Minimally invasive monitoring in patients under general anesthesia
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Noninvasive pulse pressure and stroke volume variation to predict fluid responsiveness at multiple thresholds: a prospective observational cohort study

Submitted for publication

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Abstract

Background. Dynamic variables such as pulse pressure variation (PPV) and stroke volume variation (SVV) can nowadays be measured noninvasively to assess fluid responsiveness (FR) in anesthetised, ventilated patients. Yet, the influence of the actual definition of FR on its prediction is not well studied. Also, assessment of inconclusive values of PPV and SVV (the “grey zone”) might improve individual FR prediction. We explored these grey zones of PPV and SVV measured noninvasively by the volume clamp method (Nexfin®) for the prediction of FR and we assessed the influence of multiple thresholds for the definition of FR on its predictive ability.

Methods. In this prospective observational study, 90 patients undergoing general surgery were included and received a 500 ml fluid bolus as deemed clinically required by the attending anesthetist. A minimal relative increase in Stroke Volume Index (↑SVI) was used to define FR with different thresholds from 10% to 25%. PPV, SVV and SVI were measured using noninvasive volume clamp method.

Results. Areas under the ROC curve gradually increased for PPV / SVV with higher threshold values (from 0.818 / 0.760 at 10% ↑SVI to 0.928 / 0.944 at 25% ↑SVI). Limits of the grey zone were narrower at higher ↑SVI thresholds (9% – 16% / 18% – 21% at 10% and 25% ↑SVI for PPV and 5 – 13% / 14 – 16% at these respective ↑SVI thresholds for SVV).

Conclusion. Noninvasive PPV and SVV allow an acceptable FR prediction although the reliability of both variables is dependent on the intended increase in SVI and improves substantially, with concomittant smaller grey zones, for higher ↑SVI thresholds.
Introduction

Determination of fluid responsiveness (FR), i.e. predicting whether cardiac output will increase in response to fluid administration, has been the subject of extensive research in the past decade in the field of anesthesia and critical care. Dynamic preload variables, which rely on the heart-lung interaction during volume controlled mechanical ventilation, have been shown to be good predictors of FR. Pulse pressure and stroke volume variation (PPV, SVV) are the most well-known and validated dynamic preload variables and are usually derived invasively using an arterial line, restricting its use to patients in whom invasive, advanced hemodynamic monitoring is applied. The Nexfin® device (Edwards Lifesciences, Irvine, CA, USA) provides a completely noninvasive measurement of arterial blood pressure continuously and noninvasively using an inflatable finger cuff. Its principle is based on “vascular unloading” using the volume-clamp method with additional physiological calibration (PhysioCal). Ultimately, this device reconstructs the applied brachial arterial waveform to determine arterial blood pressure, with subsequent calculation of PPV and provides cardiac output and stroke volume values based on pulse contour analysis, allowing calculation of SVV. Multiple studies have shown that dynamic variables, noninvasively obtained by this device and by comparable noninvasive techniques, are as good as invasively obtained dynamic variables in predicting fluid responsiveness.

To distinguish fluid responders from non-responders following fluid administration it is common practice to pre-define a specific cut-off value of a dynamic preload variable such as PPV or SVV. The use of such a ‘binary’ analysis may often be inappropriate regarding different patient’s comorbidities and clinical conditions. This problem may be partially overcome by the use of a grey zone approach, which identifies a range of values of the dynamic preload variables that cannot give a conclusive prediction of fluid responsiveness. For such inconclusive values of dynamic preload variables, the assessment whether or not (extra) fluid should be administered to the patient might be predominantly dependent on e.g. patient co-morbidity, fluid ‘history’ and other hemodynamic variables, such as blood pressure, heart rate or patient fluid history. Furthermore, substantial differences exist in the literature regarding the chosen numerical definition of fluid responsiveness, which additionally troubles a sound comparison of studies investigating fluid responsiveness and makes a straightforward translation of study results into clinical-decision making algorithms difficult.

