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## Fluid Therapy in Resuscitated Sepsis\*

### Less Is More

Lakshmi Durairaj, MD; and Gregory A. Schmidt, MD, FCCP

**Fluid infusion may be lifesaving in patients with severe sepsis, especially in the earliest phases of treatment. Following initial resuscitation, however, fluid boluses often fail to augment perfusion and may be harmful. In this review, we seek to compare and contrast the impact of fluids in early and later sepsis; show that much fluid therapy is clinically ineffective in patients with severe sepsis; explore the detrimental aspects of excessive volume infusion; examine how clinicians assess the intravascular volume state; appraise the potential for dynamic indexes to predict fluid responsiveness; and recommend a clinical approach.** (CHEST 2008; 133:252–263)

**Key words:** fluids; fluid responsiveness; preload resuscitation; sepsis

**Abbreviations:** CVP = central venous pressure; EGDT = early goal-directed therapy; FACTT = Fluid and Catheter Treatment Trial; GEDV = global end-diastolic volume; LVEDV = left ventricular end-diastolic volume; MAP = mean arterial pressure; PAC = pulmonary artery catheter; PAOP = pulmonary artery occlusion pressure; PEEP = positive end-expiratory pressure; PLR = passive leg raising; PPV = pulse pressure variation; Pra = right atrial pressure; RVEDV = right ventricular end-diastolic volume; ScvO<sub>2</sub> = central venous oxyhemoglobin saturation; SPV = systolic pressure variation; SvO<sub>2</sub> = mixed venous oxyhemoglobin saturation; TEE = transesophageal echocardiography

“O Lord, methought what pain it was to drown,  
what dreadful noise of waters in my ears!  
What sights of ugly death within my eyes!”

Clarence, in Shakespeare’s Richard III, act 1, scene 4, l. 21–3

#### FLUIDS IN EARLY SEVERE SEPSIS

In the first hours of severe sepsis, venodilation, transudation of fluid from the vascular space into

tissues, reduced oral intake, and heightened insensible loss combine to produce hypovolemia. Along with ventricular dysfunction, arteriolar dilation, and vascular obstruction, volume depletion contributes to impaired global perfusion, threatening the function of critical organs. Treating hypovolemia is a central tenet of early management of severe sepsis<sup>1</sup>: fluid should be infused to raise the intravascular volume, augment tissue perfusion, stave off organ failure, and enhance survival.

A study of sepsis resuscitation emphasizes the pivotal role of early and aggressive fluid therapy. Subjects presenting with severe sepsis or septic shock were randomized to 6 h of “standard therapy” guided by central venous pressure (CVP) [ $\geq 8$  to 12 mm Hg] and mean arterial pressure (MAP) [ $\geq 65$  mm Hg], or to 6 h of early goal-directed therapy (EGDT) guided also by central venous oxyhemoglobin saturation (ScvO<sub>2</sub>) [ $\geq 70\%$ ].<sup>2</sup> By targeting resuscitation to ScvO<sub>2</sub>, rather than simply to the conventional hemodynamic indexes, the EGDT subjects were administered more fluid in the first 6 h ( $4,981 \pm 2,984$  mL vs  $3,499 \pm 2,438$  mL;  $p < 0.001$ ), as well as more dobutamine and packed RBC transfusion. Standard treatment (relying on CVP and MAP) was clearly inferior, leading to more persis-

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tent lactic acidosis, greater organ dysfunction, and higher in-hospital mortality (46.5% vs 30.5%).<sup>2</sup>

This study has changed practice in many emergency departments, where there is greater emphasis on recognizing sepsis early, measuring  $ScvO_2$ , and resuscitating urgently.<sup>3,4</sup> It is far less clear how these results should inform ICU practice, however. First, the hemodynamic state of subjects in the EGDT trial differed dramatically from that of the typical ICU patient with severe sepsis. Most notably, subjects presenting to the emergency department had a mean  $ScvO_2$  of 49%, a value indicating a gross deficit of oxygen transport in relation to demand and far lower than the usual septic ICU patient (in whom the  $ScvO_2$  is usually  $> 65\%$  and often  $\geq 80\%$ ).<sup>5,6</sup> Second, time may be an important factor. The EGDT protocol was terminated after 6 h of severe sepsis, following which subjects were managed by clinicians blinded to the study group assignment. Thus, any impact of EGDT derives from this 6 h of treatment, not later ICU care. In a metaanalysis<sup>7</sup> of studies of hemodynamic optimization in critically ill subjects, most studies with early interventions (defined as before the occurrence of organ failure, within 24 h of trauma or within 12 h after surgery) showed lower mortality rates. In contrast, targeting supranormal cardiac index and oxygen delivery later conferred no benefit whatsoever.<sup>8–10</sup> In the largest of these trials with negative findings, Gattinoni and colleagues<sup>10</sup> randomized 762 subjects to three goal-directed arms: normal cardiac index, supranormal cardiac index, or mixed venous oxyhemoglobin saturation ( $SvO_2$ )  $\geq 70\%$ . There was no difference in morbidity or mortality between any of the treatment groups. Since the target in both the Gattinoni et al<sup>10</sup> trial and the EGDT trial of goal-directed hemodynamic therapy was nearly equivalent ( $ScvO_2$  is quite similar, although not identical, to  $SvO_2$ ), the disparate results are intriguing. Several key differences between these studies may explain their results (*eg*, the EGDT study enrolled only septic subjects, whereas the earlier trial included other subsets of critical illness), but the element of time (and the difference in initial hemodynamic state) stands out as a biologically plausible hypothesis. The point to emphasize is that what is beneficial early (more fluids) is not necessarily beneficial later in the course of critical illness.

