Review Article

Blood gas analysis as a surrogate for microhemodynamic monitoring in sepsis

Jingyi Wang[1,2], Li Weng[2], Jun Xu[1], Bin Du[2]

[1] *Emergency Department, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100730, China*

[2] *Medical Intensive Care Unit, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100730, China*

Corresponding Authors: *Jun Xu, Email: xujunfree@126.com; Bin Du, Email: dubin98@gmail.com*

BACKGROUND: Emergency patients with sepsis or septic shock are at high risk of death. Despite increasing attention to microhemodynamics, the clinical use of advanced microcirculatory assessment is limited due to its shortcomings. Since blood gas analysis is a widely used technique reflecting global oxygen supply and consumption, it may serve as a surrogate for microcirculation monitoring in septic treatment.

METHODS: We performed a search using PubMed, Web of Science, and Google scholar. The studies and reviews that were most relevant to septic microcirculatory dysfunctions and blood gas parameters were identified and included.

RESULTS: Based on the pathophysiology of oxygen metabolism, the included articles provided a general overview of employing blood gas analysis and its derived set of indicators for microhemodynamic monitoring in septic care. Notwithstanding flaws, several parameters are linked to changes in the microcirculation. A comprehensive interpretation of blood gas parameters can be used in order to achieve hemodynamic optimization in septic patients.

CONCLUSION: Blood gas analysis in combination with clinical performance is a reliable alternative for microcirculatory assessments. A deep understanding of oxygen metabolism in septic settings may help emergency physicians to better use blood gas analysis in the evaluation and treatment of sepsis and septic shock.

KEYWORDS: Sepsis; Microcirculation; Blood gas analysis; Emergency service

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INTRODUCTION

Sepsis is defined as life-threatening tissue hypoperfusion and organ dysfunction caused by a dysregulated host response to infection.[1] Sepsis and septic shock are major health problems in the emergency department (ED), and early recognition and interventions are essential for improving patient outcomes. Hemodynamics, comprising macrocirculation and microcirculation, is the foundation of septic resuscitation. Although ED physicians routinely depend on macrocirculation, microcirculation has recently been proposed to play a key role in the pathogenic mechanisms of sepsis-induced organ dysfunction.[2,3] Previous studies suggested that the occurrence of microcirculatory abnormalities in early sepsis, despite well-preserved macrocirculation, might result in multi-organ failure and poor outcomes.[2,3] Microcirculation perfusion can be measured by parameters including perfused vessel density (PVD), the proportion of perfused vessels (PPV), microcirculatory flow index (MFI), and heterogeneity index. PVD, PPV, and MFI comprehensively describe the functional perfusion of microvessels, while the heterogeneity index quantifies the heterogeneity of perfusion.[4] However, the availability of these advanced microcirculatory measures in clinical settings is limited because the techniques are difficult to use and lack uniformly defined endpoints.[5] Viable practical clinical surrogates are therefore needed, particularly for rapid

assessment and decision-making in the ED. Blood gas analysis and its derived indicators, linked to systemic oxygen (O_2) metabolism, may reflect the relationship between tissue O_2 delivery (DO_2) and consumption (VO_2), and may thus provide alternative tools for microcirculatory assessment and for hemodynamics optimization during septic resuscitation.

Based on the pathophysiological mechanisms and the current findings, this review provides an overview of the use of blood gas analysis to assess microcirculatory status, detect early tissue hypoxia, and optimize hemodynamic treatment in sepsis.

METHODS

We performed a search using PubMed, Web of Science, and Google scholar. The studies and reviews that were most relevant to septic microcirculatory dysfunctions and blood gas parameters were identified and included. Based on the pathophysiology of oxygen metabolism, the included articles provided a general overview of employing blood gas analysis and its derived set of indicators for microhemodynamic monitoring in septic care.

