Chapter

Assessment and Management of Hypoperfusion in Sepsis and Septic Shock

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Abstract

Diagnosis of organ hypoperfusion in patient with sepsis is not always straightforward which makes septic shock definition, diagnosis, and early treatment are major challenges that emergency physicians and intensivist must deal with in their daily practice. Normal blood pressure does not always mean good organ perfusion, which means patient might develop septic shock, yet they are not hypotensive. There are several indices that could be used in combination to diagnose and manage hypoperfusion in patients with septic shock. Fluid resuscitation and vasopressor administration along with infection sources control are the cornerstones in septic shock management. This chapter will cover indices that can be used to diagnose hypoperfusion, type and amount of fluid and vasopressor that can be used in resuscitating septic shock patients.

Keywords: septic shock, hypoperfusion, fluid resuscitation, vasopressor

1. Introduction

Sepsis is defined as life-threatening condition caused by a dysregulated host response to infection, resulting in organ dysfunction while septic shock is circulatory, cellular, and metabolic abnormalities in septic patients, presenting as fluid-refractory hypotension requiring vasopressor therapy with associated tissue hypoperfusion [1]. Septic shock has high mortality rate and constitutes 20% of all global deaths [2]. Mortality associated with septic shock range from 24–41% [3–6]. Increased morbidities and decreased functional status of septic shock patients after hospital discharge are major concerns and related to poor management [7]. Management of Septic shock include early recognition, source control with antibiotic and surgical intervention if needed, adequate perfusion and vital organ support including renal and respiratory support [8]. Patient in the early stage of septic shock required individualized fluid resuscitation and early administration of vasopressor to ensure tissue perfusion.

2. Indices of Hypoperfusion

Progression of sepsis to septic shock occur very quickly and leads to hypoperfusion, end organ failure and death. **Figure 1** summaries the pathophysiology of sepsis and septic shock [9–11]. Hemodynamic, clinical and laboratory indices could be used to determine the level of hypoperfusion and its response to resuscitation. **Table 1** summaries the perfusion indices of and their targets during resuscitation.

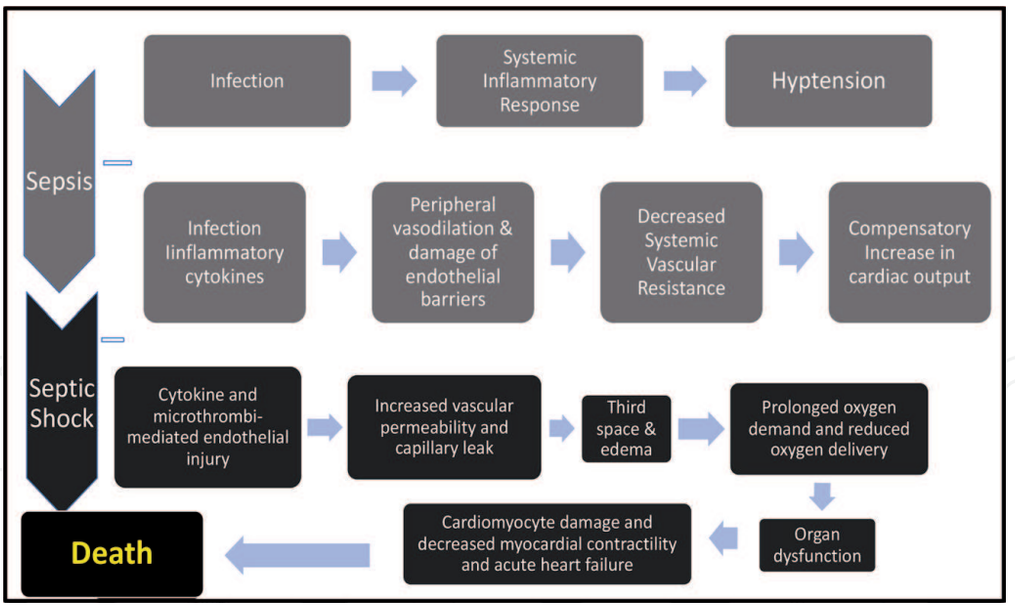

Figure 1.
Pathophysiology of sepsis and septic shock.

