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REVIEW

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Early peripheral perfusion monitoring in septic shock

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Abstract

Septic shock is a frequent critical clinical condition and a leading cause of death in critically ill individuals. However, it is challenging to identify affected patients early. In this article, we discuss new perspectives on the methods and uses of peripheral perfusion monitoring, considering the concept of a dysregulated response. Physical examination, and visual and ultrasonographic techniques are used to measure peripheral microcirculatory blood flow to reflect tissue perfusion. Compared with other monitoring techniques, peripheral perfusion monitoring has the benefits of low invasiveness and good repeatability, and allows for quick therapeutic judgments, which have significant practical relevance. Peripheral perfusion monitoring is an effective tool to detect early signs of septic shock, autonomic dysfunction, and organ damage. This method can also be used to evaluate treatment effectiveness, direct fluid resuscitation and the use of vasoactive medications, and monitor vascular reactivity, microcirculatory disorders, and endothelial cell damage. Recent introductions of novel peripheral perfusion monitoring methods, new knowledge of peripheral perfusion kinetics, and multimodal peripheral perfusion evaluation methods have occurred. To investigate new knowledge and therapeutic implications, we examined the methodological attributes and mechanisms of peripheral perfusion monitoring, in this study.

Keypoints

1. Peripheral perfusion monitoring enables early detection of alterations in microcirculation, which can indicate changes in tissue perfusion.
2. Peripheral perfusion kinetics indicate that peripheral perfusion parameters undergo regular dynamic changes that can be used to track the effects of therapeutic interventions and monitor disease progression.
3. Peripheral perfusion monitoring can assess autonomic function and serve as the foundation for appropriate treatment.
4. New technologies for measuring peripheral perfusion, such as laser and ultrasound technology, are being developed.
5. Further investigation into peripheral perfusion monitoring is warranted due to our improved understanding of the underlying mechanisms and its potential to optimize perfusion and systemic hemodynamic variables in the management of septic shock.
6. Peripheral perfusion may have a wider clinical role thanks to multimodal assessment.

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Introduction

Septic multiorgan dysfunction is understood to result from an abnormal systemic response, aligning with the current definition of sepsis as life-threatening organ dysfunction resulting from a dysregulated host response to infection [1]. According to Singer et al. [2], the focus of sepsis pathophysiology should shift from merely identifying the disease's root cause to addressing the abnormal and overwhelming organ response. In this article, we introduced the idea of the host/organ unregulated response, suggesting that this response contributes to sepsis through mechanisms including inflammatory reactions, coagulation abnormalities, metabolic disturbances, and cellular dysfunction. Consequently, modulating an individual's response emerges as a critical objective in optimizing sepsis therapy [3]. Historically, septic shock was regarded as a distinct subtype of sepsis, characterized by microcirculatory dysfunction and alterations in cellular metabolism, with a significantly higher case-fatality rate compared to other subtypes [4]. Even after fluid resuscitation, while macrocirculation may show improvement, microcirculation often remains impaired, which may indicate a poor prognosis [5]. This phenomenon can be attributed to the body's response, involving the release of various inflammatory mediators, metabolites, and cytokines, as well as immune and autonomic dysfunction. These changes directly damage endothelial cells, increase vascular permeability, and subsequently impair microcirculatory perfusion. Moreover, microcirculatory alterations precede macrocirculatory changes in the early stages of sepsis, serving as a critical factor in the progression to shock and multi-organ failure [6]. The presence of these early changes suggests a potential window of opportunity for slowing disease progression.

Peripheral perfusion monitoring is a hemodynamic monitoring technique that uses physical examination, and optical, ultrasonographic, and other techniques to monitor blood flow in the peripheral microcirculation, which provides a visual assessment of tissue perfusion. Peripheral perfusion monitoring evaluates the peripheral microcirculation of the skin, nail bed, and sublingual and other tissues, and is now frequently used clinically because of its non-invasiveness and simple access, and because it permits a quick therapeutic response. Alterations in peripheral perfusion represent the final response in reperfusion following resuscitation therapy and the earliest sign of hypoperfusion at the onset of septic shock, based on the pathophysiological characteristics of the condition [7, 8]. Clinically, there is currently a pressing need for reliable methods to monitor patient status, as current tools lack an intuitive means to track the body's responses, endothelial cell activation, and subsequent abnormalities. Peripheral perfusion monitoring fulfills this need by serving as an early diagnostic tool for shock, offering a severity index that can track the efficacy of therapeutic interventions, thus enabling guided hemodynamic therapy and continuous evaluation of treatment outcomes.

Recent studies have demonstrated a strong correlation between autonomic dysfunction and peripheral vascular reactivity, attributed to the body's response in septic shock [9, 10]. The accuracy and effectiveness of peripheral perfusion monitoring have been significantly improved with advancements in ultrasound technology [11–13]. A multimodal assessment of capillary refill time (CRT) kinetics and peripheral perfusion has been proposed following extensive research into the pathophysiological mechanisms underlying septic shock, leading to several innovative approaches in the application of this technique [14, 15]. This article delves into the methodological aspects and mechanisms of peripheral perfusion monitoring, offering a contemporary understanding of the technology, its clinical utility, and the potential for future advancements based on recent findings.

Pathophysiological mechanisms associated with peripheral perfusion

Recent insights into the physiological responses of critically ill patients have demonstrated that septic shock arises from microcirculatory damage due to an imbalanced host response [3]. This phenomenon is primarily observed in the onset of systemic inflammatory response syndrome (SIRS), which triggers the release of a multitude of inflammatory mediators into the bloodstream. These mediators can directly damage vascular endothelial cells, leading to disruption of the microcirculation. For example, tumor necrosis factor-α (TNF-α) can induce the release of elastase from neutrophils and the cleavage of vascular endothelial (VE)-cadherin by cathepsin G, which damages vascular endothelial cells, disrupts the endothelial barrier, and increases vascular permeability [16]. Furthermore, autonomic dysfunction impacts vascular tone and reactivity by impairing autonomic function [17]. Sympathetic overexcitation further harms the endothelium, impairs microcirculatory function, and exacerbates overall dysfunction. For instance, Jiang et al [18] examined changes in autonomic function and found that vagal nerve stimulation can have a protective effect in sepsis, while autonomic dysfunction, particularly sympathetic hyperexcitability, causes inflammation and harms endothelial cells. Impaired microcirculatory function leads to inadequate tissue oxygenation, exacerbating tissue damage and triggering the release of metabolites that further deteriorate the microcirculation [19–21]. Endothelial cell damage also induces coagulation dysfunction, resulting in the formation of microthrombi that

obstruct microvessels and impair peripheral perfusion [22, 23].

