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Macrocirculatory and Microcirculatory Endpoints in Sepsis Resuscitation

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Abstract

Sepsis is a common disease process encountered by physicians. Sepsis can lead to septic shock, which carries a hospital mortality rate in excess of 40%. Although the Surviving Sepsis Guidelines recommend targeting a mean arterial pressure (MAP) of 65 mmHg and normalization of lactate, these endpoints do not necessarily result in tissue perfusion in states of shock. While MAP and lactate are commonly used markers in resuscitation, clinicians may be able to improve their resuscitation by broadening their assessment of the microcirculation, which more adequately reflects tissue perfusion. As such, in order to achieve a successful resuscitation, clinicians must optimize both macrocirculatory (MAP, cardiac output) and microcirculatory (proportion of perfused vessels, lactate, mottling, capillary refill time) endpoints. This review will summarize various macrocirculatory and microcirculatory markers of perfusion that can be used to guide the initial resuscitation of patients with sepsis.

Keywords

shock, sepsis, review

Introduction

Sepsis is one of the most common disease processes encountered by physicians. Sepsis can lead to septic shock, which carries a hospital mortality rate in excess of 40%.[1] Septic shock is characterized by sepsis with persistent hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) greater than 65 mmHg and a serum lactate level >2 mmol/L despite adequate volume resuscitation.[1] This definition of septic shock highlights 2 important concepts of organ perfusion that are crucial in the management of these patients: the macrocirculation (MAP) and microcirculation (lactate). Accordingly, the Surviving Sepsis Guidelines recommend targeting a MAP of 65 mmHg (1C) in the first hour of resuscitation.[2] In patients with a lactate >2, they recommend repeating lactate levels every 2-4 hours and targeting a normalization of lactate (2C).[2,3] However, despite these recommendations, these management goals are not always compatible, especially in shock states.[4-6] Achieving a MAP of 65 mmHg does not always lead to adequate perfusion of the microcirculation, which is crucial for tissue oxygenation and organ perfusion.[4-8] Careful attention to optimizing both macro and microcirculatory flow is critical to a successful resuscitation in patients with septic shock. In addition, clinicians should also focus on optimizing cardiac function, central nervous system and systemic oxygen consumption, and delivery of oxygen to cells. This narrative review will focus on markers of impaired organ perfusion that can be used to guide the resuscitation of patients with sepsis. The emphasis will be on distinguishing between macrocirculatory versus microcirculatory markers of perfusion, and how both components are crucial to the initial resuscitation of patients with sepsis. Summary tables addressing select randomized controlled trials discussed in this paper are shown in Tables 1 and 2.

Macrocirculation

Common indicators of macrocirculation including MAP and cardiac output may help guide the initial resuscitation. However, neither of these measurements assess tissue

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Table 1. Summary of Select Randomized Controlled Trials Assessing Macrocirculation in This Review.

Trial	Population	Intervention	Control	Conclusion	Other findings
Asfar *et al*—High versus low blood-pressure target in patients with septic shock[9]	≥18 years with septic shock	MAP 80-85	MAP 65-70	No significant difference in 28 day mortality in higher versus lower MAP target group (HR 1.07, 95% CI, 0.84-1.38; p = 0.57)	Increased rate of atrial fibrillation in higher MAP versus lower MAP group (6.7% vs. 2.8%, p = 0.02)Lower doubling of serum creatinine in higher MAP group (38.9% vs. 52.0%; p = 0.02)Lower rate of renal replacement therapy in higher MAP group (31.7% vs. 42.2%; p = 0.046, NNT 9.5)
Lamontagne *et al*—Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension[10]	≥65 years with septic shock	MAP 60-65	Usual care at	discretion of treating clinician	No difference in 90 day mortality in hypotensive group compared to usual care (41.0% vs. 43.8%, ARR −2.85%; 95% CI −6.75 to 1.05; p = 0.15)
Harvey *et al*—Assessment of clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man)[11]	≥16 years with shock admitted to intensive care unit	Pulmonary artery catheter	No	pulmonary artery catheter	No difference in hospital mortality (68.4% *vs* 65.7%, p = 0.39; adjusted HR 1.09, 95% CI 0.94–1.27).

