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ORIGINAL ARTICLE

Prediction of volume responsiveness using pleth variability index in patients undergoing cardiac surgery after cardiopulmonary bypass

Sebastian Haas · Constantin Trepte · Martin Hinteregger · Rebecca Fahje · Bjoern Sill · Lena Herich · Daniel A. Reuter

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Abstract
Background The pleth variability index (PVI) is derived from analysis of the plethysmographic curve and is considered to be a noninvasive parameter for prediction of volume responsiveness. The aim of our prospective clinical study was to evaluate if volume responsiveness can be predicted by PVI in patients undergoing cardiac surgery after cardiopulmonary bypass.
Methods Eighteen patients were prospectively studied. Directly after cardiac surgery, PVI, stroke volume variation (SVV), and cardiac index (CI) were recorded. Colloid infusion (4 ml/kg body weight) was used for volume loading, and volume responsiveness was defined as increase of CI more than 10 %.
Results SVV and PVI measures were found to be highly correlated at $r = 0.80$ ($p < 0.001$). Receiver operating characteristics curve (ROC) analysis resulted in an area under the curve of 0.87 for SVV and 0.95 for PVI, which values did not differ statistically significant from each other ($p > 0.05$). The optimal threshold value given by ROC analysis was ≥11 % for SVV with a sensitivity and specificity of 100 % and 72.2 %. For PVI, optimal threshold value was ≥16 % with a sensitivity and specificity of 100 % and 88.9 %. Positive and negative predictive values estimating an increase of CI ≥10 % for SVV were 44.4 % and 100 % and 66.7 % and 100 % for PVI.
Conclusions For consideration of fluid responsiveness PVI is as accurate as SVV in patients after cardiopulmonary bypass. Methodological limitations such as instable cardiac rhythm after cardiopulmonary bypass and right- or left ventricular impairment seem to be responsible for low specificity and positive predictive values in both parameters PVI and SVV.

Keywords Hemodynamic monitoring · Volume responsiveness · Pleth variability index · Stroke volume variation

S. Haas (✉) · C. Trepte · M. Hinteregger · R. Fahje · D. A. Reuter
Department of Anesthesiology,
Center of Anesthesiology and Intensive Care Medicine,
University Medical Center Hamburg-Eppendorf,
Martinistrasse 52, 20246 Hamburg, Germany
e-mail: shaas@uke.de

B. Sill
Department of Cardiovascular Surgery,
University Medical Center Hamburg-Eppendorf,
Hamburg, Germany

L. Herich
Department of Medical Biometry and Epidemiology,
University Medical Center Hamburg-Eppendorf,
Hamburg, Germany

Introduction

Because pressure-based parameters of preload such as central venous pressure (CVP) or pulmonary capillary occlusion pressure were identified to be insufficient for prediction of volume responsiveness, functional parameters of preload such as pulse pressure variation (PPV) and stroke volume variation (SVV) came to be a field of interest [1–3]. However, for assessment of these parameters, invasive blood pressure monitoring requiring arterial cannulation is necessary. Based on these parameters, a new parameter was developed, the pleth variability index (PVI). PVI quantifies the variations of the pulse oximeter waveform amplitude in mechanically ventilated patients. Therefore, in the broadest sense PVI can be interpreted as a noninvasive approach of

PPV assessment. Recent clinical trials confirmed the ability of PVI to predict volume responsiveness in major abdominal surgery and critically ill patients as well as in children with congenital heart disease before heart surgery [4–7]. Furthermore, PVI-based goal-directed fluid management was able to reduce intraoperative and postoperative lactate levels [8]. Nonetheless, in other clinical trials PVI failed to predict volume responsiveness reliably [9–11]. To our knowledge, the validity of PVI to predict volume responsiveness in patients undergoing cardiac surgery after cardiopulmonary bypass, i.e., after ischemia–reperfusion injury, has not been previously investigated. On an intensive care unit, hemodynamic instability is a common clinical challenge in the first hours after cardiopulmonary bypass, and optimization of volume status is essential to provide consequently adequate macrocirculation and microcirculation. In this situation, PVI would be a parameter easy to assess and helpful for prediction of volume responsiveness. Therefore, the aim of our study was to explore prediction of fluid responsiveness using PVI directly after cardiac surgery requiring cardiopulmonary bypass.

