A pilot study of the epidemiology and associations of pulse pressure variation in cardiac surgery patients

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

ABSTRACT

Background: Pulse pressure variation (PPV) is an accepted measure of intravascular filling. It can now be estimated automatically. However, there is limited knowledge of the epidemiology and associations of such estimates in cardiac surgery patients.

Methods: We conducted a pilot prospective observational study of the epidemiology and associations of automatically estimated PPV in 30 cardiac surgery patients admitted to the intensive care unit of a tertiary hospital. The study was conducted in June and July 2010. We collected automated monitor-estimated PPV values every 15 minutes during mandatory ventilation in patients after cardiac surgery. We simultaneously collected data on all relevant haemodynamic values, hourly fluid balance, tidal volume (V_T) and peak airway pressure. We made a total of 205 measurements on 30 patients. A PPV value $\geqslant 13\%$ was selected as defining a likely fluid responsiveness (FR) state. Clinicians were not informed of the study.

Results: PPV values $\geqslant 13\%$ were present in 38% of measurements, and the average duration of this physiological state was 38 minutes per patient. Higher PPV values correlated with negative fluid balance ($P < 0.001$), lower mean pulmonary arterial pressure ($P = 0.018$), lower cardiac index ($P = 0.013$), higher peak airway pressure ($P < 0.001$) and higher V_T ($P < 0.001$).

Conclusions: In a tertiary ICU, among patients who had recently had cardiac surgery, automated PPV values in the likely FR range were present in over a third of measurements. Correlations with other haemodynamic and ventilation values were logical and expected.

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Assessment of intravascular volume is an important aspect of the care of critically ill patients. Dynamic parameters of fluid responsiveness (FR) 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 in patients on mechanical ventilation, appear superior to static parameters such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) for predicting FR.[1-4] But despite this superiority, dynamic parameters have not, until recently, been commonly used in the clinical setting. In contrast, static parameters such as CVP and PAOP are still widely used to assess FR, 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 in mechanically ventilated patients.[9,10] Second, they require the patient 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, PPV is not widely used and thus there is limited knowledge of its epidemiology and its associations with other relevant variables.

Recently, monitoring software has been developed that enables the automated estimation and display of PPV[11,12] as well as SVV.[13,14] Unlike SVV, PPV can be estimated using standard radial arterial lines, making it less expensive and easier to obtain. However, its physiological "validity" remains unknown.

Accordingly, using automated continuous PPV estimation, we performed a prospective observational study. We aimed to assess the incidence of PPV values in the likely FR range and their association with other relevant haemo-

Abbreviations

CI	Cardiac index
CVP	Central venous pressure
FR	Fluid responsiveness
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
V_T	Tidal volume

dynamic, ventilatory and fluid-based parameters in patients immediately after cardiac surgery. We hypothesised that it would be relatively common for such patients to have an automated PPV value in the likely FR range, and that such a value would show physiologically logical and expected correlations with relevant haemodynamic, fluid-related and mechanical ventilation-dependent variables that have been described for non-automated PPV measurements.

Methods

We studied 30 mechanically ventilated patients in the intensive care unit of a tertiary hospital following cardiac surgery in June–July 2010. 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, in all patients, a continuous cardiac index (CI) measurement-capable pulmonary artery catheter (CCOmbo Catheter, Edwards Lifesciences, Irvine, Calif, USA) and a peripheral arterial catheter (Arrow International, Reading, Pa, USA) were inserted during cardiac surgery in the operating theatre. CI and pulmonary arterial pressure (PAP) were continuously measured via transducer (ITL Healthcare, Melbourne, VIC, Australia) and Vigilance monitors (Edwards Lifesciences, Irvine, Calif, USA). Pressure transducers were zeroed at the mid chest level to atmospheric pressure. CVP was measured at end-expiration using the right atrial port of the pulmonary artery catheter.

Automated estimation of arterial pulse pressure variation

Automated PPV values were calculated in real time every 15 minutes 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 pressures (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:

$$(PP_{max} - PP_{min}) \div PP_{mean}.$$

PPV values provided by the monitor were continuously transferred into the main computer. We defined a PPV value in the likely FR range as $\geq 13\%$ of pulse pressure.[16] Patients were divided into two groups: those with PPV values below this range ($< 13\%$) and those with PPV values within this range ($\geq 13\%$).

