# Assessment of indices of preload and volume responsiveness

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**Purpose of review**

To summarize the relevant peer-reviewed publications over the past year that addressed issues of when to give (or not give) fluid to the critically ill patient.

**Recent findings**

Clinical data from several studies underscore the inability of measures of ventricular filling to assess either preload or preload responsiveness. Whereas less invasive monitoring techniques than pulmonary arterial catheterization demonstrate better discrimination with estimates of both preload and preload responsiveness. Measuring dynamic changes in stroke volume, descending aortic flow, and both superior and inferior vena caval diameters during ventilation provides good predictive value in defining preload responsiveness. One study demonstrated that resuscitation protocols keyed to esophageal flow measures improved outcome in postoperative cardiac surgery patients.

**Summary**

Preload is not preload responsiveness. Functional measures of preload responsiveness exist and are superior to traditional measures of filling pressures in driving resuscitation in critically ill patients.

**Keywords**

clinical trials, critical illness, hemodynamic monitoring, resuscitation

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**Abbreviations**

| | |
|---|---|
| **CVP** | central venous pressure |
| **PPAO** | pulmonary artery occlusion pressure |
| **$ScvO_2$** | central venous $O_2$ saturation |
| **$SvO_2$** | mixed venous $O_2$ saturation |


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## Introduction

Hemodynamic monitoring is a central aspect of cardiovascular diagnosis and titration of care. Circulatory shock results primarily in inadequate tissue blood flow. Although most forms of shock may show some increase in cardiac output initially in response to fluid loading, fully one-half of all hemodynamically unstable intensive care unit patients are not preload responsive [1]. Furthermore, volume overload often worsens cor pulmonale and can induce pulmonary and peripheral edema in heart failure states. To review the relevant new clinical data addressing this important clinical issue, PubMed was searched (www.ncbi.nlm.nih.gov/PubMed) for all papers published in 2004 using the key words 'resuscitation and hemodynamic monitoring, preload, fluid responsiveness, and circulatory shock.' The search was then narrowed to include only nonreview papers published in English that reflected clinical studies of patients within the intensive care unit or operating department. All of the 88 papers identified were reviewed and only those of particular relevance to the topic of assessing preload and preload responsiveness are summarized here. One older review paper and one position paper are also cited but only to place the current studies in proper perspective.

## Assessing ventricular performance

Fundamental to hemodynamic monitoring is the interpretation of the measured and derived data within the context of expected and known physiologic constructs, such as Starling's law of the heart and global $O_2$ supply and demand relationships. These assumptions were directly addressed in recent publications.

### Preload is not preload responsiveness

Kumar *et al.* [2••] demonstrated that neither central venous pressure (CVP) nor pulmonary artery occlusion pressure (PPAO) values nor their changes in response to fluid challenges reflected their respective ventricular end-diastolic volumes or changes, respectively, in patients receiving a fluid challenge for hemodynamic insufficiency. Presumably, nonlinear ventricular diastolic compliance relations and an incomplete knowledge of actual transmural ventricular filling pressures are the reasons for this failure. Starling's law of the heart, however, was still operative in this study. If end-diastolic volume increased in response to volume loading, then stroke volume increased as well. Thus, one should not use either CVP or PPAO values to define the state of ventricular filling or the potential

to response to a fluid challenge. Furthermore, changes in either CVP or PPAO did not correlate with each other or with changes in either stroke volume or end-diastolic volume of their respective ventricles. These findings of discordance between pulmonary artery catheter–derived data and directly measured indices of ventricular performance were duplicated, in a fashion, by Bouchard *et al.* [3•], who compared right and left ventricular stroke work index with echocardiographic-derived indices of left ventricular performance, i.e., fractional area change in 64 intraoperative cardiac surgery patients before and after bypass and before and after volume loading. A total of 186 simultaneous measurements were analyzed and compared. Correlations between right and left ventricular stroke work index changes were poor ($R = -0.28$–$0.16$, $P$ values 0.31–0.94), as were the correlations between left ventricular stroke work index changes and fractional area change changes ($R = -0.62$–$0.22$, $P$ values 0.07–0.95). Thus, not only is preload not preload responsiveness, but there is also a significant discrepancy and limited relation between the hemodynamic and echocardiographic evaluation of left ventricular performance. In the position paper entitled 'Surviving sepsis' [4•], sponsored by the major critical care societies, it was nevertheless recommended to use invasive monitoring as part of the assessment of circulatory shock and its response to therapy. This blue-ribbon panel also accentuated monitoring other related hemodynamic variables, however, such as cardiac output and mixed venous $O_2$ saturation ($SvO_2$).

