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Microcirculation Detection Technology and its Application Progress in Septic Shock

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Abstract: With the development of the theory of hemodynamic incoherence, the microcirculation has been found to be of great significance in the occurrence, development, and prognosis of septic shock. The key to multiple organ failure caused by septic shock is microcirculatory dysfunction, and organ failure is closely related to the mortality of septic shock. Therefore, microcirculation assessment has become a key focus in patients with septic shock. This article introduces the concept of microcirculation and the pathophysiology of microcirculatory disorders, reviews the current application status of commonly used clinical microcirculation monitoring indicators and techniques in septic shock, and points out the shortcomings and future prospects of microcirculation monitoring, aiming to provide new perspectives for the practice and scientific research of microcirculation monitoring in septic shock.

Keywords: Septic Shock; Microcirculation Monitoring; Sublingual Microcirculation.

1. Introduction

Septic shock is one of the main diseases treated in intensive care unit (ICU), characterized by high morbidity and high mortality. The NICE guidelines emphasize that rapid identification, assessment, and treatment can improve survival rates and outcomes for patients with septic shock. However, mortality remains high even among patients receiving aggressive early treatment[1][2]. Professor Ince[3] proposed the concept of "hemodynamic coherence," referring to the hemodynamic consistency between the macrocirculation and the microcirculation, which is often lost in septic shock. Even when macrocirculatory hemodynamic parameters are restored, persistent tissue hypoperfusion may still exist, and these persistent changes can lead to organ failure. The dissociation between the macrocirculation and microcirculation necessitates the assessment of end-organ tissue perfusion in patients with septic shock. This need has promoted the use of microcirculation monitoring technology in septic shock.

2. Definition of Microcirculation

The microcirculation is a network of small blood vessels (diameter <100μm) comprising arterioles, capillaries, and venules. This intricate system includes endothelial cells, smooth muscle cells (predominantly located in arterioles), red blood cells (RBCs), white blood cells, and platelets. The microcirculation plays a crucial role in delivering oxygen to tissues, facilitating the exchange of nutrients and waste products, as well as regulating inflammation and coagulation processes. Endothelial cells are pivotal in governing microcirculatory function; they regulate microvascular thrombosis and fibrinolysis, leukocyte adhesion, recruitment and migration, vasodilation, nutrient transport, and capillary permeability. [4].

3. Pathophysiology of Microcirculatory Dysfunction in Septic Shock

The essence of normal microcirculation lies in a perfused capillary network, which is capable of maintaining microcirculatory flow independently of fluctuations in systemic blood pressure through the mechanism of autoregulation. Vascular integrity is influenced by the interactions between endothelial cells and components such as the extracellular matrix, glycocalyx, and supporting cells. In patients experiencing septic shock, infection triggers a dysregulated host immune response that releases an abundance of endogenous inflammatory mediators. This cascade damages endothelial cells, leading to a loss of vascular autonomous rhythmic contraction and relaxation, as well as abnormal distribution of blood flow. Furthermore, detachment of the glycocalyx alters the colloid osmotic gradient between the vascular lumen and the protein-rich region safeguarded by this layer. Consequently, this results in increased capillary leakage along with enhanced adhesion and aggregation of platelets and neutrophils, ultimately forming microthrombi. Such processes exacerbate microcirculatory dysfunction and can trigger disseminated intravascular coagulation (DIC), culminating in microcirculatory failure and multi-organ dysfunction. These alterations manifest primarily in two aspects. The first aspect encompasses histological changes characterized by reduced blood flow density, weakened or stagnant circulation patterns, vascular endothelial injury alongside a procoagulant state that is anti-fibrinolytic and pro-adhesive; additionally observed are formations of microthrombi, capillary leakage phenomena, leukocyte rolling behavior, red blood cell rouleaux formation, all contributing to inadequate tissue perfusion. The second aspect highlights how these morphological changes disrupt overall microcirculatory function—impairing oxygen delivery while hindering nutrient transport as well as carbon dioxide removal along with metabolic waste clearance. This culminates in heterogeneous blood flow distribution where regions exhibiting adequate perfusion coexist with non-

perfused zones—a hallmark characteristic associated with septic shock's regional manifestations[5][6][7][8].

