

CHEST[®]

Official publication of the American College of Chest Physicians



Fluid Therapy in Resuscitated Sepsis: Less Is More

Lakshmi Durairaj and Gregory A. Schmidt

Chest 2008;133;252-263
DOI 10.1378/chest.07-1496

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
<http://chestjournal.org/cgi/content/abstract/133/1/252>

CHEST is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright 2007 by the American College of Chest Physicians, 3300 Dundee Road, Northbrook IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder (<http://www.chestjournal.org/misc/reprints.shtml>). ISSN: 0012-3692.

A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

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; LVEDA = left ventricular end-diastolic area; MAP = mean arterial pressure; PAC = pulmonary artery catheter; PAOP = pulmonary artery pressure; PEEP = positive end-expiratory pressure; PLR = passive leg raising; PPV = pulse pressure variation; Pra = right atrial pressure; RVEDVI = right ventricular end-diastolic volume index; ScvO₂ = central venous oxyhemoglobin saturation; SPV = systolic pressure variation; SvO₂ = 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 sepsis¹: 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) [≥ 8 to 12 mm Hg] and mean arterial pressure (MAP) [≥ 65 mm Hg], or to 6 h of early goal-directed therapy (EGDT) guided also by central venous oxyhemoglobin saturation (ScvO₂) [$\geq 70\%$].² By targeting resuscitation to ScvO₂, 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-

*From the Division of Pulmonary Diseases, Critical Care, and Occupational Medicine, University of Iowa Carver College of Medicine, Iowa City, IA.

This work was done at the University of Iowa, Carver College of Medicine.

The authors have no conflicts of interest to disclose.

Manuscript received June 13, 2007; revision accepted August 1, 2007.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml).

Correspondence to: Gregory A. Schmidt, MD, FCCP, Professor of Medicine, Division of Pulmonary Diseases, Critical Care, and Occupational Medicine, University of Iowa Carver College of Medicine, Iowa City, IA 52242; e-mail: gregory-a-schmidt@uiowa.edu

DOI: 10.1378/chest.07-1496

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

This study has changed practice in many emergency departments, where there is greater emphasis on recognizing sepsis early, measuring ScvO₂, and resuscitating urgently.^{3,4} 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 ScvO₂ 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 ScvO₂ is usually > 65% and often ≥ 80%).^{5,6} 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 metaanalysis⁷ 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.^{8–10} In the largest of these trials with negative findings, Gattinoni and colleagues¹⁰ randomized 762 subjects to three goal-directed arms: normal cardiac index, supranormal cardiac index, or mixed venous oxyhemoglobin saturation (SvO₂) ≥ 70%. There was no difference in morbidity or mortality between any of the treatment groups. Since the target in both the Gattinoni et al¹⁰ trial and the EGDT trial of goal-directed hemodynamic therapy was nearly equivalent (ScvO₂ is quite similar, although not identical, to SvO₂), 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.^{2,11} 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 SvO₂. 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, ScvO₂, 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.”¹²

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,^{13,14} 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^{15,16} or sepsis.¹⁷ In a study¹⁸ 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 study¹⁹ 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.²⁰ It is of some interest that, in the trial² of EGD_T, those randomized to resuscitation guided by the ScvO₂ (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 trial²¹ (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^{22,23} 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),²³ randomized 1,001 subjects with acute lung injury²⁴ 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.²³ 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 study²⁵ 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 FACTT²³ (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).²³ 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).²³ Because metabolic abnormalities were more common in the conservative arm, care should be taken to monitor serum electrolytes, especially potassium concentration.

