Fluid Responsiveness and the Six Guiding Principles of Fluid Resuscitation

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The advanced life support technology, which is provided in the ICU, is intended to provide temporary physiologic support for patients with reversible organ dysfunction allowing homeostatic mechanisms to return the patients to their previous level of functioning (1). The introduction of the pulmonary artery catheter in the early 70s ushered in a style of critical care medicine that can best be characterized as "aggressive"; if some care is good, more care is even better. Aggressive fluid resuscitation titrated to the central venous pressure (CVP) or pulmonary artery occlusion pressure became regarded as the cornerstone of resuscitation. This approach ushered in an era of rigid protocolized care, where critically ill and injured patients received large amounts of crystalloids regardless of their hemodynamic status (2–4). However, an emerging body of evidence suggests that aggressive fluid resuscitation leads to severe tissue edema that compromises organ function and leads to increased morbidity and mortality (5, 6). A recent global cohort study that evaluated the approach to fluid resuscitation in 46 countries concluded that the "current practice and evaluation of fluid management in critically ill patients seems to be arbitrary… is not evidence-based and could be harmful." (7) This article presents a rational, physiological approach to fluid resuscitation, which is based on six fundamental principles. If one is considering giving a fluid bolus, I would recommend using dynamic rather than static measures to assess the patient according to the principles listed below.

1. FLUID RESPONSIVENESS: THE FOUNDATION OF FLUID RESUSCITATION

Fundamentally, the only reason to give a patient a fluid challenge is to increase their stroke volume (SV); if this does not happen, fluid administration serves no useful purpose and is likely to be harmful (8). A patient is considered to be fluid responsive if his/her SV increases by at least 10% following a fluid challenge (usually 500 cc of crystalloid) (8). Fluid administration will only increase SV if two conditions are met, namely 1) if the fluid bolus increases the stressed blood volume causing the mean circulating filling pressure to increase greater than the increase in CVP and thereby increasing the gradient for venous return (9, 10) and 2) if both ventricles are functioning on the ascending limb of the Frank-Starling curve (8).

Studies in heterogeneous groups of critically ill and injured patients and those undergoing surgery have reproducibly and consistently demonstrated that only about 50% of hemodynamically unstable patients are fluid responsive (5, 11, 12). This is a fundamental concept that is not widely appreciated (2, 3, 13) and challenges the widely accepted notion that fluid administration is the "cornerstone of resuscitation." (2, 3) These observations dictate that only patients who are fluid responsive should be resuscitated with fluid boluses. This concept represents a major paradigm shift and places 'fluid responsiveness" center stage in the management of critically ill and injured patients and those undergoing surgery.

2. CLINICAL SIGNS, THE CHEST RADIOGRAPH, THE CVP, AND ULTRASONOGRAPHY CANNOT BE USED TO DETERMINE FLUID RESPONSIVENESS

Although clinical signs, such as a hypotension, tachycardia, narrow pulse pressure, poor skin perfusion, and slow capillary refill, may be helpful for identifying inadequate perfusion, these signs are unable to determine volume status or fluid responsiveness (14). The CVP or change in CVP following a fluid challenge is no more accurate in predicting fluid responsiveness than flipping a coin and should be abandoned for this purpose (11). It should also be recognized that the change in the mean arterial pressure (MAP) following a fluid bolus is poorly predictive of fluid responsiveness (12, 15). Although widely recommended (4), ultrasonography of the vena cava and its respiratory variation are no more predictive than the CVP for assessing fluid responsiveness

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(16). Echocardiography has limited utility for assessing volume status and fluid responsiveness. Transthoracic measurements of left ventricular outflow tract velocities (VTI) for the estimation of SV require considerable expertise and are not easily obtainable or reproducible in ICU patients (17). Furthermore, the VTI is not ideal for detecting rapid changes in SV following a passive leg raising (PLR) maneuver or fluid challenge.

3. THE PLR MANEUVER OR A FLUID CHALLENGE COUPLED WITH REAL-TIME SV MONITORING IS THE ONLY ACCURATE METHOD FOR DETERMINING FLUID RESPONSIVENESS

Currently, there are only two techniques that are widely available, practical, easy to perform, and physiologically based, which can be used to determine fluid responsiveness with a high degree of accuracy, namely, the PLR maneuver and the fluid challenge (8, 18). These techniques are best coupled with minimally invasive or noninvasive cardiac output monitors, which can track changes in SV dynamically and in real time (8, 19). The PLR is simple to perform taking less than 5 minutes to complete. Beyond its ease of use, this method has the advantage of reversing its effects once the legs are returned to the horizontal position (18). A metaanalysis, which pooled the results of 21 studies, confirmed the excellent diagnostic value of the PLR to predict fluid responsiveness in critically ill patients with a global area under the receiver operating characteristic curve of 0.94 (12). The gold standard to determine fluid responsiveness is the change in SV following a fluid challenge (8). As crystalloids redistribute very rapidly, the fluid bolus should be given as quickly as possible and ideally within a 10–15 minute period. A bolus of between 200 and 500 cc is recommended. Large fluid boluses of 20–30 mL/kg, although still widely recommended (3, 4), are unphysiologic and likely to lead to marked volume overload with severe tissue edema (5, 6).