Index	Target
Heart Rate	60–90 Beats per minute
Mean arterial pressure MAP	≥65 mmHg
Diastolic arterial pressure (DAP)	≥50 mmHg
Skin examination	Normal color worminess
Temperature	≥ 36oC
Capillary Refill Time (CRT)	< 3 seconds
Urine Output (OUP)	≥ 0.5 ml/kg/hour
Central Venous Pressure (CVP)	< 6–8 mmHg in spontaneous breathing > 12–15 mmHg in ventilated patient
Serum Lactate	< 2.2 mmol/L

Table 1.
Indices of hypoperfusion and their targets.

2.1 Heart rate

Tachycardia is common sign of septic shock, and it predicts poor prognosis of septic shock patient. It is caused by stimulation of α- and β-adrenergic receptors increases in response to venodilattion and could be also related high temperature. Tachycardia is a sign impaired arterial tone [12]. It increases oxygen consumption, decreases diastolic filling and coronary perfusion, and increases arrhythmia [13]. Patients with septic shock and persistent tachycardia despite resuscitation measures has high mortality and morbidity rate [14].

2.2 Blood pressure

Blood pressure is easy to measure and monitor. Blood pressure is determined by cardiac output, systemic vascular resistance, and arterioles pressure and coronary perfusion and heart flow depend upon diastolic arterial pressure (DAP) [15].

Hypotension reflects decrease cardiac output, but it could be a delayed sign of hypoperfusion, and its absence does not necessarily rule out hypoperfusion. Hypotension triggers resuscitation. Low diastolic arterial pressure, in septic shock indicates impaired arterial tone. Optimizing blood pressure is one of the goals of fluid resuscitation and associated with better outcome [16]. Prolonged hypotension, low mean arterial pressure (MAP) and DAP associated with high mortality in septic shock patient [17, 18]. Normal MAP and DAP should be targeted to improve survival of septic shock patients [15]. No evidence what the best target level of DBP is but common approach is to titrate vasopressors in septic shock to keep DAP ≥50 mmHg [19]. Resuscitation should target MAP of 65 mmHg per the septic shock guidelines [20]. Hypoperfusion may persist even when pressure is restored so personalization approach to target blood pressure should consider other indices of perfusion [21].

2.3 Skin changes

Skin examination including its color, blanching and worminess is one of the most important physical examination to determine level of skin perfusion which reflect vital organ perfusion. Anterior aspect of the knee is one body area that commonly examined for skin perfusion Mottling score is one of indices of hypoperfusion and associated with worse outcome regardless of vasopressor use [22, 23]. Normalization of skin color and disappearance of mottled skin are targets of resuscitation and related to higher survival rate of septic shock patient [24, 25].

2.4 Skin temperature

Skin temperature is one of the most accessible markers of skin perfusion and hence tissue perfusion [26]. Hypothermia in circulatory shock is associated with impaired outcome [27].

2.5 Capillary refill time (CRT)

CRT is the time taken to regain distal capillary bed color after blanching by pressure. Normally should be less than 3 seconds. It has been shown in in study of 783 critically ill patients that CRT is sensitive sign of decrease cardiac output measured by echocardiogram [28]. Capillary refill time is one of the best indices of adequate perfusion [29, 30]. And could be used as screening tool to predict sick patient that might need admission to critical care area. In one study, CRT and lactate are similar in predict survival [31]. In other study prolonged CRT associated with decrease perfusion of the liver, kidneys, gut and spleen [32]. CRT more than 4 seconds associated with higher mortality rate of septic shock patients [33]. In a randomized controlled study of septic shock patients with high lactate level but with a normal CRT had lower day-28 mortality when compared to prolonged CRT and high lactate level and survival of patients is higher with when resuscitation is guided by capillary refill time but not lactate levels [34]. When CRT used as index as optimal resuscitation it led to decrease mortality rate and should be used to guide fluid resuscitation in septic shock patient [34–36]. Septic shock patients failing to normalize their CRT after the first fluid bolus in ED had high mortality [37].

2.6 Passive leg raise

Passive Leg Raise (PLR) Can assist in identifying preload dependence. Utilization of the passive leg raise as index of resuscitation lead to reduce net

fluid balance, acute kidney injury and pulmonary edema and may improve outcomes [38].

PLR became more popular and easier to use in different sitting including emergency department sitting [39].