Following the FACTT,²³ 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, ScvO₂, or some other clinically relevant parameter reflecting perfusion (BP reflects poorly whether perfusion truly rises²⁶). 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.^{1,27} Whichever is given, the impact is often underwhelming. In a two-part study,²⁸ 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,²⁸ 500 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, Svo₂, 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.^{29,30}

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.³¹ In only 65 instances (43%) did cardiac index rise at least 15%. These results are typical of prospective studies³²⁻⁴¹ 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, ³³ 1998 | 35 | 60 | dDown (SPV) |
| Sakka et al, ³⁵ 1999 | 57 | 46 | ITBVI |
| Michard et al, ³² 2000 | 40 | 40 | PPV |
| Feissel et al, ³⁴ 2001 | 19 | 53 | ΔV _{peak} |
| Michard et al, ³⁶ 2003 | 66 | 48 | GEDVI |
| Feissel et al, ³⁷ 2004 | 39 | 41 | ΔIVC |
| Vieillard-Baron et al, ³⁹ 2004 | 66 | 30 | SVC collapsibility |
| Barbier et al, ⁴⁰ 2004 | 20 | 50 | ΔIVC |
| Perner and Faber, ⁴¹ 2006 | 30 | 47 | SVV |
| Feissel et al, ³⁸ 2007 | 28 | 64 | ΔP _{plet} |
| Osman et al, ³¹ 2007 | 150 | 43 | CVP/PAOP |

*dDown = fall in systolic pressure compared with end-expiratory baseline; ITBVI = intrathoracic blood volume index; ΔV_{peak} = 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_{plet} = 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.^{2,26} Nevertheless, a large number of studies^{26,32,42-44} 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,²⁶ 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 guidelines¹ (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 investigators³¹ 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%.³¹ 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 . . .”³¹

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 al⁴⁵ 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.⁴⁶ Surprisingly, even in normal volunteers, PAOP fails to reflect preload,⁴² 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.^{32,33,43} In septic subjects, PAOP < 12 mm Hg predicts a rise in cardiac output with a positive predictive value of only 54%.³¹

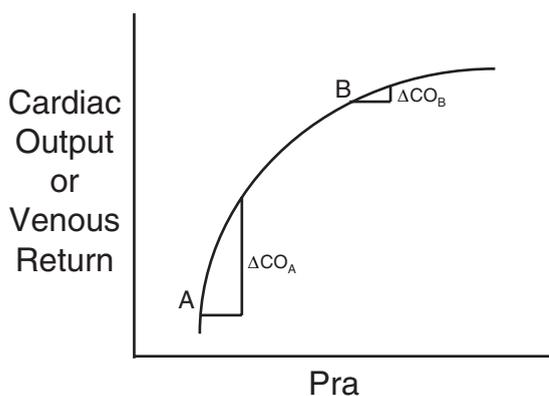


FIGURE 1. Cardiac output (CO) [and, similarly, venous return] depend on Pra. However, this relationship depends critically on where the heart is operating on its function curve. For example, when the heart is at point A, small increments in Pra raise cardiac output greatly. In contrast, augmenting Pra 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.³¹ 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 SvO₂ (or ScvO₂) in judging the adequacy of perfusion or changes in perfusion. Despite continued widespread use, several randomized trials^{47–51} 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.⁵² Attempts to use this measure of right ventricular preload have yielded conflicting results. Some investigators⁴³ have reported a correlation between baseline RVEDVI and fluid responsiveness, with a value of 140 mL/m² distinguishing those who will or will not have a positive response to fluid. In contrast, others⁴⁴ 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 mL/m². Several studies^{53,54} 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.⁵⁵

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.^{56–59} However, as with other static measures, LVEDA is an unreliable predictor of volume responsiveness.^{33,56,59,60} Compared to the PAC, TEE is less invasive and often requires less time to perform.⁶¹ 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).⁶² 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).³⁶ The mathematically related intrathoracic blood volume ($GEDV \times 1.25$), 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,⁶³ 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

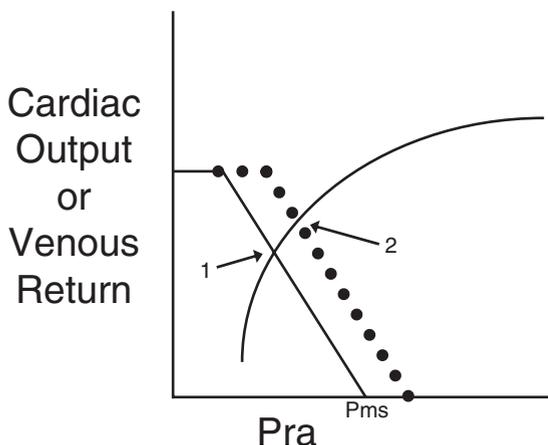


FIGURE 2. Venous return function curve superimposed on the cardiac function curve. For this heart, the current state is described by the intersection point of the cardiac function and venous return function curves (arrow 1). Raising mean systemic pressure (for example, by infusing fluids or raising the 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).⁶⁴ 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.^{65,66}

