Septic shock in ICU: update in hemodynamic monitoring

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ABSTRACT

In recent decades, new and important concepts have emerged for the diagnosis and management of the pediatric patient with septic shock, although the basic principles have remained similar over time. Attending physicians in the pediatric intensive care unit (PICU) must be fully aware of these concepts in order to improve patient care in the critical care unit. Hemodynamic monitoring is a tool that not only allows detection of the source of hemodynamic instability but also guides treatment and assesses its effectiveness. Fluid loading is considered the first step in the resuscitation of hemodynamically unstable patients. Nevertheless, clinical determination of the intravascular volume can be extremely difficult in a critically ill patient. Studies performed have demonstrated that cardiac filling pressures are unable to predict fluid responsiveness. Dynamic tests of volume responsiveness use the change in stroke volume during mechanical ventilation assessing the patients’ Frank-Starling curve. Through fluid challenge the clinician can assess whether the patient has a preload reserve that can be used to increase the stroke volume. In this review we updated the available information on basic and functional hemodynamic monitoring.

Key words: sepsis, septic shock, functional hemodynamic monitoring, fluid challenge, stroke volume, volume responsiveness.

INTRODUCTION

Septic shock is a clinical challenge both in the emergency department as well as in the pediatric intensive care unit. Early diagnosis that allows for a rapid therapeutic intervention is essential in order to obtain improvement in the prognosis of these patients. Current treatment includes the use of fluids, vasopressors in resuscitation and adjuvants such as hydrocortisone. New therapies also appear to be promising, although their efficacy and safety still remain a topic of debate. A transcendental part in the overall focus of the septic patient is hemodynamic monitoring. This has great significance because, together with detection of the origin of the hemodynamic instability, it allows for guidance and evaluation of the efficacy of the treatment used.

The objective of this review is to summarize the present status of basic and functional hemodynamic monitoring, emphasizing in the latter the new indices called dynamic indices of fluid response, which have been progressively incorporated into clinical practice.

HEMODYNAMIC PARAMETERS FOR GUIDING FLUID THERAPY

One of the cornerstones of treatment of the patient in shock is the use of intravenous fluids. However, its use and dosage is still carried out empirically. Fundamentally, the only reason for providing fluids to a critically ill patient is to increase the systolic volume (SV) and, in this manner, the cardiac output (CO). However, taking into consideration that only 50% of critical patients respond to fluid expansion, due to myocardial dysfunction and altered adrenergic sensibility, the hemodynamic parameters for deciding on administration of these fluids should identify those patients (responsive patients) who would benefit and at the same time avoid useless and potentially harmful treatments for those who would not respond.

The risk of an insufficient dose of fluids is tissue hypoperfusion which, in an uncorrected picture of hypovo-
leemia, would cause the inappropriate use of vasopressors that exacerbate even more the hypoperfusion. In contrast, an excessive amount of fluids may alter oxygen delivery ($DO_2$) and also be associated with a series of complications that will result in a longer stay in the ICU or in the hospital and in an increase in mortality. We should point out that the inadequate use of fluids occurs in the circumstances noted below:

1. When administered based on the macrohemodynamics of the patients without any real evidence of hypoperfusion
2. Once the hypoperfusion is corrected, when the volemia continues to be expanded
3. When attempting to revert with fluids a state of hypoperfusion that is not dependent on fluids (cardiovascular dysfunction)
4. When fluids are given in a context where the risk/benefit ratio is unfavorable such as in acute respiratory distress syndrome (ARDS) or abdominal compartment syndrome (ACS)

Multiple publications have demonstrated that a positive fluid balance is associated with a poor prognosis in adults and children. Boyd et al. demonstrated that both at 12 h as well as at the fourth day of evolution, larger fluid balance values are associated with a significant increase in mortality. Flori et al., in a post-hoc analysis, concluded that a persistently positive fluid balance is deleterious in pediatric patients with acute lung injury (ALI) because it causes more days on mechanical ventilation (MV) and higher mortality, independent of the magnitude of the oxygenation failure or severity of the organ failure.

In the same way, Arikan et al. demonstrated that patients with a greater percentage of fluid overload had greater deterioration of oxygenation, greater duration of MV and longer stay in ICU, independent of the age, gender and degree of severity.

In order to decide on the amount of fluids to administer, it is essential to determine whether or not there are signs of hypoperfusion. This is occasionally easy due to the presence of evident signs of shock. However, on other occasions there are more subtle signs of hypoperfusion.

