

# Resuscitation incoherence and dynamic circulation-perfusion coupling in circulatory shock

Huai-Wu He<sup>1</sup>, Yun Long<sup>1</sup>, Da-Wei Liu<sup>1</sup>, Can Ince<sup>2</sup>

<sup>1</sup>Department of Critical Care Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Science, Beijing 100730, China;

<sup>2</sup>Department of Intensive Care, Erasmus MC University Hospital Rotterdam, Rotterdam 3015 CE, the Netherlands.

## Abstract

**Objective:** Poor tissue perfusion/cellular hypoxia may persist despite restoration of the macrocirculation (Macro). This article reviewed the literatures of coherence between hemodynamics and tissue perfusion in circulatory shock.

**Data sources:** We retrieved information from the PubMed database up to January 2018 using various search terms or/and their combinations, including resuscitation, circulatory shock, septic shock, tissue perfusion, hemodynamic coherence, and microcirculation (Micro).

**Study selection:** The data from peer-reviewed journals printed in English on the relationships of tissue perfusion, shock, and resuscitation were included.

**Results:** A binary (coherence/incoherence, coupled/uncoupled, or associated/disassociated) mode is used to describe resuscitation coherence. The phenomenon of resuscitation incoherence (RI) has gained great attention. However, the RI concept requires a more practical, systematic, and comprehensive framework for use in clinical practice. Moreover, we introduce a conceptual framework of RI to evaluate the interrelationship of the Macro, Micro, and cell. The RI is divided into four types (Type 1: Macro-Micro incoherence + impaired cell; Type 2: Macro-Micro incoherence + normal cell; Type 3: Micro-Cell incoherence + normal Micro; and Type 4: both Macro-Micro and Micro-cell incoherence). Furthermore, we propose the concept of dynamic circulation-perfusion coupling to evaluate the relationship of circulation and tissue perfusion during circulatory shock.

**Conclusions:** The concept of RI and dynamic circulation-perfusion coupling should be considered in the management of circulatory shock. Moreover, these concepts require further studies in clinical practice.

**Keywords:** Circulatory shock; Shock; Tissue perfusion; Microcirculation; Hemodynamic coherence; Resuscitation incoherence

## Background

Circulatory shock is a common disease, with high morbidity and mortality rates in clinical practice.<sup>[1]</sup> In 1971, Weil and Subin<sup>[2]</sup> defined four typical types of circulatory shock according to the alterations in the macrocirculatory hemodynamics and pathophysiological state. The possibility that normalized microcirculatory parameters might not be parallel to improved tissue perfusion in the resuscitation of circulatory shock has been well recognized. Numerous clinical studies also found that normalized macrocirculatory parameters did not guarantee the restoration of microcirculatory perfusion and cellular O<sub>2</sub> metabolism in the resuscitation of circulatory shock, the failure of which is associated with poor outcomes.<sup>[3-9]</sup> Therefore, according to the concept of critical hemodynamic therapy, the diagnosis and treatment of circulatory shock should be expanded from macrocirculation (Macro) to microcirculation (Micro) and extended further into the depths of cellular oxygen metabolism.<sup>[10]</sup>

The assessment and treatment of impaired tissue perfusion present substantial challenges for physicians in clinical practice once the Micro has been restored. Recent clinical studies also questioned the value of hemodynamic data or targets that focused solely on the correction of global circulation parameters in the resuscitation of septic shock.<sup>[11,12]</sup> Thus, using microcirculatory targets or other surrogate variables to guide resuscitation (eg, lactate-guided or sublingual PCO<sub>2</sub>-guided resuscitation) has garnered increasing attention in experimental and clinical studies.<sup>[13-15]</sup> Importantly, the interactive relationship between the circulation and tissue perfusion plays a critical role in circulatory shock. Here, we stress that from a holistic perspective of resuscitation, both global and local (macro and micro) parameters should be considered. The alteration of microcirculatory perfusion or oxygen metabolism parameters (eg, poor peripheral perfusion or a high lactate level) might serve as early indicators that demand immediate attention; however, when combined with

## Access this article online

Quick Response Code:



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10.1097/CM9.0000000000000221

**Correspondence to:** Dr. Da-Wei Liu, Department of Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, 1 Shuaifuyuan, Dongcheng District, Beijing 100730, China  
E-Mail: tjmuhhw@163.com