#### FLUIDS IN RESUSCITATED SEPSIS

Initial resuscitation transforms a hypovolemic, hypodynamic circulation into one where oxygen transport is normal or high, at least at the whole-body level, in most septic adults.<sup>2,11</sup> In contrast to the average patient entering the EGDT trial, once fluids,

antimicrobials, vasoactive drugs, and perhaps blood have been administered, these resuscitated patients usually display elevated CVP, cardiac output, and  $SvO_2$ . There is no longer global hypoperfusion as judged by any measure of oxygen transport, even when hypotension, lactic acidosis, and organ dysfunction persist. Nevertheless, the circulation remains grossly impaired, and MAP rarely is restored to normal. Indeed, persistent hypotension and progressive organ failures often prompt further fluid administration. It is this state of “resuscitated sepsis” that we emphasize here.

This clinical scenario (severe sepsis following initial resuscitation, but with persistent hypotension, oliguria, or other potential marker of incomplete fluid therapy) occurs daily in any busy ICU. When given additional fluid, some patients will respond: BP, cardiac output, oxygen delivery,  $ScvO_2$ , or urine output increases. Other patients will not: hemodynamics fail to improve and the fluid bolus is ineffective, at best. Moreover, ineffective fluid challenges often lead to additional boluses, culminating in a grossly edematous patient (still hypotensive and oliguric). How can we ensure sufficient volume resuscitation of those who will benefit, while limiting potential harm in those who will not? How to manage fluids in such a patient is an everyday problem that has been little studied and is probably little informed by studies of unresuscitated patients in their first 6 h. This important clinical dilemma was described recently as “a real challenge.”<sup>12</sup>

#### FLUIDS MAY BE HARMFUL IN CRITICAL ILLNESS

Fluid infused into the vascular space ultimately equilibrates with other fluid compartments. Unnecessary fluid (*ie*, fluid that does not enhance perfusion) will cause or exacerbate edema in lungs, heart, gut, skin, brain, and other tissues. At times, this creates clinically obvious organ failure, such as respiratory failure, abdominal compartment syndrome,<sup>13,14</sup> or cerebral edema and herniation. Further, there is some evidence that excess fluid can be harmful by more subtle means. Multiple studies have correlated positive fluid balance with reduced survival in ARDS<sup>15,16</sup> or sepsis.<sup>17</sup> In a study<sup>18</sup> of critically ill patients (45% of whom had sepsis) a pulmonary artery catheter (PAC) was compared with pulse contour analysis for hemodynamic monitoring. While the monitoring technique had no effect on several outcomes, a secondary logistic regression analysis identified positive fluid balance as a significant predictor of mortality (odds ratio, 1.0002 for each milliliter per day,  $p = 0.0073$ ). Positive fluid balance may also impede liberation from mechanical ventilation. In a study<sup>19</sup> of 87 patients receiving venti-

lation, both cumulative and short-term positive fluid balance were associated with failure of a spontaneous breathing trial. Negative fluid balance was as predictive of weaning outcomes as the rapid shallow breathing index. This association has also been noted in critically ill surgical patients.<sup>20</sup> It is of some interest that, in the trial<sup>2</sup> of EGD<sub>T</sub>, those randomized to resuscitation guided by the ScvO<sub>2</sub> (who had improved survival) received significantly less fluid between 6 h and 72 h, whereas they had been given more fluid between 0 h and 6 h.

These retrospective or uncontrolled analyses leave open the question as to whether positive fluid balance contributed to death or was merely a marker of severity of illness. We believe that further controlled study is warranted. In a prospective perioperative trial<sup>21</sup> (elective colorectal surgery), fluid restriction improved outcome. Subjects were randomized to typical intraoperative fluids, including preloading, maintenance fluids, and replacement of blood and third-space losses, or to restrictive fluids (no preload or third-space replacement, less blood replacement). The restrictive approach reduced minor, major, cardiopulmonary, and tissue-healing complications. Two prospective trials<sup>22,23</sup> in subjects with ARDS have shown that diuresis improves outcome, including time on the ventilator and ICU length of stay. The second of these trials, the Fluid and Catheter Treatment Trial (FACTT),<sup>23</sup> randomized 1,001 subjects with acute lung injury<sup>24</sup> or ARDS to conservative (CVP < 4 or pulmonary artery occlusion pressure [PAOP] < 8 mm Hg) vs liberal (CVP, 10 to 14 mm Hg; or PAOP, 14 to 18 mm Hg) fluid management. Care was taken to ensure validity of the hemodynamic measurements, while ventilator management and weaning were controlled by protocol. Although there was no difference in 60-day mortality (the primary outcome), the conservative fluid strategy improved lung function, increased ventilator-free days, and reduced ICU length of stay.<sup>23</sup> Of course, all of these subjects had pulmonary edema, a condition expected to respond to diuresis, and only some of them had severe sepsis. Moreover, active fluid management was only performed when subjects were hemodynamically stable. Nevertheless, since many patients with sepsis have acute lung injury, it is likely that more fluid leads to more lung edema.

