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Describing right ventricular function

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ABSTRACT: In pulmonary hypertension and other conditions, such as acute respiratory distress syndrome and left heart failure, right ventricular dysfunction is a prognostic determinant. Therefore, functional parameters pertaining to the right heart alone, *i.e.* independent of its loading conditions, should be used to quantify right ventricular disease progression and the results of treatment. Two methods to quantitatively describe right ventricular function are reviewed, the pressure–volume relationship and the pump function graph; examples of each method are given. How to estimate wall stress and how to describe diastolic ventricular properties are also discussed.

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In 1943, STARR *et al*. [1] showed that, in dogs, following electrocautery ablation of the right ventricle free wall pulmonary venous pressure changed little, and the dogs survived. Based on this finding they concluded that the right ventricle functions only as a passive conduit, since there were "no increments of venous pressure". This study suggested to many researchers that the right ventricular pump may be neglected and this might explain why so little attention was paid to the right ventricle in the following decades. In recent years, however, this view has changed dramatically, mainly because it became clear that not only in pulmonary hypertension, but also in other conditions, like acute respiratory distress syndrome and left heart failure, right ventricular function is a prognostic determinant [2]. In addition, the importance of the right ventricle in determining maximal exercise capacity became clear [3]. Most of the studies investigating the right ventricle in different disease conditions and at exercise characterise the right ventricle by parameters obtained by imaging alone. Examples of parameters obtained from imaging are stroke volume (SV) as a measure of global cardiovascular performance, right ventricular ejection fraction, *i.e.* SV over end-diastolic volume, and tricuspid annular plane systolic excursion, as measures of right heart function [4–6]. More recent advances allow measurement of regional myocardial shortening by means of speckle echocardiography or strain analysis by magnetic resonance imaging (MRI)

through tagging [7, 8] and calculation of wall stress to get more insight into (changes in) muscle properties *per se*. Although the advantage of such noninvasive approaches is clear, and helps to improve our insight into right ventricular function, their disadvantage is that they describe right ventricular function in relation to its preload and afterload, and thus, cannot be considered a quantification of right ventricular function *per se*.

Functional parameters that pertain to the right heart alone, and that are thus independent of its loading conditions, are important for several reasons. First, preload (filling) and afterload (arterial load) vary between patients. Secondly, since most pulmonary arterial hypertension (PAH)-specific treatments will affect either preload or afterload, or both, the possible impact of the treatment on the right ventricle requires characterisation in a load independent manner. For example, to predict right ventricular function after lung transplantation a load independent characterisation of right ventricular function is mandatory.

Therefore, this short review will focus on the principles of measuring right heart function independent of its load and how these principles can be applied in the clinic.

CHARACTERISATION OF THE RIGHT HEART
Systole
The pressure–volume relationship: figure 1 shows the so-called pressure–volume relationship of the right ventricle [10, 11]. This relationship is
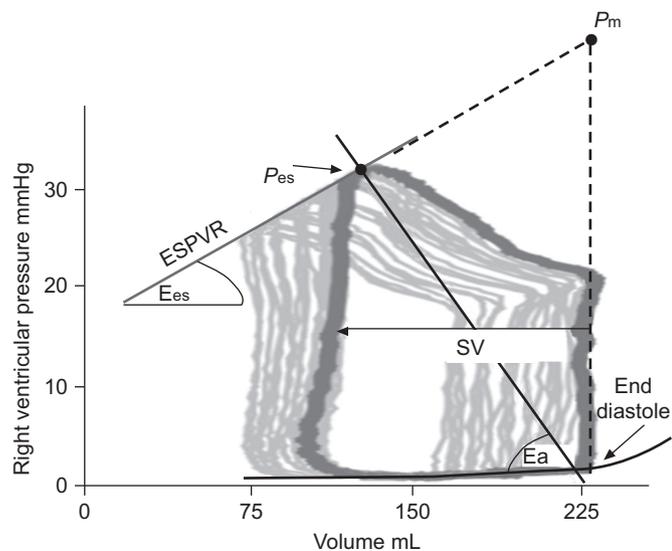

