Fluid and Volume monitoring

Pat Brophy, MD
Juan Padilla, MD
Emil Pagannini, MD
Neesh Pannu, MD
Michael R. Pinsky, MD*

A. What are the criteria for sufficient volume?

Sufficiency of volume is that volume/vasomotor tone/contractile performance that sustains tissue perfusion relative to its metabolic needs.

1. Why is blood volume an issue in determining organ perfusion?

Although an adequate intravascular volume is essential for tissue perfusion and oxygenation, excessive intravascular volume promotes pulmonary edema which itself impairs gas exchange. Thus, one balances euvolemia between hypovolemic shock and volume overload. Importantly, the total blood volume is not as important and the effective circulating blood volume and its associated vasomotor tone and cardiac contractility. Total body water is distributed into three main anatomical parts, the intravascular space, interstitial space and cellular and matrix mass. Although volume overload primarily affects only the intravascular and interstitial spaces, hypovolemia, if prolonged, can promote a generalized loss of volume from the cellular space as well. In healthy subjects with free access to water, normal thirst mechanisms and diuresis control maintain adequate hydration without volume overload. However, with decreased mental status and critical illness, hypovolemia can occur and induce renal hypoperfusion and, if sustained, renal failure. Hemorrhage, hyper-emesis, diarrhea, burns and sepsis

*Authors are listed in alphabetic order. *Denotes group facilitator.
all promote intravascular volume loss. Severe injury states, such as major trauma and sepsis, are also associated with a generalized systemic inflammatory response that causes marked impairment of vasomotor tone through generalized vascular endothelial injury, induction of inducible nitric oxide synthase, which produces massive amounts of the potent vasodilator nitric oxide, and the release from both immune effector cells and the inflamed vascular endothelium of numerous vasodilators (e.g. prostacyclin) and vasoconstrictors (e.g. HETE). These processes induce an impaired vasoregulatory response primarily characterized by loss of vasomotor tone with its resultant increase in unstressed volume and impaired autoregulation of blood flow distribution. Thus, for the same circulating blood volume effective circulating blood volume is reduced decreasing venous return and thus cardiac output; and for the same cardiac output, increasing blood flow to metabolically active tissues is impaired owing to loss of normal autoregulatory feedback. Furthermore, in subjects with impaired renal reserve, hypervolemia may rapidly occur if excessive fluid is ingested, infused or resorbed from the interstitial space. These events occur with polydypsia, over aggressive resuscitation efforts and following resolution of a generalized cardiovascular inflammatory stress (e.g. cardiopulmonary bypass or sepsis), respectively. Finally, hemodialysis with ultrafiltration removes solutes and water from the intravascular space, independent of renal excretion. Although this type of artificial diuresis is an essential aspect of fluid and electrolyte management of patients with renal insufficiency, overly aggressive ultrafiltration can and often does induce functional hypovolemia with its attendant circulatory shock manifestations, including exacerbation of renal injury. Thus, defining when a subject is developing functional hypovolemia, independent of their overall body volume status is an essential aspect of titration of diuresis therapies. Accordingly, fluid management reflects both intravascular fluid resuscitation to restore effective circulating blood volume and forced diuresis under conditions of overly expanded blood volume that carries with it the risk of pulmonary edema.

2. Problems with fluid resuscitation

   a. Identifying occult hypoperfusion

A fundamental quality of adaptive autonomic response is to maintain an adequate central arterial pressure to sustain coronary and cerebral blood flow. Thus, although
hypotension is always pathological normotension does not mean cardiovascular stability. So how does one identify occult tissue hypoperfusion? Clearly, related signs of sympathetic hyper-reactivity, such as tachycardia, vasoconstriction, diaphoresis, and anxiety, are easy to identify. Tachycardia is a sensitive but non-specific marker of increased sympathetic tone, whereas hyperlactecemia is a sensitive but non-specific marker of tissue hypoperfusion. Recently, increased interest in measuring venous $O_2$ saturation as a guide to identifying tissue hypoperfusion and defining when to stop resuscitation has become popular. Central venous $O_2$ saturation (ScvO$_2$) as a rough estimate of mixed venous $O_2$ saturation (SvO$_2$), can identify tissue hypoperfusion if less than 70%, and can drive a treatment protocol that improves outcome from septic shock (1). Clearly, the underlying principal of any method that attempts to assess the adequacy of blood flow uses surrogate makers regional performance and oxygen extraction. Newer approaches such as non-invasive measures of tissue SO$_2$, using near infrared oximetry (2), and differences in sublingual PCO$_2$ and arterial PCO$_2$ can identify tissue hypoperfusion (3).

b. Defining preload-responsiveness

Kumar et al. (4) demonstrated that neither central venous pressure (CVP) or pulmonary artery occlusion pressure (Ppao) values nor their changes in response to fluid challenges reflected their respective ventricular end-diastolic volumes or changes, respectively in patients receiving a fluid challenge for hemodynamic insufficiency. Presumably, non-linear ventricular diastolic compliance relations and an incomplete knowledge of actual transmural ventricular filling pressures are the reasons for this failure. However, Starling’s Law of the Heart was still operative in this study. If end-diastolic volume increased in response to volume loading, then stroke volume increased as well. Thus, one should not use either CVP or Ppao values to define the state of ventricular filling or the potential to response to a fluid challenge. Furthermore, changes in either CVP or Ppao did not correlate with each other or with changes in either stroke volume or end-diastolic volume of their respective ventricles.