4. Microcirculation Monitoring

Typically, the hemodynamic indicators used for resuscitation in patients experiencing septic shock are derived from macrocirculatory hemodynamic parameters, including heart rate, mean arterial pressure, and central venous pressure. However, due to the heterogeneous nature of blood flow distribution, these macro-circulatory parameters may present as favorable even when microcirculatory impairments persist, which can ultimately lead to organ failure. It is important to note that microcirculation cannot be accurately predicted through systemic hemodynamic assessments and therefore remains undetectable by conventional hemodynamic tools. Currently, methods for monitoring microcirculation can be categorized into three distinct approaches: indirect assessment via clinical manifestations, direct visualization techniques, and ultrasound-based evaluations, [9], as illustrated in Table 1.

Table 1. Common Microcirculation Detection Methods

Category	Name
Indirect Assessment via Clinical Signs	Central Venous Oxygen Saturation ($ScvO_2$) or Mixed Venous Oxygen Saturation (SvO_2)
	Venous-to-Arterial Carbon Dioxide Difference (pCO_2 gap)
	Blood Lactate
	Capillary Refill Time (CRT)
	Skin Mottling Score
	Peripheral Perfusion Index (PPI)
	Urine Output
	Level of Consciousness and Mental Status
Direct Monitoring via Visualization	Orthogonal Polarization Spectral Imaging (OPS)
	Sidestream Dark Field Imaging (SDF)
	Incident Dark Field Imaging (IDF)
	Near-Infrared Spectroscopy (NIRS)
	Hyperspectral Imaging (HSI)
Ultrasound-Based Assessment	Contrast-Enhanced Ultrasound (CEUS)
	Echocardiography
	Doppler Ultrasound of Various Organs

4.1. Indirect Assessment of Microcirculation via Clinical Signs

Clinical manifestations can be broadly defined as indirect assessments of tissue oxygenation, serving as surrogate markers for microcirculatory function. Examples include central venous oxygen saturation ($ScvO_2$), mixed venous oxygen saturation (SvO_2), and the partial pressure of carbon dioxide gap (pCO_2-gap). These parameters offer valuable insights into tissue perfusion, oxygen delivery, and oxygen consumption.

Clinically, three primary assessment windows are utilized: the skin (evaluated through temperature gradient, capillary refill time, and mottled appearance), kidneys (assessed via urine output), and brain (monitored through consciousness and mental status). The skin is the organ with the highest blood flow in the human body; consequently, peripheral skin perfusion is typically among the first to be affected during pathological states and also one of the last to recover. Therefore, skin can serve as an indirect monitor of microcirculation, with its perfusion status reflected by variations in temperature gradient, capillary refill time, and signs of mottling [10][11].

4.1.1. Skin Mottling Score:

Mottling is a distinctive discoloration of the skin that occurs as a result of reduced blood flow, and it is regarded as an important indicator of shock. Evaluating the mottling score—based on the extent of mottled areas observed in the distal limbs during episodes of shock—can serve as a predictive tool for assessing the prognosis of patients experiencing shock. However, it is essential to note that this assessment can be significantly influenced by factors such as ethnicity and skin color[12][13] Multiple studies[14][15] have demonstrated that the mottling score functions as a reliable semi-quantitative instrument, aiding in the identification of critically ill patients with poor prognoses while also facilitating monitoring changes throughout resuscitation efforts.

