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Review

How to integrate hemodynamic variables during resuscitation of septic shock? ☆

Jean-Louis Teboul

Service de Médecine Intensive-Réanimation, Hôpital de Bicêtre, GHU AP-HP, Université Paris-Saclay, Paris 94270, France

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ABSTRACT

Resuscitation of septic shock is a complex issue because the cardiovascular disturbances that characterize septic shock vary from one patient to another and can also change over time in the same patient. Therefore, different therapies (fluids, vasopressors, and inotropes) should be individually and carefully adapted to provide personalized and adequate treatment. Implementation of this scenario requires the collection and collation of all feasible information, including multiple hemodynamic variables. In this review article, we propose a logical stepwise approach to integrate relevant hemodynamic variables and provide the most appropriate treatment for septic shock.

Introduction

Septic shock is characterized by profound alteration of the cardiovascular system at macrocirculatory and microcirculatory levels. Macrocirculatory abnormalities include hypovolemia, vascular tone depression, and myocardial dysfunction. Hemodynamic disturbances eventually lead to tissue hypoxia and multiple organs failure. The aim of resuscitation of patients with septic shock is to correct tissue hypoxia, which can be related to a decrease in tissue oxygen delivery and/or impairment of local oxygen extraction. A decrease in tissue oxygen delivery can be secondary to a decrease in global oxygen delivery (DO_2) and/or a decrease in microcirculatory blood flow and/or to insufficient organ perfusion pressure.

Correcting tissue hypoxia can be achieved through increasing DO_2 or restoring sufficient organ perfusion pressure, because there are currently no therapeutic interventions for microcirculation and/or oxygen extraction. In all cases of septic shock, absolute and/or relative hypovolemia is present and contributes to tissue hypoxia. Therefore, administration of intravenous (IV) fluids should be urgently performed; however, in most cases, this is not sufficient to restore adequate hemodynamic conditions. The severity of each of component of circulatory failure (hypovolemia, vascular tone depression, myocardial depression, altered microcirculation, and impaired oxygen extraction) varies among patients and in each patient over time. Therefore, it is crucial to assess the degree of each cardiovascular disturbance. Clinical examination cannot fully identify the predominant component of the circulatory failure, hence other variables need to be obtained non-invasively or invasively.

Moreover, integration of multiple hemodynamic variables can facilitate improved assessment of the benefit/risk balance of any hemodynamic intervention and allow selection of the most appropriate therapy.

Relevant Hemodynamic Variables during Resuscitation of Septic Shock

Arterial blood pressure

In patients with shock, insertion of an arterial catheter is recommended to monitor the arterial pressure in real-time.[1,2] It is thus possible to obtain continuously reliable values of systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and pulse pressure (PP), which all provide vital information on the cardiovascular status.

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E-mail address: jean-louis.teboul@aphp.fr

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SAP

Among all the variables available at the bedside, SAP is the best estimate of left ventricular afterload. SAP is frequently used in some definitions of shock rather than as a therapeutic target in shock states. SAP at the central level is lower compared with that at the periphery due to the pulse wave amplification (PWA) phenomenon; thus, SAP measured in the femoral artery is lower than that in the radial artery. However, the PWA phenomenon is attenuated in elderly patients.[3]

DAP

DAP has two major meanings for the clinical practice. First, DAP is a good marker of arterial tone.[3] Decreased arterial tone is associated with decreased DAP and can also be due to bradycardia (prolonged diastolic time) or marked arterial stiffness. In a patient with shock and a normal or high heart rate, a low DAP is highly indicative of a markedly reduced arterial tone, which is essential for identifying the type of shock and knowing whether to commence early vasopressor treatment. An arbitrary DAP value of <40 mmHg has been proposed to identify the appropriate time to commence administration of a vasopressor.[4] Second, DAP is the upstream pressure for left ventricular perfusion. In patients with coronary artery disease, a low DAP may induce myocardial ischemia and thus is another reason to start administration of a vasopressor. Owing to the PWA phenomenon, DAP measured in the femoral artery is slightly higher compared with that in the radial artery.

MAP

Unlike SAP and DAP, the MAP is nearly constant in the arterial bed from the aorta to the arterioles; it is, by nature, slightly higher in the aorta compared with that in the periphery. Clinically, the MAP reflects the upstream pressure for perfusion of most vital organs. In cases where MAP is lower than the autoregulation threshold, the perfusion of organs such as the brain and kidneys can be reduced, even when cardiac output is high. In healthy conditions, the MAP is markedly higher than the central venous pressure (CVP), which reflects the downstream pressure for perfusion of most organs, thus MAP is considered the organ perfusion pressure. However, in some shock states such as cardiogenic shock, MAP is low and CVP is high, meaning that MAP underestimates the organ perfusion pressure; in such cases, the difference between MAP and CVP (i.e., MAP−CVP) is considered the organ perfusion pressure.[5]

PP

PP at the aortic level depends on stroke volume and arterial stiffness.[6] In elderly patients, the peripheral PP accurately reflects the central PP owing to the attenuated PWA phenomenon.[3] In such patients, the large arteries are stiff, and PP is usually increased except if stroke volume is low. Thus, a normal PP (40–50 mmHg) and *a fortiori* a lower-than-normal PP in these patients are the indicators of a low stroke volume.

