Comparison of arterial pressure and plethysmographic waveform-based dynamic preload variables in assessing fluid responsiveness and dynamic arterial tone in patients undergoing major hepatic resection

Modified from

Jaap Jan Vos, Alain F Kalmar, Michel M.R.F. Struys, J.K. Götz Wietasch, Herman G.D. Hendriks, Thomas W.L. Scheeren

Department of Anesthesiology, University of Groningen, University Medical Center Groningen
Chapter 2

Abstract

Background. Dynamic preload variables to predict fluid responsiveness are based either on the arterial pressure waveform (APW) or on the plethysmographic waveform (PW). We compared the ability of APW-based variations in stroke volume (SVV) and pulse pressure (PPV) and of PW-based plethysmographic variability index (PVI) to predict fluid responsiveness and to track fluid changes in patients undergoing major hepatic resection. Furthermore, we assessed if the PPV/SVV ratio, as a measure of dynamic arterial elastance (E_{a_{dyn}}), could predict a reduction in noradrenaline requirement after fluid administration.

Methods. Thirty patients received fluid (15 ml kg^{-1} in 30 minutes) after hepatic resection and were considered responders when stroke volume index (SVI) increased ≥ 20 % after fluid administration. SVV and SVI were measured by the FloTrac-Vigileo® device, PVI by the Masimo Radical 7 pulse co-oximeter®. PPV was calculated using an automated algorithm.

Results. The areas under the ROC curve (AUROC) of SVV, PPV and PVI were 0.81, 0.77 and 0.78, respectively. In responders, all dynamic variables, except PVI, decreased after fluid administration. E_{a_{dyn}} predicted a reduced noradrenaline requirement with an AUROC of 0.81.

Conclusions. In patients undergoing major hepatic resection, both APW- and PW-based dynamic preload variables predict fluid responsiveness (preload) to a similar extent. Most variables (except PVI) also tracked fluid changes. Additionally, E_{a_{dyn}} might be additionally useful clinically to assess the degree of arterial elastance (afterload) to distinguish the origin of hypotension.
Introduction

An adequate assessment of volume status in patients undergoing major surgery is imperative to prevent both inadvertent hypovolaemia and fluid overload, both of which are associated with increased morbidity and mortality. Static indicators of cardiac preload, such as central venous pressure (CVP) and pulmonary artery occlusion pressure, have repeatedly been shown to be inaccurate for an adequate assessment of volume status and are unable to predict fluid responsiveness reliably. Instead, current research focuses on the use of dynamic preload variables for the prediction of fluid responsiveness, i.e. to predict if fluid administration will increase cardiac output. These dynamic preload variables are based on the heart-lung interaction and are derived from circulatory fluctuations secondary to changes in intrathoracic pressure during volume controlled mechanical ventilation. Dynamic preload variables are either pressure-based (e.g. pulse pressure variation; PPV), flow-based (e.g. stroke volume variation; SVV) or volume-based (plethysmographic variability index; PVI) and are obtained either from the arterial pressure waveform (APW; semi-invasive) or from the plethysmographic waveform (PW; non-invasive). A comparable ability to predict fluid responsiveness between APW- and PW-derived PPV has recently been demonstrated in critically ill patients. A recent report however showed the reduced accuracy of dynamic preload variables to predict fluid responsiveness under ‘normal’ clinical conditions in the intraoperative setting and another report illustrated that in less than 30% of intraoperative cases, all conditions are met for the use of dynamic preload variables to predict fluid responsiveness. In addition, even when preload dependency is assessed correctly, an assessment of cardiac afterload, i.e. arterial tonus, might be additionally useful for guidance of appropriate (vasopressor or fluid) therapy to guarantee adequate organ perfusion. Recently, the ratio between the pressure-based PPV and the flow-based SVV has been proposed to reflect dynamic arterial elastance (Ea\textsubscript{dyn}), i.e. a surrogate of cardiac afterload. By this means it becomes possible to differentiate arterial vasodilatation from hypovolaemia as a cause of hypotension.

