal control subjects (21). In these subjects, maximum workload was 138 ± 46 W, mPAP was 15 ± 3 mm Hg at rest and 28 ± 5 at maximum exercise, and $\dot{Q}$ was 5.2 ± 1.2 at rest and 13.8 ± 2.5 L·min at maximum exercise. The availability of 11 ± 2 minute-by-minute mPAP–$\dot{Q}$ measurements per subject during exercise (total of 269 measurements) permitted precise evaluation of pressure–flow relationships and pulmonary vascular distensibility. The slope of mPAP–$\dot{Q}$ was 1.5 ± 0.3 mm Hg·min·L^{-1}, and α was 1.4 ± 0.5% mm Hg^{-1} (Figure 2). These values are remarkably similar to those of noninvasive echocardiographic studies. Furthermore, in this limited-size healthy-subject group, α was higher in women (n = 9) compared with men (n = 15) (1.6 ± 0.5 vs. 1.3 ± 0.4 mm Hg^{-1}) and decreased in older subjects (1.6 ± 0.5 < 50 yr [n = 9] vs. 1.2 ± 0.4 mm Hg^{-1} > 50 yr [n = 15]), also very much in keeping with noninvasive measurements.

It can be seen from these noninvasive and invasive measurements that an mPAP of 30 mm Hg remains an acceptable approximation upper limit of normal at exercise as long as $\dot{Q}$ remains below 10 L·min^{-1}.

Another important aspect of these studies is that mPAP and $\dot{Q}$ rapidly return to resting values, essentially within the first 5 minutes of recovery (17). This is illustrated in Figure 3. Rapid return to normal of pulmonary vascular pressures and flows decreases the relevance of postexercise measurements as a reflection of exercise-induced changes (8).

On the other hand, as illustrated in Figure 4, the workload–$\dot{Q}$ relationship is quite variable. It is therefore preferable to express mPAP at exercise as a function of $\dot{Q}$ rather than of workload to define the functional state of the pulmonary circulation.

In summary, both invasive and noninvasive studies show a large interindividual variation of mPAP–$\dot{Q}$ relationships, with SDs in the order of the means, which makes it difficult to estimate the limits of normal. Available studies until now have been too limited in size. This is particularly true for older subjects. Noninvasive approaches allow for the recruitment of larger numbers but may be less reliable than "gold standard" invasive measurements. With all these limitations in mind, it appears that a reasonable upper limit of normal of mPAP–$\dot{Q}$ relationships is 3 mm Hg·min·L^{-1}, corresponding to a maximum exercise total PVR of 3 Wood units. Further studies will show if this limit has to be increased in older healthy subjects and for what age range this might be.

LEFT ATRIAL PRESSURE

Until the 1980s, the opinion prevailed that LAP does not change during exercise (3). However, Bevegaard and colleagues had reported an increase in wedge PAP (PAW) up to 25 mm Hg in exercising athletes (22), whereas Granath and colleagues had observed PAW over 30 mm Hg in exercising elderly subjects (23, 24). This increase in PAW with exercise has been repeatedly confirmed and found to be strongly correlated to right atrial pressure (RAP), even though RAP increases less than PAW (25–27). In their analysis of the pulmonary vascular pressure–flow relationships from at least three points during exercise, Reeves and colleagues found a linear increase in PAW with $\dot{Q}$, with a high correlation between these measurements during either supine or upright exercise, and slopes very close to one, suggesting a one-for-one mm Hg upstream transmission of changes in LAP to changes in mPAP (14). This was subsequently confirmed by Lewis and colleagues (21).