4.1.2. Capillary Refill Time (CRT):

CRT is an essential tool for evaluating the severity of acute illness. In intensive care units, Shirley Eduardo et al. reported that assessing prolonged capillary refill time (CRT) (>3 seconds) and adjusting resuscitation strategies accordingly can enhance patient outcomes[15][16].In the ANDROMEDA-SHOCK tria[17], CRT was validated as a novel resuscitation target, demonstrating superiority to lactate in several aspects. It is important to note that CRT may be influenced by various factors, including environmental conditions, age, and compression intensity; thus, standardized measurement practices are necessary. Overall, when utilized as a qualitative variable (indicating the presence or absence of prolongation), CRT serves as a reliable triage tool that swiftly identifies critically ill patients at risk through positive results.

Renal perfusion is primarily monitored through changes in urine output, while cerebral perfusion can be assessed by observing levels of consciousness and mental status. The brain exhibits minimal tolerance to hypoxia; consequently, alterations in mental status and consciousness often manifest early during episodes of reduced perfusion.

4.2. Direct Monitoring via Visualization Techniques

With the continuous advancement of technology, visual instruments for monitoring microcirculation are becoming increasingly accessible. Handheld electron microscopes are being utilized in clinical settings, accompanied by ongoing technical enhancements. Furthermore, emerging monitoring techniques such as laser Doppler imaging and near-infrared spectroscopy imaging are gaining traction. These technological innovations facilitate direct observation of microcirculatory changes in patients experiencing septic shock.

4.2.1. Orthogonal Polarization Spectral (OPS), Sidestream Dark Field (SDF), and Incident Dark Field (IDF) Imaging

Multiple studies have demonstrated[18] that sublingual mucosal microcirculation and intestinal mucosal microcirculation exhibit a strong correlation with the overall

circulation of patients, enabling non-invasive assessment. Consequently, current efforts in microcirculation detection predominantly concentrate on the evaluation of sublingual mucosal microcirculation.

Commonly utilized sublingual microcirculation parameters encompass Total Vessel Density of small vessels (TVD), Perfused Vessel Density of small vessels (PVD), Proportion of Perfused Vessels among small vessels (PPV), and Microvascular Flow Index (MFI)[19][20]. Published studies[21] have rigorously validated microcirculation as a crucial early warning indicator for sepsis. Multiple investigations examining sublingual microcirculatory parameters in critically ill patients experiencing septic shock[22][23] demonstrated that levels of sublingual microcirculation—including PVD, PPV, MFI, and TVD—were significantly diminished in septic shock patients compared to those with uncomplicated sepsis. This finding suggests that alterations in sublingual microcirculation are closely associated with patient prognosis, thereby enhancing the identification and assessment of disease progression in individuals suffering from septic shock.

In a meta-analysis involving 25 articles and 1,750 subjects focused on sublingual microcirculation and its prognostic implications for sepsis[24], the predictive capability of the PPV parameter regarding sepsis-related mortality was evaluated through summary receiver operating characteristic (SROC) curves, pooled sensitivity analyses, and pooled specificity assessments. The analysis concluded that sublingual microcirculation was notably poorer in non-survivors and patients with severe sepsis when contrasted with survivors and those exhibiting non-severe sepsis. Consequently, PPV demonstrates substantial predictive value concerning mortality outcomes in patients afflicted by sepsis.

However, monitoring of sublingual microcirculation also presents certain limitations. 1) The acquired microcirculation images only capture the state at the moment of monitoring and do not allow for dynamic observation of changes in microcirculation; 2) While sublingual monitoring provides insights into microcirculation under non-invasive conditions, the reliability of the sublingual mucosa as a representative window for vital organ microcirculation requires further investigation; 3) Achieving high-quality image acquisition can be somewhat challenging, and image quality significantly impacts statistical outcomes; 4) Even when disturbances in microcirculation are identified, there is a lack of specific therapeutic interventions aimed at "micro-hemodynamic" resuscitation.[25][26].

Currently, sublingual microcirculation is often used in combination with ultrasound or blood indicators for assessment. A study involving 80 patients on the application effect of a sublingual microcirculation imaging system combined with ultrasound in volume assessment of septic shock[27] concluded that the combination guided volume assessment in septic shock patients, improved lactate levels, oxygen levels, organ function status, promoted patient recovery, and reduced mortality, with effects superior to either method used alone.