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obtained by changes in ventricular filling. The details of the relationship and how to obtain the relationship are given in the figure caption. The slope of the end-systolic pressure–volume relationship (systolic elastance: E_{es}) is a generally accepted load-independent characterisation of the cardiac pump. Changes in filling pressure by vena cava occlusion are the best approach but are often not practical or desirable. Therefore, methods have been developed to obtain E_{es} from measurement of right ventricular pressure (catheterisation) and volume (MRI) of a single beat [12–14], making it a practical method to obtain a load-independent functional characterisation of the right heart. The pressure–volume loop of the right ventricle is, in general, more of a trapezoidal shape than the more rectangular shape of the left ventricle, probably as a result of the very compliant pulmonary tree [15].

In the pressure–volume diagram (fig. 1) the line connecting the end-diastolic volume point with the end-systolic pressure–volume point can be drawn and its slope, E_a, gives the so-called arterial elastance. This term is confusing since E_a is not characterising the elasticity of the arterial system but is related to total pulmonary vascular resistance (R), mean pulmonary artery pressure (mPAP) over cardiac output (CO), R=mPAP/CO.

End-systolic ventricular pressure (P_{es}) is closely related to mean pulmonary artery pressure, and therefore the simplification that $P_{es} \approx$ mPAP [16] is sometimes assumed (see limitations), so that $E_a \approx$ mPAP/SV=R/T, where T is the heart period (R-R interval).
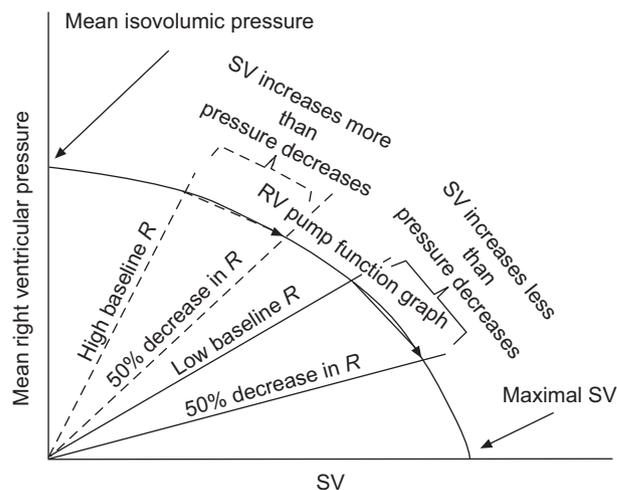
The pressure–volume relationship is also used to estimate ventriculo-arterial coupling. It has been shown that when the ratio E_a/E_{es}=1 external work is maximised, while for E_a/E_{es}=0.5 cardiac efficiency is maximal [17]. In this context it should be mentioned that ejection fraction (EF), rather than being a characterisation of the ventricle, is a coupling parameter. It turns out that EF is more closely related to E_a/E_{es} and to E_a [11].

Applying an even further simplification, SANZ et al. [18] calculated E_{es} by assuming that the intercept with the volume axis is negligible, thus giving E_{es}=P_{es}/ESV, where ESV is the end systolic volume. This assumption, however, underestimates E_{es} in a contractility dependent manner [14] and leads to E_a/E_{es}=1/EF-1 [11]. The pump function graph: figure 2 shows the so-called pump function graph that relates mean ventricular pressure and SV (for details see caption) [19]. This graph is obtained by changes in cardiac load. Again in practice this may not be possible or desirable, but the same single-beat methods [12, 13] can be used to find the (mean value of) maximal pressure to obtain a second point on the graph. The two points can then be fitted by a parabola [20]. The slope of the pump function graph is related to E_{es}. From the pump function graph maximal efficiency (close to optimal power output of the ventricle), is found when mean pressure is 66% of maximal pressure or SV is 58% of maximal SV (intercept of horizontal axis) [21, 22].

The relationship between the end-systolic pressure–volume relationship and the pump function graph have been discussed previously [11].