By moving the patient from a semi-recumbent position, lowering the trunk and raising the patient's legs to 45°, an amount of ~300 mL of blood is transferred to the ventricles, thereby increasing the cardiac preload. If CO increases of at least 10% compared to baseline, the patient is considered preload responsive, thus capable of displaying a CO increase following administration of fluid. The change in cardiac output changes in is measured by thermodilution, echocardiography, pulse contour analysis or pulse pressure variation. Passive leg rising is shifts venous blood from the legs to the intrathoracic compartment. This response can predict the response to a fluid challenge. Passive leg-raise test is accurate and has excellent sensitivity and specificity, for that it is recommended to determine fluid responsiveness [20, 40]. A meta-analysis of 21 studies and 991 adult patients showed that a 10% 2% increase in cardiac output with PLR predicted fluid responsiveness [41].

2.7 Urine output

Oliguria which is urine output less than 0.5 ml/kg/hour is one of the main triggers for fluid challenges in septic shock patient [16]. Oliguria is one of signs of acute renal failure which is an independent risk factor associated with increased mortality during sepsis. Low UOP may reflect low renal perfusion pressure. UOP 30–50 mL/h in adult patient with septic shock should prompt further fluid resuscitation or other measures to increase cardiac output in a non–fluid-responsive patient [42]. UOP should not be taken alone as fluid resuscitation may not increase urinary output and cause positive fluid balance in patients with septic shock [20].

2.8 Central venous pressure (CVP)

Venodilation and hypovolemia cause decrease in ventricular preload which is signaled by decrease in central venous pressure. CVP reflect the right atrial pressure [43]. CVP alone is a poor variable to predict fluid responsiveness [44, 45]. The target CVP is < 6–8 mmHg in spontaneous breathing patient and > 12–15 mmHg in mechanically ventilated patient [46].

2.9 Lactate

Lactates reflect the onset of anaerobic metabolism. In experimental conditions, lactate increases when oxygen consumption increased and oxygen delivery decreased. Lactate also elevated in beta-adrenergic stimulation, leading to an accelerated glycolysis and liver failure. Lactate >2 mmol/L associated tissue hypoperfusion (lactate >2 mmol/L) [47]. Clinical studies show high lactate levels are associated with a high mortality, independently of its cause [48]. Lactate is easy to measure and can be used in emergency department triage and as a goal of early sepsis therapy [49]. Repeating lactate measurements is a trigger of resuscitation [20]. Lactate-guided resuscitation has emerged after the observation that the higher the decrease in lactate levels, the best the outcome [50].

Indices of hypoperfusion are combinations of pressure and flow measurements and clinical markers. They should be taken together and not to rely only on one index to diagnose and mange hypoperfusion [51].