Blood Lactate

Increased blood lactate concentration can be due to either overproduction (from increased anaerobic metabolism, increased aerobic metabolism, or mitochondrial dysfunction) or to a decrease in clearance. In sepsis and septic shock, all these mechanisms may occur and increased blood lactate is therefore not always due to tissue hypoxia. Nevertheless, hyperlactatemia is associated with a poor outcome, and a subsequent decrease in blood lactate concentration following intervention suggests that the selected therapeutic strategy is effective.[7]

Mixed Venous Blood Oxygen Saturation (SvO_2) and Central Venous Oxygen Saturation

SvO_2 is related to arterial blood oxygen saturation (SaO_2), oxygen consumption (VO_2), cardiac output, and hemoglobin concentration (Hb) according to the formula derived from the Fick equation applied to oxygen: $SvO_2 = SaO_2 - [VO_2/(\text{cardiac output} \times Hb \times 13.4)]$. Thus, SvO_2 is an integrative variable that reflects the balance between DO_2 and VO_2. In healthy subjects, SvO_2 ranges from 70% to 75%. A decrease in SvO_2 can be due to a decrease in SaO_2 or Hb or to an increase in VO_2 if cardiac output does not compensate for these changes. In addition, a decrease in SvO_2 can be due to a decrease in cardiac output itself and no acute compensation from other variables would be expected to occur in this situation.

An increase in SvO_2 above the normal range is generally associated with a decrease in the oxygen extraction capacities leading to decrease in VO_2. In this context, the value of SvO_2 can be very high, especially if DO_2 is high due to increased cardiac output. This latter condition can be encountered in hyperdynamic septic shock. These points highlight that (1) SvO_2 is not 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 shock states due to impaired oxygen extraction capacities. Thus, a normal of high SvO_2 does not exclude the presence of tissue hypoxia.[8] Finally, during resuscitation of shock states, an increase in VO_2 is expected to result from the increase in DO_2 such that SvO_2 does not change markedly until DO_2 has exceeded a critical value. Above this value, a further increase in DO_2 should no longer change VO_2 and the SvO_2 should increase in parallel with the increase in DO_2.[8]

SvO_2 requires a pulmonary artery catheter, the use of which is declining; consequently, it has been proposed to replace SvO_2 with central venous blood oxygen saturation ($ScvO_2$). Although both variables represent different entities, an acceptable agreement between the variables[9] and their changes[10] was reported. $ScvO_2$ is no longer recommended as a therapeutic target in the resuscitation of septic shock by the Surviving Sepsis Campain;[2] however, the use of this variable should not be totally abandoned.[1,11] Indeed, a normal $ScvO_2$ or a higher-than-normal $ScvO_2$ suggests that oxygen extraction capacities are impaired or markedly impaired. In such conditions, it is illusory to expect correction of tissue hypoxia after an increase in DO_2. Conversely, a lower-than-normal $ScvO_2$ clearly suggests that DO_2 is inadequate and measures should be applied to increase it, mostly through an increase in cardiac output.[11] Therefore,

knowledge of $ScvO_2$ should be very helpful for orienting the resuscitation strategy.

Mixed Venous Blood (or Central Venous Blood) Minus Arterial Blood Carbon Dioxide Pressures Differences

According to the Fick equation applied to carbon dioxide (CO_2), the production of CO_2 (VCO_2) equals the product of cardiac output and the difference between the mixed venous blood CO_2 content and the arterial blood CO_2 content. Assuming that the relationship between CO_2 content and CO_2 pressure (PCO_2) is almost linear, it has been proposed to substitute CO_2 pressure for CO_2 content in the Fick equation. Therefore, the difference between the mixed venous blood PCO_2 and the arterial blood PCO_2 (also called PCO_2 gap) equals $k \times VCO_2$/cardiac output, where k is a factor defining the relationship between CO_2 content and PCO_2.[12] Therefore, the PCO_2 gap should increase when VCO_2 is abnormally increased and the cardiac output cannot compensate for this increase (e.g., marked exercise) or when the venous flow (cardiac output) is not sufficient to clear the CO_2 produced at the periphery (CO_2 stagnation phenomenon). In normal conditions, the PCO_2 gap is ≤6 mmHg.