Thus, on the face of signs of inadequate tissue perfusion, usually a first step in the resuscitation process is fluid administration. The expected result of the expansion would be an increase in SV and CO because as the preload is greater, the SV is greater (Frank-Starling Law). It should be remembered that, physiologically, the preload is understood as all the factors that contribute to the passive stress (tension) of the ventricular wall at the end of the diastole and is one of the main determinants of CO. In turn, the optimal preload is defined as the degree of maximal stretching or tension of the myocardial fibers before the start of the ventricular contraction. In clinical practice this definition is not easily applicable, for which reason the intracavitary pressures or telediastolic volumes are substituted, assuming that these two parameters exactly reflect the elongation of the muscular fibers.

However, it must be considered that the relationship between the preload and the SV is not linear. Therefore, once a determined value of the preload is reached, the increases after that will not have a significant translation in the SV (Figure 1). Two parts can be identified in this curve: an ascending or dependent preload zone and another flat or independent preload zone. Under normal conditions, both ventricles operate in the ascending part of the curve. This is the mechanism that allows us to have

![Figure 1. Schematic representation of the cardiac function curve (Starling curve).](https://www.medigraphic.org.mx)
a functional reserve under stress conditions.\textsuperscript{18} During states of hypoperfusion, the positive response will be an increase of the SV. However, this will only occur if both ventricles are operating on the ascending part of the curve. When a positive response is observed, the patient will be categorized as “fluid responsive”; however, if there is no response the fluid load may be harmful. Therefore, repetitive “fluid boluses” should be discontinued if the patient does not respond or if there is a significant increase of the extravascular lung water observed if there is a possibility of monitoring the latter.\textsuperscript{10} Nevertheless, the increase of the SV as a result of a fluid test depends not only on the increase in the preload, but also on the ventricular function and ventricular afterload. Reduction of the contractility decreases the degree of the slope of the relationship between the preload and the SV (Frank-Starling curve) (Figure 2).\textsuperscript{19}

Static parameters such as central venous pressure (CVP), which is most frequently used, are traditionally used to guide fluid therapy. Based on the mistaken principle that the CVP reflects the intravascular volume,\textsuperscript{20} it is widely assumed that patients with “low CVP” are volume depleted, whereas patients with “high CVP” have volume overload.

CVP is a good approximation of the right atrial pressure (RAP), which in turn, is a major determinant of right ventricular (RV) filling. As the stroke volume of the RV determines the filling of the left ventricle (LV), it is assumed as an indirect measure of the preload of the LV. However, due to various factors such as changes in venous tone, the magnitude of the intrathoracic pressures, distensibility of the ventricles, stressed and non-stressed blood volume and mean systemic pressure,\textsuperscript{21} there is a poor relationship between the CVP and the volume of the end diastolic pressure of the right ventricle.

It has been documented that the real value of the CVP is a poor predictor of the volemic state. There is a superimposition among the values of the CVP in the group of responsive and non-responsive patients to fluids, without the possibility of establishing a differential threshold value for the groups.\textsuperscript{22,23} Recently, a systematic review confirmed that there is no association between the CVP and the circulating blood volume and does not predict the fluid response in a wide spectrum of clinical conditions.\textsuperscript{24}

Like the CVP, the pulmonary artery occlusion pressure (PAOP) is not a reliable parameter for evaluating the fluid response because its relationship with CO is influenced by the distensibility of the LV, the contractility of the myocardium or the juxtacardiac pressure.\textsuperscript{5,25-27}

Other static indices for evaluating fluid response are the volume and ventricular areas of end diastole (tele-diastolic volumes of the right and left ventricle, global end-diastolic volume index, LV end-diastolic area).\textsuperscript{17,28} However, similar to the filling pressures, they are poor predictors of fluid response.

In conclusion, static parameters (whether volumetric or pressure) are not reliable predictors of fluid response because, on being isolated measures, the curve of the ventricular function and in which zone it is found are unknown. Therefore, they should not be used routinely to guide fluid therapy.