The aim of this study was to assess an estimate of both cardiac preload and dynamic arterial elastance in a clinical setting of patients undergoing major hepatic resection. Therefore, we provide a comparison of the ability of the most commonly used APW- and PW-based dynamic preload variables to predict fluid responsiveness and to track its changes following fluid administration. We hypothesized that PVI was as good as the arterial pressure based dynamic preload variables in predicting and tracking changes induced by fluid administration. In addition, we assessed whether Ea\textsubscript{dyn} was able to predict changes in arterial tone in response to changes in noradrenaline requirement after fluid administration.

Methods

We performed this analysis in 30 patients involved in a previous study in which we investigated the accuracy of continuous non-invasive measurement of total haemoglobin concentration using the Masimo Radical 7 device (Masimo Inc., Irvine, USA), which additionally records the plethysmographic variability index (PVI) with the same waveform. In these patients, the other cardiac output-based data were obtained as part of routine clinical monitoring. Each patient served as his/her own control. The original study was approved by the local ethics committee (Ref: 2009/174, University Medical Centre Groningen, The Netherlands) and was registered at clinicaltrials.gov (NCT01060683).
All eligible ASA I – III patients scheduled for major hepatic resection were included into this study after written informed consent had been obtained.

Patients with intra-operatively diagnosed incurable disease, cardiac dysrhythmia or patients who required additional intravenous fluids to maintain haemodynamic stability before the fluid bolus was administered (the latter required for the aim of the original study), were excluded.

All patients received a standardised general anaesthesia after placement of a thoracic epidural catheter, as previously described. A radial artery was cannulated (20G) for continuous monitoring of arterial blood pressure and for blood gas analysis and the right internal jugular vein was cannulated (7F triple lumen) for monitoring CVP and drug infusion. Both pressure transducers were, after zeroing, adjusted to the height of the right atrium.

Noradrenaline was administered when mean arterial pressure (MAP) dropped below 60 mmHg and adjusted to keep MAP between 60 and 80 mmHg. Patients were mechanically ventilated with a mixture of O₂ (FiO₂ 0.30-0.35), air and isoflurane in a volume controlled mode with minimal tidal volumes of 8 ml kg⁻¹ adjusted to lean body mass and a PEEP of 5 cm H₂O. The respiratory rate was adjusted to maintain end-tidal CO₂ pressure between 4.5 and 5.5 kPa. Respiratory settings were not changed throughout the measurements.

Directly after the end of hepatic resection, all patients received a fluid bolus of 15 ml⁻¹ kg⁻¹ within 30 min. As per original protocol, patients were allocated to receive a fluid bolus of either colloids (n=15) or crystalloids (n=15). Patients were considered fluid-responsive when stroke volume index (SVI, stroke volume divided by body surface area for normalisation) increased by at least 20% after fluid administration compared to the value before administration of fluid. SVI was measured continuously using the FloTrac-Vigileo device (Edwards Lifesciences, Irvine, USA).

**Dynamic preload variables:**

The FloTrac-Vigileo® device (software V03.02) analyses continuously the arterial pressure waveform for calculation of cardiac output (CO) and cardiac index (CI). The device also calculates SVV over a 20 second time frame using the formula: \( SVV = SV_{max} - SV_{min} / SV_{mean} \).

The FloTrac sensor was attached to the arterial catheter and the Vigileo® was connected to the vital signs monitor (Philips MP70; Philips, Eindhoven, Netherlands) for continuous data registration.

The Masimo Radical 7 SET (V7.6.0.1, sensor version R2-25, RevE) uses transcutaneous multi-wavelength analysis for non-invasive measurement of arterial oxygen saturation and total haemoglobin concentration using a finger clip. This device also calculates PVI, which is based on the perfusion index (PI). PI represents the ratio between pulsatile and non-pulsatile blood and is a measure of local blood flow. PVI is subsequently calculated as \( ((PI_{max} - PI_{min}) / PI_{max}) \times 100 \) over a period of time sufficient to include multiple respiratory cycles. The Masimo sensor was attached to the index finger contralateral to the arterial catheter according to the manufacturer’s instructions.