In hypodynamic shock states (decreased cardiac output), the PCO_2 gap should be increased, whereas in hyperdynamic shock states (normal or high cardiac output), the PCO_2 gap should be normal.[13]

Therefore, a normal PCO_2 gap suggests that aiming to increase cardiac output cannot be a priority in the therapeutic strategy, whereas a high PCO_2 gap suggests that increasing cardiac output may be an appropriate therapeutic option.

Indices of Fluid Responsiveness

Approximately half of all critically ill patients are fluid responders, i.e., their cardiac output increases by >15% after fluid administration.[14] Fluid infusion may result in deleterious effects (e.g., pulmonary edema and tissue edema) in fluid non-responders and fluid overload in general is associated with poor outcomes in critically ill patiens;[15–17] thus, it is crucial to predict fluid responsiveness before any fluids are administered. Numerous indices or tests of fluid responsiveness have been developed during the last two decades. Some of these indices use the heart-lung interactions in patients under mechanical ventilation. The general principle is that if the heart is preload responsive, the stroke volume changes markedly over the respiratory cycle due to changes in preload.[18] As changes in PP may reflect changes in stroke volume,[19] the changes in PP during mechanical ventilation, called PP variation (PPV), have been proposed as an index of fluid responsiveness,[20] and the value of this index in many studies was reported in meta-analyses.[21,22] PPV can be calculated automatically and displayed in real-time on the screen of bedside hemodynamic monitoring devices. A notable advantage of PPV is that it can be obtained from a simple arterial catheter without the need of any sophisticated cardiac output monitoring device. However, there are numerous factors limiting the use of PPV to predict fluid responsiveness, such as the presence of cardiac arrhythmia, persistence of spontaneous breathing activity, low tidal volume ventilation, and low compliance of the respiratory system.[23] Recently, it was proposed to calculate the changes in PPV during a tidal volume challenge that consisted of increasing the tidal volume transiently (from 6 mL/kg to 8 mL/kg) to overcome the limitation of PPV in cases of low tidal volume ventilation.[24] Excellent results have been reported in critically ill patients in supine[25,26] and in prone positions[27] and in patients undergoing surgery.[28,29] The end-expiratory occlusion test is another approach that uses heart-lung interaction in mechanically ventilated patients and can reliably predict fluid responsiveness[30], even in cases of spontaneous breathing activity[31] or low lung compliance.[32] The passive leg raising (PLR) test, which does not use heart-lung interactions, reliably predicts fluid responsiveness in all situations[33] except cases of intra-abdominal hypertension.[34] The PLR test involves moving the patient's bed from the semi-recumbent position to a position where the trunk and the head are horizontal, and the lower limbs elevated at 45° This maneuvre results in a venous blood shift from the lower limbs and the abdomen toward the thorax. This endogenous volume challenge has the same effects as fluid loading on the venous return determinants (mean systemic pressure, CVP, and resistance to venous return)[35] and thus represents an excellent test to predict fluid responsiveness. However, some rules must be respected for the PLR test results to be properly interpreted.[36] Sympathetic stimulation should be avoided to prevent an increase in cardiac output that is unrelated to passive mobilization of venous blood and would result in misleading interpretation. The absence of an increase in heart rate during PLR ensures that the test results can be properly interpreted. Furthermore, as the effects of PLR are transient, a real-time hemodynamic assessment is mandatory. Most studies that showed excellent accuracy of PLR to predict fluid responsiveness used the real-time changes in cardiac output during PR.[33] Changes in arterial pressure waveform-based cardiac output[32] or in velocity-time integral (VTI) using echocardiography[37] are particularly suitable. More recently, it was reported that the decrease in PPV during PLR is a good indicator of fluid responsiveness in patients receiving mechanical ventilation.[26] The advantage of this method is that no cardiac output measurement is required to interpret the test results.

Echocardiographic Variables

Echocardiographic examination is recommended to be performed as soon as possible in patients with shock as it can rapidly provide information about the systolic and diastolic functions of the left and of the right ventricles, and no other bedside method is better for that purpose. The most used echocardiographic variables in critically ill patients are the left ventricular ejection fraction (LVEF), the VTI, the left ventricular size, the right ventricular end-diastolic area (RVEDA)/left ventricular end-diastolic area (LVEDA), the early wave of transmitral diastolic blood flow (E), the atrial wave of transmitral diastolic blood flow (A), the E/A, the maximal diastolic early velocity by tissue Doppler imaging at the mitral annulus (E′), the E/E′, the tricuspid annulus systolic excursion (TAPSE), the paradoxical septal motion, the pulmonary artery systolic pressure (PAPs), the left ventricular strain or strain rate, and the inferior vena cava diameter. Cardiac output can be obtained from VTI and the cross-sectional area of the left ventricular outflow tract. In addition, echocardiographic examination can rapidly detect other disturbances such as pericardial effusion and cardiac valve dis-

eases, which can sometimes contribute to the circulatory failure. Furthermore, as well as assessing cardiac function and diagnosing cardiac disease, echocardiography can also assess preload responsiveness. For example, the changes in VTI during PLR reliably predict fluid responsiveness.[37]

