Chapter 3

Accurate assessment of load-independent right ventricular systolic function in patients with pulmonary arterial hypertension

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ABSTRACT

Background

End-systolic elastance (E\textsubscript{es}), a load-independent measure of ventricular function, is of clinical interest for studies on the right ventricle (RV) in patients with pulmonary arterial hypertension (PAH). The objective of this study is to determine whether in PAH patients E\textsubscript{es} can be estimated from mean pulmonary artery pressure (mPAP) and end-systolic volume (ESV) only.

Methods

Right heart catheterisation was used to measure mPAP. Maximal isovolumic pressure (P\textsubscript{iso}) was estimated from RV pressure curves with the so-called single-beat method as published by Sunagawa. Cardiac MRI was used to assess RV end-diastolic and end-systolic volumes (EDV and ESV). E\textsubscript{es} was then calculated as: E\textsubscript{es} = (P\textsubscript{iso}-mPAP)/(EDV-ESV), and as E\textsubscript{es,VO=0} = mPAP/ESV (simplified method, with V\textsubscript{O}=0 is negligible volume at zero pressure). Right ventricular volume at zero pressure (V\textsubscript{0}) was then defined as the intercept of the end-systolic pressure-volume relation (single-beat method) with the horizontal axis.

Results

E\textsubscript{es,VO=0} was significantly lower compared to E\textsubscript{es} (0.61 vs. 1.34 mmHg/ml respectively, p < 0.01). A modified Bland-Altman analysis showed a contractility-dependent difference between E\textsubscript{es,VO=0} and E\textsubscript{es}. Moreover, V\textsubscript{0} ranged from -8 up to 171 ml, and a moderate and good correlation was found between V\textsubscript{0} and EDV, and V\textsubscript{0} and ESV respectively (r = 0.65 and r=0.87, p < 0.01).

Conclusions

These findings illustrate that V\textsubscript{0} is dependent on RV dilation. Therefore, the assumption that V\textsubscript{0} is negligible in PAH is incorrect. Consequently, for an accurate assessment of load independent RV systolic function, RV volumes and pressure curves are required.
INTRODUCTION

Pulmonary arterial hypertension (PAH) is a condition characterized by increased pulmonary artery pressure as a result of pulmonary vascular remodeling. Although it is the pulmonary vasculature that is affected, patients die of right heart failure. The importance of right ventricular (RV) function in PAH is further reflected by the prognostic significance of RV ejection fraction and other RV functional parameters. Although useful, all of these parameters are dependent on loading conditions and therefore do not characterize intrinsic RV function. An RV functional parameter that is accepted as load-independent is end-systolic elastance ($E_{es}$), a measure of myocardial contractility. Because of the load-independency, this parameter is of potential interest for studies on the right ventricle in PAH. From a clinical point of view, the assessment of RV function independent of load is important for the estimation of RV function after normalization of arterial load, such as after lung transplantation in patients with severe pulmonary hypertension.

Until now, the clinical use of $E_{es}$ in PAH patients is still very limited since accurate determination of $E_{es}$ is hampered by the requirement of invasive interventions. Namely the classical approach to determine $E_{es}$ requires pressure-volume loop analysis with (partial) vena cava occlusion, which is not only technically demanding but also dangerous in PAH patients. A simplified single-beat approach has been developed by Sunagawa et al. (FIGURE 3.1, left), not requiring pressure-volume loops and vena cava occlusion. Although proven to be accurate for the right ventricle, this method still requires measurement of RV pressure curves in combination with the assessment of RV volumes or pulmonary artery flow. Since cardiac MRI and RV pressure curves are not available in every PAH-center, this method is still not widely applicable.

