Pulmonary Vascular Function During Exercise
Progressing Toward Routine Clinical Use

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It is widely recognized that a disproportionate increase in pulmonary artery pressure (PAP) during exercise is an important clinical finding with diagnostic and prognostic utility in many cardiac and pulmonary vascular conditions.[1] It is a real clinical entity that lacks a real definition. Abnormal increases in PAP were removed from recent iterations of pulmonary hypertension definitions,[2,3] not because of a lack of clinical significance, but rather because of questionable specificity resulting from widely variable methodologies. In particular, early definitions of exercise-induced pulmonary hypertension failed to consider that PAP increases with exercise intensity in a near-linear manner in healthy individuals.[1,2] Furthermore, some investigators focused on systolic PAP (sPAP),[4,5] others on mean PAP (mPAP),[6] while estimates of right atrial pressure have been variably incorporated.[7,8] Thus, the accuracy and precision of echocardiographic PAP estimates during exercise have been much debated.

See Article by van Riel et al

The data of van Riel et al[9] in this issue of *Circulation: Cardiovascular Imaging* interrogate the accuracy of exercise estimates of pulmonary vascular hemodynamics during exercise and provides further confidence for the incorporation of exercise assessments in the assessment of the breathless patient. They performed echocardiographic estimates of PAP with simultaneous gold standard invasive pressure measurements in patients with unexplained exercise intolerance. In addition to the typical echocardiographic assessment of sPAP using the peak transtriscupid regurgitation (TR) velocity and modified Bernouilli equation, the authors estimated mPAP by tracing the TR spectral Doppler envelope. Based on the quality of the Doppler signal, the envelopes were graded as quality A, B, or C using 2 predefined criteria: (1) extension of the signal for at least half of systole and (2) well-defined border. High-quality (grade A) signals, meaning that both criteria were met, were observed in 68% of subjects at rest and in 34% of subjects at peak exercise. This distinction based on the quality of the TR signal was clinically important as the agreement of echocardiographic and invasive sPAP and mPAP measurements at peak exercise was high in subjects with grade A quality TR signals, but poor in subjects with lower quality (grade B and C) Doppler signals. In the patients with high-quality Doppler signals, abnormal pulmonary vascular reserve, defined as an increase in mPAP of >3 mm Hg/L of cardiac output by invasive assessment, was best predicted by the mPAP:workload ratio (cutoff 1.4 mm Hg/10 W). In contrast, single peak exercise sPAP and mPAP values had low specificity to differentiate between a normal and abnormal pulmonary hemodynamic response to exercise in subjects with grade B or C Doppler signals.

The findings of this study are in line with recent consensus documents that measurements of flow (cardiac output) or exercise intensity should be incorporated in the assessment of the PAP response to exercise (see Figure 1 for illustration).[1,10] Both invasive and noninvasive studies have consistently demonstrated a near-linear relationship between changes in PAP and cardiac output[1,11–13] with an expected increase in mPAP of ≈1 to 2 mm Hg/L per minute of cardiac output representing a normal pulmonary vascular response and any value >3 mm Hg/L per minute being suggestive of pathology—either in the pulmonary vasculature or further downstream in the left ventricle.[1] The data by van Riel et al[9] corroborate previous findings of our group by demonstrating that pulmonary vascular reserve can also be expressed by mPAP as a function of workload rather than flow, thereby compensating for possible inaccuracies in cardiac output measurements by echocardiography.[8] In general, determination of pulmonary vascular function by pressure–flow relationships is preferred because the determinant of PAP is flow and not workload. There is considerable interindividual variability in the relationship between cardiac output and work related to differences in body size, muscle mass, and exercise (in this case cycling) efficiency. On the contrary, there are potential advantages in using mechanical work as the denominator given that estimates of cardiac output introduce another source of calculation error, and in our aim to translate these measures into routine clinical practice, there are advantages in aiming for the simplest methodology with least off-line calculations. Finally, although there may be considerable interindividual variability in the relationship between cardiac output and work at any point in time, the relationship between the change in both variables is likely more constant. This is one of the main advantages of exercise measures—the errors involved in any single measure are attenuated by assessing trends across multiple measures. We have previously shown that the increase in cardiac output relative to the increase in workload is in fact similar between subjects.[8] Therefore, assessing the mPAP:workload or sPAP:workload ratio may be a simpler and more pragmatic

