

REVIEW

Open Access



Beyond macrocirculatory targets: a multimodal framework for microcirculatory and organ perfusion monitoring in sepsis

Xuebin Yin^{1,2} , Haowen Guan², Ming Zhou², Lisha Fan¹, Qiuxia Liu¹, Ruping Zhou³, Gefan Wu², Man Chen¹ and Wei Fang^{1*}

Abstract

Background Microcirculatory dysfunction may persist despite restoration of conventional macrocirculatory targets in sepsis, reflecting loss of hemodynamic coherence. This review synthesizes current microcirculatory monitoring approaches according to the physiological information they provide and examines how complementary modalities may be integrated to characterize persistent or regional tissue hypoperfusion.

Main body A narrative review of PubMed-indexed literature was conducted, with emphasis on bedside peripheral perfusion assessment, tissue oxygenation and superficial perfusion imaging, direct microvascular visualization, and organ- or tissue-specific monitoring. Recent studies were prioritized together with landmark methodological and validation studies. Available techniques interrogate distinct but overlapping components of the circulation. Bedside peripheral measures provide rapid information on skin reperfusion and vascular tone; spectroscopic and optical techniques characterize tissue oxygenation, reactivity, and spatial perfusion heterogeneity; direct microvascular imaging enables assessment of microvascular density and flow; and organ-specific approaches provide information on renal, cerebral, or retinal perfusion and oxygenation. Discordance between these domains may persist despite improvement in blood pressure or cardiac output, supporting serial multimodal rather than single-variable interpretation. However, substantial heterogeneity in acquisition protocols, measurement sites, devices, analytical methods, and proposed thresholds limits comparability and clinical implementation.

Conclusion Microcirculatory monitoring should currently be viewed as a complementary framework for identifying persistent or heterogeneous tissue hypoperfusion beyond conventional macrocirculatory targets. Its integration into individualized resuscitation remains promising but requires standardized methodology, external validation, and prospective interventional evidence before any single modality or multimodal strategy can be adopted as a validated resuscitation endpoint.

Keywords Microcirculation, Multimodal monitoring, Resuscitation, Sepsis, Tissue perfusion

*Correspondence:

Wei Fang
doctorfang@163.com

¹Department of Critical Care Medicine, Shandong Provincial Hospital
Affiliated to Shandong First Medical University, Jinan, Shandong
250000, China

²Shandong First Medical University, Jinan, Shandong 250117, China

³Department of Pulmonary and Critical Care Medicine, Respiratory
Intensive Care Unit, Qilu Hospital of Shandong University, Jinan,
Shandong 250012, China



© The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Background

During sepsis, sustained activation of inflammatory signaling pathways such as toll-like receptor 4/nuclear factor kappa B (TLR4/NF- κ B) promotes endothelial inflammation. Destabilization of vascular endothelial cadherin (VE-cadherin)–catenin adherens junctions, endothelial glycocalyx degradation, and cytoskeletal remodeling jointly impair endothelial barrier function [1]. Multiple inflammatory mediators further promote endothelial glycocalyx degradation and shedding [2, 3]. Together, these processes damage the vascular endothelial barrier, leading to hypotension and tissue edema [4]. Other contributory mechanisms include impaired microvascular vasomotor function and reactivity, endothelial apoptosis, mitochondrial dysfunction, and microthrombus formation associated with excessive platelet activation [5–8]. These structural and functional microvascular abnormalities underlie the defining features of microcirculatory dysfunction: reduced functional capillary density, heterogeneous blood flow, and impaired oxygen extraction. They ultimately result in tissue hypoxia and metabolic dysregulation and promote the development and progression of multiple organ dysfunction syndrome (MODS) [5, 7, 8]. Direct monitoring of the microcirculation may therefore enable detection of the functional consequences of these pathological changes and provide complementary tissue-level information for individualized physiological assessment.

Red blood cells (RBCs) are not merely oxygen carriers; their rheological behavior also contributes to capillary blood flow and tissue oxygen transport. RBC deformability and aggregation are major cellular determinants of blood rheology and microvascular flow. In sepsis, oxidative stress, inflammatory mediators, disturbances in intracellular Ca^{2+} and ATP homeostasis, and alterations in membrane and cytoskeletal properties may reduce RBC deformability and increase aggregation, potentially impairing capillary transit and contributing to heterogeneous microvascular oxygen delivery [9, 10]. Clinical studies have demonstrated reduced RBC deformability and increased aggregation early after ICU admission in patients with sepsis [11]. Moutzouri et al. reported greater impairment of deformability with increasing disease severity, whereas serial measurements in a subset of patients paralleled clinical deterioration or improvement [12]. Donadello et al. further showed that persistent or progressive reductions in RBC deformability were associated with poor outcome [13]. More recent exploratory data have also identified altered RBC morphology, impaired deformability, and reduced membrane CD35 expression in sepsis [14]. These observations further illustrate that tissue oxygen transport depends not only on macrocirculatory blood flow, but also on the availability

of RBCs within the microcirculation and on their rheological properties, cellular integrity, and viability.

Consistent with this tissue-level perspective, the 2025 European Society of Intensive Care Medicine (ESICM) guidelines define shock as life-threatening acute circulatory failure characterized by decreased tissue perfusion, resulting in inadequate oxygen delivery and/or oxygen utilization relative to cellular metabolic demands. Importantly, hypotension, although commonly present, is not required to define shock [15].

Microcirculatory abnormalities may persist despite apparently restored systemic hemodynamics, and persistent impairment has been associated with organ failure and mortality in septic shock [16, 17]. This loss of hemodynamic coherence between the macrocirculation and microcirculation is a recognized feature of sepsis and septic shock.

Ince [17] first proposed that fluid resuscitation in patients with sepsis should seek to maintain hemodynamic coherence between the macrocirculation and microcirculation, a concept now widely accepted. Fluid resuscitation remains a cornerstone of sepsis management and aims to correct microcirculatory hypoperfusion and improve oxygen delivery. Even when macrocirculatory variables improve after fluid resuscitation, regional microvascular perfusion may remain impaired [18]. The 2026 Surviving Sepsis Campaign supports serial lactate assessment during resuscitation while emphasizing frequent reassessment and individualized fluid administration after the initial resuscitation phase [19]. However, lactate is influenced by production, clearance, hepatic function, adrenergic stimulation, and mitochondrial metabolism and therefore cannot be interpreted as a direct measure of microcirculatory perfusion.

Against this background, this review summarizes current peripheral, tissue-level, direct microvascular, and organ-specific monitoring approaches and considers their complementary roles within the framework of hemodynamic coherence.

This review was informed by a narrative PubMed search prioritizing recent evidence together with landmark methodological and validation studies, as detailed below.

Literature search strategy

A narrative literature search was conducted in PubMed using combinations of controlled vocabulary and free-text terms related to sepsis, septic shock, microcirculation, tissue and peripheral perfusion, hemodynamic coherence, and individual monitoring modalities. Technique-specific searches included capillary refill time, peripheral perfusion index, mottling score, snuffbox artery resistive index, laser Doppler flowmetry, near-infrared spectroscopy, hyperspectral imaging, laser

speckle contrast imaging, sidestream and incident dark-field imaging, contrast-enhanced ultrasound, and optical coherence tomography angiography. Additional targeted searches included red blood cell/erythrocyte availability, deformability, aggregation, rheology, hemorheology, viability, eryptosis, and related functional-assessment methods, as well as macro-to-microcirculatory coupling and organ-specific perfusion monitoring. Recent evidence was prioritized, while older landmark or methodologically important studies were retained when relevant. Because this was a narrative review, no formal risk-of-bias assessment or systematic study-selection procedure was undertaken.

ChatGPT (OpenAI) was used to assist with English-language editing and to improve the clarity, concision, and organization of selected passages. All AI-assisted content was critically reviewed, revised, and verified by the authors, who take full responsibility for the final manuscript.

Peripheral and tissue microcirculation monitoring

Capillary refill time

Capillary refill time (CRT) is among the simplest measures of peripheral perfusion. It is assessed by observing the time required for color to return after pressure is applied to the fingertip, knee, or earlobe, thereby providing an indirect measure of skin microvascular reperfusion. A prolonged CRT, commonly > 3 s, suggests impaired peripheral perfusion and has been associated with adverse outcomes in sepsis [20–22]. Because CRT is noninvasive, rapid, and requires no additional equipment, it is particularly useful in emergency departments, intensive care units (ICUs), and resource-limited settings. Recent randomized trials have further explored the use of peripheral perfusion targets within individualized hemodynamic resuscitation. ANDROMEDA-SHOCK-2 used CRT normalization as the central perfusion target within a multicomponent, phenotype-based algorithm in which pulse pressure, diastolic arterial pressure, fluid responsiveness, and bedside echocardiography were used to characterize the underlying hemodynamic profile and guide the selection of fluids, vasopressors, or inotropes. These findings support the incorporation of CRT into individualized bedside perfusion assessment, but should not be interpreted as validating CRT alone as an independent therapeutic target [23].

By contrast, TARTARE-2 S evaluated a targeted tissue perfusion strategy incorporating several concurrent targets, including CRT, peripheral skin temperature, motting, arterial lactate, urine output, and a lower mean arterial pressure (MAP) range, and found no significant difference in the primary composite outcome or pre-specified secondary outcomes compared with MAP-guided standard care [24]. The two trials therefore should

not be viewed as directly validating or invalidating CRT itself, because both evaluated multicomponent treatment strategies with substantially different treatment architectures. Current evidence supports CRT as one component of an individualized hemodynamic and tissue-perfusion assessment framework, but does not establish CRT alone as a sufficient basis for decisions regarding fluids, vasoactive drugs, or other resuscitation therapies.

