A pilot study of the epidemiology and associations of pulse pressure variation among non-cardiac surgery critically ill patients

In Byung Kim, Nigel Fealy, Ian Baldwin and Rinaldo Bellomo

ABSTRACT

Background: A pulse pressure variation (PPV) ⩾ 13% of mean arterial pressure (MAP) is an accepted marker of a fluid-responsive state. However, there is no study of its epidemiology and associations among non-cardiac critically ill patients.

Objectives: To conduct a pilot study of the epidemiology and associations of a PPV ⩾ 13% among non-cardiac critically ill patients.

Design: Prospective observational study.

Setting: Intensive care unit of a university hospital.

Patients: Cohort of 37 sedated critically ill patients undergoing mandatory ventilation.

Main outcome measures: PPV values, tidal volume and peak airway pressure, MAP, heart rate (HR) and central venous pressure (CVP) collected every 15 minutes; fluid balance collected hourly; correlation between PPV and these variables.

Results: 450 PPV measurements were collated. The PPV value was ⩾ 13% in 86 (19%) measurements and was observed in two consecutive measurements in 68 (15%) of cases. On multivariable analysis, mean PPV was significantly correlated with CVP ($P = 0.04$), HR ($P < 0.001$) and peak airway pressure ($P = 0.001$), but not fluid balance ($P = 0.3$).

Conclusions: Among non-cardiac surgery mechanically ventilated patients, a PPV in the fluid-responsive range was present in one-fifth of measurements and showed logical correlations with relevant haemodynamic and mechanical ventilation-related variables. Our results provide a rationale for a more comprehensive evaluation of PPV measurement in suitable critically ill patients.

Crit Care Resusc 2011; 13: 156–161

The assessment of intravascular volume is an important aspect of the care of critically ill patients. Dynamic parameters of fluid responsiveness, such as pulse pressure variation (PPV), systolic pressure variation (SPV), stroke volume variation (SVV) or respiratory variations in plethysmographic variability index (PVI), which are based on cardiopulmonary interactions among patients on mechanical ventilation, have been shown to be superior to static parameters such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) in predicting fluid responsiveness.[1-4]

Despite their superiority in predicting a response of cardiac output to fluid loading, until recently, dynamic parameters were not routinely used in the clinical setting. In contrast, static parameters, such as CVP and PAOP, are still widely used to assess fluid responsiveness, despite many studies showing that they are poor predictors of response to volume expansion.[5-8] Thus, evidence and practice appear dissociated.

One reason why dynamic parameters are not more widely used is that they have several limitations. First, they have only been validated for mechanically ventilated patients receiving mandatory ventilation and making no spontaneous respiratory efforts.[9,10] Second, they require patients to be in sinus rhythm.[3] Third, they have not been made available on monitoring screens through automated estimation and display. Because of these practical obstacles, there is limited knowledge of the epidemiology of PPV and its associations with other relevant variables. This is particularly true for non-cardiac surgery critically ill patients, among whom the epidemiology of PPV has not yet been studied.

Recently, monitoring software has been developed that enables automated estimation and display of PPV[11,12] and SVV.[13,14] Unlike SVV, however, such automated PPV can be estimated using standard arterial lines, making it less expensive and easier to obtain, and enabling the study of the epidemiology of a likely fluid-responsive state among non-cardiac surgery patients receiving mandatory mechanical ventilation.

Accordingly, we performed a prospective observational study using automated PPV estimation. We aimed to assess the incidence of PPV values in the likely fluid-responsive range (⩾ 13% of mean arterial pressure [MAP]) and their association with other relevant parameters among non-cardiac surgery critically ill patients.

Abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
CVP	Central venous pressure
HR	Heart rate
MAP	Mean arterial pressure
PAOP	Pulmonary artery occlusion pressure
PAP	Pulmonary arterial pressure
PP	Pulse pressure
PPV	Pulse pressure variation
PVI	Plethysmographic variability index
SPV	Systolic pressure variation
SVV	Stroke volume variation

We hypothesised that a PPV value in the likely fluid-responsive range would be relatively uncommon, and that such value would show logical correlations with relevant haemodynamic, fluid-related and mechanical ventilation-dependent variables.

Methods

The hospital human research ethics committee approved the study protocol (approval no. H2010/04137) and waived the need for informed consent. We studied 37 critically ill patients in the intensive care unit who were receiving mandatory ventilation and making no spontaneous respiratory efforts. All data were collected prospectively. Clinicians were not informed of the study and did not use PPV for patient management.