The aim of this prospective observational cohort study was to determine the ability of noninvasively volume clamp derived PPV and SVV to predict fluid responsiveness using the grey zone approach. Secondly, because different SVI values should be pursued depending on patient co-morbidities, we investigated the influence of the definition of fluid responsiveness on the actual prediction of fluid responsiveness.

Methods

The local medical ethics committee approved the use of the Nexfin® device for use in this prospective observational study in April 2011 (METc2011.052; University Medical Center Groningen, University of Groningen, Groningen, Netherlands). In this prospective observational cohort study in patients requiring colloid administration for clinical reasons, adult patients under general anesthesia undergoing general surgery were included if the following criteria were met:
Chapter 3

- Tracheal intubation and mechanical ventilation in a volume controlled mode with tidal volumes ≥ 8 ml kg⁻¹ lean body mass.
- Requirement for administration of a fluid bolus on clinical reasons, e.g. clinical signs of hypovolemia, anticipated blood loss.
- No clinical signs of cardiac arrhythmia.
- No open chest surgery or procedures associated with high intrathoracic or intra-abdominal pressure (e.g. laparoscopy).

All patients signed informed consent agreeing to the use of their data for analysis. General anesthesia was induced with propofol and sufentanil or remifentanil, while anesthesia was maintained with target controlled infusion of propofol or with sevoflurane in combination with target controlled infusion of sufentanil or remifentanil. In general, patients received between 1 - 3 ml kg⁻¹ hr⁻¹ crystalloid solution as basic maintenance infusion according to hospital standards. Volume-controlled mechanical ventilation was performed with a mixture of O₂/air (inspired oxygen fraction 0.3 – 0.4). Respiratory rate was adjusted to maintain normocapnia (end tidal CO₂ between 4.5 and 5.5 kPa).

The Nexfin® finger cuff was attached to the intermediate phalanx of either the left or right hand. The technology of the Nexfin® device is based on the volume clamp technique. In short, the pressure of the finger cuff is adjusted to keep arterial blood volume of the finger – which is measured by plethysmography - at a constant level (i.e. volume clamping). By using a high-speed feedback loop, the cuff pressure is adjusted to keep the arterial wall “unloaded”, and cuff pressure reflects arterial blood pressure. The device incorporates an algorithm (Physiocal) aimed to ascertain the “unloaded state” and this algorithm is regularly performed to compensate for any changes in vasomotor tone which might influence the pressure-volume relationship between the finger cuff and arterial blood volume. A 5 minute time period to attain maximal vascular unloading of the finger and for calibration of the Nexfin® device was respected before the fluid bolus was administered.

In addition, the Nexfin® incorporates a heart reference system to correct for hydrostatic pressure differences between the finger and the level of the heart and in this study, it was adjusted so that it was continuously located at the level of the right atrium. More in-detail information on the technology behind the volume clamp technique has comprehensively been described elsewhere. Measurements were performed in a hemodynamically stable phase during maintenance of anesthesia, at least 20 minutes after anesthesia induction. The decision to administer fluid bolus was made by the attending anesthetist, not involved in the study, based on routine clinical care (see above). The anesthetist was blinded for all Nexfin® data other than blood pressure. All patients received a standardized single colloid infusion of 500 ml 6% hydroxyethyl starch solution (Voluven®, Fresenius, Bad Homburg, Germany) within 5-10 min. No changes in ventilator setting, table positioning or in dosage of anesthetic and vasoactive medication were made around or during the period of fluid administration.