Methods

Approval for this study was provided by the Ethics Committee of the Hamburg Medical Board (Aerztekammer Hamburg). All patients gave written informed consent.

Patients

In this prospective study 18 patients (13 male, 5 female) undergoing elective cardiac surgery with the use of cardiopulmonary bypass (11 patients undergoing aortic-coronary bypass grafting, 5 patients undergoing valve surgery, and 2 patients undergoing a combination of aortic-coronary bypass grafting and valve surgery) were investigated. Impairment of ventricular function was not an exclusion criterion for this study. Exclusion criteria were atrial fibrillation and known arterial occlusive disease of the upper limb.

Hemodynamic monitoring and anesthesia

In all patients a central venous line was placed into the internal jugular vein for the continuous monitoring of CVP, drug administration, and injection of cold indicator for thermodilution. A 5-Fr. thermistor-tipped catheter (PiCCO, PV2025L20; Pulsion Medical Systems, Munich, Germany) was inserted into the femoral artery and connected to a hemodynamic monitor ($PiCCO_2$; Pulsion Medical Systems) for continuous measurement of SVV and arterial pressure and intermittent assessment of cardiac index (CI). Thermodilution measurements were performed by three sequential central venous injections of 10 ml cold saline solution (<8 °C). All thermodilution curves were examined, and measurements were accepted if none of the three consecutive values differed by more than 10 % from the mean.

PVI was recorded using the Masimo Radical-7 monitor (Masimo Corporation, Irvine, CA, USA). Tidal volumes were set at 8 ml/kg, inspiration to expiration ratio at 1:1.6, and positive end-expiratory pressure at 5 cmH_2O. End-expiratory pCO_2 was continuously controlled and maintained at 35–42 mmHg by adjusting respiration rate. During the period of data acquisition anesthesia was maintained with sevoflurane 2 % in oxygen and sufentanil as needed. Body temperature was measured by the arterial catheter and kept >36 °C by warming blankets and by prewarming of the infusions if required.

Study protocol

Directly after completion of cardiac surgery and thoracic closure, CI, SVV, and PVI were recorded. Site of measurement of PVI in all PVI measurements was the index finger. After accomplishment of baseline measurement, volume loading was performed, consisting of a colloid infusion of 4 ml/kg to assess volume responsiveness. Volume responsiveness was defined as an increase of CI of more than 10 % (responder, $\Delta CI \geq 10$ %; non-responder, $\Delta CI < 10$ %). After a period of stabilization of 3 min, measurements were repeated within 5 min and again PVI, SVV, and CI were recorded. During the 5 min of measurement, extrasystoles were counted and reported as extrasystoles per minute. This procedure was repeated until volume loading no longer resulted in an increase of CI of more than 10 %. Based on this protocol, a total number of 22 measurement time points were recorded.

Statistical methods

Patient characteristics are presented as arithmetic means and standard deviation. Student's t test was used for the comparison of hemodynamic data before and after volume loading. The relationship between SVV and PVI was analyzed using linear regression analysis and calculation of Pearson correlation coefficient.

The prognostic capacities of SVV and PVI to predict positive volume responsiveness were assessed by use of area under the receiver operation characteristic (ROC) curves. ROC curves were compared statistically by the method of DeLong et al. [12]. The response to volume administration was considered positive if CI increased by ≥10 % (criterion value). Threshold values were determined by considering values that yielded the greatest sensitivity and specificity.

Table 1 Hemodynamics of non-responders and responders before volume loading and after volume loading

Factor	HR (/min)	MAP (mmHg)	GEDI (ml/m^2)	SVI (ml/m^2)	CI (l/min/m^2)	ELWI (ml/kg)	SVR (dyn × s/cm^5)
Non-responder before volume loading ($n = 18$)	85.8 ± 9.1	70.1 ± 4.3	684.7 ± 137.8	31.3 ± 5.2	2.7 ± 0.4	8.7 ± 2.4	982.3 ± 312.7
Responder before volume loading ($n = 4$)	93.8 ± 9.3	68.7 ± 7.1	588.4 ± 104.8	23.6 ± 2.9	2.2 ± 0.2	7.1 ± 1.4	1100.8 ± 130.9
p value (t test)	0.13	0.63	0.23	0.031	0.026	0.25	0.13
Non-responder after volume loading	85.0 ± 10.1	77.1 ± 7.5	683.2 ± 137.2	32.1 ± 6.2	2.7 ± 0.5	8.6 ± 2.8	1017.7 ± 416.5
Responder after volume loading	93.0 ± 9.7	78.3 ± 7.0	772.8 ± 263.5	29.3 ± 3.5	2.7 ± 0.4	6.6 ± 0.9	1236.3 ± 278.7
p value (t test)	0.17	0.79	0.41	0.51	0.79	0.23	0.10