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Chinese Medical Journal 2019;132(10)

Received: 20-11-2018 Edited by: Ning-Ning Wang

macrocirculatory parameters, they might elucidate the reasons for the alteration and what should be done next. The conceptual framework of hemodynamic coherence (HC) was proposed to describe the relationship between the Macro and Micro.<sup>[16]</sup> Moreover, the HC concept attracted substantial attention regarding hemorrhagic shock, sepsis, burn, perioperative, and pediatric patients.<sup>[17-20]</sup> However, the HC concept primarily focuses on using microcirculatory hemodynamics to describe the relationship between the Macro and Micro using handheld vital microscopy.<sup>[16]</sup> A comprehensive and practical concept is required to further interpret resuscitation coherence during circulatory shock. Therefore, we further introduce a classification of the resuscitation incoherence (RI) based on information regarding the following three domains: Macro, Micro, and cell. Moreover, a dynamic circulation-perfusion coupling (CPC) score was proposed to assess the effects of medical interventions and determine the therapeutic direction for circulatory shock.

### Loss of Resuscitation Coherence in Circulatory Shock

The early goals of resuscitation are to restore global oxygen delivery (DO<sub>2</sub>), global blood flow, and organ perfusion pressure, with the ultimate aim of improving microcirculatory perfusion and cellular oxygen metabolism in circulatory shock. However, the preset expected targets (eg, microcirculatory perfusion, tissue oxygenation, and lactate) might be disassociated from the improved Macro targets, termed the RI. Tissue perfusion is always improved with global circulation in hypovolemic, cardiogenic, and obstructive shock if the Macro is restored at the early stage. In contrast, when tissue hypoxia is not corrected expeditiously and continues for a long time, the ischemia-reperfusion injury may further cause a severe RI. Moreover, the lack of resuscitation coherence is common in sepsis conditions. Many studies demonstrated that the correction of the Macro did not restore the Micro in septic shock patients after early goal-directed resuscitation.<sup>[8,21-24]</sup> The disordered tissue perfusion is to some extent independent of global circulation in sepsis.

Here, we stress that the RI might occur in different stages and various types of circulatory shock. The early identification of RI might reduce the risk of overresuscitation. In theory, RI always results from impaired autoregulatory mechanisms of the Micro and/or of cellular oxygen metabolism. The potential pathophysiologic mechanisms include unchecked cascade inflammation, cytokine storm, reactive oxygen species generation, glycocalyx degradation and shedding, endothelial dysfunctional capillary leakage, and mitochondrial dysfunction.<sup>[25,26]</sup> Although the phenomenon of RI has garnered attention, related diagnostic standards remain lacking in clinical practice. Moreover, the concept of RI should be more practical, systematic, and comprehensive.

### Macro, Micro, and Cellular Oxygen Metabolism Parameters in Resuscitation

Macrocirculatory, microcirculatory, and cellular oxygen metabolism parameters have become potential targets in the circulatory resuscitation of shock. These parameters

are also commonly used to help physicians identify the phenomenon of RI in clinical practice. The relevant parameters are summarized in the following subsections.

#### Macro parameters

The primary macrocirculatory parameters during resuscitation focus on global DO<sub>2</sub>, blood flow, and perfusion pressure targets, with the aim of restoring tissue perfusion.<sup>[10]</sup> A cutoff value of central venous oxygen saturation (ScvO<sub>2</sub>) ≥70% is used to assess whether the global DO<sub>2</sub> is meeting the oxygen consumption, and a central venous-arterial carbon dioxide difference (P(v-a)CO<sub>2</sub>) gap ≤6 mmHg is suggested as an indicator of global flow to assess whether global blood flow is meeting tissue perfusion demands. Moreover, a mean arterial pressure value >65 mmHg and/or an individual value is suggested as a proper perfusion pressure target. In theory, the potential contribution of macrocirculatory factors to poor tissue perfusion should be totally excluded before diagnosing RI. Here, microcirculatory normalization should be guided by normal physiologic ranges in a healthy population, and personalized targets should be considered to optimize the macrocirculatory targets. Moreover, the medical history and current pathophysiologic status are important to determine how to optimize the Macro target. Finally, the “normalization/optimization” of microcirculatory targets should not be viewed as actual “health” given that the “normalization/optimization” of global circulation is usually achieved by ongoing fluid and/or catecholamine therapy.