The majority of the endothelial cell damage and dysfunction underlying microcirculatory disorders can be attributed to the aforementioned factors. During septic shock, the glycosaminoglycan, proteoglycan, and glycoprotein layers that normally cover the endothelial cell surfaces are degraded, leading to the thinning of these protective structures [24–27]. The breakdown of glycoproteins also exacerbates macrocirculatory dysfunction, promoting circulating cell adhesion, microthrombosis, and increased vascular permeability [28, 29]. The main symptoms comprise an increase in the percentage of microvessels with interrupted or stagnant perfusion, a decrease in the density of functional microvessels, and a notable rise in perfusion heterogeneity.

Recently, several studies have found that even with treatment for septic shock, disturbances in tissue microcirculatory perfusion may persist. These disturbances are linked to poor prognosis, even when conventional macrocirculatory parameters are deemed satisfactory by clinicians [5]. The idea of "hemodynamic coherence" was first suggested by Ince [30], who contended that increased macrocirculation should be accompanied by concurrent improvement in microcirculatory perfusion. "Hemodynamic dysharmony" refers to the imbalance between the macrocirculation and microcirculation in septic shock. Several studies have reported high mortality rates associated with a lack of synchronization between macro- and microcirculation [31]. Microcirculatory dysfunction plays a critical role in the clinical outcomes of septic shock [32]. However, careful consideration is required to determine the specific areas of microcirculation that need to be monitored. In the early stages of sepsis, when peripheral perfusion is compromised to preserve vital organ perfusion, the body's response is primarily governed by compensatory mechanisms [33]. Microcirculation in peripheral, nonvital organs that occur to protect vital organs such as the heart and brain, undergoes the first alterations in the circulatory system. Nonetheless, the macrocirculatory state must also be taken into account during hemodynamic assessment. Clinically, patients with adequate hemodynamic coordination may not have moderately severe conditions and may nonetheless be experiencing concurrent progressive macro- and microcirculation deterioration [34]. However, categorizing the connection between micro- and macrocirculation at this stage is premature. Thus, in patients with septic shock, a thorough evaluation of the coordination between micro- and macrocirculation should be conducted based on the patient's hemodynamic status. It is crucial to rapidly assess, analyze, and interpret the conditions of both macro- and microcirculations, adjust resuscitation strategies accordingly, evaluate resuscitation effectiveness, and accurately determine the required volumes of resuscitation fluids. The persistence of abnormal systemic oxygen metabolism indicators, despite treatment for septic shock, underscores the presence of cellular oxygen metabolism dysfunction in sepsis patients, even when macro–microcirculatory congruency appears restored and tissue perfusion seems normal. This indicates that cellular metabolism levels and microcirculatory activity may not be fully aligned.

Bakker et al. [35] have highlighted that lactate levels can still be elevated even when both macrocirculation and microcirculation are well-coordinated. In an intra-abdominal hypertension model, researchers observed a significant increase in lactate levels (6.9 ± 2.8 mmol/L), despite normal cardiac output (CO) and adequate perfusion of the sublingual and mucosal microcirculation [36]. This finding suggests impaired cellular oxygen uptake, indicating that dysregulated cellular metabolism may persist independently of macro- and microcirculatory functions. Since cellular metabolic issues often coexist with microcirculatory insufficiency, distinguishing between these two conditions can be clinically challenging. It is plausible that patients with septic shock experience reduced mitochondrial function due to cellular anaerobic metabolism, which persists even with improved peripheral tissue perfusion.

These mechanisms indicate that peripheral perfusion monitoring can be used to observe microcirculation and endothelial function, and provide a target for resuscitation and streamline rehydration to protect the endothelium (Fig. 1). Moreover, these mechanisms highlight that peripheral perfusion monitoring can focus on the hemodynamic management of the "last mile of critical illness," addressing the continuum from endothelial injury to microcirculatory dysfunction and cellular metabolic disorders, thus underscoring the fundamental principle of critical care therapy: "protection first."

Commonly used peripheral perfusion monitoring techniques and their characteristics

Multiple studies have demonstrated that peripheral perfusion monitors have good consistency and can permit an intuitive response to tissue perfusion [15, 37]. The majority of these monitors are non-invasive, have the advantages of sensitivity and simplicity of operation, and may be used extensively in critical care bedside assessment. These monitors can also be used at any time, and repeatedly and quickly. For instance, peripheral perfusion index (PPI), sublingual microcirculation evaluation, skin mottling score, and CRT evaluation all enable economical and effective clinical actions by providing crucial information in a matter of seconds or minutes [38–41].

