Current haemodynamic management of septic shock

Jean-Louis Vincent, Diego Orbegozo Cortés, Angela Acheampong

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Erasme University Hospital, université libre de Bruxelles, Department of Intensive Care, route de Lennik 808, 1070 Brussels, Belgium

Correspondence:
Jean-Louis Vincent, Université Libre de Bruxelles, Erasme University Hospital, Department of Intensive Care, route de Lennik 808, 1070 Brussels, Belgium.
jlvincen@ulb.ac.be

Summary

Early and adequate resuscitation of patients with acute circulatory failure is important to restore the balance between oxygen needs and delivery. Haemodynamic management can globally be separated into three categories according to the VIP mnemonic – Ventilate, Infuse, Pump – which should be considered simultaneously in the patient with shock. Sufficient oxygen should be given early, and endotracheal intubation and mechanical ventilation performed without hesitation if there is any indication that oxygenation is inadequate. Fluids should be administered using the SOSD mnemonic – Salvage, Optimization, Stabilization, De-escalation. After initial liberal administration, ongoing requirements should be guided by repeated fluid challenges using a combination of balanced crystalloid solutions and colloid. Noradrenaline is the vasopressor of choice and should be started early. Dobutamine may be needed to improve myocardial contractility and cardiac output. Haemodynamic support should be personalized according to individual patient characteristics and global and regional parameters of haemodynamic and oxygenation status.

Introduction

Shock can be defined as “the clinical expression of circulatory failure that results in inadequate cellular oxygen utilization” [1]. The aim of haemodynamic management in patients with shock, including septic shock, is thus to restore tissue oxygenation. To achieve this goal requires establishment of an adequate tissue perfusion pressure and an optimal oxygen delivery (DO₂). DO₂ is determined by three factors: cardiac output, haemoglobin concentration and the haemoglobin oxygen saturation. Each of these factors must, therefore, be taken into consideration when approaching the patient with shock. Importantly, treatment must be started early to prevent deterioration of organ function.

In this review we will discuss the key aspects of haemodynamic management, including some of the more recent changes in this field. We will base our considerations on the mnemonic proposed by Weil and Shubin [2] many years ago, but still very relevant today: VIP – Ventilate,
Infuse, Pump. Importantly, although we will discuss these three elements separately, in practice they are considered simultaneously.

**Haemodynamic management**

**Ventilate**
The term “ventilate” encompasses provision of oxygen by any method. It is crucial that sufficient oxygen is available in the blood in order to insure adequate $\text{DO}_2$. Initial provision of oxygen to patients with sepsis is relatively straightforward and can now be achieved with high flow oxygen through nasal cannulas [3] instead of non-rebreathing masks. However, the presence of respiratory failure indicates need for endotracheal intubation and early use of mechanical ventilation – there is no real place for non-invasive mechanical ventilation or continuous positive airway pressure (CPAP) in patients with shock; these situations are life-threatening, and respiratory arrest would rapidly lead to cardiac arrest. Mechanical ventilation has the additional benefit of decreasing the oxygen demand of the respiratory muscles and thus potentially improving the overall oxygen delivery: uptake balance. Hence, there should be no real hesitation before endotracheal intubation is performed. The only real precaution is that hypotension should be corrected in patients suspected of being hypovolemic, as the increase in intrathoracic pressure may further reduce venous return and result in even more profound hypotension.

There have been recent questions about the harmful effects of a very high arterial pressure of oxygen ($\text{PaO}_2$). High $\text{PaO}_2$ levels can indeed induce vasoconstriction and, therefore, impair the microcirculation [4]. There have also been some concerns about the harmful effects of high $\text{PaO}_2$ on the brain, notably after traumatic brain injury [5]. Nevertheless, there are several reasons why oxygen administration should still be generous in the early stages of shock resuscitation. The first is that there is no good evidence that hyperoxia is harmful in shock states. Second, in septic shock in particular, brain perfusion is relatively well preserved (the brain is a vital organ), so that brain sequelae are not prominent. Third, because pulse oximetry is often unreliable in shock states when skin perfusion is altered, these patients are usually monitored using repeated blood gases so that $\text{PaO}_2$ levels can be accurately measured and hyperoxia avoided.

**Infuse**
Fluid administration is essential to correct absolute and relative hypovolemia. Absolute hypovolemia may be due to external (sweating, diarrhea…) or internal (oedema formation, intra-peritoneal reaction) losses; relative hypovolemia is due to vaso-dilation. The typical haemodynamic pattern of distributive shock is a high cardiac output (associated with vaso-dilation and normal or high mixed venous oxygen saturation ($\text{SvO}_2$)), so fluid administration is a physiologically sound intervention.