ARR, absolute risk reduction; HR, hazard ratio; MAP, mean arterial pressure; NNT, number needed to treat.

hypoperfusion at the microvascular level, which is the driver of organ dysfunction in sepsis.[4-6]

MAP

The Surviving Sepsis Guidelines recommend targeting resuscitation to achieve a MAP of 65 mmHg.[2] However, this blood pressure target is based largely on a small number of observational studies that showed a mortality benefit in patients with a MAP of 65 mmHg or greater.[14,15] To date, there have been no randomized controlled trials that have shown a higher MAP target is associated with improved outcomes compared to lower MAP targets. SEPSISPAM was one of the first randomized controlled trials that compared septic patients at different MAP targets (higher MAP 80-85 mmHg versus lower MAP 60-65 mmHg).[9] In their study, they reported no significant difference in 28 day mortality in the higher versus lower target group (hazard ratio 1.07, 95% CI, 0.84-1.38; p = 0.57).[9] Limitations to this study include it being underpowered secondary to a lower than expected mortality in the cohort, and no standardization of corticosteroid use. Furthermore, there was no data collected on stroke incidence, which may have important clinical implications as there was an increased rate of atrial fibrillation in the higher MAP versus lower MAP group (6.7% vs 2.8%, p = 0.02).[9]

In a more recent study, Lamontagne *et al* looked at the effect of reduced exposure to vasopressors on 90-day mortality in elderly patients with septic shock.[10] In their study, patients were randomized to the reduced vasopressor group (target MAP 60-65; "hypotensive group") versus usual care (at discretion of physician). This study found no difference in 90-day mortality in the hypotensive group (41.0% hypotensive group vs. 43.8% usual care, absolute relative risk (ARR) −2.85%; 95% CI −6.75 to 1.05; p = 0.15).[10] It is important to note that this study only looked at patients over the age of 65, and as such this data cannot be extrapolated to a younger population. Furthermore, although the Surviving Sepsis Campaign recommends vasopressin as the second line vasopressor in septic shock, the second most commonly used vasopressor in this trial was metaraminol (primarily alpha-receptor agonist).[3] As such, the findings from this study must be interpreted with these important caveats in mind.

Moreover, patients with chronic hypertension may benefit from higher MAP targets, though this recommendation is limited to expert opinion.[3,16] In theory, this subset of patients has a circulation adapted to a higher MAP, and they may require a higher pressure to autoregulate their blood flow and organ perfusion. In a subgroup analysis of SEPSISPAM, they found that among patients with chronic hypertension, those in the higher MAP group had lower doubling of serum creatinine (38.9% vs. 52.0%; p = 0.02, NNT 7.6) and a lower rate of renal

Table 2. Summary of Select Randomized Controlled Trials Assessing Microcirculation Discussed in This Review.

Trial	Population	Intervention	Control	Conclusion	Other findings
Jones *et al*—Lactate clearance vs. central venous oxygen saturation as goals of early sepsis therapy[12]	≥18 years with severe sepsis or septic shock	Lactate clearance (normalize CVP, MAP ≥65, lactate clearance of at least 10%)	ScvO2 group (normalize CVP, MAP ≥65, ScvO2 ≥70%)	Mortality rates lactate clearance group vs. ScvO2 group (16.7% vs. 22.6%); did not reach-10% threshold in ITT analysis	
Hernández *et al*—Effect of a resuscitation strategy targeting peripheral perfusion status vs. serum lactate levels on 28-day mortality among patients with septic shock[13]	≥18 years with septic shock admitted to the intensive care unit	Normalization of CRT (≤3 seconds)	Normalize or decrease lactate by 20% every 2 hours	CRT-guided therapy non-inferior to lactate guided therapy (HR 0.75, 95% CI 0.55-1.02; p = 0.06)	Trend toward improved mortality in the CRT group (34.9% vs. 43.4%; p = 0.06) In patients with chronic hypertension, large proportion of patients achieved resuscitation goals with increased MAP