Haemodynamic measurements

As part of our routine monitoring, a peripheral arterial and a central venous catheter (Arrow International Inc, Reading, Pa, USA) were inserted for all patients. Pressure transducers were zeroed to atmospheric pressure at anterior axillary line level. CVP was measured at end expiration.

PPV values were calculated in real time by the Philips IntelliVue MP70 monitor (Philips Medical Systems, Suresnes, France). The algorithm used has been previously published.[13,15] Briefly, the method is based on automatic detection algorithms, rank-order filters and kernel smoothing. Maximum, minimum and mean pulse pressure (PP_{max}, PP_{min} and PP_{mean}) are determined over a window of 8 seconds and the values from four consecutive windows (32 seconds) are used to calculate an averaged PPV as $(PP_{max} - PP_{min})/PP_{mean}$. In this study, the PPV value provided by the monitor was continuously transferred from the monitor into the main computer.

Data collection

We started data capture from arrival in the ICU. We collected demographic and clinical data and disease severity score (Acute Physiology and Chronic Health Evaluation [APACHE] II and APACHE III scores). Every 15 minutes, we recorded heart rate (HR), MAP, pulmonary arterial pressure (PAP), CVP, tidal volume, peak airway pressure, and cardiac index. Every hour, we recorded cumulative fluid balance (total input – total output).

We collected these data for each patient for 2 consecutive hours daily during a variable convenience period between 09:00 and 17:00 hours, while the patient was sedated and mechanically ventilated with a mandatory mode of ventilation.

Statistical analysis

Data are expressed as mean (SD). Non-normally distributed data were compared using the Mann–Whitney test. Categorical data were compared using Fisher's exact test. We defined a PPV value in the likely fluid-responsive range as $\geqslant 13\%$ of MAP.[16] We classified patients into two groups according to mean PPV. We assessed patients as "high PPV" if they had at least two PPV measurements $\geqslant 13\%$ during any 2-hour observation period and as "low PPV" if they only had one or no measurements $\geqslant 13\%$. The relationship between PPV and cardiac index, PAP_{mean}, HR, MAP, CVP, tidal volume, peak airway pressure and fluid balance were evaluated using Spearman's correlation test.

We performed multivariable linear regression analysis with PPV as the dependent variable to identify independent factors that might affect its value. Changes in variables over time were compared using analysis of variance. $P < 0.05$ was considered statistically significant.

Results

During the study period, we recorded 450 PPV measurements in 37 critically ill patients. The 37 patients studied were admitted to the ICU with a medical diagnosis (26 patients), surgical diagnosis (7) or trauma (4). Table 1 shows the patients' baseline characteristics and haemodynamic parameters.

Table 2 shows changes in the mean value for PPV and other haemodynamic parameters during the 2 hours of daily observation; PPV did not significantly change over time during the observation period ($P = 0.9$) (Figure 1A, $P = 0.5$; Figure 1B, $P = 0.5$). A likely fluid-responsive state was seen during 86 measurements (19.1%). Patients with PPV values $\geqslant 13\%$ had a greater APACHE II score, faster HR, lower MAP, and higher peak airway pressure (Table 3). Fluid balance, CVP and tidal volume, however, were not significantly different. In addition, on 68 measurements (15.1%), a value of $\geqslant 13\%$ was seen consecutively, suggesting a persistent state of likely fluid responsiveness. Finally, no values $\geqslant 13\%$ were ever detected in 29 of the 37 patients (78%). Table 4 shows the univariate correlation between PPV values and other haemodynamic parameters. On multivariable linear regression analysis, the mean value of automated PPV correlated with CVP, HR and peak airway pressure (Table 5).

When patients with high and those with low PPVs were compared in terms of outcome, there were differences in terms of time on mechanical ventilation and time in the ICU, but no differences in ICU or hospital survival (Table 6).

Discussion

In our study of non-cardiac surgery critically ill patients, we found that the incidence of a PPV value in the likely fluid-responsive range was about 20% of all measurements and persisted in about 15% of measurements. Further, we found a logical and significant negative independent correlation between PPV and MAP and CVP, and a similarly logical significant positive correlation with faster HR and higher peak airway pressure. Patients with high PPV values in the fluid-responsive range had a longer time on mechanical ventilation and a longer duration of ICU stay.