RESULTS

Circulatory pathophysiology of sepsis

The principal role of the circulation is to deliver O_2 and nutrients to peripheral tissues and remove metabolites. Circulatory dysfunction is common in sepsis, and its current management mainly aims to improve macrohemodynamic indicators, such as the mean arterial pressure, central venous pressure, and cardiac index.[1,6] However, abnormal microcirculation might persist despite improved or restored macrohemodynamic indicators,[7-9] highlighting a loss of coherence between the macrocirculation and microcirculation.[10] The microcirculation comprises a network of O_2 exchange between peripheral tissues and blood circulation, and it is the main site for tissue oxygenation. When sepsis occurs, the microcirculatory network is disrupted by factors such as endothelial glycocalyx dysfunction, activation of microthrombosis and leukocytes, increased microvascular rigidity, and pathologic formation of arteriovenous shunts,[11,12] leading to impaired blood flow and deteriorated heterogeneity of tissue perfusion (Figure 1). Consistently sluggish or absent blood flow will compromise DO_2 in related tissues or disrupt the balance between DO_2 and VO_2.

The DO_2/VO_2 balance is the cornerstone of hemodynamic stability. DO_2 represents the arterial supply of O_2 to tissues (DO_2=Q × CaO_2, where Q is blood flow and CaO_2 is arterial O_2 content), while VO_2 represents O_2 removed from arterial blood for use by the tissues (VO_2=Q × [CaO_2−CvO_2], where CvO_2 is venous O_2 content [Supplementary Figure S1]). Both DO_2 and VO_2 are affected by multiple factors, resulting in a dynamic balance (Figure 2 and Supplementary Table S1). Under normal circumstances, aerobic cell metabolism only requires a small fraction of DO_2 (Figure 2A). Under conditions of an inadequate DO_2/VO_2 (decreased DO_2, and/or increased VO_2), VO_2 initially remains satisfied as O_2 extraction increases adaptively, known as DO_2/VO_2 independency. At this stage, aerobic metabolism is preserved, but CvO_2 decreases (Figure 2B). However, if the inadequacy persists, the compensatory O_2 extraction

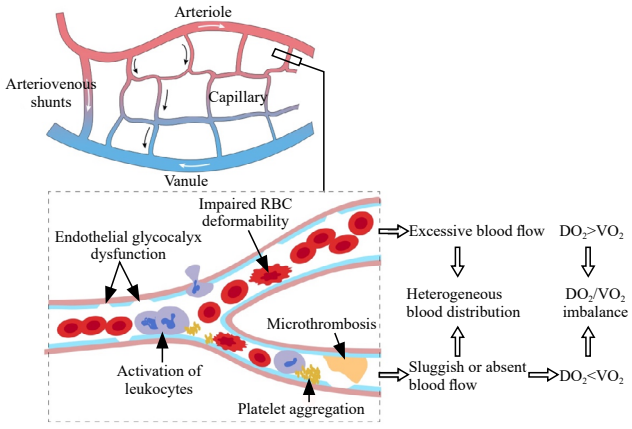

Figure 1. Microcirculatory alterations in sepsis. RBC: red blood cell; DO_2: O_2 delivery; VO_2: O_2 consumption.

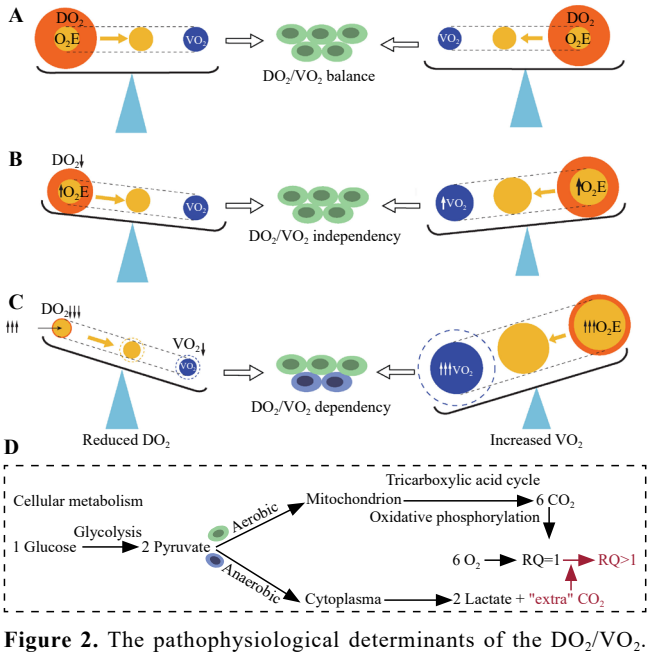

Figure 2. The pathophysiological determinants of the DO_2/VO_2. A: DO_2/VO_2 balance; B: DO_2/VO_2 independency; C: DO_2/VO_2 dependency; D: cellular metabolism. DO_2: O_2 delivery; VO_2: O_2 consumption; O_2E: O_2 extraction; RQ: respiratory quotient.

