

How to Titrate Vasopressors Against Fluid Loading in Septic Shock

Benoît Vallet, MD, Hervé Tytgat, MD, and Gilles Lebuffe, MD

Department of Anaesthesiology and Intensive Care Medicine, University Hospital of Lille, Lille, France

The initial management of patients with septic shock includes ensuring oxygen supply, fluid therapy, consideration of inotrope or vasopressor therapy, and specific treatments to address the cause. The assessment and treatment of septic shock is confounded by the fact that shock may be present with a normal blood pressure, and patients in septic shock may present with a high or low cardiac output (CO), and a variable amount of intravascular volume depletion. Thus, vasopressors and fluid loading should be used to maintain tissue perfusion, rather than maintaining blood pressure. This review describes the assessment of circulatory function and initial management of patients with septic shock, and specifically details the process of titrating vasopressors against fluid loading in septic shock. The appropriate weaning of patients from vasopressors is also discussed. The authors present several arguments for the monitoring of CO in order to facilitate the best course of treatment in septic shock patients.

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In clinical practice, the terms "hypotension" and "shock" are often used interchangeably. However, it is important to stress that shock may be present despite a normal blood pressure. Correspondingly, blood pressure may be low without shock being present. Hypotension can be defined as a drop in systolic blood pressure of >40–50 mmHg from baseline, a systolic value of <90 mmHg, or a mean arterial pressure (MAP) of <65 mmHg. Hypotension can result from either a low cardiac output (CO) and/or a low systemic vascular resistance (SVR) because MAP is determined by both CO and SVR ($MAP = CO \times SVR$). Hypotension does not necessarily equate to shock but, in the critically ill patient, is often associated with a reduction in the level of oxygen transport (TO_2) to tissues or its utilization therein. A low CO is likely to be associated with a low TO_2 ($TO_2 = CO \times CaO_2$, where CaO_2 is arterial oxygen content). When TO_2 decreases, ventilatory oxygen consumption (VO_2) is maintained (at least initially) by an increase in oxygen extraction (EO_2). Increased EO_2 is consistent with adapted vascular reactivity, increased SVR, and redistribution of blood flow. In contrast, low vascular resistance is often associated with impaired EO_2 by tissues; this may be associated with mitochondrial pathology. When TO_2 decreases beyond a certain threshold it induces a decrease in VO_2 . This point is known as the critical TO_2 (TO_{2crit}), below which there is a state of oxygen uptake-to-supply dependency (shock or dysoxia). TO_{2crit} is higher when EO_2 is lower. Below the TO_{2crit} , a decrease in VO_2 is associated with an increase in lactic acid production and an inadequate supply of adenosine triphosphate (ATP) relative to cellular requirements. In sepsis, as in carbon monoxide or cyanide poisoning, dysoxia may also occur as a consequence of mitochondrial damage or inhibition where oxygen is available, but not consumed [1].

In the clinical setting, the mixed venous oxygen saturation (SvO_2) can be used to assess the whole body VO_2 - TO_2 relationship. In the absence of a pulmonary artery (Swan-Ganz) catheter (PAC), the central venous oxygen saturation ($ScvO_2$) is being increasingly used as a reasonably accurate surrogate. Tissue VO_2 can be calculated according to the Fick equation: $VO_2 \approx CO \times (SaO_2 - SvO_2) \times Hb \times 1.34$, where SaO_2 represents arterial oxygen saturation and Hb represents hemoglobin; SvO_2 can be derived using the calculation: $SvO_2 \approx SaO_2 - VO_2 / (Hb \times 1.34 \times CO)$.

Cardiogenic, hypovolemic, and obstructive etiologies are generally associated with low-CO states and have corresponding clinical features. The circulation of a patient who has hypotension with a septic cause is usually hyperdynamic. However, profound myocardial depression (from excess nitric oxide production and release of myocardial depressant factors), major third space fluid losses (capillary leak, with additional fluid and electrolyte depletion from a variety of routes, e.g. sweat, vomit, diarrhea), and/or extreme vasodilatation (due to excessive activation of macrophages, neutrophils, or endothelium and over-production of pro-inflammatory mediators such as prostanoids, nitric oxide, kinins, and pyrogens) may produce a low-flow state. Vascular hyporeactivity is related to decreased responsiveness to catecholamines and variable degrees of endocrine dysfunction (notably adrenocortical). Thus, patients in septic shock may present with a high or low CO, and a variable amount of intravascular volume depletion [1].