Perel et al. suggested that one access systolic pressure variation (SPV) during positive-pressure breathing to identify those subjects who would be preload responsive (5). They
reasoned that the natural variation in venous return induced by positive-pressure ventilation must induce a subsequent change in systolic arterial pressure. Michard et al. (6,7) reasoned that arterial pulse pressure variation (PPV) reflects changes in LV stroke volume during positive-pressure ventilation between than SPV because PPV is not influenced by the intrathoracic pressure-induced changes in both systolic and diastolic arterial pressure. They compared SPV with PPV as predictors of the subsequent increase in cardiac output in response to fluid loading in septic ventilator-dependent patients. Their data demonstrated that both PPV and SPV of ≥15% were far superior to measures than either Pra or Ppao in predicting an increase in cardiac output response to volume loading. Furthermore, the greater the PPV or SPV, the greater was the increase in cardiac output. However, PPV claimed a slight, though significant, advantage over SPV in terms of greater precision and less bias. Since PPV attempts to monitor LV stroke volume changes, it was not surprising that Feissel et al. (8) demonstrated that aortic flow variation, as measured by transesophageal 2-D echocardiography pulsed Doppler of the aortic outflow tract, followed a similar response to PPV in response to fluid loading. The flow variation data are very important because, flow it is the primary variable from which SPV and PPV derive their validity. Though less invasive than arterial pressure monitoring, echocardiographic analysis is far from ideal as a hemodynamic monitoring tool. It requires the continuous presence of an experienced operator. Echocardiography requires using expensive and often scare equipment. And finally, measures of aortic root flow variation cannot be made on-line or continuously over prolonged periods of time. Still, recent minimally invasive esophageal pulsed Doppler techniques have been developed that measure continuously descending aortic flow on a beat-to-beat basis. To the extent that descending aortic flow varies proportionally with aortic outflow, then these measures of descending aortic flow accurately access stroke volume variation (SVV).

One can use this test to identify when subjects become effectively hypovolemic as well. Consider a patient receiving hemodialysis in which some degree of intravascular volume depletion is necessary to drive fluid from the interstitium into the vascular space. If the ultrafiltration becomes too vigorous then the patient may develop functional hypovolemia.
Unfortunately, measures of SPV, PPV and SVV all require that the subject be supported on mechanical ventilation and have a fixed R-R interval, such that stroke volume changes reflect dynamic changes in preload during to ventilation. Thus, none of these parameters accurately predict fluid responsiveness in spontaneously breathing subjects and/or in those with frequent ventricular ectopic beats or atrial fibrillation. To address this issue, Monnet et al. demonstrated that the change in mean aortic flow, estimated by esophageal Doppler measures of descending aortic flow, predicted volume responsiveness (119). Specifically, if mean aortic flow increased by at least 10%, these subjects were preload responsive, even though they were breathing spontaneously or have arrhythmias. Although they measured mean aortic flow with an esophageal Doppler probe, similar results should if one estimates dynamic changes in mean flow using estimates of stroke volume from arterial pulse pressure analysis.

3. End-points of resuscitation

Resuscitation from circulatory and respiratory failure represents the mainstay of emergency and critical care management. However, laboratory studies have demonstrated that restoration of total blood flow, arterial oxygenation and even arterial pressure to otherwise normal levels by the use of vasoactive agents is not universally good for either organ function and host outcome (9). Exogenous vasopressor therapy impairs normal autoregulation of blood flow among organs and may induce occult tissue ischemia in vital but silent vascular beds, such as the gut mucosa and renal subcortex. Furthermore, microcirculatory oxygen utilization is more a function of local metabolic demands and capillary flow than global blood flow or arterial O$_2$ content. Regrettably, significant regional ischemia or rescue can occur without perceptible changes in global O$_2$ uptake (VO$_2$). Although fluid and vasopressor therapies may normalize organ perfusion pressure they may not induce normal organ perfusion nor prevent organ dysfunction. Still, it is clear from numerous clinical studies that tissue hypoperfusion is bad and that avoidance of ischemia improves outcome from stress states. Thus, the rapid restoration of normal hemodynamics by conventional means, including fluid resuscitation and surgical repair, results in a superior outcome than inadequate or delayed resuscitative efforts. Since critically ill patients often have abnormal blood flow regulation, increasing oxygen delivery (DO$_2$) to what would otherwise be considered supranormal levels theoretically may treat the lethal occult tissue hypoxia that is a
hallmark of many forms of circulatory shock. Accordingly, interest centered on “hyper-resuscitation” such that $DO_2$ is exogenously increased to supranormal levels, levels often seen in subjects who spontaneously survive acute circulatory insults, the so-called “survivor levels of $DO_2$.” Most studies that have aimed at augmenting $DO_2$ or $VO_2$ to “survivor levels” have documented that if $DO_2$ can increase, subjects do better (10). However, this improvement in survival appears to be independent of whether the subject was part of the group with intentional augmented $DO_2$ (11). Furthermore, aggressive therapies aimed at augmenting $DO_2$ may actually increase mortality in experimental groups (12). Thus, a low $DO_2$ in a critically subject is probably a marker of critical illness, rather than a parameter of effective resuscitative therapy. Interestingly, the most impressive beneficial outcomes from clinical trials have all included prevention of hypoperfusion rather than resuscitation from shock. Finally one recent prospective clinical trial has documented that early aggressive resuscitation base don a logical physiological paradigm markedly improved survival in patients in septic shock (1). In that study and others, the appropriate assessment of circulatory performance is to define as adequate or inadequate based on end-organ measures of tissue perfusion such as $SvO_2$, lactate and changes in other metabolic markers. Thus, aggressive hemodynamic therapies in patients in septic shock or at risk for development of multiple organ dysfunction and death improve survival. Often these benefits are seen without measurable differences in $DO_2$ or $VO_2$ during therapy. The cumulative data to date suggests that a major benefit of aggressive resuscitation therapy would be realized if efforts were directed at more rapid identification of subjects at risk from the general hospital population and the more rapid emergency resuscitation, transport and definitive therapy of subjects in the field. However, once circulatory shock and/or organ dysfunction has occurred there appears to be little additional benefit and real risk of harm from aggressive resuscitation therapies that increase $DO_2$ or $VO_2$ to levels above which would otherwise be considered normal.