CRT, capillary refill time; ITT, intention to treat; HR, hazard ratio; MAP, mean arterial pressure; ScvO2, central venous oxygen saturation.

replacement therapy (31.7% vs. 42.2%; p = 0.046, NNT 9.5) compared to the lower MAP group. Similar findings were found in the ANDROMEDA-SHOCK trial.[13] In this large multicenter randomized controlled trial, septic shock patients were randomized to a resuscitation strategy targeting peripheral perfusion (capillary refill time [CRT] guided strategy [target ≤3 seconds] vs. lactate-guided strategy [target lactate ≤2 mmol/L or 20% decrease at 2 hours]).[13] In patients with chronic hypertension, after adequate fluid resuscitation, the study protocol prescribed a "vasopressor test," where clinicians were instructed to increase the MAP targets to 80-85 mmHg and assess for response. A large proportion of these patients met resuscitation goals with the increased MAP (44.0% in CRT group vs. 38.0% in lactate group; p = 0.86).

These studies highlight that MAP, when taken in isolation, may lead to suboptimal resuscitation in patients with septic shock. Some patients may require different MAP targets (eg, elderly patients and patients with chronic hypertension) for adequate organ perfusion, and other macro- or microcirculatory markers may be helpful.

Cardiac Output

Cardiac output can be a valuable measure to monitor in a resuscitation as it is one of the key variables that affects oxygen delivery to tissues. Cardiac output can be measured invasively with a pulmonary artery catheter (eg, thermodilution or Fick's method), though these devices are not routinely used in sepsis resuscitation due to a demonstrated lack of mortality benefit.[11,12,17] Non-invasive tools to assess cardiac output include bedside echocardiography, which can provide qualitative and quantitative measures of cardiac output.[18,19]

Although cardiac output is important for organ perfusion, adequate cardiac output may be variable among patients in the shock state. In sepsis, the predominant etiology of shock is vasoplegia; and as a result, cardiac output early in sepsis naturally increases to compensate for a reduction in systemic vascular resistance to maintain blood pressure. As such, although it is important to identify a cardiogenic component in septic shock and to optimize the factors affecting myocardial oxygen demand and consumption, cardiac output alone cannot inform an assessment of adequate resuscitation.

Microcirculation

The microcirculation is comprised of small vessels (arterioles, capillaries, and venules) where diffusion takes place to allow for tissue perfusion and oxygenation.[4,5,7,8] In sepsis, the ultimate goal is to supply adequate oxygenation to tissues to improve perfusion and organ function. A detailed description of the physiology of tissue oxygenation will not be covered in this review. Sepsis causes dysfunction of microcirculatory autoregulation, which results in heterogenous abnormalities in blood flow. When this occurs, some capillaries are under perfused, whereas others receive a disproportionately increased amount of blood flow.[5,8] This imbalance leads to microcirculatory units becoming hypoxic, resulting in an oxygen extraction deficit and subsequent tissue malperfusion.[4,5,7,8] Sepsis also affects the nitric oxide system and can lead to mitochondrial failure, which can contribute further to tissue distress and organ dysfunction.[20] Furthermore, sepsis can cause a wide spectrum of disseminated intravascular coagulation as a result of microvascular thrombosis.[21,22] There is a growing body of literature supporting the use of various microcirculation measurements in addition to the concurrent optimization of macrocirculatory markers in the management of patients with sepsis. Microcirculatory markers that can be readily obtained at the bedside or with rapid laboratory testing include proportion of

Table 3. Differential for Elevated Lactate.[27]