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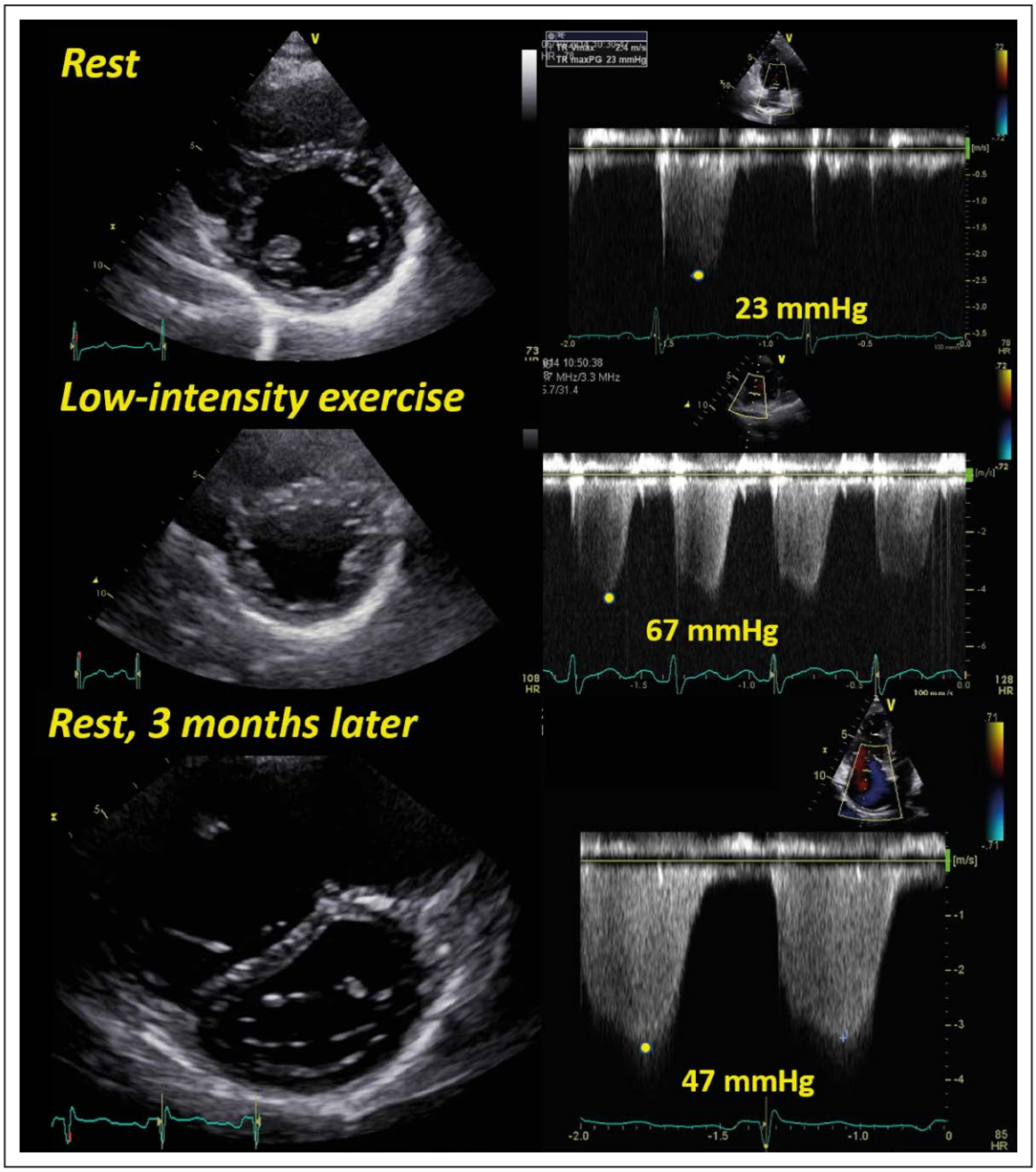