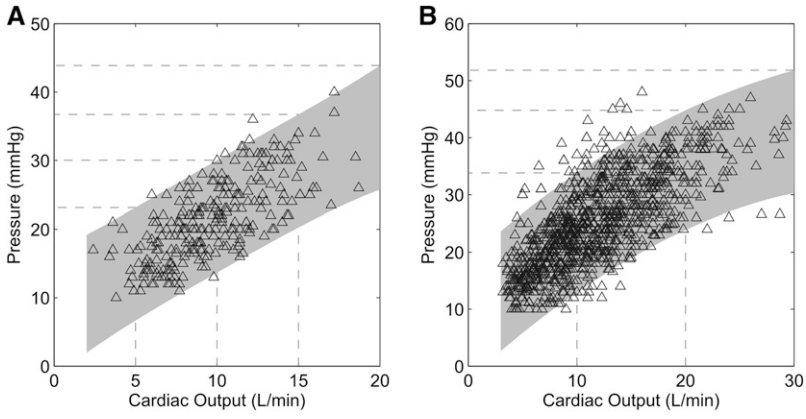

Figure 2. (*A*) Mean pulmonary artery pressure (mPAP)–$\dot{Q}$ relationships at rest and at progressively increased workloads in normal subjects measured by echocardiography (n = 113). (*B*) mPAP–$\dot{Q}$ relationships at rest and at progressively increased workloads in normal subjects measured by right heart catheterization (n = 24). The prediction bands are shown by the shaded areas. mPAP at $\dot{Q}$ values of 10, 20, and 30 L/min are shown by the stippled lines. There was a good agreement on limits of normal between noninvasive and invasive measurements. Upper limits of normal are estimated as a slope of linearized mPAP–$\dot{Q}$ of 3 mm Hg·min·L^{-1} or mPAP less than 30 mm Hg at a $\dot{Q}$ less than 10 L·min^{-1}. Adapted by permission from Reference 16.

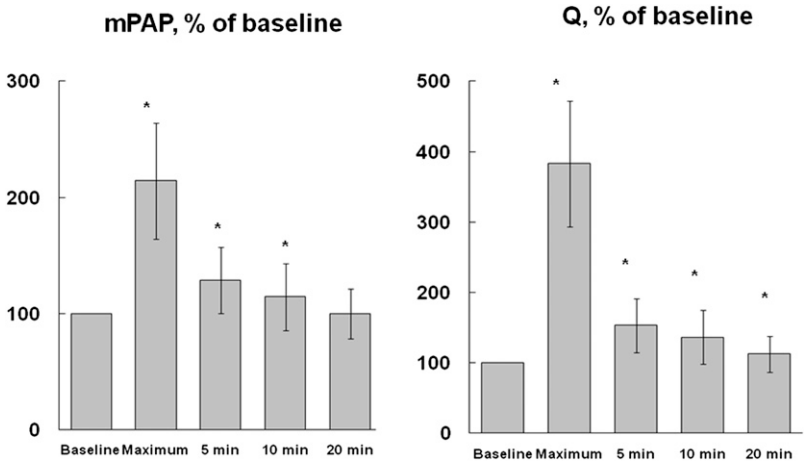

Figure 3. Changes in mean pulmonary artery pressure (mPAP) and $\dot{Q}$ at maximum exercise and after 5, 10, and 20 minutes' recovery in 25 healthy subjects. Both mPAP and $\dot{Q}$ are almost back to baseline 5 minutes after maximum exercise. Reprinted by permission from Reference 17.

There has been discussion as to whether these observations are valid in the presence of higher intrathoracic pressure swings at exercise, particularly regarding the reliability of the estimation of LAP from PAW. However, positive and negative intrathoracic pressures at high levels of ventilation likely cancel each other out in normal subjects, and LAP is probably correctly estimated by a PAW in zone III lungs at high levels of $\dot{Q}$ (14). Previous studies have reported a good agreement between PAW and LAP prospectively measured over a wide range of pressures at exercise (8, 28), even though this is not always confirmed in current retrospective quality-control studies (29).

As for the cause of increased PAW or LAP at exercise, this is likely explained by the left ventricle (LV) using the Starling mechanism matching of its flow output to peripheral demand (25). Left ventricular diastolic compliance decreases with increasing diastolic volume, which reaches a maximum at mild to moderate levels of exercise (30). This is due to the intrinsic mechanical properties of the LV, with contribution of competition for space with the right ventricle within the relatively nondistensible pericardium and possible sympathetic nervous system activation. Elite endurance athletes present with parallel increases of LAP and RAP, which occur at higher levels of exercise than in less well trained or sedentary subjects (25), suggesting that pericardial constraint is acting in the elite athletes at very high levels of exercise but not the latter group. This theory is supported by studies on athletic animals showing that when the pericardium is removed, peak end-diastolic volume, stroke volume, and maximal oxygen uptake are increased (31).