Type A: Inadequate Oxygen Delivery	Type B: No Evidence of Inadequate Tissue Oxygen Delivery
Anaerobic muscular activity • Exercise • Generalized convulsions Tissue hypoperfusion • Cardiac arrest • Regional hypoperfusion • Shock Reduced tissue oxygen delivery • Hypoxemia • Anemia	Associated with underlying disease • Diabetic failure • Hepatic failure • Infection • Leukemia • Lymphoma • Pancreatitis • Renal failure • Short bowel syndrome • Thiamine deficiency Associated with drugs and toxins • Acetaminophen • Anti-retroviral drugs • Beta-agonists • Biguanides • Carbon monoxide • Cyanide • Epinephrine • Fructose • Isoniazid • Lactate-based dialysate • Metformin • Methanol • Nitroprusside infusion • Salbutamol • Salicylates • Sorbitol Associated with inborn errors of metabolism

perfused vessels, lactate, skin mottling, and capillary refill time. Other markers such as central venous oxygen saturation, venous-to-arterial carbon dioxide, median flow index, and peripheral perfusion index are additional markers of microcirculation, but will not be discussed in this review.

Proportion of Perfused Vessels

New technologies such as dark field microscopy allow for direct visualization and measurement of small vessel perfusion, and have led to studies assessing the impact of proportion of perfused vessels in patients with sepsis.[4,5,7,8,14] De Backer *et al* assessed the relationship between sublingual microcirculation measurements and mortality in patients with severe sepsis.[6] Their results showed similar MAPs between survivors compared to non-survivors (71 [95% CI, 66-78] vs. 69 [95% CI, 64-75]; $p = 0.11$). However, survivors had a significantly higher proportion of perfused vessels compared to non-survivors (71% [95% CI, 65-78] vs. 50% [95% CI, 40-66]; $p = 0.001$). Furthermore, proportion of perfused vessels was the best predictor of ICU outcome (AUC 0.82, 95% CI 0.77-0.87). Hernandez *et al* also utilized sublingual microcirculation measurements to assess the relationship between microcirculation to mortality and organ dysfunction.[23] They found no significant differences in MAP among patients in the lowest quartile of small vessel perfusion compared to second to fourth quartiles of small vessel perfusion (67 [95% CI 63-73] vs. 70 [95% CI 64-77]; $p = 0.21$). However, patients in the lowest quartile of small vessel perfusion had worse organ dysfunction (as depicted by Acute Physiology And Chronic Health Evaluation II [APACHE II] and Sequential Organ Failure Assessment [SOFA] scores) and higher mortality (OR 8.7, 95% CI 1.14-66.78; $p = 0.037$).

These studies highlight the important role of the microcirculation when treating patients with sepsis. The findings suggest that compared to macrocirculatory markers such as MAP, markers of poor microcirculation are more strongly associated with patient outcomes in sepsis. Furthermore, achieving hemodynamic goals does not necessarily result in achieving small vessel perfusion, which are the predominant determinants of organ perfusion. These studies are not without limitations. They are retrospective, single center trials, and have large confidence intervals likely secondary to small patient populations. Moreover, the technology used to measure PPV is not available at all centers. These studies, nonetheless, convey the importance of microcirculation when treating sepsis, especially in conjunction with restoration of macrocirculation markers (eg, MAP).

Lactate

An elevated lactate is often the result of a mismatch between relative oxygen supply and tissue demand.[24,25] However, lactate metabolism is complex and its production may be necessary for both glycolysis and gluconeogenesis, especially in states of shock.[25,26] Lactate can also be elevated secondary to common medications, such as epinephrine, beta-agonists, and metformin.[24] Furthermore, as lactate is cleared by the liver (60-70%) and kidneys (30%), in patients with organ dysfunction, lactate clearance is hindered and may be difficult to interpret.[23,24] As such, when interpreting an elevated lactate, clinicians must consider type A (inadequate oxygen delivery) versus type B (no signs of inadequate oxygen delivery) lactic acidosis (Table 3).[27]

