

## How Do I Integrate Hemodynamic Variables When Managing Septic Shock?

Olfa Hamzaoui, M.D.<sup>1</sup>, and Jean-Louis Teboul, M.D., Ph.D.<sup>2</sup>

<sup>1</sup>Service de Réanimation Polyvalente, Hôpital Antoine Bécère, Hôpitaux universitaires Paris-Sud, Assistance Publique-Hôpitaux de Paris. Clamart,

<sup>2</sup>Service de Réanimation Médicale, Hôpital Bicêtre, Hôpitaux universitaires Paris-Sud, Assistance Publique-Hôpitaux de Paris. Le Kremlin-Bicêtre, France

Hemodynamic management of sepsis-induced circulatory failure is complex since this pathological state includes multiple cardiovascular derangements that can vary from patient to patient according to the degree of hypovolemia, of vascular tone depression, of myocardial depression and of microvascular dysfunction. The treatment of the sepsis-induced circulatory failure is thus not univocal and should be adapted on an individual basis. As physical examination is insufficient to obtain a comprehensive picture of the hemodynamic status, numerous hemodynamic variables more or less invasively collected, have been proposed to well assess the severity of each component of the circulatory failure and to monitor the response to therapy. In this article, we first describe the hemodynamic variables, which are the most relevant to be used, emphasizing on their physiological meaning, their validation and their limitations in patients with septic shock. We then proposed a general approach for managing patients with septic shock by describing the logical steps that need to be followed in order to select and deliver the most appropriate therapies. This therapeutic approach is essentially based on knowledge of physiology, of pathophysiology of sepsis, and of published data from clinical studies that addressed the issue of hemodynamic management of septic shock.

**Key Words:** hemodynamics; hemodynamic monitoring; lactates; shock, septic; veno-arterial carbon dioxide gap; venous oxygen saturation.

### Introduction

Septic shock is characterized by multiple cardiovascular abnormalities including absolute and relative hypovolemia, vascular tone depression, myocardial dysfunction, derangements in regional blood flow distribution and microcirculatory disorders. Septic shock is often associated with multiple organ failure, including mainly respiratory and renal failures. The degree of severity of each of these disorders is variable from patient to patient. Early and adequate hemodynamic support is crucial to prevent further worsening of organ dysfunction. Therefore, it is important to assess the degree of each component of the hemodynamic failure in order to select the appropriate therapeutic measures. Multiple

hemodynamic variables are available to manage patients with septic shock. The main issue for the physician is to properly integrate these variables in order to optimize the therapy. Some of the hemodynamic variables are used to make or confirm the diagnosis of shock and others are used to guide therapy and to evaluate the response to it. In this review, we describe a wide variety of hemodynamic variables and we propose how to integrate them in a thera-

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**Correspondence to:** Jean-Louis Teboul, Service de Réanimation Médicale, Hôpitaux universitaires Paris-Sud, Hôpital de Bicêtre, 78, rue du Général Leclerc, Le Kremlin-Bicêtre, F-94270, France  
Tel: +33-145213543, Fax: +33-145213551  
Email: jean-louis.teboul@aphp.fr

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peutic strategy for septic shock patients.

## What are the most relevant hemodynamic variables during resuscitation of septic shock?

### 1) Blood Lactate

Lactate is mainly released by the skeletal muscles, the adipose tissue and the brain and in a smaller proportion by the lung and the heart. Daily, 20 mmol/kg of lactate is produced, released in the blood stream and transported to the liver and the kidney, where it is subsequently metabolized in two main energy (ATP)-producing processes: glycolysis and oxidative phosphorylation. Lactate arises from the metabolism of glucose. Glycolysis metabolizes glucose to pyruvate in the cellular cytosol. Further metabolism of pyruvate follows one of two routes. First, pyruvate enters mitochondria and is converted to acetyl-coenzyme A by pyruvate dehydrogenase, which enters the Krebs's cycle allowing generation of 38 ATP molecules for each molecule of metabolized glucose. The second route for pyruvate is conversion to lactate in the cytosol. This reaction is bi-directionally catalyzed by lactate dehydrogenase, resulting in a normal lactate/pyruvate ratio of approximately 10.

