Implications of arterial pressure variation in patients in the intensive care unit

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Positive-pressure ventilation alters stroke volume by transiently increasing intrathoracic pressure and thereby decreasing preload. This phasic variation in stroke volume results in a cyclic fluctuation in arterial pressure with a phase length equal to the respiratory rate. Measuring ventilation-induced arterial pressure variation allows the clinician to predict the cardiovascular response to changes in intravascular volume status. Thus, one may predict preload responsiveness because the greater the amount of ventilation-associated arterial pressure variation, the greater the patient's preload responsiveness. This variation in arterial pressure can been defined as a variation in either systolic pressure or pulse pressure. Although pulse pressure gives a clearer signal, systolic pressure variation may be easier to measure bedside without invasive hemodynamic monitoring. Newer methods of quantifying this arterial pressure variation include the respiratory systolic variation test, which can performed without an apneic baseline, and the pulse pressure variation, a potentially more accurate measure of preload responsiveness. Curr Opin Crit Care 2001, 7:212–217

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Abbreviations

CI	cardiac index
CVP	central venous pressure
LVEDA	left ventricular end-diastolic area
LVEDV	left ventricular end-diastolic volume
LVSV	left ventricular stroke volume
PEEP	positive end-expiratory pressure
P_{PAO}	pulmonary artery occlusion pressure
PPV	pulse pressure variation
SPV	systolic pressure variation

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Mean arterial pressure is determined by blood flow and arterial vasomotor tone, whereas arterial pulse pressure (*ie*, arterial systolic and diastolic pressure) is determined by left ventricular stroke volume (LVSV), heart rate, and arterial tone. Because arterial tone and heart rate remain relatively constant over the course of a single breath, arterial pressure variation is largely due to transient changes in stroke volume resulting from a positive pressure breath. However, if marked respiratory sinus arrhythmia exists, changes in pulse pressure may also reflect reciprocal changes in heart rate. Positive-pressure breathing increases intrathoracic pressure and lung volume, both of which decrease preload and ultimately LVSV in the preload-dependent heart. The only determinant of a change in arterial pulse pressure from one beat to the next is a proportionally similar change in LVSV [1,2]. Vascular tone, arterial resistance, and elastance will modulate the slope of the relation between arterial pressure and LVSV over time, but not on a beat-to-beat basis. Thus, the only causes of arterial pulse pressure variation during positive-pressure ventilation are changes in LVSV. Ventilation-induced systolic arterial pressure variation, or pulsus paradoxus, is defined as the variation in the arterial systolic pressure waveform as measured from an apneic baseline to its highest and lowest point after a positive-pressure breath.

A common therapeutic goal in hemodynamically unstable patients is the rapid increase in cardiac index (CI) using fluid resuscitation. Massive fluid resuscitation carries measurable risks, including volume overload, iatrogenic pulmonary edema, and dilutional acidosis (from excess chloride loading). Titration of resuscitative therapies is commonly based upon some measure of ventricular preload as an estimate of left ventricular end-diastolic volume (LVEDV). Traditionally, measures of preload have included pulmonary artery occlusion pressure (P_{PAO}), right ventricular end-diastolic volume, and estimates of left ventricular end-diastolic area (LVEDA) using echocardiography. These diagnostic measures have met with varying degrees of success in estimating preload, absolute LVEDV, or the subsequent response to fluid challenge.

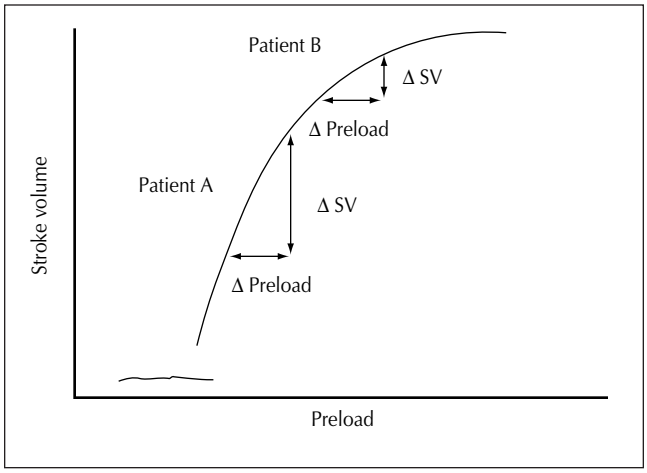
Previously studies documented that P_{PAO} does not correlate well with LVEDV [3–5]. Very high or very low values for P_{PAO} provide a qualitative assessment, but most intermediate readings give little useful information. Measurement of right ventricular end-diastolic