#### Micro parameters

The microcirculatory parameters focus on capillary refill time (CRT), peripheral perfusion index (PI), tissue oxygen saturation, peripheral temperature, skin mottling, transcutaneous partial pressure of oxygen, transcutaneous oxygen challenge test, and sublingual microcirculatory parameters (microvascular flow index, proportion of perfused vessels, and density of perfused vessels). Here, we stress that the critical values of microcirculatory perfusion should not be misconstrued as the normal values of the healthy population. The critical value of tissue perfusion serves as a sensitive indicator of tissue hypoxia and requires immediate attention, whereas the normal value of a healthy population might indicate the cutoff value to exclude “tissue hypoperfusion” and identify the loss of resuscitation coherence of cellular O<sub>2</sub> energy metabolism. For similar physiologic parameters of tissue perfusion, the critical cutoff values in critically ill patients are not always equal to the normal cutoff values in healthy populations. For example, the normal value of CRT is equal to or less than 2 s in healthy populations, whereas the critical value of CRT might be more than 5 s in critically ill patients<sup>[27,28]</sup>; the normal value of PI is more than 1.4, whereas the critical value might be less than 0.6<sup>[9]</sup>; and the normal value of tissue oxygen saturation is 87%, whereas the critical value might be less than 70%.<sup>[29,30]</sup> Moreover, in critically ill states, the sacrifice of peripheral circulation perfusion is a self-protection mechanism; therefore, the impairment of peripheral circulation perfusion might be acceptable to some extent. In contrast, the normalization of tissue perfusion may be an indicator for

fluid deresuscitation.<sup>[31]</sup> Therefore, blindly pursuing a total normalization of microcirculatory perfusion might also induce overresuscitation, and the targets of microcirculatory perfusion might be referred to as the personalized physiological requirement and cellular oxygen metabolism indicators.

**Cell parameters**

Both lactate and central venous-arterial carbon dioxide difference/arterial-central venous oxygen difference (P(v-a)CO<sub>2</sub>/C(a-v)O<sub>2</sub>) ratio are used to identify the cellular oxygen metabolism in clinical practice. It is important to determine whether the cellular hypoxia is dependent on the increase of DO<sub>2</sub>. Studies have questioned whether high lactate levels are markers indicating anaerobic metabolism, which did not originate from cellular hypoxia in circulatory shock.<sup>[32-34]</sup> Rimachi *et al*<sup>[34]</sup> reported the presence of hyperlactatemia in 65% of patients with septic shock; however, only 75% of these patients exhibited an increased lactate/pyruvate ratio, confirming that hyperlactatemia might be not due to hypoxia, particularly during the early stages of shock. Recently, the P(v-a)CO<sub>2</sub>/C(a-v)O<sub>2</sub> was suggested as a supplemental indicator to reflect anaerobic metabolism, and studies reported that a high P(v-a)CO<sub>2</sub>/C(a-v)O<sub>2</sub> is an independent risk factor for mortality in septic shock patients.<sup>[35,36]</sup> Studies also found that the evaluation of the P(v-a)CO<sub>2</sub>/C(a-v)O<sub>2</sub> ratio might provide additional infor-

