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Pulmonary Arterial Hypertension and Sex in the Right Ventricle: It Is an Interesting Picture!

Right ventricle (RV) function determines clinical course and long-term prognosis in patients with pulmonary arterial hypertension (PAH) (1). Though PAH is common in females, it has been established that RV function is inferior in male patients with PAH when compared with female patients with PAH. On cardiac magnetic resonance imaging, despite having a similar degree of pulmonary vascular disease, male patients with PAH have lower RV ejection fraction than age-matched female patients with PAH (2, 3). In addition, the improvement in RV function after pulmonary vasodilator therapies is less in male versus female patients with PAH (3). The difference in RV function response to pulmonary vasodilator therapies partially explains the survival disadvantage in male PAH patients (3). In fact, similar sex differences in RV function have also been documented in healthy individuals (4), patients with pulmonary hypertension because of left heart disease (5), and patients with pulmonary hypertension secondary to chronic lung disease (6). However, all prior studies assessing sex differences in RV function are based on load-dependent measures, which are not a true measure of RV contractility (i.e., when the RV afterload is high, the load-dependent measures can be lower despite normal RV contractile function) (7).

There is growing recognition of the importance of the interaction between the RV and the pulmonary arterial system in PAH, which is referred to as RV–pulmonary artery (RV-PA) coupling (8). RV-PA coupling represents efficient delivery of the power generated by the RV contractility into the pulmonary arterial system. In other words, it is a measure of RV adaptation to the increased afterload. During the early stages of PAH, the RV undergoes concentric hypertrophy and increases its contractile function to match the increase in afterload. This RV adaptation maintains a normal RV-PA coupling (9). However, with progression of PAH, the RV can no longer undergo hypertrophy or increase its contractile function to match the afterload. This leads to RV-PA uncoupling, RV failure, and eventually death (9).

The best measure of RV-PA coupling is the relationship between end-systolic elastance (Ees), a load-independent measure of intrinsic RV contractility, and effective arterial elastance (Ea), a measure of RV afterload (9). These measures are calculated from invasive RV pressure–volume loop analysis obtained using high-fidelity micromanometer catheters. An ideal RV-PA coupling (Ees/Ea) is 1.5–2, and an Ees/Ea ratio <0.8 defines RV-PA uncoupling (10). In addition to RV-PA coupling, pressure–volume loop analysis can assess RV diastolic function by measuring Tau and RV end-diastolic elastance (Eed) (9). Eed is a load-independent measure of RV diastolic function. It is calculated from the relationship of change in pressure and volume at end-diastole (9). Tau is a load-dependent measure of RV diastolic function. It is calculated from the reciprocal of the natural logarithm of the early maximal fall in ventricular pressure during the isovolumetric phase of diastole (9). Though load-dependent measures of RV systolic function are lower in male patients with PAH, it is unknown whether there are similar sex differences in load-independent measures of intrinsic RV contractility, RV-PA coupling, and RV diastolic function in patients with PAH.

In this issue of the *Journal*, Tello and colleagues (pp. 1042–1046) dig deeper to better understand sex differences in RV function in patients with PAH using pressure–volume loop analysis (11). They prospectively studied 57 patients with PAH, of whom 33 (58%) were females. The pressure–volume relationships were assessed using the single-beat method (12) in all 57 patients and the multibeat technique (8) with inferior vena cava occlusion in 37 patients. All patients except two also had a cardiac magnetic resonance imaging. Despite similar RV afterload (Ea), female patients had higher RV contractile function (Ees) and better RV-PA coupling (Ees/Ea) than male patients. Tau was lower in females than in males, indicating better RV diastolic function; however,

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there was no difference in Eed. The authors noted similar findings when they restricted their analysis to idiopathic PAH patients only. There were no differences between males and females in the traditional clinical, echocardiographic, cardiac magnetic resonance imaging, and hemodynamic measures of RV function.

Tello and colleagues should be commended for their extensive work and novel finding. RV pressure–volume loop measurements are cumbersome and difficult to perform. To our knowledge, this is the largest series of PAH patients with RV pressure–volume loop assessments. The male and female patients were matched for age. The authors used the gold-standard multibeat method in the majority of the patients (63%), which is an additional strength. Unlike the single-beat method, there are no assumptions in the calculation of Ees in the multibeat method (13). Furthermore, the current study demonstrates the increased sensitivity of pressure–volume loop analysis to uncover RV dysfunction compared with the traditional hemodynamic or imaging measures. This study clearly establishes that female patients with PAH adapt better to the increased afterload by increasing RV contractility than male patients with PAH. The Ees/Ea ratio in female patients was above the RV-PA uncoupling threshold of 0.8.

However, it still remains unclear whether RV diastolic adaptation is also better in female patients compared with male patients with PAH. Though Tau was lower (i.e., better relaxation) in females, there was no difference in RV Eed, which is a better measure of RV diastolic function (9, 13). This is unexpected, as RV diastolic dysfunction, in general, occurs before RV systolic dysfunction (14). It is possible that the authors were not able to elucidate a sex difference in RV diastolic function because of the small number of patients in this study, but this needs to be assessed in the future. Similarly, it is unclear whether the sex difference in RV-PA coupling by itself can explain the better survival in female patients with PAH compared with male patients with PAH. Finally, when the authors restricted their analysis to patients with idiopathic PAH only, the difference in Ees between females and males narrowed. This was mainly driven by a reduction in Ees in females with no change in Ees in males. This raises a question of whether the female versus male difference in Ees is more marked in patients with associated PAH.

Now having established that females have better RV systolic adaptation in PAH, we need to better understand the mechanisms underpinning this sex difference. Solving this enigma can help us develop novel therapies targeted to improve RV function in patients with PAH. Preclinical and clinical data, to date, link sex hormones to the difference in RV function (15–17). Based on this, in fact, there are two ongoing clinical trials that are altering sex hormones as a treatment option for PAH (ClinicalTrials.gov identifiers: NCT03229499 and NCT03648385). In the interim, we need to monitor RV function more closely in our male patients with PAH and treat them aggressively. ■

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