Respiratory systolic variation test in acutely impaired cardiac function for predicting volume responsiveness in pigs

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Editor’s key points

- In critically ill patients, it is difficult to predict cardiac output after third administration.
- Using a pig model, these authors showed that fluid response could be predicted using functional parameters of cardiac preload.
- Respiratory systolic variation was as good as other measures.

Background. Predicting the response of cardiac output (CO) to volume administration remains difficult, in particular in patients with acutely compromised cardiac function, where, even small amounts of i.v. fluids can lead to volume overload. We compared the ability to predict volume responsiveness of different functional haemodynamic parameters, such as pulse pressure variation (PPV), stroke volume variation (SVV), the static preload parameter right atrial pressure (RAP), and global end-diastolic volume (GEDV) with the recently proposed respiratory systolic variation test (RSVT) in acutely impaired cardiac function.

Methods. In 13 mechanically ventilated pigs, cardiac function was acutely reduced by continuous application of verapamil to reach a decrease in peak change of left ventricular pressure over time (dP/dt) of 50%. After withdrawal of 20 ml kg⁻¹ BW blood to establish hypovolaemia, four volume loading steps of 7 ml kg⁻¹ BW using the shed blood and 6% hydroxyethylstarch 130/0.4 were performed. Volume responsiveness was considered as positive, if CO increased more than 10%.

Results. Receiver operating characteristic curve analysis revealed an area under the curve (AUC) of 0.88 for the RSVT, 0.84 for PPV, 0.82 for SVV, 0.78 for RAP, and 0.77 for GEDV.

Conclusions. Functional parameters of cardiac preload, including the RSVT, allow prediction of fluid responsiveness in an experimental model of acutely impaired cardiac function.

Keywords: functional haemodynamic monitoring; heart–lung interaction; impaired cardiac function; RSVT; volume responsiveness

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In critically ill patients, assessing volume responsiveness, that is, to predict the response of left ventricular cardiac output (CO) to volume administration is not reliably possible with conventional parameters of preload, such as right atrial pressure (RAP), pulmonary artery occlusion pressure (PAOP), or global end-diastolic volume (GEDV).¹–³ Undoubtedly, fluid administration is possible to increase CO and to reduce hypoperfusion in hypovolaemic and haemodynamically unstable patients.⁴ However, unnecessary volume loading, in terms of not leading to a further increase in CO, may cause significant deterioration in myocardial function. Pulmonary or intestinal oedema also are a frequent consequence.⁵ ⁶ New methods of haemodynamic assessment have been developed, since static parameters of cardiac preload have shown to be of little value in predicting the response to volume administration. These methods including pulse pressure variation (PPV) and stroke volume variation (SVV), summarized as functional haemodynamic monitoring, are based on the assessment of the heart–lung interactions during mechanical ventilation. Basically, the changes in stroke volume (SV) during varying intrathoracic pressure caused by mechanical ventilation are quantified. As a further step, the respiratory systolic variation test (RSVT) was proposed: the RSVT quantifies the decrease in systolic pressure in response to a standardized manoeuvre consisting of three consecutive mechanical breaths with increasing airway pressure.⁷ Basic prerequisites for the performance of RSVT are the presence of an arterial line and mechanical ventilation. The idea of utilizing heart–lung interactions for the prediction of cardiac preload has been accomplished before by the measurement of SVV and PPV, both based on the continuous analysis of the arterial pulse waveform, calculating the variation between maximum and minimum SV or pulse pressure during one mechanical breath.⁸ However, in practice, the use of those functional haemodynamic parameters has certain inherent limitations, such as the influence of the depth of tidal

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volume, the need for a regular cardiac rhythm, and the inclusion of the initial increase in SV in early inspiration, which is even more prominent in the failing heart.

The RSVT was proposed to eliminate the dependency from tidal volume and the SV augmentation in the early inspiration and might therefore have an advantage in the accuracy of predicting volume responsiveness, especially in ventilated patients with compromised cardiac function.

Hence, the aim of this study was to evaluate the ability of RSVT to predict volume responsiveness using an animal model of acutely impaired cardiac function and to compare its precision with that of SVV, PPV, RAP, and GEDV.

Methods

The study was approved by the local Institutional Review Board for animal research. The animals received care, as outlined by the United States Public Health Service Policy on Humane Care and Use of Laboratory Animals and the Guide for the Care and Use of Laboratory Animals (1996), prepared by the National Academy of Sciences’ Institute for Laboratory Animal Research.