#### USUAL ICU CARE LEADS TO FLUID OVERLOAD

Critically ill septic patients are often receiving nutrition, sedatives, analgesics, antimicrobials, vasoactive drugs, insulin infusions, and agents to reduce the risk of gastric hemorrhage, all of which contribute to fluid intake. Some ICUs still encourage

“maintenance” fluids, an approach that compounds the problem of fluid overload. What is surprising is the amount of fluid comprised by all of these treatments. For example, in a study<sup>25</sup> comparing midazolam to lorazepam for ICU sedation, the mean daily volume attributed just to the sedative was between 1.2 L and 1.3 L. One subject was administered 3.6 L/d at peak sedative infusion. In the conservative arm of the FACTT<sup>23</sup> (which did not allow maintenance fluids and otherwise sought to restrict volume), subjects nevertheless were exposed to a mean daily volume of 3.5 L over the first week of study. The liberal fluid arm subjects received > 4 L/d. The consequence of this was a 7-day net negative fluid balance in the conservative arm (− 136 mL), compared to a positive fluid balance of 7 L in the liberal arm.

It is important to emphasize that the conservative arm, performed through fluid restriction and aggressive diuretic therapy, was safe. The oft-stated quandary to “save the kidney or save the lungs” turned out to be a false dilemma. For example, the conservative arm did not compromise the circulation, there being no fewer cardiovascular failure-free days (19.0 days vs 19.1 days;  $p = 0.85$ ).<sup>23</sup> Further, although BUN and creatinine values were somewhat higher (statistically significant only for BUN) in the conservative arm, there was no difference in the incidence of renal failure (10% vs 14%;  $p = 0.06$  in favor of the conservative arm).<sup>23</sup> Because metabolic abnormalities were more common in the conservative arm, care should be taken to monitor serum electrolytes, especially potassium concentration.

Following the FACTT,<sup>23</sup> fluid balance in the earlier ARDS Network trials was examined and found to be essentially superimposable on the liberal arm of the FACTT. Since fluid therapy was uncontrolled in these earlier studies, the liberal arm seems to represent “usual management,” at least for patients with acute lung injury or ARDS treated at very good academic centers. Thus routine critical care is associated with large fluid loads and a very substantial net positive fluid balance.

#### IMPACT OF A FLUID BOLUS

The most direct means to assess whether additional fluid will raise perfusion is to perform a “fluid challenge”: infuse a fluid bolus and measure cardiac output, ScvO<sub>2</sub>, or some other clinically relevant parameter reflecting perfusion (BP reflects poorly whether perfusion truly rises<sup>26</sup>). Fluid challenges are a regular part of ICU management, but there are few data to guide how much of what fluid constitutes an adequate challenge. We will not cover here the



continuing debate regarding whether to prefer crystalloid or colloid for fluid management in the ICU, except to comment that neither seems clearly superior on an efficacy basis.<sup>1,27</sup> Whichever is given, the impact is often underwhelming. In a two-part study,<sup>28</sup> fluid boluses were examined for a period of 1 month in two medical-surgical ICUs. In the course of 470 patient-days, 159 rapid boluses were infused, confirming how common this practice is. The mean infused volume was only 390 mL (median, 500 mL; crystalloid in two thirds of instances). In the second part of this study,<sup>28</sup> 500 mL of saline solution was infused rapidly in 13 subjects (when a fluid bolus was deemed necessary), while hemodynamic parameters were monitored. Although PAOP increased slightly, there was no change in MAP, heart rate, cardiac output, CVP, Svo<sub>2</sub>, pulmonary artery pressure, oxygen delivery, oxygen consumption, or left ventricular end-diastolic area. In three subjects who were oliguric, urine output did not increase. The authors concluded that the hemodynamic effect of a typical fluid bolus was surprisingly small. Similarly modest responses to a fluid bolus have been reported by others.<sup>29,30</sup>

Not only is the average impact of a fluid bolus small, but many patients with resuscitated sepsis simply do not respond. For example, 150 fluid boluses were studied in 96 subjects receiving mechanical ventilation for severe sepsis over a 3-year period.<sup>31</sup> In only 65 instances (43%) did cardiac index rise at least 15%. These results are typical of prospective studies<sup>32–41</sup> of fluid challenge, in which meaningful hemodynamic effects are seen in fewer than half of subjects (Table 1). This means that more than half of the fluid boluses judged to be clinically indicated are actually ineffective and potentially harmful.

#### ASSESSING INTRAVASCULAR VOLUME AND PREDICTING FLUID RESPONSIVENESS

Since fluid challenge fails to help many septic patients and may cause harm, predicting the likelihood of response could be of great clinical value. Historically, clinicians have generally used static hemodynamic values (*eg*, CVP or PAOP) to judge whether fluids are likely to boost the circulation. As discussed below, however, these measures have almost no ability to distinguish fluid responders from nonresponders. Of more current interest are dynamic indexes, such as pulse pressure variation (PPV), because these have much higher positive and negative predictive values (Table 1). We will examine the clinical evidence regarding both static values, such as CVP, and dynamic values, such as the respiratory variation in pulse pressure.

**Table 1—Studies of Fluid Responsiveness in Septic Patients\***

Study	Fluid Challenges, No.	Responders, %	Test Used
Tavernier et al, <sup>33</sup> 1998	35	60	dDown (SPV)
Sakka et al, <sup>35</sup> 1999	57	46	ITBVI
Michard et al, <sup>32</sup> 2000	40	40	PPV
Feissel et al, <sup>34</sup> 2001	19	53	ΔV <sub>peak</sub>
Michard et al, <sup>36</sup> 2003	66	48	GEDVI
Feissel et al, <sup>37</sup> 2004	39	41	ΔIVC
Vieillard-Baron et al, <sup>39</sup> 2004	66	30	SVC collapsibility
Barbier et al, <sup>40</sup> 2004	20	50	ΔIVC
Perner and Faber, <sup>41</sup> 2006	30	47	SVV
Feissel et al, <sup>38</sup> 2007	28	64	ΔP <sub>plet</sub>
Osman et al, <sup>31</sup> 2007	150	43	CVP/PAOP

\*dDown = fall in systolic pressure compared with end-expiratory baseline; ITBVI = intrathoracic blood volume index; ΔV<sub>peak</sub> = variation in aortic peak flow velocity; GEDVI = global end-diastolic volume index; ΔIVC = inferior vena cava collapsibility; SVC = superior vena cava; SVV = stroke volume variation; ΔP<sub>plet</sub> = plethysmographic pulse wave variation.