Data collection

We started data capture as soon as possible after a patient's post-operative arrival in the ICU (within 30 minutes in all cases). Demographic and clinical data were recorded. Every 15 minutes, we recorded heart rate, mean arterial pressure (MAP), PAP, CVP, tidal volume (V_T), peak airway pressure and CI. Every hour, we recorded cumulative fluid balance (total input minus total output), including fluid balance in the operating theatre. We collected these data over a 2-hour period.

Statistical analysis

All data were expressed as mean ± SD. Comparison between groups (lower PPV and higher PPV) was performed using the Mann–Whitney test. Relationships between PPV and CI, mean PAP, heart rate, MAP, CVP, V_T, peak airway pressure and fluid balance were evaluated using Spearman's correlation test. We also performed multivariable linear regression analysis with (i) PPV and (ii) length of stay in the ICU as the dependent variable, to identify independent factors that might affect its value. Changes in variables over time were compared using analysis of variance. A P value of < 0.05 was considered statistically significant.

Ethics approval

The Human Research Ethics Committee of Austin Hospital approved our study protocol and waived the need for informed consent.

Results

During the study period, we recorded 205 automated PPV measurements on 30 cardiac surgical patients. The 30 patients were admitted to the ICU in the immediate postoperative period after coronary artery bypass graft surgery ($n = 17$), valvular surgery ($n = 7$), or both ($n = 6$). Only one of the 30 patients did not survive to hospital discharge.

Baseline characteristics and haemodynamic parameters of patients are shown in Table 1. Changes in mean PPV values and other haemodynamic parameters over the 2-hour observation period are shown in Table 2. The mean automated PPV value did not significantly change over time during this period (Figure 1).

There were 79 episodes of automated PPV values $\geq 13\%$ (38% of all measurements). In patients with PPV values $\geq 13\%$, V_T and peak airway pressure were significantly higher and CI was significantly lower (Table 3). However, differences between the two groups with respect to cumulative fluid balance, MAP, mean PAP, heart rate and CVP were not significant.

The correlation of automated PPV values with other haemodynamic parameters is summarised in Table 4. A higher automated PPV value was significantly correlated with negative fluid balance, lower mean PAP, lower CI, higher peak airway pressure and higher V_T. The correlation between automated PPV and CI is shown in Figure 2. The distribution of PPV in the 10 patients who had PPV ⩾ 13% at initial measurement is shown in Figure 3.

On multivariable linear regression analysis, the mean automated PPV value was significantly correlated with cumulative fluid balance and peak airway pressure (Table 5). On multivariable linear regression analysis, length of stay in the ICU was not significantly correlated with mean PPV, cumulative fluid balance or CI (Table 6).

Table 1. Baseline characteristics of study patients (*N* = 30)

Variable	Mean (SD)*
Mean age, years	54.8 (14.3)
Male sex, *N* (%)†	23 (76.7%)
Operative type, *N*†	30
Coronary artery bypass surgery	17
Valve surgery	7
Both	6
PPV classification, *n* (%)‡	
< 13%	127 (62%)
⩾ 13%	78 (38%)
Cardiac rhythm, *N* (%)†	
Normal sinus rhythm	16 (53.3%)
Pacing rhythm	14 (46.7%)
Discharged from ICU, *N* (%)†	29 (96.7%)
Length of stay in ICU, days	2.2 (2.5)
Length of stay in hospital, days	12.7 (7.4)
APACHE II score	14.7 (4.3)
APACHE III score	53.1 (17.2)
SAPS	26.7 (9.2)
Mean pulse pressure variation, %	11.8 (5.7)
Mean cardiac index, L/min/m^2	2.7 (0.6)
Mean heart rate, beats/minute	82.6 (11.5)
Mean arterial pressure, mmHg	76.8 (9.9)
Mean pulmonary artery pressure, mmHg	23.1 (6.9)
Mean fluid balance, mL	– 342.3 (1026.8)
Mean central venous pressure, mmHg	10.4 (3.8)
Mean tidal volume, mL/kg	7.5 (1.3)
Mean peak airway pressure, mmHg	22.1 (4.2)

APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. PPV = pulse pressure variation. SAPS = Simplified Acute Physiology Score. * Data are mean (SD) unless otherwise indicated. † *N* = number of patients. ‡ *n* = number of measurements.

Discussion

Statements of key findings

In our study, the incidence of automated PPV values in the likely FR range (⩾ 13%) was about 40%. There was a physiologically logical and expected significant negative correlation between automated PPV values and cumulative fluid balance, CI, and mean PAP, and a positive correlation between PPV values and higher V_T and peak airway pressure. On multivariable linear regression analysis (also as physiologically logical and expected), greater cumulative fluid balance and higher peak airway pressure were independently associated with higher automated PPV values.