\textbf{FUNCTIONAL HEMODYNAMIC MONITORING AND CARDIOPULMONARY INTERACTIONS DURING MECHANICAL VENTILATION}

Dynamic parameters, as opposed to static parameters, provide a functional evaluation of the cardiac output on the face of preload modifications also allowing determination of which zone of the Frank-Starling curve both ventricles operate.
**DYNAMIC CHANGES IN THE STROKE VOLUME**

**Stroke volume variation and pulse pressure variation**

A large number of studies have demonstrated that the variation of the stroke volume, (SVV, stroke volume variation) (derived from the arterial pulse contour analysis), the pulse pressure variation (PPV) (derived from the analysis of the arterial wave) and the variation of the amplitude of the plethysmographic wave of the pulse oximetry are measurements highly predictive of the fluid response.

This is based on cardiopulmonary interaction during the use of mechanical ventilation where intermittent positive pressure ventilation induces cyclic biventricular changes.

The main mechanism occurs in the RV during inspiration where the increase in intrathoracic pressure results in a decrease of the preload to hinder venous return by decreasing the pressure gradient between the mean systemic pressure and the atrial pressure. At the same time, the afterload increases in relation to the inspiratory increase of the transpulmonary pressure (TPP). This finally determines a fall of the EV of the RV (which is minimal at the end of the inspiratory period). On the other hand, the blood volume contained in the lung is “squeezed” towards the LV, increasing its preload and its EV during inspiration. After the interval of two or three beats (blood pulmonary transit time), a decrease in the filling of the LV is noted. Thus, the fall of the preload of the LV induces a decrease of its stroke volume, which is minimal during the expiratory period (Figure 3).

SVV can be determined by the use of hemodynamic monitoring devices based on arterial pulse contour analysis. A variation of >10% is predictive of a positive response to the administration of fluids with high sensitivity and specificity in the majority of published studies.

Some authors describe the maximum systolic volume. This consists of administering multiple fluid loads to identify the flat part of the curve of the LV function. This is an important concept to understand because even though researchers use the term “maximum”, what they are really looking for is to increase the systolic volume in at least 10% to allow a judicious quantity of fluids, which has shown improvement in results perioperatively.

Pulse pressure (systolic pressure minus diastolic pressure) and its variation (PPV) is defined as the amplitude of cyclical changes in arterial pulse pressure (Figure 4). At the aortic level, pulse pressure is directly related with the SV of the LV and is inversely related to aortic compliance. Assuming the aortic compliance does not vary during the breathing cycle, changes in pulse pressure exclusively reflect variations of the SV. Typically, hemodynamic effects of the positive-pressure mechanical ventilation. Cyclical changes in left ventricular systolic volume (LVSV) are mainly related to the decrease in LVSV preload during expiration due to decreased right ventricular (RV) filling during inspiration. The magnitude of these changes is proportional to the degree of preload-dependence, i.e., they are more pronounced when the ventricles operate on the ascending part of the Frank-Starling curve. Finally, the magnitude of the respiratory changes in the stroke volume of the left ventricle (LV) are indicators of biventricular preload dependence.

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**Figure 3. Cardiopulmonary interactions.**
patients undergoing mechanical ventilation have a small PPV (1-5%). In a study by Michard et al., it was determined that changes >13% allow for discrimination between responsive and non-responsive patients with a 94% sensitivity and 96% specificity. At the same time, the baseline PPV value correlated closely with the increase in cardiac index in response to the fluid expansion: the higher the PPV before expansion, the greater the increase in the cardiac index.

However, these parameters may not be used in any patient because they have limitations as mentioned below:

1. Need for controlled mechanical ventilation. If there is spontaneous respiratory activity, the pressure it creates would overlap with the ventilator effect, making its interpretation difficult. This has been demonstrated in at least three studies in critically ill patients.
2. Cannot be used in patients with cardiac arrhythmias.
3. Needs a tidal volume >8 ml/kg of ideal weight because in this way there would be a significant modification in intrathoracic pressure to cause a change in the preload.

4. In the presence of right ventricular dysfunction, increased transpulmonary pressure and the consequent increase in RV postload during inspiration may cause a decrease in the EV of the RV unrelated to the preload dependency.

5. Not applicable in patients with high-frequency ventilation (HFOV). In conventional mechanical ventilation, decreased LV filling secondary to the decrease of the EV of the RV during inspiration occurs two to four beats later, being manifested during expiration. In HFOV, these two events may occur during the same period of the respiratory cycle.

**End-expiratory occlusion test (EEOT)**

It is hypothesized that upon interrupting mechanical ventilation at the end of expiration for a period of 15 sec, the preload increases due to an increase of the venous return in such a way sufficient to predict a fluid response. Recently, Monnet et al. validated this hypothesis in patients with circulatory failure. Responsive patients demonstrated an increase of the pulse pressure and cardiac index with this maneuver.