Anaesthesia

Each of the 13 pigs was fasted for 14 h before start of the experiment. After i.m. premedication with ketamine (8 mg kg⁻¹), midazolam (0.5 mg kg⁻¹), and azaperone (9 mg kg⁻¹), anaesthesia was induced with fentanyl (0.02 mg kg⁻¹) and propofol (7 mg kg⁻¹). Pancuronium 0.2 mg kg⁻¹ was given to facilitate orotracheal intubation with a cuffed tube. For maintenance of anaesthesia, the animals received fentanyl (0.05 mg kg⁻¹ h⁻¹) and propofol (10 mg kg⁻¹ h⁻¹) throughout the entire protocol.

All animals were monitored with a five-lead electrocardiograph and pulse oximetry. Controlled mechanical ventilation was performed in a pressure-controlled setting with tidal volumes of 8–12 ml kg⁻¹ inspiration to expiration ratio of 1:2, and PEEP of 5 cm H₂O (Evita XL, Drägermedical, Lübeck, Germany) in a circle system. End-expiratory Pco₂ was continuously controlled and maintained at 35–40 mm Hg. Hydration was maintained by a continuous infusion of 0.9% saline at a rate of 10 ml kg⁻¹ h⁻¹. After completing the experimental protocol, all animals were killed by i.v. injection of high-dose potassium during deep anaesthesia until asystole was observed by electrocardiogram.

Surgical preparation

Animals were placed in the supine position. An 8 F central venous catheter (Arrow, Reading, PA, USA) was introduced into one jugular vein for injection of the cold indicator for transcardiopulmonary thermodilution. An electronic micro-tip catheter (SPC 350, Millar Instruments, Houston, TX, USA) was introduced via the other side of jugular vein into the right atrium of the heart to monitor RAP continuously. A second micro-tip catheter (Millar) for evaluating left ventricular pressure and measurement of peak changes in left ventricular pressure over time (dP/dt), for assessment of left ventricular contractility, was introduced in the left ventricle via one carotid artery. In the femoral artery, a 20 G arterial catheter (Abbocath-T G718-A01, Abbott, Ireland) was placed for invasive arterial pressure monitoring. Finally, a 4 F thermostipped catheter (PICCO, PV 2015L20, Pulsion, Germany) was placed into the other side femoral artery for pulse contour analysis and transcardiopulmonary thermodilution.

Measurements

Respiratory systolic variation test

In our study, for the first time, the RSVT manoeuvre was performed automatically by the ventilator (Evita XL, Drägermedical) with newly developed software, which controls the application of this standardized manoeuvre after initiation by the user. During RSVT, the ventilator administers three consecutive pressure-controlled mechanical breaths of gradually increasing pressures (10–20–30 cm H₂O). The airway pressure curve and the arterial pressure wave form are analysed by the RSVT software at the same time. The minimum systolic arterial pressure value after each mechanical breathing cycle is plotted against the corresponding airway pressure and the slope of this line (RSVT angle in degrees) is calculated from the first and third point in the following way:

\[
\text{Slope} = \frac{P_{\text{arterial}3} - P_{\text{arterial}1}}{P_{\text{insp,mean}3} - P_{\text{insp,mean}1}}
\]

In the software algorithm, inspiration is defined by the airway pressure value at the threshold of 1.5 cm H₂O above PEEP for the start and at the threshold of 1.0 cm H₂O above PEEP for the end of inspiration. The changed order of indices assures positive values. A screenshot is presented in Figure 1. In our study protocol, at each point of measurement, three RSVT manoeuvres (each consisting of three respiratory cycles) were performed and the mean was documented.

Pulse contour analysis and thermodilution

Online pulse contour analysis was performed using the PICCO plus System (version 6.0, Pulsion Medical Systems, Munich, Germany). CO, SV, PPV, and SVV were registered. Transcardiopulmonary thermodilution measurements were performed after three sequential central venous injections of 10 ml cold saline solution (<8 °C) randomly administered throughout the respiratory cycle to assess GEDV and CO. Measurements were accepted for statistical analysis if none of the three values differed by more than 10% from the mean. All parameters were recorded on a notebook using the PICCO Win Version 6.0.1.5 software (Pulsion Medical Systems).

