The effect of fluid resuscitation on the effective circulating volume in patients undergoing liver surgery

Submitted for publication

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Abstract

Background. Dynamic preload variables, e.g. pulse pressure variation and stroke volume variation (PPV, SVV) allow predicting fluid responsiveness, i.e. whether cardiac output would increase after fluid administration. Recently, bedside assessment of the mean systemic filling pressure analogue (Pmsa) allows the calculation of the venous return driving pressure (Pvr = Pmsa minus central venous pressure). We aimed to compare the ability of Pvr to predict fluid responsiveness with that of PPV and SVV. Secondly, we assess changes in Pmsa, Pvr and heart performance (Eh) after a fluid bolus.

Methods. A post-hoc analysis of data from 30 patients undergoing major hepatic surgery was performed. Patients received 15ml kg⁻¹ fluid in 30 minutes. Fluid responsiveness was defined as an increase of 20% or greater in cardiac index (CI). CI was measured by the FloTrac-Vigileo®, Pmsa, Pvr and Eh were calculated subsequently.

Results. 18/30 patients were fluid responsive. In both responders and non-responders, Pmsa increased following fluid administration (from 13(3) to 17(4) mmHg and from 14 (4) to 17 (4) mmHg, respectively). Pvr, which was lower in responders before fluid administration (6(1) vs. 7(1) mmHg), only increased after fluid administration in responders (from 6(1) to 8(1) mmHg). Eh only decreased in the non-responders group (from 0.56 (0.17) to 0.45 (0.12)). The Area under the ROC curve (AUROC) of Pvr for predicting fluid responsiveness was 0.75 while that of PPV and SVV was 0.73 and 0.72, respectively.

Conclusions. Pvr allows a comparable ability to predict fluid responsiveness as the dynamic preload variables PPV and SVV. In situation in or in patients which PPV and SVV are regarded unreliable for guiding fluid administration, Pvr might provide a suitable alternative. Furthermore, changes in Pvr and Eh allow a further differentiation between fluid responders and non-responders.
Introduction

Fluid administration in the perioperative phase in patients undergoing major surgery should be titrated to the individual needs of the patient to ensure adequate organ perfusion by maintaining or increasing cardiac output (CO). An individual, goal-directed fluid therapy aimed at optimizing CO can prove beneficial to reduce the incidence of postoperative complications as has been shown repeatedly, which requires an appropriate recognition of volume status. Fluid responsiveness can until now best be predicted by dynamic preload variables such as pulse pressure and stroke volume variation (PPV, SVV respectively). Nevertheless, neither PPV nor SVV gives a quantitative estimate of the volume status of an individual patient and the use of these variables is limited by several factors that are frequently present in critically ill and (post-)surgical patients.

According to Guyton’s concept of CO regulation, CO equals venous return under steady state conditions. Following this concept, venous return is determined by the effective circulating volume, the resistance to venous return and the pressure within the right atrium. The effective circulating volume is the result of vascular filling and vascular tone resulting in a driving pressure for the return of blood to the heart that resides in the system when there is no flow. This pressure is referred to as the mean circulatory filling pressure (Pmsf).

Subsequently, the truly driving force of the circulation of blood – according to this model – is the pressure gradient for venous return (Pvr), i.e. the pressure difference between Pmsf and the right atrial pressure (or central venous pressure).

Recently, several studies have validated the use of an algorithm to estimate Pmsf that had previously been described. This algorithm incorporates a cardiovascular model calculating an analogue of Pmsf (Pmsa), adjustable by actually measured conventional hemodynamic variables (MAP, CVP, CO) and patient characteristics (age, sex, weight, length). The algorithm also allows calculation of heart performance (E), which is defined as Pvr / Pmsa. The significance of Pmsa, Pvr and E in FR compared to the frequently used PPV and SVV have not been studied yet.

Therefore, the aim of this study was to compare the ability of Pvr to predict fluid responsiveness with that of the dynamic preload variables PPV and SVV.