Transpulmonary Thermodilution Variables

The European Society of Intensive Care Medicine[1,11] has recommended the use of transpulmonary thermodilution monitoring in complex patients, especially those with circulatory shock and associated acute respiratory distress syndrome (ARDS). Transpulmonary thermodilution systems provide intermittent measurements of cardiac output. However, a single value of cardiac output has limited value as it depends on the metabolic conditions; thus, cardiac output can be low but adequate in states of low oxygen demand or can be high but inadequate in cases of high oxygen demand. Therefore, a cardiac output value should always be interpreted with $ScvO_2$ or PCO_2 gap. The most important transpulmonary thermodilution variables are 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.[38] Transpulmonary thermodilution systems also provide intermittent measurements of global end-diastolic volume (a volumetric marker of global cardiac preload) and cardiac function index (a marker of systolic function of the whole heart). The pulse contour analysis method, which is coupled to transpulmonary thermodilution, provides continuous and real-time cardiac output and PPV monitoring. Pulse contour analysis is beneficial for tracking the short-term changes in cardiac output during preload responsiveness tests such as PLR or end-expiratory occlusion tests, which are helpful when PPV is unreliable.

Pulmonary Artery Catheter Variables

The pulmonary artery catheter is an invasive tool that is now used less frequently compared with in the 20th century. When used in complex patients, this tool can provide measurements of important hemodynamic variables such as pulmonary artery pressure, pulmonary artery occlusion pressure (PAOP), right atrial pressure, SvO_2, $PvCO_2$, intermittent cardiac output, and continuous cardiac output. However, the continuous cardiac output monitoring provided by the pulmonary artery catheter is not a real-time monitoring and therefore cannot be used for interpreting dynamic preload responsiveness tests such as PLR or end-expiratory occlusion tests.

How should we integrate the hemodynamic variables to manage patients with septic shock? (*Figure 1*)

Step 1: identify the presence of shock

Clinical assessment is essential to identify patients with shock. When present, hypotension is a good marker of shock although arterial blood pressure can remain almost normal in the early phase of shock due to compensatory mechanisms. Clinical signs of skin hypoperfusion such as mottling and increased capillary refill time (CRT) are variable but when present they are valuable since they are associated with a low cardiac output shock state.[39] Hyperlactatemia is an important biological marker of global tissue hypoxia, although it may have other origins than tissue hypoxia. The decrease in hyperlactatemia over time is a sign of favorable evolution of shock and is an important recognized target for hemodynamic resuscitation in shock states.[2,7] However, a multicentre, randomized controlled trial recently demonstrated that a resuscitation strategy targeting normalization of CRT was at least as pertinent as a strategy targeting serum lactate levels in terms of outcome of patients with septic shock.[40] A Bayesian analysis of the study showed that CRT-targeted resuscitation may result in lower mortality and faster resolution of organ dysfunction when compared with a lactate-targeted resuscitation strategy.[41] Finally, in the same study, patients with normal CRT at baseline received more therapeutic interventions and presented more organ dysfunction when allocated to the lactate group.[42] Collectively, these data emphasize the importance of peripheral perfusion indices such as CRT to diagnose shock, to assess its severity and to follow the effects of the therapies.

Step 2: start fluid infusion and simultaneously measure MAP−CVP

Severe hypotension can be responsible for organ hypoperfusion, independently of cardiac output. In the case of septic shock, it is recommended to achieve a MAP target of at least 65 mmHg to limit hypotension-induced hypoperfusion.[1,2] In some pathological conditions, the backpressure for organ perfusion is increased so that the organ perfusion pressure is much better reflected by the difference between MAP and CVP than by the sole MAP. Thus, if CVP is high, its value should be taken into account to estimate the actual organ perfusion pressure. In critically ill patients, it was demonstrated that the mean perfusion pressure (MAP−CVP) but not MAP was associated with the progression of acute kidney injury, with a threshold value of 60 mmHg.[43] Therefore, if CVP is 0 mmHg, a MAP of 65 mmHg could be sufficient to maintain kidney perfusion, but a CVP of 15 mmHg would not. To ensure an adequate organ perfusion pressure, the best option would be to decrease CVP when feasible since this would also decrease or prevent development of interstitial tissue edema and hence prevent organ dysfunction. For example, if a patient is mechanically ventilated with positive end-expiratory pressure (PEEP), which increases CVP by a variable degree, the question of slightly decreasing the level of PEEP to improve the mean perfusion pressure, should arise. As the risk of decreasing PEEP is impairment of arterial oxygenation, the benefit/risk of such an intervention should be carefully assessed. The alternate option to increase the mean perfusion pressure is to achieve a higher MAP target. Other pathological conditions where a higher MAP target would be required for kidney function is the presence of abdominal hypertension or the existence of prior chronic hypertension.[44]