HR heart rate, *MAP* mean arterial pressure, *GEDI* global end-diastolic volume index, *CI* cardiac index, *ELWI* extravascular lung water index, *SVR* systemic vascular resistance

Additional analysis was performed taking into account intrapatient correlation between measurements when evaluating SVV and PVI prognostic capacities. As the findings did not differ from unadjusted results, the output is omitted.

Statistical tests were two tailed; significance was considered at $p < 0.05$. Data were analyzed using Stata/MP 12.0 (StataCorp LP, College Station, TX, USA).

Results

Patient characteristics

Patient data presented with mean age of 67.5 ± 10.8 years; mean patient height was 173.1 ± 9.5 cm and mean patient weight was 79.0 ± 11.5 kg. Body temperature at the time point of measurement was 36.3 ° ± 0.3 °C. In five patients, left ventricular function was impaired, reflected by an ejection fraction (EF) below 40 %. Duration of surgery was 261.1 ± 57.8 min. Five patients showed multiple atrial or ventricular extrasystoles (>3/min) during the measurement period.

Hemodynamics

Four patients responded to volume loading (ΔCI ≥ 10 %). In 18 steps of measurement, there was no response to volume loading (ΔCI < 10 %). Thirteen patients required catecholamine administration (10 non-responders, 3 responders). Dosage of epinephrine was 0.024 ± 0.036 in the non-responder group and 0.003 ± 0.006 μg/kg/min in the responder group. Dosage of norepinephrine was 0.056 ± 0.077 μg/kg/min in the non-responder group and 0.055 ± 0.046 in the responder group. Catecholamine dosage was not changed after volume administration. There was no statistically significant difference of blood pressure between the responder group and the non-responder group both before volume loading and after volume loading compared by Student's t test ($p > 0.05$). Detailed information on hemodynamics is shown in Table 1.

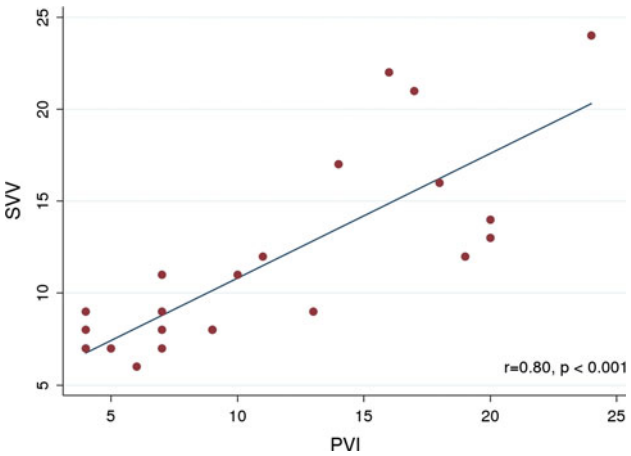

Fig. 1 Scatter plot including linear regression analysis for 22 paired stroke volume variation (SVV) and pleth variability index (PVI) values. The relationship between the two parameters can be described by SVV = 4.04 + (0.678 × PVI)

Regression analysis

Linear regression analysis revealed the following relationship between SVV and PVI: SVV = 4.04 + (0.678 × PVI). There was a statistically significant correlation between SVV and PVI ($r = 0.80$, $p < 0.001$) (Fig. 1).

Receiver operating characteristics curves

Area under the curve was 0.87 for SVV and 0.95 for PVI. Comparison of the areas under the ROC curves did not show a statistically significant difference ($p = 0.31$). Area under the curve for CVP was 0.19 (Fig. 2).