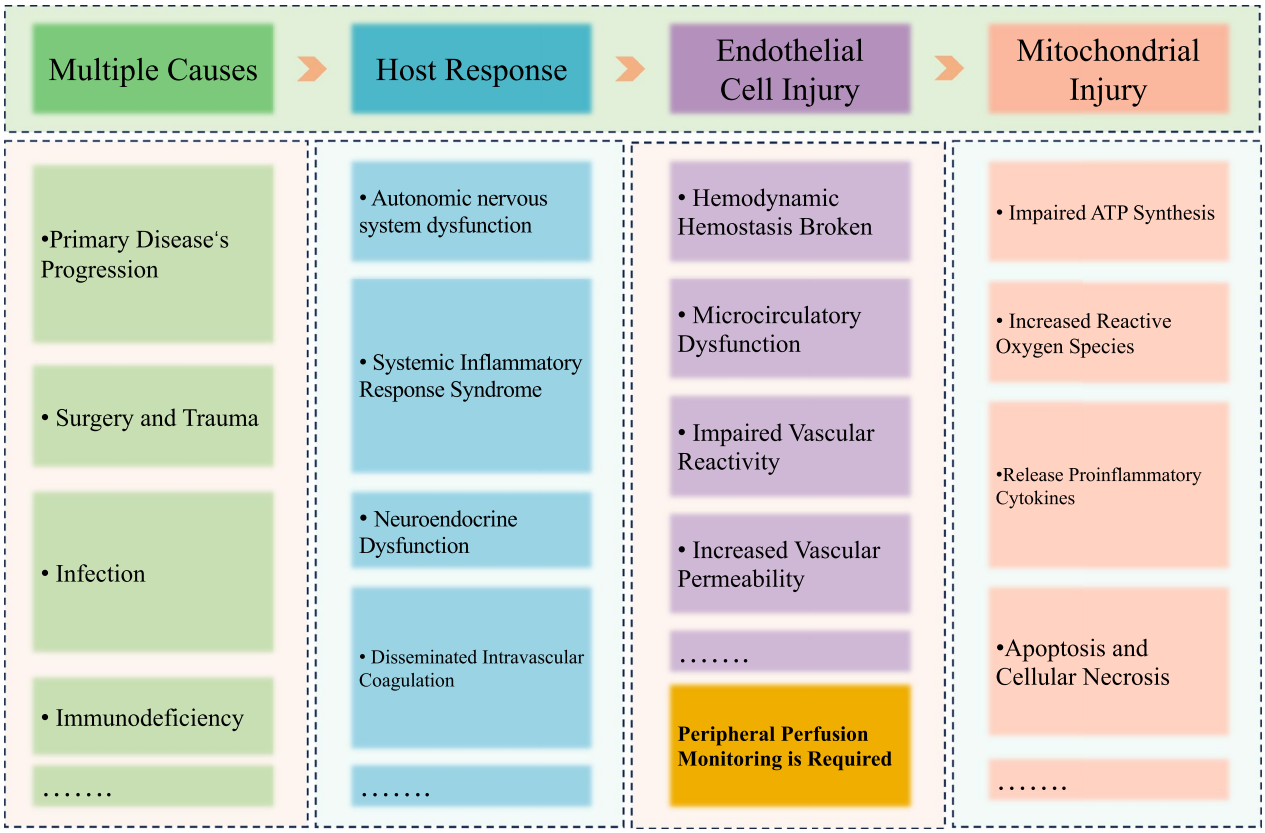

Fig. 1 In the pathogenesis from injury to critical illness, timely peripheral perfusion monitoring can detect microcirculatory dysfunction, which reflects endothelial injury and serves as a bridge between endothelial and mitochondrial damage. Peripheral perfusion indices also mirror the systemic inflammatory response and macro–microcirculatory discoordination, linking central hemodynamics with microvascular perfusion abnormalities

We begin by introducing the most commonly used techniques for monitoring peripheral perfusion in clinical settings. First, Capillary Refill Time (CRT) is a technique that consistently predicts outcomes across various conditions, proving the reliability of peripheral perfusion monitoring [42]. Microcirculatory perfusion can be assessed by observing the color recovery time after applying pressure to the fingertip or earlobe. Its advantages include simplicity, ease of execution, and non-invasiveness [41].

Next is the PPI, an indicator measured by a pulse oximeter that reflects changes in peripheral blood perfusion [43]. Based on photoplethysmography (PPG), PPI calculates the peripheral microcirculation status by measuring the ratio of pulsatile to non-pulsatile blood flow. Its advantages include being easy to operate and non-invasive. However, it is susceptible to external factors such as patient movement and ambient light, and it can only reflect local blood perfusion.

The mottling score is also commonly used to assess microcirculatory dysfunction by observing mottling on the skin's surface [44]. Its advantages include not requiring special equipment, being simple and intuitive, and having good prognostic value for sepsis patients. However, it is highly subjective, influenced by the observer's experience, and can be affected by environmental light and the patient's body temperature.

Temperature gradient assessment evaluates microcirculatory perfusion by measuring the temperature differences across various skin sites using methods such as infrared thermography and skin thermometers [45]. It is non-invasive, easy to operate, and user-friendly, making it suitable for evaluating peripheral circulation in postoperative and critically ill patients. However, the temperature gradient is susceptible to environmental temperature and the specific measurement site, limiting its accuracy and precision in providing detailed microcirculatory function data.

In addition to these, there are several more advanced techniques that have been gradually popularized in clinical settings in recent years. NIRS (near-infrared spectroscopy) uses near-infrared light to irradiate

tissues, assessing tissue oxygen saturation and blood perfusion by leveraging the light absorption characteristics of different wavelengths [46]. It is non-invasive, easy to operate, and capable of real-time monitoring of local tissue blood flow and oxygenation. NIRS is applicable in various clinical and research settings, such as cerebral blood flow and muscle perfusion assessment.

Side-stream dark field (SDF) imaging uses a specific optical design and side-stream dark field illumination to visualize blood cells in the microcirculation, allowing real-time observation of microvascular structures and blood flow dynamics [47]. It provides clear visualization of the microcirculation but requires expensive equipment and skilled technicians for operation and image analysis. Therefore, SDF is primarily used in clinical research and microcirculatory assessment in complex cases.

Nailfold Capillaroscopy (NC) uses a microscope to observe the microvascular morphology and blood flow dynamics at the base of the fingernail, allowing for the assessment of microcirculatory function [48]. It is non-invasive, easy to perform, and capable of visually observing microvascular structures and blood flow changes. NC is widely used in diagnosing and evaluating systemic sclerosis and other microcirculation-related diseases. However, the results are highly dependent on the observer's experience and technical skill, and it requires specialized microscopic equipment. Therefore, NC is suitable for research and clinical diagnosis of microcirculatory abnormalities.

