

Fluid challenge revisited

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Explain the signs of hypovolemia.
2. Describe how to administer a fluid challenge.
3. Use this information in a clinical setting.

Both authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

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Objective: To discuss the rationale, technique, and clinical application of the fluid challenge.

Data Source: Relevant literature from MEDLINE and authors' personal databases.

Study Selection: Studies on fluid challenge in the acutely ill.

Data Extraction: Based largely on clinical experience and assessment of the relevant published literature, we propose that the protocol should include four variables, namely 1) the type of fluid administered, 2) the rate of fluid administration, 3) the critical end points, and 4) the safety limits.

Conclusions: A protocol for routine fluid challenge is proposed with defined rules and based on the patient's response to the volumes infused. The technique allows for prompt correction of fluid deficits yet minimizes the risks of fluid overload. (*Crit Care Med* 2006; 34:1333–1337)

KEY WORDS: fluid administration; central venous pressure; resuscitation

Acutely ill patients frequently require fluid repletion. Fluids are primarily administered for reversal of hypovolemia. Hypovolemia may be due to external fluid losses caused by bleeding or losses from the gastrointestinal or urinary tracts, skin surface, or internal losses due to extravasation of blood or exudation or transudation of body fluids. Relative hypovolemia follows increases in venous capacitance due to release of inflammatory mediators as in sepsis or as a side effect of drugs. In these distributive forms of cir-

culatory failure, the intravascular volume may be normal, but the increases in the capacity of the vascular bed preclude adequate venous return. In each instance, volume repletion may be essential to restore critical levels of cardiac output and arterial pressure, resulting in more normal perfusion of vital organs and tissues.

The cause of hypovolemia after exsanguination from hemorrhage due to trauma or acute gastrointestinal bleeding is self-evident. In these settings, however, the benefit/risk of fluid repletion must be assessed, particularly in the light of recently demonstrated benefits of delayed resuscitation (1). Even after large volumes of nonsanguinous fluids have been administered and cardiac filling pressures are increased, red cell deficit precludes reversal of the oxygen deficit. On the other hand, persistent hypovolemia will result in multiple organ dysfunction syn-

drome (2), the end result of critically reduced organ perfusion (3). Moreover, fluid repletion is typically more effective for restoring effective circulation during hypovolemic states (4, 5) but is less effective in later stages (6). A method for guiding volume repletion has been available for >25 yrs based on measurements of the patient's response to a fluid load. We herewith present our viewpoint regarding the current role of what was then termed the "fluid challenge" (7) as a method of assessing response to fluid infusion.

In the Absence of Overt Hypovolemia, Which Patient Is Likely to Respond Favorably to Fluid Administration?

The likelihood that there will be a favorable response to fluid administration is initially estimated on the basis of con-

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Table 1. Clinical and biological factors suggesting that a patient may require fluid administration

Static evaluation
Signs of dehydration
Diminished skin turgor
Thirst
Dry mouth
Dry axillae
Hypernatremia, hyperproteinemia, elevated hemoglobin/hematocrit
Circulatory signs of hypovolemia
Tachycardia
Arterial hypotension (severe cases)
Increased serum lactate (severe cases)
Decreased toe temperature
Decreased renal perfusion
Concentrated urine (low urine sodium concentration, high urine osmolarity)
Increased blood urea nitrogen relative to creatinine concentration
Persistent metabolic alkalosis
Dynamic evaluation
Orthostatic hypotension
Respiratory variations in arterial pressure or stroke volume (during mechanical ventilation, in the absence of ventilatory dyssynchrony or arrhythmias)
Passive leg raising
Positive response to fluid challenge

ventional clinical examination. Nevertheless, the history, physical signs, and routine laboratory tests summarized in Table 1 have limited sensitivity and specificity. Signs of dehydration (diminished skin turgor, thirst, dry mouth, hypernatremia, hyperproteinemia, elevated hemoglobin/hematocrit) are especially misleading. Extravascular volume deficits do not become clinically apparent until they exceed 10% of body weight. Arterial hypotension is a nonspecific sign, which may be due to heart failure, vascular obstruction, as in the instance of a massive pulmonary embolism, or vasodilation quite independent of intravascular volume. Volume deficits are typically compensated for by increases in heart rate, which maintain cardiac output when stroke volumes are reduced. This response is inconsistent, especially in patients with intrinsic heart disease and during treatment with commonly used antiarrhythmic drugs. Stress, pain, fever, anemia, or drugs produce endogenous adrenergic stimulation with compensating increases in heart rate and vasoconstriction, further limiting the value of heart rate and blood pressure for assessing the severity of hypovolemia.