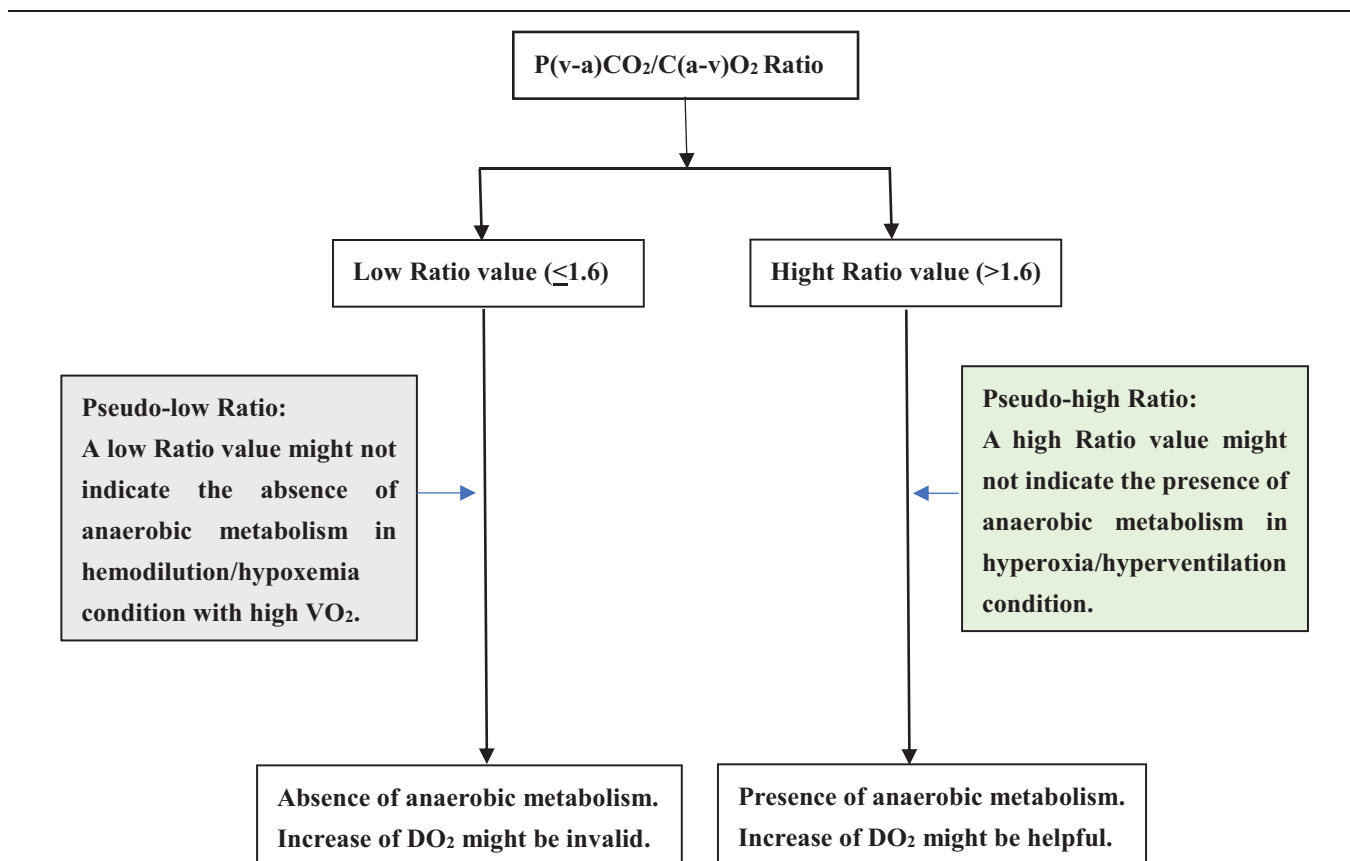
mation to identify nonhypoxic hyperlactatemia and optimize lactate clearance.<sup>[37,38]</sup> Moreover, several factors (hyperoxia, hyperventilation, hemodilution, and hypoxemia) might confound the performance of P(v-a)CO<sub>2</sub>/C(a-v)O<sub>2</sub> ratio.<sup>[39,40]</sup> In Figure 1, we summarized a schematic diagram to interpret P(v-a)CO<sub>2</sub>/C(a-v)O<sub>2</sub> ratio in clinical practice.

**Classification of RI**

The Micro is coupled with the Macro, and the cell is coupled with the Micro under normal physiologic regulatory mechanisms. In theory, several combinations of coherence loss may exist among Macro-Micro and Micro-cell in circulatory shock. Here, we define the following four types of RI in clinical practice.

**Type 1: Macro-Micro incoherence + cell hypoxia**

In this type, the Micro is disassociated from the Macro. When tissue hypoperfusion/tissue hypoxia is continuously present after microcirculatory improvement, RI at a microcirculatory level should be suspected. Moreover, the cellular oxygen metabolism was decompensated and impaired. Importantly, the cell oxygen metabolism is dependent on the microcirculatory perfusion and the increase of local DO<sub>2</sub>. The uncoupling of Macro-Micro is always caused by the impaired microcirculatory functions of recognition and autoregulation in local blood flow, DO<sub>2</sub>, and cellular hypoxia.<sup>[26]</sup>



**Figure 1:** Schematic diagram to interpret P(v-a)CO<sub>2</sub>/C(a-v)O<sub>2</sub> ratio in clinical practice. DO<sub>2</sub>: Oxygen delivery; P(v-a)CO<sub>2</sub>/C(a-v)O<sub>2</sub>: Central venous-arterial carbon dioxide difference/arterial-central venous oxygen difference; VO<sub>2</sub>: Oxygen consumption.