Diastole

The diastolic pressure–volume relationship determines filling and thus cardiac output (Frank–Starling mechanism). The

FIGURE 1. The pressure–volume relationship. A pressure–volume loop consists of four phases. Starting at end-diastole these phases are: isovolumic contraction, ejection, isovolumic relaxation and filling phase (black loop). The shallow diastolic phase shows large increases of volume with small increases in pressure. When diastolic filling is decreased by vena cava occlusion multiple loops are obtained (grey loops). The line connecting the end-systolic pressure–volume points is the end-systolic pressure–volume relationship (ESPVR). Its slope, E_{es}, is a measure of systolic ventricular function (contractility). The slope of the line connecting end-diastolic volume and end-systolic pressure, E_a, is called arterial elastance but is actually close to pulmonary vascular resistance over heart period: R/T. The ratio E_{es}/E_a is a measure of ventriculo-arterial coupling. Maximal isovolumic pressure (P_m) is determined with the single-beat method (see text), and with this method E_{es}=(P_m-P_{es})/SV. P_{es}: end systolic pressure; SV: stroke volume. Reproduced and modified from [9] with permission from the publisher.

FIGURE 2. The pump function graph relates mean ventricular pressure and stroke volume (SV) and can be obtained by changes in arterial load. The slopes of the straight lines, are pulmonary vascular resistance, indicated by R, and are a measure of pulmonary arterial load and are proportional to $E_a \times$ T (where T=heart period). The (mean) isovolumic pressure can be obtained by means of the single-beat method. The relationship explains the effect of decreasing the arterial load on pressure and SV (and thus also on flow). When baseline R is high, a decrease in R mainly causes an increase in SV, while at lower baseline R pressure is more affected. E_a: arterial elastance.

pressure–volume inherently contains the information, but again, changes in filling are not practical. A straight line approach as a description of the diastolic pressure–volume relationship is not sufficiently accurate. Several descriptions of the curved diastolic pressure–volume relationship have been proposed. The best relationship is $P=P_0(e^{\beta(V-V_d)}-1)$, with V_d the volume at negligible (transmural) pressure and P_0 and β the amplitude and curvature, respectively. Approximations have been used, such as $P=P_0e^{\beta V}$, a "asymptotic model" [23] and even simpler $P=P_0e^{\beta V}$ [24]. The third formula has only two parameters and can be used with, in principle, two data points. A single beat approach requires more simplifying assumptions, and is not yet available.

Wall stress

When information on the cardiac muscle is desired (segmental) wall shortening and wall stress are required. Wall shortening can be quantitatively obtained by echocardiography or cardiac MRI. Wall stress is not directly measurable and needs quantitative information on ventricular shape and size (*e.g.* radius of curvature (r) and wall thickness (h)). Laplace's law, $T=Pr/h$, with T stress, and P (transmural) pressure allows for a rough estimate of wall stress [10]. The right ventricular radius varies greatly with location which makes accurate calculations doubtful. No generally accepted calculation of wall stress exists. At present a simple, easy to calculate estimate of wall stress is $T=(1+3V_{lumen}/V_{wall})\,P$ [25].

Direct ventricular interaction

Direct ventricular interdependency mediated *via* the interventricular septum plays an important role in right ventricular pressure overload. Therefore a complete description of cardiac function should take ventricular interdependency into account. However, it was shown that leftward septal bowing [26] is a consequence of prolonged right ventricular contraction, and occurs after pulmonary valve closure [27] and it is, therefore, unlikely that ventricular interdependence affects the description of right ventricular systolic function as described above.

POSSIBLE LIMITATIONS OF THE PROPOSED METHODS

Although the above described methods are, at present, the most optimal descriptions of right ventricular function they have limitations, which need further attention.