Another important role of CRT is the dynamic assessment of treatment response. CRT responses vary markedly among individuals after norepinephrine dose escalation or an increase in MAP; improvement in cardiac output does not necessarily shorten CRT [25]. Similarly, CRT often improves after rapid fluid administration in fluid-responsive patients, whereas responses to a vasopressor test are highly heterogeneous in fluid-unresponsive patients with chronic hypertension and septic shock [26]. These findings suggest that serial CRT can provide information on changes in peripheral perfusion following a fluid challenge or vasopressor test and may help determine whether improvements in macrocirculatory hemodynamics are accompanied by peripheral reperfusion. Such responses should be interpreted within the broader hemodynamic context rather than used in isolation to mandate fluid administration, vasopressor adjustment, or MAP escalation.

The principal limitation of CRT is its subjectivity. Measurements are also influenced by ambient temperature, anatomical site, compression technique, and skin condition, making standardized measurement and staff training essential [21]. Objective approaches, including automated CRT devices and laser Doppler monitoring of skin blood flow, have therefore attracted increasing interest [27, 28]. Skin blood-flow variables show some correlation with changes in CRT and lactate, suggesting that objective peripheral perfusion monitoring may complement CRT; however, its clinical value requires further validation.

Perfusion index

The perfusion index (PI) is derived from the pulse oximetry plethysmographic signal and is calculated as the ratio of pulsatile to non-pulsatile components, providing a continuous and noninvasive measure of peripheral perfusion. Compared with CRT, PI is objective, continuous, and readily repeatable. Available studies indicate that a low or persistently declining PI is associated with adverse outcomes in sepsis [29, 30], and early changes across multiple time points may better reflect disease progression and response to resuscitation than a single measurement [30]. A 2026 meta-analysis of 22 studies involving 2,727 patients found that a reduced peripheral perfusion index was associated with 28-day mortality (OR, 5.05; 95% CI, 3.65–6.98) and in-hospital mortality (OR, 4.56;

95% CI, 3.32–6.26) [22]. Although these odds ratios were numerically larger than those reported for prolonged CRT and elevated mottling score, differences in populations, thresholds, and measurement timing preclude direct conclusions regarding comparative discriminatory performance.

Dynamic changes in PI may also assist in assessing fluid responsiveness. During passive leg raising (PLR) or a fluid challenge, changes in PI have shown some correlation with changes in cardiac output or aortic velocity–time integral [31–33]. Thus, Δ PI may reflect the peripheral perfusion response to a short-term hemodynamic intervention but should not be regarded as a surrogate for cardiac output. Rasmy et al. reported that $PI \leq 0.3$ predicted vasopressor requirement during early resuscitation [34]. A recent prospective cohort similarly associated $PI \leq 0.3$ with vasopressor use within 24 h [35]. Together, these findings suggest that a low PI may help identify patients with persistent peripheral hypoperfusion and a greater likelihood of requiring vasopressor support. However, this evidence is derived mainly from small, single-center studies, and the generalizability of the proposed thresholds requires validation in multicenter studies.

PI is affected by both systemic hemodynamics and local conditions. Skin and ambient temperature, peripheral vascular disease, probe position, nail polish, ambient light, pain, and stress may all introduce measurement error [36–42]. Moreover, the optimal PI threshold remains uncertain. PI is therefore better interpreted as a continuous trend than used as an independent treatment trigger based on a single threshold, and should be considered alongside CRT, lactate, blood pressure, urine output, and other clinical variables.

Mottling score

The mottling score has shown prognostic value for mortality in sepsis [43, 44]. A 2026 meta-analysis of 22 studies involving 2,727 patients found that elevated mottling scores were associated with both 28-day mortality (OR, 2.27; 95% CI, 1.79–2.87) and 14-day mortality (OR, 1.96; 95% CI, 1.32–2.91) [22]. However, heterogeneity in assessment timing and scoring protocols currently precludes the use of a universal intervention threshold. In a post hoc analysis of the SEPSISPAM trial, assignment to a higher MAP target was not associated with higher lactate concentrations or worse mottling scores [44].

However, the score is highly dependent on the assessor and is susceptible to ambient light, temperature, skin pigmentation, and other factors. Although attempts have been made to standardize the assessment procedure, substantial subjectivity limits its widespread clinical use.

Snuffbox artery resistive index

At the anatomical snuffbox, the radial artery lies superficially, enabling Doppler acquisition with a small insonation angle. The snuffbox artery resistive index (SBRI) is calculated as (peak systolic velocity – end-diastolic velocity)/peak systolic velocity and reflects local downstream arterial impedance rather than capillary perfusion directly. Ban et al. found a strong correlation between RI and vascular resistance in an in vitro vessel-phantom model incorporated into a mock circulation system. In 15 postoperative cardiac-surgery patients, SBRI correlated with SVRI, whereas no significant overall correlations were observed for resistive indices measured at the brachial artery or wrist radial artery [45]. These findings should be regarded as proof-of-concept evidence because of the small postoperative cohort and repeated within-patient measurements.

In 44 patients with septic shock, Wang et al. found that SBRI was higher in patients with < 20% reduction in lactate at 6 h [46]. A cutoff of 1.09 yielded an AUC of 0.805, with 68.8% sensitivity and 85.7% specificity, but this single-center threshold was based on a surrogate endpoint and has not been externally validated.

Qin et al. reported a mean SBRI estimate with a 95% confidence interval of 0.72–0.75 in healthy volunteers [47]. This interval reflects the precision of the estimated group mean and should not be interpreted as an individual reference interval or treatment threshold. ICU patients had higher RI and lower end-diastolic velocity than healthy volunteers, but snuffbox Doppler variables did not differ significantly between patients with and without shock. Lower end-diastolic velocity was associated with 28-day mortality. SBRI should therefore be regarded as an investigational measure of local peripheral arterial impedance and interpreted alongside CRT, PI, lactate, vasoactive-drug exposure, temperature, and macrocirculatory variables rather than used as an independent resuscitation endpoint.

Red blood cell availability, viability, and functional assessment

RBC availability can be considered at both systemic and microcirculatory levels. Hemoglobin concentration, hematocrit, and RBC count characterize the circulating erythrocyte pool, whereas microvascular RBC distribution and transit can be further characterized by capillary recruitment, RBC velocity, and local capillary hematocrit [48]. Sepsis-related inflammatory and oxidative injury may also alter RBC membrane integrity and functional properties [10]. During septic-shock resuscitation, hemoglobin concentration may decrease, with the volume of intravenous fluid administered showing a weak association with this decline, consistent with a contribution from hemodilution [49].

Intrinsic RBC properties still require predominantly *ex vivo* assessment. Ektacytometry can assess RBC deformability [11, 14], whereas aggregation can be quantified using complementary rheological methods [11]. Flow-cytometric approaches can characterize RBC morphology and selected membrane alterations [14]. Sepsis-related RBC injury may also promote eryptosis and premature erythrocyte clearance [10, 50]. Eryptosis-related changes can be assessed *ex vivo* by flow-cytometric detection of phosphatidylserine exposure [50].

Emerging microfluidic and automated analytical platforms can reduce sample requirements and characterize selected RBC mechanical or flow-related properties *ex vivo* [51–53], but their clinical validation in sepsis remains limited. *In vivo* microvascular imaging provides complementary information on RBC behavior within the intact microvascular network. Chalkias et al. quantified sublingual RBC velocity using handheld vital microscopy (HVM) and estimated microvascular wall shear stress from vessel geometry and an assumed pressure difference across the capillary [54]. Such measurements characterize RBC transit rather than intrinsic cellular properties such as deformability or membrane mechanics.

Spectroscopic monitoring of tissue oxygenation and perfusion

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) exploits differences in the absorption of near-infrared light by oxyhemoglobin and deoxyhemoglobin to assess local tissue oxygenation continuously and noninvasively. Key variables include tissue oxygen saturation (StO_2), oxyhemoglobin (HbO_2), and deoxyhemoglobin (HbR); some devices can also estimate tissue water content. Unlike lactate, which reflects systemic metabolic status, NIRS primarily characterizes dynamic changes in local oxygen supply–demand balance and microvascular reactivity.

Studies of NIRS in septic shock show that reduced StO_2 may coexist with increased tissue water content and that tissue oxygenation variables do not always change in parallel with MAP, suggesting that improved macrocirculatory hemodynamics do not necessarily indicate recovery of local tissue oxygenation [55, 56]. NIRS has also been used to investigate tissue autoregulation and individualized blood-pressure targets. Available studies suggest that NIRS-derived indices may capture impaired cerebral autoregulation during inflammation, and that the optimal MAP (MAP_{opt}) derived from cerebral and skeletal-muscle measurements may differ [57, 58]. These findings further suggest that perfusion requirements vary between tissues and that a fixed MAP target may not be appropriate for every patient or organ.

When combined with a vascular occlusion test (VOT), NIRS can assess microvascular reactivity using variables

such as the reoxygenation slope. In a preliminary study, the NIRS-derived reoxygenation slope improved from baseline after albumin administration but not after crystalloid administration; however, the between-group difference was not statistically significant [59]. The weak agreement between NIRS and SDF variables suggests that these techniques may assess different physiological domains. NIRS is therefore most valuable for continuous monitoring of local tissue oxygenation and functional microvascular reactivity, rather than as a substitute for direct microcirculatory imaging or an independent resuscitation endpoint. Clinical translation remains limited by measurement site, tissue edema, subcutaneous adiposity, and substantial device- and algorithm-dependent variability. Importantly, the InSpectra StO_2 platform (Hutchinson Technology) was reported as no longer commercially available in 2021 [60]. Because absolute values and dynamic responses may differ across NIRS platforms, thresholds derived from historical studies cannot necessarily be extrapolated to contemporary devices [61]. These limitations, together with limited prospective interventional validation, constrain the routine application of peripheral NIRS in adult ICUs. Further validation using currently available platforms is required before NIRS-derived variables can be incorporated reliably into individualized fluid or blood-pressure management.

