Dynamic Measures to Determine Volume Responsiveness: Logical, Biologically Plausible, and Unproven

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Let us get the easy stuff out of the way. Dynamic measures to guide fluid resuscitation are physiologically based, biologically plausible, and have been shown in many studies to be reasonably well predictive of whether a patient will respond to a fluid challenge. I and many other clinicians use them in clinical practice. This physiologically based argument is backed by the surrogate outcome measure of improved stroke volume, cardiac index, and blood pressure and serves as supporting evidence for the contrary viewpoint argued by Dr. Marik in this journal. Unfortunately, using dynamic measures to guide fluid therapy is, similar to many things that clinicians do in the ICU, logical, backed by some theory and data but is unproven as a measure to improve the clinical outcomes of critically ill patients.

POTENTIAL METHODS TO DELIVER VOLUME RESUSCITATION

Clinicians have at their disposal a number of ways to determine whether a critically ill patient will require additional volume. First, they can use clinical judgment that involves patient history and patient examination, including presence of tachycardia or hypotension, orthostatic, jugular venous pressure, capillary refill, mucous membranes, and peripheral cyanosis. For example, a patient would have been eligible to receive a fluid challenge in the Saline versus Albumin Fluid Evaluation (SAFE) and Crystalloid versus Hydroxyethyl Starch Trial (CHEST) trial comparing albumen to saline or hydroxyethyl starch or saline, respectively, if they had hypotension, impaired capillary refill, or decreased urine output (1, 2). A recent European observational trial of fluid resuscitation demonstrated that clinical judgment and examination was the most common method to prompt a fluid challenge (3). A second method to determine whether to give fluids is to empirically provide a certain amount of fluids to patients who meet certain diagnostic criteria. For example, in the Protocolized Care for Early Septic Shock trial, patients enrolled later in the trial were required to receive at least 1 liter of fluid before enrollment (4). The recommendation to deliver 30 cc/kg fluid bolus as part of sepsis treatment guidelines provides another example of empiric fluid therapy (5)

A third method to determine whether patients receive fluids is to use static pressure measures to determine whether patients require volume resuscitation. For example, in the SAFE and CHEST trials, a low central venous pressure (CVP) was a potential criterion for need for fluid resuscitation. Similarly, in the Surviving Sepsis Guidelines, one of the goals of treatment was to maintain a CVP greater than 8–12 mm Hg (5). In the Fenice observational study, roughly one third of patients received fluid resuscitation based on static filling pressures (3). Finally, one can use dynamic measures to assess whether patients require additional volume resuscitation. This would include measures such as pulse contour analysis, passive leg raise, and measurements of inferior vena cava variability with respiration. These were used by one fifth of the clinicians in the Fenice study. **Table 1** reports potential benefits and downsides of each of these methods for deciding whether to deliver a fluid bolus.

RATIONALE SUPPORTING USE OF DYNAMIC OVER STATIC MEASURES TO DETERMINE NEED FOR VOLUME RESUSCITATION

For many years, people have used static measures of filling pressures as a mechanism to determine whether patients require additional volume resuscitation. These static measures have been used in clinical trials in patients with sepsis (6), and as part of treatment guidelines (5, 7) It has been well shown that static measures of filling pressures are a poor surrogate for whether a patient or a normal volunteer will respond to a fluid bolus (8–10). This has been shown in normal volunteers and critically ill patients and is well described in Dr. Marik's viewpoint (9, 11).

Dynamic measures have been shown to predict whether patients will respond to a fluid bolus by increasing blood

Key Words: clinical trials; fluids; hypovolemia; mortality

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Dr. Sevransky disclosed other support (that he is an Associate Editor for *Critical Care Medicine*). His institution received grant support from the Food and Drug Administration.

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DOI: 10.1097/CCM.0000000000001997

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TABLE 1. Advantages and Limitations of Common Methods to Assess Need for Volume Resuscitation

Method to Assess Need for Fluid Resuscitation	Advantages	Limitations
Clinical examination	Simple, readily available	Difficult to quantify or standardize
		Not proven to demonstrate improvement in patient outcomes
Empiric	Simple	Not individualized
		Not proven to demonstrate improvement in patient outcomes
Static measures	Frequently used and readily available	Not correlated with response to volume challenge
	Used in clinical algorithms that have led to improvement in patient clinical outcomes	Invasive
Dynamic measures	Validated to predict response to therapy	Some are invasive
		Not proven to demonstrate improvement in patient clinical outcomes

pressure and stroke volume. This appears true across several platforms, including passive leg raising, monitors that assess pulse contour analysis in mechanically ventilated patients in sinus rhythm, echocardiographic measurement of inferior vena cava variation in responsive to respiration, and esophageal Doppler assessment of stroke volume (12–18). In many but not all critically ill patient populations, pulse pressure variation appears to be predictive of whether a patient will respond to a fluid challenge with increased stroke volume, cardiac index, and blood pressure (19, 20). Additional limitations of pulse pressure variation include the need for mechanical ventilation and absence of cardiac arrhythmias. The passive leg raise appears to be somewhat effective at predicting response to volume challenge in patients who are spontaneously breathing without positive pressure ventilation and have cardiac arrhythmias (21).