More recently, an approach to estimate RV $E_{es}$ (FIGURE 3.1, right) in PAH patients has been used. This approach, first applied to the left ventricle and thereafter frequently used, estimates $E_{es}$ by dividing mean pulmonary artery pressure (assumed equal to end-systolic pressure) by end-systolic volume (ESV). With this method $E_{es}$ can be easily calculated in large groups of PAH patients. Furthermore, ventricular-arterial coupling, a measure of how well cardiac and vascular function are matched, can be then be assessed non-invasively. In spite of its advantages, the method has never been validated with an accepted standard for the assessment of RV function. Therefore, the aim of this study is to determine whether RV $E_{es}$ can be estimated from mPAP and ESV only.
FIGURE 3.1 Schematic presentation of a pressure-volume loop showing the two methods to calculate $E_{es}$. A. Single-beat estimation of $E_{es}$. The grey area represents the triangle which is used to calculate the slope ($E_{es}$) of the end-systolic pressure-volume relation (ESPVR) which is the line connecting $P_{iso}$ with mPAP. With this method, the line can be continued until it intercepts the horizontal axis at a certain value. This value represents the volume at zero pressure ($V_0$) and can either be a negative or a positive value. B. $E_{es}$ estimated by mPAP/ESV. The line of ESPVR is drawn through the origin of the graph, thereby neglecting $V_0$. In every patient $V_0$ is assumed to be zero. $P_{iso}$: RV isovolumic pressure, mPAP: mean pulmonary artery pressure, EDV: RV end-diastolic volume, ESV: RV end-systolic volume, $V_0$: volume at zero pressure, $E_{es}$: end-systolic elastance.

METHODS

Subjects
Patients referred to the VU university medical center for evaluation of PAH and patients with PAH undergoing follow-up analysis were retrospectively included in this study. Standard clinical care included right heart catheterization with digital recordings of pressures and cardiac MRI. A total of 28 patients were selected based on: 1. diagnosis of idiopathic pulmonary arterial hypertension (IPAH), and 2. available recordings of qualitative good RV pressure curves and cardiac MRI (for RV volumes) within two days of each other. Inclusion period was January 2003 to April 2009. Idiopathic PAH was defined as pulmonary hypertension for which no cause could be identified with a measured mean...
pulmonary artery pressure (mPAP) > 25 mmHg and a pulmonary capillary wedge pressure (PCWP) < 15 mmHg. Due to the retrospective character of the study using data obtained for clinical purposes the Medical Ethics Review Committee of the VU University Medical Center did not consider this study to fall within the scope of the Medical Research Involving Human Subjects Act. Therefore, no additional approval was acquired.

Right heart catheterization

Under local anesthesia, a balloon-tipped Swan-Ganz catheter (Edwards Lifesciences, LLC, Irvine, CA) was inserted via the jugular vein and brought into position. Under constant ECG monitoring, pulmonary artery and right ventricular pressures were measured. Alongside the standard pressure recordings, pressure curves were registered using a Powerlab data acquisition system (AD Instruments, Sydney, Australia). For our measurements we used shielded pressure transducers with a resistance serially connected to increase damping. For each measurement we assured that no oscillations were obtained in the pressure signal. Moreover, the catheter was repeatedly flushed with heparin to avoid potential underdamping due to blood clots.

Mean PAP was averaged over at least two respiratory cycles. Cardiac output was measured by the direct Fick method in 26 patients and by thermodilution in 2 patients. Stroke volume was calculated as cardiac output divided by heart rate. Cardiac output and stroke volume were indexed for body surface area (BSA). PCWP was taken at end-expiration. Pulmonary vascular resistance was calculated as the difference between mPAP and PCWP divided by cardiac output.

Cardiac magnetic resonance imaging

All MR images were acquired with a 1.5 Tesla Avanto or Sonata MRI system equipped with a 6-element phased array coil (Siemens Medical Solutions, Erlangen, Germany). A stack of short-axis images was taken at breath-hold per slice, with a slice thickness and interslice gap of 5mm. Both ventricles were covered. To obtain RV volumes, endocardial borders were manually drawn at end-diastole and end-systole using Mass Analysis software (MEDIS Medical Imaging Systems, Leiden, The Netherlands). End-diastole was defined as the onset of the R-wave of the ECG. End-systole was determined visually as the smallest volume during the cardiac cycle. Volume measurements were indexed for body surface area (BSA). RV ejection fraction (RVEF) = RVEDV-RVESV*100%, where RVEDV is RV end-diastolic volume and RVESV is RV end-systolic volume.
Data analysis and calculations

End-systolic elastance

RV isovolumic pressure \( (P_{iso}) \) per beat was determined according the single-beat method of Sunagawa\textsuperscript{11-13}. An inverted cosine wave was fitted over the RV pressure curve using the isovolumic contraction period (from end-diastole to the point of maximal rate of pressure rise \( (dP/dt_{max}) \)) and the isovolumic relaxation period (from minimal \( dP/dt \) to start diastole) by a semi-automatic Matlab R2008a program (The MathWorks, Natick, MA). The point of end-diastole was identified using the R-wave of the ECG, and when needed manually shifted to the point before the upslope of the ascending limb. To compensate for beat-to-beat variations, the so calculated RV isovolumic pressures were averaged over at least five heartbeats. Beats with significant catheter artefacts were excluded.