Lactate for risk stratification. In sepsis, observational trials have shown that an elevated lactate can be useful for risk stratification, both as a threshold (lactate >2 mmol/L) and as a degree of elevation (lactate $\geq$4 mmol/L).[28-30] Mikkelson et al. assessed the relationship between lactate (low <2.0, intermediate 2.0-3.9, high $\geq$4.0) and in-hospital mortality for septic patients with and without shock.[29] In the non-shock group, they saw that relative to the low lactate group, patients in the intermediate (OR 2.05, 95% CI 1.1-3.8; $p = 0.024$) and high (OR 4.87, 95% CI 2.6-9.3; $p < 0.001$) groups were associated with increased mortality at 28 days. In the shock group (defined as systolic blood pressure less than 90 mmHg despite 1500 mL fluid resuscitation or the use of vasoactive agents), they saw a similar relationship with the intermediate (OR 3.27, 95%CI 1.2-9.1; $p = 0.022$) and high (OR 4.87, 95% CI 1.9-12.7;

p = 0.001) groups associated with increased mortality at 28 days. The ARISE investigators saw that patients in cryptic shock (lactate >4 mmol/L in absence of refractory hypotension) had increased mortality compared to patients with isolated hypotension (relative risk 1.7, 95%CI 1.2-2.5; p = 0.003).[30] These studies highlight that an elevated lactate (>2 mmol/L) can be used as a threshold of increased mortality in sepsis. Furthermore, a highly elevated lactate (≥4 mmol/L) should prompt clinicians that these patients are critically ill, even in the absence of concomitant hypotension. However, it is important to note limitations to these studies. There were few patients in these studies with liver or renal failure, both of which can be associated with elevated lactate levels. There was also limited data collected on medication use, which could iatrogenically increase lactate levels. As such, when interpreting elevated lactates, physicians must consider the lactate in context of patient comorbidities (renal failure, liver failure), medication use (eg, metformin, beta-agonists), and other potential causes of lactic acidosis (Type A vs. Type B).

Lactate clearance. The Surviving Sepsis Campaign suggests guiding resuscitation to normalize lactate in patients with elevated lactate levels.[2,3] Lactate clearance is easy to trend and there are similarities between venous and arterial values. Furthermore, lactate clearance has been shown to be non-inferior to central venous oxygen saturation (ScvO2), allowing for quantitative resuscitation without the need for central line placement; a procedure which is not without complications.[12]

Lactate clearance and lactate normalization in the first 6 hours are strong predictors of survival in patients with sepsis.[12,31-36] Nguyen *et al* reported a 2-fold increase in mortality for patients who cleared <10% of their lactate in the first 6 hours.[35] Furthermore, they reported an 11% decrease in mortality for every subsequent 10% lactate clearance in the first 6 hours. Puskarich *et al* examined lactate kinetics and concluded that at 6 hours, both lactate normalization (OR 6.3, 95% CI 2.4-17.0; p = 0.005) and a lactate clearance of 50% (OR 4.3, 95% CI 1.8-10.2; p = 0.005) were most strongly associated with survival.[36] Overall, lactate clearance at 6 hours can be utilized as a marker of successful resuscitation. However, a patient population that requires special attention are those with liver and/or renal dysfunction, as they were under-represented in these studies. These patients are at risk of over-resuscitation with intravenous fluids if lactate clearance is the only marker utilized. Further research is needed to discern the use of lactate clearance in this patient population.

Skin Examination

A thorough examination of the skin can provide important clinical information regarding hypoperfusion at the bedside. Skin mottling and capillary refill time (CRT) provide quick and useful information that can be used for risk stratification and help guide resuscitation.[37-39] These tools are especially helpful in low resource settings and in time sensitive scenarios of a resuscitation before laboratory values (such as lactate) have returned.

Mottling. Mottling is patchy skin discoloration that reflects blood flow reduction and skin hypoperfusion. Studies have used laser Doppler imaging to analyze skin perfusion according to mottling extension in patients with sepsis. Results showed that skin perfusion was inversely related to mottling, and that mottling extension was related to skin perfusion and cutaneous microcirculation impairment.[40] Clinically, the most common location for mottling to be visually assessed is peripherally at the knees. The mottling score is a tool that provides a semi quantitative evaluation of mottling based on skin area extension on legs: score 0 no mottling, score 1 small mottling area (coin size) localized to the center of the knee, score 2 mottling area that does not exceed the superior edge of the knee cap, score 3 mottling area that does not exceed the middle thigh, score 4 mottling area that does not exceed the fold of the groin, and score 5 otherwise.[41] This score has been externally validated, and studies have shown a strong inter-rater reliability (κ 0.87, CI 95% 0.72-0.97).[41] Studies have also shown an association between an increased mottling score and higher lactate levels and decreased urine output.[41-43] Furthermore, the mottling score at 6 hours has been shown to be associated with increased mortality (OR 2.26, 95%CI 1.72-2.96; p < 0.001).[42]