#### STATIC MEASURES TO PREDICT FLUID RESPONSIVENESS

##### *CVP or Right Atrial Pressure*

CVP is probably the most used parameter for judging whether fluids should be administered.<sup>2,26</sup> Nevertheless, a large number of studies<sup>26,32,42–44</sup> show that CVP fails to discriminate responders from nonresponders. When CVP is significantly elevated (> 10 mm Hg), fluids are generally quite unlikely to raise perfusion,<sup>26</sup> but there are occasional exceptions. Moreover, these studies have generally failed to consider carefully the effect of mechanical ventilation or high levels of positive end-expiratory pressure (PEEP) in terms of a threshold value for CVP that predicts little likelihood of response.

Following the EGDT trial and publication of the Surviving Sepsis Campaign guidelines<sup>1</sup> (which propose a CVP target > 8 mm Hg for patients not receiving ventilation and ≥ 12 mm Hg for patients receiving ventilation), a group of French investigators<sup>31</sup> examined the role of cardiac filling pressures as predictors of fluid responsiveness in 96 septic subjects receiving ventilation. Overall, the predictive

power of the CVP was poor: when CVP was  $< 12$  mm Hg, the positive predictive value was only 47%.<sup>31</sup> Even when CVP was much lower in these patients receiving ventilation ( $< 5$  mm Hg), the positive predictive value was still only 47%. The lack of predictive value of the CVP has been so thoroughly documented that we agree with these authors that its use as a target "... for volume resuscitation must be discouraged, at least after the early phase of sepsis ...".<sup>31</sup>

These results should not be surprising. Raising CVP can only augment perfusion when cardiac function is not limited, as can be seen by examining the relationship of CVP to cardiac output (Fig 1). While "low" CVP tends to indicate a point on the steep portion of the cardiac function curve in a population, huge individual variation makes specific values of little use in any specific patient.

### Wedge Pressure or PAOP

Since the original description of the flow-directed balloon catheter by Swan et al<sup>45</sup> in 1970, PACs have been used widely for monitoring critically ill, heart failure, and postoperative patients. Although many clinicians consider the PAOP to be the "gold standard" for determining left ventricular preload (and judging volume status), the correlation of PAOP and left ventricular end-diastolic volume is feeble.<sup>46</sup> Surprisingly, even in normal volunteers, PAOP fails to reflect preload,<sup>42</sup> thought to be due to wide variation in diastolic compliance even in health. More importantly, values of PAOP are no better than those of CVP in predicting the response to fluid challenge.<sup>32,33,43</sup> In septic subjects, PAOP  $< 12$  mm Hg predicts a rise in cardiac output with a positive predictive value of only 54%.<sup>31</sup>

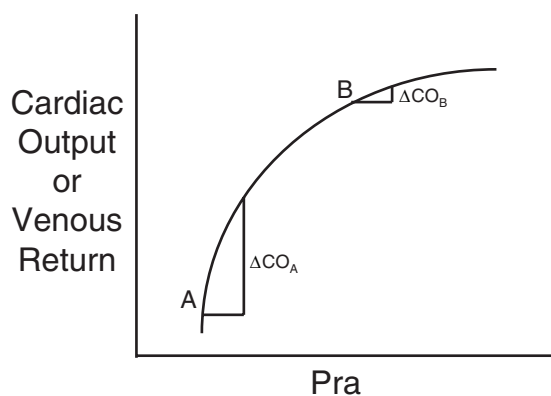


FIGURE 1. Cardiac output (CO) [and, similarly, venous return] depend on  $P_{ra}$ . However, this relationship depends critically on where the heart is operating on its function curve. For example, when the heart is at point A, small increments in  $P_{ra}$  raise cardiac output greatly. In contrast, augmenting  $P_{ra}$  when the heart is at point B has little impact on cardiac output.

Like the CVP, PAOP should not be used to judge the volume state in severe sepsis or to predict the role for further fluid administration. It is possible that combining PAOP with other values calculated from the PAC might guide management, but even adding knowledge of the stroke volume index does not lead to a satisfactory positive predictive value.<sup>31</sup> More obviously, because the PAC measures perfusion, it can serve to detect the response to fluid boluses or other cardiovascular interventions and, in this regard, it could prove useful. However, since the measured cardiac output (or index) fails to integrate the tissue oxygen demand, one would not expect these values to be as useful as  $SvO_2$  (or  $ScvO_2$ ) in judging the adequacy of perfusion or changes in perfusion. Despite continued widespread use, several randomized trials<sup>47–51</sup> have failed to detect any clinically meaningful benefit of the PAC in critically ill, perioperative, or heart failure patients.