Laser Speckle Imaging (LSI) assesses blood flow dynamics by using laser illumination on the skin or tissue and analyzing changes in speckle patterns [49]. The dynamic changes in speckle patterns reflect blood flow velocity and perfusion status. LSI is non-invasive, provides real-time monitoring, and delivers high-resolution blood flow images, making it suitable for monitoring blood flow in various tissues and organs. However, the equipment is complex and expensive, requiring high technical proficiency for operation and image processing. Therefore, LSI is primarily used in cerebral blood flow, skin perfusion, and postoperative monitoring.

In a clinical trial, Iizuka et al. [50] evaluated CRT and PPI as peripheral perfusion monitoring methods and successfully predicted hypoperfusion and showed good correlation between the methods and clinical confirmation [37]. There were no appreciable differences in the sublingual vascular distribution across patients with various underlying diseases in a study by Dubin et al [37], who evaluated sublingual microcirculation to monitor peripheral perfusion. Peripheral perfusion monitoring can also be used to track a patient's response to pain, therapy, and environmental stimuli [15, 51–53].

Recent studies have shown that ultrasonography can also be used for peripheral perfusion monitoring. Doppler ultrasonography is valuable to determine PPI to evaluate peripheral perfusion using blood flow resistance monitoring in the snuffbox artery. The systemic vascular resistance index and the flow resistance index at the snuffbox showed a significant correlation in the ultrasonographic assessment of 15 patients. However, when the patients' individual data were analyzed, a stronger correlation was observed [54], suggesting that the snuffbox flow resistance index may serve as a better indicator of peripheral perfusion compared to other body regions. In addition, the snuffbox resistance index shows a strong correlation with lactate and PPI, suggesting that Doppler ultrasonographic monitoring of this index can predict lactate clearance more accurately than using PPI alone [11].

The arteries at the fingertips may also be evaluated as a peripheral perfusion monitoring approach. Kibo et al. [55] confirmed that peripheral perfusion may be monitored using ultrasonic angiography. Both laser speckle imaging and laser Doppler blood flow imaging are promising methods for evaluating the microcirculation and enable the continuous real-time assessment of microvascular blood flow changes [56, 57]. These methods are also capable of accurately assessing the degree of peripheral perfusion of the skin. Guven et al. [49] examined and compared blood flow variations under various settings while modeling the relationship between laser speckle imaging and laser Doppler flow imaging. The authors found a significant correlation and accuracy between the two methods for determining skin perfusion. Furthermore, recent research has showed that fluorescence monitoring and urine monitoring methods are both effective for determining peripheral perfusion [58, 59].

Clinical applications of peripheral perfusion

Early identification and determination of prognosis

Peripheral perfusion monitoring can assess the type of macro- and microcirculatory discoordination, identify endothelial cell injury, identify microcirculatory dysfunction, and predict prognosis. Lima et al. [60] found that even when macrocirculatory parameters are stable, assessing peripheral microcirculatory indicators, such as skin temperature, can help predict organ failure and hyperlactatemia. The skin temperature gradient from forearm to fingertip (Tskin-diff) was 4.6 ± 2.8 °C in patients with abnormal peripheral microcirculation, compared to -0.2 ± 2.8 °C in normal patients ($p < 0.01$). The central-to-toe temperature difference (Tc-toe) was 10 ± 4.1 °C in patients with abnormal peripheral microcirculation, compared to 6.5 ± 3.4 °C in normal patients ($p < 0.01$). The peripheral flow index (PFI) was 0.7 ± 0.8

in patients with abnormal peripheral microcirculation, compared to 2.3 ± 1.6 in normal patients ($p < 0.01$). These findings indicate that assessing skin temperature and other peripheral microcirculatory indicators can significantly predict the progression of organ failure and hyperlactatemia. After initial fluid resuscitation, Lara et al. [61] showed that sepsis patients with abnormal CRT values had a mortality rate that was nearly six times higher than that of patients with normal CRT values. Sebat et al. [41] found a significant correlation between prolonged CRT and mortality, criticality of disease progression, and prolonged hospital stay. Dubee et al. [62] discovered that the preintubation skin mottling score, in particular, was the best predictor of hemodynamic worsening among the skin perfusion-related parameters. SDF imaging can also be used to assess the microcirculatory response to resuscitation, to identify organ dysfunction and the risk of death. This method offers an accurate and intuitive view of the state of the microcirculation by revealing details that are not visible using other methods [37]. Numerous studies have shown that poor peripheral perfusion is independently associated with a poor prognosis and that, in sepsis management, peripheral perfusion parameters play an important role in the restoration of hemostasis.

Fluid resuscitation therapy

One of the treatment choices for shock is fluid resuscitation, which has a surprising degree of success and can increase the survival rate. Re-injury owing to tissue perfusion results from improper timing of resuscitation, fluid excess, or fluid insufficiency, which can negatively impact the prognosis.

A patient's fluid responsiveness during the fluid stimulation test is the current benchmark for deciding whether to perform fluid resuscitation. The main goal is to evaluate cardiac output by observing whether it increases after rehydration therapy. The fluid stimulation test has its limits, and to follow the hemodynamic effects of the volume of rehydration, cardiac output must be measured in real time. However, changes in PPI values are fairly responsive to cardiac output because PPI is regulated by cardiac output. Passive leg-raising increased cardiac output in one study, which in turn increased PPI values [63], in patients who passed the leg-raising test. Hasanin et al. [64] found a significant correlation between ΔPI(Delta Perfusion Index) and ΔVTI(Delta Velocity–Time Integral) in their study. After a 200 mL fluid load, the Spearman correlation coefficient between ΔPI and ΔVTI was 0.39 (95% confidence interval [CI] 0.14–0.58, $p = 0.003$). Following a 500 mL fluid load, the correlation coefficient increased to 0.57 (95% CI 0.36–0.72, $p < 0.001$). PPI may be a useful tool for assessing fluid responsiveness. However, Raia et al. [15] showed that baseline CRT was longer in non-survivors than that in survivors during passive leg-raising to predict the impact of rehydration on peripheral tissue perfusion. Jacquet-Lagrèze et al. [65] also showed that CRT-passive leg raising was a straightforward, affordable, and non-invasive diagnostic method for anticipating the response of peripheral perfusion to volume expansion in peripheral perfusion-targeted resuscitation protocols. Therefore, peripheral perfusion monitoring techniques for quick therapeutic judgments can be widely used in resource-constrained settings to assess fluid responsiveness easily, non-invasively, and quickly.