Most previous studies compared dynamic and static parameters. These studies focused on the ability of PPV to predict fluid responsiveness in different groups. Their results show that, among patients on mechanical ventilation, dynamic parameters (PPV, SPV or PVI) are superior to static parameters (CVP, PAOP) in predicting fluid responsiveness.[1-4,10] Despite such evidence, dynamic parameters are not routinely used in the clinical setting, and only a few studies have evaluated the impact of PPV-guided or SPV-guided fluid management.[17-20] Furthermore, to our knowledge, no research has prospectively assessed the epidemiology of PPV in non-cardiac surgery critically ill patients and PPV's association with relevant haemodynamic, fluid-related and mechanical ventilation-dependent variables in such patients. This lack of information is unfortunate, because such patients are more common than cardiac surgery patients. It also makes it difficult to appreciate how often, in the absence of PPV monitoring, non-cardiac surgery critically ill patients might be in a PPV-predicted likely fluid-responsive state. Such appreciation is the first crucial step toward establishing whether PPV monitoring might be desirable. It is also an important step toward gaining a quantitative appreciation of the incidence of "hypovolaemia" in such patients. Finally, it helps clinicians appreciate how often fluid therapy would be a physiologically appropriate intervention for non-cardiac surgery mechanically ventilated patients.

Our study shows that a PPV-predicted likely fluid-responsive state is uncommon (about 20% of measurements and about 15% of measurements if persistence is considered) in non-cardiac surgery critically ill patients. These observations suggest that a "likely fluid-responsive/hypovolaemic state" might be relatively uncommon in such patients. As such, they provide a clinical rationale for the monitoring of PPV in non-cardiac surgery patients receiving mandatory mechanical ventilation in order to avoid the unnecessary administration of intravenous fluid loading.

Our findings support the notion that automated PPV measurements are similar in nature, and have similar logical

Table 1. Baseline characteristics and haemodynamic parameters of 37 critically ill patients

Variables	
Mean age, years (SD)	55.0 (16.2)
Male sex, no. (%)	23 (62%)
Mean APACHE II score (SD)	20.2 (8.5)
Mean APACHE III score (SD)	72.7 (33.5)
Admitting diagnostic group	
Medical	26
Surgical	7
Trauma	4
CRRT	
CRRT, no. of measurements (%)	92 (20%)
No CRRT, no. of measurements (%)	358 (80%)
Pulse pressure variation	
No. of measurements < 13% (%)	364 (81%)
No. of measurements ⩾ 13% (%)	86 (19%)
Mean pulse pressure variation, % (SD)	8.7 (4.8)
Mean cardiac index, L/min/m^2 (SD)	5.0 (0.6)
Mean heart rate, beats/min (SD)	82.4 (21.3)
Mean arterial pressure, mmHg (SD)	78.9 (11.0)
Mean hourly fluid balance, mL (SD)	10.3 (1092.0)
Mean central venous pressure, mmHg (SD)	10.0 (2.7)
Mean tidal volume, mL/kg (SD)	7.5 (1.7)
Mean peak airway pressure, mmHg (SD)	21.3 (5.0)

APACHE = Acute Physiology and Chronic Health Evaluation.
CRRT = continuous renal replacement therapy.

Table 2. Changes in pulse pressure variation and other haemodynamic parameters during the study period*

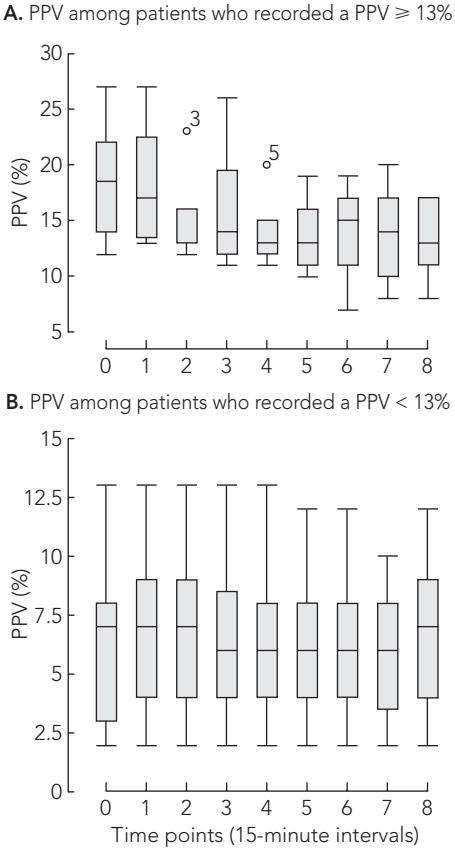
Parameter	Initial	30 minutes	60 minutes	90 minutes	120 minutes	*P*
PPV, %	8.8 (5.3)	8.4 (4.6)	9.0 (4.6)	7.9 (4.3)	9.0 (4.3)	0.90
Heart rate, beats/min	82.7 (20.7)	82.7 (21.3)	85.0 (23.0)	78.7 (20.0)	79.8 (19.3)	0.71
MAP, mmHg	80.0 (13.7)	78.8 (10.9)	78.8 (9.1)	80.4 (11.3)	78.4 (11.0)	0.96
Fluid balance,† mL	61.8 (1081.3)	—	58.6 (1376.8)	—	–25.8 (1074.5)	0.86
Peak airway pressure, mmHg	21.2 (5.1)	21.2 (4.9)	20.4 (5.3)	21.7 (5.1)	22.0 (5.2)	0.87
CVP, mmHg	10.2 (2.5)	10.1 (2.5)	9.6 (2.5)	10.1 (2.5)	9.9 (3.1)	0.93