Given the hyperbolic relationship between diastolic ventricular pressure and volumes, it is curious that available data rather suggest a linear relationship between PAW and $\dot{Q}$ during exercise (14). A possible explanation for this apparent paradox is in the limited number of individual PAW–$\dot{Q}$ and mPAP–$\dot{Q}$ coordinates reported, making adequate linearity testing difficult. This issue was addressed by Stickland and colleagues in an invasive study in healthy athletes (26). Neither PAW nor RAP increased above normal before V_{O_2} values of approximately 30 $ml \cdot kg^{-1} \cdot min^{-1}$, corresponding to $\dot{Q}$ in the range of 20 $L \cdot min^{-1}$. Above this level of exercise, both PAW and RAP increased rapidly in the less-fit subjects but was very much delayed in the fittest subjects, in whom, as expected, stroke volume continued to increase.

Although Stickland and colleagues favored the hypothesis that elite athletes present with a lesser increase in mPAP because of a higher LV compliance, La Gerche and colleagues recently added the notion of the individual variability in exercise-induced decrease in PVR (32). They found that the lowest exercise PVR was associated with pulmonary shunting of agitated contrast, which could be explained by more pronounced vascular distension. They also found that lower exercise PVR and shunting of agitated contrast were associated with lower brain natriuretic peptide levels, in keeping with the notion that more pulmonary vascular distension would allow for lesser right ventricle loading conditions at high $\dot{Q}$.

Argiento and colleagues calculated LAP from transmitral mitral Doppler and mitral annulus tissue Doppler ratio of E and E′ waves in normal exercising individuals and could not find a significant change over a range of Qs from 10 to 26 $L \cdot min^{-1}$, mean 18 $L \cdot min^{-1}$ (17, 18). Although the measurement has been validated during exercise (33), the authors wondered if this negative result might have been artifactual or related to the fact that most subjects did not exercise at levels high enough to be associated with a significant increase in LAP (18).

In summary, on the basis of available exercise measurements in normal subjects, it appears that both mPAP and LAP increase in a broadly linear fashion with $\dot{Q}$. A slight curvilinearity is disclosed by attentive examination of multipoint mPAP–$\dot{Q}$ plots.

EXERCISE STRESS TESTS FOR THE DETECTION OF EARLY OR LATENT PULMONARY HYPERTENSION

Recommendations derived from the 2008 Dana Point conference warned against invasive as well as noninvasive exercise stress

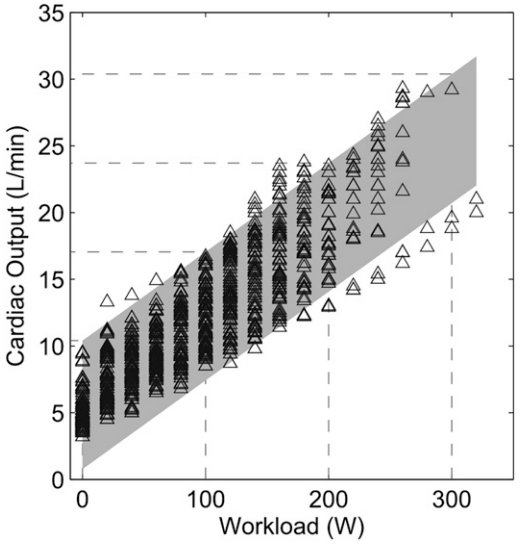

Figure 4. Cardiac output versus workload (W) relationships at exercise. There is wide range of cardiac output values at any given workload. Reprinted by permission from Reference 18.

testing for early detection of pulmonary hypertension, because of insufficient evidence (34–36). However, more recent recommendations of European and North American societies of echocardiography include exercise stress testing for the detection of pulmonary hypertension in subjects with unexplained dyspnea or valvular heart disease (37). More data are currently being gathered as concepts evolve (16).