To select the most appropriate treatment for increasing MAP, it is essential to consider the DAP. As mentioned above, low DAP is most often due to low vascular tone[3] and this should prompt urgent administration of a vasopressor, namely norepinephrine. In normal vascular tone conditions, DAP should be higher than normal in cases of tachycardia owing to the low diastolic time. Consequently, low DAP in the presence of tachycardia suggests

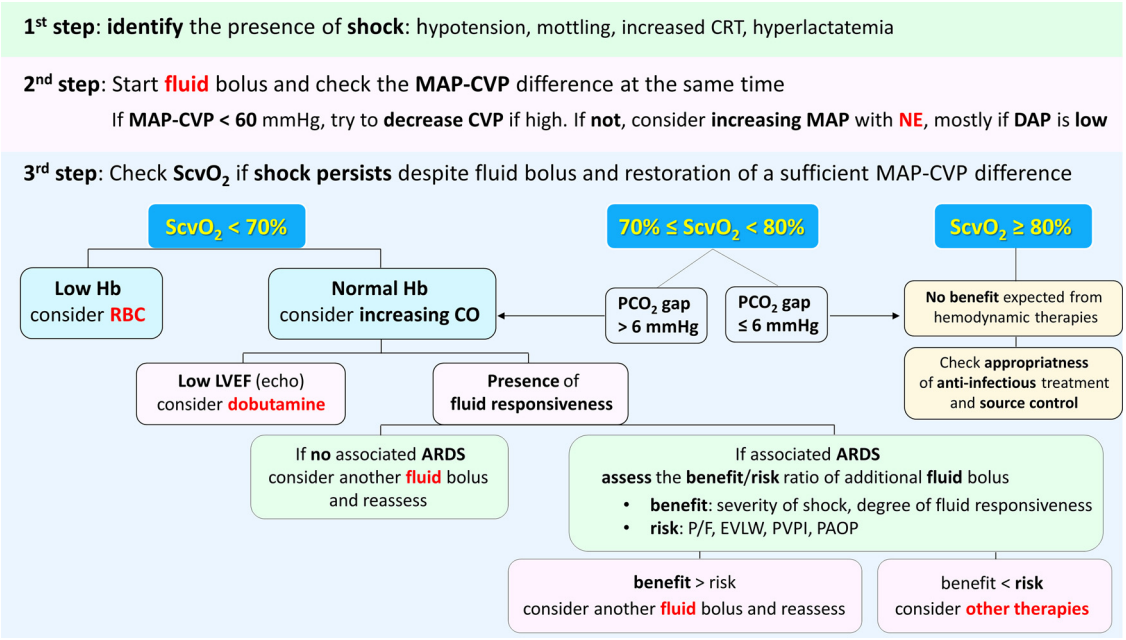

Figure 1. Stepwise approach to integrate hemodynamic variables for the resuscitation of septic shock.
ARDS: Acute respiratory distress syndrome; CO: Cardiac output; CRT: Capillary refill time; CVP: Central venous pressure; DAP: Diastolic arterial pressure; EVLW: Extravascular lung water; Hb: Hemoglobin concentration; LVEF: Left ventricular ejection fraction; MAP: Mean arterial pressure; P/F: Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; PAOP: Pulmonary artery occlusion pressure; PCO_2 gap: Central venous blood – arterial blood carbon dioxide pressure difference; PVPI: Pulmonary vascular permeability index; RBC: Red blood cells; $ScvO_2$: Central venous blood oxygen saturation.

that the arterial tone is markedly depressed and immediate administration of norepinephrine is needed.[45]

If DAP is not very low, low MAP is likely to be associated with an insufficient cardiac output due to a low stroke volume. 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 with stiff arteries.

Step 3: measure $ScvO_2$, a marker of the VO_2/DO_2 balance

If the initial fluid infusion and correction of hypotension are not sufficient to reverse signs of shock, it is important to check $ScvO_2$, a marker of the VO_2/DO_2 balance.

$ScvO_2$ is <70%

If $ScvO_2$ is low (<70%), it indicates that DO_2 is inadequate to VO_2, and it is logical to consider increasing DO_2. At this stage, there are two options: (1) if Hb is low, then blood transfusion can be considered and (2) if Hb is not low, then the inadequate DO_2 should be due to an insufficient cardiac output, related either to insufficient preload or to altered cardiac contractility. If available, indices or tests of fluid responsiveness (see above) can be used. Transthoracic echocardiography is advantageous in that it can help detect fluid responsiveness (changes in VTI during PLR) and diagnose cardiac dysfunction. If fluid responsiveness is still present, fluid administration can be considered, particularly if there is no risk of pulmonary edema formation. A low LVEF (<45%) strongly suggests that septic shock is associated with myocardial depression, and in this context, administration of an inotropic drug, namely dobutamine, can be considered. Right ventricular dysfunction can be suspected when the RVEDA/LVEDA ratio is high (>0.6).[46] A specific therapy can be administered after diagnosing the underlying mechanism using echocardiography.