4. THE HEMODYNAMIC RESPONSE TO A FLUID CHALLENGE IS USUALLY SMALL AND SHORT LIVED

Fluid boluses are most frequently administered to patients with hypotension (7). However, it is not widely recognized that the hemodynamic response to a fluid challenge is usually small and short lived. Nunes et al (20) evaluated the duration of the hemodynamic effect of a fluid bolus in patients with circulatory shock. In this study, 65% of patients were fluid responders whose cardiac index increased by 25% at the end of the infusion (30 min). However, the cardiac index had returned to baseline 30 minutes after the end of the infusion. Glassford et al (21) performed a systematic review that examined the hemodynamic response of fluid boluses in patients with sepsis. These authors reported that although the MAP increased by 7.8 ± 3.8 mm Hg immediately following the fluid bolus, the MAP had returned close to baseline at 1 hour with no increase in urine output. In a retrospective analysis of the ARDSnet Fluid and Catheter Treatment Trial, Lammi et el (22) examined the physiological effect of 569 fluid boluses in 127 patients. According to the protocol, fluid challenges were given for hypotension or oliguria. In this study, the MAP increased by 2 mm Hg following the bolus with no increase in urine output. These data indicate that fluid boluses are generally an ineffective treatment strategy for hypotension, circulatory shock, and oliguria.

5. FLUID RESPONSIVENESS DOES NOT EQUATE TO THE NEED FOR FLUID BOLUSES

Most healthy humans are normally fluid responsive and function on the ascending limb of the Frank-Starling curve; they have preload reserve and do not require fluid "to live" on the flat part of the curve to function optimally. Similarly, critically ill and injured patients and those undergoing surgery do not need to be pushed to the top of their Frank-Starling curve. Patients should only receive a fluid bolus if they are preload responsive and likely to benefit from the fluid bolus, that is, the potential benefits and risk should be evaluated prior to each fluid bolus. Patients should only continue to receive fluid boluses if the hemodynamic benefits are likely to outweigh the risks of an accumulating positive fluid balance. Patients should not receive repeated fluid boluses until they are no longer fluid responsive. As patients "ascend" the Frank-Starling curve, the adverse effects begin to outweigh the benefits as atrial pressures increase with increasing release of natriuretic peptides and increasing hydrostatic edema (**Fig. 1**). Because of the small and short lived effect of a fluid bolus, it may be preferable to treat the fluid responsive septic patient with norepinephrine (23). Norepinephrine will increase venous return, SV, and MAP, thereby increasing organ perfusion while limiting tissue edema (23).

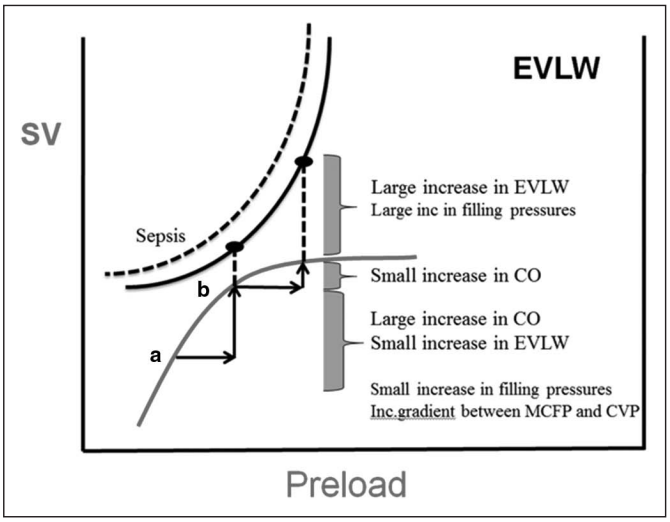

Figure 1. Superimposition of the Frank-Starling and Marik-Phillips curves demonstrating the effects of increasing preload on stroke volume (SV) and lung water in a patient who is preload responsive (a) and nonresponsive (b). With sepsis, the extravascular lung water (EVLW) curve is shifted to the left. CO = cardiac output, CVP = central venous pressure, MCFP = mean circulating filling pressure. Reproduced with permission from Marik and Lemson (24).