The APW-based Pulse Pressure Variation (PPV) was recorded online by the clinically used vital signs monitor and calculated off-line afterwards using dedicated software developed by the authors. For the interested reader, also Systolic Pressure Variation (SPV; APW-based) as well as the PW-based variation in peak amplitude (PW_{peak}) and pulse amplitude (PW_{pulse}) were calculated. The results of these three dynamic preload variables are presented in supplementary results. All dynamic preload variables were, after synchronisation, calculated over a time frame of 20 seconds. Obvious artefacts were eliminated by visual inspection of waveforms. \( Ea_{dyn} \) was calculated as the SVV/PPV ratio, as previously described.
Data recording:
Data were recorded by a Windows XP based medical grade personal computer running RugLoop II data-collection software (Demed Engineering, Temse, Belgium). RugLoop II output files were exported to Microsoft Excel 2010 (Microsoft, Redwood, USA) and PASW Statistics 18 (IBM Inc., Chicago, USA) for further analysis. All discrete variables (SpO₂, tidal volume, heart rate, MAP, CVP, SVI, CO, CI, SVV and PVI) were recorded with a sampling rate of 1 Hz, whereas the original APW and PW were stored with a sampling rate of 100 Hz and later used for calculation of dynamic preload variables.

Statistical analysis:
All continuous variables were tested for normal distribution using the Kolmogorov–Smirnoff test. The Student T test was used for normally distributed continuous variables and the Mann-Whitney test for non-normally distributed variables. For categorical variables, the Fisher’s Exact test was applied. The Wilcoxon Signed Rank test was used to compare haemodynamic variables before and after fluid administration. We assessed the ability of dynamic preload variables to predict fluid responsiveness using receiver operating characteristic (ROC) analysis and subsequently calculated the areas under the ROC curve (AUROC’s). AUROC’s were compared using the DeLong methodology.

Optimal cut-off values maximising appropriate classification were calculated using the Youden index (calculated as: sensitivity + specificity -1), along with its sensitivity and specificity.
In addition, the ability of Ea dyn to predict a decrease in noradrenaline requirement at the end of fluid administration was assessed using calculation of its AUROC.

Results
A total of 30 patients were included and analysed. Patient characteristics, except for blood loss and surgery duration, were normally distributed as previously described.

Changes in static variables during fluid administration:
MAP remained stable (74 (11) vs. 74 (9) mmHg). CVP increased from 6 (3) to 9 (4) mmHg (p<0.05). Mean SVI increased from 36 (12) ml m⁻² at the start of fluid administration to 45 (13) ml m⁻² at the end of fluid administration (p<0.05). The mean percentage increase of SVI was 9% with a range from -14% to 33%. In total, 17 out of 30 patients showed an increase in SVI of at least 20% after fluid administration and were considered fluid-responsive.

Haemodynamic effects of fluid administration in fluid responders and non-responders:
All dynamic preload variables as well as heart rate were higher in responders than in non-responders at the start of the fluid administration, while SVI was lower in these patients (table 1). MAP and CVP were not different between groups.
In fluid responders, all dynamic preload variables except PVI decreased at the end of fluid administration (p<0.05); CVP increased slightly (p<0.05). Of note, the decrease of PPV was more pronounced than the decrease of SVV (-14% vs. -10%, respectively).
In non-responders, both SVV and PPV also decreased (p<0.05) but again being more pronounced for PPV. CVP increased slightly (p<0.05). PVI and static preload variables did not change.
Haemodynamic variables of fluid-responders and non-responders before and after administration of the fluid bolus

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-responders (n=13)</th>
<th>Responders (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>SVI (ml m$^{-2}$)</td>
<td>44 (12)</td>
<td>45 (13)</td>
</tr>
<tr>
<td>Heart rate (beats min$^{-1}$)</td>
<td>76 (15)</td>
<td>78 (11)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>73 (9)</td>
<td>72 (9)</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>7 (4)</td>
<td>9 (4) *</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>12 (6)</td>
<td>9 (5) *</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>16 (9)</td>
<td>8 (4) *</td>
</tr>
<tr>
<td>PVI (%)</td>
<td>10 (7)</td>
<td>8 (6)</td>
</tr>
</tbody>
</table>

Table 1: Data are presented as mean (SD). SVI: stroke volume index; MAP: mean arterial pressure; CVP: central venous pressure; SVV: stroke volume variation; PPV: pulse pressure variation; PVI: plethysmographic variability index. * p<0.05, responders vs. non-responders. # p<0.05, value after fluid bolus administration vs. value before.