**Type 2: Macro-Micro incoherence + occult cell hypoxia**

In this type, a mildly impaired Micro always accompanies normal cellular oxygen metabolism function. Because of the physiologic compensatory mechanisms in the critically ill state, cellular oxygen metabolism might be preserved in type 2. Hence, the lactate level always is normal. Importantly, the potential cellular hypoxia is dependent on the increase of DO<sub>2</sub>. To some extent, impaired microcirculatory perfusion might be acceptable in the critically ill. Furthermore, the impaired Micro might be considered an early alarm indicator, and attention should be directed toward the potential factors that contributed to the impaired Micro.

**Type 3: Micro-cell incoherence + normal Micro**

Cellular oxygen metabolism is disassociated from microcirculatory perfusion in this type. When cellular oxygen metabolism dysfunction persists after the restoration of tissue perfusion, the RI of the Micro and cellular oxygen metabolism should be suspected. Profoundly disordered cellular oxygen energy metabolism in type 3 might arise from independent oxygen utilization dysfunction from mitochondrial cytopathy and accelerated aerobic metabolism from stress.<sup>[41]</sup> Albuszies *et al*<sup>[42]</sup> found that

microcirculatory restoration allowed the maintenance of gut and liver microvascular perfusion and an increase of capillary oxygenation after fluid resuscitation, although hepatic metabolic capacity remained impaired in a murine model of septic shock. Moreover, cellular derangements might occur in some toxic conditions such as cyanide poisoning under normal tissue perfusion conditions. Thus, impaired cellular oxygen metabolism might independently occur, despite improved microcirculatory perfusion in the resuscitation. Additionally, nonhypoxic hyperlactatemia indicates the Micro-cell RI. The early identification of nonhypoxic hyperlactatemia may provide information to avoid overresuscitation of Macro and Micro targets.

**Type 4: “Macro-Micro + Micro-cell” incoherence**

Both the Micro and the cellular functions are impaired in type 4, notwithstanding the restoration of the global circulation. Type 4 is also termed microcirculatory and mitochondrial distress syndrome in conditions of sepsis.<sup>[43]</sup> However, the diagnostic differentiation of type 1 and type 2 based on clinical parameters is difficult. For example, a poor Micro and cellular oxygen metabolism response might occur in type 1 during resuscitation, which is similar