### Right Ventricular End-Diastolic Volume Index

Right ventricular end-diastolic volume index (RVEDVI) is calculated from right ventricular ejection fraction measured by thermodilution technique using a modified PAC.<sup>52</sup> Attempts to use this measure of right ventricular preload have yielded conflicting results. Some investigators<sup>43</sup> have reported a correlation between baseline RVEDVI and fluid responsiveness, with a value of  $140 \text{ mL/m}^2$  distinguishing those who will or will not have a positive response to fluid. In contrast, others<sup>44</sup> report a lack of difference in baseline RVEDVI between responders and nonresponders as well as a significant response to fluid challenge in four of nine subjects with a value  $> 138 \text{ mL/m}^2$ . Several studies<sup>53,54</sup> have shown RVEDVI to predict better than PAOP the response to fluid challenge. Further, this parameter correlated better than PAOP with cardiac index at high levels of PEEP.<sup>55</sup>

### Left Ventricular End-Diastolic Area

Transesophageal echocardiography (TEE) has been used in the critical care setting since the early 1990s for evaluation of hemodynamic instability. Left ventricular end-diastolic area (LVEDA) is used to approximate left ventricular end-diastolic volume (by making assumptions regarding ventricular geometry), a surrogate for preload. LVEDA has been studied often in the intraoperative setting.<sup>56–59</sup> However, as with other static measures, LVEDA is an unreliable predictor of volume responsiveness.<sup>33,56,59,60</sup> Compared to the PAC, TEE is less invasive and often requires less time to perform.<sup>61</sup> However, TEE yields information at only a single time point, so that the impact of changing status or therapeutic interventions cannot be ascertained readily.

A single-indicator, transpulmonary thermodilution technique uses injected cold saline solution and a thermistor-tipped arterial catheter to estimate the maximal cardiac (four-chamber) volume, termed *global end-diastolic volume* (GEDV).<sup>62</sup> In a series of septic subjects, GEDV was a modestly accurate predictor of fluid responsiveness (positive predictive value of 0.77 when GEDV was in the lowest tercile; negative predictive value of 0.77 when GEDV was in the highest tercile).<sup>36</sup> The mathematically related intrathoracic blood volume ( $\text{GEDV} \times 1.25$ ), which represents the sum of GEDV and pulmonary blood volume, would be expected to be of similar accuracy.

#### DYNAMIC MEASURES TO PREDICT FLUID RESPONSIVENESS

As confidence in static preload measures has faded over the last 20 years, interest in dynamic predictors has heightened. Rather than relying on fixed hemodynamic values, these measures utilize changes in the mean systemic pressure, which is the intravascular pressure averaged over the entire circulation,<sup>63</sup> or right atrial pressure (Pra) [manipulated during breathing] to infer the position of the heart on the Starling function curve. Since (in steady state) cardiac output equals venous return and, because both are functions of Pra, these curves can be superimposed on the same axes (Fig 2). The point where the

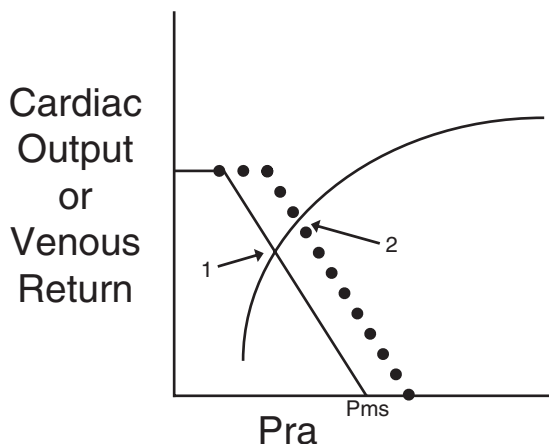


FIGURE 2. Venous return function curve superimposed on the cardiac function curve. For this heart, the current state is described by the intersection point of the cardiac function and venous return function curves (arrow 1). Raising mean systemic pressure (for example, by infusing fluids or raising the legs) shifts the venous return function curve rightwards. The new state (higher Pra and higher cardiac output) is represented by the new intersection point (arrow 2).

two curves intersect describes the current hemodynamic state (*ie*, Pra and cardiac output).

Since pleural pressure surrounds the heart, respiratory effects can be used to shift the cardiac function curve. The Pra of the Starling curve is referenced to atmospheric pressure (which is always constant), yet during spontaneous inspiration, the pressure surrounding the heart (the pleural pressure) falls. This inspiratory fall in pleural pressure raises the transmural Pra, giving the appearance of a leftward shift in cardiac function, moving the point of intersection of cardiac function and venous return. Therefore, spontaneous inspiration will raise (transiently) the cardiac output and lower the Pra if and (this is the key point) only if the heart is operating on the steep portion of its function curve (*ie*, it is responsive to preload augmentation) [compare Fig 3, *top*, *a*, and *bottom*, *b*].

Similarly, passive lung inflation during controlled mechanical ventilation (by tidal inflation or PEEP) shifts the cardiac function curve rightwards (Fig 4).<sup>64</sup> If the heart is preload responsive, this will (transiently) lower cardiac output. This is the major feature that causes pulse pressure, a very good surrogate for stroke volume, to vary cyclically during passive breathing (Fig 5). For respiration to produce measurable changes in stroke volume, the pleural pressure must be sufficiently perturbed. This generally requires that tidal volume be transiently raised, especially in patients receiving ventilation with a lung-protective tidal volume.<sup>65,66</sup>

There are now several studies testing these dynamic predictors, generally using respiration to probe the circulation while gauging the effect by displaying the change in Pra, pulse pressure, echocardiographic vena cava diameter, or Doppler ultrasound arterial blood flow (Table 1). Echocardiographic predictors have been reviewed.<sup>67</sup> Many but not all of these studies have been conducted in septic subjects.