Importantly, Lopes et al. showed that resuscitation guided by PPV reductions to < 10% markedly improved outcomes in high risk surgery patients (120). Thus, one can use simple measures of complex physiological processes to guide effective fluid resuscitation therapies.
B. Monitoring Volume Status

Monitoring of volume status and the utilization of fluid therapy in patients at risk for developing or with established acute kidney injury (AKI) including those that are critically ill is an important clinical issue. Indeed, several studies including those performed on pediatric patients have implicated that excess fluid may be related to adverse outcomes in critically ill patients particularly those with AKI requiring CRRT (13,14,15,16). It is not clear from the literature, however, whether fluid overload is a cause of increased morbidity or mortality or a marker representing the severity of underlying illness. What is clear is that volume status monitoring is imperative in order to prevent or manage patients developing AKI, particularly those who have not required the initiation of renal replacement therapy. To date management has been based on local standard of care. The following provides a description of the tools available for appropriate fluid monitoring.

1. What are the indicators of sufficient volume?

Indicators of “sufficient volume” as previously defined need to be tailored in regard to patient acuity and clinical diagnosis. As patient acuity increases so does the invasive component and hence accuracy of monitoring. While filling pressure measurements (central venous pressure (CVP) and pulmonary artery occlusion pressure (Ppao) have been popular surrogate markers of preload and continue to be utilized as measures of preload responsiveness, in general static measurements are not sensitive indicators of hypovolemia. Their measurement may however crudely parallel effective circulating volume. While low values can be indicative of hypovolemia, high values do not necessarily mean that the patient is volume replete, and neither high or low values are useful in predicting preload responsiveness (17-25). Changes in the pericardial restraint, thoracic compliance or alterations in ventricular compliance can effect the relation between filling pressures and ventricular end-diastolic volume. Thus, neither absolute measures of filling pressure nor their change provide the clinician adequate information to determine sufficient volume status and may lead to incorrect therapeutic decisions in the most critically ill patients. Indeed recently, pulmonary artery catheter guided therapy has been demonstrated to be associated with more complications and did not positively impact survival (26). That is why such static hemodynamic indicators have been largely replaced by dynamic indicators such as: inspiratory decrease in right atrial pressure
(ΔRAP), expiratory decrease in arterial systolic pressure (Δdown), respiratory changes in pulse pressure (i.e. PPV) and respiratory changes in aortic blood velocity (ΔVpeak). All of these measures are noted to be elevated in patients that are volume responders. (Table 1)(27). Although dynamic parameters should be preferentially utilized over static indicators in order to better predict fluid responsiveness, they do possess some limitations in that, distorted signals due to fluid-filled catheters and arrhythmias may reduce the precision of the measurements (28).

Table 1 Dynamic change in measured hemodynamic variables during ventilation to predict preload responsiveness

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Best threshold</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>ΔRAP</td>
<td>1 mm Hg</td>
<td>Magder (16)</td>
</tr>
<tr>
<td>ΔDown</td>
<td>5 mm Hg</td>
<td>Tavernier (17)</td>
</tr>
<tr>
<td>ΔRAP</td>
<td>1 mm Hg</td>
<td>Magder (18)</td>
</tr>
<tr>
<td>PPV</td>
<td>13 %</td>
<td>Michard (19)</td>
</tr>
<tr>
<td>ΔVpeak</td>
<td>12 %</td>
<td>Feissel (20)</td>
</tr>
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Sufficient volume must be assessed within the context of the following variables  i) Tissue wellness, ii) Vasomotor tone, iii) Contractility, and iv) Preload responsiveness. Measurement and monitoring of plasma volume, along with other commonly used variables to assess fluid status particularly with respect to AKI must also be considered.

In terms of approaches to volume deficit/overload both in the presence and absence of RRT, the following will serve as a guide as to at what point these monitoring tools may be implemented and analyzed. Several important points must also be considered in monitoring sufficient volume status.

   a. Monitoring is context specific
The choice of indicators used to evaluate sufficient volume in AKI will depend on the health status of the patient, including: the presence of pre-existing renal disease (AKI superimposed upon chronic kidney disease); the place, a patient on the general hospital ward will require different monitoring tools than one in the intensive care unit; the etiology, a patient with AKI on admission will require a different fluid monitoring approach than one developing AKI after admission; and finally the physiology, monitoring may be continuous or intermittent, invasive or non-invasive.

b. **Therapy should be goal-directed**
   The indicators should allow us to prescribe therapy aimed at restoring tissue perfusion and preventing tissue hypoperfusion.

