When it all comes down to pressure: right ventricular ejection fraction at cardiac catheterisation

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In the present issue of the *European Respiratory Journal*, Heerdt *et al.* [1] report on the validation of right ventricularejection fraction (RVEF) calculated from a pressure curve at cardiac catheterisation. This is of great interest as right ventricular (RV) function is the main determinant of symptomatology and outcome in pulmonary hypertension [2], and RVEF accordingly adds significantly to risk stratification in these patients [3]. However, ejection fraction (EF) is a ratio of stroke volume (SV) to end-diastolic volume (EDV), with no pressure in the equation. So, how is it possible to calculate a volume ratio from pressure measurements?

As recently reviewed [4–6], the adequacy of coupling of RV function to the pulmonary circulation is defined by a ratio of end-systolic to arterial elastances (Ees/Ea). End-systolic elastance is a ratio of end-systolic pressure (ESP) to end-systolic volume (ESV). Arterial elastance is a ratio of ESP to SV. Both Ees and Ea have pressure or volume terms in common, so that the ratio of elastances can actually be simplified as either a pressure or a volume ratio [7, 8]:

$$\mathrm{Ees/Ea} = (\mathrm{ESP/ESV})/(\mathrm{ESP/SV}) = \mathrm{SV/ESV} = (\mathrm{Pmax/ESP}) - 1$$

where Pmax is the maximum pressure of a non-ejecting beat calculated by nonlinear extrapolation of the isovolumic portions of a RV pressure curve [9].

The pressure-only (Pmax/ESP)−1 and volume-only SV/ESV estimations of the Ees/Ea ratio have been shown to agree well with gold standard multi-beat or single beat methods [10], with no (pressure-only) or minimal (volume-only) biases as shown by a Bland–Altman analysis. However, the same analysis showed rather wide limits of agreement, particularly for the volume-only method. In the Bland–Altman analysis, bias is a measure of accuracy and limits of agreement a measure of precision [11]. It may be noted that replacing ESP with the easier to measure mean pulmonary artery pressure (mPAP) as previously proposed [7], and applied to show exercise-induced RV–pulmonary arterial (PA) uncoupling in pulmonary

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hypertension patients [12], introduces a pressure-dependent bias which can be approximated following the equation [13]:

$$ESP = (1.65 \times mPAP) - 7.79$$

Since ESV is equal to EDV minus SV, the SV/ESV ratio is inversely related to EF [14]:

$$SV/ESV = EF/(1 - EF)$$

and accordingly, EF as calculated by Heerdt *et al.* [1] from a RV pressure curve only is indeed equal to:

$$EF = 1 - (ESP/Pmax)$$

Heerdt *et al.* [1] validated this pressure-only measurement of EF in 15 anaesthetised swine with RVEF ranging from 18 to 59% by manipulation of afterload or pharmacological interventions and in six patients, three with heart failure and three with pulmonary arterial hypertension (PAH) with RVEF ranging from 30 to 70%, who underwent standard diagnostic right heart catheterisations and magnetic resonance imaging [1]. Based on the experimental animal data, the prediction of EF from RV pressure curves was very good, with (in absolute values of EF) a small bias of −2% and limits of agreement of −9 to +13%, reduced to −3 to +7% when corrected for repeated measures. The overall error on the measurement was estimated at 12.5%. However, the clinical data were less convincing in relation to small and inhomogeneous sample size and impact of tricuspid regurgitation on imaging but not pressure-derived EF. As acknowledged by the authors, the concept of volume estimations from pressure curves may hold true pending further clinical validation.

The method itself may be more complicated than it seems. A critical step is the offline inspection of pressure curves to define isovolumic portions for the determination of Pmax [9]. For this purpose, most studies have relied on the first derivative of dP/dt and manual identification of end and onset of diastole [9, 10, 13]. A newly introduced automated method relying on the second derivative of dP/dt decreases the variability of the measurement, but underestimates Pmax by an average of 13% [15]. Such an underestimation is necessarily associated with an overestimation of ESP and may therefore result in an underestimation of Ees/Ea [16, 17]. Heerdt *et al.* [1] developed an alternative automated approach based

