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Dynamic indices do not predict volume responsiveness in routine clinical practice

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Editor’s key points

- Dynamic cardiac indices indicate i.v. fluid responsiveness under controlled conditions.
- In this prospective observational study, dynamic indices were determined by pulse contour analysis in 29 ventilated cardiac surgery patients in response to fluid challenge.
- Lower tidal volumes, cardiac arrhythmias, and specific calculation method reduced predictive value of this method.

Background. Dynamic indices, including pulse pressure, systolic pressure, and stroke volume variation (PPV, SPV, and SVV), are accurate predictors of fluid responsiveness under strict conditions, for example, controlled mechanical ventilation using conventional tidal volumes (TVs) in the absence of cardiac arrhythmias. However, in routine clinical practice, these prerequisites are not always met. We evaluated the effect of regularly used ventilator settings, different calculation methods, and the presence of cardiac arrhythmias on the ability of dynamic indices to predict fluid responsiveness in sedated, mechanically ventilated patients.

Methods. We prospectively evaluated 47 fluid challenges in 29 consecutive cardiac surgery patients. Patients were divided into different groups based on TV. Dynamic indices were calculated in various ways: calculation over 30 s, breath-by-breath (with and without excluding arrhythmias), and with correction for TV.

Results. The predictive value was optimal in the group ventilated with TVs >7 ml kg⁻¹ with correction for TV, calculated breath-by-breath, and with exclusion of arrhythmias [area under the curve (AUC)=0.95, 0.93, and 0.90 for PPV, SPV, and SVV, respectively]. Including patients ventilated with lower TVs decreased the predictive value of all dynamic indices, while calculating dynamic indices over 30 s and not excluding cardiac arrhythmias further reduced the AUC to 0.51, 0.63, and 0.51 for PPV, SPV, and SVV, respectively.

Conclusions. PPV, SPV, and SVV are the only reliable predictors of fluid responsiveness under strict conditions. In routine clinical practice, factors including low TV, cardiac arrhythmias, and the calculation method can substantially reduce their predictive value.

Keywords: cardiac output; dynamic indices; fluid therapy; haemodynamics

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Estimating the intravascular volume status of the intensive care unit (ICU) patients remains a clinical challenge. While hypovolaemia can result in inadequate organ perfusion and organ dysfunction, inappropriate fluid administration can result in pulmonary and interstitial oedema and contribute to further tissue injury, organ dysfunction, and eventually death.1–6 Therefore, reliable predictors of fluid responsiveness are highly relevant.

Various dynamic indices, based on cardiopulmonary interactions in ventilated patients, have been shown to accurately predict fluid responsiveness.5–9 These dynamic indices are induced by mechanical ventilation when the heart operates on the steep portion of the Frank–Starling curve10 11 and include pulse pressure variation (PPV), systolic pressure variation (SPV), and stroke volume variation (SVV).

Although several studies5–9 have shown excellent accuracy for these dynamic indices, most of the study populations were strictly controlled, including controlled mechanical ventilation with no spontaneous breathing, tidal volumes (TVs) >7 ml kg⁻¹, breath-by-breath calculation, and no cardiac arrhythmias. However, recent research including more than 12,000 consecutive patients undergoing surgery12 showed that only 39% of patients met the criteria for monitoring fluid responsiveness, with pulse pressure measured invasively or non-invasively.13 This is in part because patients are ventilated with low TVs of 6–8 ml kg⁻¹14–16 and calculation of dynamic indices is not performed on a breath-by-breath basis, and patients often show spontaneous breathing activity. In addition, cardiac arrhythmias can occur on an irregular basis.
Nevertheless, dynamic indices are often used in routine clinical practice while the exact effects of these non-ideal circumstances on the predictive value of dynamic indices are unclear. This emphasizes the need for quantification of their influence on dynamic indices in the general cardiac ICU patient.

The aim of the present study was to evaluate the effects of regularly used ventilator settings, cardiac arrhythmias, and different calculation methods on the predictive value of dynamic indices on fluid responsiveness in sedated, mechanically ventilated patients after cardiac surgery.

**Methods**

**Patients**

Thirty patients on controlled mechanical ventilation after isolated coronary artery bypass surgery were prospectively studied from the time of admission to the ICU. Because of the observational and non-invasive character of this study, the local medical ethics committee waived the need for informed consent. Fluid challenges were administered by the attending physician based upon the presence of at least one clinical sign of inadequate tissue perfusion [low mean arterial pressure (MAP), low urine production, cold extremities, elevated lactate level, or low central venous oxygen saturation]. Patients were excluded if they did not receive a single fluid challenge, showed spontaneous respiratory efforts, or had an intra-aortic balloon pump.