Hyperspectral imaging

Hyperspectral imaging (HSI) is a noncontact optical imaging technique that acquires tissue reflectance spectra across multiple wavelength bands to generate spatially resolved information on tissue oxygenation, hemoglobin distribution, tissue water content, and near-infrared perfusion-related features. Unlike single-point measures such as CRT and PI, HSI depicts the spatial heterogeneity of tissue oxygenation and perfusion. However, it does not directly measure microvascular blood flow; instead, it infers local oxygenation and perfusion from tissue spectral characteristics.

Direct clinical evidence for HSI in sepsis remains limited. Using hand HSI data from more than 400 ICU patients, Seidlitz et al. [62] developed a deep-learning model for identifying sepsis and predicting mortality risk. Predictive performance improved when HSI was combined with clinical variables, suggesting that HSI may provide data for noninvasive optical phenotyping and artificial intelligence (AI)-based risk stratification. Animal studies further showed that HSI could capture changes in tissue oxygenation and water content associated with shock, fluid resuscitation, and high-dose vasoactive drugs [63]. A study in a trauma resuscitation room provided preliminary evidence of feasibility in acute and critical-care settings [64]. Kazune et al. [65] found that higher mottling scores were associated with lower

HSI-derived microcirculatory hemoglobin oxygen saturation, although considerable overlap existed between score categories. However, these translational findings do not establish that HSI can guide resuscitation in sepsis.

Overall, HSI is currently better viewed as an emerging technology for tissue spectral phenotyping and multimodal data acquisition than as a mature tool for guiding resuscitation. Its clinical application is constrained by limited direct evidence; inadequate standardization of devices and algorithms; susceptibility to motion artifacts, skin characteristics, and environmental conditions; and complex image-processing workflows. Future studies should assess whether HSI can monitor dynamic microcirculatory changes and treatment responses in sepsis, and should explore its integration with conventional perfusion measures, hemodynamic variables, and AI models. Further device miniaturization and simplified image-processing workflows may improve the feasibility of mobile and bedside HSI.

Microcirculatory blood-flow imaging and direct visualization

Laser doppler flowmetry

Laser Doppler flowmetry (LDF) uses Doppler frequency shifts in light scattered by moving red blood cells to provide continuous, noninvasive assessment of local cutaneous microvascular flux/perfusion, generally expressed in relative perfusion units. In critically ill patients, fingertip LDF-derived skin blood flow has been closely associated with CRT and lactate but not with cardiac output, supporting its potential to detect peripheral perfusion abnormalities that are not captured by systemic hemodynamic variables [27]. In a prospective cohort of patients with circulatory shock, Mongkolpun et al. further showed that reduced fingertip skin blood flow and impaired vasodilatory response to thermal challenge were associated with ICU mortality, while serial measurements demonstrated the feasibility of dynamic bedside assessment [66]. More recently, changes in skin blood flow during passive leg raising predicted the subsequent peripheral microvascular response to volume expansion in patients with sepsis [67]. Earlier proof-of-concept data also showed increased laser-Doppler flow following fluid administration in stroke-volume responders [68]. However, LDF samples a small, localized tissue volume and provides relative rather than absolute blood-flow measurements; its results are influenced by measurement site, temperature, motion, and probe positioning, limiting assessment of spatial heterogeneity. It therefore remains an adjunctive or research technique rather than a validated independent resuscitation target.

Laser speckle contrast imaging

Laser speckle contrast imaging (LSCI) is a noncontact technique for imaging superficial blood flow. It quantifies local perfusion by analyzing changes in the contrast of dynamic speckle patterns generated when coherent laser light illuminates tissue. Unlike single-point measures such as CRT and PI, LSCI provides two-dimensional spatial information that may help identify heterogeneity in superficial tissue perfusion. Available evidence suggests that LSCI variables can distinguish patients with shock from healthy controls and may identify hypoperfusion not detected by conventional MAP or systolic blood pressure measurements [69]. In sepsis and septic shock, LSCI-derived perfusion variables have also shown some prognostic value [70]. However, most studies are single-center or exploratory, and LSCI predominantly reflects superficial perfusion; its performance is affected by limited penetration depth, motion artifacts, measurement site, and lack of standardized image analysis. LSCI is therefore more appropriate as a rapid, noncontact method for assessing superficial perfusion than as an independent resuscitation endpoint.

Sidestream dark-field imaging and incident dark-field imaging

Sidestream dark-field imaging (SDF) and incident dark-field imaging (IDF) enable direct visualization of sublingual microvascular blood flow and quantification of total vessel density (TVD), perfused vessel density (PVD), proportion of perfused vessels (PPV), microvascular flow index (MFI), and heterogeneity index (HI). Compared with SDF, IDF systems have demonstrated improved image-acquisition quality, including better focus and stability [71]. More recent analysis of full-frame high-resolution IDF images using advanced computer-vision tools has further improved capillary detection and quantitative analysis [72].

Available studies suggest that sublingual microcirculatory variables such as PPV are associated with sepsis severity and mortality risk, although findings regarding their prognostic value are not consistent across studies [73, 74]. This suggests that a single measurement or brief monitoring window may not adequately capture dynamic changes in the microcirculation or organ-level heterogeneity. Moreover, microvascular morphology, estimated wall shear stress, and perfusion may remain abnormal despite macrohemodynamic optimization [54]. These findings are consistent with loss of hemodynamic coherence in sepsis.

Dedicated sublingual videomicroscopy systems can provide an indirect glycocalyx-related measure through the perfused boundary region (PBR). In patients with sepsis, PBR was increased, and PBR in the smallest capillary diameter class was inversely correlated with TVD

and PVD [75]. These findings suggest a possible relationship between glycocalyx injury and microcirculatory alterations, although the clinical interpretation of PBR remains investigational.

Overall, SDF/IDF provide microvascular structural and perfusion information that is unavailable from conventional hemodynamic monitoring. The 2025 ESICM guidelines acknowledge that visualization of the sublingual microcirculation may reveal persistent perfusion abnormalities after macrocirculatory-targeted resuscitation, although evidence that its use improves clinical outcomes remains insufficient [15]. However, HVM remains limited by challenging image acquisition, operator dependence, motion and pressure artifacts, and incomplete standardization of analysis. Automated HVM analysis may reduce the burden of manual image interpretation [76], while the recently introduced OxyCam integrates image stabilization, automated analysis, and microvascular RBC oxygen-saturation imaging. Its initial validation was preclinical, however, and its clinical utility in patients with sepsis remains to be established [77]. Despite these advances, HVM remains primarily a research and adjunctive assessment tool rather than a routine bedside resuscitation modality.

Organ-specific microcirculatory monitoring: from peripheral perfusion to organ-specific assessment

Most bedside microcirculatory monitoring techniques assess relatively accessible sites such as the skin, sublingual mucosa, or skeletal muscle. However, sepsis-associated organ dysfunction is heterogeneous, and organs differ substantially in blood-flow regulation, capillary density, oxygen-extraction capacity, and inflammatory responses. Improved peripheral perfusion therefore does not necessarily imply concurrent recovery of the renal, cerebral, hepatic, or intestinal microcirculation [58, 78, 79]. Organ-specific microcirculatory monitoring aims to characterize this regional heterogeneity and provide physiological information beyond systemic and peripheral perfusion assessment.

Renal microcirculation: CEUS and renal cortical perfusion

The kidney is among the organs most commonly affected in sepsis. Although urine output and serum creatinine reflect changes in renal function, these changes are often delayed and do not directly represent renal cortical microcirculatory perfusion. Contrast-enhanced ultrasound (CEUS) uses microbubble contrast agents to assess renal cortical perfusion dynamically, providing an organ-specific monitoring approach for sepsis-associated acute kidney injury (AKI). Evidence indicates that reduced renal cortical perfusion in severe AKI can occur independently of renal blood flow, cardiac output, and sublingual microcirculatory changes [78], suggesting that neither

systemic hemodynamic nor sublingual microcirculatory variables fully represent renal microcirculation. Renal CEUS may therefore identify inadequate renal cortical perfusion despite apparently adequate macrocirculatory variables and may provide complementary organ-specific physiological information. However, CEUS is limited by operator expertise, contrast-agent requirements, equipment availability, and inability to provide continuous monitoring. It is therefore currently more appropriate as a research tool or adjunctive assessment in selected high-risk patients.

Microcirculation in the brain and other tissues: NIRS and OCTA

Cerebral and skeletal-muscle NIRS represent another group of organ- or tissue-specific monitoring approaches. Cerebral NIRS can continuously assess cerebral tissue oxygenation and can use dynamic changes in oxyhemoglobin and deoxyhemoglobin to explore cerebral autoregulation. A human endotoxemia model in healthy volunteers showed changes in NIRS-derived dynamic cerebral autoregulation despite the absence of detectable changes with conventional TCD/arterial blood pressure-based analysis in the same experimental setting [57]. However, this observation requires validation in patients with sepsis-associated encephalopathy. Skeletal-muscle NIRS is convenient and is often used as a window onto peripheral tissue oxygenation and microvascular reactivity, allowing dynamic assessment of StO_2 , ReOx , DeOx , and tissue water content. Studies in septic shock suggest that reduced tissue oxygenation may coexist with tissue edema [55, 56], while ICU pilot data indicate that MAPopt estimates may differ between skeletal-muscle and cerebral measurements [58]. A single MAP target or a single monitoring site may therefore not fully represent the perfusion requirements of multiple organs.