It is also possible to apply this test to patients with arrhythmia in whom a partial ventilatory modality is being used or in patients with ARDS with low pulmonary compliance where the use of the PPV and SVV do not present greater usefulness.

**Passive leg elevation**

On occasions where the PPV and SVV are not applicable, for example, in patients with spontaneous breathing, this maneuver can be performed. Its use is based on gravitational transfer of blood from the lower extremities and abdominal compartment to the intrathoracic compartment. It has been shown that the amount of blood transported to the heart (equivalent to 4.3 ml/kg fluid infusion) is sufficient to increase the LV preload and thus assess the Frank-Starling curve. The advantage of this operation is that it can be considered as reversible autotransfusion.

The maximum hemodynamic effect, the increase of the CO (evaluation in real time), occurs between 30 and 90 sec after the maneuver is carried out. It is considered positive if the CO increases at least 10% during the maneuver, which could predict an increase of the CO >15% with a fluid load.
Lukito et al. documented that in children (1-8 years, 27% with mechanical ventilation, evaluated with transthoracic Doppler echocardiography) an increase of 10% of the CO during this maneuver was associated with an increase >10% of the CO in response to a fluid load, with a sensitivity of 55% and specificity of 85%. In turn, the authors verified that neither changes in systolic pressure nor in heart rate during this maneuver predicts a response to fluids. This reaffirms that the PPV in patients with spontaneous ventilation is not sufficiently sensitive to detect changes in the EV.

**FLUID CHALLENGE**

Critically ill patients frequently require fluids that are administered to reverse the hypovolemia. However, many times the quantity given is insufficient or excessive, which leads to adverse effects. The fluid challenge (FC) allows the physician to give fluids and at the same time evaluate the cardiovascular response, which allows for identification of those patients who probably would benefit from an increase in the intravenous volume. The difference with respect to the fluid load is that it consists of giving volume without evaluating the real-time response.

It must be emphasized that if a septic patient responds to a fluid test, it does not necessarily mean that a fluid bolus is necessary. It is necessary to first determine if the patient needs fluid intake or not. It is thus concluded that the response to fluids should not be confused with need for fluids.

This test is reserved for hemodynamically unstable patients and offers three advantages:

1. Quantify the cardiovascular response during fluid infusion
2. Allow for the correction of fluid deficits
3. Utilize a small quantity of fluids, minimizing the risk of overload and its potential adverse effects, especially at the pulmonary level

The FC is done with the intent to increase the SV or CO. To evaluate the cardiovascular response generated by the FC, there are multiple indicators available that are used both as guides for the administration, as predictors, goals and limits of safety. To choose one or the other depends on the clinical situation or on the availability of the particular monitoring of each ICU.

For the FC, colloids as well as crystalloids can be used as there are no demonstrated advantages of one over the other. It was recently reported that the use of colloids does not reduce the risk of death, compared with the crystalloids. Therefore, the need for the type of fluid used will depend on the clinical condition.

However, more important than the type and amount of fluid administered is the rate of administration. Small amounts are provided, usually 3 ml/kg (maximum 250 mL) in 5 to 10 min. A patient will be considered to be responsive when the SV increases by 10-15%. Despite using small aliquots, these should be sufficient to increase end-diastolic volume of the right ventricle. If these are insufficient, the SV cannot increase and there is the risk of a false negative.

In conclusion, the FC is neither new nor complex. It allows evaluation of the cardiovascular response at the patient’s bedside and, simultaneously, prevents fluid overload.