Development of hyperlactatemia in sepsis is multifactorial. It can be due to an overproduction of lactate via either anaerobic or aerobic metabolism or to a decrease in its clearance. During sepsis, impaired ability of the tissues to extract oxygen and endothelial inflammatory processes result in microcirculatory dysfunction so that regional  $DO_2$  is not matched with oxygen demand and tissue hypoxia develops.[1] When sufficient oxygen is not available, the Krebs's cycle cannot metabolize pyruvate so that lactate is generated. In addition, mitochondrial dysfunction may occur during sepsis so that, even in tissues with adequate oxygenation, pyruvate is shunted toward lactate production. In addition, the resting metabolic rate can be increased during sepsis leading to increased metabolism of glucose.[2] Glycolytic flux can exceed the capacity of pyruvate dehydrogenase to

catalyze conversion of pyruvate into acetyl coenzyme A. Therefore, pyruvate is converted to lactate by lactate dehydrogenase. Finally,  $\beta_2$  adrenergic stimulation can activate the sodium-potassium-adenosine triphosphatase (Na-K-ATPase) activity and this increased the glycolytic flux.[3] These results are supported by the observation that lactate production is reduced by  $\beta_2$ -receptors antagonists such as esmolol and by Na/K-ATPase inhibitors (ouabain) in septic shock or when glycolysis is induced by epinephrine.[4] Finally, hyperlactatemia might also be the result of impaired lactate clearance during sepsis. [5] This may become an important issue in patients with significant pre-existing or new hepatic dysfunction.

### 2) Arterial blood pressure

Arterial catheterization (radial or femoral artery) is recommended as soon as possible during acute circulatory failure to monitor the arterial pressure waveform in real-time and also to easily sample arterial blood.[6,7] This provides direct measurements of systolic arterial pressure and diastolic arterial pressure (DAP) and from these two values, estimation of mean arterial pressure (MAP) and of pulse pressure (PP). Monitoring these four pressures provides important information on the hemodynamic status and the cardiac function.

#### (1) Mean arterial pressure

The MAP is considered as the upstream pressure for perfusion of most vital organs such as the brain and the kidney. As a result, when MAP falls below the lower limit of autoregulation, regional blood flow becomes linearly dependent upon MAP. In some pathological settings, and in specific vascular areas, MAP underestimates the true perfusion pressure, because of marked increases in the downstream venous pressure or in the extravascular pressure at the outflow level. There is no universally admitted MAP threshold ensuring that blood flow is independent of arterial blood pressure in most vital organs. Indeed, the critical level of MAP probably differs among organs and depends on numerous factors including age, previous history of hypertension, neuro-vegetative state

and vasoactive therapy. However, in septic shock, current resuscitation guidelines recommend to initially achieve  $\text{MAP} \geq 65$  mmHg, in order to avoid additional organ hypoperfusion[6,8] and suggest a higher value in patients having prior chronic hypertension, a pathological state characterized by a rightward shift of the autoregulation curve. Recently, a multicenter randomized open-label trial was conducted to compare two MAP targets in patients with septic shock: 65-70 mmHg and 80-85 mmHg[9]. There was no difference between the two groups in 28-day mortality rates.[9] There was no difference either in the overall rate of serious adverse events, except a slightly higher rate of atrial fibrillation in the high MAP target group.[9] In the predefined stratum of patients with chronic hypertension, those with a MAP target of 80-85 mmHg exhibited a more pronounced improvement in renal function and fewer requirements for renal replacement therapy.[9] This study thus suggests that in patients with history of chronic hypertension, a MAP between 80-85 mmHg is a reasonable target. A MAP target higher than 65 mmHg should also be considered in cases of high central venous pressure (CVP), which reflects a high outflow venous pressure within organs. Indeed, in such cases, it could be important either to increase the MAP or to decrease CVP in order to maintain an adequate driving pressure for organ perfusion. Similarly, in intra-abdominal hypertension syndromes, the increased intra-abdominal pressure can represent the outflow pressure of intra-abdominal organs, necessitating then a higher than normal MAP target to preserve their adequate perfusion unless therapeutic reduction of the intra-abdominal pressure is feasible.