Estimates of intravascular volume based on any given level of filling pressure do not reliably predict a patient's response to fluid administration. Admittedly, reduced filling pressures in the right atrium or pulmonary artery are more likely in settings of hypovolemia, and increased filling pressures are more likely in settings of either right or left heart failure. However, neither is suffi-

ciently reliable for predicting response to a fluid load.

This lack of reliability based on a static measurement led to the concept of measuring changes in pressures after a specified bolus volume of fluid, a more dynamic measure, which had a greater likelihood of unmasking hypovolemia. This dynamic test is easily performed at the bedside. The technique is not unlike that of postural maneuvers for detecting orthostatic hypotension in ambulatory patients.

Various dynamic techniques have been proposed in an effort to unmask hypovolemia or relative hypovolemia. Increased variations in arterial pressure with breathing reflect changes in the stroke volume contingent on the respiratory cycle and may help to predict the response to fluid repletion (8–11). This technique is applicable in mechanically ventilated patients and only during quiet breathing, after patients are sedated and paralyzed. Cardiac arrhythmias also invalidate the method (12). The tidal volume during mechanical ventilation may also influence the response (13). Passive leg raising may also be used to assess the response to a volume load. However, in alert patients, this method induces endogenous adrenergic responses that reduce its reliability.

The technique we propose herein is a provocative test in which fluid is administered over defined intervals and the effect on right-sided filling pressures is quantitated. The concept parallels that of feeding a crying baby who may be thirsty or hungry. The baby's response to feeding

is rapidly apparent as a need is satisfied. This trial therefore represents a test for evaluating the baby's need for fluid and nourishment. In the event that the baby continues to cry, the parent is prompted to search for an alternative explanation for the baby's discomfort. We extend this concept to the initial fluid management of the acutely ill patient who presents with signs of hypoperfusion. When a protocol of fluid repletion fails, other causes are likely, typically with correspondingly more dire prognoses.

Misconceptions

We cite five of the more common misconceptions about fluid administration in the critically ill.

- *Fluid administration should be withheld because the central venous pressure is high.* Unfortunately, the response to fluids is not reliably predicted from any given level of filling pressure (14, 15). Filling pressures may paradoxically decline during volume repletion, presumably as a result of decreased sympathetic stimulation.
- *Fluid administration should be withheld because there is evidence of lung edema on the chest roentgenogram.* Pulmonary edema may represent volume overload but may also be the cause of hypovolemia (16). Accordingly, pulmonary edema is not an absolute contraindication to the administration of fluids. If the radiographic abnormalities are due to acute cardiogenic pulmonary edema, the extravasation of fluid into the interstitium and alveoli of the lung reduces plasma volume and therefore the total blood volume. Graded fluid administration may, in fact, reverse hypovolemia and even hypovolemic shock (16).
- *Fluid administration should be withheld because the patient has already received a large volume in a short time interval.* The question remains as to whether this amount of fluid already given was insufficient or excessive. The patient's objective response to fluid administered over a defined interval, representing the "fluid challenge," rather than the quantity previously administered is likely to resolve this issue.

- *Tachycardia is due to fluid deficit and should prompt increases in fluid administration.* As cited above, tachycardia has diverse causes and does not represent a specific indication for fluid administration. Stress, high environmental temperatures, intrinsic heart disease, and the effects of medications and especially beta-adrenergic agonists may all explain tachycardia. However, if there is a fluid deficit, prompt intervention is appropriate and the fluid challenge is likely to reduce the heart rate.