Experimental protocol

After surgical preparation, cardiac preload was optimized. The animals were volume loaded by repeated administration of a colloid solution (Voluven®, hydroxyethylstarch 6%, 130/0.4, Fresenius Kabi, Germany) until SVV was <10% for 30 min (baseline). After baseline measurements, cardiac function was impaired by an i.v. bolus of the calcium channel blocker verapamil (0.14 mg kg⁻¹) followed by a continuous infusion (0.24 mg kg⁻¹ h⁻¹), until dP/dt constantly reached
50% of baseline value for a minimum of 30 min. Thereafter, the verapamil infusion rate was kept constant throughout the entire protocol. After induction of impaired cardiac function, haemodynamic parameters were measured (Baseline CI). Thereafter, 20 ml kg\(^{-1}\) BW of blood were withdrawn over 20 min to establish hypovolaemia and measurements were repeated (hypovolaemia). Consecutively, volume loading (VLS) was performed in four steps over 20 min, each consisting of 7 ml kg\(^{-1}\) BW using the shed blood and hydroxyethylstarch 6% 130/0.4, followed by haemodynamic data acquisition after each step (VLS 1–4). Hereby, volume responsiveness was assessed. Haemodynamic measurements followed each VLS after an equilibration period of 5 min.

**Statistical analysis**

Data were analysed using SigmaStat for Windows 3.5 (Systat Software Inc., San Jose, CA, USA). Normal distribution of all data was tested with the Kolmogorov–Smirnov test. Normally distributed data were analysed with a one-way analysis of variance for repeated measurements (ANOVA); non-normally distributed parameters were analysed with the Friedman repeated-measures ANOVA on ranks. Post hoc testing was performed using Tukey’s test. Normally distributed variables were expressed as mean and standard deviation (SD), otherwise as median and inter-quartile range (IQR). The assessment of tested parameters to predict positive volume responsiveness was performed by generating receiver operating characteristic (ROC) curves. The response to VLS was considered positive, if CO increased by at least 10% (criterion value).

**Results**

Thirteen animals with a body weight of 31 (3.8) kg were studied. Haemodynamic data and their changes throughout the experimental protocol at baseline, after impairment of cardiac function, after establishment of hypovolaemia, and following each VLS are presented in Table 1.

With application of a verapamil bolus ($0.14 \text{(0.09–0.22)} \text{mg kg}^{-1}$) followed by a continuous infusion ($0.24 \text{(0.18–0.34)} \text{mg kg}^{-1} \text{h}^{-1}$), left ventricular contractility decreased, as specified by protocol, below 50% of the initial values. At the same time, heart rate (HR), CO, SV, and mean arterial pressure decreased significantly and SVV, PPV, RSVT, RAP, and GEDV remained statistically unchanged.

**Prediction of volume responsiveness**

In each animal, 4 VLS were performed, in total, 52 VLS. Fifteen of the 52 VLS resulted in an increase in CO >10% (10 to first VLS, 3 to second VLS, none to third, and 2 to fourth VLS).

The areas under the ROC curve (AUC) for an increase in CO >10% of all investigated parameters were significantly larger than 0.5. In detail, for RSVT angle, the AUC was 0.88 (95% confidence intervals 0.77–0.98), for PPV 0.84 (95% confidence intervals 0.72–0.96), for RAP 0.80 (95% confidence intervals 0.68–0.93), and for GEDV 0.78 (95% confidence intervals 0.65–0.91).
surgical patients. Various studies have clearly demonstrated the importance of identifying clinical parameters for reliable prediction of volume responsiveness, particularly in high-risk patients with acutely impaired cardiac function. One reason for the reduced effectiveness of SVV and PPV might be the inclusion of the maximal increase in SV in the beginning of inspiration (delta-up), which is not related to volume responsiveness.

SVV, PPV, and RSVT are limited by the prerequisite of a mechanically ventilated patient without cardiac arrhythmias. The required tidal volume for a dependable SVV is 8 ml kg⁻¹ and hence higher than recommended tidal volumes for critically ill patients. The RSVT is independent of a given tidal volume.