### (2) Diastolic arterial pressure

The DAP is also important to monitor since it is the driving pressure for the left ventricular perfusion. In addition, DAP is a marker of arterial tone. It is also influenced by arterial compliance and heart rate. A low DAP can thus exist in cases of decreased vasomotor tone (e.g. sepsis), reduced arterial compliance and bradycardia. Therefore, in case of sepsis with tachycardia, a low DAP

(i.e.  $< 40$  mmHg) is an indicator of a profoundly depressed arterial tone.

### (3) Pulse pressure

At the level of aorta, PP is dependent on stroke volume and arterial stiffness. Due to the pulse wave amplification (PWA) phenomenon, which increases the peripheral PP compared to the aortic PP, the relation between peripheral PP and stroke volume is weaker except in old patients or in those with chronic hypertension, diabetes or arteriosclerosis, in whom the PWA is minimal. In those patients, PP should be higher than normal (60-80 mmHg) if stroke volume is normal due of the increased arterial stiffness. Thus, a lower than normal PP (30-40 mmHg) in such patients means that stroke volume is low.

### 3) The mixed venous blood oxygen saturation (SvO<sub>2</sub>) and the central venous oxygen saturation (ScvO<sub>2</sub>)

The SvO<sub>2</sub>, which is measured in the mixed venous blood is an integrative variable that reflects the global balance between arterial oxygen delivery (DO<sub>2</sub>) and the whole-body oxygen consumption (VO<sub>2</sub>) since cardiac output (CO), hemoglobin concentration (Hb) and arterial blood oxygen saturation (SaO<sub>2</sub>) are the key determinants of DO<sub>2</sub>. Indeed, SvO<sub>2</sub> is related to arterial SaO<sub>2</sub>, VO<sub>2</sub>, CO and Hb according to the formula derived from the Fick equation applied to oxygen:  $\text{SvO}_2 = \text{SaO}_2 - (\text{VO}_2 / [\text{CO} \times \text{Hb} \times 13.4])$ . In healthy subjects at rest with normal SaO<sub>2</sub> and Hb, the value of SvO<sub>2</sub> ranges from 70 to 75%. SvO<sub>2</sub> can be considered as a marker of oxygen extraction. Indeed, the whole-body oxygen extraction ratio (OER) is defined as the ratio of the whole-body VO<sub>2</sub> to the whole-body DO<sub>2</sub>:  $\text{OER} = \text{VO}_2 / \text{DO}_2$ . As DO<sub>2</sub> equals approximately  $\text{CO} \times \text{Hb} \times 13.4$ , then SvO<sub>2</sub> equals  $\text{SaO}_2 - (\text{VO}_2 / \text{DO}_2)$ . When SaO<sub>2</sub> is close to 1 (100%), SvO<sub>2</sub> can thus be used to estimate OER:  $\text{SvO}_2 = 1 - \text{OER}$ .

By considering that SvO<sub>2</sub> reflects OER, SvO<sub>2</sub> changes can be interpreted as follows:

A decrease in SvO<sub>2</sub> means that OER has increased to make the whole-body VO<sub>2</sub> matched with the whole-body oxygen demand. This increase in OER can be trig-

gered by either a drop in  $DO_2$ , or an increase in oxygen demand, or both. If, in spite of this normal adaptation,  $VO_2$  does not match oxygen demand, tissue hypoxia and anaerobic metabolism appear.[10] However, no precise value of  $SvO_2$ , can be defined as the “critical”  $SvO_2$  below which tissue hypoxia occurs.[10]

Conversely, an increase in  $SvO_2$  means that OER has decreased as a consequence of either an increase in  $DO_2$  with maintained  $VO_2$  or a decrease in  $VO_2$  with maintained or increased  $DO_2$ . This latter situation is typically encountered in hyperdynamic septic shock, where the decrease in  $VO_2$  (despite a high whole-body oxygen demand) does not result from a reduced  $DO_2$ , but rather from impairment of the  $O_2$  extraction capabilities. These points underline the fact that: 1)  $SvO_2$  cannot be a reliable marker of the adequacy between  $DO_2$  and global oxygen demand in shock states, where  $VO_2$  is lower than oxygen demand, and 2) interpretation of  $SvO_2$  can be misleading in hyperdynamic states.[11] Finally, it should be kept in mind that during resuscitation of shock states, increase in  $DO_2$  is expected to result in parallel increase in  $VO_2$  such that  $SvO_2$  does not change markedly unless a critical level of  $DO_2$  is reached. Above this critical level of  $DO_2$ , a further increase in  $DO_2$  is associated with a marked increase in  $ScvO_2$  but no anymore change in  $VO_2$ . [11]