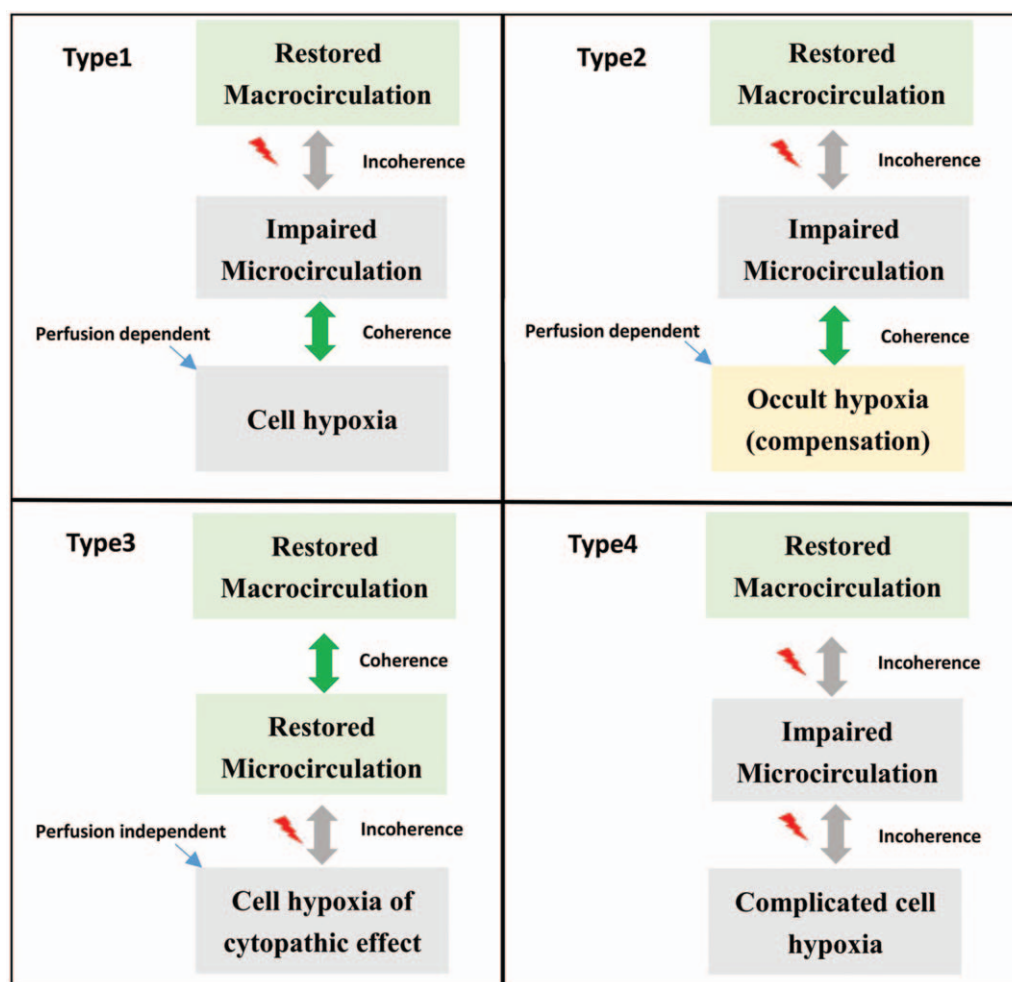


Figure 2: Schematic diagram of the classification of resuscitation incoherence.

to type 4. Thus, future experimental technology to directly assess the local Micro and cellular functions might aid type 4 identification.

A schematic diagram of the classification of RI is shown in Figure 2. Here, we stress that this classification might help describe the coupled relationship among Macro, Micro and cell according to data from a single timepoint after resuscitation; moreover, it might provide a simple and relevant evaluation of RI in circulatory shock. Characteristics of Macro, Micro, and cell of RI classification are summarized in Table 1. Moreover, some potential standards for determining the status of Macro, Micro, and cell are proposed in a clinically practical perspective. As the

standards used to identify the severely/normal/mildly impaired status of Macro/Micro/cell function remain controversial and undetermined in clinical practice, additional studies are required to validate the efficacy of the RI classification.

### Dynamic GPC

Coherence always is defined in a binary (coherence or incoherence) mode regarding the resuscitation of circulatory shock.<sup>[16]</sup> However, because different degrees of tissue perfusion response to improved global circulation exist in clinical practice, using a binary (coherence or incoherence) method to classify resuscitation coherence might be