- *I gave fluids to increase the central venous pressure to 12 mm Hg to exclude an underlying hypovolemia.* Not so! The adequacy of intravascular volume cannot be guided by any one central venous or even pulmonary artery occlusive pressure level. Precision and reliability are limited by variable zero reference, the effects of afterload, and increases in intrathoracic pressure, especially in patients with positive-pressure ventilation. Limitations in the relationships between intravascular volume and filling pressures further underscore that there is no linear relationship between pressure and volume in a vascular bed that can expand or contract its vascular capacitance three-fold. For this reason, intravascular volume may be insufficient or excessive over wide ranges of right heart pressures. If the patient responds without increasing right heart filling pressures during fluid administration, it is appropriate to continue infusion until signs of hypoperfusion are reversed. On the other hand, if there is no increase in arterial pressure and cardiac output with fluid infusion, there is little indication for continued fluid administration. If the central venous pressure alters by as little as 2 mm Hg in response to fluid boluses and remains at or below that level, the course is more favorable.

Each of these issues may be avoided if the clinician's focus is on changes in filling pressures during administration of graded volumes of fluid, especially when there is limited understanding of the volume status and of the underlying cause. Accordingly, we favor protocols in which

the response to fluid administration is routinely measured.

What Is a Fluid Challenge?

A fluid challenge should be distinguished from conventional fluid administration for patients who are not acutely ill, who receive fluids as part of a diagnostic study, or for less acutely ill patients in whom fluid administration can be guided by fluid intake and output recordings. In critically ill or injured patients, the critical issues relating to fluid replacement apply only to patients who demonstrate cardiorespiratory failure. The fluid challenge is, therefore, reserved for hemodynamically unstable patients and offers three major advantages:

1. Quantitation of the cardiovascular response during volume infusion.
2. Prompt correction of fluid deficits.
3. Minimizing the risk of fluid overload and its potentially adverse effects, especially on the lungs.

What Kind of Measurement Does It Suppose?

As already stated, cardiac filling pressures do not always accurately reflect preload. Filling pressures represent the net effect of intravascular volume preload, ventricular compliance, and afterload. The afterload is contingent on vascular resistance. The effects of increases in preload, decreases in ventricular compliance, and increases in afterload in turn determine ventricular diastolic volumes and diastolic (filling) pressures. If the left filling pressures are greatly increased, blood is backed up and the pressures are conducted to the pulmonary capillaries. If pressures are increased in the right heart, peripheral edema and anasarca may be present. To that extent, intracardiac pressures are useful measurements, even though they represent a complex summation of effects. Because the primary purpose of fluid administration is to increase blood flow to vital organs, the intent is to prevent or reduce adverse effects on cardiac function. In accord with the Frank-Starling principle, the effects of fluid infusion on stroke volume usually predominate over increases in filling pressures. However, if filling pressures increase, they may become life threatening, with increases in left ventricular diastolic pressures specifically resulting in acute pulmonary edema. Ac-

cordingly, the clinician's focus should be on the dual end points of filling pressures and forward blood flow (i.e., filling pressures and the combination of stroke volumes and heart rates, representing cardiac output). Closely related are arterial pressure and urine output. Noninvasive estimates of cardiac output are helpful, together with arterial pulse pressures as surrogates for stroke volumes. Peripheral resistance may be estimated. It is important for the clinician to identify the filling pressure levels at which stroke volumes are increased rather than decreased and, yet, vital organ blood flow is preserved, when the fluid challenge can be stopped.

Initial Fluid Challenge Technique

Several decades ago, Weil and Henning (7) proposed the fluid challenge technique, based on the 2–5 rule using central venous pressure and the 3–7 rule for the pulmonary artery occlusion pressure. According to this scheme, the corresponding filling pressure was measured at 10-min intervals. If the change in pulmonary artery occlusion pressure was <3 mm Hg (2 mm Hg for central venous pressure), the infusion was continued, if it was in the 3–7 mm Hg range (2–5 mm Hg for central venous pressure), the infusion was interrupted and reevaluated after a 10-min wait. If the change was an increase of >7 mm Hg (5 mm Hg for central venous pressure), the infusion was stopped.