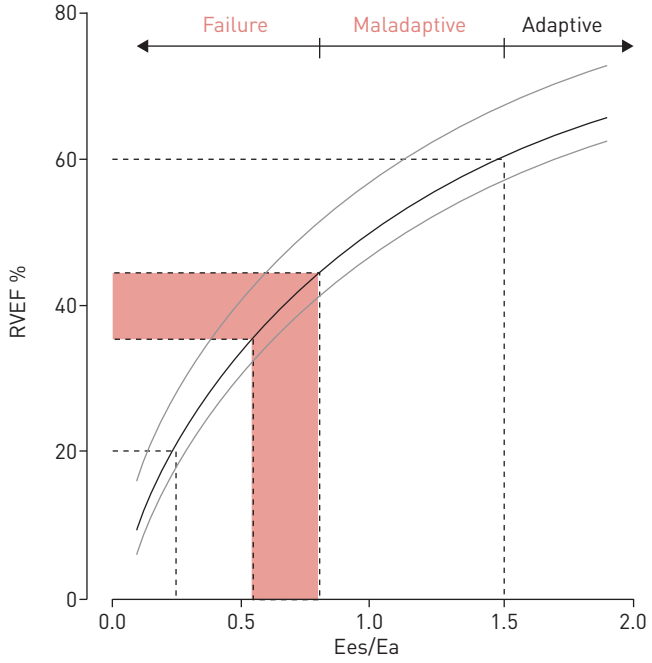

FIGURE 1 Relationship between right ventricular ejection fraction (RVEF) and ratio of end-systolic to arterial elastances (Ees/Ea) predicted from the equation Ees/Ea=EF/(1−EF), rearranged as EF=Ees/(Ees+Ea), during progression from normal to maladaptation and failure. The shaded area defines a zone of uncoupling below which right ventricular dimensions increase above normal and right heart failure symptomatology develops.

also on the second derivative of dP/dt but with a refined distribution function (the so-called "4 parameter Weibull peak fit") replacing more conventional sinusoid function. In addition, the authors determined ESP rigorously as the point of maximum elastance, which is superior to a recalculation from mPAP [13] or graphical determination by a tangent from Pmax to the systolic portion of a pressure–volume curve [9]. All these refinements probably improved the prediction of EF, but did not completely correct for a negative bias, which remained at 6–8%.

The RV adapts to increased afterload in pulmonary hypertension by a matched increase in contractility, which initially preserves flow output, dimensions and thus also EF. This homeometric adaptation eventually fails, so that the RV then relies on a heterometric increase of dimensions to maintain flow output (*i.e.* Starling's law of the heart) but at the price of increased filling pressures, systemic congestion, negative ventricular interactions and irremediable decrease in cardiac output [4–6]. It has been shown that RV–PA coupling has a lot of reserve, as the Ees/Ea ratio has to be decreased from normal values of 1.5–2.0 down to 0.8–0.9 before RV volumes increase above normal and survival decreases [18]. The same study showed that RVEF decreases along with the decrease in Ees/Ea down to 35%, below which it is necessarily associated with increased EDV and ESV at preserved SV [18]. The theoretical hyperbolic decrease in EF with decreased Ees/Ea and progression from maladaptation to failure in pulmonary hypertension patients is illustrated in figure 1. Taken into account the error on the estimate determined by Heerdt *et al.* [1] from animal experiments, there is a zone of uncoupling which actually corresponds to either higher EF or lower Ees/Ea than previously determined from direct measurements in pulmonary hypertensive patients [18]. This is possibly explained by the assumption of linearity of the ESP/ESV relationship leading to unrealistic unstressed volume extrapolation [7]. The ventricular–vascular coupling is more than "EF in disguise", as has been once suggested [19], and remains the gold standard for the assessment of RV function adaptation to loading conditions [4–6]. However, in clinical practice, it is not possible to obtain Ees and Ea on a routine basis, and clinicians have to be satisfied with surrogate EF.

A decrease in RVEF, however measured, is an independent predictor of decreased survival in heart failure [20] and in PAH [21–24]. A cut-off value of EF of 35% associated with increased RV volumes [14] is also the ROC-derived determinant of good *versus* poor survival in PAH at initial diagnosis and during follow-up [23, 24]. A decreased EF is associated with increased RV dimensions [14] and, as such, is an integrated measure of RV remodelling. Treatment-induced reversal of RV remodelling (in that study assessed by echocardiography) has been shown to markedly improve the prognosis of PAH patients [25]. However, reversal of RV remodelling and sufficient improvement in EF is not commonly achieved in PAH under single drug treatment targeting the pulmonary circulation [26, 27]. Association of two targeted therapies with preferably a parenteral prostacyclin analogue is more likely to be effective, in proportion to a more important decrease in pulmonary vascular resistance (PVR) [28, 29]. It has recently been shown that in PAH patients with initial non-reversible disease as assessed by a vasodilator challenge, triple upfront combinations of targeted therapies decrease PVR by more than 50% [30, 31]. This effect is associated with a marked clinical improvement and decreased mortality in relation probably to sufficient increase in RVEF and complete reversal of right heart dilatation [31].

In conclusion, measurement of RVEF is critically important to guide therapies in pulmonary hypertension. Heerdt *et al.* [1] are to be commended for showing that this information can be obtained by RV pressure analysis at right heart catheterisation. The method will require automation in order to be routinely applicable in the catheterisation laboratory, and needs further validation against the gold standard of magnetic resonance imaging. Yet, this provocative thought may bring about clinically useful steps forward in the pathophysiological understanding and management of severe pulmonary hypertension.

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