CVP = central venous pressure. MAP = mean arterial pressure. PPV = pulse pressure variation. * All values are expressed as mean (SD). † Fluid balance calculated every 60 minutes.

physiological links with relevant variables, to manual PPV measurement. This suggests that they are likely of sufficient quality for clinical use for non-cardiac surgery critically ill patients. In addition, our observations show that using such technology, clinicians can identify situations where there is a likely fluid-responsive/hypovolaemic state, which they are currently unable to detect with routinely available screen-displayed variables, and that such states occur 15% to 20% of the time. Finally, they suggest that a likely fluid-responsive state may be relatively uncommon among non-cardiac surgery mechanically ventilated patients.

To our knowledge, our study is the first to define the epidemiology and associations of automated PPV measurements among non-cardiac surgery critically ill patients. Our findings appear of clinical and practical importance and can lead to application in the care of such patients and provide a perception of the likelihood that such patients would be in a physiological state likely to lead to increased cardiac output with additional fluid loading.

Figure 1. Distribution of pulse pressure variation (PPV) according to time ($P = 0.5$)



Despite such utility, this study has some limitations. First, it is not a randomised controlled trial. Therefore, no conclusions can be drawn about the clinical utility of automated PPV measurements. Second, it is a single-centre study. Thus, our findings may not apply to other units, where fluid, ventilatory and haemodynamic management might differ. However, pilot studies such as this are needed to justify wider-ranging investigations. Our clinicians were unaware of the study, which enabled us to assess PPV in an unmodified clinical environment. Third, the automated measurement of PPV may be incorrect or misleading. However, the methodology used by the monitor and its associations have been previously demonstrated to be physiologically logical, suggesting otherwise.[11] Fourth, we only recorded PPV values every 15 minutes. More frequent recording may have detected a greater incidence of elevated PPV values. However, we considered that values that are not sustained for a sufficient period are unlikely to be clinically important. Finally, the detection of a likely fluid-responsive state does not imply the need to administer fluids. It simply alerts the clinician to the fact that there is relatively high probability that, if a fluid bolus is administered, the cardiac output will increase by over 15%. Whether such a gain in cardiac output is worth pursuing at the cost of a 500 mL bolus of colloidal fluid remains a decision that should be made based on clinical judgement.

Our findings need to be confirmed in other institutions. If these studies confirm that a PPV system provides physiologically logical information and that a PPV in the likely fluid-responsive range is as uncommon as shown by our study, then additional fluid resuscitation in such patients may be physiologically illogical. Randomised controlled trials where patients are allocated to having or not having PPV values displayed on their monitor may provide useful initial information on whether PPV availability changes practice.

Conclusions

Among non-cardiac surgery critically ill patients, a PPV value in the likely fluid-responsive range is uncommon. Our pilot findings suggest that, for non-cardiac surgery mechanically ventilated patients, additional fluid loading is generally unlikely to be needed, and provide a rationale for more comprehensive evaluation of PPV measurement in suitable critically ill patients.

