Right ventricular strain – a better window into the working of the heart in pulmonary hypertension

Brief Title: The physiological correlates of RV strain

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NO CONFLICTS OF INTEREST

Strain is increasingly used as a biomarker for both systolic and diastolic ventricular function[1, 2]. Although mainly used to asses the left ventricle, right ventricular (RV) strain has also been used to

assess patients with pulmonary hypertension (PH) and congenital heart disease[3,4]. Echocardiographic and CMR studies have shown that strain is abnormal in PH patients and predicts both outcome and exercise capacity[5, 6]. However, few studies have delved into the physiological correlates of RV strain. In this edition of JACC cardiovascular imaging, Tello et al have have investigated these relationships by comparing RV strain to pressure volume (P-V) loop derived metrics, as well as conventional CMR and catheter measures.

Pressure volume loops are the reference standard method of assessing load independent ventricular function, vital for a better understanding of the heart's intrinsic 'health'. Evaluation of the pressure volume relationship at end systole (Figure 1) allows measurment of ventricular contractility, independent of afterload (end-systolic elastance [E_{es}]). The pressure volume relationship in diastole (Figure 1) provides a measure of ventricular compliance that is independent of preload (end diastolic elastance [E_{ed}]). Pressure volume loops can also be used to calculate arterial load (arterial elastance – E_a) and ventricular arterial coupling (E_{es}/E_a ratio). However, construction of P-V loops is technically challenging, requiring simultaneous acquisition of high temporal fidelity pressure and volume data. Thus, simple non-invasive correlates of P-V loop metrics are required. In their carefully conducted study, the authors demonstrated that RV strain (particularly longitudinal strain) correlated with ventricular arterial coupling (E_{es}/E_a ratio) and arterial load (E_a), but not with load independent contractility (E_{es}). This led the authors to conclude that i) RV strain is a marker of ventricular arterial coupling, ii) lower RV strain in patients with PH was a reflection of an uncoupled phenotype, possibly due to an inability for E_{es} to completely compensate for increases in E_a and iii) ventricular arterial uncoupling results in RV dysfunction as demonstrated by the relationship between RV ejection fraction (RVEF) and E_{es}/E_a. However, there is an important caveat to this line of reasoning. Several studies have shown that ventricular arterial coupling can also be estimated as end systolic volume divided by stroke volume – the ventricular vascular coupling ratio (VVCR)[7]. However, VVCR equals 1/RVEF-1 and therefore, RVEF is also a physiological measure of ventricular arterial coupling[7]. The fact that RVEF and RV strain are both markers of coupling is unsurprising as they fundamentally reflect the same process, namely myocardial contraction. The difference is that RVEF is a volumetric representation, whilst RV strain is a length representation. In fact, the relationship between RV strain, RVEF and E_{es}/E_a might be better understood as a product of the force velocity relationship[8], inadequate remodelling and myocyte dysfunction. Specifically, increased wall tension secondary to higher afterload results in reduced myocyte shortening and consequently lower RVEF or strain. Initially, hypertrophy will compensate for increased afterload, but eventually myocyte dysfunction will limit the ability of the myocardium to contract. The force velocity relationship also explains why RV strain, which is affected by load, does not correlate with E_{es}, which is a load independent measure of

contractility. If RVEF and RV strain are measures of the same process, one might ask what is the benefit of one over the other? This study demonstrates that the separate components of RV strain do not have a simple relationship with RVEF. This is likely due to the more lengthwise arrangement of fibres in the RV[9], explaining the strong association between longitudinal strain and RVEF. Thus, strain may offer an early warning sign of oncoming global RV dysfunction and better predict outcome or functional capacity.

Another interesting finding in this study was association between RV strain and invasive measures of diastolic dysfunction. It is well recognised that the initial response to increased afterload is RV hypertrophy and wall thickening[10]. This normalises systolic wall stress and partly maintains contraction in the face of increased cavity pressure. Unfortunately, the cost normalising systolic function is reduced ventricular compliance and diastolic dysfunction. Over time, this effect may be compounded by RV fibrosis, which would result in greater RV stiffness and a further deterioration of diastolic function[11]. Poor diastolic function limits RV filling (particularly during exercise) and increases right atrial pressure with resultant right atrial dilation. Studies have shown that right atrial pressure is highly prognostic in PH[12], possibly due to it's effect on coronary perfusion pressure. Thus, it is likely that RV diastolic function is an important cause of morbidity and mortality in PH. Several echocardiographic metrics including tricuspid inflow assessment, tissue doppler imaging, and strain imaging have been shown to be useful in PH[13]. However, CMR metrics of RV diastolic function have not been fully developed. The traditional CMR techniques used to assess strain are tagging, displacement encoded imaging and tissue phase mapping. Unfortunately, these techniques are based on specialist sequences and often require long breath holds that are difficult for PH patients to perform. In this study, RV strain was measured using conventional cine imaging and was shown to correlate with both the diastolic relaxation constant (Tau) and Eed. This opens up the possibility of routine evaluation of diastolic dysfunction in these patients without the need for extra scanning. One exciting possibility is that RV strain may provide a novel method of evaluating new therapies that specifically target diastolic dysfunction and fibrosis.

This study elegantly investigates the connection between non-invasive measures of right heart function and load independent, invasive reference standards. However, for these findings to have impact, RV strain must be shown to correlate with exercise capacity and predict outcome. Although studies have investigated the prognostic value of RV strain[5, 6], larger multicentre studies are required to demonstrate true clinical value. The main advantage of CMR for large scale studies is reproducibility and ease of visualization of the RV. The disadvantage of CMR is that it is an expensive technology, which is not readily available at every site. Nevertheless, new fast acquisition and post-processing technologies are making CMR cheaper, quicker and more accessible[14]. Another issue that

must be addressed is the variability in strain measurements provided by different commercial software platforms[15]. This is a significant impediment to clinical uptake and must be resolved if RV strain is to become a widely used biomarker.

In conclusion, Tello and colleagues have made important steps in defining the physiological underpinnings of RV strain. However, it remains to be seen whether RV strain will usurp RV volumetric measures as the biomarker of choice in pulmonary hypertension.

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