Methods

The current study is a post-hoc analysis of a trial in 30 patients undergoing major hepatic resection in whom we investigated the ability of invasive and non-invasive dynamic variables to predict fluid responsiveness. The original study was approved by the local ethics committee (Ref: 2009/174, University Medical Centre Groningen, The Netherlands) and has been registered at clinicaltrials.gov (NCT01060683).

In the original study, cardiac output-based data were obtained as part of routine clinical monitoring. Furthermore, each patient served as his/her own control.

Only ASA I – III patients who were scheduled for major hepatic resection were included after written informed consent had been obtained. Exclusion criteria were intra-operatively diagnosed incurable disease, cardiac dysrhythmia or requirement of additional intravenous fluids to maintain hemodynamic stability before the fluid bolus was administered (the latter required for the aim of the original study).

Fluid responsiveness was defined as an increase in CO, indexed to BSA (Cardiac Index, CI) by at least 20% after fluid administration.
Anesthetic management:
All patients received a standardized balanced general anesthesia after placement of a thoracic epidural catheter, as previously described. Thereafter, only a brief summary of relevant parts is given here. During the phase of hepatic resection, all patients received 6 ml kg\(^{-1}\) hr\(^{-1}\) crystalloids (NaCl 0.9%, Baxter, Deerfield, IL, USA). Noradrenaline was titrated to keep MAP between 60-80 mmHg. Patients were allocated to receive a 500ml fluid bolus of either crystalloids (n=15) or colloids (n=15) in 30 minutes directly after completion of hepatic resection.

Hemodynamic monitoring:
MAP was monitored invasively using a 20G radial artery catheter and the pressure transducer was connected to the vital signs monitor (Philips MP70; Philips, Eindhoven, Netherlands). The FloTrac-Vigileo® device (software V03.02) was connected to the arterial pressure transducer for continuous calculation of CO using an automated auto-calibrated analysis of the arterial pressure waveform. Additionally, this device calculates stroke volume variation (SVV) over a 20 second period using the formula: SVV = \((SV_{\text{max}} - SV_{\text{min}}) / SV_{\text{mean}}\). PPV was calculated subsequently over the equivalent time frame as PPV = \((PPV_{\text{max}} - PPV_{\text{min}}) / PPV_{\text{mean}}\), using dedicated software developed by the authors. Obvious artefacts were eliminated by visual inspection of waveforms.
CVP was continuously recorded after cannulation of the right internal jugular vein using a 7F triple lumen catheter.
Both the arterial and central venous pressure transducers were zeroed and thereafter adjusted to the height of the right atrium.

Data recording:
Handling of data recording of the hemodynamic data was described previously. All data were synchronized and were exported to Microsoft Excel 2010 (Microsoft, Redwood, MS, USA) for statistical analysis.

Statistical analysis:
Continuous variables were tested for normal distribution using the Kolmogorov – Smirnoff test. Normally distributed variables were tested using the paired or unpaired Student’s t-test. Non-normally distributed data were tested using the (paired) Mann-Whitney test or (unpaired) Kruskal-Wallis test.
Correlation between relevant variables was depicted as a scatter plot and coefficients of correlation \((r^2)\) values were calculated.
The ability of dynamic preload variables and Pvr to predict fluid responsiveness was assessed using receiver operating characteristic (ROC) analysis. The areas under the ROC curve (AUROC’s) were compared using the DeLong methodology. Statistical significance was set at \(p<0.05\).
Results

A total of 30 patients (14 male, 16 female) received a fluid bolus and were included for analysis. Mean (SD) age of all patients was 57 (13) year, mean height and weight were 176 (7) cm and 80 (13) kg, respectively.

18/30 patients demonstrated an increase in CI > 20% and were regarded fluid responsive; consequently, 12/30 patients were regarded non-responders.

Hemodynamic variables before and after fluid administration in both fluid responders and non-responders are summarized in table 1.

Table 1: Hemodynamic variables before and after fluid bolus administration

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-responders (n=12)</th>
<th>Responders (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>80 (14)</td>
<td>79 (10)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>75 (11)</td>
<td>71 (9)</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>7 (4)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>CI (L min(^{-1}) m(^{-2}))</td>
<td>3.1 (0.8)</td>
<td>3.2 (1.0)</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>16 (9)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>12 (6)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Pmsa (mm Hg)</td>
<td>14 (4)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>Pvr (mm Hg)</td>
<td>7 (1)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>(E_H)</td>
<td>0.56 (0.17)</td>
<td>0.45 (0.12)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD).