Initial management of septic shock

Owing to the lack of specificity of key clinical features in the classification of hypotension, diagnosis and treatment should be considered simultaneously since a good response to treatment helps to confirm the working diagnosis. Immediate management includes

treatment helps to confirm the working diagnosis. Immediate management includes ensuring oxygen supply, fluid therapy, assessment of the need for inotrope or vasopressor therapy, and consideration of specific treatments to deal with the direct cause.

Proposed monitoring

In life-threatening situations, empirical treatment should not be delayed while monitoring devices are being inserted. Basic cardiorespiratory monitoring comprises measurement of heart rate and blood pressure, and pulse oximetry. Arterial blood pressure should be recorded at a minimum of 5-min intervals but ideally it should be monitored continuously, and whenever possible invasively, in the unstable patient [2]. Noninvasive measurements are often unreliable in shock states, and invasive arterial pressure monitoring should be instituted as soon as possible.

Central venous catheter

A central venous catheter allows measurement of central venous pressure (CVP). A static measurement of CVP is not particularly useful in deciding the need for fluid administration, although it is generally indicative when the pressure is <5 mmHg. The response of CVP to a fluid bolus is more useful (as is discussed below). The central venous catheter also allows monitoring and/or sampling of blood for measurement of ScvO₂ (the surrogate for mixed SvO₂), depending on whether or not an oximetry catheter is being used. A central venous catheter is simpler to insert, and generally safer and cheaper than a PAC.

The four determinants responsible, either alone or in combination, for a decrease in SvO₂ (or ScvO₂) are: hypoxemia (decrease in SaO₂), an increase in VO₂ without an increase in TO₂, a fall in CO, and a decrease in Hb level. The normal range for SvO₂ is 68–77% (+5% for ScvO₂). An increase in VO₂ without an increase in CO or TO₂, or a decrease in TO₂ and no change in oxygen requirements, will result in an increase in EO₂ and a fall in SvO₂. EO₂ and SvO₂ are linked by a simple equation: $EO_2 \approx 1 - SvO_2$, assuming $SaO_2 = 1$ [3].

Tissue dysoxia is usually present when SvO₂ falls below 40–50%; however, this may also occur at higher levels of SvO₂, when EO₂ is impaired. Therefore, other markers of cellular O₂ inadequacy should be sought, such as hyperlactatemia. Usually, efforts to correct CO (fluids or inotropes), Hb level, SaO₂, VO₂, or a combination of the parameters must target a return of SvO₂ (ScvO₂) from 50% to 65–70% [2].

CO monitoring

A PAC, which may be equipped with continuous CO- and SvO₂-monitoring modalities, and/or any less invasive flow assessment technique (e.g. transesophageal echocardiogram, esophageal Doppler, LiCO, or peripheral transpulmonary dilution) is recommended when hypotension persists or a precise CO optimization is required (e.g. for fluid loading). Fluid challenges should be repeated until the top of the Frank–Starling curve is reached – that is, when stroke volume does not increase >10% following a 250-mL colloid challenge. At this point, the ventricle becomes preload-independent [4].

Echocardiography

Echocardiography may provide a rapid insight into the differential diagnosis, particularly when the true problem is unclear. For example, in the context of congestive heart failure, myocardial ischemia, or sudden collapse, it may diagnose any potentially reversible ventricular, valvular, or obstructive pathology. It provides information on both left and right ventricular function and can provide an initial assessment of preload and the presence of any regional wall-motion abnormalities. Echocardiography should not be considered simply within the context of CO assessment, but within the context of global cardiac performance, which can be altered in sepsis [5]. However, it is possible that bedside bidimensional echocardiography is still not available in all general intensive care units (ICUs).

Systolic pressure, pulse pressure, and stroke volume variations

In the sedated, intubated, and ventilated patient, recordings of systolic pressure variation (SPV), pulse pressure variation (Δ PP), stroke volume variation (SVV), or a combination of these can be helpful in the absence of flow-monitoring technology; the left ventricle remains preload-dependent until the SPV is <10 mmHg (SVV variation threshold of 10%), Δ PP is <13%, or SVV is <10%. Unfortunately, arrhythmias or spontaneous breathing preclude this type of evaluation [6].