volume is affected by tricuspid regurgitation, which is common in the ICU setting [6]. Two-dimensional echocardiography has been advanced as an alternative to estimating left ventricle volumes with mixed success [7–10]. However, even if traditional measures of preload or LVEDV are accurate, they still do not reliably differentiate between preload responsiveness (*ie*, fluid challenge leads to an increase CI) and preload unresponsiveness (*ie*, fluid challenge leads to no change or decrease in CI) in patients with acute circulatory failure [11•]. Knowledge of the LVEDV or absolute preload does not necessarily allow for accurate prediction of the hemodynamic response to alterations in preload.

Ventilation and arterial pressure variations

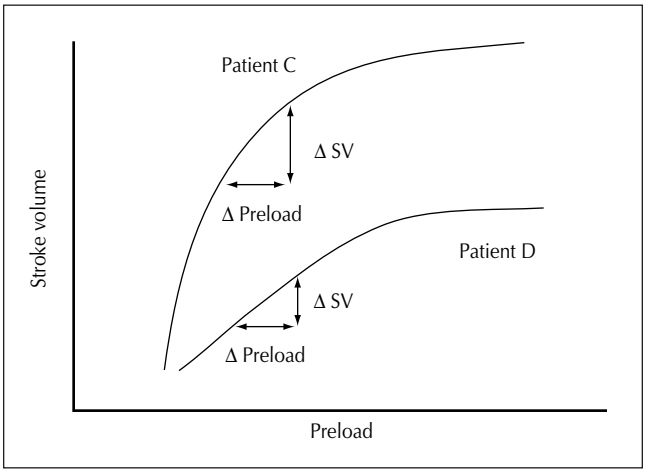
By transiently decreasing preload, positive-pressure ventilation alters LVSV indirectly through its associated reduction in venous return [1,2]. As illustrated in Figure 1, the degree to which LVSV decreases during a positive-pressure breath is proportional to the slope of the Starling curve. Patient A's LVSV, in this example, is on the "steep portion" of the Starling curve; changes in preload will result in large changes in LVSV and a greater change in systolic arterial pressure and pulse pressure. Patient A would have an increased LVSV in response to measures that increase preload (*eg*, fluid loading). In other words, this patient is preload-responsive. In contrast, patient B's Starling curve is relatively flat. Identical changes in preload will not alter LVSV as much as they would for patient A. Patient B is not preload-responsive. As seen in Figure 2, Patients C and D have different Starling curves. Given an identical change in absolute preload, patient C has a greater change in LVSV than does patient D. Patient C is preload-responsive and therefore has a greater variation in the arterial pressure even though absolute changes in LVEDV are identical for these two patients.

Figure 1. Stroke volume and preload for patients A and B



Δ Preload, change in preload after a positive pressure breath; Δ SV, change in stroke volume resulting from a positive pressure breath.

Figure 2. Stroke volume and preload for patients C and D



Δ Preload, change in preload after a positive pressure breath; Δ SV, change in stroke volume resulting from a positive pressure breath.

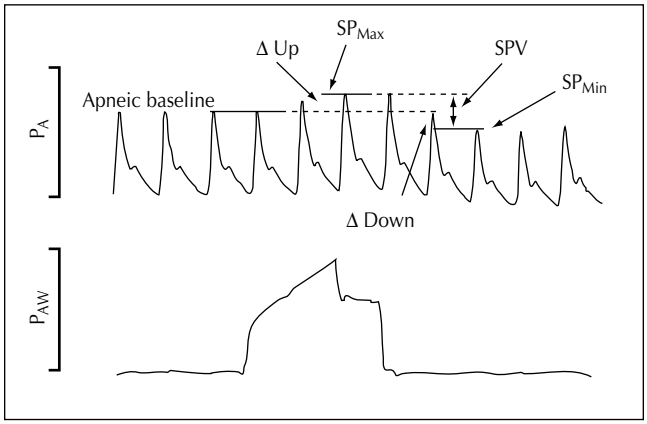
The relation between ventricular volume and pressure may not be constant between patients or even for one patient as that patient's cardiovascular status changes. Interindividual variability in ventricular cavity size and left ventricular systolic and diastolic function make any single-point estimate of preload that is based on surrogates of LVEDV subject to a wide range of "normal" values. Low left ventricular preload indicated by low P_{PAO} or LVEDA, even if accurately demonstrating a low LVEDV, can still be associated with fluid unresponsiveness if a patient's Starling curve is relatively flat. Conversely, high left ventricular filling pressures or dimensions do not necessarily connote adequate fluid resuscitation or lack of further preload-responsiveness.