Although the fluid challenge as initially proposed was widely accepted, it evolved before the availability of continuous measurements with multilumen central venous and pulmonary artery catheters. We now recognize that the protocol may be updated and even simplified; however, the objective rules should be followed. In practice, we have found them to be technically undemanding.

Modified Fluid Challenge Technique

The updated fluid challenge rules incorporate four decision phases:

1. *Type of Fluid.* Crystalloids or colloids can be used, and we defer discussion of the advantages and disadvantages of either type of solution to the extensive literature on this subject (17–19). Colloid molecules are retained within the intravascular compartment for longer intervals than crystalloids. Therefore, fluid challenges with colloids allow for more

Table 2. Critical components of the fluid challenge and one example of their application in a hypothetical patient with arterial hypotension (mean arterial pressure [MAP] of 65 mm Hg) and a central venous pressure (CVP) of 15 mm Hg; two possible types of response are presented

Example	Example 1			Example 2		
	Baseline	+10 mins	+20 mins	Baseline	+10 mins	+20 mins
1. Type of fluid: Ringer's lactate						
2. Rate of infusion: 500 mL/30 mins						
3. Clinical end points: MAP of 75 mm Hg	MAP 65	MAP 70	MAP 75	MAP 65	MAP 67	MAP 60
4. Pressure safety limits: CVP of 15 mm Hg	CVP 12	CVP 13 Continue	CVP 14 Stop	CVP 12	CVP 14 Continue	CVP 15 Stop
	Successful fluid challenge			Unsuccessful fluid challenge		

rapid completion of the challenge. However, colloid solutions are admittedly more expensive, especially human albumin. In the recent SAFE study (20), the mortality rate was identical for patients who received albumin and those who received crystalloid solution. However, hypoalbuminemia is associated with higher morbidity (21), and a meta-analysis, authored by one of us (JLV), indicated that albumin administration may reduce complications in critically ill patients (22). From the SAFE trial, there was an important trend toward improved survival with albumin in patients with sepsis (relative risk of death, 0.87; 95% confidence interval, 0.74–1.02; $p = .06$) who are often hypoalbuminemic, thus raising the possibility that albumin may be beneficial in this subset of critically ill patients.

There is also the option of fluid challenge with a synthetic colloid solution. Hydroxyethyl starch solutions are less expensive, but these also may have adverse, although minor, effects on blood clotting (23). Gelatins, with their smaller molecular weight, are less effective plasma expanders but have the advantage of low cost. They are not currently marketed in North America. Physiologic (0.9%) salt solution (saline) may increase serum chloride concentrations (24). Accordingly, so-called balanced salt solutions like Ringer's lactate have been used (sometimes called Hartmann's solution, after the American pediatrician who first proposed this solution, especially for babies with diarrhea (25)). Balanced salt solutions are, however, mildly hypotonic, and there is concern that they may exacerbate cerebral edema in patients with brain injury.

We recognize that there is no intravenous fluid solution that is ideal in all clinical settings, and no secure data support a preference for one over another. For the present, the choice is best made

contingent on the underlying disease, the type of fluid that has been lost, the severity of circulatory failure, the serum albumin concentration of the patient, and the risk of bleeding.

2. Rate of Fluid Administration. It is important to define the amount of fluid to be administered over a defined interval. The original fluid challenge technique prescribed administration of fluid with the aid of an infusion pump that allowed close control of the rate of infusion. The pump rate was typically set at 600 or 999 mL/hr (instead of 1000, as the pump displays were limited to 3 digits!). There is consensus that the protocol may be liberalized. For example, the guidelines of the Surviving Sepsis Campaign (26) for the management of severe sepsis and septic shock recommend 500–1000 mL of crystalloids or 300–500 mL of colloids over 30 mins.