In patients who do not respond sufficiently to the initial treatment or in those suffering from severe ARDS, it has been suggested to obtain additional information owing to the complexity of the situation.[1,8] In such cases, advanced hemodynamic monitoring technologies such as the transpulmonary thermodilution systems or pulmonary artery catheterization can provide vital information to assess the benefit/risk balance of therapeutic interventions such as fluid therapy.[8] In cases of ARDS, knowledge of EVLW and PVPI (transpulmonary thermodilution) or PAOP (pulmonary artery catheter) can facilitate assessment of the risk of fluid infusion[38] and sometimes curb the administration of IV fluids, even in the presence of fluid responsiveness. To make the appropriate decision, clinicians should consider the degree of fluid responsiveness, the severity of the circulatory failure and of the subsequent organ dysfunctions (e.g., renal dysfunction), the severity of pulmonary edema based on EVLW, PVPI, and PAOP, and the severity of hypoxemia.

$ScvO_2$ is between 70% and 80%

If $ScvO_2$ is within the normal range (between 70% and 80%) in the presence of tissue hypoxia, it is likely that the oxygen extraction capabilities are impaired. In such cases, knowledge of PCO_2 gap is essential as this marker of the adequacy of cardiac output with the global metabolic conditions is only slightly affected by impairment of oxygen extraction capacities. If PCO_2 gap is increased (>6 mmHg), increasing cardiac output is a therapeutic option. The appropriate therapy to increase cardiac output (fluids or dobutamine) should be selected after testing fluid responsiveness using dynamic indices and after assessing cardiac function using echocardiography, and in some complex cases, after inserting advanced hemodynamic monitoring de-

vices as detailed above. If PCO_2 gap is normal (≤6 mmHg) in the context of shock, it is likely that microcirculation and cellular metabolism disturbances are responsible for tissue hypoxia, and increasing cardiac output cannot be a priority.

$ScvO_2$ is ≥80%

If $ScvO_2$ is higher than normal (≥80%) in cases of shock, it suggests there is marked impairment of oxygen extraction capacities, and this is associated with poor outcomes.[47] Thus, increasing cardiac output and DO_2 is illogical in this situation. However, it is important to ensure adequate anti-infectious treatment and source control, while maintaining appropriate organ-supportive therapies.

Conclusions

Septic shock is a complex pathological state that includes multiple macrocirculatory and microcirculatory disturbances that can vary over time and from patient to patient. Consequently, it is important to obtain all relevant information that can help to identify the presence and degree of each of these disturbances and then select the most appropriate hemodynamic treatment. Integration of hemodynamic variables is essential to assess the benefit/risk balance of each therapeutic intervention.

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Conflicts of Interest

Prof Jean-Louis Teboul is a member of the Medical Advisory Board of Pulsion Medical Systems.

References

[1] Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med 2014;40(12):1795–815. doi:10.1007/s00134-014-3525-z.

[2] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47(11):1181–247. doi:10.1007/s00134-021-06506-y.

[3] Lamia B, Teboul JL, Monnet X, Osman D, Maizel J, Richard C, et al. Contribution of arterial stiffness and stroke volume to peripheral pulse pressure in ICU patients: an arterial tonometry study. Intensive Care Med 2007;33(11):1931–7. doi:10.1007/s00134-007-0738-4.

[4] Pottecher T, Calvat S, Dupont H, Durand-Gasselin J, Gerbeaux P. Haemodynamic management of severe sepsis: recommendations of the French Intensive Care Societies (SFAR/SRLF) Consensus Conference, 13 October 2005, Paris, France. Crit Care 2006;10(4):311. doi:10.1186/cc4965.

[5] Wong BT, Chan MJ, Glassford NJ, Mårtensson J, Bion V, Chai SY, et al. Mean arterial pressure and mean perfusion pressure deficit in septic acute kidney injury. J Crit Care 2015;30(5):975–81. doi:10.1016/j.jcrc.2015.05.003.

[6] Chemla D, Hébert JL, Coirault C, Zamani K, Suard I, Colin P, et al. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. Am J Physiol 1998;274(2):H500–5. doi:10.1152/ajpheart.1998.274.2.H500.

[7] Vincent JL, Quintairos E, Silva A, Couto L Jr, Taccone FS. The value of blood lactate kinetics in critically ill patients: a systematic review. Crit Care 2016;20(1):257. doi:10.1186/s13054-016-1403-5.