process approaches its maximum capacity, and DO_2 fails to meet the demand of tissue oxygenation, leading to DO_2/VO_2 dependency and O_2 debt.[13] At this point, aerobic metabolism switches to anaerobic metabolism (Figure 2C), resulting in further reduction of CvO_2, elevated lactate levels, and abnormal carbon dioxide (CO_2)-related parameters (Figure 2D).

As the post-metabolism part of the circulation, venous blood includes the O_2 left after cellular metabolism, thus providing valuable information on tissue oxygenation. "Venous blood" in this review refers exclusively to mixed or central venous blood. Mixed venous blood is the blood that travels through all the systemic capillary beds and returns to the right ventricle and is acknowledged to reflect global O_2 metabolism by combining venous blood from the superior vena cava (SVC) and inferior vena cava. However, measurement of mixed venous parameters requires a pulmonary artery catheter, which is invasive and not feasible in all patients.[14] Central venous blood includes blood that returns via the SVC and thus only represents the O_2 metabolism of the upper body; [15] however, it is easier to obtain via a central venous catheter (CVC) and may thus be used as a substitute for mixed venous blood. Notably, despite controversy regarding the ability to substitute mixed and central venous blood (e.g., venous O_2 saturation [SvO_2]);[16-19] when the CVC tip is close to the right atrium, central SvO_2 ($ScvO_2$) was an excellent estimate of mixed SvO_2 ($SmvO_2$), with a difference between the two parameters of about 1%.[19] Central venous blood is thus an acceptable substitute for mixed venous blood when the placement of the CVC is appropriate.

Parameters of DO_2/VO_2 independency

Despite a shortage of DO_2 relative to VO_2 during DO_2/VO_2 independency, tissue oxygenation is nevertheless satisfactory due to improved O_2 extraction. Early signs of hypoxia include a decrease in venous blood O_2 content and an increase in O_2 extraction capability.

Venous O_2 saturation (SvO_2)

SvO_2 reflects the O_2 content in venous blood after cellular metabolism. SvO_2 varies among organs, from up to 90% in the kidney to 40% in the myocardium, depending on the O_2 demands of the tissues.[15] Under normal conditions, $SmvO_2$ is about 75%, while $ScvO_2$ is usually 2%–3% lower, because the lower body consumes less O_2 than the upper body.[15] In contrast, $ScvO_2$ will exceed $SmvO_2$ during shock as blood is redistributed from the hepatosplanchnic region to support coronary or cerebral circulation.[20] Despite the lack of consensus regarding the best cutoff value for SvO_2 in resuscitation, $SmvO_2$ ≥65% or $ScvO_2$ ≥70% is still advocated in clinical practice.[21,22]

Several studies have investigated the relationship between SvO_2 and microcirculatory perfusion. In septic patients, an increase in $SmvO_2$ following norepinephrine treatment was paralleled by improvements in PVD and MFI.[23] A recent meta-analysis showed that initiation of blood cell transfusion by lower $SmvO_2$ rather than lower hemoglobin level maximized the benefit to microcirculatory blood flow in septic patients,[24] suggesting that $SmvO_2$ may be a reliable index of microcirculatory perfusion. However, SvO_2 reflects cellular oxygenation indirectly, by measuring the remaining O_2 content in venous blood. It thus provides little information on the complex O_2 metabolism within peripheral tissues. Several studies showed that higher $ScvO_2$ was also linked to increased mortality.[25,26] High SvO_2 is probably caused by impaired O_2 utilization or pathological shunting in sepsis.[25,27,28] Aggressive resuscitation with fluids, vasopressors, and oxygen therapies may also result in a prompt rise in DO_2 and a high SvO_2.[29,30] Hence, SvO_2 should be interpreted with caution, especially for high values.