Retinal OCTA provides noninvasive, depth-resolved visualization of retinal vascular plexuses and generates relative flow-related metrics rather than absolute blood-flow measurements [80]. Evidence in human sepsis remains limited, with most data derived from animal shock models and ICU feasibility studies [80]. In rodent models, retinal or choroidal flow-related indices decreased during sepsis, whereas in hemorrhagic shock they decreased during shock and showed an initial recovery after resuscitation [81]. In an ovine hemorrhagic-shock model, superficial retinal flow density decreased during shock and recovered after fluid resuscitation [82]. Noncontact acquisition and layer-resolved images are technically attractive, but the measurements are device- and algorithm-dependent. Current acquisition remains intermittent and is affected by eye movement, pupil status, optical-media abnormalities, and segmentation algorithms; OCTA should therefore be regarded as an

Table 1 Overall comparison of microcirculatory monitoring techniques in sepsis

Monitoring technique or measure	Principle	Key variables	Physiological domain	Main advantages	Main limitations	Current clinical role
CRT	Time to return of skin color after compression	CRT (s)	Peripheral skin reperfusion	Rapid, noninvasive, and equipment-free; suitable for resource-limited settings	Subjective; affected by temperature, compression technique, and skin condition	Rapid bedside identification of peripheral hypoperfusion and dynamic assessment of response to resuscitation
PI	Ratio of pulsatile to non-pulsatile components of the pulse oximetry plethysmographic signal	PI, Δ PI	Peripheral pulsatile perfusion	Continuous, objective, and readily integrated into monitoring devices	Affected by skin temperature, vascular tone, probe position, and motion artifacts	Trend monitoring of peripheral perfusion and adjunctive assessment during hemodynamic interventions
Mottling score	Extent of violaceous skin mottling around the knee	0–5 score; serial change	Visible peripheral skin hypoperfusion	Rapid, equipment-free, and prognostically informative	Subjective; affected by pigmentation, light, and temperature	Bedside risk stratification and serial peripheral assessment
Snuffbox artery Doppler/SBRI	Doppler ratio of systolic and end-diastolic velocities	SBRI, peak systolic velocity, end-diastolic velocity	Local peripheral arterial impedance or vascular tone	Noninvasive; superficial vessel; repeatable waveform acquisition	Operator- and angle-dependent; affected by temperature and vasoactive drugs	Investigational adjunct for peripheral vascular-tone assessment
NIRS	Near-infrared absorption differences are used to assess tissue oxygenation	StO ₂ , HbO ₂ , HbR, THI, ReOx, DeOx	Local tissue oxygenation, oxygen supply–demand balance, and microvascular reactivity	Noninvasive and continuous; supports functional VOT	Affected by subcutaneous adiposity, tissue edema, probe position, and algorithms	Adjunctive/research assessment of tissue oxygenation and microvascular reactivity; individualized fluid or MAP management remains investigational
HSI	Multiband reflectance spectra are analyzed to characterize tissue oxygenation and perfusion-related spectral features.	StO ₂ , NIR perfusion, THI, TWI, AI-derived features	Tissue oxygenation, water content, perfusion-related spectral features, and spatial heterogeneity.	Noncontact, two-dimensional spatial mapping; suitable for AI analysis	Complex devices and algorithms; limited direct evidence in sepsis	Emerging tissue spectral-phenotyping technique and data source for AI-based risk stratification
Laser Doppler flowmetry (LDF)	Doppler frequency shifts in coherent laser light scattered by moving RBCs	Cutaneous microvascular flux/perfusion units; response to provocation	Local superficial skin microvascular RBC flux/perfusion	Noninvasive; continuous; sensitive to dynamic local perfusion changes	Small sampling volume; relative flow units; affected by site, temperature, motion, and probe position; limited spatial heterogeneity assessment	Research or adjunctive bedside assessment of cutaneous perfusion and reactivity; not a validated independent resuscitation target
LSCI	Speckle-contrast changes after coherent laser illumination are analyzed	ROI diff, ROI ₂ /diff, LSCI-derived PI	Superficial tissue blood-flow perfusion	Noncontact, rapid, two-dimensional imaging	Shallow penetration; affected by motion artifacts and analysis workflow	Rapid assessment of superficial perfusion and exploratory prognostic stratification
SDF/IDF	Handheld in vivo microscopy directly visualizes sublingual microvascular blood flow	TVD, PVD, FCD, PPV, MFI, HI, De Backer score, RBCv, tRBCp	Microvascular density, proportion perfused, and flow heterogeneity	Closest to direct observation of the microcirculation	Operator-dependent; difficult acquisition; insufficient standardization	Research tool and adjunctive advanced ICU monitoring

Table 1 (continued)

Monitoring technique or measure	Principle	Key variables	Physiological domain	Main advantages	Main limitations	Current clinical role
Renal CEUS	Microbubble contrast kinetics within the renal cortex	Wash-in, peak intensity, time to peak	Renal cortical microvascular perfusion	Organ-specific, dynamic bedside imaging	Contrast and expertise required; intermittent and operator-dependent	Research tool or adjunct in selected high-risk patients
Retinal OCTA	Motion contrast from repeated optical coherence scans	Vessel density, flow density, relative flow-related indices	Retinal microvascular structure and relative flow-related perfusion	Noninvasive, depth-resolved, noncontact imaging	Intermittent; motion, media, pupil, and segmentation dependent	Investigational organ-specific imaging

Abbreviations: AI, artificial intelligence; CEUS, contrast-enhanced ultrasound; CRT, capillary refill time; DeOx, deoxygenation slope; FCD, functional capillary density; HbO₂, oxyhemoglobin; HbR, deoxyhemoglobin; HI, heterogeneity index; HSI, hyperspectral imaging; ICU, intensive care unit; IDF, incident dark-field imaging; LDF, laser Doppler flowmetry; LSCI, laser speckle contrast imaging; MAP, mean arterial pressure; MFI, microvascular flow index; NIR, near-infrared; NIRS, near-infrared spectroscopy; OCTA, optical coherence tomography angiography; PI, perfusion index; Δ PI, change in perfusion index; PPV, proportion of perfused vessels; PVD, perfused vessel density; RBC, red blood cell; RBCv, red blood cell velocity; ReOx, reoxygenation slope; ROI, region of interest; SBRI, snuffbox artery resistive index; SDF, sidestream dark-field imaging; StO₂, tissue oxygen saturation; THI, tissue hemoglobin index; tRBCp, tissue red blood cell perfusion; TVD, total vessel density; TWI, tissue water index; VOT, vascular occlusion test

investigational organ-specific imaging technique rather than a continuous bedside monitor. Retinal OCTA has not been validated as a surrogate for cerebral microcirculation or as a resuscitation endpoint in sepsis.

Limitations of deep-organ microcirculatory monitoring

Compared with the kidney, brain, and skeletal muscle, direct bedside monitoring of the hepatic, intestinal, and pulmonary microcirculation remains more challenging. Intestinal microcirculatory dysfunction may impair mucosal barrier integrity and facilitate bacterial translocation [83]. Hepatic and intestinal microcirculatory abnormalities may persist despite apparently improved systemic hemodynamics [79]. Pulmonary microvascular dysfunction may contribute to sepsis-associated ALI/ARDS through impaired capillary perfusion, endothelial barrier disruption, and ventilation–perfusion mismatch [84–86]. Because these organs are deep, mobile, and structurally complex, continuous, noninvasive, organ-specific microcirculatory monitoring tools suitable for widespread ICU use remain unavailable. Future research should further investigate organ-specific monitoring techniques and determine whether they can guide fluid resuscitation, vasoactive therapy, and organ-protection strategies.

The physiological domains, advantages, limitations, and current clinical roles of the monitoring approaches discussed above are summarized in Table 1.

Clinical integration and current limitations

The loss of hemodynamic coherence in sepsis means that optimization of macrocirculatory variables cannot be assumed to reflect restoration of tissue and microcirculatory perfusion. Over the past two decades, studies of septic shock resuscitation have increasingly highlighted the limitations of strategies centered on fixed, isolated

physiological targets, contributing to a shift from single-target optimization toward more dynamic and individualized physiological assessment [87]. Accordingly, the value of microcirculatory monitoring should not be viewed as identifying a new single variable to replace conventional hemodynamic targets, but rather as providing complementary tissue-level physiological information that cannot be fully captured by routine systemic monitoring.

Similarly, different microcirculatory monitoring modalities should not be regarded simply as competing or interchangeable techniques, because they interrogate related but distinct physiological domains. In a small observational study of nine patients, Zuccari et al. found that SDF-derived PVD increased at 6 and 24 h and TVD at 24 h, whereas NIRS-derived indices of tissue oxygenation and microvascular reactivity showed no significant changes over the same period [88]. Although the study was limited by its small sample size and important confounding factors, the findings illustrate that microvascular flow, tissue oxygenation, and vascular reactivity may follow different recovery trajectories. Accordingly, discordance between monitoring modalities should not automatically be interpreted as measurement failure, but may instead reflect temporal dissociation among different physiological domains.

Similar heterogeneity may also occur across tissues and organs. Although SDF/IDF imaging is among the most extensively studied approaches for direct bedside visualization of the sublingual microcirculation, microcirculatory responses across vascular beds are not necessarily synchronous, and improvement in the sublingual microcirculation cannot be assumed to indicate recovery of perfusion in internal organs [78, 79]. Organ-specific approaches, including renal CEUS, cerebral NIRS, and retinal OCTA, should therefore be considered

complementary to peripheral or sublingual monitoring rather than substitutes for them, as they provide additional information on regional or organ-specific physiology.

Nevertheless, a substantial gap remains between obtaining richer physiological information and translating that information into clinically actionable decisions. Most available technologies lack adequate validation in large prospective interventional studies. Even SDF/IDF imaging, despite being among the most extensively studied methods for direct microcirculatory assessment, remains constrained by technical complexity, incomplete standardization, and uncertainty regarding the extent to which local measurements represent systemic or organ-specific perfusion.

Bedside clinical indices such as CRT and the perfusion index are readily repeatable but provide relatively nonspecific information on peripheral perfusion; LDF provides continuous local assessment of cutaneous microvascular flux but samples only a small tissue volume; whereas techniques such as NIRS, HVM, HSI, and organ-specific imaging may provide tissue-oxygenation, direct microvascular, spatially resolved, or organ-related physiological information, with varying requirements for equipment, operator expertise, availability, and continuous monitoring. Accordingly, the principal bedside value of these techniques currently lies in serial reassessment, recognition of persistent or heterogeneous hypoperfusion, and identification of discordance between systemic hemodynamics and tissue-level perfusion, rather than in the use of isolated threshold values to mandate treatment escalation.