Table 3. Comparison of variables according to PPV group*

	PPV < 13% ($n = 364$)	PPV ⩾ 13% ($n = 86$)	P
APACHE II score	19.6 (8.5)	24.7 (9.4)	0.001
APACHE III score	70.5 (32.6)	91.0 (37.6)	0.001
HR, beats/min	79.7 (20.1)	94.5 (23.1)	0.001
MAP, mmHg	79.8 (11.0)	75.0 (10.2)	0.001
Peak airway pressure, mmHg	20.7 (4.9)	24.6 (5.0)	0.001
Fluid balance, mL	12.5 (1169.3)	–25.4 (789.9)	0.82
CVP, mmHg	10.0 (2.4)	9.9 (3.7)	0.74
Tidal volume, mL/kg	7.5 (1.7)	7.3 (1.9)	0.20

APACHE = Acute Physiology and Chronic Health Evaluation. CVP = central venous pressure. HR = heart rate. MAP = mean arterial pressure. PPV = pulse pressure variation. * All values are expressed as mean (SD).

Table 4. Univariate correlation of pulse pressure variation and other parameters*

	PPV	Peak airway pressure, mmHg	HR, beats/min	MAP, mmHg	CVP, mmHg	Fluid balance, mL	Tidal volume, mL/kg	APACHE II score
Peak airway pressure	0.275†	—	—	—	—	—	—	—
HR	0.438†	–0.007	—	—	—	—	—	—
MAP	–0.162†	–0.209†	0.001	—	—	—	—	—
CVP	–0.05	0.080	0.117†	0.104†	—	—	—	—
Fluid balance	0.018	–0.160†	0.005	–0.098	0.059	—	—	—
Tidal volume	0.049	0.026	0.115†	0.065	–0.061	–0.015	—	—
APACHE II score	0.192†	0.190†	–0.1†	–0.305†	–0.108†	0.150‡	–0.196†	—
APACHE III score	0.241†	0.175†	–0.014†	–0.293†	–0.098†	0.097	–0.173†	0.871†

APACHE = Acute Physiology and Chronic Health Evaluation. CVP = central venous pressure. HR = heart rate. MAP = mean arterial pressure. PPV = pulse pressure variation. * All values are Spearman's correlation coefficient. † Correlation is significant at the 0.01 level (2-tailed). ‡ Correlation is significant at the 0.05 level (2-tailed).

Table 5. Multivariable linear regression analysis of correlation of PPV with other parameters

Independent variables	Correlation coefficient (95% CI)	*P*
CVP	–0.29 (–0.55 to –0.04)	0.03
MAP	–0.05 (–0.11 to 0.05)	0.07
Peak airway pressure	0.24 (0.10 to 0.37)	0.001
HR	0.09 (0.05 to 0.12)	< 0.001
Tidal volume	0.06 (–0.35 to 0.46)	0.79
Fluid balance	0.00 (0.000 to 0.001)	0.31
APACHE II score	–0.06 (–0.23 to 0.11)	0.48
APACHE III score	0.03 (–0.01 to 0.07)	0.17

APACHE = Acute Physiology and Chronic Health Evaluation. CVP =central venous pressure. HR = heart rate. MAP = mean arterial pressure. PPV = pulse pressure variation.

Table 6. Comparison of variables according to PPV ⩾ 13% two or more times (high PPV) or not (low PPV) during a 2-hour observation period

	Low PPV (29 patients)	High PPV (8 patients)	*P*
Mean age, years (SD)	57.0 (15.9)	46.9 (15.2)	0.12
Male sex (%)	18 (62%)	5 (63%)	0.66
CRRT used (%)	3 (10%)	3 (38%)	0.99
Mean APACHE II score (SD)	20.4 (8.4)	22.7 (10.1)	0.73
Mean APACHE III score (SD)	73.8 (30.9)	90.8 (42.7)	0.24
Mean time on MV, hours (SD)	132.0 (199.3)	382.3 (278.9)	0.05
Mean time in ICU, days (SD)	5.6 (5.1)	15.5 (10.6)	0.001
Survived to ICU discharge	21	6	0.88
Survived to hospital discharge	20	6	0.74

APACHE = Acute Physiology and Chronic Health Evaluation. CRRT = continuous renal replacement therapy. ICU = intensive care unit. MV = mechanical ventilation. PPV = pulse pressure variation.

Authors' contributions

Rinaldo Bellomo and In Byung Kim devised the study. In Byung Kim performed the investigations. Nigel Fealy and Ian Baldwin helped perform the investigations. In Byung Kim and Rinaldo Bellomo analysed the results and cowrote the final draft. Nigel Fealy and Ian Baldwin reviewed the draft and assisted with its completion.

Competing interests

None declared.

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