Describing right ventricular function

A. Vonk-Noordegraaf and N. Westerhof
Department of Pulmonology
Institute for Cardiovascular Research VU University Medical Center,
VU University, Amsterdam, The Netherlands

Corresponding author:
A. Vonk-Noordegraaf
Department of Pulmonology
VU University Medical Center
De Boelelaan 1117
1081 HV Amsterdam
The Netherlands
Email: a.vonk@vumc.nl
Tel: +31 20 444 44710
Introduction

In 1943 Starr et al. showed that in dogs following electrocautery ablation of the RV free wall pulmonary venous pressure changed little and dogs survived[1]. Based on this finding they concluded that the RV 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 has been paid to the right ventricle in the following decades. In recent years, however, this view changed dramatically, mainly because it became clear that not only in pulmonary hypertension but also in other conditions like ARDS 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 exercise characterize the right ventricle by parameters obtained by imaging alone. Examples of so-obtained parameters are stroke volume as a measure of global cardiovascular performance, right ventricular ejection fraction, i.e., stroke volume over end-diastolic volume, and Tricuspid Annular Plane Systolic Excursion (TAPSE), as measures of right heart function [4,5,6]. More recent advances allow measurement of regional myocardial shortening by means of speckle echocardiography or strain analysis by MRI through tagging [7,8] and calculation of wall stress to get more insight in (changes) in muscle properties per se. Although the advantage of such (noninvasive) approaches is clear, and help to improve our insight in right ventricular function, their disadvantage is that they describe right ventricular function in relation to its pre-and afterload and thus cannot be considered a quantification of right ventricular function per se. Functional parameters that pertain to the right heart alone, thus independent of its loading conditions are important for several reasons. First, preload (filling) and afterload (arterial load) vary between patients. Second, since most PAH-specific treatments will affect either preload or afterload, or both, the possible impact of the treatment on the right ventricle requires characterization in a load independent manner. For example to predict right ventricular function after lung transplantation a load independent characterization of right ventricular function is mandatory.

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

Characterization of the right heart

Systole

The Pressure-Volume Relation Figure 1 shows the so-called pressure-volume relation of the right ventricle [9,10]. This relation is obtained by changes in ventricular filling. The details of the relation and how to obtain the relation are given in the caption. The slope of the End-Systolic Pressure-Volume Relation ($E_{es}$, systolic elastance) is a generally accepted load-independent characterization of the cardiac pump. Changes in filling pressure by vena cava occlusion are the best approach but often not practical or desirable. Therefore methods have been developed to obtain $E_{es}$ from measurement of right ventricular pressure (catheterization) and volume (MRI) of a single beat [11,12,13], making it a practical method to obtain a load-independent functional characterization 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 [14].
In the pressure-volume diagram (Figure 1) also the line connecting the end-diastolic volume point with the end-systolic pressure-volume point can be drawn and its slope, \( E_s \), gives the so-called arterial elastance. This term is confusing since it not characterizing the elasticity of the arterial system but related to total pulmonary vascular resistance, mean pulmonary artery pressure over Cardiac Output, \( R = mPAP/CO \). End-systolic ventricular pressure, \( P_{es} \), is closely related to mean pulmonary artery pressure, and therefore the simplification that \( P_{es} \approx mPAP \) [15] is sometimes assumed (see limitations), so that \( E_s \approx mPAP/SV = R/T \), with \( SV \) Stroke Volume, and \( T \) heart period (R-R interval).

The pressure-volume relation is also used to estimate ventriculo-arterial coupling. It has been shown that when the ratio \( E_s/E_{es} = 1 \) external work is maximized, while for \( E_s/E_{es} = 0.5 \) cardiac efficiency is maximal [16]. 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 \( E_s/E_{es} \) and to \( E_s \) [10]. Applying an even further simplification Sanz et al. [17] calculated \( E_{es} \) by assuming that the intercept with the volume axis is negligible, thus giving \( E_{es} = P_{es}/ESV \), with \( ESV \) End Systolic Volume. This assumption, however, underestimates \( E_{es} \) in a contractility dependent manner [13P.] and leads to \( E_s/E_{es} = 1/EDF - 1 \) with \( EDF \) Ejection Fraction [10]. The pump Function Graph Figure 2 shows the so-called pump function graph that relates mean ventricular pressure and Stroke Volume (for details see caption) [18] This graph is obtained by changes in cardiac load. Again in practice not possible or desirable, but the same single-beat methods [11,12] 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 [19]. The slope of the pump function graph is related to \( E_s \). 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 is or stroke volume is 58% of maximal stoke volume (intercept of horizontal axis) [20,21]. The relation between the End-Systolic Pressure-Volume relation and the Pump Function Graph can be found in [10].

Diastole

The diastolic pressure-volume relation determines filling and thus cardiac output (Frank-Starling mechanism). The pressure volume is inherently containing the information, but again, changes in filling are not practical. A straight line approach as description of the diastolic pressure volume relation is not sufficiently accurate. Several descriptions of the curved diastolic Pressure-Volume Relation have been proposed. The best relation is \( P = P_0(e^{B(V-Vd)} - 1) \), with \( V_d \) the volume at negligible (transmural) pressure and \( P_0 \) and \( B \) amplitude and curvature. Approximations have been used, such as \( P = P_0e^{BV} - a \), `asymptotic model` [22] and even simpler \( P_0e^{BV} \) [23]. The third formula has only two parameters and can do 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 Magnetic Resonance Imaging. 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 \( T = (1+3V_{\text{lumen}}/V_{\text{wall}}) P \) [24].