### Alternatives to mixed venous oxygen saturation

Several studies over the past year have addressed alternatives to $SvO_2$ as well as attempting to find less invasive means to define preload and preload responsiveness. Recent interest in using central venous $O_2$ saturation ($ScvO_2$) as a surrogate for $SvO_2$ has raised the issue of covariability of these two measures and the use of a specific threshold $ScvO_2$ to identify tissue ischemia (usually identify by an $SvO_2$ <70%). Reinhart *et al.* [5•] compared both $SvO_2$ and $ScvO_2$ in 29 patients instrumented with both catheters followed continuously for more than 1000 hours using both fiberoptic and in-vitro measures. Importantly, they found that the central venous $O_2$ catheter more accurately estimated $ScvO_2$ than spot in-vitro measures and was not affected by either simultaneous infusion of fluids through the catheter or by changes in hematocrit, temperature, or blood pH. More importantly, although $ScvO_2$ tracked $SvO_2$, it tended to be 7 ± 4% higher. Furthermore, changes in $ScvO_2$ paralleled $SvO_2$ changes 90% of the time when $SvO_2$ changed by 5% or more. Thus, $ScvO_2$ values of 74% may be associated with $SvO_2$ values of 68%. Accordingly, if threshold values of $ScvO_2$ are to be used to guide therapy, then higher threshold values need to be used to detect potential tissue hypoperfusion.

### Alternatives to right-sided heart catheterization

In an attempt to bypass the need for right-sided heart catheterization, Combes *et al.* [6] demonstrated in 333 mechanically ventilated patients that a single transpulmonary thermal injection from a central venous site using the peripheral continuous cardiac output (PiCCO) system (Pulsion Ltd, Munich) gave estimates of cardiac function index and global ejection fraction that were similar to measures of left ventricular ejection fraction made by transesophageal echocardiography ($R = 0.87$ and 0.82, respectively). Potentially, estimates of left ventricular systolic function can be made without the need for a pulmonary artery catheter. Importantly, patients with right ventricular dysfunction were excluded, because PiCCO-derived parameters include right ventricular function whereas echo-derived measures are specific for left ventricular performance. Thus, extrapolation of these data to mechanically ventilated patients, many of whom may have right ventricular dysfunction associated with acute respiratory failure, may not be warranted.

If one does not need a pulmonary artery catheter, does one even need a central venous catheter? Desjardins *et al.* [7] compared an anticubital vein–transduced pressure with CVP in 19 cardiac surgery patients with or without mechanical ventilation. They found that CVP and peripheral venous pressure were similar (mean pressure differences 0.72–0 mm Hg). Thus, peripheral venous pressure is a readily available surrogate for CVP. Since CVP values of less than 10 mm Hg are associated with a decrease in cardiac output if positive end-expiratory pressure is subsequently increased, these data have clinical utility. Staal *et al.* [8] attempted to bypass invasive catheterization completely using cardiac impedance techniques. They compared angiographically measured left ventricular volumes, using the Simpson rule, with transcardiac conductance measured from surface skin electrodes in 10 subjects undergoing angiography. Reliably stable data were available in eight of 10 subjects and gave good agreement in the estimate of left ventricular volumes ($R^2 = 0.78$). It remains to be seen, however, if this technique gives a general volume measure or can detect clinically relevant changes in left ventricular volume over time and in response to therapy.

An interesting study came from Gabbanelli *et al.* [9], who used the time–activity curve of glucose dilution following a bolus infusion to estimate circulating blood volume. They compared glucose decay curves with PiCCO-derived measures of central blood volume daily for 5 days in 20 critically ill patients. Surprisingly, they demonstrated a good correlation between the two techniques ($R^2 = 0.79$). To the extent that measures of central blood volume, as a surrogate for preload, are clinically useful, then this safe technique using a readily available intravascular marker may be worth considering.

## Functional hemodynamic monitoring

If absolute measures of cardiovascular values cannot be used effectively as parameters describing cardiovascular status or responsiveness, then more provocative maneuvers need to be employed to improve the utility of these measures. Such provocative approaches comprise the broad field of monitoring techniques, referred to as *functional hemodynamic monitoring*.