Prediction of fluid responsiveness:
Figure 1 depicts the ROC curve for the prediction of fluid responsiveness of SVV, PPV, and PVI. All individual AUROC’s were different from zero (p<0.05); the associated confidence intervals are also shown in figure 1. Comparison between all the AUROC’s of the dynamic preload variables revealed no significant differences using Hanley & McNeil analysis.
In table 2 optimal cut-off values, as determined by the Youden index, are shown for dynamic preload variables along with the associated sensitivity and specificity. Additionally, the AUROC of CVP was 0.46 (CI: 0.24-0.68; p=0.71) and was significantly different from AUROC’s of all dynamic preload variables.

<table>
<thead>
<tr>
<th>Optimal cut-off value of dynamic preload variables for predicting fluid responsiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal cut-off value</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>SVV</td>
</tr>
<tr>
<td>PPV</td>
</tr>
<tr>
<td>PVI</td>
</tr>
</tbody>
</table>

Table 2: All presented variables are reported as percentages. SVV: stroke volume variation; PPV: pulse pressure variation; PVI: plethysmographic variability index.
Influencing factors on haemodynamic variables:
Median (range) noradrenaline dosages at the start of fluid administration were similar between responders (0.15 (0.02- 0.55) µg kg⁻¹ min⁻¹) and non-responders (0.15 (0.01- 0.74) µg kg⁻¹ min⁻¹; p=0.3), as was the reduction of noradrenaline dosage at the end of fluid administration (0.13 (0.12- 0.46) µg kg⁻¹ min⁻¹ vs. 0.12 (0.01 – 0.51) µg kg⁻¹ min⁻¹, respectively; p=0.7) to keep MAP between 60 and 80 mmHg. In addition, the mean tidal volume was 10.5 (1.8) ml kg⁻¹ lean body mass at the start and end of the fluid administration, while the mean heart rate/ respiratory rate was 7.9 (1.7) at the start and 7.8 (1.3) at the end of the fluid administration.

Agreement between dynamic preload variables:
All dynamic preload variables were significantly correlated with each other at the start of the fluid administration (table 3, light grey boxes). After fluid administration (table 3, dark grey boxes), PVI did not correlate significantly with SVV. All other investigated dynamic preload variables were correlated significantly.

Table 3: Pearson correlation coefficient (R values) between individual dynamic preload variables. Light grey boxes are R values before fluid bolus administration, while dark grey boxes are R values thereafter. *indicates p < 0.05. SVV: stroke volume variation; PPV: pulse pressure variation; PVI: plethysmographic variability index.
Association $E_{a\text{ dyn}}$ with noradrenaline requirement and MAP:

$E_{a\text{ dyn}}$ was neither associated with MAP at the start of fluid administration ($R=0.28$, n.s.) nor with the absolute difference in MAP between the end and start of fluid administration ($R=-0.1$, n.s.). In patients in whom noradrenaline could be decreased at the end of fluid administration ($n=15$), mean (SD) $E_{a\text{ dyn}}$ was 1.6 (0.4), while $E_{a\text{ dyn}}$ was 1.2 (0.4) in patients in whom noradrenaline requirement was at least equal to the required dose at the start of fluid administration ($p<0.05$). Furthermore, $E_{a\text{ dyn}}$ was significantly correlated with the noradrenaline requirement ($R=0.47$) and was also inversely correlated with the difference in noradrenaline requirement before and after fluid administration ($R=-0.55$).

The AUROC of $E_{a\text{ dyn}}$ to predict a decrease in noradrenaline requirement ($n=15$) was 0.81 (CI: 0.65-0.97; $p<0.05$). The optimal cut-off $E_{a\text{ dyn}}$ value was found at 1.25 with a sensitivity of 80% and a specificity of 73%.

Discussion

In the present study, we investigated the ability to predict fluid responsiveness of dynamic preload variables that were either arterial pressure waveform (APW) based or plethysmographic waveform (PW) based. We found all of these dynamic preload variables to have a similar ability to predict fluid responsiveness in patients undergoing major hepatic resection, although optimal cut-off values seem to be somewhat different. Furthermore, all the APW based dynamic preload variables, but not PVI, decreased after fluid administration, i.e. were able to track the haemodynamic changes associated with this intervention.