Figure 1. Exercise-induced pulmonary hypertension enables early diagnosis. A 24-y-old woman presented with breathlessness and while resting studies were normal (**top**); she had an exaggerated increase in pulmonary artery pressures at very low exercise intensity. Her echo also demonstrated inducible right ventricular (RV) dysfunction and septal flattening (**middle**). Three months later, she presented with overt pulmonary hypertension and marked RV remodeling (**bottom**).

approach to screen for abnormal pulmonary vascular function in clinical practice. There is an important caveat in variability in ergometer and cycling position. Upright cycling, for example, is more efficient and thus a higher sPAP/work relationship might be expected. It may be necessary for imaging laboratories to determine their own normal references for PAP/work, whereas the PAP/cardiac output relationship should be more transferable between investigators and clinical settings.

Although van Riel et al[9] found good agreement between echocardiographic and invasive PAP measurements in the subjects with high-quality TR signals, grade A quality signals could only be obtained in a minority (34%) of subjects. This could potentially hinder the implementation of this approach into clinical practice as the accuracy and predictability of PAP measurements was poor in patients with quality B and C Doppler signals. One explanation for the relatively low feasibility of PAP estimation may be related to the particular approach of tracing the TR Doppler envelope, which requires a well-defined border throughout systole, rather than measuring the peak velocity signal and applying the Chemla formula to derive mPAP from sPAP.[6] Hence, when the authors used the Chemla formula instead of the velocity time integral method,