The Nexfin®-derived primary outcome measures (PPV and SVV as dynamic preload variables and stroke volume index (SVI) as a measure of flow) and other hemodynamic variables were recorded beat-to-beat and subsequently extracted using Nexfin®PC software (BMEYE, Amsterdam, Netherlands; Edwards Lifesciences, Irvine, CA). Finally, all data were imported into Microsoft Excel 2010® (Microsoft, Redmond, WA). After graphical representation, data were plotted for visual inspection and for correction of obvious atypical values caused by artefacts.
**Statistical analysis:**
All statistics were performed using Microsoft Excel 2010® and PASW Statistics 18 (SPSS Inc, Chicago, IL). All individual data were synchronized to the start of fluid administration and pooled for analysis. Normality of continuous variables was assessed by the Kolmogorov-Smirnov test. Data were expressed as mean (SD) for parametric data, as median (interquartile range (IQR)) for non-parametric data or as number of patients (%), for categorical variables. A 30-second median was calculated for heart rate, mean arterial pressure (MAP), SVV, PPV and SVI prior to start and after the end of fluid administration. The paired T-test was used to compare hemodynamic variables before and after fluid administration.

The correlation between both PPV and SVV and the percentage change in SVI after fluid administration was depicted in a scatter plot and coefficients of determination ($R^2$) were calculated.

All subsequent analyses were performed for every 5% step increase in SVI threshold (abbreviated as $\uparrow$SVI) in the range of 10% - 25%. For each threshold value, patients were split in groups of fluid responders and non-responders. Subsequently, receiver operator characteristics (ROC) analysis was performed for all investigated SVI thresholds and the areas under the ROC curve (AUROC's) were calculated together with confidence intervals. ROC analysis was performed with values obtained after averaging 1000 bootstrapped populations to give more robust estimates of AUROC values and grey zones by limiting the influence of outliers. Bootstrapping was performed using R software and ROC curves were generated using the ROCR software package.\textsuperscript{19, 20} Grey zones were calculated as previously described\textsuperscript{12} using two methods: 1) by calculating the range of values for which sensitivity and/or specificity is < 90% (inconclusive results) and 2) by calculating the 95% confidence interval around the calculated optimal threshold for determining fluid responsiveness using the Youden-Index (sensitivity + specificity – 1). The widest interval of one of these methods was selected as the grey zone.

Sample size calculation revealed that 82 patients were to be included if an increase of 10% in SVI were to be detected. Sample size calculation was based on this SVI threshold value as it is one of the most frequently used threshold values in studies on fluid responsiveness. Statistical significance level was set at $p<0.05$.

**Results**
Measurements were performed in 90 patients, of whom 9 were excluded for further analysis because of either new cardiac arrhythmia (n=3) – troubling an accurate calculation of PPV and SVV – or because of technical difficulties with data recording (n=6), either because of insufficient waveform quality (n=4) or because of failure of the data management system, independent of the Nexfin device (n=2).

Characteristics of the analysed patients (n=81) are shown in table 1.
Median duration of fluid bolus infusion was 385 seconds with an interquartile range of 315 to 529 seconds. In addition, mean tidal volume was 10.8 (1.2) ml kg$^{-1}$ lean body mass (range: 7.5 to 13.2 ml kg$^{-1}$).
Table 1: Main characteristics of the patients.

<p>| | |</p>
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<td>Gender</td>
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<tr>
<td>Age (yr)</td>
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<td>II</td>
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<tr>
<td>Abdominal</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>15</td>
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</tbody>
</table>

Data are presented as mean (SD) or as absolute numbers. ASA class: American Society of Anesthesiologists classification.

Hemodynamic response to fluid administration:
Mean heart rate was 68 (15) bpm before fluid administration and 67 (14) bpm in the 30 seconds following the end of it, while MAP increased from 75 (15) to 81 (17) mmHg (p<0.05).
SVI increased from 40 (11) to 45 (10) ml m⁻² (p<0.05). The relative change of SVI after fluid administration was 16 (12) % and ranged from -11 to 46 % in individual patients.
PPV and SVV were 14 (7) % and 12 (6) % before volume expansion and 7 (4) % and 6 (3) % thereafter.
Correlations between PPV and SVV values before volume expansion and relative change in SVI were significant for both dynamic variables (p<0.05) with an $R^2$ of 0.41 and 0.39, respectively (figure 1).