Additionally we found the dynamic arterial elastance ($E_{a\text{ dyn}}$) capable of predicting a reduction in noradrenaline requirement at the end of fluid administration, suggesting that $E_{a\text{ dyn}}$ is able to estimate the influence of noradrenaline administration on intrinsic arterial tone after volume expansion.

In recent years, many studies have shown the superior ability of dynamic preload variables over static preload variables (e.g. CVP) for the prediction of fluid responsiveness.\textsuperscript{2,3,5,6} Data from the present study are in line with these previous studies as the AUROC for the prediction of fluid responsiveness of CVP we found was not significant and only 0.46 whereas all dynamic preload variables performed much better. Interestingly, CVP increased both in fluid-responders and in fluid non-responders significantly, although the observed increase, i.e. from 6 to 9 mmHg and from 7 to 9 mmHg respectively, was not clinically important.

PPV and SVV are the best-known dynamic preload variables. In our population, the optimal cut-off values for SVV and PPV to predict fluid responsiveness were 15% and 14%, respectively. A meta-analysis considering studies that investigated these APW-based dynamic preload variables found that, in general, optimal cut-off SVV and PPV values are between 11-13% with a pooled AUROC of 0.84 and 0.94, respectively, which are somewhat higher than the AUROC values we found (0.81 and 0.77, respectively).\textsuperscript{14} In general, most of the studies performed for assessing the ability of dynamic preload variables to predict fluid responsiveness are performed under optimal circumstances either during surgery or on the intensive care unit and are often accompanied with a high sensitivity and specificity (>90%).\textsuperscript{5,15,16} For the correct interpretation of dynamic preload variables, patients must be in cardiac sinus rhythm and be mechanically ventilated in a volume controlled mode with tidal volumes $>$ 8 ml kg$^{-1}$ and a heart rate / respiratory rate ratio above 3:6.\textsuperscript{14} Frequently in routine clinical care, particularly in the intraoperative setting, these criteria are not met\textsuperscript{10} resulting in a decreased ability of dynamic preload variables to predict fluid responsiveness.\textsuperscript{9} Despite the fact that all our
patients met these criteria during the period of fluid administration, we found lower AUROC’s for both SVV and PPV compared to the literature. Our data were obtained in patients under general anaesthesia undergoing extensive hepatic surgery: during upper-abdominal hepatic surgery, the surgeon can easily manipulate central veins (i.e. the inferior caval vein), which can subsequently cause alterations in cardiac venous return influencing preload and thus influencing dynamic preload variables. Although measurements were obtained only after hepatic resection was completed, we cannot rule out some influence of the surgery being performed at the time of measurement causing lower sensitivity and specificity of SVV and PPV. Therefore, the data presented here might give a realistic impression of the ability of both APW- and PW-based dynamic preload variables to predict fluid responsiveness during “real life” clinical circumstances. Though, only in 23% and 39% of surgical cases all conditions are met for applying APW- and PW-based dynamic preload variables, respectively. A previous report investigated the ability of PPV to predict fluid responsiveness in patients undergoing liver surgery. Here, the AUROC of PPV either derived from the APW or from the non-invasive Finapres® device (Ohmeda Monitoring Systems, Englewood, USA) were 0.79 and 0.81 respectively (comparable to our data), but the AUROC of PW-based “PPV” was only 0.68. In contrast, we demonstrated in our population that all PW-based dynamic preload variables, calculated either using proprietary algorithms (PVI) or using automated algorithms (PW\textsubscript{peak}, PW\textsubscript{pulse}, see supplementary results) predict fluid responsiveness to a similar extent. Importantly, we observed relatively wide 95% confidence intervals of AUROC’s of the studied dynamic preload variables. This finding most probably reflects the inclusion of a limited number of patients (n=30) in the current study and is a result of the requirements for the original study. In addition, we demonstrated that all individual dynamic preload variables were significantly correlated to each other before fluid administration (table 3) and, most importantly, could predict fluid responsiveness to a similar extent, irrespective of the fact whether these variables were derived from the APW or from the PW. This finding is compatible with some previous studies investigating simultaneously both APW- and PW-based variables, while it is noteworthy that we assessed almost all of the most common dynamic preload variables altogether in one population. One of these studies in critically ill patients assessed the ability to predict fluid responsiveness of APW-based PPV and “PPV” calculated by the CNAP-device. Considering important differences in methodology compared to the present study, this study elegantly demonstrated the agreement between APW- and PW-based dynamic preload variables in the intensive care setting. One aspect not frequently taken into account in studies involving dynamic preload variables is the ability of these variables to track changes induced by fluid administration, despite its obvious clinical importance. In the present study, we observed the APW-based dynamic preload variables, but not PVI, to decrease after fluid administration in fluid responsive patients. In addition, also the correlation of PVI with SVV was lost (table 3), suggesting PVI is unable to track changes induced by fluid administration. As per original protocol, patients were randomised to receive a fluid bolus of either colloid (n=15) or crystalloid (n=15) solution and based on this, we and others previously reported that colloid solution might influence the accuracy of haemoglobin measurement by the Masimo Radical 7 device. This might also be true for calculation of PVI, given the inability of this dynamic preload variable to track changes induced by fluid administration. Nevertheless, because of the limited sample size per group, we cannot draw a firm conclusion on this issue. The finding that the Masimo Radical 7 device is unable to track changes after fluid administration despite providing an adequate prediction of fluid responsiveness, is however of major clinical importance: if an anaesthetist were using this device alone, one may conclude that no significant haemodynamic effect resulted from a fluid bolus and that the patient is either a non-responder or is in need for more fluid; both of which are of course incorrect if fluid did produce an adequate effect.
on stroke volume index.
From a physiological viewpoint it may be speculated that the flow-derived dynamic variable (i.e. SVV) is more important than pressure-based (i.e. PPV) or volume-based variables (i.e. PVI), since blood flow is the main determinant of oxygen delivery. Of interest, while the volume-based PVI was not able at all to track changes after volume expansion, the pressure-based PPV did track changes in volume-responders, but also gave a high percentage of false positive results in non-responders (specificity 62%, table 2). The flow-based SVV both tracked changes after volume expansion adequately and also had the largest AUROC in predicting fluid responsiveness.