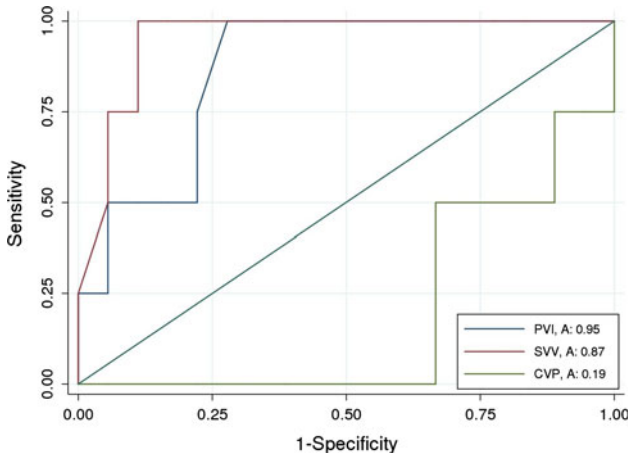

Fig. 2 Receiver operating characteristic (ROC) curves comparing the ability of SVV, PVI, and central venous pressure (CVP) to predict an increase of CI of more than 10 %. *A* area under the curve. Areas under the curve for SVV and PVI did not differ significantly statistically ($p = 0.31$)

Table 2 Contingency tables for pleth variability index (PVI) and stroke volume variation (SVV) calculating sensitivity, specificity, positive predictive value, and negative predictive value

Value	CI		
	<10 %	≥10 %	
PVI[a]			
<16	16	0	16
≥16	2	4	6
	18	4	22
SVV[b]			
<11	13	0	13
≥11	5	4	9
	18	4	22

CI cardiac index

[a] Sensitivity 4/4 = 100 %, specificity 16/18 = 88.9 %, positive predictive value 4/6 = 66.7 %, negative predictive value 16/16 = 100 %

[b] Sensitivity 4/4 = 100 %, specificity 13/18 = 72.2 %, positive predictive value 4/9 = 44.4 %, negative predictive value 16/16 = 100 %

Contingency tables

The optimal threshold value given by ROC analysis was ≥11 % for SVV and ≥16 % for PVI. Using these thresholds, the estimated sensitivity and specificity to predict an increase of CI ≥10 % were 100 % and 72.2 % for SVV and 100 % and 88.9 % for PVI, respectively, in contingency table analysis. The positive and negative predictive values for SVV were 44.4 % and 100 %. For PVI, positive and negative predictive values were 66.7 % and 100 %, respectively (Table 2).

Table 3 Summary of clinical studies evaluating threshold of PVI for volume responsiveness

Source	Threshold of PVI	Number of patients	Study group
Renner et al. [6]	>13 %	27	Infants after induction of general anesthesia before congenital heart surgery
Broch et al. [10]	>13 %	81	After induction of general anesthesia before CABP surgery
Loupec et al. [5]	Finger >17 %	40	Critically ill patients on ICU
Zimmermann et al. [4]	Finger >9.5 %	20	After induction of anesthesia before major abdominal surgery
Cannesson et al. [7]	>14 % Forehead >15 %	25	After induction of general anesthesia before CABP surgery
Desgranges et al. [14]	Ear >16 % Finger >12 %	28	After induction of general anesthesia
Haas et al. (this study)	Finger >16 %	18	After cardiopulmonary bypass and thoracic closure

Site of PVI measurement is given when described by the authors

CABP coronary artery bypass

Discussion

In the first line, our data show that both SVV and PVI are of similar validity in prediction of volume responsiveness in patients in the specific situation directly after cardiopulmonary bypass. SVV and PVI also showed a statistically significant correlation. However, SVV and PVI had nonequivalent cutoff points for optimal volume prediction, ≥11 % for SVV and ≥16 % for PVI. Because optimal threshold for SVV to predict volume responsiveness is reported to be 9–12.5 % [13], our results are in concordance with prior studies also revealing higher threshold values for PVI (Table 3) [5–7, 9]. Only one study demonstrated a lower threshold value of PVI [4]. Furthermore, results of all previous studies assessing PVI as predictor for volume responsiveness demonstrated a high variability of threshold, ranging from 9.5 % to 17 %. One reason seems to be the different settings in which the studies have been performed (before and after cardiac surgery, major abdominal surgery, ICU patients, and infants). Another reason might be that PVI is much more affected by external conditions such as low cardiac output, hypothermia, vasoactive drugs, and peripheral vascular disease as the parameter SVV [10]. This variability underlines that the

validity of PVI has to be interpreted with caution and that intra- and interindividual variability must be documented [4].