All patients arrived on the ICU with a central venous catheter in the internal jugular position and a radial arterial catheter (20 G). Mechanical ventilation was performed with the Servo 300 (Macquet, Rasstat, Germany). Vasoactive medication was administered according to standard clinical protocols.

**Haemodynamic monitoring**

Arterial pressure (AP), central venous pressure (CVP), and EKG were monitored (Merlin M1046A monitor, Hewlett Packard, Palo Alto, CA, USA) and inspiratory pressure (including $P_{\text{peak}}$, $P_{\text{plate}}$, and PEEP) and inspiratory flow were collected on a computer using the serial port of the Servo 300 ventilator. Both haemodynamic and ventilator parameters were continuously recorded on a laptop computer and stored on a hard disk with a sample rate of 200 Hz by an A/D converter (NI USB-6211, National Instrument, Austin, TX, USA). Afterwards, cardiac output (CO) and stroke volume (SV) were derived offline with the pulse contour method using the same algorithm incorporated in the BMEYE Nexfin Monitor (BMEYE, Amsterdam, The Netherlands).

From the recorded AP and SV, the PPV, SPV, and SVV were calculated offline. Dynamic indices are defined by the relative difference in maximal and minimal pulse pressure ($PP_{\text{max}}/PP_{\text{min}}$), systolic pressure ($SP_{\text{max}}/SP_{\text{min}}$), and SV ($SV_{\text{max}}/SV_{\text{min}}$) for PPV, SPV, and SVV, respectively, according to:

$$100 \times \frac{Q_{\text{max}} - Q_{\text{min}}}{(Q_{\text{max}} + Q_{\text{min}})/2}$$

with $Q=\text{PP}$, $\text{SP}$, $\text{SV}$ for PPV, SPV, and SVV, respectively (Fig. 1). All indices were automatically detected by an algorithm written in Matlab (Matlab R2009b, MathWorks Inc., Natick, MA, USA). The maxima and minima calculated by the software were visually inspected for errors.

**Study design**

All patients were mechanically ventilated using the pressure-regulated volume control mode. Recording of physiological data started immediately after arrival on the ICU and included every fluid challenge administered. The volume challenge consisted of the infusion of 250 ml of 130/0.4 6% HES solution (Voluven, Fresenius Kabi, 's-Hertogenbosch, The Netherlands).

Patients were identified as a responder to fluid challenge if their SV increased by $>10\%$.20 Baseline measurement was performed 3 min before start of the fluid challenge, and response was measured within 3 min after the infusion was completed.

To investigate the influence of TV, patients were analysed in three different groups according to their TV. One analysis included all patients (all TVs). Subsequently, we analysed patients with TV higher and lower than 7 ml kg$^{-1}$, a threshold used earlier.5 To investigate the influence of the calculation method and arrhythmias, for all the three TV groups, the
Dynamic indices do not predict volume responsiveness

**Table 1** Patient characteristics and ventilatory parameters

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (male)</td>
<td>29 (25)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67</td>
<td>61–71</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>91</td>
<td>74–99</td>
</tr>
<tr>
<td>Ventilatory mode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure-regulated volume control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate (bpm)</td>
<td>12.6</td>
<td>12.2–14.3</td>
</tr>
<tr>
<td>Inspiratory pressure (cm H2O)</td>
<td>16.6</td>
<td>15.3–18.8</td>
</tr>
<tr>
<td>PEEP (cm H2O)</td>
<td>5.3</td>
<td>4.6–6.9</td>
</tr>
<tr>
<td>Tidal volume (ml·kg⁻¹)</td>
<td>7.0</td>
<td>4.0–10.0</td>
</tr>
<tr>
<td>Fluid challenges (#)</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Infusion volume (ml)</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>Infusion time (min)</td>
<td>7</td>
<td>4–10</td>
</tr>
</tbody>
</table>

Dynamic indices were calculated in four different ways. First, dynamic indices were calculated breath-by-breath and averaged over a selected period of 5 breaths, excluding cardiac arrhythmias. Secondly, the indices were calculated over a period of 30 s (excluding cardiac arrhythmias) by using the mean of four maximal and four minimal PP, SP, and SV values to calculate the PPV, SPV, and SVV, respectively. The same method for the calculation over 30 s was used again for the third analysis only now without excluding cardiac arrhythmias occurring within the 30 s around baseline. Finally, dynamic indices were calculated breath-by-breath and divided by the delivered TV to correct for the use of different TVs, excluding cardiac arrhythmias. This resulted in a total of 12 different analyses per dynamic index (Fig. 2).