Randomized evidence in this field should be interpreted according to the intervention strategy actually tested. In trials of perfusion-guided resuscitation, a monitored variable may be embedded within a multi-component treatment algorithm, and the observed clinical effects therefore cannot be attributed to that variable alone [23, 24]. Trial results may additionally depend on patient selection, timing of intervention, comparator care, separation between treatment groups, protocol adherence, and outcome definitions. Conversely, randomized or trial-derived studies in which microcirculatory measurements are used primarily to characterize physiological responses or to assess the feasibility of a monitoring technology do not establish that the measured variable is an effective therapeutic target [44, 59, 64]. Accordingly, prognostic value, responsiveness to an intervention, or incorporation into a resuscitation algorithm should not be equated with evidence that treatment decisions based on that marker alone will improve patient outcomes.

The integration of these measures for selected clinical questions is summarized in Table 2, and a conceptual

framework for multimodal interpretation within hemodynamic coherence is illustrated in Fig. 1.

Perspectives

Different peripheral perfusion measures provide partly overlapping and partly complementary information, supporting multimodal rather than single-variable interpretation [89]. Future research should first strengthen the standardization and clinical validation of microcirculatory monitoring techniques, including measurement reproducibility, comparability across devices and acquisition sites, and external validation of proposed parameters in multicenter populations. More importantly, prospective interventional studies are needed to determine whether treatment adjustments based on these signals—including fluid administration, vasopressor titration, or other hemodynamic interventions—can improve organ function and patient-important outcomes rather than merely normalize surrogate perfusion measures. Future efforts should also move beyond the search for optimal thresholds for individual modalities and investigate how complementary information from peripheral perfusion, tissue oxygenation, direct microvascular imaging, and organ-specific monitoring can be integrated to characterize dynamic perfusion phenotypes across physiological domains. Finally, wider clinical translation will require technological advances that improve portability, acquisition speed, operator independence, automated analysis, and real-time bedside interpretability.

Conclusions

Sepsis-associated microcirculatory dysfunction cannot be adequately characterized by macrocirculatory variables or any single microcirculatory measure. Bedside clinical indices, tissue oxygenation methods, direct microvascular imaging, and organ-specific techniques interrogate different physiological dimensions and should be interpreted as complementary. At present, their strongest role is to identify persistent or regionally heterogeneous hypoperfusion and to support multimodal phenotyping; none is sufficiently validated as a stand-alone resuscitation endpoint. Standardized acquisition and analysis, serial monitoring, external validation, and prospective interventional studies are required before microcirculatory data can be incorporated reliably into individualized precision resuscitation.

Table 2 Integrating microcirculatory monitoring for selected clinical questions

Clinical question	Relevant measures or techniques	Information provided	Clinical relevance	Key considerations
Early recognition of hypoperfusion	CRT, PI, mottling score, lactate	Peripheral and systemic evidence of hypoperfusion and circulatory dysfunction	Rapid screening for shock risk in emergency departments, ICUs, and resource-limited settings	No single measure defines tissue hypoperfusion or the need for further resuscitation; interpret in clinical context.
Assessment of response to fluid resuscitation	Dynamic CRT, PI during PLR or fluid challenge, LDF-derived skin blood-flow response, NIRS-VOT, and serial lactate change	Changes in peripheral perfusion, tissue oxygenation, and oxygen supply–demand balance after fluid administration	May help distinguish systemic fluid responsiveness from the peripheral or tissue perfusion response	Fluid responsiveness is not equivalent to microcirculatory responsiveness; no measure alone determines the need for fluids
Individualized vasoactive therapy and MAP targets	CRT response to a vasopressor test, PI, NIRS-derived MAP _{opt} , SDF/IDF; SBRI as an investigational adjunct	Whether vasoactive therapy improves the peripheral or local microcirculation	Supports contextual interpretation of perfusion responses during vasoactive therapy and exploration of individualized MAP targets	Optimal MAP may differ by organ; SBRI is not a treatment target
Identification of loss of hemodynamic coherence	SDF/IDF, NIRS, CRT, PI, LDF, LSCI, HSI	Whether local perfusion abnormalities persist after MAP or CO targets are achieved	Helps identify persistent tissue-level hypoperfusion despite apparently adequate systemic hemodynamics	Dynamic monitoring is required; a single measurement has limited value
Prognostic stratification	CRT, PI, mottling score, NIRS, LSCI, SDF/IDF, HSI plus AI	Associations with mortality, organ dysfunction, or vasopressor requirement, depending on the modality	Supports identification of high-risk patients	Most techniques still lack validation against interventional outcomes
Organ-specific perfusion assessment	Renal CEUS, cerebral NIRS, skeletal-muscle NIRS, retinal OCTA	Local kidney, brain, muscle, and retinal perfusion or oxygenation	Provides organ-specific physiological information beyond systemic or peripheral measures	Peripheral or sublingual microcirculation cannot fully represent every organ
Multimodal perfusion assessment	Serial peripheral perfusion measures, metabolic markers, and selected advanced microcirculatory or organ-specific techniques	Integrated assessment of perfusion, oxygenation, metabolism, and organ function	Potentially supports integrated interpretation of perfusion status across physiological domains	Requires standardized data, external validation, and clinical trials

Abbreviations: AI, artificial intelligence; CEUS, contrast-enhanced ultrasound; CO, cardiac output; CRT, capillary refill time; HSI, hyperspectral imaging; ICU, intensive care unit; IDF, incident dark-field imaging; LDF, laser Doppler flowmetry; LSCI, laser speckle contrast imaging; MAP_{opt}, optimal mean arterial pressure; NIRS, near-infrared spectroscopy; OCTA, optical coherence tomography angiography; PI, perfusion index; PLR, passive leg raising; SBRI, snuffbox artery resistive index; SDF, sidestream dark-field imaging; VOT, vascular occlusion test

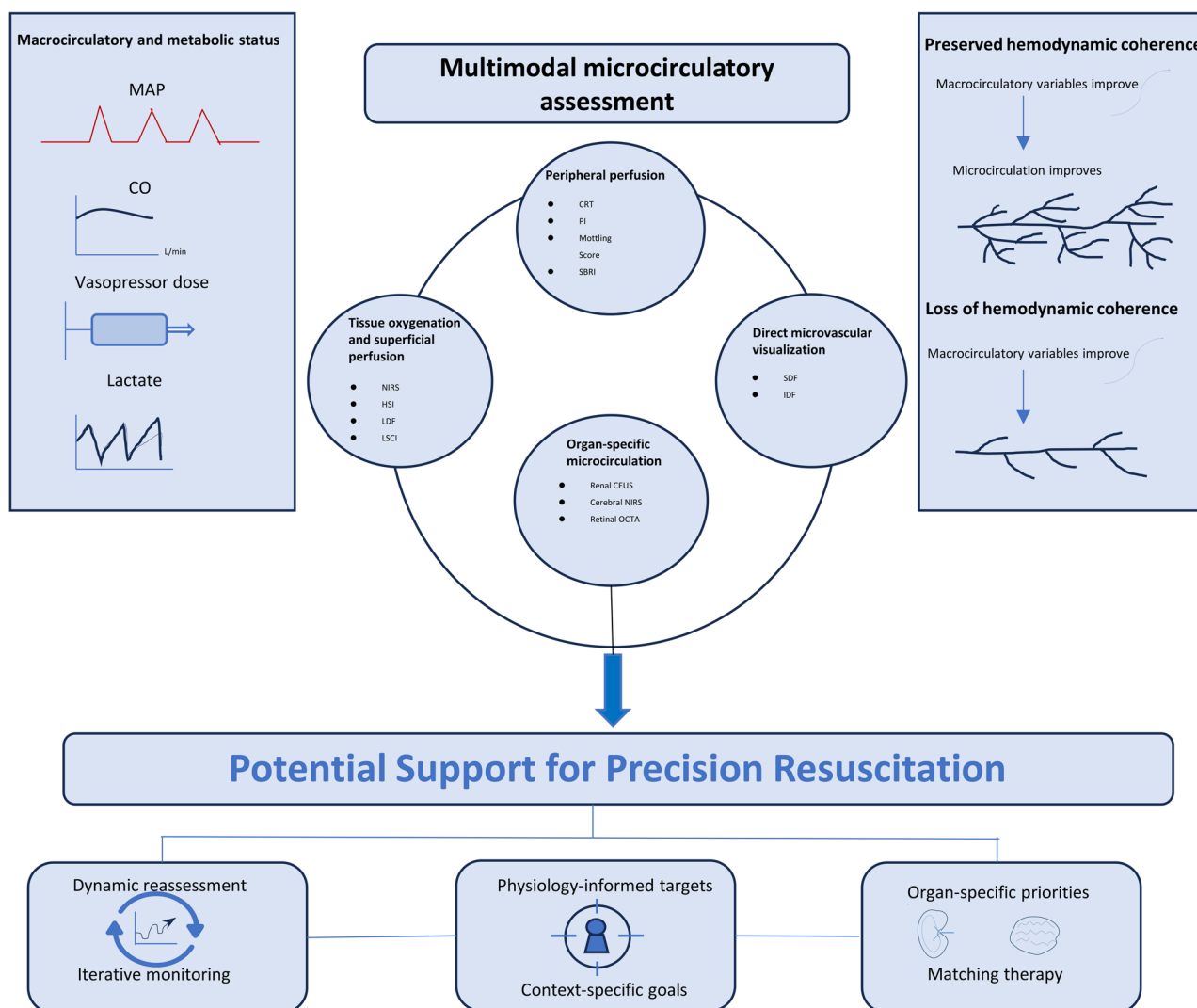


Fig. 1 Multimodal framework for microcirculatory perfusion monitoring in sepsis. The framework links conventional macrocirculatory and metabolic assessment with four complementary monitoring domains: peripheral perfusion, tissue oxygenation and superficial perfusion, direct microvascular visualization, and organ-specific microcirculation. When hemodynamic coherence is preserved, improvement in macrocirculatory variables is accompanied by improvement in the microcirculation; when coherence is lost, microcirculatory abnormalities may persist despite apparent macrocirculatory restoration. Serial multimodal assessment may therefore support physiology-informed interpretation and help characterize discordant perfusion phenotypes, but the depicted modalities should not be interpreted as independently validated treatment targets or as a validated multimodal resuscitation endpoint. MAP, mean arterial pressure; CO, cardiac output; CRT, capillary refill time; PI, perfusion index; SBRI, snuffbox artery resistive index; NIRS, near-infrared spectroscopy; HSI, hyperspectral imaging; LDF, laser Doppler Flowmetry; LSCI, laser speckle contrast imaging; SDF, sidestream dark-field imaging; IDF, incident dark-field imaging; CEUS, contrast-enhanced ultrasound; OCTA, optical coherence tomography angiography