Another important aspect of intra-operative haemodynamic optimisation is the assessment of cardiac afterload, for which we calculated the pressure / flow ratio (PPV/SVV ratio; $E_{\text{d}y\text{n}}$). In a recent study in ICU patients with acute circulatory failure, $E_{\text{d}y\text{n}}$ was shown to accurately predict an increase in MAP ($\geq 15\%$) following fluid administration with an AUROC of 0.986. Also, $E_{\text{d}y\text{n}}$ was related in this study to the increase in MAP after fluid administration and was different in MAP-responders and non-responders. In our study, noradrenaline was titrated to obtain a MAP above 60 mmHg and because noradrenaline was reduced during fluid administration meticulously in accordance with the MAP on clinical reasons, we found no clear relationship between $E_{\text{d}y\text{n}}$ and MAP. We could however demonstrate that $E_{\text{d}y\text{n}}$ was associated with the reduced noradrenaline requirement after fluid administration. Additionally, $E_{\text{d}y\text{n}}$ proved to be able to predict a decrease in noradrenaline requirement at the end of fluid administration and $E_{\text{d}y\text{n}}$ was significantly higher in those patients ($n=15$) in whom noradrenaline requirement decreased. We speculate that these patients requiring less vasopressor support after volume expansion had more intrinsic vascular tone thereafter, as reflected by the $E_{\text{d}y\text{n}}$ value, which is simply calculated as the PPV/SVV ratio. These findings suggest the $E_{\text{d}y\text{n}}$ value being able to assess vascular tone and might subsequently aid in the decision whether a patient requires afterload support using vasopressors (e.g. noradrenaline) after preload is assessed and optimised using assessment of fluid responsiveness by dynamic preload variables.

**Study limitations:**
SVI was calculated from the measured cardiac index by the FloTrac-Vigileo® device, which calculates cardiac index from auto-calibrated pulse contour analysis of the arterial pressure waveform. As a limitation, every device monitoring cardiac index has an intrinsic variability, for which a generally allowed inter-device percentage error as high as up to 30% is considered reasonable. The accuracy of cardiac index calculation by this device is generally believed to be within this accuracy limit. Though, irrespective of its accuracy, we used relative instead of absolute SVI values in this study. Therefore, we suppose our study results are not affected by the absolute value of cardiac index and stroke volume index.