**Statistical analysis**

Changes in haemodynamic and respiratory parameters due to volume expansion were analysed using the Wilcoxon rank test. Differences in baseline and response to fluid challenge between responders and non-responders were assessed using the Mann–Whitney U-test. Linear correlations were tested using the Spearman rank method. Receiver operator characteristic (ROC) curves were constructed for the dynamic indices to evaluate the predictive value together with the sensitivity, specificity, and positive and negative likelihood ratio. P-values of <0.05 were considered statistically significant. Because of the small number of patients, no formal statistical tests on the ROC curves from the different subgroups were performed. Statistical analysis was performed using SPSS 18 for windows (SPSS Inc., Chicago, IL, USA).

**Results**

One patient was excluded because of spontaneous breathing activity. The remaining study population consisted of 29 patients receiving a total of 47 fluid challenges. Patient characteristics, relevant ventilator parameters, and data concerning fluid challenges are presented in Table 1. Seven fluid challenges (15%) resulted in an increase in SV >10% (responders).

Baseline haemodynamic parameters were not significantly different between responders and non-responders except for a higher MAP in non-responders. Figure 3 shows the haemodynamic variables at baseline and after volume expansion in all responders and non-responders. MAP and CVP increased significantly in response to fluid administration for both responders and non-responders, whereas HR decreased significantly in both groups. The change in HR and SVI was significantly higher in responders compared with non-responders.

In general, baseline measurements of PPV, SPV, and SVV were significantly different between responders and non-responders, and also the decrease in these parameters as a result of fluid challenge (Fig. 4). Figure 5 illustrates that including patients ventilated with lower TVs decreases the predictive value of all three dynamic indices. For example, for PPV (Fig. 5a), adding patients ventilated with all TV (n=47) to the patient group ventilated with TV >7 ml·kg⁻¹ (n=23) decreased the area under the curve (AUC) from 0.92 to 0.80, and further to 0.69 in patients ventilated with TV <7 ml·kg⁻¹ (n=24). When changing the calculation method from breath-by-breath analysis to calculation over 30 s without excluding cardiac arrhythmias, the AUC for PPV in patients ventilated with TV >7 ml·kg⁻¹ decreased from 0.92 to 0.79. On the other hand, correction of the PPV for TV improved the AUC from 0.92 to 0.95 with a sensitivity and specificity of 100% and 93%, respectively. This particular group also showed the highest values for SPV (AUC=0.93, Fig. 5a) and SVV (AUC=0.90, Fig. 5c). SPV was least influenced by the varying circumstances. The ROC curves in Figure 5d show the decrease in predictive value of PPV in four characteristic groups.

**Discussion**

The present study confirms previous reports that show that the ability of dynamic indices to predict volume responsiveness is very good under strictly regulated conditions. In
In addition, the main finding of our study is that factors present in routine clinical practice, such as the use of lower TVs, cardiac arrhythmias, and the method of calculation, negatively influence the predictive value of dynamic indices. Unrestricted use of dynamic indices is therefore not without pitfalls since almost half of the TVs applied nowadays are < 7 ml kg⁻¹.

Dynamic indices are mostly calculated automatically using various haemodynamic monitors that lack respiratory data and therefore calculate dynamic indices over a period of 30 s. This also increases the risk of including cardiac arrhythmias into the calculation period because an unnecessary long time interval is analysed. Therefore, in routine clinical practice, liberal use of dynamic indices to support the clinical decisions to administer fluid results in a false sense of security.

**Influence of TV**

The effect of TV on the absolute value of dynamic indices has been acknowledged earlier, but to what extent TV influences the predictive value of the dynamic indices is sparsely studied. In a meta-analysis, most of the studies included also used a TV of 8–10 ml kg⁻¹, and they suggest this range when using dynamic indices to predict fluid responsiveness. In one study, it was shown that PPV is only reliable when TV > 8 ml kg⁻¹ (difference in sensitivity and specificity of 22% and 24%, respectively, in the high vs low TV group). This is most likely caused by a non-linear compliance of the chest wall resulting in less variation in intrathoracic pressure with decreased TVs. However, since in clinical practice, it is preferred to ventilate with lower TV than traditionally used, we evaluated the use of dynamic indices...
Dynamic indices do not predict volume responsiveness

Fig 4 Comparison of dynamic indices at baseline and after volume expansion in responders and non-responders (breath-by-breath analysis in group with all tidal volumes, cardiac arrhythmias excluded). Significance is indicated (*$P<0.05$) for the difference between baseline and after fluid loading (left and right significance mark), difference in baseline between responder and non-responder (upper significance mark), and difference in change of the parameter because of the volume expansion between responders and non-responders (lower significance mark).