An overview of studies of exercise stress tests of the pulmonary circulation for detection of abnormal responses is presented in Table 1. Methods and approaches were highly variable. Some studies relied on Doppler echocardiographic determination of a systolic PAP (sPAP) from maximum velocities of tricuspid regurgitant jets. Abnormal responses were defined by an sPAP greater than 40 mm Hg during exercise (38–41), an sPAP 46 mm Hg immediately after exercise (42), or a postexercise increase in sPAP by greater than 20 mm Hg (43). The measurements were sometimes combined with a determination of maximum oxygen uptake (V_{O_2}max) (41) and eventually confirmed at right heart catheterization in a proportion of patients (41, 43, 44). Some studies added detailed echocardiographic analysis of left ventricular structure and function (42) or lung function tests (43). Some reported on sPAP and $\dot{Q}$ measured at several levels of exercise, which appeared to refine the diagnosis of abnormal responses. There were patients with systemic sclerosis with increased slopes of mPAP–$\dot{Q}$ but unremarkable maximum sPAP because of a lower exercise capacity (44). A decreased α coefficient was calculated from multipoint mPAP–$\dot{Q}$ plots in a small preliminary study on asymptomatic carriers of a bone morphogenetic protein receptor–2 mutation, which is associated with a high risk of idiopathic pulmonary arterial hypertension (PAH) (45).

Invasive studies showed that increased LAP could be a common cause of increased PAP at exercise, particularly in patients with systemic sclerosis (41, 43, 46). Invasive measurements of PAP, $\dot{Q}$, PAW, and V_{O_2} have improved the understanding of the role of increased PAW as a cause of increased PAP in patients with heart failure (16), suggested that increased slopes of mPAP–$\dot{Q}$ or mPAP–workload associated with exercise intolerance (47), and shown that high PAP associated with excessive dyspnea at exercise may be predicted by high-normal resting mPAP in a substantial proportion of patients (48, 49).

Although the exercise stress test based solely on sPAP and workload measurements has shown interest in screening programs, the approach is not satisfactory because PAP is a flow-dependent variable, and the $\dot{Q}$ achieved at a given workload varies from one subject to another (8, 18) (Figure 4). Furthermore, the maximum velocity of tricuspid regurgitation is dependent on stroke volume, so that an sPAP higher than 40 to 44 mm Hg, generally accepted at the upper limit of normal at exercise in a general population (38–41), is easily exceeded by exercising athletes (17, 18, 50, 51). Furthermore, sPAP increases with aging and body weight in relation to decreased left ventricular diastolic compliance and associated increase in LAP (52).

How often abnormally increased mPAP at exercise can simply be predicted by upper limit of normal or borderline resting values has not been thoroughly evaluated. However, isolated resting measurements may be more prone to errors in the evaluation of the resistive properties of the pulmonary circulation than multipoint pressure–flow relationships because of the already discussed inherent limitations of isolated PVR calculations (14, 19, 20). Furthermore, exercise-induced pulmonary vasoconstriction, upstream transmission of LAP, and increased intrathoracic pressures are obvious causes of increased slopes of mPAP–$\dot{Q}$ relationships (2, 7). Accordingly, "out of proportion" increases in mPAP have been reported in subjects acutely or chronically exposed to environmental hypoxia (53) or in patients with either chronic lung diseases (7, 54) or left heart conditions (2, 8, 21, 29). Patients with chronic obstructive lung diseases are particularly prone to develop dynamic hyperinflation with predominantly positive intrathoracic pressures at exercise, which increases the slope of mPAP–$\dot{Q}$ (55).

Exercise-induced pulmonary vasoconstriction, increased intrathoracic pressures, or upstream transmission of exercise-induced increase in LAP may be disclosed by negative extrapolated pressure intercepts of (mPAP-PAW)–$\dot{Q}$ relationships caused by "out of proportion" increase in mPAP at the highest levels of flow (56–58). This is illustrated in Figure 5, drawn from mPAP and PAW measurements at several levels of flow in patients with advanced left heart failure (groups I and II) or resting pulmonary vascular disease (group III) (56). The zero-flow intercept of (mPAP-PAW)–$\dot{Q}$ plots represents the lowest inflow pressure of the pulmonary circulation required to generate a pulmonary blood flow and thus cannot be lower than LAP or PAW taken as the outflow pressure of the pulmonary circulation (56–58). Patients with severe pulmonary hypertension may be prone to exercise-induced pulmonary vasoconstriction because of the combined effects of decreased mixed venous P_{O_2}, acidosis, and sympathetic nervous system activation (58). This problem might