**The importance of the time factor**
Too little fluid is clearly associated with worse outcomes, but too much fluid can also be detrimental potentially leading to systemic and peripheral oedema and their associated consequences, including pulmonary oedema with reduced oxygenation, poor wound healing, and reduced gut function. Fluid administration can thus be considered in different stages according to the patient’s resuscitation phase [1]. Essentially, more fluid should be given in the early phases of resuscitation and less later on as summarized by the SOSD mnemonic: Salvage, Optimization, Stabilization, De-escalation. In the Salvage phase, speed is of the essence and there is no time for repeated monitoring so a quick bolus of about 25-30 mL/kg of fluid should be given. In the Optimization phase, fluid needs should be determined by the results of repeated fluid challenges [6]. In mechanically ventilated, profoundly sedated patients, signs of fluid responsiveness can be used. For example, fluctuations in arterial pressure can be visually appreciated, without need for complex calculations, if an arterial catheter is in situ; or if a cardiac output monitor is in place that allows measurement of stroke volume variation (SVV), then an SVV of at least 10–13 % is very suggestive of fluid responsiveness [7]. However, these measures are only accurate in the absence of spontaneous ventilation, which generally implies the use of sedative agents, although sedation should, whenever possible, be avoided in septic shock, as all sedative agents (with the possible exception of ketamine, which has other problems) can induce alterations in myocardial contractility and vascular tone. Passive leg raising makes sense physiologically (“internal fluid challenge”) and can be used in non-mechanically ventilated patients, but it is not easily accomplished in practice [8]; it also requires a cardiac output monitor that measures SV beat by beat, because the changes in SV are very transient.

Once the patient has been stabilized, fluids should be de-escalated when possible. Several recent studies have shown that excessive fluid administration resulting in positive fluid balances can be associated with worse outcomes [9-11]. Acheampong and Vincent [11] recently reported that persistence of a positive daily fluid balance over time was quite strongly associated with a higher mortality rate in patients with sepsis (figure 1) and that a positive fluid balance was independently associated with higher mortality (adjusted hazard ratio: 1.014 [1.007-1.022] per mL/kg increase, $P < 0.001$).

**Which fluid?**
The optimal type of fluid to give remains controversial despite years of research. It is clear that colloid solutions, which have large molecules that escape less from the interstitium, result in less oedema formation [12], but all colloids have potential detrimental effects, so that a mixture of crystalloids and colloids may be preferable, and may even be associated with better long term outcomes [13]. So-called balanced crystalloids, such as...
Ringer’s lactate or plasmalyte, which are designed to more closely resemble the electrolyte composition of plasma, are preferred over normal saline [14], which can induce hypernatremia and hyperchloremic metabolic acidosis [15], potentially leading to reduced renal blood flow velocity and renal cortical tissue perfusion [16]. Which type of colloid to choose is a little clearer than it was several years ago. Artificial colloids are used less than in the past: dextrans, a carbohydrate-based colloid, has been nearly completely abandoned; hydroxyethyl starch solutions (HES), derived from the starch of maize or potatoes, may be associated with some harmful renal effects (although this is not definitively proven) and were associated with increased mortality rates in one study [17], so that they should not be used in septic shock; with their relatively small molecular weight, gelatins, derived from bovine gelatin, are less effective colloids although are probably fairly safe (although this has never been well studied). Albumin, the only natural colloid, has been considered as costly but in relative terms the costs are not so high today, and it may have beneficial effects in patients with sepsis in addition to volume expansion [18].

Blood transfusions may be considered in anaemic patients, although a recent study randomizing patients with septic shock to a liberal (when the haemoglobin concentration was < 9 g/dL) or restrictive (haemoglobin concentration was < 7 g/dL) transfusion strategy suggested that this approach may not be beneficial [19]. However, as about two-thirds of the patients in the restrictive group and virtually all in the liberal group received a blood transfusion, the key message from that study [19] is that overtransfusion should be avoided. Decisions to transfuse should be made for each individual patient based on specific factors including age, cardiac comorbidity and clinical status [20].

### Pump

The first priority when considering this aspect of haemodynamic management is the need to restore a minimal tissue perfusion pressure. However, it is difficult to define an optimal pressure for all patients. In a large multicenter French trial, patients with septic shock were randomized to resuscitation with a mean arterial pressure (MAP) target of 80–85 mmHg or 65–70 mmHg [21]. There were no differences in outcome between the groups, illustrating that this is not a “one size fits all” effect, rather we need to individualize therapy (personalized medicine). A history of arterial hypertension may suggest a need to maintain a higher arterial pressure; clinical evaluation (skin perfusion, urine output, mentation) can also help to determine the optimal level. Nurses, who are more regularly present at the bedside, are often in the best position to notice these changes.

Noradrenaline is the drug of choice to restore tissue perfusion pressure [22], as it has primarily alpha-adrenergic properties, thus restoring vascular tone, but still some beta-adrenergic properties, which help maintain cardiac output in the presence of the increased afterload represented by the increased arterial pressure. In the not so distant past, vaspressors were recommended and administered only when the response to fluid therapy was insufficient. However, recent data have indicated that any period of hypotension should be avoided, so that there is nothing wrong with giving noradrenaline transiently at the same time as initial fluid resuscitation. Indeed, early noradrenaline administration has been associated with better outcomes [23,24]. However, vaspressors should not be continued when the response to fluids remains positive.