Comparison with previous studies

Most previous studies of PPV have compared dynamic parameters with static parameters. These studies mainly focused on the ability of PPV values greater than 12% or 13% to predict FR in different groups. Results of these studies show that, in patients on mechanical ventilation, dynamic parameters (PPV, SPV or PVI) are superior to static parameters (CVP, PAOP) in predicting FR.[1-4,10] Despite such evidence, dynamic parameters such as PPV are still infrequently used in the clinical setting. Furthermore, few studies have evaluated the clinical impact of PPV-guided or SPV-guided fluid management.[17-20]

No previous studies have prospectively assessed the epidemiology of PPV in cardiac surgery patients and its association with relevant haemodynamic, fluid-related and mechanical ventilation-dependent variables. This lack of information makes it difficult to appreciate how often, in the absence of PPV monitoring, patients who have had recent cardiac surgery may be in a likely FR state. Such appreciation is the first crucial step towards establishing whether automated PPV monitoring may be desirable.

Our study shows that it is fairly common for cardiac surgery patients immediately after the operation to have PPV values in the likely FR range. Moreover, during the first 2 hours after arrival in the ICU, cardiac surgery patients spend, on average, more than half an hour in such physiological conditions. These observations suggest that automated PPV monitoring may be useful for detecting patients who are in a likely FR state and whose clinicians may not appreciate their physiological condition.

It is also important to consider whether automated PPV measurement is of sufficient quality to justify its application in the clinical setting. While this can only be addressed by a randomised controlled trial, our study provides indirect evidence that automated PPV values may be as clinically useful as previously reported non-automated PPV measurements. In particular, in our study, automated PPV values had physiologically logical relationships with several other inde-

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

Variable	Initial value	30 min	60 min	90 min	120 min	*P*
Mean PPV (%)	12.5 (5.9)	11.7 (5.6)	11.4 (5.2)	12.4 (4.4)	10.2 (4.5)	0.80
Mean MAP (mmHg)	78.7 (11.5)	77.2 (8.6)	76.7 (8.7)	75.7 (11.5)	78.9 (9.7)	0.95
Mean PAP (mmHg)	22.2 (6.4)	23.6 (6.6)	23.4 (7.2)	22.6 (8.1)	21.4 (4.8)	0.85
Mean CI (L/min/m^2)	2.7 (0.8)	2.6 (0.6)	2.7 (0.6)	2.8 (0.5)	2.8 (0.5)	0.98
Mean CVP (mmHg)	10.4 (3.9)	10.0 (3.0)	10.5 (4.6)	10.1 (3.8)	10.2 (3.5)	0.99

CI = cardiac index. CVP = central venous pressure. MAP = mean arterial pressure. PAP = pulmonary arterial pressure. * Data are mean (SD).

pendently measured haemodynamic, fluid-related and mechanical ventilation-related variables. Several variables (eg, V_T, peak inspiratory pressure) that affected PPV in our study are known to affect PPV in general.[9,10]

Significance of our findings

By showing that automated PPV measurements have the same logical expected correlations with known determinants of PPV, our findings support the notion that automated PPV measurements are likely to be of sufficient quality for clinical use. They also show that, using such technology, clinicians can potentially identify situations in which (as demonstrated by previous studies of PPV) patients are in a likely FR state — a state that is currently undetectable by routinely available screen-displayed static haemodynamic variables. Finally, our study demonstrates that the duration of such a likely FR state is substantial (occupying about 25% of observation time in the first 2 hours after the patient's arrival in the ICU).

Our observations do not establish whether the availability of PPV values for patients in the likely FR state can deliver improved clinical outcomes. Furthermore, the presence of a PPV value in the likely FR range does not necessarily imply that fluid administration is desirable. These important clini-