Variation in the arterial pressure waveform reflects the dynamic response of the cardiovascular system to varying levels of preload. Arterial pressure variation is a better predictor of the cardiovascular response to changing preload than is single-point estimation of LVEDV, whether obtained by filling pressure or echocardiographic area. In other words, absolute preload is not preload-responsiveness.

Systolic pressure variation

Systolic pressure variation (SPV) is defined as the difference between the maximum and minimum systolic pressure following a positive-pressure breath [12•] (Fig. 3). The exact physiologic mechanism behind the initial increase in systolic pressure after a positive pressure breath has yet to be proven. However, likely causes include decreased left ventricular afterload as a consequence of

Figure 3. Systolic pressure variation



Δ Down, the subsequent decrease in systolic pressure; Δ Up, the increase in systolic pressure immediately after the positive pressure breath; P_A, arterial pressure; P_{AW}, airway pressure; SP_{Max}, maximum systolic pressure after a positive pressure breath; SP_{Min}, minimum systolic pressure after a positive pressure breath; SPV, the difference between the SP_{Max} and SP_{Min} or the sum of Δ Up and Δ Down.

increased intrathoracic pressure and slightly increased left ventricular preload as a result of changed transpulmonary pressure associated with a positive-pressure breath [11•]. Subsequently decreased systolic arterial pressure below the apneic baseline results from increased intrathoracic pressure that leads to decreased right ventricular preload and right ventricular stroke volume. This smaller stroke volume is seen through the left ventricle after a small transit delay through the pulmonary circulation.

In the first study to quantify SPV and correlate it with hypovolemia, Perel *et al.* [12•] found that SPV increased with graded hemorrhage in a canine model and that SPV showed a stronger correlation to the degree of hemorrhage than did heart rate, mean arterial pressure, central venous pressure (CVP), or P_{PAO}. Perel *et al.* [12•] subsequently showed that SPV was greater during hemorrhagic hypotension than during hypotension induced by sodium nitroprusside infusion, supporting alterations in LVSV as the mechanism behind SPV rather than decreased arterial tone [13]. Rooke *et al.* [14] showed that SPV and Δ down in systolic pressure increase with controlled hemorrhage and then decrease with volume challenge in anesthetized, mechanically ventilated humans.

Ornstein *et al.* [15] have shown that SPV and systolic pressure Δ down correlated with decreased CI after controlled hemorrhage in postoperative cardiac surgical patients (r = 0.85 and 0.71, respectively) and that the Δ down component of SPV was a better predictor of the decrease in CI with controlled hemorrhage than was P_{PAO} or CVP. Tavernier *et al.* [16••] evaluated in a prospective fashion the ability of systolic pressure Δ down to predict increases in CI after volume loading. In their investigation, 16 patients with septic shock were progressively volume loaded. Before each volume challenge P_{PAO}, LVEDA, SPV, and systolic pressure Δ down were recorded. Using receiver-operating curve analysis, the authors found that a Δ down of 5 mm Hg was a more accurate predictor of increase in CI than was either P_{PAO} or EDA.

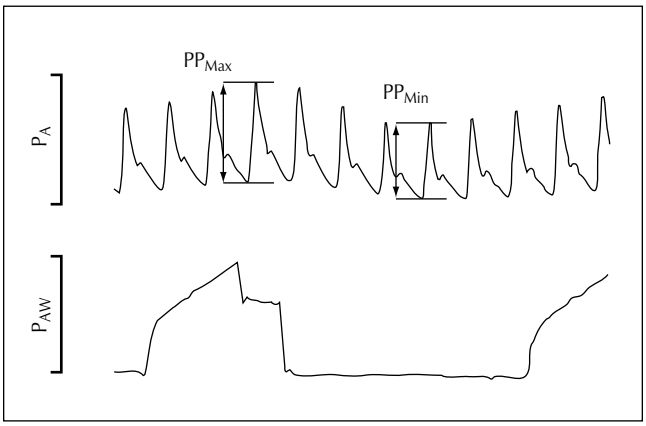
Respiratory systolic variation test

Recently, Perel *et al.* [17] described a new technique to measure preload responsiveness without the need for an apneic pause. They used sequential increases in positive-pressure tidal volumes to induce sequentially greater changes in LVSV. They call this technique the *respiratory systolic variation test* (RSVT). The advantage of RSVT is that it can be obtained without the short period of apnea required for measuring SPV or pulse pressure variation (PPV). The test is performed by the successive delivery of four pressure-controlled breaths of increasing size (5-, 10-, 15-, and 20-cm H_2O driving pressure). A line of best fit is then drawn through the successive minimal systolic pressures that result from these positive-pressure breaths. The slope of this line increases with increasing volumes of hemorrhage in a canine model [18]. In addition, the RSVT shows a correlation (r = 0.82) with increasing CI after fluid bolus in vascular surgery patients [19].