Setting fluid resuscitation objectives is also important. Currently, the lactate level is the primary clinical reference. The link between macro- and microcirculations has been examined in this article, and we consider there is space to improve resuscitation that is lactate level-oriented. Notably, there are many non-specific causes for hyperlactatemia, such as the existence of non-hypoxic lactate elevation in situations of impaired hepatic clearance, malignancy, and drug-induced hyperlactatemia. In addition, because blood lactate fluctuates slowly, it is challenging to offer fast feedback to inform clinical decision-making, and the primary use of lactate measurement is to assess the overall response. However, attempting to achieve normal lactate levels can lead to fluid overload [66], which can result in interstitial edema, glycocalyx shedding, and other problems that restrict oxygen delivery to the tissues, raise the risk of organ malfunction, and increase the possibility of a poor prognosis.

There was no discernible difference in patient mortality between fluid resuscitation directed by serum lactate levels versus fluid resuscitation directed by CRT in the ANDROMEDA-SHOCK trial [67]. This finding was supported by research by Castro et al., [51] who evaluated 42 patients with fluid-responsive septic shock who received 6 h of rehydration. This finding supports the idea that fluid resuscitation using CRT-guided peripheral perfusion is therapeutically helpful and that its inherent convenience and efficiency are very important. The ANDROMEDA-SHOCK study showed that CRT responded quickly to fluid resuscitation, enabling prompt modification of the therapeutic approach; in addition, patients in the peripheral perfusion group received significantly less fluid in the first 8 h compared with those in the serum lactate group. Furthermore, when the incidence of organ dysfunction was compared after 72 h of different resuscitation techniques, the combination of peripheral perfusion monitoring and lactate-targeted resuscitation significantly reduced the incidence of organ dysfunction.

According to Kattan et al., [66] lactate level-guided resuscitation of patients with septic shock led to more

unnecessary procedures and, as a result, to higher fatality rates compared with CRT monitoring. The authors showed that fluid resuscitation directed by blood lactate levels resulted in increased organ damage in individuals with normal CRT in a post hoc analysis of the ANDROMEDA-SHOCK study data. A Bayesian analysis of the data revealed that all patients were treated using the 28-day peripheral perfusion-guided resuscitation approach. In every instance, the posterior probability of the superiority of the peripheral perfusion-guided approach over lactate-guided resuscitation exceeded 90% [68]. Compared with the lactate-guided approach, peripheral perfusion-guided resuscitation may be associated with a lower mortality rate and hasten the recovery of organ function. A peripheral perfusion-guided fluid resuscitation strategy was found safe by van Genderen et al. [69] in a randomized controlled trial comparing two resuscitation protocols, one using peripheral perfusion and the other using standard management of 30 critically ill patients. The treatment group received significantly lower resuscitation fluid volumes compared with the control group, which was associated with less organ dysfunction.

Guidance on the use of vasoactive drugs

Early use of vasoactive medications can somewhat alleviate "Hemodynamic Dysharmony"; however, the key to successful treatment is prompt identification and reversal of tissue hypoperfusion. Norepinephrine can be used to boost tissue microcirculatory perfusion in cases of early microcirculatory abnormalities, which in turn improves prognosis. Although it is challenging to further enhance microcirculatory perfusion, increasing the dose of norepinephrine can increase mean arterial pressure while also improving cardiac index, systemic vascular resistance, and left heart function [70]. However, increasing the dose of vasoactive medications can be dangerous in septic shock patients with unbalanced bodily reactions. Wang et al. [71]. showed that overly high doses of norepinephrine induced tissue perfusion impairment because of peripheral microvascular constriction. This effect was a risk factor for a worse outcome in a clinical investigation of 423 patients with septic shock. Therefore, a guide for the proper application of vasoactive medications to treat tissue hypoperfusion is needed, while considering patients' physiological responses and hemodynamic status.

Accordingly, Wang et al. have highlighted that the use of PPI to guide the use of norepinephrine may help improve prognosis. The authors found that PPI could sensitively detect and document microcirculatory changes in the case of a mismatch between PPI and norepinephrine dosage, with high PPI being a protective factor and low PPI being associated with higher doses of norepinephrine. According to Lima's research, a straightforward bedside peripheral perfusion assessment was useful to gauge how well nitroglycerin improved tissue perfusion and to titrate nitroglycerin doses [72]. Therefore, peripheral perfusion monitoring can be used to titrate the dosage of vasoactive medicines to accurately treat microcirculatory abnormalities and prevent organ function loss. However, further study is needed to determine how to use peripheral perfusion to gauge a drug's effectiveness and adjust the dosage.

Monitoring of autonomic dysfunction

Autonomic dysfunction, which plays an important role in septic shock, is a usual pathophysiological mechanism in dysregulated body responses, as we described. Pain stimulation caused variations in PPI values in patients with various levels of sedation, according to research by Kang et al. [52]. The authors found that comparable stimulation caused a steady decrease in the change in peripheral perfusion levels as sedation deepened. Hamunen et al. and Hasanin et al. analyzed the pain scores connected with PPI changes and found that they were congruent [73, 74]. The authors of both studies also found a subsequent drop in PI in response to pain stimulation. PPI was used in a study by Ajayan et al. [53] to monitor peripheral perfusion and evaluate the vasodilatory effects of isoflurane and sevoflurane on human autonomic function. The study showed that peripheral perfusion monitoring was useful to evaluate autonomic function and that using this method is convenient and accurate even with no discernible change in cardiac output in response to a painful stimulus (Fig. 2).