TABLE 1. REVIEW OF EXERCISE STRESS STUDIES OF THE PULMONARY CIRCULATION IN PATIENTS WITH UNEXPLAINED DYSPNEA WITH OR WITHOUT RISK FACTORS OF PULMONARY ARTERIAL HYPERTENSION

Risk Factor	n	Exercise Measurement	Method	Reference
HAPE	9	sPAP > 40 mm Hg	Echo	Grünig and colleagues (38)
PAH relative	52	sPAP > 40 mm Hg	Echo	Grünig and colleagues (39)
SSc	24	sPAP > 40 mm Hg, mPAP–$\dot{Q}$	Echo	Huez and colleagues (44)
SSc	54	↑ sPAP > 20 mm Hg post Ex	Echo	Steen and colleagues (43)
Dyspnea	78	mPAP > 30 mm Hg, V_{O_2}max	RHC	Tolle and colleagues (47)
PAH relative	291	sPAP > 40 mm Hg	Echo	Grünig and colleagues (40)
SSc	29	mPAP–$\dot{Q}$	Echo/RHC	Kovacs and colleagues (48)
SSc	52	sPAP > 40 mm Hg, V_{O_2}max	Echo/RHC	Kovacs and colleagues (41)
SSc	57	mPAP > 30, TPG > 15 mm Hg	RHC	Saggar and colleagues (46)
SSc	172	sPAP > 46 mm Hg post Ex	Echo	D'Alto and colleagues (42)
CHF	60	mPAP–$\dot{Q}$ mPAP–W	RHC	Lewis and colleagues (21)
Dyspnea, CTEPH	38	mPAP > 30 mm Hg	RHC	Whyte and colleagues (49)
COPD	98	PAP–$\dot{Q}$ or PAP–W	RHC	Mykland Hilde and colleagues (54)

Definition of abbreviations: CHF = congestive heart failure; CTEPH = chronic thromboembolic pulmonary hypertension; echo = echocardiography; Ex = exercise; HAPE = high-altitude pulmonary edema; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; RHC = right heart catheterization; sPAP = systolic pulmonary artery pressure; SSc = systemic sclerosis; TPG = transpulmonary pressure gradient; W = workload.

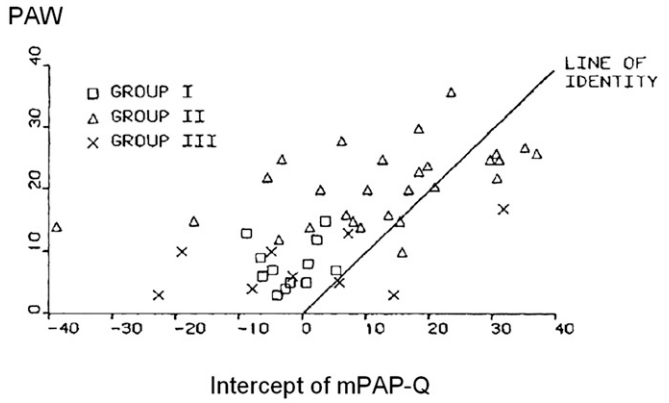

Figure 5. Negative extrapolated pressure intercepts of mean pulmonary artery pressure (mPAP)–flow plots in patients with left heart failure. Group I and II: patients with left ventricular conditions and mPAP less than or greater than 19 mm Hg, respectively. Group III: pulmonary vascular disease. Extrapolated pressure intercepts of mPAP–$\dot{Q}$ plots lower than left atrial pressure suggest pulmonary vasoconstriction at high pressures or flows. PAW = pulmonary artery wedge pressure. Reprinted by permission from Reference 56.

possibly be avoided by using low-dose dobutamine to increase $\dot{Q}$ (58), but there are no reported data to assess this alternative approach to multipoint mPAP–$\dot{Q}$ relationships.

Exercise to increase $\dot{Q}$ has to be dynamic. Resistive exercise is associated with increased systemic vascular resistance and intrathoracic pressure changes with unpredictable effects on the pulmonary circulation (59). Another important issue is in the timing of the measurements. As already mentioned, the postexercise return to normal of PAP and $\dot{Q}$ is rapid, with values almost back to baseline after only a few minutes' rest (17). Finally, even though V_{O_2} and workload are linearly related to $\dot{Q}$ (6), the measurements cannot be used as surrogates to define the functional state of the pulmonary circulation because the linearity of the relationship is lost at high levels of exercise in heart failure (8, 21) and because the mechanical efficiency of the work varies considerably from one subject to another (17).