O_2 extraction rate (O_2ER)

An increased O_2ER, calculated as $[CaO_2-CvO_2]/CaO_2$), is typically a marker of reduced DO_2 during early-stage shock, with a normal value of 25%–30%.[31] O_2ER increases in hypoxic settings to match the metabolic demand, with an upper limit of 40%–50%.[32]

O_2ER is almost equal to $1-SvO_2$ when arterial O_2 saturation (SaO_2) is 100%. However, because of the non-negligible effect of SaO_2, SvO_2 is not considered a good estimator of O_2ER in hypoxic individuals. Measuring O_2ER thus compensates for SvO_2 deficits. Negative correlations between increased systemic O_2ER and deteriorating microcirculatory parameters including PPV, PVD, and MFI were observed in an animal model of septic shock.[33] In contrast, another animal experiment produced the opposite conclusion, showing no correlation between systemic O_2ER and these microcirculatory indicators, despite parallel variations in mesenteric O_2ER and jejunal-villi PPV and mesenteric lactate.[33,34] This discrepancy was likely caused by differences in microcirculation perfusion between the two studies.[34] Further research is required to determine the reliability of using O_2ER to identify microcirculatory abnormalities.

Parameters of DO_2/VO_2 dependency

Anaerobic metabolism manifests at the point of DO_2/VO_2 dependency, when DO_2 is severely compromised but O_2ER has reached its upper limit. Anaerobic metabolism products, including lactate and abnormal respiratory quotient (RQ), serve as indicators of persistent hypoxia.

Lactate

Lactate is the end-product of anaerobic metabolism. The generation and clearance of lactate are equal under normal circumstances, maintaining a serum lactate level of around 2 mmol/L.[35] Excess lactate generated by increased anaerobic glycolysis is the primary cause of hyperlactatemia in hypoxic environments, while sepsis-induced aerobic glycolysis is also a significant source of lactate, independent of tissue hypoxia.[36] The underlying mechanisms include epinephrine-dependent activation of Na^+-K^+-adenosine triphosphatase and inflammatory cytokine-dependent stimulation of cellular glucose uptake, both of which stimulate lactate production in aerobic glycolysis.[37,38] Hyperlactatemia in sepsis is therefore assumed to arise from various sources, not solely due to hypoxia/hypoperfusion.

Despite its complicated production processes, lactate is widely applied in clinical research and practice. Ospina-Tascon et al[39] discovered that decreased lactate following fluid delivery was consistent with improvements in PVD and PPV, with no corresponding changes in cardiac index or mean arterial pressure. A similar correlation between lactate and microcirculation perfusion was reported in septic patients without hypotension.[40] However, clinicians should remain aware that several distinct factors contribute to hyperlactatemia, and lactate only accurately reflects changes in the microcirculation for hyperlactatemia mainly caused by hypoperfusion.[41]

Respiratory quotient (*RQ*)

RQ is the volume of CO_2 (VCO_2) released divided by the volume of O_2 (VO_2) consumed during metabolism (normal range 0.7–1.0, depending on the types of substrates oxidized).[42] Under hypoxic conditions, RQ is >1.0 because of the anaerobic CO_2 production. The underlying processes include increased buffering between bicarbonate and H^+ as a result of lactate accumulation and accelerated high-energy phosphate hydrolysis, and extra CO_2 produced by decarboxylation of intermediate substrates such as α-ketoglutarate during incomplete oxidation.[43]

RQ measurement currently requires indirect calorimetry, which is costly and vulnerable to patient and environmental conditions, and equipment, thus limiting its practical utility in critical patients.[44,45] According to the Fick equation, VCO_2 equals the product of blood flow and the difference between venous and arterial CO_2 content ($Cv\text{-}aCO_2$). Likewise, VO_2 is the product of blood flow and the difference between arterial and venous O_2 content ($Ca\text{-}vO_2$). RQ can thus be determined using the $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio. Moreover, given the quasi-linear curve between CO_2 content and CO_2 tension (PCO_2) within a physiological range (Supplementary Figure S2),[46] the easily accessible $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio is considered a surrogate for the $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio.