Figure 1. Distribution of mean pulse pressure variation (PPV) values over time

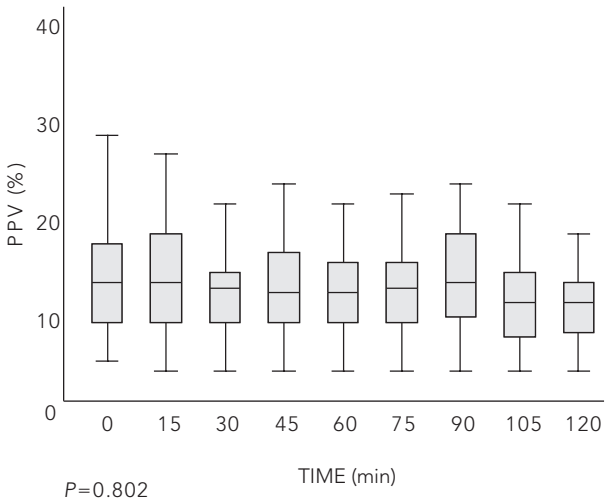


Table 3. Comparison of variables, by pulse pressure variation (PPV) group*

Variable	PPV < 13%	PPV ⩾ 13%	*P*
Cardiac index (L/min/m^2)	2.8 (0.6)	2.6 (0.5)	< 0.001
Tidal volume (mL/kg)	7.3 (1.4)	8.0 (1.2)	< 0.001
Peak airway pressure (mmHg)	20.9 (4.1)	23.6 (4.0)	< 0.001
Fluid balance (mL)	– 160.6 (1137.4)	– 517.6 (775.2)	0.11
Mean arterial pressure (mmHg)	76.7 (9.3)	77.8 (11.1)	0.56
Mean pulmonary arterial pressure (mmHg)	23.1 (6.9)	22.8 (6.8)	0.85
Heart rate (beats/min)	81.3 (11.6)	85.0 (11.1)	0.20
Central venous pressure (mmHg)	10.2 (3.3)	10.4 (4.4)	0.85
Acute Physiology and Chronic Health Evaluation II score	16.1 (3.8)	13.0 (4.3)	0.07
Acute Physiology and Chronic Health Evaluation III score	57.8 (14.4)	47.2 (19.2)	0.13
Simplified Acute Physiology Score	28.7 (9.6)	24.3 (8.5)	0.22

* Data are mean (SD).

Table 4. Correlation of pulse pressure variation (PPV) with other physiological and mechanical ventilation parameters

	PPV (%)	Peak airway pressure (mmHg)	PAP (mmHg)	Heart rate (beats/min)	MAP (mmHg)	Cardiac index (L/min/m^2)	CVP (mmHg)	Fluid balance (mL)
Peak airway pressure (mmHg)	0.31*							
Mean PAP (mmHg)	– 0.14†	0.43*						
Heart rate (beats/min)	0.19*	0.24*	0.24*					
MAP (mmHg)	0.02	– 0.06	– 0.15†	0.05				
Cardiac index (L/min/m^2)	– 0.2*	– 0.31*	– 0.12	0.26*	0.19*			
CVP (mmHg)	0.01	0.45*	0.60*	0.15†	– 0.13	– 0.03		
Fluid balance (mL)	– 0.33*	0.07	0.39*	–0.21	0.04	– 0.17	0.18	
Tidal volume (mL/kg)	0.35*	0.23*	– 0.21*	0.35*	– 0.21*	– 0.17*	0.01	0.00

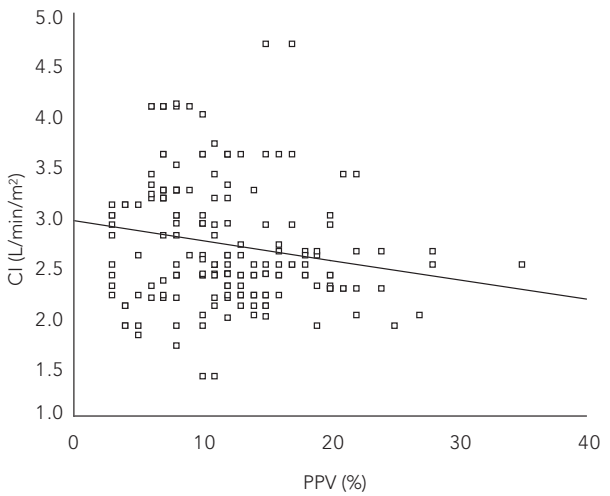
CVP = central venous pressure. MAP = mean arterial pressure. PAP = pulmonary arterial pressure. * Correlation significant at 0.01 level (2-tailed).
† Correlation significant at 0.05 level (2-tailed).

cal issues can only be addressed though randomised controlled trials. However, our observations establish the physiological "validity" of automated measurements, their potential clinical usefulness and the incidence and duration of a condition that requires PPV measurement for diagnosis.