6. A HIGH CVP IS A MAJOR FACTOR COMPROMISING ORGAN PERFUSION

Organ blood flow is driven by the difference in the pressure between the arterial and venous sides of the circulation. The MAP minus the CVP is the driving force for organ blood flow. However, when the MAP is within an organ autoregulatory range, the CVP becomes the major factor determining organ and microcirculatory (5). The kidney is particularly affected by increased venous pressure, which leads to increased renal subcapsular pressure and lowered renal blood flow and glomerular filtration rate (25). Legrand et al (26) demonstrated a linear relationship between increasing CVP and acute kidney injury (AKI), with a high CVP being the only hemodynamic variable independently associated with AKI. In critically ill patients and those with heart failure, a CVP of greater than 8 mm Hg has been demonstrated to be highly predictive AKI. There are now compelling data that the primary hemodynamic goal in critically ill and injured patients and those undergoing surgery is an MAP of greater than 65 mm Hg and a CVP of less than 8 mm Hg. Remarkably, this CVP target contradicts current guidelines that recommend targeting a CVP of greater than 8 mm Hg (3, 4). Furthermore, fluid loading oliguric patients with a low CVP with the goal of achieving a CVP of greater than 8 mm Hg may paradoxically increase the risk of progression to AKI.

CONCLUSIONS

Fluid resuscitation is the defining skill of intensivists, emergency medicine physicians, surgeons, and anesthesiologists, yet many of these clinicians have a poor understanding of the fundamental principles involved in fluid administration resulting in conflicting, inconsistent, and potentially harmful treatment strategies. Fluid administration should be guided by an assessment of fluid responsiveness combined with the determination of the potential benefits and harms of fluid administration. Large fluid boluses should be avoided.

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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

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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.

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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We are most grateful to Drs. Price and Anwar (1) for their interest in our study as well as their observations and thoughtful suggestions.

Firstly, we would like to address the valid suggestion that blinding during cardiac arrest would have strengthened our study (2). Although we agree, however, this was not feasible. The activity of the cerebral oximetry sensor needs to be closely observed by research staff at all times during cardiopulmonary resuscitation (CPR). At times, the sensors may come loose from the forehead (especially when subjects are profusely sweaty), or they may be mistakenly removed by clinical staff engaged in resuscitation (e.g., during intubation). The only practical way to detect an issue with a sensor that may require a timely intervention is to observe the regional cerebral oxygen (rSo_2) readings during CPR. For this reason, we could not cover the monitors and blind the research staff from the rSo_2 readings. However as alluded to in the article, the devices were almost always kept on the floor and a short distance away from the patient. Consequently, the monitor was not in the field of vision of the clinical resuscitation staff. Furthermore, it should be pointed out that staff collecting research data were not clinically involved with resuscitation efforts. This combined with the fact that at the participating sites, people engaged with CPR were mostly unfamiliar with the application of this technology, meant that it was not generally used to adjust resuscitation efforts.

In our experience, aside from anesthesiologists engaged with cardiothoracic surgery, most others are not intimately involved with cerebral oximetry. In our study, most anesthesiologists who attended cardiac arrest were often junior doctors and not typically from a cardiothoracic background. Furthermore, the anesthesiologists did not manage the running of cardiac arrests and often left the scene after the airway had been secured.

Unfortunately, data collection for this study had to be limited to working hours, as research staff are usually not available to ensure patient recruitment beyond working hours. To our knowledge, very few centers offer 24 of seven critical care research staffing coverage at present. However, we again agree that this would have been ideal and would certainly have helped with ensuring broader generalizability of our findings.

Finally, we would like to point out that as with peripheral oxygen saturation monitoring, cerebral oximetry levels during cardiac arrest should be used as a dynamic rather than a static marker of resuscitation quality. Consequently, any decision to prognosticate or withdraw care would be best made with this important point in mind. Our data suggest that in the ideal setting, every effort and intervention should be made (beyond the relatively basic recommendations highlighted in Advanced Cardiac Life Support training) to enhance vital organ perfusion and oxygen delivery in real time in order to elevate rSo_2 levels to greater than 65%. However, if despite all efforts rSo_2 levels cannot be elevated to at least a minimum level, that is, greater than 30%, then return of spontaneous circulation is extremely unlikely. We appreciate that in view of the enormous variations in cardiac arrest care, this ideal may not always be achievable. Although this may in part reflect the unfortunate differences in the availability of resources and expertise, however, we believe this level of vital organ and in particular cerebral perfusion and consequently oxygen delivery should be sought in every case of cardiac arrest before a decision is made to prognosticate.