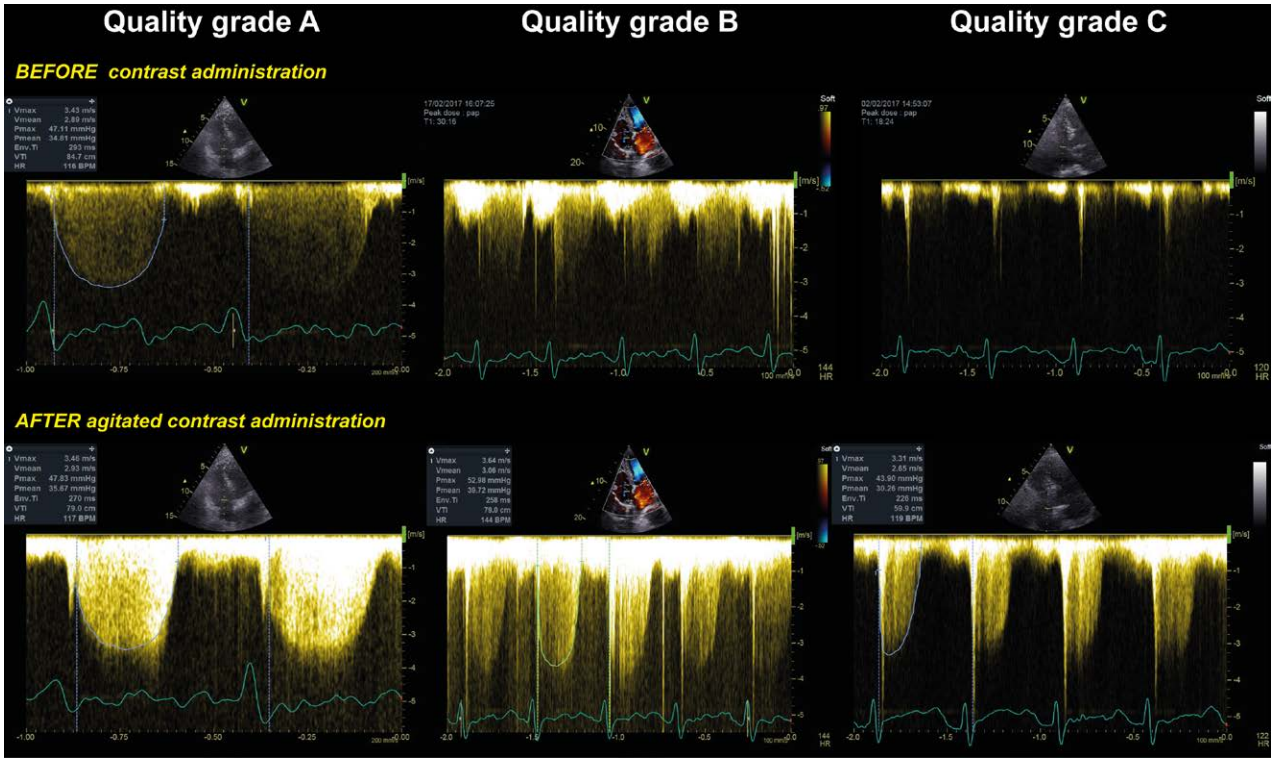

Figure 2. The value of agitated colloid contrast enhancement to improve visualization of the transtricuspid regurgitation jet. The **left** shows an example of a subject with a grade A (high-quality) Doppler signal, whereas grade B and C quality signals are depicted in the **middle** and **right**, respectively. The **top** panels show Doppler signals before administration of contrast, whereas the images in the **bottom** panels are acquired after contrast administration. In the subject with a high-quality transtricuspid regurgitation signal, similar values are obtained in the pre- and post-contrast setting. However, in both grade B and C quality signals, administration of contrast dramatically improves the visualization of the signal and the Doppler envelope can be accurately traced. Care should be taken not to overestimate pressure because of broadening of the spectral Doppler signal after contrast administration.

mPAP measurements could be obtained in all individuals and the bias tended to be lower. A second way to explain the low proportion of high-quality TR signals may be related to the lack of use of agitated contrast to enhance the TR Doppler signal. Previously, using colloid agitated contrast, we were able to obtain peak exercise PAP measurements in 69% of subjects,[8] as illustrated in Figure 2. A further important limitation in the approach taken by van Riel et al[9] is the reliance on a single measure of peak PAP. The entire assessment of exercise hemodynamic is based on an assessment at a point in which variability of measures is greatest. Other investigators have used linear regressions of multiple measures during exercise.[1,2,8,11,12] This would seem preferable given that the relationship between PAP and cardiac output (or workload) approximates a linear relationship and thus accuracy of the relationship can be refined by measures taken early in the exercise bout when measurements are less challenging. Again, this requires more off-line calculations and may be less feasible for routine clinical practice but would seem particularly important for equivocal cases or those in which the Doppler signal is less consistently excellent. It is also critical to note that measurements taken early post-exercise should not be used to assess these relationships; the rapidity and variability in recovery of hemodynamics introduces massive confounding.

What comes next? Exercise-induced pulmonary hypertension is an important entity that has suffered to gain clinical traction because of false starts with definitions and methodologies for accurate diagnosis. It is now widely accepted that it is imperative that PAPs be considered in relation to some measure of flow, either cardiac output or the indirect surrogate of physical work. van Riel et al[9] provide yet more confidence for the adoption of noninvasive assessments of pulmonary vascular hemodynamics in patients presenting with breathlessness. This will not replace invasive measures. Rather, like resting measures, exercise tests are likely to be included in a clinical workflow in which exercise testing is an important part of the early diagnostic process in which patients with abnormal or equivocal results may be considered for confirmation with invasive testing.

Disclosures

None.

References

1. Lewis GD, Bossone E, Naeije R, Grünig E, Saggar R, Lancellotti P, Ghio S, Varga J, Rajagopalan S, Oudiz R, Rubenfire M. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. *Circulation*. 2013;128:1470–1479. doi: 10.1161/CIRCULATIONAHA.112.000667.
2. Naeije R, Vanderpool R, Dhakal BP, Saggar R, Saggar R, Vachiery JL, Lewis GD. Exercise-induced pulmonary hypertension: physiological basis and methodological concerns. *Am J Respir Crit Care Med*. 2013;187:576–583. doi: 10.1164/rccm.201211-2090CI.
3. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, Manes A, Satoh T, Torres F, Wilkins MR, Badesch DB.

Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 suppl):D42–D50. doi: 10.1016/j.jacc.2013.10.032.
4. Grünig E, Janssen B, Mereles D, Barth U, Borst MM, Vogt IR, Fischer C, Olschewski H, Kuecherer HF, Kübler W. Abnormal pulmonary artery pressure response in asymptomatic carriers of primary pulmonary hypertension gene. *Circulation*. 2000;102:1145–1150.
5. Nagel C, Henn P, Ehlken N, D'Andrea A, Blank N, Bossone E, Böttger A, Fiehn C, Fischer C, Lorenz HM, Stöckl F, Grünig E, Egenlauf B. Stress Doppler echocardiography for early detection of systemic sclerosis-associated pulmonary arterial hypertension. *Arthritis Res Ther*. 2015;17:165. doi: 10.1186/s13075-015-0673-7.
6. Chemla D, Castelain V, Humbert M, Hébert JL, Simonneau G, Lecarpentier Y, Hervé P. New formula for predicting mean pulmonary artery pressure using systolic pulmonary artery pressure. *Chest*. 2004;126:1313–1317. doi: 10.1378/chest.126.4.1313.
7. Argiento P, Chesler N, Mulè M, D'Alto M, Bossone E, Unger P, Naeije R. Exercise stress echocardiography for the study of the pulmonary circulation. *Eur Respir J*. 2010;35:1273–1278. doi: 10.1183/09031936.00076009.
8. Claessen G, La Gerche A, Voigt JU, Dymarkowski S, Schnell F, Petit T, Willems R, Claus P, Delcroix M, Heidbuchel H. Accuracy of echocardiography to evaluate pulmonary vascular and RV function during exercise. *JACC Cardiovasc Imaging*. 2016;9:532–543. doi: 10.1016/j.jcmg.2015.06.018.
9. van Riel ACMJ, Opotowsky AR, Santos M, Rivero JM, Dhimitri A, Mulder BJM, Bouma BJ, Landzberg MJ, Waxman AB, Systrom DM, Shah AM. Accuracy of echocardiography to estimate pulmonary artery pressures with exercise: a simultaneous invasive–noninvasive comparison. *Circ Cardiovasc Imaging*. 2017;10:e005711. doi: 10.1161/CIRCIMAGING.116.005711.
10. Herve P, Lau EM, Sitbon O, Savale L, Montani D, Godinas L, Lador F, Jaïs X, Parent F, Günther S, Humbert M, Simonneau G, Chemla D. Criteria for diagnosis of exercise pulmonary hypertension. *Eur Respir J*. 2015;46:728–737. doi: 10.1183/09031936.00021915.
11. La Gerche A, MacIsaac AI, Burns AT, Mooney DJ, Inder WJ, Voigt JU, Heidbüchel H, Prior DL. Pulmonary transit of agitated contrast is associated with enhanced pulmonary vascular reserve and right ventricular function during exercise. *J Appl Physiol (1985)*. 2010;109:1307–1317. doi: 10.1152/japplphysiol.00457.2010.
12. Argiento P, Chesler N, Mulè M, D'Alto M, Bossone E, Unger P, Naeije R. Exercise stress echocardiography for the study of the pulmonary circulation. *Eur Respir J*. 2010;35:1273–1278. doi: 10.1183/09031936.00076009.
13. Lewis GD, Murphy RM, Shah RV, Pappagianopoulos PP, Malhotra R, Bloch KD, Systrom DM, Semigran MJ. Pulmonary vascular response patterns during exercise in left ventricular systolic dysfunction predict exercise capacity and outcomes. *Circ Heart Fail*. 2011;4:276–285. doi: 10.1161/CIRCHEARTFAILURE.110.959437.

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