3. Fluid resuscitation of septic shock patient

Crystalloid intravenous fluid either ringer lactate or 0.9% normal saline is the first and the main step in restoring hemodynamic instability. Septic shock patient in the initial stage should be considered fluid responsive and receive fluid bolus [52]. Not all septic shock patient will respond to the initial fluid resuscitation, hence additional pharmaceutics intervention is needed to augment of fluid resuscitation to restore the hemodynamic and improve organ perfusion [53, 54]. Fast intravenous (IV) crystalloid infusion has a slower redistribution rate. Interstitial distribution is hypothesized to be greater in sepsis than in healthy volunteers due to sepsis pathophysiology [55] (**Figure 1**). The maximal effect of IV crystalloid bolus achieves at one minute and return to baseline after 30 minutes. Only one third of septic shock patient will have risen in MAP after fluid challenge [56, 57]. Amount of IV fluid resuscitation in patients with septic shock is not known. In one retrospective study found large amount of fluid more than 5 liter per day associated with increase mortality rate and need of ventilatory support [58, 59]. 50% 0f septic shock patients will be non-fluid responsive, where a condition where the administration of more fluid bolus may lead to fluid accumulation, impaired oxygen delivery, and worsening hypoperfusion [60]. How fast fluid should be administered in septic shock resuscitation is not known. Mainly retrospective studies shows failure to complete 30 mL/kg of IV crystalloid over 3 hours was associated with increased mortality [61]. In multi-center study found IV fluid administration within six hours was associated with decreased mortality [62]. regarding type of fluid in resuscitating septic shock patient, the current guideline recommends both sodium chloride and balanced crystalloids [20]. Studies within the critically ill have shown lower risk of in-hospital or 30-day mortality, AKI, or major adverse kidney event in the first 30 days with the use of balanced crystalloids over sodium chloride solutions [63, 64]. SMART trial, compared the two solutions in 15,802 critically ill patients, reported a lower rate of death from any cause, renal-replacement therapy, or renal failure with using balanced crystalloids versus normal saline [63]. In secondary analysis of SMART study among 1,641 patients were admitted to the medical ICU with a diagnosis of sepsis, balanced crystalloids was associated with a lower 30-day in-hospital mortality rate, renal failure, and a higher number of vasopressor free days compared with use of saline [64]. Amount of fluids resuscitation should be decided to minimize the complication of over resuscitation as pulmonary edema, brain edema, abdominal compartment syndrome and third space edema which will lead resulting in end-organ hypoperfusion by decrease oxygen delivery, capillary blood flow and lymphatic drainage. Which explain worse outcomes in shock with a positive fluid balance [55, 65, 66]. Collapsible inferior vena cava can along with other hypoperfusion indices can be used to monitor fluid and resuscitation of septic shock patient [67]. Resuscitation of septic shock patient with high volume of normal saline is associated with hyperchloremia, AKI, multiorgan dysfunction, and high mortality [68, 69]. Fixed amount of fluid hardly suitable for all septic shock patients, Teboul and Monnet proposed to administer crystalloid about 10 mL/kg within the first 30 to 60 min and monitor patient [52]. If patient develop any signs of respiratory failure stop further boluses. In case CRT is still prolonged, tachycardia or low blood pressure reading, skin mottling increase in the infusion rate [70].

Perfusion indices should be used to individualize fluid administration approach in balanced crystalloid is recommended over normal slain in septic shock resuscitation.

4. Vasopressors in septic shock management

Vasopressor increases systemic vascular resistance (SVR), cardiac output CO, and heart rate (HR) and rapidly restore organ perfusion [71]. Vasopressors either catecholamine- or non-catecholamine-based agents. Dopamine, norepinephrine, epinephrine, and phenylephrine are catecholamine-based vasopressors while vasopressin is a non-catecholamine-based vasopressors [72]. Norepinephrine is the first-line vasopressor for patients with septic shock [20]. Early vasopressors administration in septic shock patients revert the severely impaired arterial tone and associated with lowest mortality rate occurred when vasoactive agents were started 1 to 6 hours of septic shock identification [20, 73–76]. CENSER trial shows early NE administration is associated with increased shock control over the first 6 hours [76]. Addition of vasopressin to norepinephrine in the few hours of shock when doses of norepinephrine dose is ≥1 μg/Kg/min, may decrease mortality, arrhythmia, hypotension and need for renal replacement therapy [77, 78]. Addition of vasopressin to norepinephrine is more effective in early septic shock management and reach MAP target faster and lower incidence of atrial fibrillation [79, 80]. Possible complication of vasopressor includes dysrhythmias tachycardia or atrial fibrillation. Hyperlactatemia and hyperglycemia [80, 81]. Peripheral administration of vasopressors includes extravasation and peripheral ischemia given their potent vasoconstrictive properties [82]. Extravasation was uncommon if vasopressors are administered peripherally for less than 22 hours. Peripheral administration of vasopressors in upper arm using 20 gauge or larger is safe and feasible in the initial hours of resuscitation [82–84]. Vasopressor treatment can be initiated on a peripheral venous line with non-invasive BP monitoring, and shifted, as soon as possible, to central venous catheter with arterial pressure monitoring [85].

Early norepinephrine administration should be started in septic shock patient with slow response to fluid resuscitation. Vasopressin is recommended in when norepinephrine dose is ≥1 μg/Kg/min.

5. Conclusion

Septic shock is life threatening condition complicated with hypoperfusion, Indices of hypoperfusion are combinations of pressure and flow measurements and clinical markers. Indices should be taken together and not to rely only on one index to diagnose and mange hypoperfusion. Perfusion indices should be used to individualize fluid administration approach in balanced crystalloid is recommended over normal slain in septic shock resuscitation. Early norepinephrine administration should be started in septic shock patient with slow response to fluid resuscitation. Vasopressin is recommended in when norepinephrine dose is ≥1 μg/Kg/min.

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