The RSVT is a new functional haemodynamic parameter, using intentionally generated decreases of the systolic arterial pressure under three incremental mechanical breaths and hence calculating the slope of the decrease in arterial pressure. The test is easily performed and results can be calculated online by a software that is integrated in the ventilator and presents the results on screen as RSVT angle. High values of RSVT angle represent a strong decrease in systolic arterial pressure during elevation of intrathoracic pressure and therefore postulating volume responsiveness. In a normo- or hypervolaemic patient, the decrease in arterial pressure under RSVT and consequently the RSVT angle will be small, because a heart with satisfactory preload will not be influenced as much by the increasing intrathoracic pressure under mechanical ventilation as without a decent venous filling. Therefore, additional volume challenges in the circumstance of a low RSVT will not increase CO any more, and the patient is volume unresponsive.

Data suggest that functional haemodynamic parameters show reliable prediction for volume responsiveness, although in patients with acutely impaired cardiac function, the predictive ability is lower, compared with its usage in normal cardiac function. One reason for the reduced effectiveness of SVV and PPV might be the inclusion of the maximal increase in SV in the beginning of inspiration (delta-up), which is not related to volume responsiveness.

At this point, the RSVT seems to have an advantage over SVV and PPV; because it only measures the slope created by the lowest systolic values and does not include the delta-up component. In patients with compromised cardiac function and hypervolaemia, delta-up is more prominent. This might be the reason why SVV and PPV, both embedding the delta-up component, tend to

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Baseline CI</th>
<th>Hypovolaemia</th>
<th>VLS 1</th>
<th>VLS 2</th>
<th>VLS 3</th>
<th>VLS 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>84 (14)</td>
<td>65 (7)*</td>
<td>44 (8)*</td>
<td>57 (8)</td>
<td>63 (7)</td>
<td>66 (8)</td>
<td>69 (10)</td>
</tr>
<tr>
<td>HR (beats min⁻¹)</td>
<td>90 (10)</td>
<td>80 (6)*</td>
<td>78 (9)</td>
<td>80 (10)</td>
<td>79 (9)</td>
<td>79 (9)</td>
<td>80 (9)</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>7.6 (2.0)</td>
<td>6.9 (2.1)</td>
<td>12.0 (3.8)*</td>
<td>8.3 (2.9)</td>
<td>7.1 (2.3)</td>
<td>7.1 (3.2)</td>
<td>6.1 (1.7)</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>7.8 (7–10.3)</td>
<td>6.6 (6.4–8.8)</td>
<td>12 (11–18.2)*</td>
<td>9.3 (5.8–10.6)</td>
<td>7.0 (5.3–8.7)</td>
<td>6.0 (4.3–8.6)</td>
<td>6.0 (4.3–8.6)</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>49 (10)</td>
<td>40 (6)*</td>
<td>30 (7)*</td>
<td>33 (8)</td>
<td>37 (6)</td>
<td>37 (6)</td>
<td>38 (6)</td>
</tr>
<tr>
<td>CO (litre min⁻¹)</td>
<td>4.4 (3.7–4.9)</td>
<td>3.2 (2.8–3.4)*</td>
<td>2.5 (2.0–2.6)*</td>
<td>2.6 (2.4–2.9)</td>
<td>2.9 (2.6–3.1)</td>
<td>2.9 (2.7–3.2)</td>
<td>3.0 (2.8–3.2)</td>
</tr>
<tr>
<td>GEDV (ml)</td>
<td>473 (74)</td>
<td>427 (54)</td>
<td>375 (64)*</td>
<td>409 (75)</td>
<td>430 (68)</td>
<td>439 (58)</td>
<td>452 (77)</td>
</tr>
<tr>
<td>RSVT angle (°)</td>
<td>12 (6–15)</td>
<td>12 (7–16)</td>
<td>20 (18–23)*</td>
<td>12 (9–18)*</td>
<td>11 (8–13)</td>
<td>8 (5–10)</td>
<td>6 (4–9)</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>12 (9–15)</td>
<td>10 (9–12)</td>
<td>8 (7–10)</td>
<td>12 (11–16)</td>
<td>13 (12–16)</td>
<td>15 (13–19)</td>
<td>16 (14–19)</td>
</tr>
<tr>
<td>dP/dt (mm Hg s⁻¹)</td>
<td>1874 (324)</td>
<td>736 (140)*</td>
<td>450 (123)*</td>
<td>508 (122)</td>
<td>615 (113)</td>
<td>675 (117)</td>
<td>754 (169)</td>
</tr>
</tbody>
</table>