The slope of the isochrone with maximal slope, is designated as E_{max}, and may not be equal to the slope of the end-systolic pressure–volume relationship, E_{es}, which is obtained by multiple beats [28]. The "most left-top corners" of the pressure–volume loops are to be used to obtain E_{es}. As surrogate for P_{es}, mean arterial pressure [27] can be used, and since the dicrotic notch in arterial pressure and mean arterial pressure are closely related as well [16] this pressure can be used [29]. However, in practice mean pulmonary artery pressure is the most simple to obtain and suffers little from catheter artefacts. Nevertheless, future studies should clarify these issues.

All end-systolic pressure–volume relationships are nonlinear [30] but assumed to be linear, which is a workable approximation of reality [31–33].

To calculate E_a, the P_{es} and SV can be used, and $E_a=P_{es}/SV$ [12]. It has been suggested that subtraction of left atrial (or pulmonary capillary wedge pressure) gives a better estimate of $R=E_a\times T$ [34]. However, it has not been shown which estimate of E_a is best for estimation of coupling (*i.e.* E_{es}/E_a).

In the calculation of E_{es}/E_a pressure drops out and the effects of the choice of end-systolic pressure become rather unimportant.

Systolic and diastolic ventricular function are both required for a full description of the right ventricle. Single beat methods are surrogates of the methods using changes in load: the better multiple beat methods. However, although the multiple beat method has shown its value in animal-related research, the risks of changing loading conditions in pulmonary hypertension patients are too high to use this technique in the pulmonary hypertension clinic.

End-systolic elastance is only a little different from maximal elastance [35], so that end-systolic elastance, using P_{es}, may be used in practice. Using peak (maximal) ventricular pressure as surrogate for P_{es} is not advisable, since it leads to errors. The end-systolic pressure–volume relationship is not straight, but in the working range a linear relationship seems acceptable. However, in extreme cases linearity may be lost [11].

In the single beat method, the assessment of isovolumic pressure and its maximal value in pressure–volume analysis, and mean value in the pump function graph approach, is based on the isovolumic part of the measured right ventricle pressure curve only and the fit is thus sensitive to errors and requires high quality right ventricular pressure curves. Using catheter-tip manometers and measuring more pressure curves can partially overcome this problem. The choice of the fitted curve, *i.e.* a sine wave [12–14], may also be a limitation and a "standard" isovolumic pressure curve obtained from measurements needs to be worked out [35].

The given methods describe the right ventricle in isolation. Since the right ventricle interacts on the left ventricle and *vice versa*, the question remains to be answered whether an optimal description also should incorporate ventricular direct and/or series interdependency [36, 37]. Ventricular interdependency in pulmonary hypertension needs further studies, but accounting for this effect will increase complexity, which may limit clinical usage.

The end-systolic pressure–volume relationship and the pump function graph depend on muscle contractility and ventricular wall mass. They characterise the ventricle as a whole but to derive muscle function other analyses should be carried out.

EXAMPLES

An example of the use of the pressure–volume relationship is given in figure 3 [9]. It may be seen that E_{es} is much higher in experimental pulmonary hypertension than in the control. The increase in ventricular wall thickness, and possibly also in muscle contractility causes an increase in E_{es}. The pressure–volume relationships also give information on diastolic ventricular properties (E_d) and it may be seen that E_d is also increased in pulmonary hypertension.

An example of the use of the pump function graph is shown in figure 4 [38]. The graphs are obtained through the single-beat
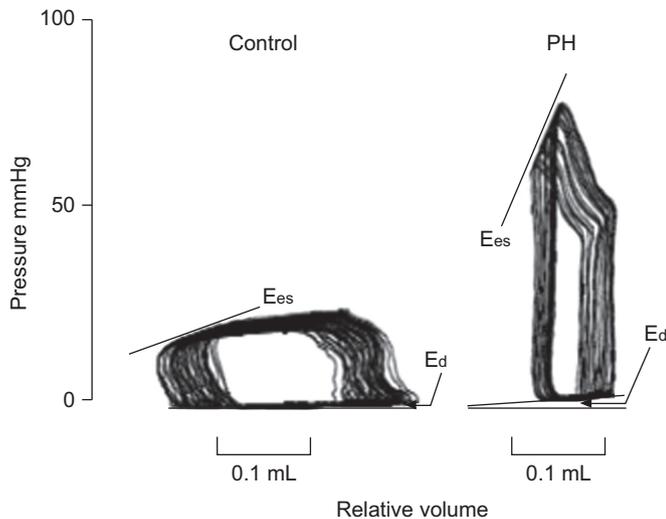
FIGURE 3. The pressure–volume relationship in a control rat (left) and in a rat with pulmonary hypertension (PH) (right). The slope of the end-systolic pressure–volume relationship (systolic elastance), E_{es}, is increased in hypertension either by increased wall thickness, muscle contractility or both. The diastolic pressure–volume relationship, E_d, also shows increased stiffness. Reproduced and modified from [9] with permission from the publisher.