Strengths and limitations of our study

To our knowledge, this study is the first to define the epidemiology and associations of automated PPV measurements in cardiac surgery patients immediately after operation. Our findings appear to be of clinical and practical importance, and open the door to the use of this new technology in patient care. But our study has some limitations. First, as it was not a randomised controlled trial, no conclusions can be drawn about the clinical impact of automated PPV measurements. Second, it was a single-centre study, and thus our findings may not apply to other units in which fluid, ventilatory and haemodynamic management differ. However, our patients and our methods of fluid management have many of the standard characteristics of cardiac surgery care in a tertiary ICU,[21] and 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 associations we demonstrate in our study are physiologically logical and suggest otherwise. Fourth, we only measured automated PPV values every 15 minutes. More frequent measurement may have detected a greater incidence of elevated PPV values. On the other hand, we considered that values that were not sustained for a sufficient period were unlikely to be clinically important.

Figure 2. Correlation between pulse pressure variation (PPV) and cardiac index (CI)*



* $r^2 = –0.12$; $P < 0.01$.

Figure 3. Distribution of pulse pressure variation (PPV) over time in 10 patients with PPV ⩾ 13% at first measurement

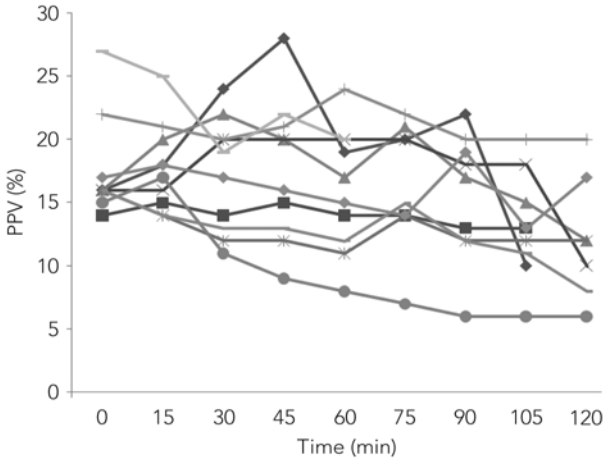


Table 5. Multivariate correlation of PPV (dependent variable) with other physiological and mechanical ventilation parameters

Independent variable	Coefficient (95% CI)	*P*
Fluid balance	– 0.254 (– 0.003 to 0.000)	0.03
Peak airway pressure	3.968 (0.437 to 1.324)	< 0.001
Mean PAP	– 3.316 (– 0.994 to – 0.246)	< 0.001
MAP	1.061 (– 0.055 to 0.179)	0.29
Cardiac index	– 0.974 (– 3.149 to 1.086)	0.33
CVP	1.653 (– 0.098 to 1.029)	0.10
Tidal volume	– 1.758 (– 2.632 to 0.169)	0.08
Heart rate	1.763 (– 0.020 to 0.315)	0.08

CVP = central venous pressure. MAP = mean arterial pressure. PAP = pulmonary arterial pressure. PPV = pulse pressure variation.

Table 6. Multivariate correlation of length of stay in ICU (dependent variable) with other physiological and mechanical ventilation parameters

Independent variable	Coefficient (95% CI)	*P*
Fluid balance	– 0.330 (– 0.002 to 0.001)	0.75
Peak airway pressure	– 0.824 (– 0.579 to 0.261)	0.43
Mean PAP	– 0.824 (– 0.353 to 0.159)	0.43
MAP	0.695 (– 0.091 to 0.176)	0.50
Cardiac index	0.558 (– 1.581 to 2.671)	0.59
CVP	0.439 (– 0.398 to 0.599)	0.67
Tidal volume	– 0.419 (– 1.262 to 0.855)	0.69
Mean PPV	– 0.796 (– 0.400 to 0.188)	0.44

CVP = central venous pressure. ICU = intensive care unit. MAP = mean arterial pressure. PAP = pulmonary arterial pressure. PPV = pulse pressure variation.

Future studies

Our findings need to be confirmed in other institutions and health care settings. More detailed data collection on a minute-by-minute basis may provide useful information. If these studies confirm that an automated PPV system provides physiologically logical information and that a PPV in the likely FR range is common, then randomised controlled trials in which patients are allocated to having or not having PPV value displays on their monitor may provide useful initial information on whether PPV availability changes practice and, perhaps, outcomes.

Conclusion

In patients immediately after cardiac surgery, a PPV value in the likely FR range is common and of considerable duration. Automated measurement of PPV provides physiologically logical and credible data. Our findings support the value of automated PPV measurements in such patients and suggest the need to investigate whether PPV display can affect patient treatment and outcome.

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Competing interests

Rinaldo Bellomo works as a paid consultant for Philips Medical.

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