The $Cv\text{-}aCO_2/Ca\text{-}vO_2$ (or $Pv\text{-}aCO_2/Ca\text{-}vO_2$) ratio has attracted increasing attention recently. Several studies indicated that an elevated ratio (>1.4) is associated with inadequate lactate clearance, progressive organ dysfunction, and a higher risk of mortality.[47-50] However, the $Cv\text{-}aCO_2/Ca\text{-}vO_2$ (or $Pv\text{-}aCO_2/Ca\text{-}vO_2$) ratio was not in excellent agreement with changes at the micro level. An early trial found only a weak correlation between an increased $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio and a decreased PPV,[51] while another study found no association between the $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio and peripheral perfusion.[52] However, they pointed out that, even in patients with a higher peripheral perfusion index, those with poor lactate clearance after resuscitation had an obviously elevated $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio.[52] These results suggested that anaerobic metabolism persisted even as perfusion improved, possibly related to impaired O_2 utilization. Taken together, the $Cv\text{-}aCO_2/Ca\text{-}vO_2$ (or $Pv\text{-}aCO_2/Ca\text{-}vO_2$) ratio is an indicator of tissue O_2 metabolism, instead of merely microcirculatory perfusion. An increased ratio may be useful for discriminating the inconsistency between tissue perfusion and O_2 utilization.

Parameters of tissue hypoxia mechanisms

Hypoxia develops when DO_2 is inadequate for VO_2. DO_2 characterizes the mechanisms of hypoxia as hypoxic (deficient O_2 supply), anemic (low hemoglobin level), and circulatory (reduced blood flow). Compared with hypoxic and anemic hypoxia, which can be directly identified by variables like SaO_2, PaO_2, and hemoglobin, the assessment of circulatory hypoxia is more challenging. Intriguingly, $Pv\text{-}aCO_2$ has been suggested as a potential marker for changes in microcirculation.

$Pv\text{-}aCO_2$ represents the difference between venous and arterial CO_2 tensions, and has been confirmed as a valid indicator of cardiac output.[53-55] In physiological settings, sufficient blood flow carries CO_2 to the alveoli where it is exhaled from the body. In contrast, pathologically reduced blood flow results in the accumulation of tissue CO_2, widening the CO_2 gap between arterial and venous blood, in accordance with the Fick equation: $Pv\text{-}aCO_2=(k\times VCO_{2tissue})/\text{blood flow}_{tissue}$, where k is a constant determining the relationship between CO_2 tension and content (Supplementary Figure S2), and $VCO_{2tissue}$ is the amount of CO_2 generated by the tissue.

Because k increases with the decreased blood flow, the inverse relationship between $Pv\text{-}aCO_2$ and blood flow is curvilinear; when blood flow is reduced to the lowest range, $Pv\text{-}aCO_2$ will increase remarkably.

[56] However, the curvilinear relationship between Pv-aCO_2 and blood flow is easily disturbed in pathological processes, because *k* is affected by various factors.[48] The theory of CO_2 stagnation during decreased blood flow compensates for the Fick equation.[56, 57] When both afferent and efferent blood flows in the capillary network are arrested, the increased anaerobic production of CO_2 from hypoxic tissues leads to increased Pv-aCO_2. In addition, a different theory stated that when blood flow was lowered, $PaCO_2$ also fell to adjust to the increased ventilation-perfusion ratio, further raising the Pv-aCO_2.[58] These theories may account for the negative correlation between blood flow and Pv-aCO_2.

The ability of Pv-aCO_2 to monitor microcirculatory dysregulation has been studied extensively. A Pv-aCO_2 >6 mmHg was associated to microcirculatory hypoperfusion in septic patients, manifested by reduced PPV, lower functional capillary density, and higher heterogeneity of microvascular blood flow.[51] Despite a $ScvO_2$ ≥70%, a Pv-aCO_2 ≥8 mmHg in post-cardiac surgery patients was linked to hepatosplanchnic hypoperfusion, as evidenced by a significantly lower plasma clearance rate of indocyanine green.[59] In addition, in patients who achieved global hemodynamic goals, Pv-aCO_2 still fluctuated with microcirculatory perfusion while there was no association between Pv-aCO_2 and cardiac output, demonstrating that Pv-aCO_2 may be a reliable indicator reflecting microcirculatory flow alterations.[51]

DISCUSSION

This review considers the application of blood gas parameters in microcirculatory monitoring based on the dynamic evolution of tissue hypoxia: (1) reduced SvO_2 and increased O_2ER indicate hypoxia; (2) hyperlactatemia and an elevated Cv-aCO_2/Ca-vO_2 (or Pv-aCO_2/Ca-vO_2) ratio are signs of deteriorating hypoxia and the emergence of anaerobic metabolism; and (3) parameters including hemoglobin, Pv-aCO_2, SaO_2, and PaO_2 may help to distinguish between various hypoxia-causing processes.