Tissue perfusion indices

Interference of sepsis-modified vasoactive drug properties by sepsis-induced microcirculatory disturbances has predominantly been investigated at the level of the splanchnic circulation using techniques such as regional capnometry, laser Doppler flowmetry, and indocyanine green dilution. Besides measurement of lactate concentration, determination of gastric tonometered-to-arterial carbon dioxide pressure (PCO₂) remains the unique clinical monitoring tool that can aid in the assessment of the efficacy of fluid loading or catecholamine infusion on tissue perfusion [7]. The venous-to-arterial carbon

dioxide difference can, to some extent, be proposed as a surrogate for tissue perfusion assessment, as suggested by Mekontso-Dessap et al. [8].

Fluid therapy

With the possible exceptions of severe heart failure and pericardial tamponade, the vast majority of hypotensive septic patients require fluid as first-line therapy because hypovolemia is nearly always present. Hypovolemia can be either absolute or relative. Absolute hypovolemia is observed with loss of intravascular fluid externally (gut or renal losses, or hyperthermia) or into extravascular compartments (capillary hyperpermeability). Relative hypovolemia is observed as a result of decreased vascular tone, resulting in an increase in the total intravascular compartment size.

The response to initial treatment dictates further management. In situations where volume loss is likely, immediate fluid resuscitation should be started before further investigations are carried out.

Fluid therapy maintains a preload level necessary to support CO and systemic TO₂. Crystalloids, colloids, blood or blood products, or a combination of these is used for this purpose. Although experts argue over the advantages and disadvantages of particular colloid or crystalloid solutions, there is consensus on the need to administer enough fluid to restore an adequate circulation [9].

Vasopressor therapy

An inotrope and/or mechanical support should be considered if an inadequate MAP persists with signs suggestive of organ hypoperfusion, such as oliguria, altered conscious state, chest pain, cardioscope changes, low SvO₂ (or ScvO₂), elevated lactate concentration, or arterial base deficit. After adequately restoring intravascular fluid volume, persistent hypotension requires the use of drugs that either improve myocardial contractility (to increase CO) and/or increase vascular tone (to increase SVR).

Owing to their short half-life (minutes) and familiarity with their use, catecholamines are usually the preferred first-line agents. Taking into account their effects on cardiac contractility (inotropism) and vascular tone (constrictor or dilator effects), they can be separated into two major classes: inodilators (inotrope plus vasodilator: low-dose dopamine and any dose of dobutamine or dopexamine), or inoconstrictors (inotrope plus vasoconstrictor: high dose dopamine, any dose of norepinephrine, and moderate-to-high doses of epinephrine).

Inodilators increase blood flow, but may actually have excessive vasodilating effects; inoconstrictors or vasopressors increase perfusion pressure and have variable effects on flow. The detection of a marked decrease in left ventricular ejection fraction using echocardiography can suggest the use of dobutamine when signs of peripheral hypoperfusion persist, despite volume resuscitation and restoration of perfusion pressure with vasopressors.

Because of a highly variable individual sensitivity to these different catecholamine agents, dose titration is strongly recommended, ideally against measurement of CO as well as blood pressure and other relevant variables such as base deficit and urine output. Non-catecholamine vasopressors such as vasopressin and its synthetic analogue terlipressin are now being evaluated in sepsis and other vasodilatory shock states. As increasing blood pressure through vaso-constriction is often associated with a decrease in CO, a trade-off is necessary between raising blood pressure and decreasing CO. This will dictate the choice and dosage of vasopressor and/or vasoconstrictor, as no purely inotropic agents exist.

The Surviving Sepsis Campaign (SSC) recommends maintaining MAP at ≥ 65 mmHg in septic shock patients [9]. It is important to emphasize that an increase in blood pressure may not be a good surrogate of clinical benefit. Indeed, in a large, placebo-controlled clinical trial, administration of the non-selective nitric oxide inhibitor NG-methyl-L-arginine in septic shock produced significant increases in both blood pressure and mortality rate [10]. Thus, the aim should be to improve tissue perfusion and not simply to increase blood pressure.