Due to the decline of the use of the pulmonary artery catheter,  $ScvO_2$  has been proposed to replace  $SvO_2$ , as a central venous catheter is recommended to be used in shock states.[6,7] Studies comparing  $SvO_2$  and  $ScvO_2$  generally found satisfactory results in terms of absolute values[12] as well as in terms of trends.[13] Confirmation of the interest of  $ScvO_2$  in the resuscitation of septic shock patients was brought by the Rivers et al’s study,[14] where a therapeutic strategy (called early goal-directed therapy) aimed at targeting a  $ScvO_2$  value  $> 70\%$  during initial resuscitation was shown to result in a better outcome than standard care.[14] Although recent multicenter randomized clinical trials did not confirm these findings,[15] it must be emphasized that  $ScvO_2$  was already higher than the 70% target in the vast majority of the included patients so that these trials could not by

nature showed any benefit of EGDT.

#### 4) Mixed venous blood (or central venous blood) minus arterial blood carbon dioxide ( $CO_2$ ) pressures differences

The Fick equation applied to  $CO_2$  indicates that the  $CO_2$  excretion (equivalent to  $CO_2$  production ( $VCO_2$ ) in a steady-state) equals the product of CO by the difference between the  $CO_2$  content in the mixed venous blood and in the arterial blood. The normal relationship between  $CO_2$  content and  $CO_2$  pressure is almost linear over the usual physiological range of the  $CO_2$  contents. Thus, by substituting  $CO_2$  pressure for  $CO_2$  content, the mixed venous blood – arterial blood  $PCO_2$  difference (also called  $PCO_2$  gap) equals  $k \times VCO_2 / CO$ , where k is a factor defining the relationship between  $CO_2$  content and  $CO_2$  pressure.[16] The relationship between CO and  $CO_2$  pressure is explained by the  $CO_2$  stagnation phenomenon that increases the venous blood  $CO_2$  pressure relatively to the arterial blood  $CO_2$  pressure at the peripheral venous level. Thus, a low CO and hence a low efferent venous blood flow should decrease the  $CO_2$  clearance rate and should result in an increased  $PCO_2$  gap for a given  $VCO_2$ . In normal conditions,  $PCO_2$  gap values range between 2 and 6 mmHg. Accordingly, in a clinical study performed in normolactatemic patients with low cardiac index at baseline, the increase in cardiac index from 1.6 to 2.2  $L \cdot min^{-1} \cdot m^{-2}$  was accompanied by a decrease in  $PCO_2$  gap from 9 to 5 mmHg, while  $VO_2$  (and thus probably  $VCO_2$ ) was unchanged.[17]

In patients with tissue hypoxia, two situations should be distinguished in function of the systemic blood flow. In case of tissue hypoxia with reduced systemic blood flow,  $PCO_2$  gap should increase, whereas in case of tissue hypoxia with maintained or high systemic blood flow,  $PCO_2$  gap should be normal.[18,19]. In the latter conditions, the high venous blood flow can easily remove the low amount of  $CO_2$  produced at the periphery.

In summary, regardless of the presence of tissue hypoxia, a normal  $PCO_2$  gap ( $\leq 6$  mmHg) is expected if CO is normal or high, and a high  $PCO_2$  ( $> 6$  mmHg) is expected if CO is too low. Thus, a normal  $PCO_2$  gap

suggests that elevation of CO cannot be a priority in the therapeutic strategy, whereas a high PCO<sub>2</sub> gap suggests that elevation of CO may be a good therapeutic option.