The issue is often raised that echocardiographic measurements of the pulmonary circulation would be inaccurate. Several studies have reported on good correlations between pulmonary vascular pressures and flows measured at echocardiography and right heart catheterization (16, 37). However, correlation coefficients largely reflect the variability of the subjects being measured. If one measurement is always twice as big as the other, they are highly correlated but do not agree. Bland and Altman addressed this problem by designing difference versus average plots, to derive the bias, or the difference between the means, and whether it is constant over the range of measurements, and the limits of agreement, or the range of possible errors (60). Thus in the Bland and Altman analysis, the bias informs about accuracy, and the limits of agreement inform about precision. Two previous studies concluded about insufficient accuracy of echocardiography compared with catheterization for the assessment of pulmonary hypertension (61, 62). However, the Bland and Altman plots showed almost no bias but large limits of agreement, rather indicating good accuracy but insufficient precision. Similar results have been reported for $\dot{Q}$ measurements by thermodilution compared with the direct Fick method (63) or for PAW compared with direct measurements of LAP (30). Insufficient precision may be in part related to spontaneous physiologic variations. For example, patients with PAH may present with spontaneous variations in up to 22% for mPAP and 36% for PVR (64). It can thus be safely stated that echocardiography of the pulmonary circulation allows for accurate measurements and that the method is valid for population studies. However, insufficient precision may limit the application of the measurements for individual diagnostic purposes. Measurements below or above cut-off values must therefore always be confronted with internal or invasively obtained controls and interpreted with caution in the context of a clinical probability.

CONCLUSIONS

Exercise stress tests of the pulmonary circulation have always been part of the diagnosis of pulmonary hypertension as a hemodynamic abnormality. The approach has allowed identification of patients with normal or marginally increased mPAP at rest but with symptomatic increases in mPAP at exercise, related to either increased resistance or increased left atrial pressure. Although this differential diagnosis is of obvious therapeutic relevance, guidelines about exercise stress studies of the pulmonary circulation have not been developed until now for lack of robust evidence allowing for a consensus on clearly defined cut-off values. Matters are further complicated by the physiological variability and interdependency of pulmonary inflow and outflow pressures and $\dot{Q}$.

However, at this stage and in view of recent years' advances brought about by invasive as well as noninvasive studies, it should be possible to reach a consensus on the following statements:

- An exercise-induced increase in mPAP greater than 30 mm Hg at a $\dot{Q}$ less than 10 L/min corresponds to a diagnosis of exercise-induced pulmonary hypertension.
- Exercise stress hemodynamic investigations should report on measurements of the components of the PVR equation, that is, mPAP, LAP (or PAW), and $\dot{Q}$, to allow for a differential diagnosis of pulmonary vascular disease versus left heart failure.
- The limits of normal of mPAP–$\dot{Q}$ relationships range from 0.5 to 3.0 mm $Hg \cdot min \cdot L^{-1}$.
- A slope of mPAP–$\dot{Q}$ greater than 3.0 mm $Hg \cdot min \cdot L^{-1}$ corresponds to a diagnosis of exercise-induced pulmonary hypertension.
- Measurements are preferably invasive but are possible using Doppler echocardiography provided invasive control measurements are performed in case of doubt.

In agreement with a recent editorial (65), it is suggested that more research is needed in the following directions:

- Improved definition of physical activity–, age-, and sex-related limits of normal of the pulmonary circulation at exercise
- Improved validation of noninvasive methods for the study of the pulmonary circulation during exercise
- Further exploration of the impact of exercise-induced pulmonary hypertension on exercise capacity as defined by a whole range of gas exchange and ventilatory variables at cardiopulmonary exercise testing
- Measurements of right ventricular function at exercise
- Natural history and effects of targeted therapies in patients with exercise-induced pulmonary hypertension in the absence of identifiable left heart or lung disease, thus possibly corresponding to early-stage PAH

Author disclosures are available with the text of this article at www.atsjournals.org.

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