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.⁶⁷ 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) ≥ 1 mm Hg served to predict responsiveness to an adequate fluid bolus.⁶⁸ 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

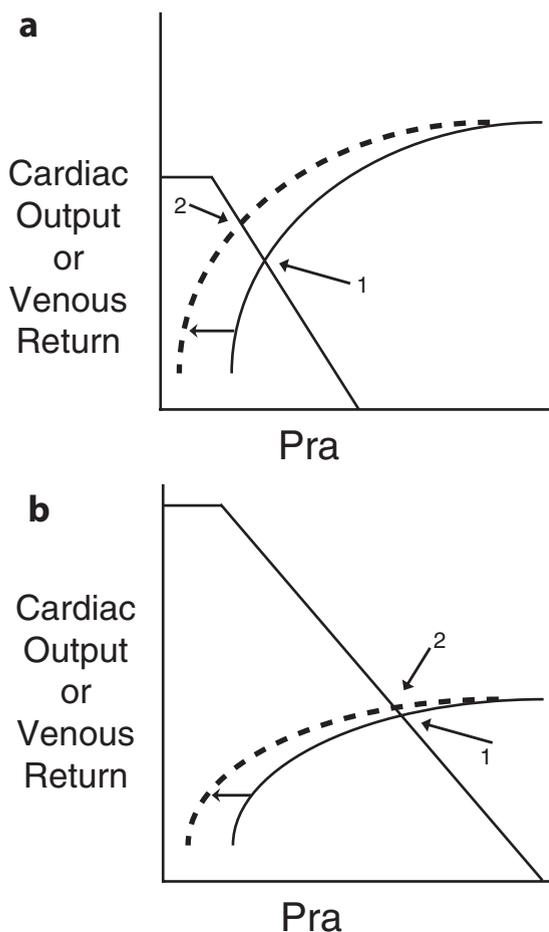


FIGURE 3. The effect of spontaneous breathing is to shift leftwards the cardiac function curve (solid line to dotted line), shifting the intersection point from arrow 1 (end-expiration) to arrow 2 (end-inspiration). When the heart is operating on the steep portion of the cardiac function curve (top, 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.⁶⁹

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-

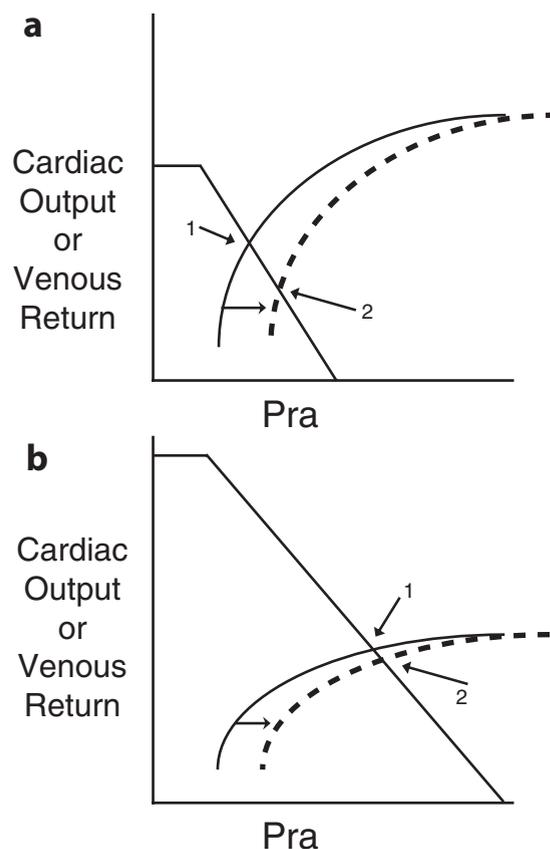


FIGURE 4. Passive ventilation shifts the cardiac function curve rightwards. The solid line represents end-expiration (intersection point 1), and the dotted line end-inspiration (intersection point 2). If the heart is preload responsive (top, a), the intersection point shifts and the resulting decrease 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.⁷⁰ In cardiac surgery patients⁷¹ and patients with sepsis,³³ 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%).³³ In one of the most influential