Fig 5 ROC curves and AUC of dynamic indices for different groups of tidal volume ($n=23, 47, \text{ and } 24$, for the groups with TV > 7 ml kg$^{-1}$, TV all, and TV < 7 ml kg$^{-1}$, respectively). (a–c) The areas under the ROC curve for PPV, SPV, and SVV for all different groups. (c) The four ROC curves for characteristic groups.
indices using TV within this lower range. The influence of TV on the absolute value of dynamic indices and their predictive value suggest that dynamic indices should be corrected for the applied TV. Indeed, when PPV is divided by the TV, the predictive value of the PPV improves. In addition, our results show an improved predictive value, not only for PPV, but also for SPV and SVV, after adjustment for TV.

**Influence of different calculation methods**

By definition, dynamic indices such as SPV, PPV and SVV represent variation of the systolic pressure, pulse pressure, and SV, respectively, over a breath. Importantly, increasing the number of breaths over which the dynamic indices are calculated can increase the calculated values, because larger and smaller pulse pressures and SVs are more likely to occur during a longer observation period, resulting in a more pronounced variation in the dynamic indices. However, clinical devices such as the Philips IntelliVue Patient Monitor (Philips Medical Systems, Eindhoven, The Netherlands), the PiCCO2 (Pulsion Medical Systems, Muenchen, Germany), and the Dräger infinity (Dräger Medical, Lübeck, Germany) use software that samples a defined time interval without identifying the number of breaths. During low respiratory rates, this leads to significant variation in PPV, which has no physiological background and should therefore be discarded. On the other hand, in other cases, the time window of 30 s leads to an unnecessary high number of breaths, which increases the chance to include cardiac arrhythmias such as premature ventricular contractions. This negatively influences the predictive value of dynamic indices. The results from the present study confirm this hypothesis, as the most pronounced decrease in predictive value of the PPV was caused by a change in calculation from breath-by-breath to a 30 s period.

**Influence of cardiac arrhythmias**

Dynamic indices reflect the influence of mechanical ventilation on cardiac preload. However, this is not the case during cardiac arrhythmias like atrial fibrillation or frequent premature ventricular contractions. Therefore, these cardiac arrhythmias should be excluded from calculations. Of importance, neglecting or interpolating the premature ventricular contraction is not advisable, since it is not known whether the neglected beat would represent a larger or smaller pulse pressure and the heart beat directly after a PVC occurs after a compensatory pause, resulting in a higher pulse pressure. For this reason, not only the specific beat, but the whole respiratory cycle should be excluded from the dynamic indices calculation. This is supported by the results of the present study. The extent to which cardiac arrhythmias influence the predictive value of dynamic indices of course depends on their incidence. In cardiac patients, the incidence of arrhythmias and thereby their influence might be higher than in other patient populations.

A technique that is less dependent on changing clinical conditions is the passive leg raising (PLR) test. Non-invasive CO monitoring during the PLR test predicts volume responsiveness with high accuracy in a broad population of ICU patients, even in patients with spontaneous breathing activity. Other alternatives independent from the TV include assessment of volume responsiveness during respiratory manoeuvres like the Valsalva manoeuvre, or the respiratory systolic variation test that uses three mechanical breaths with gradually increasing airway pressures. A disadvantage that all these alternatives have is that they are progressively labour intensive, which reduces their applicability in routine practice.

**Limitations**

Changes in CO were monitored using the pulse contour method. Although previous validation studies show excellent accuracy of this technique, and only changes in SVI were used (and not the absolute value), this method might be less reliable compared with more invasive methods. In contrast to previous studies, we found a relatively low number of responders (15%). Although other studies also used this amount of infused volume with comparable or even higher thresholds to identify volume responders, this might be related to the relatively low volume infused (250 ml). Finally, the incidence of PVCs among our cardiac patients could be higher than in non-cardiac ICU patients.

Our results are in accordance with those from other studies regarding the predictive value and limitations of dynamic indices. In addition, they demonstrate how these situations influence the predictive value of the dynamic indices in routine ICU practice.

In summary, although PPV, SPV, and SVV are reliable predictors of fluid responsiveness under strict conditions, they are not accurate predictors of volume responsiveness in mechanically ventilated patients after cardiac surgery in routine practice. This is caused by the preferent use of low TVs, presence of cardiac arrhythmias, and the applied calculation methods. Clinicians should be aware of these limitations when using dynamic indices for predicting volume responsiveness.

**Declaration of interest**

None declared.

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Dynamic indices do not predict volume responsiveness


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