MAP = Mean Arterial Pressure; CVP = Central Venous Pressure; CI = Cardiac Index. PPV = pulse pressure variation; SVV = stroke volume variation; Pmsa = mean systemic filling pressure analogue; Pvr = driving pressure for venous return; \(E_H\) = cardiac performance

* indicates \(p<0.05\) vs. non-responder group.

\(^*\) indicates \(p<0.05\) vs. value before fluid administration.

Fluid administration and changes in Pmsa, Pvr, \(E_H\) and dynamic preload variables

Pmsa was comparable between responders and non-responders before and after fluid administration (table 1). In both groups, Pmsa increased significantly following fluid administration. Pvr (= Pmsa – CVP) was lower in responders than in non-responders before fluid administration. Additionally, Pvr increased in responders after fluid administration, which was not true for non-responders. Heart Performance (\(E_H\)) was comparable between responders and non-responders before fluid administration. Importantly, \(E_H\) decreased significantly following fluid administration in the non-responders group but remained stable in the responders group.

Prediction of fluid responsiveness

For the prediction of fluid responsiveness – defined as an increase of CI > 20% – the area under the ROC curve (AUROC) of PPV was 0.73 (95% Confidence Interval (CI): 0.54 – 0.92; \(p<0.05\)), while that of SVV was 0.72 (CI: 0.53 – 0.91; \(p<0.05\)), figure 1 / table 2.

The AUROC of Pvr in predicting fluid responsiveness was 0.75 (CI: 0.57 – 0.93; \(p<0.05\), figure 1 / table 2). There were no significant differences between the observed AUROC’s. The optimal cut-off values with associated sensitivity and specificity are given in table 2.
Table 2: Characteristics of ROC analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUROC</th>
<th>Optimal cut-off (mmHg / %)</th>
<th>Sensitivity / Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pvr</td>
<td>0.75</td>
<td>7</td>
<td>72 / 75</td>
</tr>
<tr>
<td>PPV</td>
<td>0.73</td>
<td>14</td>
<td>83 / 58</td>
</tr>
<tr>
<td>SVV</td>
<td>0.72</td>
<td>16</td>
<td>56 / 91</td>
</tr>
</tbody>
</table>

Pvr = driving pressure for venous return; PPV = pulse pressure variation; SVV = stroke volume variation; AUROC = Area under the ROC (Receiver Operator Characteristics) curve

Figure 1: Receiver Operator Characteristics (ROC) Curve for assessing the prediction of fluid responsiveness by Pvr (black solid line), PPV (grey dashed line) and SVV (black dashed line).

In addition, the correlation between Pvr and CI before fluid administration was moderate with an $R^2$ value of 0.37 ($p<0.01$, figure 2). Furthermore, the change in CI following fluid administration ($\Delta$CI) was strongly correlated with the change in Pvr ($\Delta$Pvr), with an $R^2$ value of 0.93 ($p<0.01$; figure 3). Of the change in dynamic preload variables, only $\Delta$SVV correlated with $\Delta$CI ($R^2$ 0.18, $p<0.01$), whereas $\Delta$PPV did not ($R^2$ 0.05, $p=0.25$).
Figure 2: Scatter plot showing the correlation between Cardiac Index (CI, x-axis) and Pvr (y-axis) before the administration of fluid. Shown is the coefficient of correlation for all data points. Black filled circles represent responders, while white-filled circles represent non-responders.

Figure 3: Scatter plot showing the correlation between the change in CI (ΔCI, x-axis) and the change in Pvr (ΔPvr, y-axis) following administration of fluid. Shown is the coefficient of correlation for all data points. Black filled circles represent responders, while white-filled circles represent non-responders.
Discussion

In the current study, we assessed the changes in effective circulating volume following fluid administration using a cardiovascular model which is based on the “Guytonian” concepts of cardiac output regulation.

