Brief Report

Exercise Hemodynamics to Evaluate the Breathless Patient: Defining the Normal Pulmonary Arterial Wedge Pressure

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The diagnosis of heart failure with preserved ejection fraction (HFpEF) may appear to be straightforward, with the patient frequently having comorbidities, such as longstanding hypertension, symptoms and signs of heart failure, preserved left ventricular ejection fraction, evidence on echocardiography of impaired relaxation, and other structural abnormalities, such as left atrial enlargement and elevated circulating natriuretic peptides. However, in many cases the diagnosis may be less evident. In that situation, a form of stress test has been advocated to establish the diagnosis.[1] Exercise echocardiography can be used to noninvasively assess left ventricular filling pressures, pulmonary artery pressures, longitudinal systolic strain, and stroke volume changes with exercise. Another method that can be performed during exercise testing is right heart catheterization.[2] As an invasive test, it can provide a comprehensive hemodynamic assessment with right atrial, pulmonary, and pulmonary arterial wedge pressures as well as cardiac output.

As with any investigation, defining the normal values for right heart catheterization−derived hemodynamics, and in particular the pulmonary arterial wedge pressure, has therefore become an important topic and is the subject of the meta-analysis published by Esfandiari et al[3] in this issue of the *Journal of Cardiac Failure*. In this study the authors combine data from 32 studies of exercise hemodynamics in normal subjects to derive normal age- and sex-related changes in pulmonary arterial wedge pressure. To put this into context, the normal heart (without cardiac diagnoses or comorbidities such as hypertension and diabetes) undergoes significant changes with age. For instance, with the use of magnetic resonance imaging and ^{31}phosphorus spectroscopy we have shown that with normal aging there are significant alterations in left ventricular diastolic function, systolic function (abnormal torsion patterns though preserved ejection fraction), and impaired energetic reserve with a reduced ratio of phosphocreatine to adenosine triphosphate.[4] These changes are associated in part with age-related changes outside of the heart (afterload)[5] and are aggravated by hypertension[6] and diabetes.[7] Thus, defining what is a normal or abnormal pulmonary arterial wedge pressure, which can be expected to be influenced by these age-related phenomena, is an important issue.

In the meta-analysis compiling 32 studies with 424 healthy individuals (19% female) undergoing exercise right heart catheterization, data were stratified by age (>40 y or ≤40 y) and sex and divided into 3 exercise intensities (light, moderate, strenuous). In those ≤40 years of age, the weighted means of the pulmonary arterial wedge pressure with light exercise was 11 mm Hg (95% confidence interval 9−13 mm Hg) and with strenuous exercise 13 mm Hg (10−16 mm Hg). In those >40 years of age, with light exercise the pulmonary arterial wedge pressure was 19 mm Hg (17−21 mm Hg; $P < .05$ vs those ≤40 y) and with strenuous exercise 15 mm Hg (8−22 mm Hg). There were no significant differences between men and women, although the work rates with light and moderate exercise were lower in women. The authors conclude that the pulmonary arterial wedge pressure increases with exercise up to 20 mm Hg in those aged >40 years, and that an absolute cut off of 25 mm Hg should be used in that age group.

We have 2 main points of comment concerning this study. First, from a statistical view there is significant heterogeneity across the studies. This suggests that results from the included studies are not consistent. Regarding the I^2 statistic (Tables 3 and 4 in their paper) the authors report values often close to 100%. This statistic measures the percentage of total variation across studies that is due to heterogeneity rather than chance.[8] High heterogeneity is suggested by values >75%. As stated above, numerous very small studies are included (which may contribute to the heterogeneity effects), but there is 1 study that stands out in importance. Wolsk et al[9] (reference 8 in the Esfandiari et al paper) have previously reported exercise right

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heart catheterization haemodynamics in 62 healthy subjects aged 20−80 years. Interestingly, they reported that a diagnostic threshold for pulmonary arterial wedge pressure of ≥25 mm Hg was measured in 30% of healthy elderly participants (≥60 y), which contradicts the meta-analysis somewhat and thus leaves some uncertainty.

Where do these data fit into the bigger picture of diagnosis of HFpEF? As mentioned above, in most cases the diagnosis is clear based on simple clinical parameters and investigations, and invasive testing is not required. In the United Kingdom, the vast majority of these patients are seen in primary care and by general cardiologists, and right heart catheterization (especially with exercise) is performed only in the handful of transplant and pulmonary hypertension centers. Thus, exercise right heart catheterization would seem to have a limited applicability. That is not to say that current "guidelines of seeing breathless patients" with elevated levels of natriuretic peptides are perfect,[10] because in a recent report we have demonstrated that >50% of breathless patients with increased natriuretic peptides referred to an acute heart failure clinic do not have heart failure.[11] Better diagnostic noninvasive tools are needed closer to primary care. For example, a simplified exercise step test with noninvasively measured cardiac output with the use of a novel electrical signal processing technology is one possibility that is currently being investigated.[12] Thus, while Esfandiari et al's report is an important development in our understanding of HFpEF, we still have much to learn.

Disclosures

None.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016;37:2129–200.
2. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:588–95.
3. Esfandiari S, Wolsk E, Granton D, Azevedo L, Valle FH, Gustafsson F, et al. Pulmonary artery wedge pressure at rest and during exercise in healthy adults: a systematic review and meta-analysis. J Card Fail. 2018. pii: S1071-9164(18)31132-1 Published online October 23.
4. Hollingsworth KG, Blamire AM, Keavney BD, MacGowan GA. Left ventricular torsion, energetics, and diastolic function in normal human aging. Am J Physiol Heart Circ Physiol 2012;302:H885–92.
5. Parikh JD, Hollingsworth KG, Wallace D, Blamire AM, MacGowan GA. Normal age-related changes in left ventricular function: role of afterload and subendocardial dysfunction. Int J Cardiol 2016;223:306–12.
6. Parikh JD, Hollingsworth KG, Wallace D, Blamire AM, MacGowan GA. Left ventricular functional, structural and energetic effects of normal aging: comparison with hypertension. PLoS One 2017;12:e0177404.
7. Cassidy S, Hallsworth K, Thoma C, MacGowan GA, Hollingsworth KG, Day CP, et al. Cardiac structure and function are altered in type 2 diabetes and nonalcoholic fatty liver disease and associate with glycemic control. Cardiovasc Diabetol 2015;14:23.
8. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–60.
9. Wolsk E, Bakkestrom R, Thomsen JH, Balling L, Andersen MJ, Dahl JS, et al. The influence of age on hemodynamic parameters during rest and exercise in healthy individuals. JACC Heart Fail 2017;5:337–46.
10. Chronic heart failure in adults: diagnosis and management. NICE guideline [NG106]. Available at: https://www.nice.org.uk/guidance/ng106. Accessed 14 November 2018.
11. Fazal IA, Bhagra SK, Bailey KM, Dermot Neely R, MacGowan GA, Skinner JS. Impact of using different guideline recommended serum natriuretic peptide thresholds on the diagnosis and referral rates of a diagnostic heart failure clinic. Int J Clin Pract 2015;69:1349–56.
12. Charman SJ, Okwose NC, Stefanetti RJ, Bailey K, Skinner J, Ristic A, et al. A novel cardiac output response to stress test developed to improve diagnosis and monitoring of heart failure in primary care. ESC Heart Fail 2018;5:703–12.