### 5) Dynamic variables and tests predicting fluid responsiveness

The concept of prediction of fluid responsiveness has emerged since it has been demonstrated that only 50% of patients with acute circulatory failure respond to fluid administration in terms of increase in CO[20] and that fluid overload is associated with increased mortality.[21] During the last fifteen years, a number of indices able to predict fluid responsiveness at the bedside have been developed. In patients receiving mechanical ventilation, indices based on heart-lung interactions and mainly the respiratory variation of surrogates of stroke volume have been proposed.[22] The general principle is that when the heart is preload responsive, the stroke volume - or a surrogate such as PP - varies markedly over the respiratory cycle.[22] Accordingly, pulse pressure variation (PPV) was found to predict responsiveness better than cardiac filling pressures in patients with septic shock.[23] A metaanalyse including more than 800 patients showed that the prediction of fluid responsiveness by PPV is excellent in various clinical conditions with a cut-off of 12%.[24] In other words, when PPV is > 12%, CO is likely to increase by more than 15% if fluid is infused (fluid responsiveness), whereas if PPV is < 12%, no increase in CO can be expected from fluid infusion (fluid unresponsiveness). Recent functional hemodynamic monitoring devices calculate PPV automatically from the arterial pressure curve recording and display its value in real-time on their screen. Other fluid responsiveness indices such as stroke volume variation (SVV) can also be calculated and displayed by some advanced hemodynamic monitors but they have no superiority over PPV,[25] which has the great advantage to be recorded from a simple arterial catheter. However, the applicability of PPV (or SVV) for predicting fluid responsiveness is limited in the intensive care unit since it cannot be used in cases of spontaneous breathing activity, cardiac arrhythmias, low

tidal volume ventilation and low lung compliance.[26] Other tests such as passive leg raising (PLR)[27] reliably predict fluid responsiveness,[28] in particular in situations where PPV fails to do it.[29,30] Strict rules must be respected for the PLR being adequately interpreted.[27] Among them, the need of a real-time CO measurement must be emphasized. Real-time CO monitors using the arterial pressure waveform-based CO[31] as well as echocardiography (velocity-time integral)[32] are particularly suitable.

### 6) Transpulmonary thermodilution variables

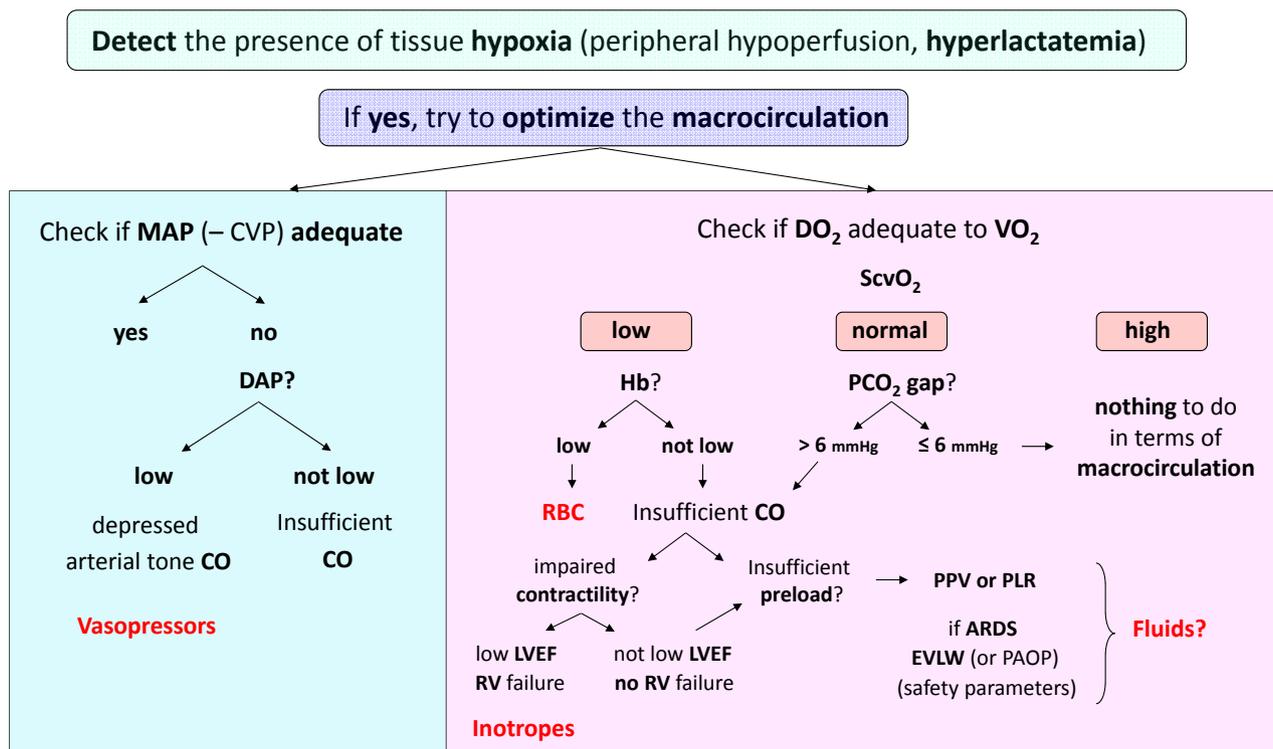
Transpulmonary thermodilution systems have been developed in the last fifteen years and are currently recommended to be used in complex patients, especially in those with circulatory shock and associated ARDS.[6,7] They take advantage of providing extravascular lung water (EVLW) and pulmonary vascular permeability index (PVPI), which represent quantitative measures of the volume of pulmonary edema and of the degree of lung capillary leakage, respectively.[33] Values of EVLW > 10 mL/kg[34] and of PVPI > 3[35] are considered as abnormally increased. In addition to EVLW and PVPI, the transpulmonary thermodilution systems provide intermittent measurements of CO and global end-diastolic volume (a volumetric marker of cardiac preload) and continuous CO and PPV, using the pulse contour analysis method.

