



## Editorial

# The Complex Relationship That Is RV-PA Coupling and Its Relevance to Managing Congenital Heart Disease

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*See article by Egbe et al., pages 914–922 of this issue.*

Although attention to the right heart in the general cardiac population has increased in recent years, it has always been an important focus in the area of congenital heart disease (CHD). The right ventricle (RV) is regularly assessed in patients with tetralogy of Fallot (TOF) and isolated pulmonary valve disease who have chronic significant pulmonary regurgitation (PR).

### Assessment of the Right Heart in Chronic PR

Transthoracic echocardiography (TTE) remains the routine imaging modality for monitoring these patients at most institutions. This can be challenging because of the retrosternal position of the RV limiting acoustic windows and variable RV geometry. The American Society of Echocardiography imaging guidelines for patients with repaired TOF suggest that RV size assessment can include: (1) RV end diastolic cross-sectional area in apical view;  $< 20 \text{ cm}^2/\text{m}^2$  is associated with an RV end diastolic volume index of  $< 170 \text{ mL}/\text{m}^2$  on cardiac magnetic resonance imaging (MRI); and (2) basal diameter  $> 42 \text{ mm}$  and midventricular diameter  $> 35 \text{ mm}$  indicates RV dilation.<sup>1</sup> Although tricuspid annular plane systolic excursion (TAPSE) and RV systolic tissue doppler velocity are important parameters for the assessment of RV systolic function, they are limited to measuring longitudinal shortening of the RV free wall while excluding the contribution of the RV septum to the overall systolic function, which is commonly abnormal in this CHD population.<sup>1,2</sup> Fractional area change (FAC) is intended to overcome these limitations but is limited by endocardial definition and volumetric modelling of the RV. Furthermore, only a modest correlation between RV FAC and cardiac MRI-derived RV ejection fraction has been shown.<sup>1</sup> Three-dimensional echocardiographic volume assessment of the RV is not routinely performed and current normative values are on the basis of

small populations. Furthermore, 3-D echocardiography has been reported to consistently underestimate RV volumes compared with cardiac MRI.<sup>3</sup>

In asymptomatic patients, the timing of pulmonary valve replacement is in large part guided by RV volumes and ejection fraction. Because of the complexity of the RV and limitations of TTE, cardiac MRI is currently the reference standard for RV assessment. The 2018 American College of Cardiology/American Heart Association Adult CHD guidelines recommend replacing the pulmonary valve in the setting of greater than mild RV dysfunction and before the RV end diastolic volume exceeds  $160 \text{ mL}/\text{m}^2$  or the end systolic volume exceeds  $80 \text{ mL}/\text{m}^2$  measured using cardiac MRI.<sup>4</sup> Intervention is also recommended on the basis of RV and left ventricle relationship parameters.<sup>4</sup>

### RV-Pulmonary Artery Coupling: Is This What We Have Been Waiting for?

RV-pulmonary artery (PA) coupling refers to the relationship between RV contractility and RV afterload. Contractility is the load-independent or intrinsic RV function. The RV and PA are “coupled” in that RV contractility should “match” the afterload. If RV afterload were to increase, the RV contractility should similarly increase (ie, through RV hypertrophy and adaptation to load), so that RV function is maintained and RV-PA coupling remains preserved. This is illustrated in a study in which the relationship between invasively derived RV ejection fraction and PA pressure in a cohort of patients with pulmonary hypertension due to left ventricular systolic dysfunction was reported.<sup>5</sup> In the presence of pulmonary hypertension but preserved RV ejection fraction, the outcomes were similar to the group without pulmonary hypertension. In contrast, in the presence of pulmonary hypertension and reduced RV ejection fraction there was a markedly worse outcome. It was not the pulmonary hypertension, but rather RV-PA uncoupling that was associated with worse outcomes. The most widely accepted index of RV-PA coupling is the relationship between arterial elastance ( $E_a$ ; a measure of afterload) and ventricular elastance ( $E_{\text{max}}$ ; a measure of contractility), determined invasively using pressure-volume loop analysis. A rising  $E_a/E_{\text{max}}$  reflects

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uncoupling of the RV-PA interaction, in which afterload is exceeding the ability of the RV function to adapt. A steady  $E_a/E_{max}$  in the face of increasing afterload reflects a concurrent compensatory increase in RV function.