Hemodynamic monitoring is a central aspect of cardiovascular diagnosis and titration of care. Circulatory shock primarily results in inadequate tissue blood flow. Although most forms of shock may show some increase in cardiac output initially in response to fluid loading, fully one-half of all hemodynamically unstable intensive care unit patients are not preload-responsive (27). Furthermore, volume overload often worsens cor pulmonale and can induce pulmonary and peripheral edema in heart failure states. To review the relevant new clinical data addressing this important clinical issue, PubMed was searched (www.ncbi.nlm.nih.gov/PubMed) for all papers published in 2004 using the key words, resuscitation and hemodynamic monitoring, preload, fluid responsiveness, and circulatory shock. The search was then narrowed to include only non-review papers published in English that reflected clinical studies of patients within the intensive care unit or operating room. All of the resultant 88 manuscripts identified were reviewed and only those of particular relevance to the topic of assessing preload and preload-responsiveness were summarized below. One older review article and one position paper were also cited but only to place the current studies into a proper perspective. Fundamental to hemodynamic monitoring is the interpretation of the measured and derived data within the context of expected and known physiological constructs, such as Starling’s Law of the Heart and global O₂ supply and demand relationships. These assumptions were directly addressed in recent publications.
2. **Preload is not preload-responsiveness** Kumar et al. (4) demonstrated that neither CVP or Ppao values nor their changes in response to fluid challenges reflected their respective ventricular end-diastolic volumes or changes, respectively in patients receiving a fluid challenge for hemodynamic insufficiency. Presumably, non-linear ventricular diastolic compliance relations and an incomplete knowledge of actual transmural ventricular filling pressures are the reasons for this failure. However, Starling’s Law of the Heart was still operative in this study. If end-diastolic volume increased in response to volume loading, then stroke volume increased as well. Thus, one should not use either CVP or Ppao values to define the state of ventricular filling or the potential to respond to a fluid challenge. Furthermore, changes in either CVP or Ppao did not correlate with each other or with changes in either stroke volume or end-diastolic volume of their respective ventricles. These finding of discordance between pulmonary artery catheter-derived data and directly measured indices of ventricular performance were duplicated, in a fashion, by Bouchard et al. (29) who compared right and left ventricular stroke work index with echocardiographic-derived indexes of left ventricular performance, i.e. fractional area change in 64 intra-operative cardiac surgery patients before and after bypass and before and after volume loading. A total of 186 simultaneous measurements were analyzed and compared. Correlations between right and left ventricular stroke work index changes were poor (R= -0.28 to 0.16, P values from 0.31 to 0.94) as were the correlations between left ventricular stroke work index changes and fractional area change changes (R= -0.62 to 0.22, P values from 0.07 to 0.95). Thus, not only is preload not preload-responsiveness, but there is also a significant discrepancy and limited relationship between the hemodynamic and echocardiographic evaluation of left ventricular performance. Still, in the position paper entitled Surviving Sepsis, sponsored by the major critical care societies, the recommendation to use invasive monitoring as part of the assessment of circulatory shock and its response to therapy was still made (30). However, this blue-ribbon panel also accentuated monitoring other related hemodynamic variables, such as cardiac output and mixed venous \( O_2 \) saturation (SvO\(_2\)). Still, the values for left and right ventricular filling pressures recommended by this panel are not predictive of preload responsiveness (31). Thus, their recommendations about \( O_2 \) delivery may need to be interpreted with caution as well.
3. Alternatives to right heart catheterization.

In an attempt to bypass the need for right heart catheterization, Combes et al. (32) demonstrated in 333 mechanically ventilated patients that a single transpulmonary thermal injection from a central venous site using the PiCCO® system gave estimates of cardiac function index and global ejection fraction that were similar to measures of left ventricular (LV) ejection fraction made by transesophageal echocardiography (R = 0.87 and 0.82, respectively). Potentially, estimates of LV systolic function can be made without the need for a pulmonary artery catheter. Importantly, patients with right ventricular (RV) dysfunction were excluded, because PiCCO-derived parameters include RV function whereas echo-derived measures are specific for LV performance. Thus, extrapolation of these data to mechanically ventilated patients, many of whom may have RV dysfunction associated with acute respiratory failure, may not be warranted.

If one does not need a pulmonary artery catheter, does one even need a central venous catheter? Desjardins et al. (33) compared an antecubital vein-transduced pressure with CVP in 19 cardiac surgery patients with or without mechanical ventilation. They found that CVP and peripheral venous pressure were similar (mean pressure differences 0.72 to 0 mm Hg). Thus, peripheral venous pressure is a readily available surrogate for CVP. Since CVP values < 10 mm Hg are associated with a decrease in cardiac output if positive-end expiratory pressure is subsequently increased, these data have clinical utility. Staal et al. attempted to bypass invasive catheterization completely (34) using cardiac impedance techniques. They compared angiographically measured LV volumes, using Simpson’s rule, with transcardiac conductance measured from surface skin electrodes in 10 subjects undergoing angiography. Reliably stable data were available in 8 of 10 subjects and gave good agreement in the estimate of LV volumes (R² = 0.78). It remains to be seen, however, if this technique gives a general volume measure or can detect clinically relevant changes in LV volume over time and in response to therapy.

An interesting study came from Gabbanelli et al. who used the time activity curve of glucose dilution following a bolus infusion to estimate circulating blood volume (35). They compared glucose decay curves to PiCCO-derived measures of central blood
volume daily for 5 days in 20 critically ill patients. Surprisingly, they demonstrated a good correlation between the two techniques ($R^2 = 0.79$). To the extent that measures of central blood volume, as a surrogate for preload, are clinically useful, then this safe technique using a readily available intravascular marker may be worth considering.

4. Functional Hemodynamic Monitoring

If absolute measures of cardiovascular values can not be used effectively as parameters describing cardiovascular status or responsiveness, then more provocative maneuvers need to be employed to improve the utility of these measures. Such provocative approaches comprise the broad field of monitoring techniques, referred to a functional hemodynamic monitoring.

Central to assessment of sufficient volume are the principles of Functional Hemodynamic Monitoring.

- Is blood flow adequate to meet metabolic demands (tissue wellness)?
- Will decreasing intravascular volume increase cardiac output and blood pressure?
- How can volume removal be increased (or decreased) to optimize fluid and solute removal?