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 [25] is a consequence of prolonged right ventricular contraction, and occurs after pulmonary valve closure [26] 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 \( E_{\text{max}} \) and may not be equal to the slope of the End Systolic Pressure Volume Relation, ESPVR, \( E_{\text{es}} \), which is obtained by multiple beats [27]. The ‘most left-top corners’ of the pressure-volume loops are to be used to obtain \( E_{\text{es}} \). As surrogate for \( P_{\text{es}} \) mean arterial pressure [26] can be used and since the dicrotic notch in arterial pressure and mean arterial pressure are closely related as well [15] this pressure can be used [28]. However, in practice mean Pulmonary Artery Pressure is most simple to obtain and suffers little from catheter artefacts. Nevertheless, future studies should clarify these issues. All ESPV-Relations are nonlinear [29] but assumed to be linear, which is a workable approximation of reality [30,31,32]. To calculate \( E_a \) the \( P_{\text{es}} \) and Stroke Volume can be used, and \( E_a = P_{\text{es}}/SV \) [11]. It has been suggested that subtraction of left atrial (or Pulmonary Capillary Wedge Pressure) gives a better estimate of PVR = \( E_a/T \) [33]. However, it has not been shown which estimate of \( E_a \) is best for estimation of coupling (i.e., \( E_{\text{es}}/E_a \)). In the calculation of \( E_{\text{es}}/E_a \) pressure drops out and the effects of the choice of end-systolic pressure becomes rather unimportant. Systolic and diastolic ventricular function both is required for a full description of the right ventricle. Single beat methods are surrogate 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 risk 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 little different from maximal elastance [34], so that end-systolic elastance, using end-systolic pressure, \( P_{\text{es}} \) may be used in practice. Using peak (maximal) ventricular pressure as surrogate for end-systolic pressure is not advisable since it leads to errors. The End-Systolic Pressure-Volume Relation is not straight, but in the working range a linear relation seems acceptable. However in extreme cases linearity may be lost [10]. In the single beat method the assessment of isovolumic pressure and its maximal value in pressure-volume analysis and mean value in 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., sine wave [11,12,13] may also be a limitation and a ‘standard’ isovolumic pressure curve obtained from measurements needs to be worked out [34]. The given methods describe the right ventricle in isolation. Since the right ventricle interacts on the left ventricle and visa versa, the question remains to be answered whether an optimal description also should incorporate ventricular direct and/or series interdependency [35,36]. Ventricular interdependency in pulmonary hypertension needs further studies, but to account for this effect will increase complexity, which may limit clinical usage.

The End-Systolic Pressure-Volume Relation and the Pump Function Graph depend on muscle contractility and ventricular wall mass. They characterize 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 relation is given in figure 3 [37]. It may be seen that $E_{es}$ is much higher in experimental pulmonary hypertension than in control. The increase in ventricular wall thickness, and possibly also in muscle contractility causes an increase in $E_{es}$. The pressure-volume relations 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 method. It may be seen that the patients with iPAH have a relation 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 mainly have been applied in animal research. Reasons 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 in the right ventricle, the 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 3-D 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 assess right ventricular function in a proper way in the clinical environment, and allowing for large scaled studies.
Nevertheless, with the above discussed methods, although having limitations, important questions such as the influence of PAH specific medication and medication aimed to target the right ventricle, can be addressed in the near future. In addition our insight in 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.
References

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Legends to the figures

Figure 1. The pressure volume relation. A pressure volume loop consists of 4 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 (gray loops). The line connecting the end-systolic pressure-volume points is the End-Systolic Pressure Volume relationship. Its slope, Ees, is a measure of systolic ventricular function (contractility). The slope of the line connecting end-diastolic volume and end-systolic pressure, Ea, is called Arterial Elastance but is actually close to Pulmonary Vascular Resistance over Heart Period: PVR/T. The ratio Ees/Ea is a measure of ventriculo-arterial coupling. Maximal isovolumic pressure is determined with the single-beat method (see text), and with this method Ees = (Pm–Pes)/SV. Adapted from [37].

Figure 2. The Pump Function Graph relates mean ventricular pressure and stroke volume and can be obtained by changes in arterial load. The straight lines, indicated by R, are a measure of pulmonary arterial load and are proportional to Ea/T. The (mean) isovolumic pressure can be obtained by means of the single-beat method. The relation explains the effect of decreasing the arterial load on pressure and stroke volume (and thus also on flow). When baseline R is high, a decrease in R mainly causes an increase in stroke volume, while at lower baseline R pressure is more affected.

Figure 3. The pressure-volume relation in a control rat (left) and in a rat with pulmonary Hypertension (right). The slope of the End-Systolic Pressure-Volume Relation, Ees is increased in hypertension either by increased wall thickness, muscle contractility or both. The diastolic relation, Ed, also shows increased stiffness. Adapted from [37].

Figure 4. The Pump Function Graph of patients with Idiopathic Pulmonary Hypertension (iPAH) and patients with Systemic Sclerosis associated Pulmonary Hypertension (SScPAH). Stroke Volume index and maximal SV index are not different but isovolumic Right Ventricular Pressure is higher in iPAH. The results are based on the single-beat method (see text). Adapted from [38].
Figure 1
Figure 2:
Figure 3
Figure 4