4.2.2. Near-Infrared Spectroscopy (NIRS)

Near-infrared spectroscopy (NIRS) leverages the attenuation of invisible wavelength light by both oxygenated and deoxygenated hemoglobin. Operating within the wavelength range of 700-1000 nm, clinically utilized wavelengths typically fall between 700-850 nm. NIRS offers a non-invasive method for continuous assessment of tissue oxygen saturation (StO_2), thereby providing an indirect evaluation of microcirculatory function. One study[28] indicated that NIRS-derived StO_2 is associated with organ failure and correlates with outcomes in septic shock. While NIRS primarily measures tissue oxygen saturation, it does not reflect temporal changes in microvascular hemoglobin content (MHC). Variations in MHC are intended to align oxygen supply with demand. In a recent experimen[29], perfusion was assessed in the quadriceps, biceps, and/or deltoid muscles by monitoring changes in optical density over time at isosbestic wavelengths for hemoglobin (798 nm). Continuous wavelet transform was applied to the hemoglobin signal to delineate frequency ranges corresponding to physiological oscillations within the cardiovascular system. This methodology enables NIRS to continuously measure MHC in intensive care units (ICUs) and capture dynamic alterations in hemoglobin distribution within microcirculation. Currently, large-scale experiments are underway to validate this novel hemodynamic parameter's utility in diagnosing microcirculatory dysfunction and monitoring peripheral perfusion effectively.

4.2.3. Hyperspectral Imaging (HSI)

Hyperspectral imaging (HSI) is a novel non-invasive optical technology capable of bedside identification of skin microcirculation changes and biochemical tissue analysis. HSI is currently mainly used in surgery and the perioperative period[30], while data on HSI technology for microcirculation diagnosis and hemodynamic therapy in critically ill patients are limited^[31]^. Preliminary experiments have demonstrated the feasibility of using the TIVITA® Tissue system (Diaspective Vision GmbH, Am Salzhaff, Germany) for HSI diagnosis, which can detect clinically relevant skin microcirculation changes in critically ill patients with sepsis and major abdominal surgery[31][32]. The TIVITA® Tissue system provides non-invasive HSI for qualitative and quantitative bedside microcirculation assessment[33]. Furthermore, Dietrich et al., in a porcine hemorrhagic shock model study, showed that HSI could detect dynamic changes in tissue oxygenation and perfusion quality. In this way, the effectiveness of resuscitation can be assessed, and negative effects of fluid and vasoactive drug therapy can be identified[34].

Visualization tools significantly enhance our understanding of microcirculatory parameters. However, their clinical adoption remains limited due to factors such as instrument size, cost, and the requisite level of operator expertise. While these tools are available in some large hospitals, they are predominantly utilized in laboratory settings or extensive clinical trials. Nonetheless, the importance of visual microcirculatory monitoring and the interpretation of its parameters in dynamic assessments merits considerable attention. With ongoing technological advancements, it is anticipated that visualization devices will become increasingly prevalent in clinical environments.

4.3. Ultrasound-Based Assessment

The microcirculation is the terminal part of the vascular system and also a component of tissues and organs. Monitoring the microcirculation also means monitoring organ perfusion. In 2020, Corradi etal.[35] proposed an ultrasound-based approach to assess organ perfusion in critically ill patients. Echocardiography is widely used to diagnose and monitor cardiac dysfunction and shock in general, by monitoring the macrocirculation and fluid responsiveness,

thereby estimating overall perfusion. However, the therapeutic goal for circulatory shock is to achieve and maintain adequate end-organ perfusion. The information obtained from echocardiography is partial and cannot accurately infer organ perfusion. Contrast-Enhanced Ultrasound (CEUS) is an emerging imaging technique in the field of critical care, using highly echogenic but inert microbubbles to delineate microvascular perfusion areas within organs. For ICU patients, CEUS can quantitatively assess changes in renal microcirculatory blood flow. In an experiment involving 50 patients with septic shock[36], assessment of renal cortical perfusion found that renal cortical hypoperfusion is a persistent feature in critically ill septic patients who develop acute kidney injury. Cortical hypoperfusion appeared unrelated to changes in sublingual microcirculation, suggesting the possibility of a specific renal pathogenesis suitable for future therapeutic intervention.