Pulse pressure variation

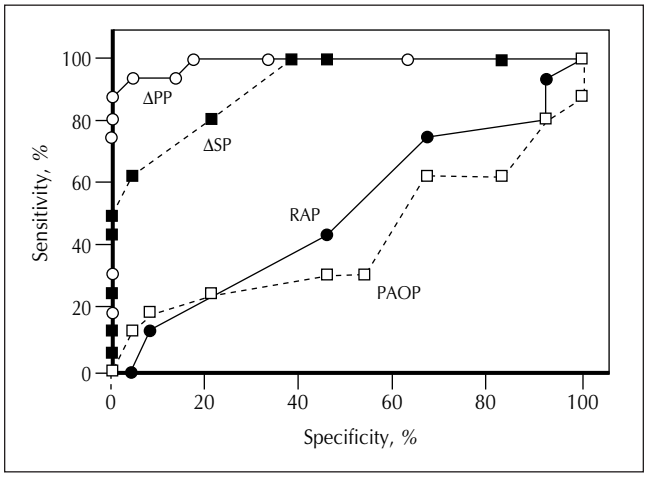
Pulse pressure variation is defined as the maximal pulse pressure less the minimum pulse pressure divided by the average of these two pressures [20•] (Fig. 4). PPV may be a more accurate metric of changes in LVSV with positive-pressure breathing because SPV may reflect variations in pleural pressure [21] and changing LVSV,

Figure 4. Pulse pressure variation



P_A, arterial pressure; P_{AW}, airway pressure; PP_{Max}, maximum pulse pressure after a positive pressure breath; PP_{Min}, minimum pulse pressure after a positive pressure breath.

Figure 5. Receiver-operating characteristic curve for central venous pressure, pulmonary artery occlusion pressure, spontaneous venous pulse, and pulse pressure variation



ΔPP, change in pulse pressure; ΔSP, change is systolic pressure; PAOP, pulmonary artery occlusion pressure; RAP, right arterial pressure. Published with permission [22••].

whereas PPV reflects only changes in transmural aortic pressure and therefore changes in LVSV on a beat-to-beat basis.

Michard *et al.* [22••] compared CVP, P_{PAO}, SPV, and PPV as predictors of preload responsiveness in a group of 40 septic, ventilator-dependent patients. Preload responsiveness was prospectively defined as a greater than 15% increase in CI after fixed volume challenge. CI is often elevated in septic, ventilator-dependent patients; although further fluid resuscitation may be useful, if it results in volume overload and hemodilution without an increase in CI then mortality may actually increase. Thus, predicting which patients could increase their CI further and by how much is important for this patient cohort. Importantly, the authors found that PPV predicted CI responses more accurately than CVP, P_{PAO}, or SPV. The receiver-operating characteristic curve for these measures demonstrates that SPV is a good predictor of preload responsiveness, as compared with either CVP or P_{PAO}. However, PPV is also superior to SPV in predicting preload responsiveness (Fig. 5). Furthermore, PPV displayed better precision and less variance than SPV (Fig. 6) in predicting preload responsiveness.

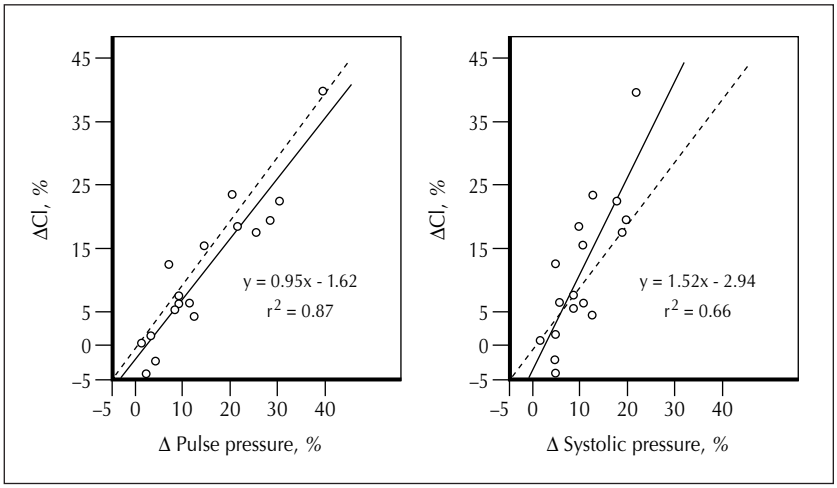
Michard *et al.* [20•] also correlated PPV to decreased CI induced by the addition of 10 cm H_2O positive end-expiratory pressure (PEEP) in 14 ventilated patients with acute lung injury. Hemodynamic measurements were performed before and 15 minutes after application of an additional 10 cm H_2O PEEP. PEEP–induced changes in CI could be predicted from the baseline PPV before adding PEEP. The greater the PPV before the PEEP level was increased, the greater the decrease in CI. Thus, by noting PPV during positive-pressure breathing, clinicians can now accurately predict which patient will have decreased CI when given PEEP and by how much CI will decrease.