**MONITORING CARDIAC OUTPUT (PICCO SYSTEM)**

The clinical signs for recognizing inadequate DO₂ are nonspecific, and the ability to estimate a reduced CO in children through physical examination is very limited.
Table 1. Global hemodynamic, systemic and regional perfusion targets.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Arterial pressure</td>
<td>Universally available. Inexpensive. Continuous measurement, reliable and reproducible.</td>
<td>No prediction of hypoperfusion states.</td>
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<tr>
<td>Central venous pressure (CVP)</td>
<td>Easy to measure. Possibly useful trends.</td>
<td>Poor correlation between CVP and preload. No prediction of fluid response.</td>
</tr>
<tr>
<td>Mixed venous saturation of oxygen (SvO₂)</td>
<td>Gold standard for measuring venous saturation of oxygen.</td>
<td>Requires instillation of a catheter in the pulmonary artery along with its inherent risks.</td>
</tr>
<tr>
<td>Central venous saturation of oxygen (SvO₂)</td>
<td>Easy to measure. Reliable alternative for SVO₂. The trend over time is useful.</td>
<td>Normal value does not exclude deterioration in local perfusion.</td>
</tr>
<tr>
<td>Arteriovenous difference of CO₂</td>
<td>Easy to measure. Inexpensive. Permits indirect evaluation of CO output.</td>
<td>Requires central venous access.</td>
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<td></td>
<td>Is inversely correlated with CO. Possible useful tendencies.</td>
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<td></td>
<td>Can complement information delivered by ScvO₂.</td>
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<tr>
<td>Lactacidemia</td>
<td>Easy to measure. Inexpensive. Time trend is prognostic.</td>
<td>Multiple mechanisms alter its value.</td>
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<tr>
<td>Base deficit</td>
<td>Easy to measure. Inexpensive.</td>
<td>Shock is not the unique factor affecting base deficit. Predictive value depends on the patient population.</td>
</tr>
<tr>
<td>Analysis of the contour of the arterial pulse wave (PICCO, Pulse-induced Index Contour Cardiac Output)</td>
<td>Minimally invasive. Continuous delivery of CO. Provides additional information on volumetric estimation of preload and EVLVW. PPV &gt;13% is highly sensitive and specific for detection of fluid response. It is validated in pediatric patients and models.</td>
<td>Validity of the measurements is affected by arrhythmias, intracardiac shunt and extreme alterations of vascular tone. Transpulmonary thermodilution is not the gold standard to measure CO. Consensus does not exist in relation to normal values for the pediatric population.</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Information in real time of anatomy and cardiac function.</td>
<td>Requires training and accreditation.</td>
</tr>
<tr>
<td>Near-Infrared Spectral Imaging, NIRS</td>
<td>Noninvasive. STO₂ of skeletal muscle presents a good correlation with measurements of systemic delivery of oxygen.</td>
<td>Expensive equipment. Is not universally accepted.</td>
</tr>
<tr>
<td>Regional capnometry</td>
<td>Minimally invasive. Immediate results.</td>
<td>Equipment in refinement. Significant variability in PCO₂ tissue levels among individuals.</td>
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</table>

EVLW, extravascular lung water; CO, cardiac output; PPV, pulse pressure variation; STO₂, tissue oxygen saturation.
should always be kept in mind that for the correct interpretation of the CO (especially low cardiac output) various factors must be considered (Figure 5).

Moreover, the measurement of CO in children is unusual, given that the methods are invasive and can present technical limitations (pulmonary thermodilution, PTD), low accuracy (direct Fick principle) or require a high level of training (echocardiography).

The PiCCO System (Pulse Index Contour Cardiac Output) refers to cardiac output by arterial pulse contour analysis (Pulsion Medical Systems, Munich, Germany). It allows for calculation of the CO in a minimally invasive manner using a CVC and an arterial catheter (usually femoral), avoiding in this way introducing a catheter in the pulmonary artery. This device is based on the same basic principle of the thermodilution to estimate CO, which uses an injection of cold intravenous fluid as an indicator (SF 0.9%, <8°C). Temperature changes in blood flow are measured in order to calculate the CO (transpulmonary thermodilution, TPTD). The CO determined in this manner correlates well with thermodilution estimates in the pulmonary artery and shows less dependent variations of the respiratory phase.50-52

The PiCCO system provides useful clinical information of a continuous hemodynamic character.53 It also allows to evaluate the volumetric preload by means of a global volume at the end diastole (global end-diastolic volume, GEDV) and the extravascular lung water index.54

It should be emphasized that the values found in the pediatric population are different from those usually involved in adult treatment algorithms. This should be considered when they are used in younger children in which the values of intrathoracic and intracardiac volume are lower in adults and the extravascular lung water values are higher.55-57

However, as in all procedures, this may present risks and complications such as the ischemia derived from arterial catheterization.58

Finally, it should be noted that all the parameters used to evaluate overall, regional hemodynamics and perfusion of the patient with septic shock, interpreted as an absolute value and individually, have limitations in adequately reflecting the hemodynamic status and tissue perfusion in patients with circulatory dysfunction (Table 1).

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