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EDITORIAL COMMENT

Progress in Exercise Stress Imaging of the Pulmonary Circulation and RV*

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Exercise stress measurements have been used since the early years of cardiac catheterization (1). A mean pulmonary artery pressure (mPAP) >30 mm Hg during exercise was an entry criterion for the U.S. National Institutes of Health's registry of primary pulmonary hypertension, now called pulmonary arterial hypertension (PAH), in the 1980s (2). However, exercise measurements fell from grace at world symposiums on pulmonary hypertension (PH) because of persistent uncertainties about limits of normal and clinical relevance (3,4). This has now been overcome. Evidence has been gathered that the upper limit of normal mPAP during exercise is 30 mm Hg, provided cardiac output (CO) is below 10 l/min, which corresponds to an mPAP-CO relationship of 3 mm Hg/l/min (5-7). Furthermore, invasive and noninvasive studies have shown that a higher than normal mPAP at exercise, or exercise-induced on pulmonary hypertension (EIPH), may be associated with dyspnea/fatigue symptoms, impaired exercise capacity, and decreased survival (5-7). Attention has now turned to exercise stress testing of the right ventricle (RV). Recent invasive studies combined with imaging have shown that the RV of patients with PH adapts to increased afterload by means of increased contractility (8-10) but fails to further do so during exercise (11). The clinical and prognostic relevance of these observations is being actively explored. This requires validation of simple noninvasive measurements.

In this respect, the report by Claessen et al. (12) in this issue of *iJACC* is timely. The authors investigated the pulmonary circulation and RV function at rest and during exercise using echocardiography alone or cardiac magnetic resonance imaging combined with simultaneous invasive pressure measurements (CMRip) in healthy volunteers and in patients. Slopes of mPAP-CO relationships by CMRip taken as the gold standard were >3 mm Hg/l/min in 1 of 28 healthy subjects, 1 of 8 healthy carriers of a bone morphogenetic protein 2 (*BMPR2*) mutation (the greatest known risk factor for PAH), 3 of 5 patients with persistent dyspnea after an acute pulmonary embolism, 12 of 14 patients with chronic thromboembolic PH, and all 6 patients after pulmonary endarterectomy. The abnormal responses were reasonably well predicted by echocardiographic estimates of mPAP and CO, as shown on receiver-operating characteristic curves. However, slopes of mPAP-CO relationships were steeper (by some 1 mm Hg/l/min) than those generated by CMRip, and echocardiographic signals of sufficient quality were recovered in only 63% of patients at peak exercise despite the use of contrast. Contractility of the RV, estimated by peak pulmonary artery pressure versus either end-systolic area (both by echocardiography) or volume (CMRip), increased 2-fold in patients with PH at rest but failed to increase adaptively during exercise. From these data, Claessen et al. (12) concluded that echocardiographic estimates of RV and pulmonary vascular function are feasible during exercise and can identify pathology. One would agree, but with a few reservations and while awaiting the test of clinical relevance.

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Steeper slopes of mPAP-CO found by Claessen et al. (12) at echocardiography were related to an underestimation of CO and, to a lesser extent, an overestimation of mPAP. Could this be better? Probably. In a study of a large number of patients with a wide range of PH at rest, D'Alto et al. (13) showed that

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echocardiographic estimates of CO output and mPAP were accurate compared with right-sided heart catheterization measurements (no bias on Bland and Altman analysis) and thus were adequate for population studies. However, that study also showed that insufficient precision (large limits of agreement on Bland and Altman analysis) could pose a problem for individual decision making. Such a rigorous comparison has not been repeated with exercise, but the same average slope of mPAP-CO plots and upper limit of normal of 3 mm Hg/l/min were found in several separate noninvasive and invasive studies (5–7). The lack of accuracy of echocardiography reported by Claessen et al. (12) underscores that exercise stress echocardiography requires a high level of training and dedication. A safer cutoff value for mPAP-CO relationships, increased to 3.5 mm Hg/l/min, for example, would limit false-positive results. Of course, invasive confirmation remains necessary in case of doubt.

Claessen et al. (12) argue that exercise stress echocardiography of the pulmonary circulation is best expressed by mPAP as a function of workload. This, of course, solves the problem of the possible inaccuracy of CO measurements. It makes sense, because workload and CO are linearly related (14). However, CO at any level of workload varies considerably from one subject to another; at a workload of 150 W, for example, CO may range from 10 to 20 l/min (15). This is explained by the individual variability of the mechanical efficiency of muscle work. Because CO increases during exercise in response to uptake of oxygen by working muscles, and pulmonary vascular pressures at any given resistance are determined by CO, it is preferable to define pulmonary vascular function by pressure-flow rather than by pressure-workload relationships (5).

There are quite a few cardiac and pulmonary conditions associated with EIPH, defined as an mPAP-CO during exercise >3 or 3.5 mm Hg/l/min (5–7). An exercise stress echocardiography EIPH, therefore, begs for further diagnostic workup (6). Could EIPH in patients with unexplained dyspnea represent early-stage PAH? Possibly, particularly in high-risk patients such as those with systemic sclerosis or a *BMPR2* mutation. However, the natural history of unexplained EIPH is not yet sufficiently known to consider targeted pharmacological interventions. As for the contractile reserve of the RV, uncertainties persist about its optimal noninvasive determination. Grünig et al. (16) showed that an insufficient increase in RV systolic pressure during exercise was associated with decreased survival in severe PH. However, this estimate of contractile reserve does not correlate well with gold standard measurements of end-systolic elastance (11). Claessen et al. (12) might be right that the ratio of systolic RV pressure to end-systolic surface area is a better surrogate. Others think of the tricuspid annular plane excursion corrected for systolic pulmonary artery pressure (17). The diagnostic and prognostic value of these measurements of RV function is likely to be further improved when combined with comprehensive cardiopulmonary exercise testing (16,17).

Claessen et al. (12) are to be commended for adding a convincing argument in favor of exercise imaging for the diagnosis of early-stage PH or RV failure. Much remains to be done, but their work is an important step in the right direction. As always with good studies, this one calls for more.

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