Carrara et al., [75] in their most recent analysis of the autonomic nervous system as a therapeutic target in septic shock, discussed how autonomic dysfunction in septic shock patients causes circulatory collapse and sympathetic nervous system overactivity, which increases catecholamine levels and is associated with a worse prognosis. The authors also proposed that monitoring and modulating autonomic function is a crucial treatment target and that resolving circulatory issues owing to autonomic dysfunction may be an important goal. Accordingly, therapies for autonomic dysfunction may include vagal nerve stimulation to reduce systemic inflammatory responses and autonomic dysfunction [76–78], and the administration of glucocorticoids in specific doses to alleviate vascular paralysis owing to autonomic dysfunction by improving the body's receptivity to catecholamines [79]. However, these therapies rely on the observation of alterations in autonomic function, peripheral perfusion, and the application of numerous additional therapeutic modalities. Peripheral perfusion monitoring, which

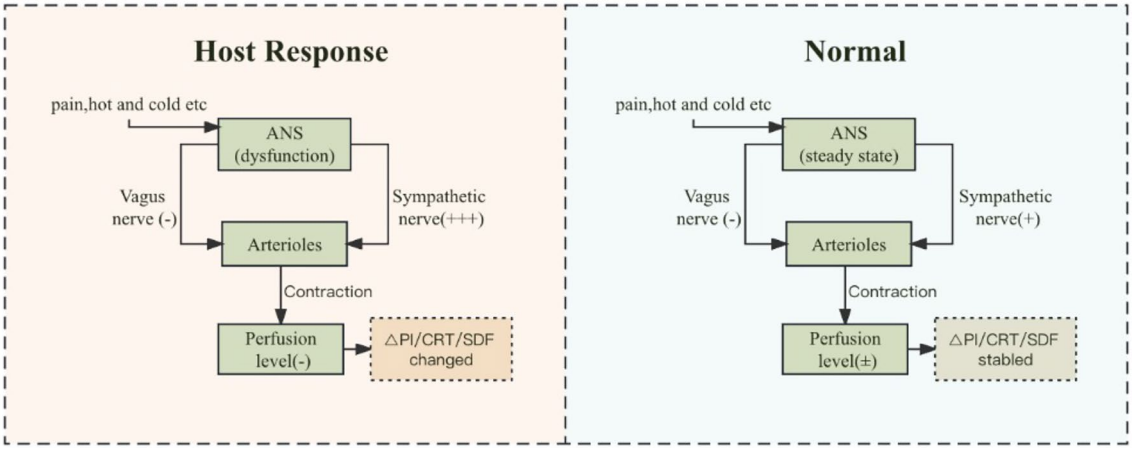

Fig. 2 In the early phase of the host response, autonomic dysfunction manifests as aberrant autonomic regulation, which can be sensitively detected by peripheral perfusion monitoring. Under nociceptive stimuli, dysautonomia leads to excessive vasoconstriction of small arteries, compromising tissue perfusion. Peripheral perfusion monitoring provides a means to promptly identify these changes. ANS: autonomic nervous system

is a pertinent hemodynamic indicator, can be sensitive to these changes, and the therapeutic regimen can be altered as a result.

Other clinical applications

Seventy-two hours after randomization in the ANDROMEDA-SHOCK study [67], there was significantly less organ dysfunction in the peripheral perfusion monitoring group compared with that in the lactate monitoring group. This suggests that CRT-guided resuscitation facilitated earlier resolution of organ failure compared with lactate monitoring. According to Brunauer et al., [80] resuscitation intended to restore peripheral perfusion in patients with septic shock also improved the vascular pulsatility indices of other organs, including the mesentery, liver, kidneys, spleen, and others. Similarly, Bouattour et al. [81] found that cardiac preload dependence was connected to decreased microcirculation following surgery. These tissue perfusion measures are linked to the degree of organ failure and are reliable indicators of a poor prognosis in the intensive care unit [39].

It is possible to determine postoperative prognosis using intraoperative surveillance. In a retrospective analysis of 1586 general surgery patients, Kang et al. [82] found that postoperative acute kidney injury was associated with low intraoperative PPI, and that patients with acute kidney injury had higher rates of intensive care unit admissions and renal replacement therapy, longer hospital stays, and higher mortality rates compared with patients without acute kidney injury. In a trial evaluating spontaneous respiration, Lofty et al. [83] found that low PPI values predicted extubation failure. Changes in PPI values might be a useful predictor of intradialytic hypotension according to Mostafa et al., [84] who found that low PPI values showed high sensitivity for doing so.

New insights into the theory of peripheral perfusion

Peripheral perfusion kinetics

Quantifying fluid resuscitation and improving its accuracy is a current crucial clinical topic. When do we begin? When do we stop? Prognosis improves in septic shock with early identification of inadequate perfusion and subsequent resuscitation. Recent research has shown that poor peripheral perfusion responds to therapy, with varying degrees of peripheral perfusion alterations associated with various therapeutic effects, which may provide useful information [64]. The ability of peripheral perfusion to respond quickly to an increase in blood flow can be used to determine the type of shock, initiate resuscitation early, and stop the process in time to precisely adjust the therapeutic regimen.

A recent study by Raia et al. [15] showed that underlying medical issues had no effect on the accuracy of CRT measurements, with a specific hemodynamic pattern of CRT variations known as "CRT kinetics". The greatest reduction in CRT occurred 10–12 min (− 0.7 s) after initiating fluid resuscitation, continued for 30 min, and occurred in the responders 6–8 min following the commencement of the infusion. CRT values at baseline were positively correlated with this shift in CRT value, with higher baseline CRT values associated with greater post-infusion CRT declines. According to Kattan et al., [85] the quick improvement in CRT with a single rehydration episode or passive leg raising was significant for both diagnostic and therapeutic purposes. This succession of

altering patterns raises the possibility that CRT could be used as a dynamic measure for fluid resuscitation monitoring and control. Therefore, peripheral perfusion monitoring enables a quicker response and more frequent repeat monitoring, both of which ultimately result in intangible advantages.