Abbreviations

AI	Artificial intelligence
AKI	Acute kidney injury
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
AUC	Area under the receiver operating characteristic curve
CEUS	Contrast-enhanced ultrasound
CI	Confidence interval
CO	Cardiac output
CRT	Capillary refill time
Δ PI	change in perfusion index
DeOx	Deoxygenation slope
HbO ₂	Oxyhemoglobin
HbR	Deoxyhemoglobin
HI	Heterogeneity index

HSI	Hyperspectral imaging
HVM	Handheld vital microscopy
ICU	Intensive care unit
IDF	Incident dark-field imaging
LDF	Laser Doppler flowmetry
LSCI	Laser speckle contrast imaging
MAP	Mean arterial pressure
MAP _{opt}	Optimal mean arterial pressure
MFI	Microvascular flow index
MODS	Multiple organ dysfunction syndrome
NIR	Near-infrared
NIRS	Near-infrared spectroscopy
NF- κ B	Nuclear factor kappa B
OCTA	Optical coherence tomography angiography
OR	Odds ratio

PBR	Perfused boundary region
PI	Perfusion index
PLR	Passive leg raising
PPV	Proportion of perfused vessels
PVD	Perfused vessel density
RBC	Red blood cell
ReOx	Reoxygenation slope
RI	Resistive index
ROI	Region of interest
SBRI	Snuffbox artery resistive index
SDF	Sidestream dark-field imaging
StO ₂	Tissue oxygen saturation
SVRI	Systemic vascular resistance index
TCD/ABP	Transcranial Doppler/arterial blood pressure
THI	Tissue hemoglobin index
TLR4	Toll-like receptor 4
TVD	Total vessel density
TWI	Tissue water index
VE-cadherin	Vascular endothelial cadherin
VOT	Vascular occlusion test

Acknowledgements

Not applicable.

Author contributions

XY: Conceptualization, literature search, writing—original draft, visualization. HG: Literature search, writing—review and editing. MZ: Literature search, writing—review and editing. LF: Literature review, funding acquisition, writing—review and editing. QL: Literature review, writing—review and editing. RZ: Literature review, writing—review and editing. GW: Literature review, writing—review and editing. MC: Literature review, writing—review and editing. WF: Conceptualization, supervision, funding acquisition, writing—review and editing. All authors read and approved the final manuscript.

Funding

This work was supported by the Shandong Provincial Natural Science Foundation, China (Grant No. ZR2021QH354 and Grant No. ZR2023MH379).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 15 August 2026 / Accepted: 19 September 2026

Published online: 23 September 2026

References

- Zhang H, Wang Y, Qu M, et al. Neutrophil, neutrophil extracellular traps and endothelial cell dysfunction in sepsis. *Clin Transl Med*. 2023;13:e1170. <https://doi.org/10.1002/ctm2.1170>.
- Alphonso CS, Rodseth RN. The endothelial glycocalyx: a review of the vascular barrier. *Anaesthesia*. 2014;69:777–84. <https://doi.org/10.1111/anae.12661>.
- Schmidt EP, Yang Y, Janssen WJ, et al. The pulmonary endothelial glycocalyx regulates neutrophil adhesion and lung injury during experimental sepsis. *Nat Med*. 2012;18:1217–23. <https://doi.org/10.1038/nm.2843>.
- Joffe J, Hellman J, Ince C, Ait-Oufella H. Endothelial Responses in Sepsis. *Am J Respir Crit Care Med*. 2020;202:361–70. <https://doi.org/10.1164/rccm.2019-0-1911TR>.
- Tang F, Zhao XL, Xu LY, Zhang JN, Ao H, Peng C. Endothelial dysfunction: Pathophysiology and therapeutic targets for sepsis-induced multiple organ dysfunction syndrome. *Biomed Pharmacother*. 2024;178:117180. <https://doi.org/10.1016/j.biopha.2024.117180>.
- Raia L, Zafrani L. Endothelial Activation and Microcirculatory Disorders in Sepsis. *Front Med (Lausanne)*. 2022;9:907992. <https://doi.org/10.3389/fmed.2022.907992>.
- Wu M, Yan Y, Xie X, Bai J, Ma C, Du X. Effect of endothelial responses on sepsis-associated organ dysfunction. *Chin Med J (Engl)*. 2024;137:2782–92. <https://doi.org/10.1097/CM9.0000000000003342>.
- Lelubre C, Vincent JL. Mechanisms and treatment of organ failure in sepsis. *Nat Rev Nephrol*. 2018;14:417–27. <https://doi.org/10.1038/s41581-018-0005-7>.
- Piagnerelli M, Boudjeltia KZ, Vanhaeverbeek M, Vincent JL. Red blood cell rheology in sepsis. *Intensive Care Med*. 2003;29:1052–61. <https://doi.org/10.1007/s00134-003-1783-2>.
- Bateman RM, Sharpe MD, Singer M, Ellis CG. The Effect of Sepsis on the Erythrocyte. *Int J Mol Sci*. 2017;18:1932. <https://doi.org/10.3390/ijms18091932>.
- Reggiori G, Occhipinti G, De Gasperi A, Vincent JL, Piagnerelli M. Early alterations of red blood cell rheology in critically ill patients. *Crit Care Med*. 2009;37:3041–6. <https://doi.org/10.1097/CCM.0b013e3181b02b3f>.
- Moutzouri AG, Skoutelis AT, Gogos CA, Missirlis YF, Athanassiou GM. Red blood cell deformability in patients with sepsis: a marker for prognosis and monitoring of severity. *Clin Hemorheol Microcirc*. 2007;36:291–9. <https://doi.org/10.3233/CHM-2007-980>.
- Donadello K, Piagnerelli M, Reggiori G, Gottin L, Scolletta S, Occhipinti G, et al. Reduced red blood cell deformability over time is associated with a poor outcome in septic patients. *Microvasc Res*. 2015;101:8–14. <https://doi.org/10.1016/j.mvr.2015.05.001>.
- Vanderelst J, Rousseau A, Selvais N, Biston P, Zouaoui Boudjeltia K, Piagnerelli M. Evolution of red blood cell membrane complement regulatory proteins and rheology in septic patients: An exploratory study. *Front Med (Lausanne)*. 2022;9:880657. <https://doi.org/10.3389/fmed.2022.880657>.
- Monnet X, Messina A, Greco M, Bakker J, Aissaoui N, Cecconi M, et al. ESICM guidelines on circulatory shock and hemodynamic monitoring 2025. *Intensive Care Med*. 2025;51:1971–2012. <https://doi.org/10.1007/s00134-025-0813-7-z>.
- Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med*. 2004;32:1825–31. <https://doi.org/10.1097/01.ccm.0000138558.16257.3f>.
- Ince C. Hemodynamic coherence and the rationale for monitoring the microcirculation. *Crit Care*. 2015;19(Suppl 3):S8. <https://doi.org/10.1186/cc14726>.
- van Genderen ME, Klijn E, Lima A, et al. Microvascular perfusion as a target for fluid resuscitation in experimental circulatory shock. *Crit Care Med*. 2014;42:e96–105. <https://doi.org/10.1097/CCM.0b013e3182a63fbf>.
- Prescott HC, Antonelli M, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2026. *Crit Care Med*. 2026;54:725–812. <https://doi.org/10.1097/CCM.0000000000000705>.
- Franzosi OS, Nunes DSL, Klanovicz TM, et al. Hemodynamic and skin perfusion is associated with successful enteral nutrition therapy in septic shock patients. *Clin Nutr*. 2020;39:3721–9. <https://doi.org/10.1016/j.clnu.2020.03.033>.
- Hernandez G, Carmona P, Ait-Oufella H. Monitoring capillary refill time in septic shock. *Intensive Care Med*. 2024;50:580–2. <https://doi.org/10.1007/s00134-024-07361-3>.
- Shi LJ, Ke SF, Fu LS, Zhu LM, Chen LY, Zhuang YN. Meta-Analysis of the Prognostic Value of Skin Perfusion Parameters in Sepsis Patients: Evidence Integration Based on the Mottling Score, Capillary Refill Time, and Peripheral Perfusion Index. *Shock*. 2026;66:303–14. <https://doi.org/10.1097/SHK.0000000000002885>.
- The ANDROMEDA-SHOCK-2 Investigators for the ANDROMEDA Research Network. Spanish Society of Anesthesiology, Reanimation and Pain Therapy (SEDAR), and Latin American Intensive Care Network (LIVEN). Personalized Hemodynamic Resuscitation Targeting Capillary Refill Time in Early Septic Shock: The ANDROMEDA-SHOCK-2 Randomized Clinical Trial. *JAMA*. 2025;334:1988–99. <https://doi.org/10.1001/jama.2025.20402>.
- Pettit V, Pfortmüller CA, Perner A, Merz TM, Wilkman E, Hästbacka J, et al. Targeted Tissue Perfusion Versus Macrocirculatory-Guided Standard Care in Patients With Septic Shock: A Randomized Clinical Trial-The TARTARE-2S Trial. *Crit Care Med*. 2026;54:24–34. <https://doi.org/10.1097/CCM.00000000000006899>.

