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The effects of vasoactive drugs on pulse pressure and stroke volume variation in postoperative ventilated patients

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Abstract

Introduction—Although pulse pressure (PPV) and stroke volume variation (SVV) during mechanical ventilation have been shown to predict preload responsiveness, the effect of vasoactive therapy on PPV and SVV is unknown.

Methods—PPV and SVV were measured continuously in 15 cardiac surgery patients for the first 4 post-operative hours. PPV was directly measured from the arterial pressure waveform and both PPV and SVV were also calculated by LiDCO Plus before and after volume challenges or changes vasoactive drug infusions done to sustain cardiovascular stability.

Results—71 paired events were studied (38 vasodilator, 10 vasoconstrictor, 14 inotropes and 9 volume challenges). The difference between the measured and LiDCO-calculated PPV was $1 \pm 7\%$ (1.96 SD, 95% CI, $r^2=0.8$). Volume challenge decreased both PPV and SVV (15 to 10%, $P<0.05$ and 13 to 9%, $P=0.09$, respectively). Vasodilator therapy increased PPV and SVV (13% to 17%, and 9% to 15%, respectively, $P<0.001$). Whereas increasing inotropes or vasoconstrictors did not alter PPV or SVV. The PPV/SVV ratio was unaffected by treatments.

Conclusion—Volume loading decreased PPV and SVV and vasodilators increased both consistent with their known cardiovascular effects. Thus, SVV and PPV can be used to drive fluid resuscitation algorithms in the setting of changing vasoactive drug therapy.

Keywords

Arterial pulse contour; minimally invasive; functional hemodynamic monitoring; LiDCO; vasopressor; vasodilator; inotrope; pulse contour analysis; vasomotor tone

Introduction

Positive-pressure ventilation-induced arterial pulse pressure variation (PPV) and left ventricular (LV) stroke volume variation (SVV) are sensitive and specific predictors of preload responsiveness (1-7). Specifically, threshold variation values exceeding 10-15%

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during 7-10 mL/kg tidal volume ventilation predict well cardiac output increases >20% in response to a 250-500 ml fluid bolus infusion. Based on these robust findings across several studies, both PPV and SVV have been proposed as reasonable parameters to guide resuscitation (25). Indeed, PPV has recently been showed to be an effective guide fluid therapy in high risk patients (24).

However, several factors commonly seen in critically ill patients can potentially influence both PPV and SVV independent of preload responsiveness. For example, since the primary driving force causing the variation on LV filling during positive-pressure breathing is the increased lung volume-induced increase in pleural pressure (8), if tidal volume were to vary, then for the same intravascular volume status PPV and SVV would also co-vary (9-13). Similarly, if vasomotor tone were to vary it may alter unstressed circulatory blood volume. Thus, the effective circulating blood volume should also vary inversely with changes in vasomotor tone (26). One would predict that vasopressors should decrease both PPV and SVV, whereas vasodilators would have the opposite effects. The hemodynamic effects of inotropic agents may have varying effects depending on their impact on LV ejection efficiency, vasomotor tone and heart rate. Finally, changes in the ratio of PPV to SVV at a constant tidal breath should parallel changes in central arterial compliance. If vasopressor therapy increased arterial stiffness then PPV/SVV should increase and vasodilators should induce the opposite effect.

Although we recently documented that inotropes do not alter PPV and SVV in an animal model (27), the effect of vasoactive agents and inotropes on PPV and SVV has not been studied in humans (14). Since critically ill patients are often resuscitated with a combination of agents including fluid, vasoactive and inotropic drugs, these interactions must have clinical relevance if PPV and SVV parameters are to be used to guide resuscitation therapy in these patients. Thus, we examined the impact of selective infusions of vasoactive agents and inotropes as compared to volume loading on PPV and SVV changes and their ratio in post-cardiac surgery patients.