The slope of the ESPVR was calculated using the single beat method \( (E_{es}) \), and estimated using mean pressure and end-systolic volume \( (E_{es,V0=0}) \) as follows (FIGURE 3.1):

\[
E_{es} = (P_{iso} - mPAP)/(EDV - ESV) = (P_{iso} - mPAP)/SV
\]

\[
E_{es,V0=0} = mPAP/ESV
\]

\( P_{iso} \) is RV isovolumic pressure estimated by the single-beat method, \( mPAP \) is mean pulmonary artery pressure taken as a surrogate of RV end-systolic pressure\textsuperscript{21-23}, EDV, ESV, and SV are RV end-diastolic, end-systolic and stroke volume, respectively.

Volume at zero pressure \( (V_0) \)

\( V_0 \) is volume at zero pressure and was defined as the intercept of the (linear) end-systolic pressure volume relationship with the horizontal axis (FIGURE 3.1a). In addition, \( V_0 \)-values of individual patients (without pulmonary hypertension) who had undergone multiple pressure-volume loop analysis together with RV volume measurements were collected from literature for comparison\textsuperscript{24}.

Statistical analysis

The data are presented as median with range. The Wilcoxon signed rank test was used to compare the values of two methods. A \( p \)-value of < 0.05 was considered significant. The correlation between the two methods and between \( V_0 \) and RV end-diastolic and end-systolic volume was assessed by the Pearson’s or Spearman’s method when data was normally or not normally distributed, respectively. Linear regressions were performed using the least-squares method. Bland-Altman analysis was performed to determine the agreement between the two methods. Since mean bias was not well
described by one value, a modified Bland-Altman analysis was applied to compute the 95% limits of agreement\textsuperscript{25}.

**TABLE 2.1 Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43</td>
<td>21-64</td>
</tr>
<tr>
<td>Male (%)</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>BSA (m\textsuperscript{2})</td>
<td>1.76</td>
<td>1.53-2.33</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>51</td>
<td>30-77</td>
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<tr>
<td>mRAP (mmHg)</td>
<td>6</td>
<td>0-18</td>
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<tr>
<td>CI (L/min/m\textsuperscript{2})</td>
<td>2.5</td>
<td>1.1-7.4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>86</td>
<td>56-101</td>
</tr>
<tr>
<td>SVI (ml/m\textsuperscript{2})</td>
<td>31</td>
<td>14-89</td>
</tr>
<tr>
<td>PVR (dyn-s-cm\textsuperscript{5})</td>
<td>800</td>
<td>188-1969</td>
</tr>
<tr>
<td>RVEDVI (ml/m\textsuperscript{2})</td>
<td>68</td>
<td>46-169</td>
</tr>
<tr>
<td>RVESVI (ml/m\textsuperscript{2})</td>
<td>42</td>
<td>24-130</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>39</td>
<td>18-65</td>
</tr>
<tr>
<td>$E_s$ (mmHg/ml)</td>
<td>1.34</td>
<td>0.36-3.88</td>
</tr>
<tr>
<td>$E_{s,V0=0}$ (mmHg/ml)</td>
<td>0.61</td>
<td>0.22-1.13</td>
</tr>
<tr>
<td>$V_0$ (ml)</td>
<td>43</td>
<td>-8-171</td>
</tr>
</tbody>
</table>

mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; $E_s$ and $E_{s,V0=0}$, end-systolic elastance measured by the single beat method and the method mPAP/ESV with $V_0=0$, respectively.

**RESULTS**

Patient characteristics and both $E_s$ and $E_{s,V0=0}$ are shown in **TABLE 3.1**. The patients (n=28) included represent IPAH patients over a wide range of disease severity, as is reflected by the range in PVR (188-1969 dynes-s-cm\textsuperscript{-5}), RV ejection fraction (18-65 %), and stroke volume index (14-89 ml/m\textsuperscript{2}). Out of 28 patients, 24 patients were under treatment at the moment of inclusion, the other 4 patients were not yet treated.