[8] Teboul JL, Hamzaoui O, Monnet X. SvO2 to monitor resuscitation of septic patients: let's just understand the basic physiology. Crit Care 2011;15(6):1005. doi:10.1186/cc10491.

[9] Reinhart K, Kuhn HJ, Hartog C, Bredle DL. Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. Intensive Care Med 2004;30(8):1572–8. doi:10.1007/s00134-004-2337-y.

[10] Dueck MH, Klimek M, Appenrodt S, Weigand C, Boerner U. Trends but not individual values of central venous oxygen saturation agree with mixed venous oxygen saturation during varying hemodynamic conditions. Anesthesiology 2005;103(2):249–57. doi:10.1097/00000542-200508000-00007.

[11] Teboul JL, Saugel B, Cecconi M, De Backer D, Hofer CK, Monnet X, et al. Less invasive hemodynamic monitoring in critically ill patients. Intensive Care Med 2016;42(9):1350–9. doi:10.1007/s00134-016-4375-7.

[12] Scheeren TWL, Wicke JN, Teboul JL. Understanding the carbon dioxide gaps. Curr Opin Crit Care 2018;24(3):181–9. doi:10.1097/MCC.0000000000000493.

[13] Vallet B, Teboul JL, Cain S, Curtis S. Venoarterial CO(2) difference during regional ischemic or hypoxic hypoxia. J Appl Physiol 2000;89(4):1317–21 1985. doi:10.1152/jappl.2000.89.4.1317.

[14] Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest 2002;121(6):2000–8. doi:10.1378/chest.121.6.2000.

[15] Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 2006;34(2):344–53. doi:10.1097/01.ccm.0000194725.48928.3a.

[16] Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med 2011;39(2):259–65. doi:10.1097/CCM.0b013e3181feeb15.

[17] Vaara ST, Korhonen AM, Kaukonen KM, Nisula S, Inkinen O, Hoppu S, et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. Crit Care 2012;16(5):R197. doi:10.1186/cc11682.

[18] Michard F, Teboul JL. Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. Crit Care 2000;4(5):282–9. doi:10.1186/cc710.

[19] Mesquida J, Kim HK, Pinsky MR. Effect of tidal volume, intrathoracic pressure, and cardiac contractility on variations in pulse pressure, stroke volume, and intrathoracic blood volume. Intensive Care Med 2011;37(10):1672–9. doi:10.1007/s00134-011-2304-3.

[20] Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 2000;162(1):134–8. doi:10.1164/ajrccm.162.1.9903035.

[21] Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med 2009;37(9):2642–7. doi:10.1097/CCM.0b013e3181a590da.

[22] Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. Crit Care 2014;18(6):650. doi:10.1186/s13054-014-0650-6.

[23] Michard F, Chemla D, Teboul JL. Applicability of pulse pressure variation: how many shades of grey. Crit Care 2015;19(1):144. doi:10.1186/s13054-015-0869-x.

[24] Myatra SN, Monnet X, Teboul JL. Use of 'tidal volume challenge' to improve the reliability of pulse pressure variation. Crit Care 2017;21(1):60. doi:10.1186/s13054-017-1637-x.

[25] Myatra SN, Prabu NR, Divatia JV, Monnet X, Kulkarni AP, Teboul JL. The changes in pulse pressure variation or stroke volume variation after a "tidal volume challenge" reliably predict fluid responsiveness during low tidal volume ventilation. Crit Care Med 2017;45(3):415–21. doi:10.1097/CCM.0000000000002183.

[26] Taccheri T, Gavelli F, Teboul JL, Shi R, Monnet X. Do changes in pulse pressure variation and inferior vena cava distensibility during passive leg raising and tidal volume challenge detect preload responsiveness in case of low tidal volume ventilation. Crit Care 2021;25(1):110. doi:10.1186/s13054-021-03515-7.

[27] Shi R, Ayed S, Moretto F, Azzolina D, De Vita N, Gavelli F, et al. Tidal volume challenge to predict preload responsiveness in patients with acute respiratory distress syndrome under prone position. Crit Care 2022;26(1):219. doi:10.1186/s13054-022-04087-w.

[28] Messina A, Montagnini C, Cammarota G, De Rosa S, Giuliani F, Muratore L, et al. Tidal volume challenge to predict fluid responsiveness in the operating room: an observational study. Eur J Anaesthesiol 2019;36(8):583–91. doi:10.1097/EJA.0000000000000998.

[29] Messina A, Montagnini C, Cammarota G, Giuliani F, Muratore L, Baggiani M, et al. Assessment of fluid responsiveness in prone neurosurgical patients undergoing protective ventilation: role of dynamic indices, tidal volume challenge, and end-expiratory occlusion test. Anesth Analg 2020;130(3):752–61. doi:10.1213/ANE.0000000000004494.