Blood gas parameters have certain limitations. First, the parameters essentially reflect global O_2 metabolism and cannot accurately follow the complex changes within the microvascular environment. Analysis of blood gas parameters must thus be combined with organ-perfusion performance. Second, the parameters are affected by multiple factors; a satisfactory value is never the ultimate target during septic treatment, and only a comprehensive assessment can reveal the tissue metabolism. Despite these limitations, blood gas analysis provides valuable information on tissue O_2 metabolism, especially when advanced technologies for microcirculatory measurements are not available.

Taken together with medical practice, the recommended interpretation of blood gas analysis is presented in Figure 3. Lactate should be included in the initial clinical evaluation, given that it is acquired from arterial blood, which involves a relatively less-invasive procedure that is readily available in the ED. Notably, physicians need to be aware that interpretations should be combined with clinical judgments, and the ultimate goal of resuscitation is to improve clinical performance, rather than correcting the specific values.

CONCLUSIONS

This review contributes to our understanding of the use of blood gas analysis as a surrogate for visualizing microcirculation and tissue O_2 metabolism. Despite its drawbacks, evidence suggests that blood gas analysis,

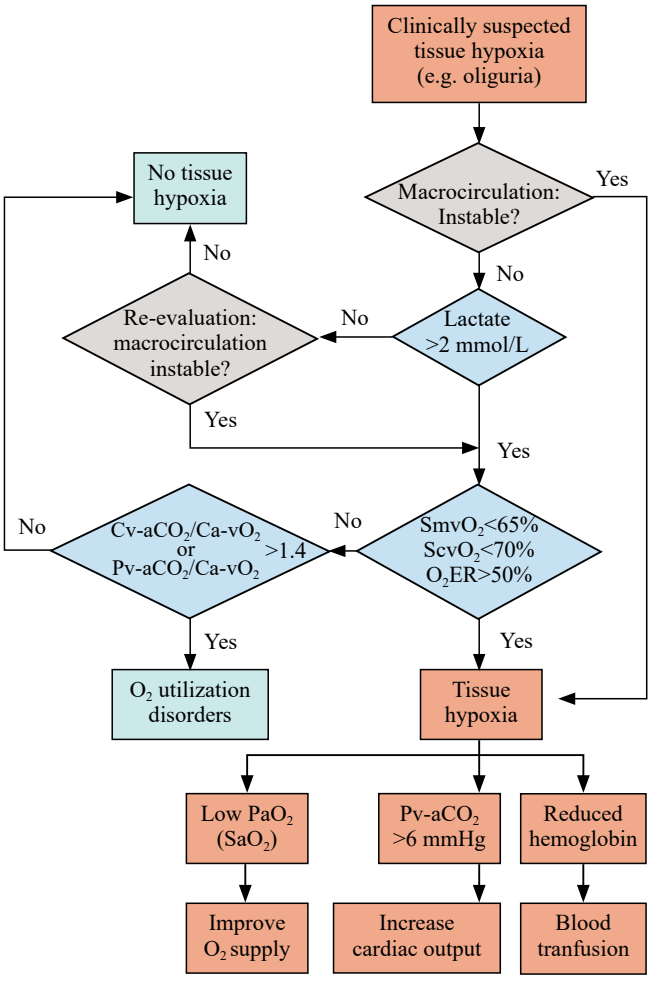

Figure 3. Integrated interpretation of blood gas analysis in hemodynamic monitoring. O_2ER: O_2 extraction rate; SvO_2: venous O_2 saturation; Pv-aCO_2: venous to arterial CO_2 tension; Ca-vCO_2: arterial to venous CO_2 content; Ca-vO_2: arterial to venous O_2 content; SaO_2: arterial O_2 saturation; $ScvO_2$: central venous O_2 saturation; SmvO2: mixed venous O_2 saturation.

combined with clinical performance, provides a feasible and reliable alternative for microcirculatory management. We believe that further insights into the DO_2/VO_2 ratio will help ED physicians utilize blood gas analysis effectively, leading to improved judgments and better decision-making in the treatment of sepsis.

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