### Pulse pressure variation and pulse contour analysis of stroke volume variation

Both Marx *et al.* [10] and Rex *et al.* [11] duplicated previous studies documenting that measures of stroke volume variation made using arterial pulse contour analysis following a transthoracic thermodilution estimate of cardiac output demonstrated that as cardiac output increased after volume loading, intrathoracic blood volume increased and stroke volume variation during positive-pressure ventilation decreased. Though not a novel observation, these data fill the files of duplicate studies of the same nonpredictive design published in previous years. Interestingly, Reuter *et al.* [12•] examined the impact of opening the chest on the value of ventilation-induced pulse pressure and stroke volume variations to predict preload responsiveness in 22 patients immediately after midline sternotomy. They determined pulse pressure and stroke volume variation, as well as left ventricular end-diastolic area index by transesophageal echocardiography, global end-diastolic volume index, and cardiac index by thermodilution before and after removal of blood (500 mL) and after volume substitution with hydroxyethyl starch 6% (500 mL). Just as one would predict for closed-chest conditions, blood removal resulted in a significant increase in both pulse pressure variation (5.2 ± 2.5% to 11.9 ± 4.6%) and stroke volume variation (6.7 ± 2.2% to 12.7 ± 3.8%, both $P < 0.001$), whereas both cardiac index (2.9 ± 0.6 $min^{-1} \cdot m^{-2}$ to 2.3 ± 0.5 $L \cdot min^{-1} \cdot m^{-2}$) and global end-diastolic volume index decreased (650 ± 98 $mL \cdot m^{-2}$ to 565 ± 98 $mL \cdot m^{-2}$, both $P < 0.025$). Left ventricular end-diastolic area index, however, did not change significantly. Then, after fluid loading both pulse pressure variation (to 5.4 ± 2.1%) and stroke volume variation (to 6.8 ± 2.2%, both $P < 0.001$) decreased significantly, while both cardiac index to 3.3 ± 0.5 $L \cdot min^{-1} \cdot m^{-2}$, $P < 0.001$) and global end-diastolic volume index increased significantly (to 663 ± 104 $mL \cdot m^{-2}$, $P < 0.005$). Again, left ventricular end-diastolic area index did not change significantly. Importantly, they found a significant correlation between the increase in cardiac index caused by fluid loading and both pulse pressure variation ($R = 0.61$) and stroke volume variation ($R = 0.74$, $P < 0.005$ both). Furthermore, to underscore the concept that preload is not preload responsiveness, they also found no correlations between values of global end-diastolic volume index or left ventricular end-diastolic area index before fluid loading and the increase in cardiac index. Although one may have predicted that following open-chest and open-pericardium conditions, heart–lung interactions would be greatly minimized, these authors showed that as long as the pleural spaces are not violated, a clinically relevant degree of heart–lung interactions persists to allow prediction of preload responsiveness.

### Esophageal Doppler monitoring of aortic flow variation

Can one do without the central venous and femoral arterial catheters necessary to make these measures, however? Echocardiography is a minimally invasive (transesophageal) to noninvasive (transthoracic) technique that may permit bypassing of the need for invasive monitoring. Recent training by intensivists in this technique has resulted in its taking a greater role in bedside diagnostic approaches [13]. Vieillard-Baron *et al.* [14] measured superior vena caval collapse using transesophageal echocardiography in 66 ventilated septic patients before and after volume challenge. A superior vena caval collapsibility of greater than 36% predicted an increase in cardiac output of at least 11% with 90% sensitivity and 100% specificity. Furthermore, this same group [15•] measured inferior vena caval collapse using transthoracic echocardiography in 23 ventilated septic patients before and after an intravascular volume challenge. The found that an inferior vena caval collapsibility of more than 18% predicted an increase in cardiac output of at least 15% with a 90% sensitivity and specificity. Regrettably, as summarized by Pinsky [16••], these echocardiographic measures carry the same limitations as do arterial pressure variation parameters, namely a dependence of the level of tidal volume and its regularity without spontaneous ventilatory efforts, the separation of preload responsiveness from the need for fluid resuscitation, and the need for an expert operator to make these echocardiographic measures. Still, with the greater use of bedside echocardiographic imaging by intensivists, this latter limitation may be minimized.