Table 1 Changes in haemodynamic parameters throughout the experimental protocol. *Significantly different from previous point of measurement (P<0.05). Data are presented as mean (SD) or median (IQR). Points of measurements are as follow: baseline, baseline cardiac impairment (CI), hypovolaemia, volume loading steps 1–4 (VLS). MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; GEDV, global end-diastolic volume; RSVT, respiratory systolic variation test; RAP, right atrial pressure; dP/dt, peak change of left ventricular pressure over time.
be less reliable with often false-positive results under these circumstances.\textsuperscript{21, 22} RSVT showed promising results in an animal model and in patients undergoing heart and major vascular surgery.\textsuperscript{5-32, 4} To our knowledge, up to now, there are no data evaluating the use of RSVT in acutely impaired cardiac function. Therefore, we investigated the value of RSVT in an animal model with acutely impaired cardiac function established by a continuous infusion of the negative inotropic calcium channel blocker verapamil. In order to quantify and to comparably realize cardiac impairment, left ventricular $\frac{dP}{dt}$ and its reduction by 50% of baseline value was targeted.

The area under the ROC curve for RSVT was significantly higher than 0.5, which demonstrates that discriminating responders to volume loading (CO increase $>$ 10%) from non-responders is possible with this parameter. Compared with the sensitivity and specificity of SVV ($A = 0.82$) and PPV ($A = 0.84$), the AUC for RSVT is the highest ($A = 0.88$), even though these differences were statistically not significant.

Our results support the assumption of RSVT being at least as accurate in predicting fluid responsiveness in acute impaired cardiac function as SVV and PPV. Even though without significant statistical differences, the RSVT tended to perform slightly superior compared with SVV and PPV in predicting volume responsiveness. This encourages the hypothesis that the early inspiratory augmentation of SV, that is, the delta-up component contributes to less accuracy of SVV or PPV under those clinical circumstances.\textsuperscript{11, 17}

In this study, static (RAP), volumetric (GEDV), and dynamic (PPV, SVV, RSVT angle) indices statistically had equal predictive value based on the ROC analysis. These findings differ from other clinical and experimental studies.\textsuperscript{16-18} In this study, which is in contrast to a cohort of critically ill patients, the slopes of the individual cardiac function curves were nearly identical: young and healthy animals without cardiac co-morbidities were investigated and the load-dependent myocardial contractile function was targeted by the pharmacological intervention. Thus, this reduction in load-dependent contractile function was not associated with structural changes, that is, ventricular dilatation or changes in compliance. This explains, why under these ideal and consistent circumstances, changes in cardiac preload were detected with remarkable accuracy also by the static parameters GEDV and RAP.

A limitation of our study is the use of an animal model. Although pigs are known to have comparable haemodynamic circumstances to humans, these results cannot be taken into clinical practice without any further questioning. As already observed in the former studies, pigs seem to react to sudden hypovolaemia to a much smaller extent with an increase in HR compared with humans, which was...
also the case in the present investigation. Further, heart–lung interactions are dependent on thoracic compliance, which is not directly transferable from this model to humans. This is especially true for proposed threshold values of ROC analysis. Furthermore, one may claim that the model of impaired cardiac function we used is not comparable with chronic heart failure in humans. The present model rather imitates acute heart failure with decreased contractility, reduced SV and CO, but unchanged ventricular dimensions and compliance. Further, acute impairment of cardiac function as described here might have led to a relative hypervolaemia influencing the presented data. However, neither GEDV nor RAP showed a significant increase immediately after verapamil infusion, making an acute hypervolaemia rather unlikely. The basic assumption was that the induction of global cardiac insufficiency leads to a decreased cardiac function curve. The remarkably small number of positive VLS is explained by the inability of the heart to increase CO after volume administration because of the acute cardiac insufficiency established beforehand. Thus, the present data cannot be transferred to chronic cardiac failure where the Frank–Starling curves are different and more homogeneous in comparison with our study population.

We conclude the RSVT as a new functional, standardized, and automated test performed comparably with other functional parameters for prediction of volume responsiveness in the presence of acutely impaired cardiac function. The RSVT might therefore be clinically useful when optimizing volume in patients with acutely compromised cardiac function.

**Conflict of interest**

Draegermedical, Lübeck, Germany, provided an unrestricted grant for performing this study. Draeger also provided the ventilator with the implemented RSVT-software.

**References**


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