Methods

The study was approved by our IRB and all subjects signed informed consent. Twenty post-cardiac surgery patients (54 to 82 years of age) were studied. Additional inclusion criteria were the presence of both an arterial and PAC (Edwards LifeSciences, Irvine, CA, USA) (either CO_{TD} or CCO). Exclusion criteria were evidence of cardiac contractility dysfunction (ejection fraction < 45% by intraoperative echocardiography), pregnancy, pacemaker/AICD, heart/lung transplant, persistent arrhythmias, severe valvular stenosis or insufficiency after surgery, intra-aortic balloon pump, or other mechanical cardiac support. Patients were admitted to ICU on assist-control ventilation with 12/min respiratory rate (no patient had a spontaneous respirations >16/min) and 6 ml/kg tidal volume, I/E time of 1:2 and 5 cm H₂O positive end-expiratory pressure. Fentanyl (25-50 mcg) was given as needed by nursing staff if patient appeared to have pain or discomfort.

Therapeutic interventions were categorized as vasodilator, vasoconstrictor, inotropic or volume loading as defined by:

1. *Volume*: any given volume ≥ 250 mL of blood products, colloid or crystalloid infused in <15 minutes
2. *Vasodilator*: any increase ≥ 0.1 mcg/kg/min in nitroprusside infusion
3. *Vasoconstrictor*: any increase ≥ 0.01 mcg/kg/min in epinephrine, norepinephrine or phenylephrine, or ≥ 1 mcg/kg/min in dopamine infusion

4. *Decrease Inotrope*: any decrease ≥ 0.01 mcg/kg/min in epinephrine, or ≥ 1 mcg/kg/min in dobutamine or dopamine infusion

These vasoactive drugs and volume were given based on a pre-set post-operative order set that defined that vasopressors and vasodilators were to be given to keep mean arterial pressure between 90 and 65 mmHg (with individual subject adjustments made on a case-by-case basis). Thus, vasodilator agents were given to reverse hypertension where as vasopressors were given before hypotension occurred to sustain mean arterial pressure >65 mmHg. In practice, subjects rarely received single interventions, with most receiving two treatments simultaneously. Since we wished to examine the selective effect of specific treatments, we excluded multi-treatment events. Thus, all reported paired pre-to-during drug infusion or pre-to-post volume loading events are single treatment events. The pre-drug infusion period was defined as the time immediately before starting treatment and the during drug infusion time was defined as that time after starting the drug at a constant infusion rate once hemodynamic parameters returned to a stable new state, as assessed by measure of continuous cardiac output, heart rate and blood pressure. Accordingly, we could analyze single therapeutic events in only 15 of the original 20 patients recruited for this study.

Upon admission to the ICU, a LiDCO Plus™ device was attached to the arterial cannula and connected to its unit via a lithium sensor as recommended by the manufacturer (LiDCO Ltd, Cambridge UK). Arterial pressure waveform was extracted from the patient bedside ICU monitor via a cable to the LiDCO device. We used lithium dilution technique to calibrate the device as recommended by the manufacturer. If calibration resulted in repeated errors in the curve acceptability (>3 errors per patient) we used PAC-derived estimates of CO. After calibration with lithium dilution CO or PAC-derived CO, the LiDCO device reported beat-to-beat CO, PPV and SVV. Both PPV and SVV are calculated as the ratio of the difference between the maximum and minimum PP and SV and their respective mean over at 20 second window (approximately 4-6 breaths).

PAC CO was measured by either CO_{TD} or CCO attached to Vigilance monitor (Edwards LifeSciences, Irvine, CA). If there was a CO_{TD} PAC in place, the measurements were done before each event and then 5 minutes after the intervention was completed. In the case of drug infusion, the second CO value was taken 5 minutes after the new drug infusion rate was set. All CO_{TD} measurements in all subjects were performed by one of the investigators, with a consistent method of a fast and constant injection of 10 mL 4°C 0.9N NaCl. At least 3 consecutive measurements started at random to the respiratory cycle were performed. Accuracy and acceptability of each thermal decay curve was judged visually on the attached ICU monitor. PAC CCO values were continuously collected in a WinDaq data acquisition system (15) in a separate computer, from the time patient arrived in ICU until the end of the study.

All the data were collected continuously in the corresponding data acquisition systems, LiDCO or WinDaq. No operator bias was involved in recording the LiDCO-derived measurements of CO, PPV or SVV. We also collected paired arterial waveform data extracted from the ICU monitor at a sampling frequency of 250 Hz into a common WinDaq data acquisition file. Using these data we calculated PPV directly by measuring the maximum and the minimum PP, the difference between diastolic and the subsequent systolic blood pressure for all beats over 20 seconds as previously described (1) at the same time intervals as data reported by the LiDCO plus device.