Dr. Parnia has disclosed that he does not have any potential conflicts of interest.

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The Frank-Starling Curve Is Not Equivalent to the Fluid Responsiveness Curve

To the Editor:

We read with interest the recent expert Viewpoint article by Marik (1) in a recent issue of *Critical Care Medicine*. An understanding of the physiologic effects of bolus fluid administration is generally ascribed to two principles: the Frank-Starling law of the heart and the Starling equation for microvascular fluid exchange. However, examination of the original studies that elucidated the form of the Frank-Starling law (cardiac function curve) and recent studies that have led to a revised form of the Starling equation suggest an alternative interpretation of the physiologic response to a fluid challenge from that provided by Marik (1).

In Starling's original isolated heart lung preparation, preload was altered by regulation of venous return from a reservoir with a resistor screw; measurements were taken of cardiac output and right atrial pressure. From these experiments, Starling concluded that "within physiological limits, the larger the volume of the heart, the greater is the energy of its contractions." With a similar arrangement for venous

return, but a more intact systemic circulation (open chest dog), Sarnoff and Berglund (2) demonstrated a curvilinear (concave upwards) stroke work to atrial pressure relation (for both ventricles), but hypothesized that the nonlinearity reflected the exponential shape of the ventricular diastolic pressure to volume relation. This hypothesis was subsequently confirmed with experiments in closed chest conscious dogs (using mostly pharmacologic manipulation of preload), showing a highly linear stroke work to left ventricular chamber volume relation (3). Furthermore, if afterload remains constant, then stroke volume can be substituted for stroke work, and there is a linear relationship between stroke volume and left ventricular volume—a linear cardiac function curve.

In practice, however, when fluid loading is used to augment preload, there is an apparent plateau in the cardiac function curve—the transition from a fluid responsive to nonresponsive state. To be consistent with the studies cited above, this cannot be due to a true plateau in cardiac function and requires an alternative explanation. In a study of repeated fluid boluses given to spontaneously breathing healthy subjects, Fujimoto et al (4) demonstrated that there was not only a smaller incremental increase in cardiac output after the second bolus than the first bolus (of the same volume), but also a smaller incremental rise in left and right sided filling pressure; contrary to what would be expected from the shape of the diastolic volume pressure relation. The most likely explanation is an increased rate of fluid extravasation after the second bolus, a hypothesis consistent with the revised Starling equation and the principle of context sensitivity—at low capillary hydrostatic pressure the rate of extravasation is constant, but above a critical inflection point the rate of extravasation increases progressively with hydrostatic pressure (5).

Thus, in Figure 1 of the article by Marik (1), the "true" Frank-Starling curve should be a straight line, and an "apparent" cardiac function curve—the fluid responsiveness curve—would show a plateau, "caused" by, and thus coincident with, an upward inflection of the Marik-Phillips extravascular lung water curve (1, 6).

The authors have disclosed that they do not have any potential conflicts of interest.

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The author replies:

I thank Drs. Wiersema and Birhari (1) for their thoughtful commentary. The relationship between left ventricular preload (left ventricular end-diatoric volume or fiber length) and stroke volume (SV) is exceedingly complex and dynamic and affected by multiple factors including diastolic compliance, ventricular interdependence, heart rate, autonomic tone, circulating catecholamine levels, alterations in cardiomyocyte intracellular signalling and contractibly related to the acute disease process (e.g., sepsis), arrhythmias, intrapericardial pressure, acid-base balance, hypoxemia, inotropic drugs, and left ventricular afterload to name just a few (2). Nevertheless, over the last two decades, it has been clearly established that only about 50% of hemodynamically unstable patients with will demonstrate an acute increase in SV (> 10–15%) in response to a 500 cc fluid challenge (3, 4). Furthermore, it is now indisputable that volume overload increases patient morbidity and mortality (5). From a purely pragmatic point of view, it is therefore critical for clinicians to determine the position of his/her patient on the patients' Frank-Starling (or cardiac function or fluid responsiveness curve) prior to fluid resuscitation (3, 4, 6). Although physiologists may argue as to the precise shape of the Frank-Starling curve (2), for the clinician at the bedside, this is less important as it is indisputable that the "fluid responsive curve" is curvilinear with a clear plateau (3, 4). This construct aligns with the length-tension relationship of cardiac muscle related to the degree of overlap of the actin and myosin myofibrils. In summary, the Frank-Starling relationship is used more to illustrate rather than explain the relationship between preloading conditions and SV change.

Dr. Marik has disclosed that he does not have any potential conflicts of interest.

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