Still, echocardiography requires the constant presence of the operator at the bedside, whereas other techniques, used as pulmonary arterial catheterization, do not. Thus, the use of an esophageal Doppler probe that does not require continued expert attendance to acquire continuous hemodynamic data is highly attractive. In this regard, an esophageal Doppler technique, wherein an esophageal probe is positioned in the esophagus to measure descending aortic flow velocity, has great potential. Dark and Singer [17] performed a systematic search of the relevant international literature on this approach, finding 21 studies encompassing 314 patients including 2400 paired measurements of cardiac output by thermodilution and esophageal Doppler monitoring. Although esophageal Doppler monitoring does not measure absolute cardiac

output, the changes in descending aortic flow velocity closely followed changes in cardiac output measured by thermodilution, with a pooled mean bias for thermodilution to Doppler monitoring of 0.19 L/min (range −0.69–2.00 L/min), whereas the pooled mean percentage of clinical agreement between the two measures was 52% for absolute cardiac output and 86% for changes in cardiac output. Since changing cardiac output is probably more important to know than absolute cardiac output values, these findings suggest that esophageal Doppler monitoring may become a major factor in future resuscitation protocols. In fact, McKendry *et al.* [18••] used esophageal Doppler monitoring to assess optimal fluid resuscitation, stopping further fluid resuscitation when aortic flow velocity no longer increased in response to bolus volume challenges. They studied 174 post–cardiac surgery patients randomly assigned to conventional hemodynamic management or to an algorithm guided by esophageal Doppler monitoring to maintain a stroke index of greater than 35 mL/m$^2$. Their protocolized group had fewer postoperative complications (17 *vs* 26, $P = 0.08$), reduced median hospital length of stay from 9 to 7 days, and the usage of intensive care beds was reduced by 23% (−8–59%). This impressive nurse-delivered protocol documents not only that esophageal Doppler monitoring may improve outcome but also that protocolized care based on such measures is a central part of the improvement process. The significance of protocol was underscored by a report by Marr *et al.* [19], who retrospectively analyzed their intensive care unit outcome data from patients in circulatory shock not initially responsive to fluid resuscitation. Such patients then get increased volume challenges until their PPAO is greater than 20 mm Hg. Such patients tended to be older (44 *vs* 34 years of age), and this resulted in an increase in PPAO from 18 ± 1 mm Hg to a maximum of 25 ± 2 mm Hg and cardiac index to increase from 3.2 ± 0.1 L/min · m$^{-2}$ to 4.5 ± 0.4 L/min · m$^{-2}$, with a resultant increase in pulmonary admixture (shunt) and peripheral edema. Thus, aggressive resuscitation, even if based on reasonable physiologic principles, if taken to extremes may have detrimental effects.

## Conclusion

The recent past has witnessed a rapid introduction of novel methods of analysis of established monitoring techniques, such as CVP and arterial pressure monitoring, applied in proactive fashion by noting their behavior in response to positive-pressure ventilation. Furthermore, we are witnessing increasing sophistication of novel and evolving monitoring techniques that bypass more invasive routes and use either the central venous or peripheral venous route, arterial catheterization, and esophageal Doppler monitors. The stage was thus set to use these techniques to drive resuscitation in a defined treatment algorithm and note improved outcome. The first of what we hope will be many such studies has now been published and documents some of the profound utility that these functional applications of hemodynamic monitoring enjoy.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest


**1** Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest 2002; 121:2000–2008.

**2** •• Kumar A, Anel R, Bunnell E, *et al.* Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. Crit Care Med 2004; 32:691–699.

Nice clinical study demonstrating the inability of CVP, pulmonary artery occlusion pressure, and their changes to predict preload responsiveness or reflect end-diastolic volume or its change in response to volume loading. Traditional bedside measures of both CVP and pulmonary artery occlusion pressures should not be used as preload indices to drive resuscitation protocols.

**3** • Bouchard MJ, Denault A, Couture P, *et al.* Poor correlation between hemodynamic and echocardiographic indexes of left ventricular performance in the operating room and intensive care unit. Crit Care Med 2004; 32:644–648.

Nice clinical study comparing stroke work measured by pulmonary arterial catheterization with fractional area of contraction, measured by echocardiography, clearly documenting that derived and indirect measures of left ventricular performance may not covary with directly measured left ventricular performance in cardiac surgery patients, especially if right ventricular performance is impaired.

**4** • Dellinger RP, Carlet JM, Masur H, *et al.* for the Surviving Sepsis Campaign Management Guidelines Committee. Surviving Sepsis Campaign Guidelines for management of severe sepsis and septic shock. Crit Care Med 2004; 32:858–873.