## How can clinicians integrate the hemodynamic variables to manage patients with septic shock?

The Fig. 1 depicts a step-by-step therapeutic approach of septic shock integrating the main hemodynamic variables.

### 1) First step: detect acute circulatory failure and tissue hypoxia

Presence of hyperlactatemia along with clinical signs of peripheral hypoperfusion (mottling, increased capillary refill time) is fundamental to detect global tissue



**Fig. 1.** Logical integration of hemodynamic variables for resuscitation of septic shock. The details of the different steps of this algorithmic therapeutic approach are given in the text. MAP: mean arterial pressure; CVP: central venous pressure; DAP: diastolic arterial pressure; CO: cardiac output;  $DO_2$ : oxygen delivery;  $VO_2$ : oxygen consumption;  $ScvO_2$ : central venous blood oxygen saturation; Hb: hemoglobin concentration;  $PCO_2$  gap: central venous blood – arterial blood carbon dioxide pressure difference; RBC: red blood cells; PPV: pulse pressure variation; PLR: passive leg raising; LVEF: left ventricular ejection fraction; RV: right ventricular; ARDS: acute respiratory distress syndrome; EVLW: extravascular lung water; PAOP: pulmonary artery occlusion pressure.

hypoxia. When present, hypotension is also a good indicator of circulatory failure, but a normal arterial blood pressure cannot rule out the diagnosis of shock at least in its early phase.[6]

As we mentioned above hyperlactatemia may have other origins than tissue hypoxia but in such a context, it is considered as an excellent quantitative marker of tissue hypoxia. The ideal tool to detect the presence of tissue hypoxia would be the lactate/pyruvate ratio (see above). If it is far above 10, this strongly suggests that hyperlactatemia is actually related to anaerobic metabolism and this should urgently prompt therapies aimed at reducing tissue hypoxia. If the lactate/pyruvate ratio is around 10, hyperlactatemia is probably due to accelerated aerobic metabolism and not to tissue hypoxia. Unfortunately in the routine practice, lactate but not pyruvate is measured so that the clinician should always interpret hyperlactate-

mia in function of the clinical context. In addition to the baseline blood lactate concentration, the blood lactate kinetics is important to assess. A decrease in blood lactate concentration with therapy is currently recognized as a valuable target for hemodynamic resuscitation in shock states.[36,37]

## 2) Second step: once the presence of tissue hypoxia is detected, check at the same time both the arterial blood pressure and the $DO_2/VO_2$ balance.