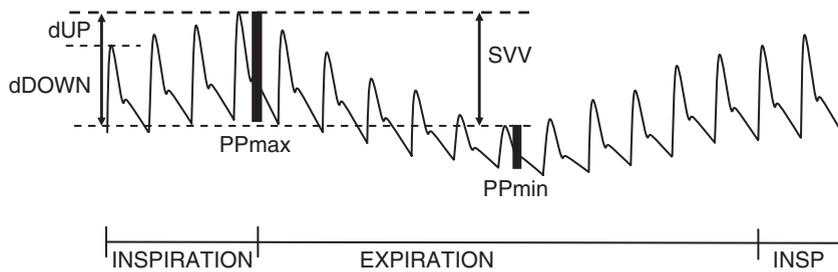


FIGURE 5. Relationship of arterial pressure wave and passive respiration. Compared to end-expiration, the systolic pressure and pulse pressure rise during inspiration (INSP), then fall during expiration. PPmax = maximal pulse pressure; PPmin = minimal pulse pressure.

studies,³² 40 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.^{33,65,66,71–73} As indicated above, PPV is only reliable when tidal volume is at least 8 mL/kg^{66,65} and when patients are receiving passive ventilation.^{69,74} 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.³⁴ 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%.⁷⁵ Accuracy can be improved by measuring (rather than estimating) aortic diameter.⁷⁶ 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.⁷⁷ 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^{37,40} 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.^{37,40} Because the superior vena cava is surrounded by pleural, rather than abdominal, pressure, it may be preferable for predicting fluid responsiveness.⁶⁷ In one study³⁹ 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 studies⁷⁴ 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%.⁷⁴ Multiple other studies^{78–80} 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 ScvO₂. Although infusing fluid until the Pra reaches 8 to 12 mm Hg is commonly recommended, the only basis for this is expert opinion.^{1,2,81} We are concerned that excessive focus on Pra will lead to underresuscitation or overresuscitation, emphasize again that ScvO₂ 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 recrudescing 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

Table 2—Recommendations for Fluid Management in Severe Sepsis

| |
|---|
| For the first 6 h of severe sepsis, infuse fluids liberally, targeting SvO ₂ or ScvO ₂ > 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 |

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, ScvO₂, 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 3.³²

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 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 $(PP_{max} - PP_{min}) / [(PP_{max} + PP_{min}) / 2] \times 100\%$ |
| A value $\geq 13\%$ 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.