Figure 1: Scatter plot of the percentage change in Stroke Volume Index (ΔSVI) after fluid administration and the associated values of PPV (black circles) and SVV (white circles) before start of fluid administration.
Influence of definition of fluid responsiveness on its predictive value:
The ROC curves and associated AUROC values for the investigated ↑SVI thresholds are shown in figure 2 for both PPV (A) and SVV (B).
At a ↑SVI threshold of 10% to define “fluid responders”, the AUROC of both PPV and SVV were at their lowest point, while the AUROC’s gradually increased for higher ↑SVI thresholds and are maximal for the 25% ↑SVI threshold (figure 2A and 2B). At 25% ↑SVI threshold, the mean AUROC of SVV was higher than the mean AUROC of PPV, while the lower limit of the confidence intervals of SVV at this thresholds was also above the mean AUROC of PPV. However, the contrary was true for the other thresholds, where the mean AUROC of PPV was higher than that of SVV and its lower limit of confidence intervals were also higher than the mean AUROC of SVV. Of the 4 investigated ↑SVI thresholds to define “responders”, the sensitivity and specificity of the full range of PPV and SVV values to predict a response to fluid administration are shown in figure 3A-B. For both PPV and SVV, lower ↑SVI thresholds are associated with a higher specificity and lower sensitivity at lower PPV / SVV values, while the contrary is true for higher ↑SVI thresholds.

Figure 2A:

Figure 2B:

Figure 2A-B: ROC-curves for the prediction of fluid responsiveness for PPV (3A) and SVV (3B), n=81. Shown are the mean ROC-curves and the AUROC values together with associated confidence intervals for the investigated ↑SVI thresholds.
Table 2A-B: Specification of the number of responders / non-responders, grey zone (=area of uncertainty) limits and percentage of patients within these limits for PPV (A) and SVV (B).

A: PPV

<table>
<thead>
<tr>
<th>↑SVI (%) threshold</th>
<th>No. of responders and non-responders</th>
<th>Limits of the grey zone (%)</th>
<th>Percentage patients below/within/above grey zone</th>
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<td>56/25</td>
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<td>28 / 41 / 31</td>
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<tr>
<td>20</td>
<td>22/59</td>
<td>14 – 17</td>
<td>54 / 17 / 29</td>
</tr>
<tr>
<td>25</td>
<td>16/65</td>
<td>18 – 21</td>
<td>72 / 7 / 21</td>
</tr>
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</table>

B: SVV

<table>
<thead>
<tr>
<th>↑SVI (%) threshold</th>
<th>No. of responders and non-responders</th>
<th>Limits of the grey zone (%)</th>
<th>Percentage patients below/within/above grey zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>56/25</td>
<td>5 – 13</td>
<td>11 / 53 / 36</td>
</tr>
<tr>
<td>15</td>
<td>34/47</td>
<td>7 – 14</td>
<td>18 / 51 / 31</td>
</tr>
<tr>
<td>20</td>
<td>22/59</td>
<td>10 – 15</td>
<td>49 / 22 / 29</td>
</tr>
<tr>
<td>25</td>
<td>16/65</td>
<td>14 – 16</td>
<td>69 / 6 / 25</td>
</tr>
</tbody>
</table>

Data are given for each definition of minimal relative increase in stroke volume index (↑SVI) for pulse pressure variation (A; PPV) and stroke volume variation (B; SVV).
Figure 3A-B: Graph showing the sensitivity (dashed curves) and specificity (solid curves) of the PPV (3A) and SVV (3B) to predict increases in stroke volume (↑SVI) after 500ml fluid administration, n=81. In addition, the range of the grey zone (dashed horizontal lines) of the PPV and SVV are shown for the different ↑SVI thresholds. The small dashed horizontal line at sensitivity / specificity of 0.9 shows the intercepts of the grey zone limits for the different ↑SVI thresholds.
Discussion

We found that the ability of noninvasively derived PPV and SVV to discriminate between fluid responders and non-responders improved substantially for larger $\uparrow$SVI thresholds. Furthermore, the associated limits of the grey zone were narrower for higher $\uparrow$SVI thresholds, suggesting that if a larger increase in SVI is intended, fluid responsiveness can be predicted with more certainty compared to a more ‘subtle’ intended increase in SVI. The current results can be used clinically to improve guiding fluid therapy in individual patients where these dynamic variables are appropriate and measured noninvasively. Furthermore, this finding is important to consider in any clinical algorithm in which a threshold for defining fluid responsiveness needs to be defined, as well as for designing studies concerning fluid responsiveness and dynamic variables as a treatment goal.