At first, we found that Pvr can predict fluid responsiveness to a similar extent as the commonly used dynamic preload variables PPV and SVV. Therefore, in patients in whom the prediction of fluid responsiveness by dynamic preload variables is limited, e.g. in spontaneously breathing patients or in patients with cardiac arrhythmia, Pvr might provide a suitable alternative method.

At second, the variables derived by the investigated model closely followed expected cardiovascular volume-induced changes and allow a further differentiation between fluid responders and non-responders. While Pmsa increased in both responders and non-responders to fluid administration, Pvr only increased in fluid responders, suggesting that in fluid responders the heart was able to handle the increase in Pmsa allowing CI to increase secondary to an increase in Pvr. Also, the decrease in heart performance (EH) in non-responders following fluid administration suggests that these patients were actually not in need of fluid and were already on the “flat” part of the Frank-Starling curve.

Prediction of fluid responsiveness

In anesthesia and intensive care medicine, an individual and rationale approach for guiding fluid management is of high clinical importance in order to prevent the development of (fluid-related) complications.\(^1,2\) An important consideration in this matter is to distinguish responders from non-responders to fluid administration: i.e. to assess whether CI increases following fluid administration (responder) or not (non-responder). Currently, in sedated and mechanically ventilated patients, dynamic preload variables like PPV and SVV are established predictors of fluid responsiveness and these variables have been found superior to the traditional static cardiac preload variables like CVP\(^3-5\).

Unfortunately, it has been shown that in a majority of the routine surgical patient population, dynamic preload variables like PPV and SVV cannot be used due to several limiting factors.\(^5\) For example, in patients who are not mechanically ventilated in a volume controlled mode, or in patients with substantial cardiac arrhythmia, or in patients undergoing surgical procedures with an open thorax, dynamic preload variables have been shown to be unreliable in predicting fluid responsiveness.\(^6\) The observation in this study that Pvr was able to predict fluid responsiveness to a similar extent as PPV and SVV, suggests that Pvr might be considered as an alternative method for the determination of fluid responsiveness in the abovementioned situations.

Importantly, Pvr does not require positive pressure mechanical ventilation, and is not limited by any of the other factors as mentioned above, and therefore we suggest that Pvr might serve as an important alternative method for predicting fluid responsiveness, especially when dynamic preload variables are unreliable, which is the case in many ‘routine’ surgical patients or in critically ill patients on the ICU. Future studies in large, perioperative patient populations, should confirm this suggestion.

Further physiologic differentiation between fluid responders and non-responders:

The calculation of Pmsa – as an analogue of the mean systemic filling pressure (Pmsf) – forms the basis of the cardiovascular model introduced by Parkin\(^13\) that was applied in this study. The underlying algorithm, introduced by Parkin, represents a “Guytonian” cardiovascular model that incorporates values of MAP, CO and CVP. We could confirm previous studies which also assessed Pmsf following fluid loading\(^10\),
as we also found that the administration of fluid increases Pmsa. These observations clearly show that – irrespective of the way Pmsf is assessed – this variable functions as an indicator of effective circulating volume and adequately follows volume changes. According to the cardiovascular model of Guyton\(^7\), CO is determined by the effective circulating volume, the resistance to venous return and the pressure within the right atrium. In this respect, Pmsf (Pmsa) can be regarded as a surrogate of effective circulating volume, which is defined as the result of vascular filling and vascular tone. As such, it provides a pressure for the determination of venous return. Subsequently, the pressure gradient between Pmsf (Pmsa) and CVP functions as a driving pressure for generating venous return and subsequently, CO. The current data confirm this as, according to our definition of fluid responsiveness (i.e. an increase in CI>20%), Pvr increased in responders but remained unchanged in non-responders – a finding that was previously observed in post-cardiac surgery patients receiving a fluid challenge.\(^10\) In physiologic terms, these observations suggest that the heart of a fluid responder can, by generating more output in response to fluid administration, handle the increase in Pmsf (Pmsa), which is numerically reflected by an increase in Pvr. In non-responders, the increase in Pmsf (Pmsa) cannot be handled by the heart and CVP – as a passive consequence of cardiac output – is allowed to increase.