REFERENCES

- 1 Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858–873
- 2 Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
- 3 Sivayoham N. Management of severe sepsis and septic shock in the emergency department: a survey of current practice in emergency departments in England. *Emerg Med J* 2007; 24:422
- 4 Nguyen HB, Corbett SW, Menes K, et al. Early goal-directed therapy, corticosteroid, and recombinant human activated protein C for the treatment of severe sepsis and septic shock in the emergency department. *Acad Emerg Med* 2006; 13:109–113
- 5 Chawla LS, Zia H, Gutierrez G, et al. Lack of equivalence between central and mixed venous oxygen saturation. *Chest* 2004; 126:1891–1896
- 6 Turnaoglu S, Tugrul M, Camci E, et al. Clinical applicability of the substitution of mixed venous oxygen saturation with central venous oxygen saturation. *J Cardiothorac Vasc Anesth* 2001; 15:574–579
- 7 Kern JW, Shoemaker WC. Meta-analysis of hemodynamic optimization in high-risk patients. *Crit Care Med* 2002; 30:1686–1692
- 8 Yu M, Levy MM, Smith P, et al. Effect of maximizing oxygen delivery on morbidity and mortality rates in critically ill patients: a prospective, randomized, controlled study. *Crit Care Med* 1993; 21:830–838
- 9 Hayes MA, Timmins AC, Yau EH, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; 330:1717–1722
- 10 Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients: SvO₂ Collaborative Group. *N Engl J Med* 1995; 333:1025–1032
- 11 Hayes MA, Timmins AC, Yau EH, et al. Oxygen transport patterns in patients with sepsis syndrome or septic shock: influence of treatment and relationship to outcome. *Crit Care Med* 1997; 25:926–936
- 12 Parker MM. Goals for fluid resuscitation: a real challenge. *Crit Care Med* 2007; 35:295–296
- 13 Malbrain ML, Chiumello D, Pelosi P, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. *Crit Care Med* 2005; 33:315–322
- 14 McNelis J, Marini CP, Jurkiewicz A, et al. Predictive factors associated with the development of abdominal compartment syndrome in the surgical intensive care unit. *Arch Surg* 2002; 137:133–136
- 15 Humphrey H, Hall J, Sznajder I, et al. Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure. *Chest* 1990; 97:1176–1180
- 16 Simmons RS, Berdine GG, Seidenfeld JJ, et al. Fluid balance and the adult respiratory distress syndrome. *Am Rev Respir Dis* 1987; 135:924–929
- 17 Alsous F, Khamiees M, DeGirolamo A, et al. Negative fluid balance predicts survival in patients with septic shock: a retrospective pilot study. *Chest* 2000; 117:1749–1754
- 18 Uchino S, Bellomo R, Morimatsu H, et al. Pulmonary artery catheter versus pulse contour analysis: a prospective epidemiological study. *Crit Care* 2006; 10:R174
- 19 Upadya A, Tilluckdharry L, Muralidharan V, et al. Fluid balance and weaning outcomes. *Intensive Care Med* 2005; 31:1643–1647
- 20 Epstein CD, Peerless JR. Weaning readiness and fluid balance in older critically ill surgical patients. *Am J Crit Care* 2006; 15:54–64
- 21 Brandstrup B, Tonnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens; a randomized assessor-blinded multicenter trial. *Ann Surg* 2003; 238:641–648
- 22 Mitchell JP, Schuller D, Calandrino FS, et al. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Respir Dis* 1992; 145:990–998
- 23 Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354:2564–2575
- 24 Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149:818–824
- 25 Pohlman AS, Simpson KP, Hall JB. Continuous intravenous infusions of lorazepam versus midazolam for sedation during mechanical ventilatory support: a prospective, randomized study. *Crit Care Med* 1994; 22:1241–1247
- 26 Magder S, Bafaqeeh F. The clinical role of central venous pressure measurements. *J Intensive Care Med* 2007; 22:44–51
- 27 Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350:2247–2256
- 28 Axler O, Tousignant C, Thompson CR, et al. Small hemodynamic effect of typical rapid volume infusions in critically ill patients. *Crit Care Med* 1997; 25:965–970
- 29 Hauser CJ, Shoemaker WC, Turpin I, et al. Oxygen transport responses to colloids and crystalloids in critically ill surgical patients. *Surg Gynecol Obstet* 1980; 150:811–816
- 30 Calvin JE, Driedger AA, Sibbald WJ. The hemodynamic effect of rapid fluid infusion in critically ill patients. *Surgery* 1981; 90:61–76
- 31 Osman D, Ridet C, Ray P, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med* 2007; 35:64–68
- 32 Michard F, Boussat S, Chemla D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med* 2000; 162:134–138