LIMITATIONS ABOUT WIDESPREAD USE OF DYNAMIC MEASURES TO ASSESS RESPONSIVENESS TO VOLUME

As mentioned above, dynamic measures appear to be able to predict whether a patient will respond to a fluid challenge with an increase in stroke volume and cardiac index and a decrease in pulse pressure variation. Following stroke volume, cardiac index and pulse pressure variation is logical and frequently done. Each of these measures may be used as a surrogate outcome for clinical improvement and patient survival. Unfortunately, in patients with critical illness, many biologically plausible, logical, physiologically sure treatments that improve surrogate outcomes measures have not led to improvements in patient's care. Examples of such surrogate endpoints that have been examined in trials performed in critically ill patients include oxygenation in the acute respiratory distress syndrome (ARDS), mean arterial pressure in septic shock, and inflammation in sepsis patients. Each of these measures has been used clinically after having biological and in some cases physiologic support in preclinical models and early clinical studies.

It makes sense to target improved oxygenation in patients with ARDS; however, delivering larger tidal volumes, which clearly does in the short term improve oxygenation, causes increased mortality compared with smaller tidal volumes in ARDS patients (22) and is associated with increased risk of ARDS in patients who are mechanically ventilated without initial ARDS (23). Other treatments in ARDS such as nitric oxide improve oxygenation without changing mortality (24). Targeting a higher blood pressure in patients with septic shock does not improve mortality, and a treatment that raised blood pressure in septic shock patients led to increased mortality (25). Other examples of biologically plausible therapies that improve surrogate outcome measures but have not shown mortality benefit in critically ill patients include raising cardiac output to higher levels in critically ill patients (26), transfusing patients with active upper gastrointestinal bleeding to a higher hemoglobin target (27) and broadly or specifically blocking inflammation in sepsis patients (28). Whether the lack of benefit to these interventions is related to failure of the intervention or failure to identify a specific patient group that might benefit is not known. A representative list of interventions in the critically ill that have shown improvements in biologically plausible surrogate outcome measures but not mortality can be found in **Table 2**.

It therefore follows use that although dynamic measures have been successfully used to assess whether patients will respond to volume challenges, it remains unclear whether response to volume by improving stoke volume or blood pressure is a surrogate endpoint for mortality in the critically ill. Whether using dynamic measures to assess responsiveness to volume resuscitation improves patient mortality, development or organ failures or any other patient-centric endpoint is unknown: there are no large scale studies to test dynamic measures to assess volume resuscitation with these outcome measures as primary endpoints.

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TABLE 2. Biologically Plausible Surrogate Outcomes Measures in Critical Illness Not Associated with Improved Mortality

Intervention	Surrogate Outcome Measure	Effect on Mortality
Larger tidal volumes in ARDS	Improved oxygenation	Increased
Inhaled nitric oxide in ARDS	Improved oxygenation	Unchanged
Nonspecific nitric oxide synthase inhibitors in septic shock	Increased blood pressure	Increased
Early goal-directed therapy in sepsis	Increased central venous oxygen saturation	Unchanged

ARDS = acute respiratory distress syndrome.

WHY DYNAMIC MEASURES TO ASSESS VOLUME RESUSCITATION ARE UNPROVEN TO IMPROVE IMPORTANT PATIENT OUTCOMES

Dynamic measures to assess fluid responsiveness have been shown in some but not all patient populations to be reasonable predictors of whether a patient will respond to a fluid challenge with an increased stroke volume, cardiac index, and blood pressure. It is possible that treatments that improve these measures may improve important patient outcomes: it certainly makes clinical and physiologic sense. However, as noted, we have many times before in critical care adopted therapies that have improved surrogate endpoints but have not been shown to help and in some cases have led to harm. We lack definitive studies to show that using dynamic measures leads to improvement in outcomes that are important to patients and clinicians such as mortality, prevention of organ failure, and improvement in long-term outcomes. Until we have those studies, using dynamic measures to assess volume status is reasonable, supported by physiology, and unproven. I use them, other clinicians use them, but whether we will continue to use them 10 years from now is unknown.

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