The commonly used indicators for tissue wellness, preload responsiveness, vasomotor tone and cardiac contractility are reviewed below and summarized in table 2.

a. Indicators of Tissue Wellness. The current trend in monitoring is toward less invasive methods and goal directed therapy [36]. Mixed venous oxygen saturation (SvO$_2$) remains the most accurate method by which to assess tissue wellness, however the declining use of pulmonary artery catheters has limited the practical application of this assessment tool in acute kidney injury. Recent interest in using central venous O$_2$ saturation (ScvO$_2$) as a surrogate for SvO$_2$ has raised the issue of co-variability of these two measures and the use of a specific threshold ScvO$_2$ to identify tissue ischemia (usually identified by an SvO$_2 < 70\%$) Rivers et al (37). Reinhart et al. (39) compared both SvO$_2$ and ScvO$_2$ in 29 patients instrumented with both catheters followed continuously for over 1000 hours making both fiberoptic and in vitro measures.
Importantly, they found that the central venous $O_2$ catheter more accurately estimated ScvO$_2$ than spot \textit{in vitro} measures and was not affected by either simultaneous infusion of fluids through the catheter, or by changes in hematocrit, temperature or blood pH. More importantly, although ScvO$_2$ tracked SvO$_2$, it tended to be $7 \pm 4\%$ higher. Furthermore, changes in ScvO$_2$ paralleled SvO$_2$ changes 90% of the time when SvO$_2$ changed by $\geq 5\%$. Thus, ScvO$_2$ values of 74% may be associated with SvO$_2$ values of 68%.

However, these global perfusion indices as well as measures of regional perfusion and/or organ function are non-specific markers of volume status since organ dysfunction and derangement in cellular metabolism may occur in the absence of tissue flow abnormalities, particularly in sepsis. The gut mucosa is one of the earliest tissues to be compromised and is especially vulnerable to hypoperfusion because of the countercurrent flow in the microcirculation. Gastric tonometry has been shown to be more sensitive than global hemodynamic parameters in detecting occult hypovolemia \cite{39,40}. The gastric mucosal-arterial pCO$_2$ gap (Pg-aCO$_2$) is the variable of choice because, it is independent of systemic acid-base disturbances \cite{41,42}.

Less invasive measures of tissue wellness include commonly used blood tests such as serum lactate levels and the development of metabolic acidosis. Newer noninvasive tools that may also be useful include monitoring of reoxygenation of tissue oxygen saturation (StO$_2$) after peripheral arterial occlusion, as well as sublingual CO$_2$ monitoring, however the application of these technologies may be limited outside of the ICU setting. Finally, clinical measures of tissue wellness include assessment of capillary refill, peripheral cyanosis, tachycardia and blood pressure, although abnormalities in these parameters are often late indicators of tissue wellness.

\textit{b. Indicators of Preload Responsiveness.} A positive response to fluid administration or preload responsiveness can be predicted by the presence of (mechanical ventilation-induced) respiratory variations of systolic pressure \cite{43-47}, pulse pressure \cite{48-52}, stroke volume \cite{53}, or aortic flow velocity \cite{54}, which are currently considered the most reliable parameters to diagnose volume deficit \cite{52,55}. In less critically ill patients
preload responsiveness can be determined by evaluating variations in pulse oximetry density and measuring intrathoracic blood volume measured with the COLD or PiCCO system (transpulmonary thermo-dye dilution or transpulmonary thermodilution). Volume-related preload indices show a better correlation with stroke volume (19,20,23,24,25,55-60). End-diastolic ventricular volume can be measured with transesophageal echocardiography. This method requires training and experience and may be subject to interobserver variability (61-63). Right ventricular end-diastolic volume can be measured with a pulmonary artery catheter equipped with a fast-response thermistor (64,65).

Dynamic tests such as fluid challenges or lifting the legs with observation of trends in filling pressure and stroke volume responses have broader application (64,65). Finally in specific circumstances urine and blood tests such the BUN/SCr ratio, the urine fractional excretion of urea (FeUrea) and the urine fractional excretion of sodium (FeNa) may also indicate insufficient renal perfusion.

c. Indicators of Vasomotor Function and Contractility. Measures of vasomotor tone and cardiac contractility can be directly assessed in the intensive care unit using a variety of both invasive and noninvasive methods, but must generally be inferred outside of the ICU setting.

d. Classical Monitoring Tools. The renal system has the primary role of maintaining fluid homeostasis on a continual basis. Perterbations in intravascular volume lead to a series of physiological changes aimed at preserving tissue perfusion. A reduction in intravascular volume results in a rapid water and sodium resorption by the kidneys. A variety of clinical parameters are available to assess such states. These include; Blood pressure, tachycardia, altered of mental state, poor capillary refill, core peripheral temperature gradient, and oliguria/anuria. Unfortunately, these tend to be rather late indicators of sufficient volume status and detect more severe states of hypovolemia (66-69). The application of such signs in terms of percent dehydration, including changes in body weight, has long been utilized in the pediatric population (70).
The use of biochemical parameters and urinary chemistries have also been employed in assessing sufficient volume status and potential AKI development in both adult and pediatric patients. History and clinical suspicion remain important. Simple tests using either urine and serum or a combination of both may help in defining sufficient volume state. Many entities leading to AKI demonstrate specific patterns of biochemical and urinary findings that are useful in assessing sufficient volume status.

5. Renal Function Tests

Renal function tests may be categorized mainly by those that measure renal blood flow, glomerular function, and/or tubular function. The latter tests measure urinary concentrating ability and sodium and urea handling. These may provide some useful indices in order to distinguish between prerenal and intrinsic AKI. Additionally these tests may be helpful in deciding whether the AKI is potentially volume responsive (71).