- 33 Tavernier B, Makhotine O, Lebuffe G, et al. Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. *Anesthesiology* 1998; 89:1313–1321
- 34 Feissel M, Michard F, Mangin I, et al. Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. *Chest* 2001; 119:867–873
- 35 Sakka SG, Bredle DL, Reinhart K, et al. Comparison between intrathoracic blood volume and cardiac filling pressures in the early phase of hemodynamic instability of patients with sepsis or septic shock. *J Crit Care* 1999; 14:78–83
- 36 Michard F, Alaya S, Zarka V, et al. Global end-diastolic volume as an indicator of cardiac preload in patients with septic shock. *Chest* 2003; 124:1900–1908
- 37 Feissel M, Michard F, Faller JP, et al. The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. *Intensive Care Med* 2004; 30:1834–1837
- 38 Feissel M, Teboul JL, Merlani P, et al. Plethysmographic dynamic indices predict fluid responsiveness in septic ventilated patients. *Intensive Care Med* 2007; 33:993–999
- 39 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
- 40 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
- 41 Perner A, Faber T. Stroke volume variation does not predict fluid responsiveness in patients with septic shock on pressure support ventilation. *Acta Anaesth Scand* 2006; 50:1068–1073
- 42 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
- 43 Reuse C, Vincent JL, Pinsky MR. Measurements of right ventricular volumes during fluid challenge. *Chest* 1990; 98:1450–1454
- 44 Wagner JG, Leatherman JW. Right ventricular end-diastolic volume as a predictor of the hemodynamic response to a fluid challenge. *Chest* 1998; 113:1048–1054
- 45 Swan HJ, Ganz W, Forrester J, et al. Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. *N Engl J Med* 1970; 283:447–451
- 46 Raper R, Sibbald WJ. Misled by the wedge? The Swan-Ganz catheter and left ventricular preload. *Chest* 1986; 89:427–434
- 47 Harvey S, Young D, Brampton W, et al. Pulmonary artery catheters for adult patients in intensive care. *Cochrane Database Syst Rev* 2006; 3:CD003408
- 48 Shah MR, O'Connor CM, Sopko G, et al. Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE): design and rationale. *Am Heart J* 2001; 141:528–535
- 49 Binanay C, Califf RM, Hasselblad V, et al. Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness: the ESCAPE trial. *JAMA* 2005; 294:1625–1633
- 50 Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003; 348:5–14
- 51 Wheeler AP, Bernard GR, Thompson BT, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 2006; 354:2213–2224
- 52 Vincent JL, Thirion M, Brimiouille S, et al. Thermodilution measurement of right ventricular ejection fraction with a modified pulmonary artery catheter. *Intensive Care Med* 1986; 12:33–38
- 53 Diebel L, Wilson RF, Heins J, et al. End-diastolic volume versus pulmonary artery wedge pressure in evaluating cardiac preload in trauma patients. *J Trauma* 1994; 37:950–955
- 54 Diebel LN, Wilson RF, Tagett MG, et al. End-diastolic volume: a better indicator of preload in the critically ill. *Arch Surg* 1992; 127:817–821
- 55 Cheatham ML, Nelson LD, Chang MC, et al. Right ventricular end-diastolic volume index as a predictor of preload status in patients on positive end-expiratory pressure. *Crit Care Med* 1998; 26:1801–1806
- 56 Tousignant CP, Walsh F, Mazer CD. The use of transesophageal echocardiography for preload assessment in critically ill patients. *Anesth Analg* 2000; 90:351–355
- 57 Thys DM, Hillel Z, Goldman ME, et al. A comparison of hemodynamic indices derived by invasive monitoring and two-dimensional echocardiography. *Anesthesiology* 1987; 67:630–634
- 58 Cheung AT, Savino JS, Weiss SJ, et al. Echocardiographic and hemodynamic indexes of left ventricular preload in patients with normal and abnormal ventricular function. *Anesthesiology* 1994; 81:376–387
- 59 Greim CA, Roewer N, Apfel C, et al. Relation of echocardiographic preload indices to stroke volume in critically ill patients with normal and low cardiac index. *Intensive Care Med* 1997; 23:411–416
- 60 Reuter DA, Felbinger TW, Schmidt C, et al. Stroke volume variations for assessment of cardiac responsiveness to volume loading in mechanically ventilated patients after cardiac surgery. *Intensive Care Med* 2002; 28:392–398
- 61 Kaul S, Stratienko AA, Pollock SG, et al. Value of two-dimensional echocardiography for determining the basis of hemodynamic compromise in critically ill patients: a prospective study. *J Am Soc Echocardiogr* 1994; 7:598–606
- 62 Sakka SG, Ruhl CC, Pfeiffer UJ, et al. Assessment of cardiac preload and extravascular lung water by single transpulmonary thermodilution. *Intensive Care Med* 2000; 26:180–187
- 63 Guyton A, Jones C, Coleman T. *Circulatory physiology: cardiac output and its regulation*. Philadelphia, PA: Saunders, 1973
- 64 Michard F, Chemla D, Richard C, et al. Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP. *Am J Respir Crit Care Med* 1999; 159:935–939
- 65 Reuter DA, Bayerlein J, Goepfert MS, et al. Influence of tidal volume on left ventricular stroke volume variation measured by pulse contour analysis in mechanically ventilated patients. *Intensive Care Med* 2003; 29:476–480
- 66 De Backer D, Heenen S, Piagnerelli M, et al. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* 2005; 31:517–523
- 67 Charron C, Caille V, Jardin F, et al. Echocardiographic measurement of fluid responsiveness. *Curr Opin Crit Care* 2006; 12:249–254
- 68 Magder S, Georgiadis G, Cheong T. Respiratory variations in right atrial pressure predict the response to fluid challenge. *J Crit Care* 1992; 7:76–85
- 69 Heenen S, De Backer D, Vincent JL. How can the response to volume expansion in patients with spontaneous respiratory movements be predicted? *Crit Care* 2006; 10:R102
- 70 Perel A, Pizov R, Cotev S. Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. *Anesthesiology* 1987; 67:498–502
- 71 Preisman S, Kogan S, Berkenstadt H, et al. Predicting fluid responsiveness in patients undergoing cardiac surgery: functional haemodynamic parameters including the respiratory

