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 (HF pEF) is usually relatively straightforward, with the patient frequently having co-morbidities such as long standing hypertension, symptoms and signs of heart failure, preserved left ventricular ejection fraction, evidence of impaired relaxation on echocardiography and other structural abnormalities such as left atrial enlargement, and elevated circulating natriuretic peptides. However, in some 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 non-invasively 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]. Whereas 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 haemodynamics, and in particular the pulmonary arterial wedge pressure, has thus become an important topic which is the subject of a meta-analysis published by Esfandiari and colleagues[3] in this issue of the *Journal of Cardiac Failure*. In this study they combine data from 32 studies of exercise haemodynamics in normal subjects to derive normal age- and gender-related changes in pulmonary arterial wedge pressure. To put this into context, the normal heart (without cardiac diagnosis or co-morbidities such as hypertension and diabetes) undergoes significant changes with age. For instance, using magnetic resonance imaging and ^{31}phosphorous spectroscopy we have shown that with normal aging there are significant changes in left ventricular diastolic function, systolic function (abnormal torsion patterns though preserved ejection fraction), and impaired energetic reserve with a reduced phosphocreatine to adenosine triphosphate (PCr/ATP) ratio[4]. These changes are in part

associated to 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 (> or $\leq$ 40 years), and gender, and divided into 3 exercise intensities (light, moderate, strenuous). In those $\leq$ 40 years of age, the weighted means of the pulmonary arterial wedge pressure with light exercise was 11 mmHg (95% confidence limits: 9-13 mmHg) and with strenuous exercise 13 mmHg (10-16 mmHg). In those >40 years of age, with light exercise was 19 mmHg (17-21 mmHg) ($P<0.05$ vs $\leq$ 40 years) and with strenuous exercise was 15 mmHg (8-22 mmHg). There were no significant differences between men and women, though 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 20mmHg in those aged >40 years, and that an absolute cut off of 25 mmHg should be used in this age group.

There are 2 main points of comment about this study. Firstly, from a statistical view there is significant heterogeneity across the studies. This suggests that results from the included studies are not consistent. Reporting the I^2 statistic (tables 3 and 4) 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 over 75%. As stated above there are numerous very small studies included (which may contribute to the heterogeneity effects), but there is one standout study that is of considerable importance. Wolsk

et al[9] (reference 8 from the Esfandiari paper) have previously reported exercise right heart catheterization haemodynamics in 62 healthy subjects aged 20 to 80 years. Interestingly they reported that a diagnostic threshold for pulmonary arterial wedge pressure of $\geq$ 25 mm Hg was measured in 30% of healthy elderly participants (60 – 79 years), which contradicts the current paper somewhat, and thus leaves some uncertainty.

Where do these data fit into the bigger picture of diagnosis of HF pEF? As mentioned above, in most cases the diagnosis is clear based on simple clinical parameters and investigations, and invasive testing is not required. Writing from the United Kingdom, where the vast majority of these patients are seen in primary and secondary care, and right heart catheterization (especially with exercise) is performed in the handful of transplant and pulmonary hypertension centres, exercise right heart catheterization seems 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], when in a recent report we have shown that over 50% of breathless patients with increased natriuretic peptides ??? referred to an acute heart failure clinic do not have heart failure[11]. Better diagnostic non-invasive tools are needed closer to primary care. For instance, a simplified exercise step test while non-invasively measuring cardiac output using a novel electrical signal processing technology is one possibility that is currently being investigated[12]. Thus, this study is an important development in our understanding of HF pEF, though we still have much to learn.

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Disclosures:

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