Statistical analysis

Paired hemodynamic data pre to post treatment were compared by ANOVA for repeated measures, with a post hoc Student's T-test for each of the 4 groups. Using Bland-Altman

analysis (16) and Pearson linear regression we compared bias, the limits of agreement, and correlation coefficient between the PPV calculated directly and measured by LiDCO device. Bias was defined as the mean difference between the values of PPV calculated directly and measured by LiDCO. Precision was defined as the upper and lower limits of agreement (± 1.96 SD of the bias). Bias and limits of agreement and correlation coefficient were calculated for the entire data set (all events) and then separately for each 4 groups of events as defined above. Differences associated with a $p < 0.05$ were considered significant.

Results

Patients demographic data displayed in Table 1. Upon admission to the ICU three subjects had mild hypothermia ($< 36^{\circ}\text{C}$) whereas the rest were normothermic. Hemodynamic values after admission to the intensive care unit at the start of the study mean cardiac output was 6.9 ± 0.2 l/min, mean arterial pressure 70.0 ± 2.1 mmHg, heart rate 89.4 ± 1.2 min⁻¹ with a PPV and SVV of 14.9 and 11.1 respectively. Eighty-one single treatment events were identified in fifteen patients. Ten events were excluded due to arrhythmias leaving 71 events for analysis. Demographics of the events and the corresponding patients are presented in Table 2 and the hemodynamic effects of the treatments are summarized in Table 3. As shown in Table 3 vasodilators decreased both mean arterial pressure (MAP) and PP, whereas increasing vasoconstrictor therapy increased only MAP. Volume loading increased PP. Decreasing inotropes had no measurable effect on the measured and derived hemodynamic variables and parameters.

The measured and calculated PPV values showed a mean difference (bias) of 1% with precision (1.96 SD, 95% CI) of $\pm 7\%$. We found a strong correlation between the two PPV methods across all conditions ($r^2 = 0.8$) (Fig. 1). There was no difference between the measured and calculated PPV ($17 \pm 8\%$ vs. $18 \pm 8\%$) for all measures pre and during intervention states. Subgroup analyses across different treatments showed similar agreement (Figs. 2 and 3).

Volume challenge was associated with a decrease in both PPV (15% to 10%, $P < 0.05$) and SVV (13% to 9%, $P = 0.09$) and an associate increase in cardiac output proportional to the pre-challenge PPV and SVV values, even though the change in SVV was not statistically significant (Fig. 4). Vasodilator treatment increased both PPV and SVV (13% to 17%, and 9% to 15%, respectively, $P < 0.001$). Vasoconstrictor agents did not alter either PPV (24 to 25%) or SVV (9 to 16%) significantly. Similarly, decreasing inotropic support did not alter either PPV (19 to 17%) or SVV (16 to 12%) significantly. Furthermore, the SD of the variance in PPV and SVV for both vasoconstrictor and inotropic support changes were greater than the mean changes in each variable, making increasing sample size highly unlikely to demonstrate significance if the sample size were increased.

Discussion

The primary findings of this study are that functional measures of preload responsiveness, PPV and SVV behave in a predictable fashion in response to volume loading and vasodilator therapy, whereas increasing vasopressor or inotropic drug infusion rates have negligible effects. These findings are important because clinicians are increasingly using PPV and SVV parameters to guide resuscitation. Our PPV and SVV findings with volume responsiveness agree with those of previous studies (1-7). In patients with a PPV $> 13\%$ or a SVV $> 10\%$ volume challenges both increase cardiac output and decrease PPV and SVV. Even though the amount of change in CO and SVV were not significant in our study, the direction of change was consistent with expected directional changes. That PPV decreased slightly though not statistically more than SVV is consistent with the expected decrease in