A second limitation of the present study is the possible impact of the use of noradrenaline on the tracking of changes by the auto-calibrated FloTrac-Vigileo® device, as has been shown in previous reports. We thus could not rule out that the results might have been biased to some extent by changes in noradrenaline administration. The value of assessing dynamic arterial tone using $E_{\text{d}y\text{n}}$ with respect to the ability of the FloTrac-Vigileo® device to track changes in cardiac output following dosage changes of vasopressors might be subjected to further research.

A third limitation, which we already discussed, is the possibly decreased accuracy of dynamic preload variables due to surgical manipulation of the upper abdomen, in particular of the great vessels. Finally, it has to be noted that the fluid bolus administered in our study, required for clinical reasons, was larger than that usually administered in a general surgical population, so that less distinct results might be expected with smaller fluid challenges.
In conclusion, PVI can predict fluid responsiveness as good as dynamic preload variables based on the arterial pressure waveform. Yet, each dynamic preload variable has a different optimal cut-off value. In addition, the APW-based dynamic preload variables, but not PVI, were able to track changes induced by fluid administration. Further technical improvements of the Masimo Radical 7 software and its sensor are necessary to reduce variability in PVI measurements and to improve the ability to track changes induced by fluid administration.

Furthermore, the pressure / flow relationship of PPV and SVV, expressed as the $E_{a,dyn}$, was able to predict a reduction of noradrenaline requirement. Thus we speculate that $E_{a,dyn}$ may serve as a sensitive indicator of intrinsic arterial tone and the influence of noradrenaline thereon in mechanically ventilated patients undergoing major hepatic resection.

### Supplementary Table 1: Data are presented as mean (SD). SPV: systolic pressure variation; PW peak and PW pulse: variation in the peak amplitude and pulse amplitude of the plethysmographic waveform, respectively. * $p<0.05$, responders vs. non-responders. ** $p<0.05$, value after fluid bolus administration vs. value before.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-responders (n=13) Before</th>
<th>Non-responders (n=13) After</th>
<th>Responders (n=17) Before</th>
<th>Responders (n=17) After</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPV (%)</td>
<td>9 (5)</td>
<td>8 (7)</td>
<td>14 (6)*</td>
<td>8 (6)†</td>
</tr>
<tr>
<td>PW peak (%)</td>
<td>11 (8)</td>
<td>9 (7)</td>
<td>23 (14)*</td>
<td>13 (5)**</td>
</tr>
<tr>
<td>PW pulse (%)</td>
<td>18 (10)</td>
<td>15 (9)</td>
<td>30 (17)*</td>
<td>18 (7)**</td>
</tr>
</tbody>
</table>

### Supplementary Table 2: All presented variables are reported as percentages. SPV: systolic pressure variation; PW peak and PW pulse: variation in the peak amplitude and pulse amplitude of the plethysmographic waveform, respectively.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SPV</th>
<th>PW peak</th>
<th>PW pulse</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV</td>
<td>8</td>
<td>88</td>
<td>62</td>
</tr>
<tr>
<td>PW peak</td>
<td>12</td>
<td>88</td>
<td>77</td>
</tr>
<tr>
<td>PW pulse</td>
<td>21</td>
<td>70</td>
<td>85</td>
</tr>
</tbody>
</table>

### Supplementary Table 3: Pearson correlation coefficient (R values) between individual dynamic preload variables. Light grey boxes are R values before fluid bolus administration, while dark grey boxes are R values thereafter. SPV: systolic pressure variation; PW peak and PW pulse: variation in the peak amplitude and pulse amplitude of the plethysmographic waveform, respectively. * indicates $p < 0.05$. 

![Correlation Table](image)
Supplementary Figure 1: ROC curves for SPV (black), PW_{peak} (black dotted line) and PW_{pulse} (grey dotted line). Shown are the AUROC with the associated confidence interval for every dynamic index. The line of SPV (APW-based) is solid, while the lines of PW-based PW_{peak} and PW_{pulse} are dashed.
References

References


