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Simple functional imaging of the right ventricle in pulmonary hypertension: can right ventricular ejection fraction be improved?

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It has been better realized in recent years that the symptomatology and the outcome of severe pulmonary hypertension are largely determined by right ventricular function (RV) (1). This has re-activated the search for physiologically robust and noninvasive bedside measurements of RV function using imaging techniques (2). The direct application of metrics of ventricular function developed in the left ventricle to the RV is difficult due to morphological differences. The gold standard metric of RV function adaptation to increased afterload in pulmonary hypertension, or ventricular vascular coupling, is the ratio of end-systolic to arterial elastance E_{es}/E_a (1–3). End-systolic elastance is a measure of RV contractility and arterial elastance is a measure of arterial afterload. In the clinical setting, E_{es} has been approximated by the ratio between end-systolic pressure (ESP) and end-systolic volume (ESV) and E_a as the ratio of ESP to stroke volume (SV). Measurements of RV ESV and SV can be obtained by cardiac magnetic resonance imaging and, more recently, 3D echocardiography. Measurements of RV pressures require a cardiac catheterization. The optimal value of E_{es}/E_a , associated with flow output at minimal energy cost between, is between 1.5 and 2 (3).

The E_{es}/E_a ratio has a common pressure term, and can thus be simplified as a ratio of stroke volume (SV) to end-systolic volume (ESV) (4).

$$ESP/ESV/ESP/SV=SV/ESV$$

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The obvious advantage of the SV/ESV ratio is that it relies only on volume measurements, minimizing the need of a right heart catheterization. However SV/ESV as a surrogate for Ees/Ea rests on several assumptions including linearity of the RV end-systolic elastance curve and the RV volume at 0 mm Hg is zero ($V_0 = 0$) (5) resulting in lower absolute values than derived from multipoint RV pressure-volume measurements (2,6). On the other hand, it can be argued that SV/ESV and more commonly used SV/EDV, or ejection fraction (EF), are necessarily linked, so that the advantage of SV/ESV over more traditional EF to assess RV function adaptation in PH is not entirely clear (7).

RVEF has repeatedly been shown to predict outcome in patients with severe pulmonary hypertension (8–10). In patients referred for pulmonary hypertension and who underwent a right heart catheterization and imaging of RV volumes, when both SV/ESV and EF were determined, SV/ESV, not EF emerged as an independent predictor of outcome (6,11). We wondered if this discrepancy could have happened by chance.

Mathematically, the simplified ventricular vascular coupling ratio SV/ESV is similar to RVEF where RVEF is the ratio of SV to end-diastolic volume (EDV) or $RVEF = SV/EDV$. To investigate the relationship between RVEF and SV/ESV, the RVEF equation can be re-arranged to solve for SV, $SV = RVEF \times EDV$ and since $SV = EDV - ESV$ then $ESV = EDV (1 - RVEF)$. Taking the ratio of these two equations results in the following relationship:

$$\frac{SV}{ESV} = \frac{RVEF \cdot EDV}{EDV \cdot (1 - RVEF)} \text{ which simplifies to } \frac{SV}{ESV} = \frac{RVEF}{(1 - RVEF)}$$

RVEF and the coupling estimate SV/ESV are mathematically linked but exhibit a non-linear relationship (Figure 1A). Thus, this relationship implies that RVEF is also a simplified estimate of ventricular vascular coupling. The non-linear relationship is a potential reason for why SV/ESV might be a better predictor of outcomes than RVEF.

Van de Veerdonk et al previously reported on 110 patients with pulmonary arterial hypertension (PAH) in whom a RVEF > 0.35 was found predictive of poorer prognosis. (10). In that study, RVEF ranged from 0.14 to 0.58 (from mean $- 2SD$ to mean $+ 2SD$). Using the relationship of SV/ESV to RVEF, we calculated a 3 times wider range of SV/ESV, from 0.18–1.5. The increased resolution of SV/ESV in subjects with a relatively normal RVEF could be important in identifying and stratifying at-risk individuals (subjects with a RVEF above cut-off value in red in Figure 1A). From the relationship between RVEF and SV/ESV, an RVEF of 0.35 corresponds to a SV/ESV of 0.539 which is similar to cut-off values of 0.515 and 0.534 that were found to be associated with increased mortality in patients referred for pulmonary hypertension (6,11). It is not surprising both RVEF and SV/ESV are predictive of outcomes below a cutpoint but the nonlinear relationship suggests a possible explanation of why SV/ESV could be more predictive because it widens the physiological range of values allowing for more resolution.

Adaptation of the ventricle to changes in afterload and disease progression is complex and nonlinear. As RVEF and SV/ESV decrease, ventricular volumes have to non-linearly increase to maintain SV (Figure 1B and C) or invoke other adaptive mechanisms such as

increasing contractility. In a 12-month follow-up study in patients with PAH, van de Veerdonk et al reported that survivors had a 3% increase in RVEF compared to a 5% decrease in the non-survivors (10). If we were to translate these values over to SV/ESV, survivors went from 0.539 to 0.613 or had a 7% increase where non-survivors went from 0.539 to 0.429 or an 11% decrease in SV/ESV. Thus the SV/ESV would be expected to be more sensitive than EF to changes over time in severe PH.

In conclusion, with current progress and expanding use of cardiac magnetic resonance and echocardiographic imaging of RV volumes in pulmonary hypertension, both RVEF and SV/ESV may be increasingly used for assessment of severity and prediction of outcome despite concerns surrounding simplification of Ees/Ea (1,2). Because of the larger physiological range and greater sensitivity to change resulting from its non-linear relationship to RVEF, SV/ESV may emerge as a more potent predictor of outcome than EF as well as a more potent clinical endpoint to follow over time, particularly in patient populations with wide range of RV function alterations.

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Take home message

SV/ESV has a larger physiological range and greater sensitivity compared to RVEF due to a non-linear relationship

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Figure 1.

A) Non-linear relationship between right ventricular ejection fraction (RVEF) and the stroke volume (SV) to end-systolic volume (ESV). The gray region shows the pulmonary hypertension RVEF range (0.15–0.60) and the red line shows the RVEF and corresponding SV/ESV cut-off value that is predictive of outcomes. B) and C) Non-linear relationship between ventricular volumes (end-diastolic volume (EDV) and ESV, and RVEF and SV/ESV at a given SV. As RVEF and SV/ESV decreases, to maintain stroke volume ventricular volumes have to increase or there needs to be changes in contractility. The red line shows the

RVEF and corresponding SV/ESV cut-off value that has been shown to be predictive of outcomes.

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