Notably, the influence of autonomic function cannot be separated from this dynamic shift in peripheral perfusion. In a review of clinical studies of autonomic function in sepsis, Sharawy et al. [86] concluded that good vascular reactivity and vascular paralysis are intimately linked to autonomic dysfunction. Carrara et al. [17] found that peripheral vascular tone was "decoupled" from macrocirculation in autonomic dysfunction, mainly as a result of major alterations in compliance, resistance, and pressure. This shift must be precisely indexed to help with the management of septic shock. We believe that these alterations in vascular reactivity are the basis for the use of CRT to track dynamic blood flow changes. In addition, a marked decline in CRT kinetics may indicate dysregulation of the body's response and the emergence of autonomic dysfunction. This finding frequently suggests that additional vasoactive medications are needed to maintain macrocirculation and signals disease progression and patient deterioration.

We consider that other measures of peripheral perfusion, such as an increase in SDF values in response to fluid resuscitation therapy, should exhibit dynamics that are comparable to those of CRT kinetics [37]. Changes in skin mottling score following therapy can also be used to gauge how a patient's condition has changed [87]. Peripheral perfusion kinetics were used to judge an appropriate level of sedation in studies which showed that painful and surgical stimuli may cause changes in peripheral perfusion kinetics associated with analgesia during anesthesia and sedation [52, 53].

Multimodal assessment

Multimodal assessment mainly refers to the thorough application of numerous techniques or indicators to evaluate specific patient characteristics. This diversified assessment can enhance the thoroughness and dependability of a study's findings and help researchers avoid the constraints of a single indicator, even those with a high clinical reference value. According to Kattan et al., [14] it is challenging for a single metric to accurately reflect overall peripheral perfusion in patients with septic shock. To fully assess micro- and macrocirculation and identify and diagnose sepsis early, a multimodal analysis is required [14]. The authors created a multimodal analysis model, with lactate representing the degree of cell/tissue hypoxia, central venous oxygen saturation representing systemic oxygen consumption, venous–arterial carbon dioxide difference representing tissue perfusion and oxygenation imbalance, CRT representing microcirculatory perfusion status, and hemodynamic coherence representing the macro–microcirculatory coordination status. These variables represent many physiological mechanisms with various kinetics, each with advantages and disadvantages. Comprehensive multi-parameter analysis can assess tissue perfusion and correctly identify sepsis and guide treatment.

Multimodal evaluation models can be used for diagnosis and to direct treatment as well as to check for variations in several resuscitation measurements to enable accurate comparisons. Castro et al. [51] used SDF imaging to assess sublingual microcirculation and measure the sublingual microcirculatory flow index during treatment using both CRT- and lactate-guided fluid resuscitation. In the CRT-guided therapy (CRT-T) group, the median MFI was 2.5 (IQR 1.5–3), while in the lactate-guided therapy (LAC-T) group, the median MFI was 3 (IQR 2.7–3), though this difference was not statistically significant ($p=0.09$). The proportion of patients who achieved perfusion targets was significantly higher in the CRT-T group compared to the LAC-T group (62% vs. 24%, $p=0.03$). The indocyanine green bilirubin plasma disappearance rate was also used to indirectly measure hepatic blood flow, and near-infrared spectroscopy was used to measure muscle tissue oxygenation. The impact and distinction between CRT and lactate-guided fluid resuscitation were then assessed by integrating the findings with sequential organ failure assessment scores derived from the clinical organ function evaluation.

Multiple factors must be considered when designing the ideal multimodal assessment model. These include peripheral perfusion indicators, such as skin temperature [45, 88], CRT [42, 89], and skin blood flow [47–49], that represent microcirculation and tissue perfusion. Multimodal assessment models can be a crucial variable in the evaluation of microcirculation. Measurements of cardiac output, arterial pressure, and mixed venous oxygen saturation are included in these models as these measurements reflect macrocirculation and pulmonary circulation. Variables characterizing cellular oxygenation, such as lactate and bilirubin, are also added [90–94]. The degree of tissue hypoxia can be indirectly determined using these models. To gauge renal perfusion, urine production and renal function must be monitored [95, 96]. To assess macro-microcirculation coordination, a dynamic evaluation of each parameter's trend and correlation must be performed. The appropriate steps in fluid resuscitation or vasoactive medication therapy are than performed in accordance with the model's results.