How to titrate fluid loading and vasopressor

The risk, when using vasopressors, is to inadequately fluid-load patients and to decrease tissue perfusion. Preload assessment in the context of increased vascular tone and vasopressor-induced reduced vascular compliance does not predict tissue perfusion. In a recent experimental study, Nouira et al. clearly demonstrated that preload independency could be artificially created by infusing norepinephrine following hemorrhagic shock [11]. In hemorrhaged dogs (in which 35 mL/kg of blood was withdrawn), norepinephrine, in the absence of fluid or red blood cell infusion, resulted in a return of Δ PP from 28% to a normal 12%, while MAP and CO were increased from 85 to 153 mmHg and from 1.98 to 3.08 L/min, respectively. Conversely, despite normalization of hemodynamics, pH and

bicarbonates fell from 7.29 to 7.24 and from 18.0 to 15.8 mmol/L, respectively. These data clearly show that oxygen-derived parameters need to be taken into account when vasopressors are used in shock states in order to accurately titrate the drugs against fluid loading.

In a landmark study by Rivers et al. [12], patients admitted to an emergency department with severe sepsis and septic shock were randomized to standard therapy (aiming for a CVP of 8–12 mmHg, MAP \geq 65 mmHg, and urine output \geq 0.5 mL/kg/h), or to early goal-directed therapy (EGDT) where, in addition to the previous parameters, an ScvO₂ of \geq 70% was targeted by optimizing fluid administration, keeping hematocrit \geq 30%, and/or giving dobutamine to a maximum of 20 μ g/kg/min (**Fig. 1**). The initial ScvO₂ in both groups was low (49 \pm 12%), which serves as a reminder that severe sepsis is often a hypodynamic condition before fluid resuscitation is started. From the first to the 72nd hour, the total fluid loading was not different between the two groups (\approx 13.4 L); in contrast, from the first to the seventh hour the amount of fluid received was significantly greater in the EGDT patients (\approx 5000 mL vs. 3500 mL). Conversely, from the first to the 72nd hour, the number of patients treated by vasopressor was significantly lower in the EGDT group (36.8% vs. 51.3%; $p=0.02$). This was also the case from the first to the seventh hour although this was not a significant difference (27.4% vs. 30.3%; $p=0.62$). In the follow-up period between the seventh and the 72nd hour, mean ScvO₂ was higher (70.6 \pm 10.7% vs. 65.3 \pm 11.4%; $p=0.02$), as was mean arterial pH (7.40 \pm 0.12 vs. 7.36 \pm 0.12; $p=0.02$) in patients receiving EGDT. Lactate plasma levels were lower in those receiving EGDT (3.0 \pm 4.4 mmol/L vs. 3.9 \pm 4.4 mmol/L; $p=0.02$), as was base excess (2.0 \pm 6.6 mmol/L vs. 5.1 \pm 6.7 mmol/L; $p=0.02$). Organ failure score was also significantly altered in patients receiving standard therapy when compared with patients receiving EGDT. Hospital mortality rates fell from 46.5% (standard group) to 30.5% in the EGDT group ($p=0.009$). Importantly, 99.2% of patients receiving EGDT achieved their hemodynamic goals within the first 6 h compared with 86% in the standard group. This was the first study demonstrating that early identification of patients with sepsis plus initiation of EGDT to achieve an adequate level of tissue oxygenation by oxygen delivery (as judged by ScvO₂ monitoring) significantly improves mortality rates. Vasopressor titration in EGDT patients combined with MAP measurement and ScvO₂ assessment helped in reducing vasopressor therapy and to increase fluid loading when compared with a more conventional approach. This was followed by a net improvement in organ failure and mortality rate. In two recent successful trials in sepsis (using activated protein C or corticoids), a more rapid decrease in vasopressor therapy was observed together with an improvement in mortality rates, suggesting that if vasopressors need to be rapidly introduced in the initial therapeutic strategy, their benefit must then be frequently challenged, and the weaning process must be rapidly considered [13,14].

In ICU-resuscitated patients, SvO₂ or ScvO₂ may not be of help to guide titration of fluid loading and vasopressor therapy. The lower sensitivity of ScvO₂ in ICU stabilized patients may be that the severity of hypovolemia/ myocardial dysfunction is usually lower at that stage. This might also be due to EODefects related to severe microcirculatory disorders, or to mitochondrial damage and/or inhibition. In that context, measurement of SvO₂ or ScvO₂ would be expected to be elevated and one could suggest using the lactate and/or the venous-to-arterial PCO₂ difference to guide fluid loading toward perfusion-derived parameters [8].

To enhance the benefit in mortality rate reduction observed in EGDT patients, adding gastric-to-arterial carbon dioxide or venous-to-arterial carbon dioxide (Δ CO) assessment to refine the Rivers et al. goal-directed protocol might therefore be useful (**Fig. 1**), although this has not yet been validated in formal studies. In order to decrease Δ CO₂ to \leq 8 mmHg, several authors have suggested specific treatments aimed at improving tissue perfusion. This can be achieved using either low-dose dobutamine or dopexamine [15], or even by administering drotrecogin alfa (activated) [16].