This critical review of the literature attempts to review the relevant data defining improved outcome from septic shock and presents evidence-based recommendations for management. Although excluding the data supporting selective decontamination of the digestive tract and recommending early goal-directed therapy as an intensive care unit centered option, though only studied in emergency department patients, this landmark paper does develop a rational and reasonable approach to the overall management of the critically ill patient.

**5** • Reinhart K, Kuhn HJ, Hartog C, *et al.* Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. Intensive Care Med 2004; 30:1572–1578.

Extensive observational study comparing $SvO_2$ with $ScvO_2$ in a mix of critically ill patients monitored continuously for more than 1000 hours, documenting the differences between these two measures and the degree to which $ScvO_2$ can be substituted for $SvO_2$. These sensitivity data should be applied in any future study using threshold values of $ScvO_2$to drive resuscitation protocols.

**6** Combes A, Berneau JB, Luyt CE, *et al.* Estimation of left ventricular systolic function by single transpulmonary thermodilution. Intensive Care Med 2004; 30:1377–1383.

**7** Desjardins R, Denault AY, Belisle S, *et al.* Can peripheral venous pressure be interchangeable with central venous pressure in patients undergoing cardiac surgery? Intensive Care Med 2004; 30:627–632.

**8** Staal EM, Baan J, Jukema JW, *et al.* Transcardiac conductance for continuous measurement of left ventricular volume: validation vs. angiography in patients. Intensive Care Med 2004; 30:1370–1376.

**9** Gabbanelli V, Pantanetti S, Donati A, *et al.* Initial distribution volume of glucose as noninvasive indicator of cardiac preload: comparison with intrathoracic blood volume. Intensive Care Med 2004; 30:2067–2073.

**10** Marx G, Cope T, McCrossan L, *et al.* Assessing fluid responsiveness by stroke volume variation in mechanically ventilated patients with severe sepsis. Eur J Anaesthesiol 2004; 21:132–138.

**11** Rex S, Brose S, Metzelder S, *et al.* Prediction of fluid responsiveness in patients during cardiac surgery. Br J Anaesth 2004; 93:782–788.

**12** • Reuter DA, Goepfert MS, Goresch T, *et al.* Assessing fluid responsiveness during open chest conditions. Br J Anaesth 2005; 94:318–323.

Concise clinical trial documenting that both fluid removal and volume resuscitation effects on cardiac output can be monitored by parallel changes in stroke volume and arterial pulse pressure variation during positive-pressure ventilation even following a midline sternotomy and opening of the pericardium.

**13** Jardin F. Ventricular interdependence: how does it impact on hemodynamic evaluation in clinical practice? Intensive Care Med 2003; 29:361–363.

**14** Vieillard-Baron A, Chergui K, Rabiller A, *et al.* Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients. Intensive Care Med 2004; 30:1734–1739.

**15** • Barbier C, Loubieres Y, Schmit C, *et al.* Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. Intensive Care Med 2004; 30:1740–1746.
Nice observational study of the correlation between respiration-induced changes in inferior vena caval diameter and the subsequent change in cardiac output following a fluid challenge. These data clearly document that variations in venous return define the pulse pressure variation used to define preload responsiveness.

**16** •• Pinsky MR. Using ventilation-induced aortic pressure and flow variation to diagnose preload responsiveness [editorial]. Intensive Care Med 2004; 30:1008–1010.
An editorial that addresses the fundamental issues in functional hemodynamic monitoring and presents all the interacting factors clearly and concisely. Good summary of the philosophy behind assessing preload responsiveness and its clinical utility.

**17** Dark PM, Singer M. The validity of trans-esophageal Doppler ultrasonography as a measure of cardiac output in critically ill adults. Intensive Care Med 2004; 30:2060–2066.

**18** •• McKendry M, McGloin H, Saberi D, *et al.* Randomised controlled trial assessing the impact of a nurse delivered, flow monitored protocol for optimisation of circulatory status after cardiac surgery. BMJ 2004; 329:258–265.
The first of what we hope will be many studies documenting that using a nurse-run flow optimization algorithm to drive fluid therapy, selective patients known to require fluid resuscitation could have their overall outcomes improved. This study demonstrates the profound utility of functional hemodynamic monitoring and the need to couple any monitoring data to a treatment protocol to realize improved outcomes.

**19** Marr AB, Moore FA, Sailors RM, *et al.* Preload optimization using 'Starling curve' generation during shock resuscitation: can it be done? Shock 2004; 21:300–305.