- systolic variation test and static preload indicators. *Br J Anaesth* 2005; 95:746–755
- 72 Solus-Biguenet H, Fleyfel M, Tavernier B, et al. Non-invasive prediction of fluid responsiveness during major hepatic surgery. *Br J Anaesth* 2006; 97:808–816
- 73 Kramer A, Zygun D, Hawes H, et al. Pulse pressure variation predicts fluid responsiveness following coronary artery bypass surgery. *Chest* 2004; 126:1563–1568
- 74 Monnet X, Rienzo M, Osman D, et al. Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med* 2006; 34:1402–1407
- 75 Monnet X, Rienzo M, Osman D, et al. Esophageal Doppler monitoring predicts fluid responsiveness in critically ill ventilated patients. *Intensive Care Med* 2005; 31:1195–1201
- 76 Monnet X, Chemla D, Osman D, et al. Measuring aortic diameter improves accuracy of esophageal Doppler in assessing fluid responsiveness. *Crit Care Med* 2007; 35: 477–482
- 77 Brennan JM, Blair JE, Hampole C, et al. Radial artery pulse pressure variation correlates with brachial artery peak velocity variation in ventilated subjects when measured by internal medicine residents using hand-carried ultrasound devices. *Chest* 2007; 131:1301–1307
- 78 Maizel J, Airapetian N, Lorne E, et al. Diagnosis of central hypovolemia by using passive leg raising. *Intensive Care Med* 2007
- 79 Lamia B, Ochagavia A, Monnet X, et al. Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity. *Intensive Care Med* 2007
- 80 Lafanechere A, Pene F, Goulenok C, et al. Changes in aortic blood flow induced by passive leg raising predict fluid responsiveness in critically ill patients. *Crit Care* 2006; 10: R132
- 81 Practice parameters for hemodynamic support of sepsis in adult patients with sepsis. *Crit Care Med* 1999; 27:639–660

Fluid Therapy in Resuscitated Sepsis: Less Is More

Lakshmi Durairaj and Gregory A. Schmidt

Chest 2008;133;252-263

DOI 10.1378/chest.07-1496

This information is current as of March 23, 2008

| | |
|---|---|
| Updated Information & Services | Updated information and services, including high-resolution figures, can be found at: http://chestjournal.org/cgi/content/full/133/1/252 |
| References | This article cites 78 articles, 29 of which you can access for free at: http://chestjournal.org/cgi/content/full/133/1/252#BIBL |
| Permissions & Licensing | Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://chestjournal.org/misc/reprints.shtml |
| Reprints | Information about ordering reprints can be found online: http://chestjournal.org/misc/reprints.shtml |
| Email alerting service | Receive free email alerts when new articles cite this article sign up in the box at the top right corner of the online article. |
| Images in PowerPoint format | Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online article figure for directions. |

A M E R I C A N C O L L E G E O F



P H Y S I C I A N S ®