RV-PA coupling should also be considered in the TOF and valvular pulmonary stenosis (VPS) populations with significant PR. The commonly used echocardiographic or MRI parameters of RV function are load-sensitive in that despite seemingly normal RV function they still do not give information on the adequacy of RV function for a given afterload. In the setting of significant PR the RV is faced with increasing preload and afterload. The preload is due to the significant PR and increasing RV end diastolic volume. The increase in RV afterload in chronic PR is not completely understood. As expected there is an initial increase in PA compliance because of the PA volume overload. Overtime and into adulthood there is likely a loss of PA elastance leading to increased stiffness and hence increased RV afterload.<sup>6</sup> Other factors could include the multiple surgical interventions that take place in the region of the PA and histologic abnormalities of the PA that can be seen in this population.<sup>6</sup> RV-PA uncoupling might help to explain why symptoms develop in an individual with otherwise relatively preserved RV volumes and ejection fraction and why some individuals have more progressive RV dilation than others. In a small study of TOF patients with significant PR, patients were reported to have invasively determined impaired RV-PA coupling or uncoupling regardless of RV ejection fraction.<sup>7</sup> Assessment of noninvasive indices of RV-PA coupling are essential to ongoing study and clinical applicability. Noninvasive measures of RV-PA coupling currently include a TTE-derived ratio of RV systolic function parameter (TAPSE or FAC) and RV afterload as measured by right ventricular systolic pressure (RVSP). This has been shown to be of prognostic importance in the setting of pulmonary hypertension and superior to TAPSE or RVSP alone in heart failure patients.<sup>8,9</sup> There have been no studies to date that have evaluated TTE-measured RV-PA coupling in the CHD population.

With all of these factors in mind, we read with great interest the recent article by Egbe et al.<sup>6</sup> This well-designed retrospective study included 84 adults with TOF and 45 adults with VPS with a previous pulmonary valve intervention. These patients all had at least moderate pulmonary valve regurgitation and a preserved RV ejection fraction (> 50%) determined using MRI. The 84 TOF patients were propensity matched with 84 patients with a normal echocardiogram (control group). RV-PA coupling was measured using TAPSE/RVSP and FAC/RVSP in all patients. Egbe et al. were successful in showing that despite a preserved RV ejection fraction and similar RV systolic function indices (TAPSE and FAC), RV-PA coupling was significantly lower in the TOF group compared with normal controls.<sup>6</sup> The findings in the VPS group were similar. These findings highlight the important pulmonary arterial changes seen in this CHD population mostly as a consequence of chronic volume loading, and are reflective of the higher afterload seen in these patients. This study is novel and begins to explore the effect of the volume load from significant PR on true RV contractile function in this CHD population. It is important to note that the RV function indices of TAPSE and FAC have limitations and can be especially challenging to acquire in CHD patients.

Also, RVSP is not entirely representative of PA compliance, and other Doppler markers of increasing afterload such as RV outflow tract Doppler notching and short RV outflow tract acceleration time should be considered.<sup>10</sup>

Egbe et al. attempted to establish a prognostic role for RV-PA coupling in this CHD population by investigating its relationship with exercise capacity. They were able to show a modest correlation of RV-PA coupling with exercise capacity in the TOF group. This finding, however, could not be shown in the VPS group. Certainly peak oxygen consumption on exercise testing, an objective measure of exercise capacity, is routinely measured and followed in this CHD population. It has been shown that reduced exercise capacity is associated with increased morbidity in the TOF population.<sup>11,12</sup> However, it remains unclear how a reduction in exercise capacity can be used to guide timing of pulmonary valve replacement. These data, however, are encouraging and does support further study addressing the prognostic value of RV-PA coupling.

### **Conclusions: Clinical Implications and Next Steps**

Patients with chronic significant PR are often young and have been exposed to chronic RV volume loading for many years. As clinicians, our goal is to intervene on the pulmonary valve before irreversible cardiac changes occur. This is balanced against intervening too early, keeping in mind that prosthetic valves have limited longevity and might need to be replaced more than once in a patient's lifetime. We have in large part focused on the RV when it comes to making this decision in asymptomatic patients. This study brings attention to the fact that there is in fact a change in PA compliance because of chronic volume loading and this in combination with an inadequate increase in RV contractile function results in RV-PA uncoupling in this CHD population.

We congratulate Egbe et al. in undertaking this important study that will serve to propel further research in this area.<sup>6</sup> The next steps in this line of inquiry will include validating additional robust noninvasive-derived measures of RV-PA coupling and establishing the prognostic value of these measures. Studies to investigate RV-PA coupling in the CHD population should consider using more robust methods of RV systolic function assessment such as 3-D echocardiography or cardiac MRI. Increasing attention to assessment of afterload should be given with consideration of using more than 1 Doppler parameter. A combined invasive/noninvasive approach could also be considered. Ultimately, is RV-PA coupling a tool that can be used in the decision-making model for pulmonary intervention? This study includes patients with chronic PR who did not independently meet the RV volume or function thresholds for pulmonary valve intervention. This is in fact the population of interest because there is likely a spectrum of RV-PA coupling, and identifying individuals with uncoupling might represent a cohort who will benefit from earlier intervention before symptoms or threshold RV dilation and dysfunction occur.

### **Disclosures**

The authors have no conflicts of interest to disclose.

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