[30] Gavelli F, Shi R, Teboul JL, Azzolina D, Monnet X. The end-expiratory occlusion test for detecting preload responsiveness: a systematic review and meta-analysis. Ann Intensive Care 2020;10(1):65. doi:10.1186/s13613-020-00682-8.

[31] Monnet X, Osman D, Ridel C, Lamia B, Richard C, Teboul JL. Predicting volume responsiveness by using the end-expiratory occlusion in mechanically ventilated intensive care unit patients. Crit Care Med 2009;37(3):951–6. doi:10.1097/CCM.0b013e3181968fe1.

[32] Monnet X, Bleibtreu A, Ferré A, Dres M, Gharbi R, Richard C, et al. Passive leg-raising and end-expiratory occlusion tests perform better than pulse pressure variation in patients with low respiratory system compliance. Crit Care Med 2012;40(1):152–7. doi:10.1097/CCM.0b013e31822f08d7.

[33] Monnet X, Marik P, Teboul JL. Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. Intensive Care Med 2016;42(12):1935–47. doi:10.1007/s00134-015-4134-1.

[34] Beurton A, Teboul JL, Girotto V, Galarza L, Anguel N, Richard C, et al. Intra-abdominal hypertension is responsible for false negatives to the passive leg raising test. Crit Care Med 2019;47(8):e639–47. doi:10.1097/CCM.0000000000003808.

[35] Guérin L, Teboul JL, Persichini R, Dres M, Richard C, Monnet X. Effects of passive leg raising and volume expansion on mean systemic pressure and venous return in shock in humans. Crit Care 2015;19:411. doi:10.1186/s13054-015-1115-2.

[36] Monnet X, Teboul JL. Passive leg raising: five rules, not a drop of fluid. Crit Care 2015;19(1):18. doi:10.1186/s13054-014-0708-5.

[37] Lamia B, Ochagavia A, Monnet X, Chemla D, Richard C, Teboul JL. Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity. Intensive Care Med 2007;33(7):1125–32. doi:10.1007/s00134-007-0646-7.
[38] Jozwiak M, Teboul JL, Monnet X. Extravascular lung water in critical care: recent advances and clinical applications. Ann Intensive Care 2015;5(1):38. doi:10.1186/s13613-015-0081-9.
[39] Hiemstra B, Eck RJ, Wiersema R, Kaufmann T, Koster G, Scheeren TWL, et al. Clinical examination for the prediction of mortality in the critically Ill: the simple intensive care studies-I. Crit Care Med 2019;47(10):1301–9. doi:10.1097/CCM.0000000000003897.
[40] Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomized clinical trial. JAMA 2019;321(7):654–64. doi:10.1001/jama.2019.0071.
[41] Zampieri FG, Damiani LP, Bakker J, Ospina-Tascón GA, Castro R, Cavalcanti AB, et al. Effects of a resuscitation strategy targeting peripheral perfusion status versus serum lactate levels among patients with septic shock. A bayesian reanalysis of the ANDROMEDA-SHOCK trial. Am J Respir Crit Care Med 2020;201(4):423–9. doi:10.1164/rccm.201905-0968OC.
[42] Kattan E, Hernández G, Ospina-Tascón G, Valenzuela ED, Bakker J, Castro R, et al. A lactate-targeted resuscitation strategy may be associated with higher mortality in patients with septic shock and normal capillary refill time: a post hoc analysis of the ANDROMEDA-SHOCK study. Ann Intensive Care 2020;10(1):114. doi:10.1186/s13613-020-00732-1.
[43] Ostermann M, Hall A, Crichton S. Low mean perfusion pressure is a risk factor for progression of acute kidney injury in critically ill patients – A retrospective analysis. BMC Nephrol 2017;18(1):151. doi:10.1186/s12882-017-0568-8.
[44] Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med 2014;370(17):1583–93. doi:10.1056/NEJMoa1312173.
[45] Hamzaoui O, Teboul JL. Importance of diastolic arterial pressure in septic shock: PRO. J Crit Care 2019;51:238–40. doi:10.1016/j.jcrc.2018.10.032.
[46] Huang S, Sanfilippo F, Herpain A, Balik M, Chew M, Clau-Terré F, et al. Systematic review and literature appraisal on methodology of conducting and reporting critical-care echocardiography studies: a report from the European Society of Intensive Care Medicine PRICES expert panel. Ann Intensive Care 2020;10(1):49. doi:10.1186/s13613-020-00662-y.
[47] Textoris J, Fouché L, Wiramus S, Antonini F, Tho S, Martin C, et al. High central venous oxygen saturation in the latter stages of septic shock is associated with increased mortality. Crit Care 2011;15(4):R176. doi:10.1186/cc10325.