central arterial tone seen with increased flow. Presumably the lack of significant SVV decrease in response to volume challenge in our study reflects the small number volume challenges we gave compared to previous studies. Still the SVV values did trend downward in response to volume loading. Importantly, vasodilator therapy increased both PPV and SVV. These changes are consistent with the known effect of vasodilators to increase unstressed circulating blood volume, thus creating a relative hypovolemic state, and decrease in left ventricular afterload, improving ventricular performance. In support of this assumption, even though PPV increased with vasodilator therapy, both MAP and pulse pressure decreased slightly, though not significantly, consistent with the known effects of pharmacological vasodilation on arterial tone. Inotropic and vasoconstrictor therapies, however, induced only minimal changes in either PPV or SVV. Presumably, the combined volumetric effects (i.e. changes in unstressed circulatory volume) of both vasopressors and inotropes could be nullified purely vasoactive and pulse pressure effects of these two groups of agents. Potentially, the small number of pure events wherein vasoconstrictors or inotropes groups or the relatively small incremental changes in drug infusion rate may have masked changes in PPV and SVV or in their ratio. The ratio of PPV/SVV should trend changes in central arterial tone, such that vasopressors should increase this value and vasodilators should decrease it. However, inspection of individual subject responses (Fig 4) reveals no obvious directional trend. Still, these vasoactive agents were given to sustain cardiovascular stability, not to alter it. Thus some of the observed lack of PPV/SVV change may reflect appropriate vasoactive drug therapy to maintain a constant vasomotor tone. Finally, PPV measured by LiDCO Plus accurately reflects directly measured PPV, this on-line continual analysis of PPV minimizing the effort needed to collect this clinically-relevant parameter.

The management of hemodynamically unstable patients can be challenging because it is often difficult at the bedside to predict either the etiology of the underlying process or the responsive to therapy. Importantly our patients did not behave in a uniform fashion during their initial post-operative period. Their highly individualized management requirements underscore the importance of having robust measures of cardiovascular status across all types of cardiovascular state when using that information to drive resuscitation decisions. Several recent studies have shown that targeted volume/inotropic treatments of patients prior to surgical stress to create an artificially high oxygen delivery state, referred to as pre-optimization (17), reduces post-operative complications and hospital length of stay. Furthermore, early goal-directed therapy reduces mortality and morbidity in patients presenting to an Emergency Department in severe septic shock by targeting, among other things, CO (18), although the reasons for these observed benefits are not known. Finally, aggressive resuscitation using volume and vasoactive therapies in the ICU following high risk surgery (post-optimization) (19,20) also reduces complications and hospital length of stay. Thus, the benefit of sustaining a relatively high oxygen delivery rate in these patients seems warranted. Regrettably, determining which treatments will effectively increase blood flow is often difficult. Cardiac filling pressures are poor predictors of preload responsiveness (21,22). A major benefit to the newly validated use of ventilation-induced PPV and SVV is that they predict accurately volume responsiveness, allowing treatment stratification between fluid resuscitation and vasoactive drug therapies (23,24). However, until this present study the impact of vasoactive and inotropic drug therapy on PPV and SVV has not been examined. These potentially confounding interactions might have reduced the utility of these preload response parameters in real-life resuscitation scenarios where volume resuscitation and drug therapy are often combined or given sequentially. Our data demonstrates in a series of unstable post cardiac surgery patients that, except for the expected increase in preload-responsiveness with vasodilator therapy and decrease in preload-responsiveness with volume loading, vasoconstrictor and inotropic therapy minimally alter either PPV or SVV. Thus, both SVV and PPV appear to be unaffected by varying doses of vasopressor and inotropic agents presumably because vasoconstrictors and

inotropes also have additional hemodynamic effects on the heart and circulation, respectively.