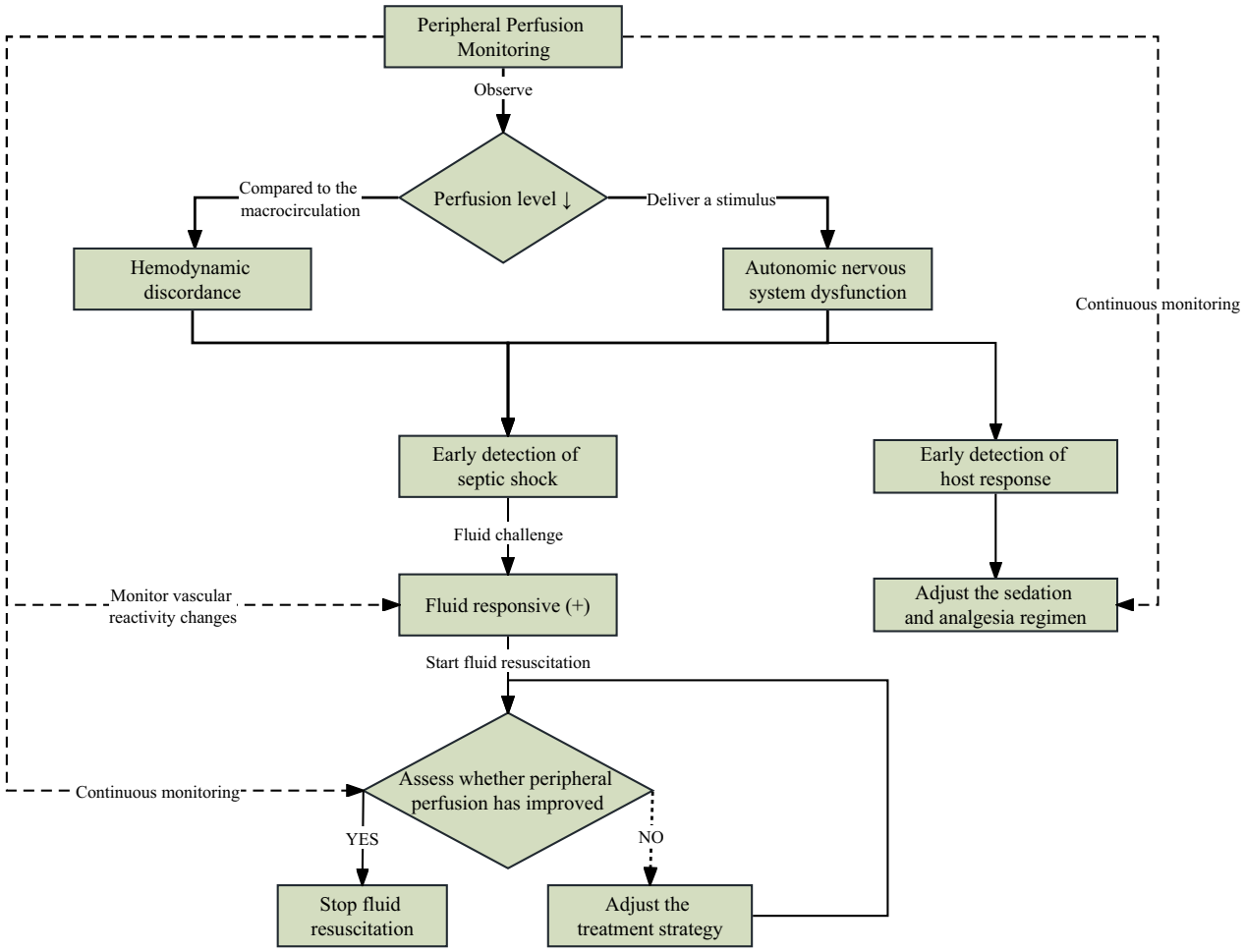

Fig. 3 Peripheral perfusion monitoring can detect autonomic dysfunction and identify systemic host responses early to identify potential septic shock patients. Peripheral perfusion monitoring assesses fluid responsiveness to guide initial fluid resuscitation and dynamically evaluate the effects. Perfusion kinetics enables evaluation of patients' responses to treatment, as well as prognosis, allowing timely adjustment or cessation of resuscitation to protect the vascular endothelium

Attainable therapeutic objectives are set, such as restoring normal skin perfusion and lowering lactate concentrations, and attention is paid to potential side effects, such as fluid overload. The model must be optimized while dynamically adjusting the assessment process. Using these models, rescue treatment can be accurately guided and enhanced by integrating assessment of micro- and macrocirculations, with other parameters for dynamic assessment and intervention.

Discussion and outlook

Peripheral perfusion monitoring can provide an accurate, real-time, and multidimensional assessment of a patient's condition. It is crucial to promptly identify dysregulation, monitor autonomic dysfunction, and determine whether the patient is in a state of homeostasis.

Alterations in microcirculation resulting from poor peripheral perfusion are mainly a result of the function of the endothelium of small arteries. The microcirculation functions as a bridge between endothelial cell dysfunction and mitochondrial injury, as well as between macrocirculatory changes and tissue injury. This is important information that needs to be further investigated.

A clinical trial by Castro et al. found no difference between fluid resuscitation volume determined by CRT or lactate over a 6-h period, which is in contrast to the findings of the ANDROMEDA-SHOCK trial. There is disagreement between these clinical trials of peripheral perfusion monitoring-guided therapy. However, both trials reported the benefits of targeting fluid resuscitation as the final treatment outcome and using CRT to evaluate responsiveness to fluid therapy in septic shock. We carefully examined the differences between the two clinical

trials. Notably, the ANDROMEDA-SHOCK trial's inclusion criterion was 4 h rather than 24 h after the diagnosis of septic shock, as in Castro et al.'s study. This suggested that the early stages of septic shock may be more indicative of tissue perfusion and may be the reason why the ANDROMEDA-SHOCK trial was unable to assess the response to fluid therapy. This difference may also explain why less fluid was administered to the CRT-guided group in the ANDROMEDA-SHOCK trial. Other discrepancies between the studies could be attributed to the addition of vasoactive medications to ANDROMEDA-SHOCK trial when resuscitation was insufficient to improve the therapeutic impact. In addition, Castro et al. trial's had a small sample size and minimal population diversity.

Peripheral perfusion monitoring has a wide range of applications owing to its many benefits. This method can provide information to aid in the early detection of hemodynamic changes and guide fluid resuscitation, adjust autonomic function, guide sedation and analgesia, or guide extubation and assess hemodynamic changes during hemofiltration. New approaches, particularly the use of various ultrasound techniques, can stimulate further innovation and aid in the monitoring of peripheral perfusion (Fig. 3).

Future work may focus heavily on elucidating changing patterns of peripheral perfusion kinetics and developing logical response techniques. The kinetics of various peripheral perfusion monitoring techniques should be further investigated to better understand patterns in kinetic changes and the clinical importance of diverse responses. The multimodal analysis model of peripheral perfusion monitoring should be improved as well to compare the benefits and drawbacks of various monitoring parameters in the evaluation of peripheral microcirculatory dysfunction and to serve as a guide for the creation of a precise assessment system. This can help increase the thoroughness and accuracy of the assessment of microcirculatory damage in sepsis. Through multilevel and overall microcirculation monitoring, the microcirculation status of patients with sepsis can be systematically evaluated to provide a basis for future research and developments in sepsis treatment.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study is a literature review based on publicly available data and information. It does not involve any new human participants or animal experiments. Therefore, it does not require special ethical approval.

Competing interests
The authors declare no competing interests.

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