Limitations

Unlike other traditional hemodynamic parameters, which are best measured during apnea, SPV and PPV depend on a positive-pressure breath and are therefore influenced by tidal volume. Szold *et al.* [23] studied the effects of increasing tidal volumes on the degree of SPV in a hemorrhagic canine model and found the SPV was dependent on the degree of hypovolemia and also the size of the tidal volume. As the RSVT demonstrates, increased tidal volumes lead to progressively greater decreases in LVSV. The RSVT will need to be standardized across ventilators and patient subgroups.

Figure 6. Spontaneous venous pulse and pulse pressure variation as predictors of preload responsiveness

Solid line denotes regression equation; dotted line denotes line of identity. ΔCI, change in cardiac output after a fixed fluid bolus. Published with permission [22••].



Arrhythmias, particularly atrial fibrillation, also interfere with the degree of arterial pressure variation by changing beat-to-beat LVSV and may limit the usefulness of arterial pressure variation analysis in predicting preload responsiveness. In addition, positive-pressure ventilation is required for accurate measurement. Spontaneous respiration has been shown to be less effective in producing reliable changes in the arterial wave form [14].

Attempts at correlating absolute levels of preload with dynamic changes in the arterial waveform have been mixed. In a set of 300 data points from 226 patients, Marik [24] has shown a moderate degree of correlation ($r^2 = 0.86$) between SPV and P_{PAO}. However, Gunn *et al.* (unpublished data, February 2001) were unable to show any correlation between SPV or PPV and conventional measures of preload, such as CVP, P_{PAO} or EDA in a group of cardiac surgical patients. This may not be a weakness but may reflect that preload responsiveness and absolute, single-point estimates of LVEDV are different physiologic concepts.

That preload responsiveness and single-point estimates of LVEDV are different is also evident when using echocardiographic measures of preload. Tousignant *et al.* [25] investigated the relation between LVSV and LVEDA by using in a population of 20 ICU patients and 21 postoperative cardiac surgical patients. They examined whether LVEDA could identify patients who would have increases of LVSV by 20% or more after 500 mL pentastarch administration. The authors found only a modest correlation ($r = 0.60$) between single-point estimates of LVEDA and response to fluid loading. However, Swenson *et al.* [26], in a hemorrhaged and then fluid-resuscitated canine model, showed a significant relation between changes in LVEDA with fluid resuscitation and changes in CI. They were unable to demonstrate a relation between changes in P_{PAO} and changes in CI. These data suggest that changes in LVEDA with fluid resuscitation can predict trends in cardiac function and therefore suggest an appropriate end-point for fluid resuscitation. Measuring alterations in preload provides more information than does single-point estimates of LVEDV. Ventilation-induced changes in LVEDA may also correlate with preload responsiveness. However, rendering accurate measures of LVEDA during ventilation is technically difficult. Future studies will need to define the role of variation in LVEDA as measured by transesophageal echocardiography during positive-pressure ventilation and its correlation with preload responsiveness. In addition, beat-to-beat variation in other modalities that measure LVSV, such as esophageal pulse Doppler stroke distance and pulse contour cardiac output, should correlate with preload responsiveness; this has yet to be proven.

Conclusions

PPV has already been shown to predict decreased CI in association with PEEP [20•] and may predict hypotension associated with hemodialysis or diuresis. Integration of SPV and PPV into automated bedside monitoring tools, similar to automated routines for measuring cardiac output or P_{PAO}, would simplify bedside quantification of arterial pressure variation. Presently there are no treatment algorithms available that use SPV or PPV as drivers for therapeutic interventions.

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