#### Inspiratory Decrement in Pra

In 33 mixed medical and surgical ICU patients, some of whom were receiving mechanical ventilation but actively inspiring (ensured by noting at least a 2 mm Hg inspiratory fall in PAOP), an inspiratory drop in Pra (measured at the base of the “a” wave)  $\geq 1$  mm Hg served to predict responsiveness to an adequate fluid bolus.<sup>68</sup> Cardiac output increased by at least 250 mL/min in 16 of 19 patients with a positive inspiratory response and only 1 of 14 patients with a negative response. The importance of an adequate inspiratory fall in pleural pressure, necessary to shift the cardiac function curve sufficiently, was emphasized by a study of 21 actively inspiring, critically ill patients receiving mechanical

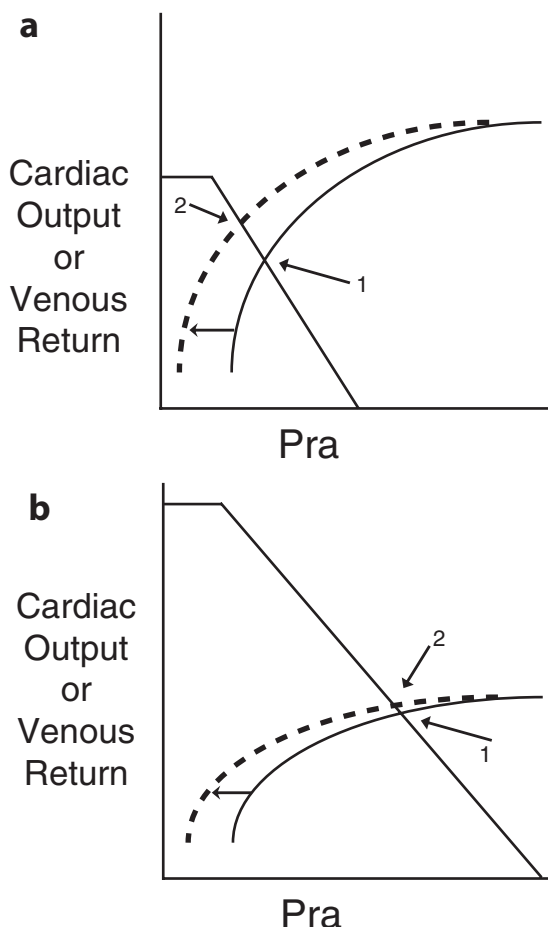


FIGURE 3. The effect of spontaneous breathing is to shift leftwards the cardiac function curve (solid line to dotted line), shifting the intersection point from arrow 1 (end-expiration) to arrow 2 (end-inspiration). When the heart is operating on the steep portion of the cardiac function curve (*top, a*), this leftward shift moves the intersection point significantly (*ie*, Pra falls and cardiac output rises). However, if cardiac function is depressed or the circulation is fluid loaded (*bottom, b*), the respiratory shift (from arrow 1 to arrow 2) has only a trivial impact on Pra and cardiac output.

ventilation. The inspiratory change in Pra did not distinguish fluid responders from nonresponders, perhaps because the ventilatory assistance prevented much fall in pleural pressure.<sup>69</sup>

#### PPV

Cyclic changes in pleural pressure during ventilation induce fluctuations in right-heart filling, pulmonary venous volume, and ventricular afterload. The rise in pleural pressure during inspiration augments left ventricular filling (due, in part, to compression of pulmonary veins and rising left ventricular compliance as the right heart fills less), and simultaneously lowers left ventricular afterload. These factors combine to transiently raise left ventricular stroke vol-

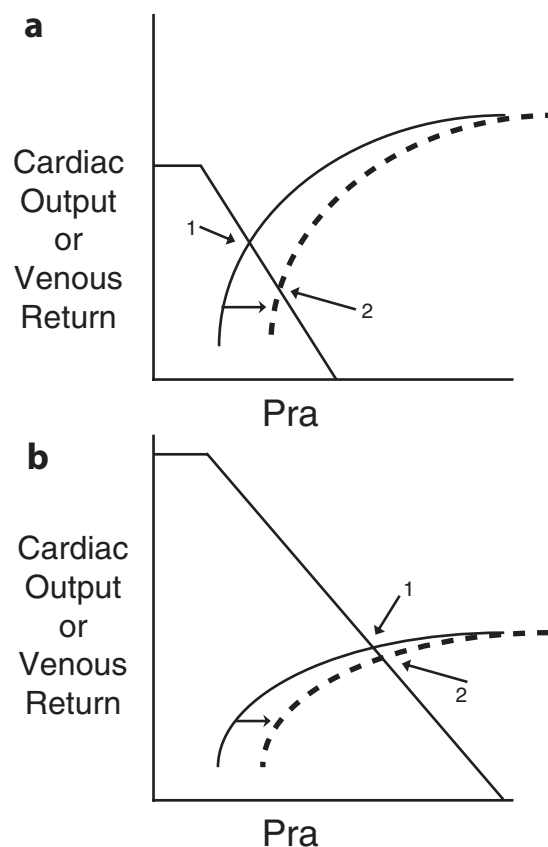


FIGURE 4. Passive ventilation shifts the cardiac function curve rightwards. The solid line represents end-expiration (intersection point 1), and the dotted line end-inspiration (intersection point 2). If the heart is preload responsive (*top, a*), the intersection point shifts and the resulting decrease in cardiac output will reveal itself in changing pulse pressure, stroke volume, and aortic or brachial artery peak flow velocity. If the heart is not preload responsive (*bottom, b*), there will be little respiratory-related decrease in cardiac output (as the intersection point shifts from arrow 1 to arrow 2).

ume and systolic arterial pressure. Also, during inspiration the rise in pleural pressure impedes right-heart filling transiently, the effects of which become evident in the arterial pressure wave several beats later (during expiration) as a fall in systolic pressure (and stroke volume).