5. Treatment Targeting Microcirculatory Dysfunction:

The primary objective of shock resuscitation is to restore normal tissue perfusion and oxygenation. Consequently, traditional approaches that focus solely on correcting blood pressure and cardiac output may not adequately address tissue hypoxia and hypoperfusion. As a result, the management and treatment of microcirculation in septic shock frequently employ individualized resuscitation strategies aimed at stabilizing the microcirculatory environment as promptly as possible, thereby improving organ ischemia and hypoxia.

Fluid resuscitation can improve the microcirculation in the early stages of septic shock, but this improvement is not significant in the later stages. Simultaneously, the optimal amount of fluid to administer remains difficult to determine, so personalized strategies are more favored. The 2021 Surviving Sepsis Campaign (SSC) guidelines[37] recommend administering at least 30 mL/kg of intravenous crystalloids within the first 3 hours after resuscitation. This recommendation has now been moved from a strong to a weak recommendation (use with caution in patients with heart failure and renal disease). The effects of vasoactive drugs on the microcirculation also vary; they can improve microcirculation in some patients. Current guidelines[37] recommend initiating peripheral vasopressor therapy to restore mean arterial pressure rather than delaying treatment. Norepinephrine remains the vasopressor of first choice. If norepinephrine does not achieve the desired therapeutic effect, vasopressin can be added to reduce the dose of norepinephrine.

New therapies to restore the microcirculation are also being actively developed. Since the nitric oxide (NO) pathway plays a crucial role in controlling microvascular perfusion[38], its regulatory pathways are among the earliest explored. However, studies testing the utility of direct or indirect nitric oxide enhancement in patients with septic shock have not shown improvements in sublingual microcirculation or organ dysfunction[39].

Additionally, modulating the arachidonic acid pathway is a future direction. Trials are currently underway to evaluate the effect of prostaglandins on vasodilation. Legrand et al.[40][41] are currently conducting a multicenter double-blind study testing iloprost (a prostacyclin analogue with vasodilatory and antithrombotic properties) in septic shock with persistent microcirculatory disorders (i.e., skin mottling or increased capillary refill time).

Ascorbic acid and several anticoagulants are also quite promising. In sepsis patients, ascorbic acid can improve microvascular perfusion. Due to the complex interaction between endothelial function, coagulation, and inflammation, various anticoagulants have been tested. Activated protein C was the most promising drug, showing significant improvement in microvascular perfusion in both experimental and clinical sepsis[42][43].

6. Discussion and Outlook

The pathophysiological mechanisms of septic shock are complex, with rapid onset, severe disease progression, and high rates of disability and mortality. Approaches focused solely on restoring systemic circulation goals no longer meet current clinical research and treatment demands. Targeted microcirculation monitoring methods and indicators represent the primary direction for future development, though consensus on monitoring and treatment strategies remains elusive. Despite numerous proposed therapeutic interventions, clinically effective, accurate, and non-invasive microcirculation monitoring tools for septic shock remain lacking. Future research should focus on exploring microcirculatory monitoring and related indicators for vital organs under non-invasive or minimally invasive conditions, developing bedside continuous microcirculation monitoring technologies. Concurrently, treatment approaches should integrate macrocirculatory and microcirculatory optimization to provide clinicians with the most comprehensive understanding of patient physiology, thereby enabling clear therapeutic pathways. Utilizing artificial intelligence to establish algorithms can assist clinicians in making treatment decisions based on microcirculatory changes. In clinical practice, healthcare provider training must be enhanced to ensure early identification of septic shock patients and proper understanding and application of microcirculation monitoring and management techniques, thereby further improving the prognosis of septic shock.

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