### (1) Check arterial blood pressure

As mentioned above severe hypotension can be responsible for further organ hypoperfusion, independently of systemic blood flow or alteration of oxygen extraction. This is why the intensivist should urgently initiate therapies aimed at avoiding prolonged hypotension. In

the case of septic shock, it has been clearly demonstrated that the area under MAP 65 mmHg was the best predictor of 30 day-mortality[38] suggesting that not only the deepness but also the duration of hypotension are important to take into account. The MAP is the driving pressure for organ perfusion when the downstream venous pressure is low. However, if the downstream venous pressure is not negligible due to organ venous congestion, the organ perfusion driving pressure is much better assessed by the difference between MAP and CVP than by the sole MAP. In other words, in case of high CVP, the CVP value should be taken into account for assessing the actual organ perfusion pressure. This could occur in some septic shock states associated with right ventricular failure or when excessive fluid resuscitation had resulted to a high CVP. When the MAP-CVP difference is considered to be too low, the clinician should consider either to decrease CVP (probably the best option when feasible) or to increase MAP or both.

To select the most appropriate treatment for increasing MAP, it is then essential to pay attention to the DAP. A low DAP is generally due to a low arterial tone and thus should prompt a vasopressive therapy urgently. As already mentioned, a low heart rate also can be responsible for lowering DAP. As a direct consequence, a low DAP in presence of tachycardia suggests that the arterial tone is totally depressed and that vasopressors should be administered in extreme urgency. When a vasopressor is administered (mainly norepinephrine), the MAP target should be individualized.[6,39] In the context of septic shock[8] or cardiogenic shock,[40] the initial MAP target should be at least 65 mmHg. The MAP target should be higher in case of history of chronic hypertension,[6,8,9,39] increased CVP or increased intra-abdominal pressure.

If the DAP is not judged as low, the low MAP is likely to be associated with an insufficient (CO) (see below). The presence of a low PP could be an additional indication of low stroke volume, although a low stroke volume can be associated with normal PP in patients having stiff arteries.

## **(2) Check ScvO<sub>2</sub>, a marker of the DO<sub>2</sub>/VO<sub>2</sub> balance**

In patients with shock, ScvO<sub>2</sub> can be low (< 70%), normal (between 70 and 80%) or high (> 80%) depending on the value of DO<sub>2</sub> and the degree of alteration of oxygen extraction capabilities.

When ScvO<sub>2</sub> is low, as DO<sub>2</sub> is inadequate to VO<sub>2</sub>, it is logical to attempt to increase DO<sub>2</sub>, especially in such conditions of oxygen debt, where VO<sub>2</sub> does not meet oxygen demand.

- If Hb is low, blood transfusion can be considered.

- If Hb is not low, the insufficient DO<sub>2</sub> should be due to an insufficient CO, either related to insufficient preload or to altered cardiac contractility. Cardiac function should be rapidly assessed by transthoracic echocardiography, which helps diagnose left ventricular dysfunction using left ventricular ejection fraction (LVEF). A low LVEF (< 45%) strongly suggests that septic shock is associated with myocardial depression and in this context, administration of an inotropic drug can be considered. Right ventricular dysfunction can be suspected when the right ventricular end-diastolic area/left ventricular end-diastolic area ratio is high (> 0.6).[41] A specific treatment can be initiated after determination of the precise underlying mechanism (mainly using echocardiography). If cardiac function is unaltered and Hb not low, the low ScvO<sub>2</sub> should be due to insufficient cardiac preload and fluid infusion could be considered in this context. In case of any doubt, dynamic predictors of fluid responsiveness may help to make the correct decision. In mechanically ventilated patients having an arterial catheter in place and if the conditions of correct applicability of PPV are met, a PPV value > 12% is highly predictive of a positive response of fluid infusion.[23,24] If PPV cannot be measured (no artery catheter) or correctly interpreted (spontaneous breathing activity, arrhythmias, low tidal volume ventilation, low lung compliance), a PLR test can be performed to predict fluid responsiveness.[27] If echocardiography is available, the response of velocity-time integral to PLR is a good predictor of fluid responsiveness.[32] In the presence of fluid responsiveness, administration of fluids should be considered. However, as for any