Contingency table analysis in our study revealed rather poor results for both SVV and PVI regarding specificity and positive predictive value. Prior studies reported higher values here [4, 5]. Cannesson and colleagues [7] also reported higher specificity and positive predictive values in patients scheduled for coronary artery bypass surgery before connection to cardiopulmonary bypass. The site of PVI measurement is known to influence the results at this point. In a recent study by Desgranges and co-workers [14], influence of the site of PVI measurement on the threshold, sensitivity, and specificity of PVI was described. In this study sensitivity and specificity were lower when PVI was measured at the finger compared to PVI measurement at the forehead or the ear. It might be assumed that in our study even higher values for specificity could have been achieved if the ear or the forehead was chosen for PVI assessment.

With regard to poor results of the specificity and positive predictive value, four aspects have to be taken into consideration:

(1) Our patients have been evaluated shortly after termination of cardiopulmonary bypass. During this phase, many patients show no continuous sinus rhythm but a higher amount of extrasystoles because of reperfusion damage and surgical manipulation of the heart. This instability of cardiac rhythm interferes with the algorithm of SVV and PVI assessment, resulting in false overestimation of these parameters [15]. In the author's opinion, this phenomenon, which was observed in five patients in our study, has to be considered mainly causative for poor results regarding specificity and positive predictive value. We intentionally did not exclude these patients from our study because they realistically reflect the clinical situation after cardiopulmonary bypass and underline the methodological limitations of these parameters. Recently, Cannesson et al. [16] successfully investigated a new SVV algorithm to predict volume responsiveness in animals with multiple extrasystoles. It will be very interesting to see this new algorithm in a clinical setting. Until now, such an algorithm is not available for PVI assessment.

(2) In most of the studies dealing with PVI as predictor for volume responsiveness, volume responders were defined by an increase in CI of 15 %. Because in our study patients with impaired left ventricular function (five patients showed an EF <40 %) were also included, we set the definition of volume responders to only 10 % in our initial study protocol. It was not reasonable to us to expect high increases of CI from our study population when patients with severe impaired left ventricular function were also included. The fact that nearly 30 % of our patients showed an EF <40 % might be one reason that only four patients were volume responders and an increase of even 10 % in CI could not be achieved. SVV is a marker of the position on the Frank–Starling curve, and a myocardium with impaired ventricular function having a modified character of the Frank–Starling curve might differ from the implications of SVV and PVI [16].

(3) It is known that impaired right ventricular function results in false-positive functional parameters of preload [17]. It has to be assumed that our patients with an EF below 40 % also suffered from an impaired right ventricular function and therefore poor positive predictive values for SVV and PVI would become more plausible.

(4) Another reason might be the rather restricted amount of volume administration of only 4 ml/kg colloid, which might have been not enough for adequate CI response. However, this rather low amount was chosen in the initial study protocol to prevent these cardiac patients from the risk of volume overload, especially because patients with impaired ventricular function were not excluded from this study.

Further, some other limitations of our study have to be discussed. PVI assessment can be affected by hypothermia, and peripheral temperature was not recorded in our study. Nevertheless, measurements were performed shortly after rewarming by the heart–lung machine, and patients were continuously warmed by warming blankets and prewarmed infusions. Therefore, peripheral hypothermia seems to be unlikely.

The number of patients evaluated is limited, and formally our study is underpowered and has to be interpreted as an explorative methodical study. Especially, the number of volume responders is low, which can limit results of ROC analysis, resulting in an inadequate high area under the curve values for SVV and PVI. However, our ROC analysis underlines that both SVV and PVI are much more valuable for prediction of volume responsiveness than CVP.

Nevertheless, the presented data give evidence that for consideration of fluid responsiveness in patients undergoing cardiac surgery after cardiopulmonary bypass, PVI is of high value, especially regarding sensitivity and negative predictive value. Thus, volume responsiveness is not to be expected when PVI is low. However, in the special situation after termination of extracorporal bypass, PVI, similar to SVV, has to be interpreted carefully, especially when these parameters are high, because of limitations such as impaired left- or right ventricular function or when an unstable cardiac rhythm with multiple extrasystoles is observed.

Conflict of interest Daniel A. Reuter is a member of the Medical Advisory Board of Pulsion Medical Systems. Apart from the conflict of interest mentioned above, all authors disclose (1) all funding sources, (2) any commercial or non-commercial affiliations, and (3) any other associations, such as consultancies. This study was funded solely by departmental sources.

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