Examples of tubular function tests:

- Urinary concentrating ability
- Urine to plasma osmolar ratio
- Free water clearance
- Urine to plasma creatinine ratio
- Urine sodium
- Fractional excretion of sodium (FeNa)
- Fractional excretion of urea
- Indices of tubular injury
  - β2 microglobulin
  - Urinary N-acetyl beta D-glucosaminidase
  - Neutrophil gelatinase associated lipocalin
  - IL-18 (72)

Even though some thresholds have been established for these tests in order to differentiate prerenal and intrarenal AKI, there is not a single test with complete efficacy. Urinary indices may be misinterpreted and unable to distinguish between volume responsive AKI and intrarenal injury (73,74).

a. Urine and blood tests. AKI may characterized by increases in blood urea nitrogen (BUN) and serum creatinine (Cr) levels. Evaluation of the pediatric patient takes on a
different dimension compared to adult patients with ARF. The normal creatinine values in pediatrics are varied and depend on age and body mass (75). Indeed, AKI in pediatric patients may go undiagnosed if the clinician doesn’t take into account the size and age of the patient as many laboratories do not specify age appropriate creatinine ranges. Creatinine clearance in children and adolescents may be approximated by using the Schwartz equation (76).

b. Serum Urea/Creatinine ratio. Urea is passively reabsorbed in the proximal tubule due to increased sodium and water reabsorption seen in hypovolemia. Thus, a high serum urea/creatinine ratio is suggestive of prerenal AKI. Where serum urea and creatinine are reported in mg/dl, a ratio exceeding 20:1 suggests prerenal causes and a ratio of 10-15:1 suggests ATN. Where serum creatinine is reported in µmol/L and urea reported in mmol/L a urea-to-creatinine ratio>0.10 and urea>10 mmol/L (60 mg/dl) is suggestive of prerenal ARF (77,78).

This ratio is of limited value in the setting of high patient catabolic rate, gastrointestinal bleeding or corticosteroid administration. Under these circumstances urea will be elevated and therefore the ratio will be elevated in the absence of hypovolemia. A high ratio may also be noted in patients with decreased muscle mass. A normal ratio cannot exclude prerenal causes of AKI in the presence of decreased protein intake or liver disease.

c. Fractional excretion of sodium (FE$_{Na}$). Urine sodium can be used to estimate the patient’s sufficient volume status. In situations of hypovolemia, urine sodium is usually less than 20 Meq/L (79). However, low urine sodium may be found in normovolemia associated with acute glomerulonephritis (80). The contrary can also be seen, where high urine sodium is noted in the face of hypovolemia in cases of diuretic use, Bartter’s syndrome, adrenal insufficiency and chronic renal disease among others (81-83). Water reabsorption also influences urine sodium. For example, in polyuric patients with diabetes insipidus, a daily normal excretion of sodium can be associated with low urine sodium due to dilution and thus labeled as hypovolemia. To avoid this situation, the renal handling of water can be assessed by using FE$_{Na}$.
FE\textsubscript{Na} is easily calculated from a random urine sample. It is often used in cases of AKI. In cases of hypovolemia, most sodium should be reabsorbed in the proximal tubule and thus the FE\textsubscript{Na} should be less than 1 percent. If the tubules are damaged as seen in acute tubular necrosis, the FE\textsubscript{Na} is often in the range of 2-3\% (79,84). The FE\textsubscript{Na} can be calculated as follows (80).

\[
FE_{\text{Na}}(\%) = \frac{\text{Quantity of Na}^+ \text{excreted}}{\text{Quantity of Na}^+ \text{filtered}} \times 100 = \frac{U_{Na} \times Pcr}{P_{Na} \times Ucr} \times 100
\]

Where, the amount of Na excreted is equal to the product of urine concentration of Na (\(U_{Na}\)) and urine volume (\(V\)); the amount of Na filtered is equal to the product of the plasma concentration of Na (\(P_{Na}\)) and the glomerular filtration rate (\(Ucr \times V/Pcr\)).

FE\textsubscript{Na} can be less than 1\% in conditions other than hypovolemia such as congestive heart failure, nephrotic syndrome or hepatic cirrhosis (79). It can also be less than 1\% in contrast nephropathy or heme pigmentation nephropathy (79). Urine sodium and FE\textsubscript{Na} are unreliable if diuretics are given. If measured, urine should be collected based on the half-life of the diuretics administered. Caution should also be exercised in the neonatal population when using this ratio. FE\textsubscript{Na} is appropriately elevated in newborns making the transition from intra to extra uterine life. This ratio is even less reliable in those infants born pre-term.

d. Fractional excretion of urea (FE\textsubscript{UN}): Due to the limited value of the FE\textsubscript{Na} in circumstances where diuretics have been administered the measurement of fractional excretion of urea (FE\textsubscript{UN}) has been proposed as an alternative. In states of clinical dehydration, the urinary excretion of urea should also decrease (85). The FE\textsubscript{UN} should be less than 35\% in hypovolemic states of prerenal AKI while in the case of ATN it should be above 50\%. A hospital based prospective study conducted comparative analysis of FE\textsubscript{Na} and FE\textsubscript{UN} in their respective abilities to differentiate between prerenal AKI and acute tubular necrosis in the presence of diuretics (86). In this study, FE\textsubscript{UN} (<35\%) had a better sensitivity and specificity (85\% and 92\%, respectively) in differentiating AKI due to pre-renal causes vs. ATN particularly where diuretics were employed. More importantly, a high positive predictive value of 98\% was noted for the FE\textsubscript{UN}. Studies evaluating FE\textsubscript{UN} in children with ARF are limited.
e. Other laboratories: While changes in hemotocrit have been thought to reveal changes in volume status, intuitively, one can recognize the limited value of this measure. The hematocrit may be elevated in patients with decreased volume status due to dehydration or quite low in those with acute hemmorhage, both states however can lead to a reduction in sufficient volume to maintain appropriate renal perfusion pressure.