The relationship between Pvr and Pmsa is reflected by the value of E\(_H\) (calculated as Pvr/Pmsa), which is a dimensionless variable – ranging from 0 to 1 – and is proposed to resemble heart performance. In responders, E\(_H\) did not change following fluid administration, while in non-responders, E\(_H\) decreased significantly following fluid administration. As explained above, this observation can indicate that in these patients the heart was unable to handle the increase in effective circulating volume and thus, these patients were not in need of fluid, i.e. these patients were likely to be (already) on the “flat” part of their (individual) Frank-Starling curve, due to “overstretching” of the cardiomyocytary actin-myocine complexes. Therefore, a decrease in E\(_H\) might indicate that the patient is on, or even beyond the flat part of the Frank-Starling curve. We therefore hypothesize that this variable might be used clinically to monitor the effects of fluid administration on cardiac performance itself. Potentially, E\(_H\) might also demonstrate the (combined) effects of fluid administration and other factors such as inotropic medication on cardiac performance. Future studies should confirm the potential use of E\(_H\).

In addition, the current data confirm that isolated pressure values – whether it is Pmsa or CVP – are not indicative of venous return itself or CI and thus, should not be used as a surrogate. Whether this is also true for Pvr (apart from its ability to predict fluid responsiveness) remains to be elucidated. In our study, these variables were moderately correlated, suggesting that it might possibly be used as surrogate at least to some extent, yet, there are no data available yet to assess whether an “optimal” Pvr value exists.

**Study limitations**

The current study was performed in patients undergoing major hepatic resection in whom a fluid bolus was administered at the end of parenchymal transection. Therefore, as surgery was ongoing, we cannot rule out that surgical manipulation (e.g. alterations of venous return) might have had some influence on the observed data. Also, if clinically required, dosages of norepinephrine were altered to maintain MAP between 60 and 80 mmHg. The dosage changes of norepinephrine can affect cardiac performance and could have affected total vascular capacitance due to arterial vasoconstriction in combination with some degree of venous vasoconstriction. Hence, Pmsa and other derived variables might be altered by this mechanism, although we could not find any correlation between dosage(s) of norepinephrine and Pmsa or related variables (data not shown). Yet, this issue deserves further elucidation in future, dedicated research.
Also, while we found no differences between PPV, SVV and Pvr in predicting fluid responsiveness, the number of patients included in this study (n=30) was relatively low (as reflected by relatively wide AUROC confidence intervals). A larger sample size might have allowed the recognition of more subtle differences in the ability of Pvr or PPV and SVV in predicting fluid responsiveness, yet with an arguable clinical relevance.

In addition, Pmsa is a theoretical variable that cannot be measured clinically to assess its validity, as real-life measurement would require circulatory arrest. Nevertheless, Pmsa values calculated by the applied algorithm have been shown\(^\text{11}\) comparable to assessments of Pmsf by two other methods: One of these methods uses inspiratory-hold maneuvers (requiring a sedated and ventilated patient) in which data pairs of CO and CVP are back-extrapolated to a zero CO state.\(^\text{16}\), while in the other method\(^\text{11}\), Pmsf is assessed using transient stop-flow arm measurements.\(^\text{11}\)

Finally, the applied algorithm incorporates values of MAP, CO and CVP and combines these with demographic parameters in order to calculate Pmsa and subsequent calculation of Pvr. As the algorithm for calculation of Pmsa is based on multiple (independent) measurements (MAP, CVP and CO), the measurement error of Pmsa is an accumulation of the individual measurement errors of MAP, CVP and CO, which might decrease its accuracy in reflecting volume status and in predicting fluid responsiveness.

In conclusion, Pvr can predict fluid responsiveness to a similar extent as PVV and SVV. Therefore, Pvr might be regarded as an alternative method for predicting fluid responsiveness, especially in situations in which either PPV or SVV is regarded unreliable. Furthermore, fluid responsiveness is reflected by an increase in Pvr, while the decrease of heart performance in non-responders demonstrates
References