Both systolic pressure variation (SPV) and PPV (maximum minus minimum pulse pressure) have proved to be reliable indicators of the response to a volume challenge, not only in sepsis but in other conditions as well. In a dog model of graded hemorrhage, SPV was a sensitive predictor of hypovolemia.<sup>70</sup> In cardiac surgery patients<sup>71</sup> and patients with sepsis,<sup>33</sup> the fall in systolic pressure was superior to LVEDA and other static parameters in predicting fluid responsiveness (a fall of > 5 mm Hg had a positive predictive value of 95% and negative predictive value of 93%).<sup>33</sup> In one of the most influential



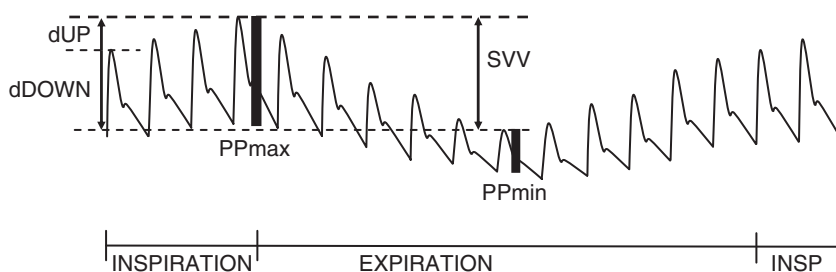


FIGURE 5. Relationship of arterial pressure wave and passive respiration. Compared to end-expiration, the systolic pressure and pulse pressure rise during inspiration (INSP), then fall during expiration. PPmax = maximal pulse pressure; PPmin = minimal pulse pressure.

studies,<sup>32, 40</sup> subjects with sepsis received mechanical ventilation (tidal volumes of 8 to 12 mL/kg), were therapeutically paralyzed, and instrumented with PACs. Four parameters (Pra, PAOP, SPV, and PPV) were judged for their ability to predict the response to a fluid challenge. The areas under the receiver operating characteristic curves for PPV and SPV (0.98 and 0.91, respectively) were outstanding and far superior to those for Pra and PAOP (0.51 and 0.40, respectively). Furthermore, a threshold value for PPV of 13% (calculated as maximum pulse pressure minus minimum pulse pressure divided by the average and converted to percentage) discriminated responders and nonresponders with excellent sensitivity and specificity. These findings seem robust, having been reproduced by several other investigators.<sup>33, 65, 66, 71–73</sup> As indicated above, PPV is only reliable when tidal volume is at least 8 mL/kg<sup>66, 65</sup> and when patients are receiving passive ventilation.<sup>69, 74</sup> Further, the cardiac rhythm must be regular so that pulse pressure does not vary because of irregular filling times.

#### Peak Aortic Blood Flow Velocity Variation

The same cyclic respiratory changes that affect the pulse pressure also impact aortic blood flow velocity. TEE was used to judge aortic flow variability prior to fluid challenge in 19 septic patients receiving ventilation.<sup>34</sup> A prebolus threshold value of 12% discriminated between responders and nonresponders. These results have been validated subsequently, albeit using a somewhat different cutoff (18%) to predict responsiveness, with sensitivity of 90% and specificity of 94%.<sup>75</sup> Accuracy can be improved by measuring (rather than estimating) aortic diameter.<sup>76</sup> Esophageal Doppler ultrasound monitoring is invasive, a limitation that could be sidestepped by monitoring arterial flow variation in other vessels. For example, peak blood flow velocity variation of the brachial artery was shown to correlate well with PPV in subjects receiving passive ventilation.<sup>77</sup> This method has an added advantage of requiring limited ultrasound training.

#### Respiratory Variation in Vena Cava Diameter

During passive mechanical ventilation, inferior vena cava diameter tends to increase during lung inflation (as Pra rises) and tends to decrease during expiration (to the extent that the heart is on the steep portion of the Starling curve). In two separate studies<sup>37, 40</sup> of septic subjects receiving ventilation, variation in vena cava diameter was highly accurate in predicting fluid responsiveness (*eg*, positive and negative predictive values of 93% and 92%, respectively). The threshold values used to distinguish fluid responders from nonresponders were slightly different (18% vs 12%), raising the issue of generalizability of these findings to other ICUs. An interesting corollary finding was that baseline inferior vena cava collapsibility correlated strongly with the magnitude of cardiac output augmentation.<sup>37, 40</sup> Because the superior vena cava is surrounded by pleural, rather than abdominal, pressure, it may be preferable for predicting fluid responsiveness.<sup>67</sup> In one study<sup>39</sup> of patients with sepsis and acute lung injury, a superior vena cava collapsibility index > 36% predicted a significant, fluid-induced rise in cardiac output with a sensitivity of 90% and specificity of 100%.

#### Passive Leg Raising

Passive leg raising (PLR) has been used in several studies as a surrogate for volume challenge due to ease of performance and lack of adverse effects related to volume overload. The largest of these studies<sup>74</sup> enrolled 71 subjects receiving ventilation, some actively breathing and some passive, and showed that a PLR increase of aortic blood flow  $\geq 10\%$  signaled a response to fluids (sensitivity, 97%; specificity, 94%). In subjects receiving passive ventilation with regular cardiac rhythm, PPV  $\geq 12\%$  was of similar value in this cohort, but in those with spontaneous breathing, the specificity of PPV was only 46%.<sup>74</sup> Multiple other studies<sup>78–80</sup> have confirmed that PLR predicts well the response to subsequent volume challenge. A downside of PLR is that it requires some measure of cardiac output

during the maneuver. Studies have generally used Doppler ultrasound techniques, but these may not be readily or widely available.