Weaning process for vasopressor therapy

Removal of catecholamines is associated with the risk of inducing relative hypovolemia and preload dependency. Mallat et al. elegantly demonstrated that the decrease in catecholamine concentration during pheochromocytoma resection was associated with large SPV, which was significantly reduced by fluid loading [17]. However, the authors did suggest that catecholamine infusion needed to be considered when the fluid loading that was titrated to reduce SPV was not sufficient to correct MAP.

Similarly, the current authors hypothesize that lowering the dose of a vasopressor such as norepinephrine could unmask preload dependency, and that a protocol based on MAP and SPV, Δ PP, or SVV should be considered (**Fig. 2**). This protocol could help in safely reducing norepinephrine dose; moreover, the authors suggest that it might be associated with improved organ perfusion and more rapid vasopressor withdrawal. Biological parameters of organ perfusion should be assessed during the process (arterial and central venous blood gas analysis, with a special emphasis on ScvO₂, lactate and bicarbonates, and arterial

blood gas analysis, with a special emphasis on SvO_2 , pH and bicarbonate, and arterial lactate) in order to ascertain that the weaning process is not deleterious. Some safety limit to fluids, especially if SVV remains $>10\%$ and MAP at <65 mmHg, may be proposed, such as maintenance of CVP ≥ 12 mmHg.

Alternatively, stress-dose ("low dose") steroid therapy (50 mg hydrocortisone administered every 6 h) should be considered if maintenance of blood pressure levels requires increasing concentrations of vasopressors. Although the adrenocorticotrophic hormone (ACTH) stimulation test has now been challenged, intravenous hydrocortisone is proposed to be administered after an ACTH test has been performed. If the clinical response is a decrease in the required vasopressor therapy together with a low baseline cortisol level and/or a subnormal response to ACTH (change in plasma cortisol level of <250 nmol/L) the corticosteroid should be continued. The duration of treatment should be 7 days, with a subsequent tapering off the drug for a further 5–7 days [16].

Conclusion

When aiming to titrate vasopressor and fluid loading in septic shock, the choice of monitoring technique to be used depends on familiarity with and availability of the procedure, the presence of exclusion criteria (e.g. dilution techniques are inaccurate in cases of moderate-to-severe tricuspid regurgitation), and potential risks (e.g. bleeding from line insertion in patients with concurrent coagulopathy). As discussed in this review, there are several arguments for monitoring CO in order to optimally titrate vasopressors and fluid loading. These are summarized here:

- Shock (dysoxia) may be present despite a normal blood pressure.
- It is easier to optimize fluid status and stroke volume in terms of constructing a Frank–Starling curve, especially with concurrent use of norepinephrine and poorly compliant lungs requiring high ventilator pressures and high positive end-expiratory pressure. This may enable earlier reduction/discontinuation of inotrope.
- In patients with critically low tissue TO_2 and supply–demand dependency with limited reserve to cope with further deterioration, CO monitoring facilitates the correct choice of treatment (including blood products, volume maintenance, and use of inotropes) and avoidance/early recognition of inappropriate and/or harmful therapies (and doses).
- An overall lack of outcome benefit may not necessarily apply to an individual case, especially in a severely ill individual.
- The pulmonary artery catheter allows assessment of preload dependency, CO, and pulmonary pressures in selected patients with severe lung injury. Continuous (or intermittent) monitoring of SvO_2 may be used to titrate therapy to improve oxygen supply–demand balance, for example, aiming for a mixed SvO_2 value >65 – 70% . Alternatives include echocardiography, esophageal Doppler, peripheral dye dilution or thermodilution techniques, and pulse contour analysis. ScvO_2 monitoring (intermittent or continuous) can be used as a surrogate for mixed SvO_2 .
- Combined CO and MAP measurement together with preload dependency and SvO_2 (ScvO_2) assessment can help in appropriately titrating vasopressor therapy and fluid loading.

Disclosures

The authors have no relevant financial interests to disclose.

Address for correspondence: Benoît Vallet, Pôle d'Anesthésie & Réanimation, Hôpital Huriez – CHRU de Lille, Rue Michel Polonovski, F59037 Lille cedex, France. Email: bvallet@chru-lille.fr

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