**$E_s$: comparison of two methods**

End-systolic elastance was significantly higher compared to the $E_{s,V0=0}$ (1.34 vs. 0.61 mmHg/ml respectively, $p < 0.01$). As shown in **FIGURE 3.2a**, a moderate correlation was found between the two
methods ($r = 0.51$, $p < 0.05$). A modified Bland-Altman analysis is given in FIGURE 3.2b, which shows that at higher values of $E_{es}$ the difference between $E_{es}$ and the $E_{es,V0=0}$ increases.

FIGURE 3.2. A. Linear regression analysis of the correlation between $E_{es}$ and $E_{es,V0=0}$. Line of equality is given. Dashed lines = 95% confidence interval. B. Modified Bland-Altman plot of agreement between $E_{es}$ and $E_{es,V0=0}$.

FIGURE 3.3 Linear regression analysis of the correlation between RV end-systolic volume and $V_0$ in this study (patients with idiopathic pulmonary arterial hypertension, open dots) and in a study published by Dell’Italia (patients referred for cardiac catheterization for evaluation of chest pain by whom no abnormalities were found, closed dots)\textsuperscript{24}.

Volume at zero pressure

$V_0$ ranged from -8 to 171 ml. A moderate correlation was found between $V_0$ and EDV ($r = 0.65$, $p < 0.01$). A stronger correlation between $V_0$ and ESV was found (FIGURE 3.3, $r = 0.87$, $p < 0.01$). We additionally plotted ESV- and $V_0$-values reported in the study published by Dell’Italia\textsuperscript{24}, and a similar dependence but a stronger correlation was found between ESV and $V_0$ (FIGURE 3.3, $r = 0.95$, $p < 0.01$). The slopes of the regression lines of these two data sets were not statistically different (this study; 0.88 ± 0.08,
Dell’Italia; 0.79 ± 0.10, p = 0.68). However, the Y-axis intercept was significantly lower in the present study (-29 ± 7 vs. 2 ± 6 mm Hg, p < 0.01).

**DISCUSSION**

Our study shows that in PAH patients, the estimation of $E_{es}$ based on mPAP and end-systolic volume strongly underestimates $E_{es}$. Therefore, this method cannot be applied in patients with PAH, as will be discussed below. Furthermore, $V_0$ was highly dependent on RV dilation suggested by the close association between RV volumes and $V_0$. The assumption that $V_0$ is negligible in PAH patients is therefore incorrect.

**$V_0$ in healthy controls and PAH patients and the consequence of neglecting its value**

The estimated $E_{es}$ is calculated by dividing mPAP by RV end-systolic volume ($E_{es,V0=0}$) and is based on the assumption that $V_0$ is negligible. $V_0$ is the volume that would be left in the ventricle after contraction against zero load, and is often called dead volume, i.e. $V_d$ or $V_0$. For the left ventricle it is known that neglecting $V_0$ in the $E_{es}$-calculation leads to a consistent and severe overestimation of $E_{es}$ as measured by multiple-loop analysis.

For the right ventricle the consequence of neglecting $V_0$ is not known. There are only a few studies reporting right ventricular $V_0$-values in humans. In a study of Dell’Italia et al. subjects without underlying cardiovascular disease underwent multiple pressure-volume loop analysis and $V_0$ was calculated using a linear ESPVR. They found right ventricular $V_0$ to range from 24 up to 89 ml. Brown et al. analyzed eight patients, also with a linear approach, and found $V_0$-values to range from -8 ml/m² to 28 ml/m². With this wide range in $V_0$ in normotensive patients there seems to be no reason to assume $V_0$ is negligible. Indeed, we show in PAH patients an even wider range of $V_0$, making it even less appropriate to neglect $V_0$ in this patient category. The assumption that $V_0$ is zero for all PAH patients has as a consequence that $E_{es}$ is severely underestimated, as is shown in FIGURE 3.1. Furthermore, the limited range in $E_{es,V0=0}$ makes this method less usable for discrimination between patients.

**Correlation of $V_0$ with RV volumes**

The wide range in $V_0$ in humans and especially in PAH patients, might be explained by the dependence of $V_0$ on muscle length at end-systole at zero load. Since muscle length is never zero, $V_0$ will never be
zero. And since muscle length is presumably increased in PAH patients in case of eccentric remodelling, this patient category will have higher $V_0$-values compared to persons with non-dilated ventricles.