Overall, mottling has been shown to be associated with mortality. One method to quantifying the mottling is through the use of the mottling score. However, there are limitations to assessment of mottling. First, patients with darker skin tones were excluded from the original trials in developing the mottling score, and as such this score cannot be used in this patient population. Secondly, utility of mottling may be limited if the source of sepsis is the lower limb, as seen in severe skin and soft tissue infections such as necrotizing fasciitis. In the patient population where mottling is difficult to assess, other markers of perfusion should be utilized. Future research on mottling should focus on assessing mottling kinetics to guide ongoing resuscitation, as well as comparison between central versus peripheral mottling.

Capillary refill time (CRT). CRT is measured by applying pressure to an extremity until it blanches and timing duration for color return, where a normal CRT is ≤3 seconds. It is most commonly measured at the distal fingertip, but can also be assessed at the knee. Observational data has shown an association between prolonged CRT and increased mortality.[13,37-39,44,45] ANDROMEDA-SHOCK was the first randomized controlled trial that compared CRT to lactate guided resuscitation.[13] CRT was measured by applying pressure to the distal phalynx with a microscope slide until blanching, holding pressure for 10 seconds before releasing and timing with a stopwatch for color return. Overall, CRT-guided therapy was non-inferior to lactate guided therapy for assessing 28-day mortality (HR 0.75, 95% CI 0.55-1.02; p = 0.06), with a trend toward improved mortality in the CRT group (34.9% vs. 43.4%; p = 0.06). Shortly after the trial, a post-hoc Bayesian analysis was done[13].

Their results favored CRT over lactate guided therapy for decreased 28- and 90-day mortality.

In the ANDROMEDA-SHOCK trial, one of the differences between the 2 groups was the amount of intravenous fluids received in the first 8 hours (CRT 2359 mL vs. lactate 2767 mL, $p = 0.01$).[13] The authors noted that patients in the lactate-guided group may have been over-resuscitated. However, this conclusion should be interpreted as hypothesis generating and was not a primary outcome of the original trial. Other important limitations to ANDROMEDA-SHOCK include comorbidities such as peripheral vascular disease not being recorded, as well as no report of inter-rater reliability among users. Overall, the literature shows that CRT can be used to guide resuscitation, and is non-inferior to lactate guided therapy with a trend toward a mortality benefit.

Conclusions

Sepsis is a complex disease process, and there is no single marker that can be used to guide resuscitation. Although clinicians traditionally rely on MAP and lactate, there are other important endpoints that should also be restored. In conjunction with traditional markers (macrocirculation: MAP, microcirculation: lactate), clinicians should focus on optimizing other microcirculatory endpoints such as CRT and mottling. Patients with increased mottling (most easily measured at the knees), and prolonged CRT >3 seconds (most easily measured at distal fingertips) are associated with increased mortality and can be used to risk stratify patients. To help guide ongoing resuscitation, clinicians can use lactate clearance and CRT. Specifically, clinicians should target normalization of lactate and CRT, as both are associated with improved mortality. It is, however, important to note that the microcirculation is only a component in the overall resuscitation of patients with septic shock, and most studies on the role of the microcirculation in shock are limited in being observational in nature. Future studies should focus on a resuscitation strategy that incorporates both macrocirculatory and microcirculatory endpoints. Clinicians must first focus on the basic components of sepsis management including cardiac optimization, central nervous system and systemic oxygen consumption, and oxygen delivery. Ultimately, the optimal resuscitation of patients with septic shock should be individualized and incorporate the assessment and ongoing monitoring of both the micro- and macrocirculation.

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