3. Goal to be Achieved. One should identify and quantitate the primary defect or defects that prompt the fluid challenge: most commonly, the presence of hypotension or tachycardia, less commonly, oliguria, which may signal decreased renal perfusion or a marked decrease in tissue perfusion. Skin perfusion, especially of the limbs, may be a useful clinical end point but is less easily quantitated at the bedside except by measurement of toe temperature (27) and sublingual CO₂. Lactate is a good measure of anaerobic metabolism and therefore the severity of perfusion failure (28), but it fails to reverse rapidly enough to serve as a real-time indicator of the reversal of perfusion failure during volume repletion.

4. Safety Limits. Pulmonary edema due to congestive heart failure is the most serious complication of fluid infusion. In searching for a threshold pressure accessible from the right heart, pulmonary artery occlusion pressure is a

more direct indicator than central venous pressure, but we nevertheless regard central venous pressure as acceptable for routine fluid challenge in patients who do not have intrinsic heart or lung disease.

The time interval for the measurements of the cardiac filling pressures in response to a defined fluid load of 100 or 200 mL was originally every 10 mins, but with the availability of continuous and simultaneous infusion and measurements, the intervals may be extended (i.e., larger volumes with correspondingly larger intervals are possible). We now have the advantage of automated alarms when the critical levels of pressure are reached.

What Are the Advantages?

The principles of the fluid challenge have been presented largely based on the authors' clinical practice. The protocol has not been subjected to controlled, multicenter evaluation. We nevertheless present our present practice as a better alternative to the less objective methods that generally guide large-volume fluid resuscitation. The proposed protocol includes the option of monitoring mean arterial pressure, heart rate, and even cardiac output as concurrent measurements but requires only the safety limits based on filling pressures. As in the example illustrated in Table 2, the fluid challenge continues for as long as safety remains within limits. As in the example, the increase in central venous pressure to 15 mm Hg, associated with an increase in blood pressure, may prompt the clinician to advance to a central venous pressure safety limit of 16 or 17 mm Hg.

There are several advantages of using the fluid challenge concept as part of the conventional management of patients with life-threatening acute circulatory failure (shock):

1. Quantitative goals together with limits are imposed, replacing the uncertain "let's see what happens and call me if you're in doubt." The structured protocol can be employed equally by experienced clinicians and trainees. The protocol exposes mechanisms and, especially, limited cardiac competence at one extreme and directs the clinician to search for causes of perfusion failure other than hypovolemia on the other. It supports the team approach, for the goals are defined for the entire team and especially for the nursing staff who typically perform the fluid challenge, often in the physician's absence. Physicians, and especially nurses, appreciate the clear end points.
2. Fluid deficits are more rapidly corrected in contrast to a protracted infusion over 12 or even 24 hrs, with lesser durations of hypovolemia and, therefore, less ischemic injury and multiple organ failure.
3. After goals are achieved, there is more predictable completeness of fluid repletion. Fears of large volumes are minimized.

What Are the Limitations and Risks?

Simply stated, we cannot identify adverse effects, excepting imprecise technique. Fluid administration predictably increases intravascular and extravascular volumes and increases cardiac output, except when limited by cardiac function. However, the technique identifies cardiac failure early, based on early increases in filling pressures to threshold levels. A later consequence of fluid challenge is failure of renal elimination of fluids, especially in settings in which excesses follow resorption of large amounts of edema. Fortunately, renal function is better preserved and the risk of renal failure is no longer necessarily life threatening with renal replacement therapy. Moreover, renal function is protected when fluid challenge restores hemodynamic stability. If there is renal failure, we now have effective renal replacement therapies to reverse fluid overload. A potentially serious limitation is in neurologically impaired patients in whom fluids may increase intracranial pressure and adversely affect intracranial disease or

traumatic brain injuries or in patients with diabetes insipidus.

Conclusion

The fluid challenge strategy is not a new or complex bedside technique. We regard it as one of the most useful, basic interventions for management of critically ill and injured patients. The updated protocol outlined above provides clearly defined options of types of fluid selected and rates of administration, with objective goals and limits for volumes and rates of infusion. The fluid challenge therefore serves as a procedure that facilitates diagnosis in the routine management of critically ill and injured patients.

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