In many studies investigating the ability of dynamic preload variables to predict fluid responsiveness, there is a substantial variation in its definition. In general, a $\uparrow$SVI cut-off value between 10 – 20% is regarded an optimal threshold for the administration of fluid to increase cardiac output in most clinical settings. Nevertheless, up to the best of our knowledge, it has not yet been investigated what the impact is of the chosen definition of fluid responsiveness on its prediction. Yet, we observed a substantial dependency on the chosen $\uparrow$SVI threshold for the discrimination of fluid responders from non-responders. E.g., at a $\uparrow$SVI threshold of 25%, both PPV and SVV have a good ability to differentiate fluid responders from non-responders, but at a $\uparrow$SVI threshold of 10%, both dynamic preload variables only have a moderate ability to predict fluid responsiveness with rather broad grey zones with a subsequently high percentage of patients presenting with inconclusive PPV / SVV values. These findings for this $\uparrow$SVI threshold may not be surprising as a high proportion of the patients predicted as fluid responder will in fact be false positively classified, assumed that the $\uparrow$SVI threshold of 10% more closely approximates physiologic variation in stroke volume. Thus, specificity, i.e. the ability of PPV or SVV to correctly predict fluid non-responders was low, while sensitivity was high when choosing a $\uparrow$SVI threshold of only 10% (figure 3). The contrary was true for higher $\uparrow$SVI thresholds as sensitivity, i.e. the ability to correctly predict fluid responders decreased and specificity increased; the definition of fluid responsiveness with the highest AUROC and the smallest grey zone (with the least proportion of patients included) was 25% $\uparrow$SVI. While this may partly be a mathematical consequence – applicable to dynamic variables derived from any monitoring device – it is important to keep this in mind when defining fluid responsiveness for implementation in a clinical decision-making algorithm as well as in the design of future clinical studies.

Therefore, it remains up to the anesthesiologist to assess to what extent an increase in cardiac output is deemed necessary in the individual patient and, more importantly, which situation should be avoided, depending on specific patient comorbidity: inadvertent hypovolemia or, on the other hand, fluid overload. For example, in a critically ill patient at high risk for pulmonary edema, it would be more deleterious to inappropriately administer fluids, while in contrast, in a patient with a serious aortic valve stenosis, hypovolemia would be deleterious, which requires an adequate recognition of fluid needs. In the first case, the clinician should privilege a high specificity, while in the second case a high sensitivity should be favoured. Consequently, higher $\uparrow$SVI threshold values may be preferred in the first case, in contrast to lower $\uparrow$SVI threshold values in the second case.

Another important point is the observation that limits of the PPV and SVV grey zones for the investigated $\uparrow$SVI thresholds were narrower for higher threshold values. Subsequently, the percentage of patients with PPV or SVV values within the grey zone (= area of uncertainty) decreased substantially for higher $\uparrow$SVI threshold values, especially at $\uparrow$SVI threshold values > 20%
(table 2). These data strongly suggest that for these higher threshold values, the observed PPV or SVV value in an individual patient will be more conclusive given the narrower range of grey zone values. Concisely stated, PPV or SVV values below the limits of the grey zone indicate that fluid should not be administered, while values above the limits of the grey zone strongly suggest that the patient will benefit from fluid administration. PPV or SVV values within the grey zone indicate an area of doubt and thus, the clinical decision whether or not to administer fluid will then be dominantly determined by patient co-morbidity or other individual clinical factors rather than the exact PPV or SVV value.