If myocardial depression is suspected, primarily on the basis of an excessive increase in cardiac filling pressure without an increase in cardiac output, then the inotrope, dobutamine, is the drug of choice. Small doses of about 5 mcg/kg/min are usually sufficient. However, vasopressors should not be continued when the response to fluids remains positive.

### Monitoring

In all cases of septic shock, an arterial catheter should be placed so that arterial pressure can be monitored reliably. Unless the shock responds very rapidly to treatment, a central venous catheter should be inserted for several reasons. First, it can be used to facilitate fluid administration; it is also preferable for vasopressor infusion. Second, the central venous pressure...
(CVP) can help to guide fluid administration (using a fluid challenge), the aim being to have a minimal increase in CVP. Third, it can be used for measurements of central venous oxygen saturation (ScvO2), which can provide some indication of the adequacy of tissue oxygenation. Measurements of the venoarterial PCO2 gradient (VAPCO2) may also be of interest, because CO2 diffuses very rapidly. For these reasons, we believe it unlikely that central venous catheters will be replaced by peripherally inserted central catheters.

The first haemodynamic tool should be echocardiography. Any intensivist should be able to use and interpret echocardiography images, especially for transthoracic echocardiography although the transoesophageal approach is not much more complex, without having to call for a specialist. The first aim of echocardiography in this context is not to obtain a sophisticated diagnosis, but just to appreciate the size of the ventricles and the global contractility (and the presence of pericardial fluid, which is common in septic shock). Very thin probes are now becoming available, which will enable the probe to be kept in the esophagus, so that a continuous image can be visualized at the bedside.

Cardiac output monitoring is important not so much to obtain an absolute value, but rather to evaluate trends in values over time. An absolute value is difficult to evaluate especially in septic shock as it is hard to define an optimal value for all patients; this will depend on the oxygen demand, oxygen extraction capabilities, and the haemoglobin level (and the haemoglobin saturation in the presence of hypoxaemia). Cardiac output monitoring is perhaps of most interest when trying to interpret the effects of a fluid challenge in the presence of the sepsis vasodilatory state. Indeed cardiac output will sometimes increase with a fluid challenge but not arterial pressure [26]. But even in these cases, one may ask whether it is not better to increase the doses of vasopressor agents rather than “pushing” fluids.

ScvO2 or ScvO2 (if only a central venous catheter is in place) is at least as important as cardiac output, because it provides information about the balance between the oxygen consumption (VO2) and the DO2. The ScvO2 is expected to be normal or high in septic shock. If this is not the case, and if the patient still has signs of altered tissue perfusion, there are three possible options (figure 2): give more fluids, transfuse, or add an inotropic agent (primarily dobutamine). This approach was the basis of the landmark study on early goal-directed therapy by Rivers et al. [27]. Subsequent large randomized controlled trials were unable to confirm the improved outcomes noted by Rivers group [28–30], but many patients in these studies already had ScvO2 close to 70% initially, in part due to better initial management of these patients. Nevertheless, some patients will still have a low ScvO2, and this variable may help to guide therapy in these circumstances. Importantly too, the fact that ScvO2 is normal or high does not necessarily mean the patient’s condition is satisfactory: indeed, prognosis may be worse in patients with a very high ScvO2 [31]. Hence, fluid administration should not necessarily be withheld when ScvO2 is normal or high [32].

Measurement of blood lactate levels is paramount to identify the presence of altered tissue perfusion and to monitor it, although lactate levels respond relatively slowly so that lactate levels alone cannot be used to guide therapy, but provide an indication that the therapeutic approach is (in)effective and the patient’s condition is (not) improving. Measurements should be made regularly, perhaps every hour during shock. People sometimes refer to “lactate clearance”, but this term is incorrect for two reasons [33]: the first is that lactate levels are based on production and elimination of lactate, not just on clearance; the second is that using the word “clearance” suggests that lactate levels can only go down, but they can, of course, also increase – hence it is the general trend in time course that must be taken into account.

**Conclusions**

The haemodynamic management of the patient with septic shock is much more than just monitoring and correcting the blood pressure. Multiple variables need to be taken into account when assessing a patient’s haemodynamic status and deciding on the most appropriate therapy. These variables and the optimal targets will vary in different patients and management must be adapted to the individual patient and not rely on standardized “cookbook” protocols. Analysis of the trends in values of any variable over time provides valuable information.
about a patient's progress and is of more value than static measures. Optimal patient management requires a team effort with all members of the care team; nurses can be of particular value in these patients as patient condition can change rapidly and (almost) continuous presence at the bedside is warranted.

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