Our study has several important limitations that limit its generalizability. Firstly, we studied unstable post-operative cardiac surgery patients emerging from general anesthesia and cardiopulmonary bypass-induced rheological changes whose instability reflected major changes in vasomotor tone, intravascular volume and to a lesser extent contractility over the initial peri-operative interval. Thus, extrapolation of these data to conscious subjects with septic shock or trauma should be done with caution. Still, the relative lack of impact of vasopressor therapy on either PPV or SVV when vasopressor agents were used to keep blood pressure, and presumable vasomotor tone, constant speaks to the robustness of these parameters in assessing volume responsiveness in the critically ill patient. Second, we did not define a common dose of vasopressor, vasodilator or inotrope to be given in every patient. Treatment was titrated to effect. However, we would argue that such an approach is more physiologically relevant because different subjects will display differing adrenergic responsiveness and vasoactive therapy is usually given to realize a defined physiologic outcome (e.g. mean arterial pressure, cardiac output, SvO₂, etc.). Third, the number of subjects receiving vasodilators and inotropic support were also small potentially making the lack of significant changes in PPV and SVV induced by inotropic agents of questionable significance. However, vasodilator therapy had a significant and predictable effect of PPV and SVV that we doubt would be lost if more subjects were enrolled in the study. Finally, on a purely mythological basis, if changes in vasomotor tone or cardiac ejection were to alter the nature of the arterial pulse power and pulse profile, calculated stroke volume and hence SVV may vary independent of actual measures of SVV. That is one of the primary reasons for reporting the PPV measures which are not prone to the same computational artifact, since they are the measures from which SVV is derived. Furthermore, we used the LiDCO device to estimate SVV specifically because its output is not dependent of pulse contour to its analysis only pulse power, a parameter not primarily altered by changes in vascular input impedance. Importantly, PPV measures parallel SVV measures in all cases. Thus, if bedside clinicians are concerned that their estimates of SVV may to artificially influenced by peripheral vasomotor tone changes, they can always revert back to PPV measures which remain unaffected.

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Figure 1. Linear regression and Bland-Altman analysis between the directly calculated PPV and LiDCO measured PPV in all events. PPV1= LiDCO measured PPV, PPV2= directly calculated PPV.

Figure 2.
Linear regression analysis between the directly calculated pulse pressure variation (PPV) and LiDCO derived PPV for each therapeutic intervention group.

Figure 3. Bland-Altman analysis between the directly calculated pulse pressure variation (PPV) and LiDCO measured PPV for each therapeutic intervention group. PPV1= LiDCO measured PPV, PPV2= directly calculated PPV.

Figure 4. PPV and SVV before and after each therapeutic intervention. Red line represents mean values (SD) for PPV and SVV before and after intervention.

Table 1**Patients Characteristics**

Age (y)	71±10
Gender (M/F)	14/6
Body mass index	29± 5
LVEF (%)	51 ±8
Type of PAC (CO _{TD} /CCO)	12/8
LiDCO calibrated against (Lithium dilution/PAC)	12/8
Calibrated against PAC (CO _{TD} /CCO)	6/2
Type of operation	Number
CABG	8
Valvular repair	5
CABG + valve repair	3
CABG +/- valve repair +/- TAAR	4

Data are presented as mean ± SD.

Abbreviations: LVEF, left ventricular ejection fraction; PAC, pulmonary artery catheter; CO_{TD}/CCO, intermittent bolus thermodilution/continuous cardiac output; CABG, coronary artery bypass grafting;; TAAR, thoracic aortic aneurysm repair. n=20

Table 2

Numbers of single treatment event and patients per different therapeutic intervention

Therapeutic intervention	Events	Patients	Events per patient
Vasodilator	38	9	2-9
Vasoconstrictor	10	5	2
Volume challenge	9	4	2-3
Inotrope decrease	14	4	2-6
Subtotal	71	15	2-11
Excluded due to constant arrhythmias	10	3	
Total	81	18	

Table 3

Hemodynamic effects of therapeutic intervention by treatment group

Therapy	PAC CO		LIDCO CO		HR		MAP		PP	
	pre	post	pre	post	pre	post	pre	post	pre	post
Vasodilator	6.4±1.4	6.8±1.3	6.4±1.4	6.8±1.3	77±18	80±20	89±10	75±12*	78±12	65±16*
Vasopressor	6.5±1.1	6.6±1.6	6.5±1.1	6.6±1.6	75±16	73±16	72±12	78±10*	65±12	72±14
Volume Challenge	4.9±0.2	5.1±2.5	4.9±0.2	5.1±2.5	74±18	70±18	89±12	91±13	67±13	75±12*
Decrease Inotrope	6.4±1.6	6.1±1.7	6.4±1.6	6.1±1.7	82±17	78±16	88±8	85±10	72±15	68±16

Values reported as mean ± SD.

* P<0.05 pre to post state.

Abbreviations: PAC, pulmonary artery catheter; CO, cardiac output (l/min); HR, heart rate (min⁻¹); MAP, mean arterial pressure (mm Hg); PP, arterial pulse pressure (mm Hg).