f. Urinalysis and Urine sediment as a determination of sufficient volume. The urinary sediment is an essential part of the work-up of AKI as it may provide clues as to the underlying pathophysiology involved. Indeed every nephrologist should be able to prepare and review spun urines in order to identify histological clues for diagnosis. Abnormalities in urinary sediment are strong indicators of Intrinsic AKI (87,88). A relatively bland acellular +/- clear hyaline casts (typically composed of Tamm-Horsfall protein secreted by epithelial cells from the loop of Henle) urine in the face of a history of low effective circulating blood volume would reaffirm the potential diagnosis of prerenal AKI (88,89). Benign sediment may be seen in patients with postrenal AKI, however hematuria and pyuria can occur, as many will have intraluminal obstruction due to stones or blood clots. Table 3 (90) provides a guide to commonly associated microscopic urinary sediment and urinalysis findings associated with prerenal, renal and postrenal AKI.

g. Novel markers of AKI: Serum creatinine is an easily measured marker of AKI. However, it is generally appreciated that serum creatinine is a relatively inaccurate marker of AKI since a rise in creatinine signifies that damage has already occurred. With improved molecular biology techniques, understanding the molecular underpinnings of AKI have been greatly enhanced in the last few years. This increased knowledge has led to the discovery of early markers of AKI and hence sufficient volume status. The principal utility of these markers is to detect early signs of injury that could lead the clinician to alter fluid management in order to prevent further damage to the kidneys. Early markers may also serve to predict severity of injury and help in monitoring the effect of intervention.
Two excellent reviews on biomarkers in AKI have been recently published (91,92). Biomarkers should ideally be non invasive, reproducible, accurate, reliable and have a high predictive ability (specific and sensitive). They should also be easy to perform and the results should be rapidly available. To date few markers have been used in prospective clinical studies and the most promising ones will be discussed.

**i. Cystatin C:** Cystatin C is a cysteine protease inhibitor protein that, unlike serum creatinine is freely filtered, completely reabsorbed and catabolized by the tubular epithelial cells, and not secreted. It is stable and not influenced by body mass, gender or age. More interestingly, its measurement is simple, automated and easily available (93). One prospective study in an adult population at risk for AKI showed that an increase of 50% in serum cystatin C level predicted AKI one to two days prior to a rise in serum creatinine (94). Another study demonstrated that cystatin C had a better correlation with GFR than serum creatinine in critically ill adults (95). Cystatin C levels were also able to predict the need for renal replacement therapy but could not differentiate among various causes of AKI. Cystatin C measurement has also been useful in kidney transplantation (96). In children, cystatin C has also been demonstrated to correlate with AKI in children suffering from malaria (97). So far, no prospective study on the value of cystatin C in predicting AKI in children has been published.

**ii. Kidney injury molecule (KIM-1):** KIM-1 is a transmembrane receptor that is cleaved and found in urine following ischemic injury (98). Based on a small study, KIM-1 measurement was able to differentiate ischemic renal injury from prerenal causes and chronic kidney disease (98). To date, no large study has validated the predictive value of KIM-1 in AKI in adults. KIM-1 is also undergoing analysis and evaluation for its usefulness as a predictive tool for AKI in children.

**iii. Neutrophil gelatinase-associated lipocalin (NGAL):** NGAL is a protein bound to gelatinase first described in neutrophils (99). Circulating NGAL is normally reabsorbed at the level of the proximal tubule and following ischemia, NGAL is secreted in the thick ascending limb and is found in the urine. A study in 71 children undergoing cardiopulmonary bypass surgery measured urinary NGAL 2 hours post surgery (100).
Twenty children had an increase in urinary NGAL and this increase preceded a rise in serum creatinine by 2 to 4 days. The specificity and sensitivity were excellent i.e.: 98% and 100%, respectively. NGAL has been recently proven to be useful predictor of AKI in patients with HUS (101). NGAL may be increased in patients with infections. Thus its value in diagnosing early AKI in complicated, septic patients may be limited. Urinary NGAL measurement has recently become commercially available.

iv. Interleukin-18 (IL-18): IL-18 is a pro-inflammatory cytokine cleaved to the mature form by caspase-1 and found in the urine following ischemia (102). Many studies have observed an increase in urinary IL-18 that predicts an increase in serum creatinine in diverse patient populations (103-105). It has also been used to differentiate among the diverse causes of ARF (103). When combined with NGAL, it predicted the duration of AKI in children following cardiac surgery (100). It’s easy to perform and a commercial assay is available.

v. Other markers: Many other markers such sodium/hydrogen exchanger isoform 3(NHE3), N-acetyl-β-glucosaminidase (NAG), matrix metalloproteinase 9 (MMP-9) may be useful in early detection of AKI but presently the assays are not easily performed nor is there enough preliminary data to support their use at this time (98,106).

h. Utility of these novel renal injury markers

The value of these markers in predicting AKI is under intense study (92,107). While urinary IL-18 and NGAL are good predictors of AKI, in situations of complex critically ill patients their value may be diminished. Serum cystatin C measurement is promising but large prospective studies in patient populations with complex diseases need to be performed before its utility can be fully established. Before these markers make a significant impact on clinical management in patients developing AKI, there is a need for simple, accurate, inexpensive and rapid methods of measuring them. Prospective studies in diverse pediatric patient groups developing AKI are in process and the results are highly anticipated.
While these predominantly classical tools for monitoring sufficient volume status and the development of AKI have been the mainstay of therapeutic fluid guidance in the past, they fail to recognize many cases of occult hypovolemia and indeed have limited value in states of established AKI where fluid overload becomes the main concern. Since cardiac function and the size of the intravascular space are variables in determining effective circulating volume, the use of blood or plasma volume monitoring techniques provide limited information of sufficient fluid status unto themselves. However, these techniques used in conjunction with the techniques outlined above and below may provide a relatively reasonable assessment of sufficient volume status during RRT and provide guidance for intervention.