25. Fage N, Moretto F, Rosalba D, et al. Effect on capillary refill time of volume expansion and increase of the norepinephrine dose in patients with septic shock. *Crit Care*. 2023;27:429. <https://doi.org/10.1186/s13054-023-04714-0>.
26. Hernández G, Valenzuela ED, Kattan E, et al. Capillary refill time response to a fluid challenge or a vasopressor test: an observational, proof-of-concept study. *Ann Intensive Care*. 2024;14:49. <https://doi.org/10.1186/s13613-024-01275-5>.
27. Morin A, Missri L, Urbina T, et al. Relationship between skin microvascular blood flow and capillary refill time in critically ill patients. *Crit Care*. 2025;29:57. <https://doi.org/10.1186/s13054-025-05285-y>.
28. Shinozaki M, Nakada TA, Saito D, Tomita K, Nomura Y, Nakaguchi T. Cut-Off Value of Capillary Refill Time for Peripheral Circulatory Failure Diagnosis. *Prehosp Disaster Med*. 2023;38:319–25. <https://doi.org/10.1017/S1049023X23005812>.
29. He HW, Liu DW, Long Y, Wang XT. The peripheral perfusion index and transcutaneous oxygen challenge test are predictive of mortality in septic patients after resuscitation. *Crit Care*. 2013;17:R116. <https://doi.org/10.1186/cc12788>.
30. Chi C, Gong H, Yang K, Peng P, Zhang X. Early peripheral perfusion index predicts 28-day outcome in patients with septic shock. *World J Emerg Med*. 2024;15:372–8. <https://doi.org/10.5847/wjemj.1920-8642.2024.081>.
31. Casazzo M, Pisani L, Md Erfan Uddin RA, et al. The Accuracy of the Passive Leg Raising Test Using the Perfusion Index to Identify Preload Responsiveness—A Single Center Study in a Resource-Limited Setting. *Diagnostics (Basel)*. 2025;15:103. <https://doi.org/10.3390/diagnostics15010103>.
32. Hasanin A, Karam N, Mukhtar AM, Habib SF. The ability of pulse oximetry-derived peripheral perfusion index to detect fluid responsiveness in patients with septic shock. *J Anesth*. 2021;35:254–61. <https://doi.org/10.1007/s00504-0-021-02908-w>.
33. Beurton A, Teboul JL, Gavelli F, et al. The effects of passive leg raising may be detected by the plethysmographic oxygen saturation signal in critically ill patients. *Crit Care*. 2019;23:19. <https://doi.org/10.1186/s13054-019-2306-z>.
34. Rasmy I, Mohamed H, Nabil N, et al. Evaluation of Perfusion Index as a Predictor of Vasopressor Requirement in Patients with Severe Sepsis. *Shock*. 2015;44:554–9. <https://doi.org/10.1097/SHK.0000000000000481>.
35. Nahiduzzaman M, Kundu S, Mazumder MK, et al. Role of Perfusion Index as a Predictor of Vasopressor Requirement in Patients With Sepsis. *Cureus*. 2025;17:e100431. <https://doi.org/10.7759/cureus.100431>.
36. Coutrot M, Dudoignon E, Joachim J, Gayat E, Vallée F, Dépret F. Perfusion index: Physical principles, physiological meanings and clinical implications in anaesthesia and critical care. *Anaesth Crit Care Pain Med*. 2021;40:100964. <https://doi.org/10.1016/j.accpm.2021.100964>.
37. Sun X, He H, Xu M, Long Y. Peripheral perfusion index of pulse oximetry in adult patients: a narrative review. *Eur J Med Res*. 2024;29:457. <https://doi.org/10.1186/s40001-024-02048-3>.
38. Okada H, Tanaka M, Yasuda T, et al. The perfusion index is a useful screening tool for peripheral arterial disease. *Heart Vessels*. 2019;34:583–9. <https://doi.org/10.1007/s00380-018-1276-4>.
39. Fine J, Branan KL, Rodriguez AJ, et al. Sources of Inaccuracy in Photoplethysmography for Continuous Cardiovascular Monitoring. *Biosensors (Basel)*. 2021;11:126. <https://doi.org/10.3390/bios11040126>.
40. Hasanin A, Mohamed SAR, El-Adawy A. Evaluation of perfusion index as a tool for pain assessment in critically ill patients. *J Clin Monit Comput*. 2017;31:961–5. <https://doi.org/10.1007/s10877-016-9936-3>.
41. Kang H, Nakae A, Ito H, et al. Effects of sedation on subjective perception of pain intensity and autonomic nervous responses to pain: A preliminary study. *PLoS ONE*. 2017;12:e0183635. <https://doi.org/10.1371/journal.pone.0183635>.
42. Hamunen K, Kontinen V, Hakala E, Tälke P, Paloheimo M, Kalso E. Effect of pain on autonomic nervous system indices derived from photoplethysmography in healthy volunteers. *Br J Anaesth*. 2012;108:838–44. <https://doi.org/10.1093/bja/aes001>.
43. Dumas G, Laviglegrand JR, Joffre J, et al. Mottling score is a strong predictor of 14-day mortality in septic patients whatever vasopressor doses and other tissue perfusion parameters. *Crit Care*. 2019;23:211. <https://doi.org/10.1186/s13054-019-2496-4>.
44. Fage N, Demiselle J, Seegers V, et al. Effects of mean arterial pressure target on mottling and arterial lactate normalization in patients with septic shock: a post hoc analysis of the SEPSISPAM randomized trial. *Ann Intensive Care*. 2022;12:78. <https://doi.org/10.1186/s13613-022-01053-1>.
45. Ban K, Kochi K, Imai K, Okada K, Orihashi K, Sueda T. Novel Doppler technique to assess systemic vascular resistance: the snuffbox technique. *Circ J*. 2005;69:688–94. <https://doi.org/10.1253/circj.69.688>.
46. Wang C, Wang X, Zhang H, Su L, Huang W, Liu D. Association Between Doppler Snuffbox Resistive Index and Tissue Perfusion in Septic Patients. *Shock*. 2020;54:723–30. <https://doi.org/10.1097/SHK.0000000000001547>.
47. Qin Y, Zhu Y, Dai X, Yin W. Critical care ultrasound evaluation of snuff-box artery vascular tension: a prospective observational study between healthy volunteers and intensive care unit patients. *Front Med (Lausanne)*. 2026;13:1722497. <https://doi.org/10.3389/fmed.2026.1722497>.
48. Favaron E, Ince C, Hilty MP, Ergin B, van der Zee P, Uz Z, et al. Capillary Leukocytes, Microaggregates, and the Response to Hypoxemia in the Microcirculation of Coronavirus Disease 2019 Patients. *Crit Care Med*. 2021;49:661–70. <https://doi.org/10.1097/CCM.00000000000004862>.
49. Maiden MJ, Finnis ME, Peake S, McRae S, Delaney A, Bailey M, Bellomo R. Haemoglobin concentration and volume of intravenous fluids in septic shock in the ARISE trial. *Crit Care*. 2018;22:118. <https://doi.org/10.1186/s13054-018-2029-6>.
50. Marcello M, Virzi GM, Marturano D, de Cal M, Marchionna N, Sgarabotto L, et al. The Cytotoxic Effect of Septic Plasma on Healthy RBCs: Is Eryptosis a New Mechanism for Sepsis? *Int J Mol Sci*. 2023;24:14176. <https://doi.org/10.3390/ijms241814176>.
51. Firat IS, Alaçayır Ö, Creutz T, Artmann GM, Damiati S, Artmann AT. A novel AI-coupled flow chamber method quantifying erythrocyte osmotic fragility. *Sci Rep*. 2026;16:7175. <https://doi.org/10.1038/s41598-026-38322-z>.
52. Recktenwald SM, Lopes MGM, Peter S, Hof S, Simionato G, Peikert K, et al. ErySense, a Lab-on-a-Chip-Based Point-of-Care Device to Evaluate Red Blood Cell Flow Properties With Multiple Clinical Applications. *Front Physiol*. 2022;13:884690. <https://doi.org/10.3389/fphys.2022.884690>.
53. Saadat A, Huyke DA, Oyarzun DI, Escobar PV, Øvreide IH, Shaqfeh ESG, et al. A system for the high-throughput measurement of the shear modulus distribution of human red blood cells. *Lab Chip*. 2020;20:2927–36. <https://doi.org/10.1039/d0lc00283f>.
54. Chalkias A, Papagiannakis N, Katsifa K, et al. Characterization of Sublingual Microvascular Tortuosity in Steady-State Physiology and Septic Shock. *Biomedicines*. 2025;13:691. <https://doi.org/10.3390/biomedicines13030691>.
55. Lin CK, Tsai YH, Kao KC, et al. Serum vascular endothelial growth factor affects tissue fluid accumulation and is associated with deteriorating tissue perfusion and oxygenation in severe sepsis: a prospective observational study. *Eur J Med Res*. 2023;28:155. <https://doi.org/10.1186/s40001-023-01119-1>.
56. Lin CK, Leu SW, Tsai YH, et al. Increased tissue water in patients with severe sepsis affects tissue oxygenation measured by near-infrared spectroscopy: a prospective, observational case-control study. *Quant Imaging Med Surg*. 2022;12:4953–67. <https://doi.org/10.21037/qims-22-127>.
57. Eleveld N, Hoedemaekers CWE, van Kaam CR, et al. Near-Infrared Spectroscopy-Derived Dynamic Cerebral Autoregulation in Experimental Human Endotoxemia—An Exploratory Study. *Front Neurol*. 2021;12:695705. <https://doi.org/10.3389/fneur.2021.695705>.
58. Mirsajadi A, Erickson D, Alias S, et al. Microvascular Autoregulation in Skeletal Muscle Using Near-Infrared Spectroscopy and Derivation of Optimal Mean Arterial Pressure in the ICU: Pilot Study and Comparison With Cerebral Near-Infrared Spectroscopy. *Crit Care Explor*. 2024;6:e1111. <https://doi.org/10.1097/CCE.0000000000000111>.
59. Cusack R, Rodríguez A, Cantan B, et al. Albumin Enhances Microvascular Reactivity in Sepsis: Insights from Near-Infrared Spectroscopy and Vascular Occlusion Testing. *J Clin Med*. 2025;14:4982. <https://doi.org/10.3390/jcm14144982>.
60. Cowling N, Woldeyohannes S, Sole Guitart A, Goodwin W. Measurement of Tissue Oximetry in Standing Unsedated and Sedated Horses. *Vet Sci*. 2021;8:202. <https://doi.org/10.3390/vetsci8100202>.
61. Chung J, Ji SH, Jang YE, Kim EH, Lee JH, Kim JT, et al. Evaluation of Different Near-Infrared Spectroscopy Devices for Assessing Tissue Oxygenation with a Vascular Occlusion Test in Healthy Volunteers. *J Vasc Res*. 2020;57:341–7. <https://doi.org/10.1159/000510072>.
62. Seidlitz S, Hölzl K, von Garrel A, et al. AI-powered skin spectral imaging enables instant sepsis diagnosis and outcome prediction in critically ill patients. *Sci Adv*. 2025;11:eadw1968. <https://doi.org/10.1126/sciadvadw1968>.
63. Dietrich M, Özdemir B, Gruneberg D, et al. Hyperspectral Imaging for the Evaluation of Microcirculatory Tissue Oxygenation and Perfusion Quality in Haemorrhagic Shock: A Porcine Study. *Biomedicines*. 2021;9:1829. <https://doi.org/10.3390/biomedicines9121829>.
64. Katzenschlager S, Dietrich M, Peterstorfer F, et al. Implementation of hyperspectral imaging in a trauma resuscitation room: a randomized controlled trial. *Scand J Trauma Resusc Emerg Med*. 2022;30:66. <https://doi.org/10.1186/s13049-022-01057-7>.