### A BEDSIDE APPROACH

We summarize here our recommendations for management of fluids in septic patients (Table 2). In the first 6 h of acute resuscitation, fluids should be infused urgently to restore perfusion, guided by the ScvO<sub>2</sub>. Although infusing fluid until the Pra reaches 8 to 12 mm Hg is commonly recommended, the only basis for this is expert opinion.<sup>1,2,81</sup> We are concerned that excessive focus on Pra will lead to underresuscitation or overresuscitation, emphasize again that ScvO<sub>2</sub> should be the target, and recommend that dynamic predictors be used (even at this early time) to gauge the likely impact of fluids.

Once the patient has been resuscitated, fluid infusion should be ceased and no maintenance fluids should be prescribed. The intravascular and total body volume state should be judged periodically (daily in a rather stable patient, more frequently in the newly admitted or unstable patient) using conventional means such as clinical examination, intake and output records, changes in weight, adequacy of urine output and perfusion, and other measures. Generally, such assessment should be followed by diuretic administration because the typical septic patient is hypervolemic. When persistent or recrudescient hypotension, tachycardia, or oliguria raise the question as to whether fluids would be helpful, the intensivist should estimate the probability of harm from a fluid bolus. For many patients, the risks of fluid expansion are trivial and, in such a case, an adequate fluid bolus should be infused rapidly while

measuring clinically relevant outcomes. For others, however, the risks of fluid infusion may be real. Pulmonary or cerebral edema, abdominal compartment syndrome, acute right-heart strain, or oliguria are all conditions that raise the potential risk. Especially when these conditions are present, the clinician should attempt to identify patients unlikely to benefit from fluids, in order to spare them potential harm.

Depending on the monitoring available (arterial line, PAC, ScvO<sub>2</sub>, echocardiography, Doppler ultrasound), one of the dynamic predictors of fluid responsiveness should be used to guide any fluid therapy. Most often this will involve PPV, as described in Table 3. Technology is available to display PPV, but care must be taken that the preconditions for reliable measurement are adhered to (passive patient, tidal volume of 8 to 12 mL/kg, regular rhythm). The patient must be assessed carefully for respiratory activity, taking into account the ventilator pressure and flow waveforms, hemodynamic tracings, and the clinical examination. We recommend that the arterial pressure wave be printed on paper, preferably along with measures of airway pressure or chest volume, for careful assessment and measurement of pulse pressures. Visually and with the aid of a ruler, we find the tallest and shortest pulse waves, ensuring that these represent the typical cyclic pattern in a long strip. Further, it is essential to be certain that the cardiac rhythm remains regular, especially when choosing values of minimum and maximum pulse pressure. We then simply measure the pulse heights in millimeters on a ruler because there is no need to perform the arithmetic in millimeters of mercury. The equation for calculating PPV is provided in Table 3.<sup>32</sup>

If the PPV is > 13%, a fluid bolus should be administered. Some reliable indicator of perfusion should be measured before and after the bolus in order to determine the effect. If the bolus is effective, the patient should be assessed again for fluid responsiveness, and the procedure repeated until dynamic measures predict no further response. If the initial bolus is not effective, the intensivist should ask whether this is because the bolus was inadequate or the patient is simply unresponsive to fluid.

**Table 2—Recommendations for Fluid Management in Severe Sepsis**

For the first 6 h of severe sepsis, infuse fluids liberally, targeting SvO <sub>2</sub> or ScvO <sub>2</sub> > 70%
Subsequently, do not use “maintenance” fluids
Judge the intravascular volume daily (at least)
For new hypotension, tachycardia, or unexplained oliguria, ascertain the cause and consider a fluid challenge:
When fluid challenge is of low risk, administer 500 to 1,000 mL of crystalloid;
When the risk of fluid challenge is not trivial (ALI/ARDS; oliguria; right ventricular dysfunction), use a dynamic predictor to guide fluid boluses
PLR for those with some measure of cardiac output;
PPV for those with regular rhythm and lack of spontaneous breathing;
Change in Pra for those with substantial inspiratory effort
Reassess the patient frequently because the hemodynamic state changes often

**Table 3—How To Measure PPV\***

Check that cardiac rhythm is regular
Raise the tidal volume to 10 mL/kg of predicted body weight
Ensure that the patient is receiving ventilation passively or adjust further the rate, tidal volume, or degree of sedation to achieve this
Display or print the arterial pressure waveform for 30 s
Measure the minimum and maximum pulse pressure
Calculate PPV (PPmax – PPmin)/[(PPmax + PPmin)/2] × 100%
A value ≥ 13% predicts fluid responsiveness

\*See Figure 5 legend for expansion of abbreviations.

## CONCLUSION

After the initial fluid resuscitation, many septic patients who have traditional indications for a fluid challenge will not actually respond. Such fluid challenges may be not only ineffective, but harmful. While further studies should attempt to confirm and quantify this harm, we think that current knowledge is sufficient to change practice safely. We advocate that fluid boluses be considered critically rather than simply being given reflexively. When a patient has indications for a fluid bolus, the potential for harm should be considered and, if there is reasonable potential for harm, a dynamic predictor should be used to limit fluid infusion only to patients who will benefit. We believe there is room for much further study to identify whether this, or some other fluid-restrictive approach, confers improved outcomes in resuscitated septic patients.

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## Fluid Therapy in Resuscitated Sepsis: Less Is More

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