method. It may be seen that the patients with idiopathic PAH have a relationship with a higher slope implying increased wall thickness and/or increased muscle contractility.

In general it holds that increased E_{es} implies increased slope of the pump function graph.

FUTURE PERSPECTIVES

Although we have shown that measuring right ventricular function is feasible in the clinic, until now these methodologies have been mainly applied in animal research. Reasons for this are that ideally measurements of high quality right ventricular pressures and volumes measured simultaneously are required. These limitations can often not be fulfilled in the clinic. Since MRI is the most accurate method to assess right ventricle volume, the technique is even in its simplified form still technically demanding. Simultaneous determination of pressure and flow is also hardly practical at present. All in all, clinical reports are sparse, and although these studies have improved our insight into the right ventricle, their clinical value remains unknown [39]. For this reason, studies containing a large number of patients measured at baseline and during follow-up are required to assess the clinical value of these load-independent ventricular parameters, and how these parameters can be used to optimise treatment strategy in PAH. Of interest are the novel advances in three-dimensional echocardiography which offer the prospect of the assessment of right ventricular volume in an accurate way in PAH. This technique offers advantages above MRI, namely that simultaneous measurements [40] can be performed during right heart catheterisation in almost every clinic, which will lower the hurdle to assessing right ventricular function in a proper way in the clinical environment, allowing for large scale studies.

Nevertheless, with the above discussed methods, although having limitations, important questions such as the influence
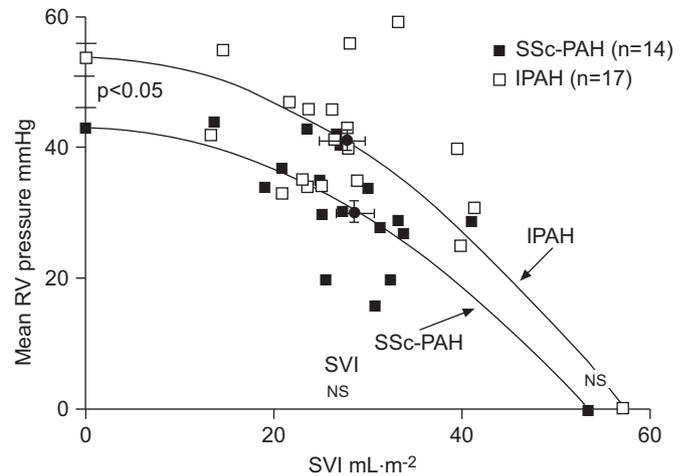
FIGURE 4. The pump function graph of patients with idiopathic pulmonary arterial hypertension (IPAH) and patients with systemic sclerosis associated pulmonary arterial hypertension (SSc-PAH). Stroke volume index (SVI) and maximal SVI are not different but isovolumic right ventricular pressure is higher in IPAH. The results are based on the single-beat method (see text). Reproduced and modified from [38] with permission.

of PAH specific medication and medication aimed to target the right ventricle can be addressed in the near future. In addition our insight into the mechanisms of right ventricular failure might improve if we combine these measurements with other meaningful parameters, such as parameters of myocardial perfusion or metabolism.

STATEMENT OF INTEREST

Conflict of interest information can be found alongside the online version of this article at www.erj.ersjournals.com

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