65. Kazune S, Caica A, Volceka K, Suba O, Rubins U, Grabovskis A. Relationship of mottling score, skin microcirculatory perfusion indices and biomarkers of endothelial dysfunction in patients with septic shock: an observational study. *Crit Care*. 2019;23:311. <https://doi.org/10.1186/s13054-019-2589-0>.
66. Mongkolpun W, Orbegozo D, Cordeiro CPR, Franco CJS, Vincent JL, Creteur J. Alterations in Skin Blood Flow at the Fingertip Are Related to Mortality in Patients With Circulatory Shock. *Crit Care Med*. 2020;48:443–50. <https://doi.org/10.1097/CCM.0000000000004177>.
67. Morin A, Urbina T, Bernier J, Raia L, Bonny V, Missri L, et al. Passive leg raising and microvascular skin blood flow to predict peripheral tissue perfusion fluid responsiveness. *Crit Care*. 2026;30:80. <https://doi.org/10.1186/s13054-026-05852-x>.
68. Klijn E, van Velzen MH, Lima AP, Bakker J, van Bommel J, Groeneveld AB. Tissue perfusion and oxygenation to monitor fluid responsiveness in critically ill, septic patients after initial resuscitation: a prospective observational study. *J Clin Monit Comput*. 2015;29:707–12. <https://doi.org/10.1007/s10877-014-9653-8>.
69. Hsieh MC, Hu JJ, Lin YR, et al. Improving the early diagnosis and clinical outcomes of shock patients via laser speckle contrast imaging assessment of peripheral hemodynamics. *iScience*. 2024;27:111307. <https://doi.org/10.1016/j.isci.2024.111307>.
70. Ruan Z, Li R, Dong W, Cui Z, Yang H, Ren R. Laser speckle contrast imaging to monitor microcirculation: An effective method to predict outcome in patients with sepsis and septic shock. *Front Bioeng Biotechnol*. 2022;10:1067739. <https://doi.org/10.3389/fbioe.2022.1067739>.
71. Gilbert-Kawai E, Coppel J, Bountziouka V, Ince C, Martin D. Caudwell Xtreme Everest and Xtreme Everest 2 Research Groups. A comparison of the quality of image acquisition between the incident dark field and sidestream dark field video-microscopes. *BMC Med Imaging*. 2016;16:10. <https://doi.org/10.1186/s12880-015-0078-8>.
72. Guerri P, Ince C, Dilken O, et al. Improved Detection of Capillaries in High-Resolution Handheld Vital Microscopy by Use of the MicroTools Advanced Computer Vision Algorithm. *Microcirculation*. 2026;33:e70045. <https://doi.org/10.1111/micc.70045>.
73. Panda A, Revadi G, Sharma JP, et al. On Admission, Microcirculation Abnormality is an Independent Predictor of Sepsis and Sepsis-related Mortality: A Hospital-based Study. *Indian J Crit Care Med*. 2022;26:294–301. <https://doi.org/10.5005/jp-journals-10071-24110>.
74. Holley AD, Dulhunty J, Udy A, et al. Early Sequential Microcirculation Assessment In Shocked Patients as a Predictor of Outcome: A Prospective Observational Cohort Study. *Shock*. 2021;55:581–6. <https://doi.org/10.1097/SHK.0000000000001578>.
75. Belousviene E, Kiudulaite I, Pilvinis V, Pranskunas A. Links between Endothelial Glycocalyx Changes and Microcirculatory Parameters in Septic Patients. *Life (Basel)*. 2021;11:790. <https://doi.org/10.3390/life11080790>.
76. Hilty MP, Akin S, Boerma C, Donati A, Erdem Ö, Giaccaglia P, et al. Automated Algorithm Analysis of Sublingual Microcirculation in an International Multicenter Database Identifies Alterations Associated With Disease and Mechanism of Resuscitation. *Crit Care Med*. 2020;48:e864–75. <https://doi.org/10.1097/CCM.0000000000004491>.
77. Ince C, Ergin B, Montomoli J, Döring M, Boegborn N, van Dam W, et al. The OxyCam: A novel hand-held vital microscope for quantitative measurement of microcirculatory perfusion and oxygenation. *J Intensive Med*. 2026;6:382–90. <https://doi.org/10.1016/j.jointm.2026.01.010>.
78. Watchorn J, Huang D, Bramham K, Hutchings S. Decreased renal cortical perfusion, independent of changes in renal blood flow and sublingual microcirculatory impairment, is associated with the severity of acute kidney injury in patients with septic shock. *Crit Care*. 2022;26:261. <https://doi.org/10.1186/s13054-022-04134-6>.
79. Edinger F, Holtz L, Schmidt G, et al. New Insights into Hepatic and Intestinal Microcirculation and Pulmonary Inflammation in a Model of Septic Shock and Veno-Arterial Extracorporeal Membrane Oxygenation in the Rat. *Int J Mol Sci*. 2024;25:7421. <https://doi.org/10.3390/ijms25137421>.
80. Courtie E, Gilani A, Veenith T, Blanch RJ. Optical coherence tomography angiography as a surrogate marker for end-organ resuscitation in sepsis: A review. *Front Med (Lausanne)*. 2022;9:1023062. <https://doi.org/10.3389/fmed.2022.1023062>.
81. Park JR, Lee B, Lee MJ, Kim K, Oh WY. Visualization of three-dimensional microcirculation of rodents' retina and choroid for studies of critical illness using optical coherence tomography angiography. *Sci Rep*. 2021;11:14302. <https://doi.org/10.1038/s41598-021-93631-9>.
82. Alnawaiseh M, Ertmer C, Seidel L, et al. Feasibility of optical coherence tomography angiography to assess changes in retinal microcirculation in ovine haemorrhagic shock. *Crit Care*. 2018;22:138. <https://doi.org/10.1186/s13054-018-2056-3>.
83. Tang AL, Shen MJ, Zhang GQ. Intestinal microcirculation dysfunction in sepsis: pathophysiology, clinical monitoring, and therapeutic interventions. *World J Emerg Med*. 2022;13:343–8. <https://doi.org/10.5847/wjem.j.1920-8642.2022.031>.
84. Yang R, Zheng T, Xiang H, Liu M, Hu K. Lung single-cell RNA profiling reveals response of pulmonary capillary to sepsis-induced acute lung injury. *Front Immunol*. 2024;15:1308915. <https://doi.org/10.3389/fimmu.2024.1308915>.
85. Fang P, Li S, Lu ZQ, et al. Histone lactylation exacerbates acute lung injury in septic mice by promoting ferroptosis in pulmonary microvascular endothelial cells. *Burns Trauma*. 2025;13:tkaf056. <https://doi.org/10.1093/burnst/tkaf056>.
86. Park I, Kim M, Choe K, et al. Neutrophils disturb pulmonary microcirculation in sepsis-induced acute lung injury. *Eur Respir J*. 2019;53:1800786. <https://doi.org/10.1183/13993003.00786-2018>.
87. Hernandez G, Hunsicker O, de Backer D, et al. Twenty-five years of septic shock hemodynamic resuscitation trials: a conceptual perspective. *Crit Care*. 2026;30:400. <https://doi.org/10.1186/s13054-026-06201-8>.
88. Zuccari S, Damiani E, Domizi R, et al. Changes in Cytokines, Haemodynamics and Microcirculation in Patients with Sepsis/Septic Shock Undergoing Continuous Renal Replacement Therapy and Blood Purification with CytoSorb. *Blood Purif*. 2020;49:107–13. <https://doi.org/10.1159/000502540>.
89. Demailly Z, Modica E, Vitali E, et al. Multimodal assessment of peripheral perfusion in critically ill patients: a pilot study. *Ann Intensive Care*. 2025;15:176. <https://doi.org/10.1186/s13613-025-01585-2>.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.