Recent new insights have resulted in a dramatic reduction in the use of synthetic colloids, and we would not advocate to systematically administer colloids to treat hypovolemia. Our conclusion on the use of PPV/SVV primarily addresses the prediction of fluid responsiveness, which is equally applicable on responsiveness to crystalloids, although larger volumes may be necessary to attain the same level of intravascular volume expansion.

Study limitations: We studied volume clamp derived SVI measurements to assess the extent of fluid responsiveness induced by fluid administration in patients undergoing surgery without the clinical need for continuous invasive arterial blood pressure measurement or (semi-) invasive cardiac output monitoring. Therefore, fluid responsiveness and dynamic variables were both determined from the same signal, which might suggest mathematical coupling of the investigated variables. Ideally, cardiac output data were obtained using an alternative, independent approach though this was not feasible in the studied patient population.

Furthermore, there are conflicting reports on the agreement of the volume clamp derived cardiac output with cardiac output values derived from reference methods.8, 21-25 Irrespective of the discussion whether trend monitoring is more important than the accuracy of the absolute value of cardiac output26, most ‘negative’ reports21, 24 were performed in patient populations rather different than the population we studied: e.g. these patients were “sicker” patients being admitted to the ICU and mostly requiring vasopressor support, or were just weaned of cardiopulmonary bypass after cardiac surgery. In addition, apart from the clinical decision of the attending anesthesiologist to administer colloids, we studied patients in an otherwise relatively stable hemodynamic phase. Also, in the current study we only used relative changes in SVI to define fluid responsiveness and we therefore expect that the influence of measurement bias to the observed results is negligible. Nevertheless, some extent of inaccuracy in measuring SVI might by itself explain some degree of differences between the subgroups of SVI thresholds.

We did not compare noninvasively derived PPV and SVV with invasively derived dynamic preload variables. Yet, we have previously shown that the ability of invasive and noninvasive dynamic variables to predict fluid responsiveness is similar9, although it was recently pointed out that invasive variables may provide the best ability to predict fluid responsiveness.27 In addition, two reports20, 25 demonstrated that Nexfin®-derived dynamic variables are closely correlated to invasively measured dynamic variables before and after volume loading in post-cardiac surgical patients. In 4 out of 90 patients (4.4%) we could not derive an adequate waveform quality by the volume clamp method, which is a limitation of this noninvasive technique. Finally, when considering all patients presenting for any type of surgery and any form of anesthesia, a valid interpretation of fluid responsiveness by noninvasive dynamic preload variables is only possible in 39%.28 Likewise, its ability to predict fluid responsiveness was reduced under routine clinical circumstances.29 However, in all included patients the required clinical criteria28 were met (i.e. cardiac sinus rhythm, volume controlled mechanical ventilation with tidal volumes ≥ 8 ml kg⁻¹, closed-chest conditions) for a valid interpretation of PPV and SVV. Also, to avoid additional hemodynamic fluctuations, no changes in the dosages of anesthetic or vasoactive medication were made around the moment of fluid administration.
Conclusion

Noninvasively determined PPV and SVV by the volume clamp method can predict fluid responsiveness adequately at all investigated $\uparrow$SVI thresholds, although this ability is substantially dependent on the chosen $\uparrow$SVI threshold and increases at higher $\uparrow$SVI thresholds, also reflected in increasingly narrow grey zone limits with a subsequently decreased range of PPV / SVV values within this "area of doubt". Therefore, these data stress the importance of considering not only values of dynamic preload variables in assessing fluid responsiveness, but also stress that the clinician considers the intended increase in cardiac output, as well as patient co-morbidity and patient-specific risk factors regarding fluid-related risks for hypo- or hypervolemia, for the ultimate decision whether or not to administer fluids.
References

27 Cannesson M, Le Manach Y. Noninvasive hemodynamic monitoring: No high heels on the farm; no clogs to the opera. Anesthesiology 2012; 115: 937-939.