other therapeutic intervention, the benefit/risk ratio of fluid infusion should be individually assessed. In patients with acute respiratory distress syndrome (ARDS), the risk of worsening pulmonary edema with fluid infusion is increased due to increased permeability of the lung capillary membrane. Knowledge of EVLW and PVPI, which as good markers of pulmonary edema and of capillary leakage are helpful to assess risk of fluid infusion in such circumstances.[33] Alternatively, pulmonary artery catheterization can be considered in such complex cases.[6,7] The value of the pulmonary artery occlusion pressure can then be taken for assessing the risk of pulmonary edema formation during fluid infusion, although it is neither a marker of the volume of pulmonary edema nor of the degree of capillary leakage. Nevertheless, these advanced hemodynamic monitoring systems are relatively invasive and costly and should be reserved to situations where shock is associated with ARDS or in case of insufficient response to the initial treatment of shock.[6,7] These devices are thus particularly helpful to assess the benefit/risk ratio of fluid infusion in complex situations.

It is noteworthy that in the rare cases of preload unresponsiveness despite low ScvO<sub>2</sub>, normal cardiac function and normal Hb, it would be important to reconsider the MAP target and attempt to reach a higher value.

Presence of a normal ScvO<sub>2</sub> while tissue hypoxia persists strongly suggests that the oxygen extraction capabilities are altered. Nevertheless, it has been clearly shown that in patients with persistent shock, hyperlactatemia and ScvO<sub>2</sub> ≥ 70%, a further increase in DO<sub>2</sub> (with fluids) might still increase VO<sub>2</sub> and decrease arterial blood lactate concentration.[42] Therefore, stopping resuscitation of shock states when ScvO<sub>2</sub> reaches a value of ScvO<sub>2</sub> 70% is a nonsense. A high value PCO<sub>2</sub> gap (> 6 mmHg) can identify situations where increasing CO can be still attempted in spite of normal ScvO<sub>2</sub>. The PCO<sub>2</sub> gap is a marker of the adequacy of CO with the global metabolic conditions that is less affected by impairment of oxygen extraction capacities than ScvO<sub>2</sub>. The choice of the therapy aimed at increasing CO should be based on the same reasoning than that followed in cases of low ScvO<sub>2</sub> and

normal Hb. Thus, assessment of cardiac function (using echocardiography) and assessment of fluid responsiveness (using dynamic tests) are also essential in this situation of normal ScvO<sub>2</sub> with increased PCO<sub>2</sub> gap. In case of normal PCO<sub>2</sub> gap, an increase in CO is unlikely to reduce tissue hypoxia and in our opinion should not be attempted. It is likely that alteration of microcirculation and cellular metabolism disorders are responsible for the severity of shock and unfortunately cannot be positively affected by conventional therapies of shock such as fluids, vasopressors and inotropes.

When ScvO<sub>2</sub> is higher than normal in case of persistent shock, severe alteration of oxygen extraction capacities such as arterio-venous shuntings and microcirculatory disorders are likely to exist and the prognosis is poor.[43] This essentially occurs in cases of severe hyperdynamic septic shock with multiple organ failure. It is thus illusory to think that a treatment aimed at increasing DO<sub>2</sub> will be effective to reduce oxygen debt. Until development of new therapies targeting the microcirculation or the cell function, the intensivist is helpless with the hemodynamic failure and can only hope for a beneficial effect action of anti-infectious treatments, while maintaining as far as possible other organ functions with appropriate supportive therapies.

## Conclusion

Hemodynamic management of sepsis-induced circulatory failure is complex since this pathological state includes multiple cardiovascular derangements that can vary from patient to patient. To make the correct therapeutic decision, clinicians need to be helped by hemodynamic variables other than those obtained from the clinical examination. Integration of these hemodynamic variables in a logical scheme is helpful to identify the main(s) hemodynamic disorder(s) and to assess the benefit/risk ratio of each therapeutic intervention at any time of the resuscitation phase.

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