**What should be the end-point of fluid resuscitation?**

Fluid resuscitation should be targeted to a specific preload, stroke volume and/or cardiac output rather than to a specific MAP. Careful assessment of the hemodynamic response to fluid challenge not only allows the diagnosis of hypovolemia but also allows titration of fluid. Parameters of preload responsiveness are probably the best variables to define the adequacy of fluid resuscitation (52,27). It is unclear whether increasing hemodynamic variables to supranormal values has a beneficial effect on outcome. Trauma and perioperative patients seem to benefit whereas septic patients do not (108). It is also not clear whether the endpoints of fluid resuscitation should be different in patients with AKI because of the limited capacity to eliminate fluid excess. Whether the use of more invasive monitoring improves outcome remains to proven. Data on the use of the PAC even suggest the opposite (67,109). A small randomized trial showed that resuscitation based on the measurement of EVLW results in a less positive fluid balance and a shorter duration of mechanical ventilation and ICU stay (110). In patients on renal replacement therapy, blood volume (111-113) and cardiac output (114,115) can be monitored with specific techniques applied to the extracorporeal circuit.

**Table 3. Characteristic Urinalysis by Renal Failure Etiology**

<table>
<thead>
<tr>
<th>ARF Diagnosis</th>
<th>URINALYSIS</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Prerenal Causes</td>
<td>Normal</td>
</tr>
<tr>
<td>----------------</td>
<td>--------</td>
</tr>
<tr>
<td>Renal (intrinsic) Causes</td>
<td>Acute Tubular Necrosis</td>
</tr>
<tr>
<td></td>
<td>Glomerulonephritis</td>
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<tr>
<td></td>
<td>Interstitial Nephritis</td>
</tr>
<tr>
<td></td>
<td>Vascular Disorders</td>
</tr>
<tr>
<td>Postrenal Causes</td>
<td>Normal or RBCs, casts, pyuria</td>
</tr>
</tbody>
</table>

**C. What should be monitored during fluid removal with RRT or with diuresis?**

The approach to volume management will need have clear and established goals which may change as the patients’ situation changes. Thus the principles of “goal directed” therapy need to be established with clear endpoints and schedules. It should be understood that the total loss or the rate of loss may or may not mirror the total intake or rate of intake. The ultimate goal of therapy for total loss is to (a) normalize organ perfusion; (b) normalize organ turgor; (c) normalize fluid compartmentalization; (d) normalize fluid composition.

The ultimate goal of therapy rate of removal is to maximize therapy effect while avoiding complications. These include (a) *intravascular disturbances* based on altered refilling rates, disease state vascular permeability variations, overly (or underly) aggressive unaltered removal, therapy choice and finally choice of dialysate/hemofiltrate replacement composition; (b) *volume composition, acid/base and nutritional changes* based in large part by therapy choice and replacement/dialysate composition and (c) *medication ineffectiveness* judged by loss across therapy variations and approaches.
Before we can judge the appropriate indicators for monitoring the therapy chosen, one needs to ask some basic questions related to the specific goal desired. These basic questions to be answered are:

What are the physiologic principles that govern fluid distribution?

What is (are) the target organ(s) considered with volume removal?

What is the total amount projected to be removed?

What method would be the most appropriate?

What time course is most appropriate at specific timeframes?

Once these issues have been established, the choice of indicators used to monitor volume removal will need to be chosen. This choice will be based upon invasive or non-invasive methods as well as target goals for specific organ function. Perhaps the most limiting factor is the compartment with which one is connected. Most extracorporeal therapy rely on the plasma space as entry to bodily fluids. It is therefore important to utilize indicators which will judge this “relative” space as a gage to entry into areas of interest. Indeed the relative changes in volume in this space may help in judging the rate dependency of the effort as well as the arrival point of therapy.

The most frequently utilized indicator is pressure. Although CVP elevations (> 10 mm Hg) reflects volume overload, if present, values < 10 mm Hg have no prognostic implications. As described above, only functional measures, like PPV and SVV during positive pressure breathings of the change in mean flow during passive leg raising of 30
reflect well preload responsiveness. Hopefully, pulse oximetry density change can be used as a surrogate for PPV, making this parameter more useful.

Another popular indicator of rate adjustment has been the relative blood volume as judged by hematocrit change in a constant RBC environment or albumin concentration variation over a timed constant ultrafiltration. Both the nature of volume removed as well as the ability of volume replenishment across compartmental barriers into this space can be projected by these relative concentration changes (see physiology). While this is extremely important in the performance of the extracorporeal therapy per se, it may be less clear whether these changes have physiological effects in avoidance of hemodynamic complications. There is also no advantage to the “absolute” blood volume determination in the dynamic state, but may have a role in end-point judgement. Overall tissue perfusion can be a relatively simple yet quite important monitor to volume management.
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Authors:

In alphabetic order:

Patrick Brophy, MD
University of Michigan
Email: pbrophy@med.umich.edu

Juan Padilla, MD
Universidad de Iberoamerica
Email: apadilla@racso.co.cr

Emil Pagannini, MD
Email: PAGANIE@ccf.org

Nees Pannu, MD
Division of Nephrology and Immunology
CSB 11-107h
E:Mail: neesh.pannu@ualberta.ca

Michael R. Pinsky, MD
University of Pittsburgh Medical Center
E-mail : pinskymr@upmc.edu