The theory above suggests a positive relation between ventricular volume and $V_0$. This relationship has never been reported for the RV though. However, for the left ventricle it is known that $V_0$ is smaller in patients with a normal ejection fraction, compared to patients with a lower ejection fraction\textsuperscript{28,29}. Patients with a low ejection fraction did have larger end-diastolic and end-systolic volumes. In our present study, a moderate correlation between RV end-diastolic volume and $V_0$, and a stronger correlation between $V_0$ and RV end-systolic volume was found. This correlation was confirmed in data from multiple pressure-volume loop analysis of Dell’Italia et al.\textsuperscript{24}. The latter is not only confirming the existence of a relationship between RV volume and $V_0$, but also underlines the reliability of the single-beat estimation of end-systolic elastance.

The stronger correlation between RV end-systolic volume and $V_0$ compared to RV end-diastolic volume and $V_0$ may be explained by the greater intra- and inter-observer variability of the quantification of RV end-diastolic volume\textsuperscript{30}. Then, the finding of the $V_0$-ESV relation raises the question whether one can estimate $V_0$ when knowing end-systolic volume. In this study a considerable scatter around the regression line of $V_0$-ESV was found. Therefore, we do not recommend to estimate $V_0$ based on ESV. However, it may be that an acceptable estimation of $V_0$ can be made using both ESV and EDV. Future studies will be needed to answer this question.

**Clinical implications**

The findings of this study imply that the estimation of RV $E_{es}$ using mPAP/ESV does not reflect RV contractility, but may rather be a load-dependent measure of systolic function. Therefore, to describe RV contractility in PAH patients the estimation should not be used. Instead, one should use the single-beat method as published by Sunagawa, and validated for the RV by Brimioulle, since no better alternative methods are presently available\textsuperscript{11,13}. Furthermore, the finding that RV-arterial coupling can be assessed non-invasively by cardiac MRI, using the simplified method, should therefore be revised\textsuperscript{15}. 
Study limitations
In the calculation of $E_{es}$ usually RV end-systolic pressure is used and not mPAP. In this study we chose to substitute RV end-systolic pressure by mPAP in both $E_{es}$-calculations and not to focus on the difference between RV end-systolic pressure and mPAP. As a consequence, the difference found between the two methods is only the result of the magnitude of $V_0$-values.

In this study, pressure and volumes could not be measured simultaneously which may have influenced the results due to differences in the patients’ stress level. However, we measured heart rates during both measurements and found an excellent correlation between the two values ($r \ 0.87, \ p<0.001$) suggesting a similar amount of stress and therefore a negligible effect of stress on the study results.

We used fluid-filled catheters to measure RV pressures, taking special care to prevent under- and overdamping of the pressure signal and excluded data showing RV pressure tracings with catheter artifacts. Kuehne et al. showed that data obtained in this way is in good agreement with data obtained by catheter-tip manometers\textsuperscript{14}.

CONCLUSIONS

In PAH patients, the estimation of right ventricular contractility using $E_{es, V_0=0}$ from the ratio of mean pulmonary artery pressure and end-systolic volume is inaccurate. Consequently, for an accurate assessment of RV systolic function, and ventriculo-arterial coupling, RV volumes and pressure curves are required.

Disclosures
No conflicts of interest, financial or otherwise, are declared by the authors.

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REFERENCES


SUPPLEMENTAL DATA

FIGURE 3.15. Schematic presentation of the single-beat estimation of RV isovolumic pressure and the calculation of end-systolic elastance.

A. RV isovolumic pressure ($P_{iso}$) per beat was determined according the single-beat method of Sunagawa.\textsuperscript{11-13} An inverted cosine wave was fitted over the RV pressure curve using the isovolumic contraction period (see pressure points within the grey area). The data points used start at end-diastole and continue to the point of maximal rate of pressure rise ($dP/dt_{max}$). In addition, the points within the isovolumic relaxation period (from minimal $dP/dt$ to start diastole) are used. The idea behind this extrapolation is based on the fact that the isovolumic part of the pressure curve of an ejecting beat is similar to these parts of a pressure curve during a non-ejecting beat (i.e. isovolumic). Consequently, one can use these data points to fit a cosine wave, that results in an estimated pressure curve of a non-ejecting beat and thus maximal isovolumic pressure.

B. A. Schematic presentation of a pressure-volume loop showing the single-beat method to calculate $E_{es}$. Using the estimated maximal isovolumic pressure, two data points on the end-systolic pressure-volume relationship (ESPVR) are obtained and the slope ($E_{es}$) can be calculated.