**Table 1: Characteristics of Macro, Micro, and cell in conceptual classification of resuscitation incoherence.**

Item	Type 1	Type 2	Type 3	Type 4
Macro				
Normal	MAP ≥ 65 mmHg (or usual level), ScvO <sub>2</sub> ≥ 70%, Pv-aCO <sub>2</sub> ≤ 6 mmHg, and CI > 2.2 L/m <sup>2</sup>	MAP ≥ 65 mmHg (or usual level), ScvO <sub>2</sub> ≥ 70%, Pv-aCO <sub>2</sub> ≤ 6 mmHg, and CI > 2.2 L/m <sup>2</sup>	MAP ≥ 65 mmHg (or usual level), ScvO <sub>2</sub> ≥ 70%, Pv-aCO <sub>2</sub> ≤ 6 mmHg, and CI > 2.2 L/m <sup>2</sup>	MAP ≥ 65 mmHg (or usual level), ScvO <sub>2</sub> ≥ 70%, Pv-aCO <sub>2</sub> ≤ 6 mmHg, and CI > 2.2 L/m <sup>2</sup>
Micro				
Normal	–	–	CRT ≤ 2 s, PI ≥ 1.4, PPV > 80%, MFI ≥ 3, mottling score 0, warm extremities Urine output > 0.5 mL·kg <sup>-1</sup> ·h <sup>-1</sup>	–
Mildly impaired	–	CRT 2–5 s, PI 0.6–1.4, PPV 60%–80%, MFI 2–3, mottling score 0–2, cold extremities Urine output 0.3–0.5 mL·kg <sup>-1</sup> ·h <sup>-1</sup>	–	–
Severely impaired	CRT < 5 s, PI < 0.6, PPV < 60%, MFI < 2, mottling score > 2, cold extremities Urine output < 0.3 mL·kg <sup>-1</sup> ·h <sup>-1</sup>	–	–	CRT < 5 s, PI < 0.6, PPV < 60%, MFI < 2, mottling score > 2, cold extremities Urine output < 0.3 mL·kg <sup>-1</sup> ·h <sup>-1</sup>
Cell				
Perfusion-dependent hypoxia	Lactate > 2 mmol/L, P(v-a)CO <sub>2</sub> /C(a-v)O <sub>2</sub> > 1.6, etc.	–	–	–
Perfusion-dependent occult hypoxia with compensation	–	Lactate < 2 mmol/L, P(v-a)CO <sub>2</sub> /C(a-v)O <sub>2</sub> < 1.6, etc.	–	–
Perfusion-independent hypoxia of cytopathic effect	–	–	Lactate > 2 mmol/L, P(v-a)CO <sub>2</sub> /C(a-v)O <sub>2</sub> > 1.6, etc.	–
Combined cell hypoxia	–	–	–	Lactate > 2 mmol/L P(v-a)CO <sub>2</sub> /C(a-v)O <sub>2</sub> > 1.6, etc.

CI: Cardiac output index; CRT: Capillary refill time; Macro: Macrocirculation; MAP: Mean arterial pressure; MFI: Microvascular flow index; Micro: Microcirculation; P(v-a)CO<sub>2</sub>/C(a-v)O<sub>2</sub>: Central venous-arterial carbon dioxide difference/arterial-central venous oxygen difference; PI: Peripheral perfusion index; PPV: Proportion of perfused vessel; ScvO<sub>2</sub>: Central venous oxygen saturation; Type 1: Macro-Micro incoherence + impaired Cell; Type 2: Macro-Micro incoherence + normal Cell; Type 3: Micro-Cell incoherence + normal Micro; Type 4: “Macro-Micro + Micro-Cell” incoherence; “–”: None.

inadequate. While “coherence” might easily be misinterpreted negatively, “coherence” might instead be a neutral term. For example, a poor Macro accompanied by a poor Micro is a condition that is coherent from a technical perspective. Thus, the concept of dynamic CPC is proposed to assess the effect of resuscitation, which might provide insights into the dynamic interaction of circulation and tissue perfusion. To evaluate dynamic CPC, global circulation is used as the independent variable, and the expected tissue perfusion targets are the dependent variables. Importantly, circulation and tissue perfusion data from two timepoints are required to determine the dynamic CPC. A dynamic CPC degree scale is summarized in Table 2 and Figure 3.

### Dynamic CPC-III

Dynamic CPC-III is defined as strong coupling between the Macro and tissue perfusion. The change in the tissue perfusion is consistent with the change in the Macro in dynamic CPC-III. That is, an improvement of macro-hemodynamic variables might result in beneficial effects on the tissue perfusion, and vice versa. Here, dynamic CPC-III is divided into dynamic CPC-IIIa and dynamic CPC-IIIb, according to the direction of the change of the Macro and tissue perfusion. In dynamic CPC-IIIa, the Macro and tissue perfusion are both restored from an impaired status after the resuscitation, and the patients with dynamic CPC-IIIa have a successful resuscitation. Moreover, once dynamic CPC-IIIa is achieved after early resuscitation, the deresuscitation also warrants consideration. Dynamic CPC-IIIb is another outcome of the consistent relationship

between the Macro and tissue perfusion. Both the Macro and Micro are disordered after the initial resuscitation. A poor Macro is well known to always result in poor tissue perfusion, organ function, and outcome.<sup>[44-46]</sup> A clinical study showed that the patients with a low PI (<0.6) and a low ScvO<sub>2</sub> (<70%) after 8 h of resuscitation had the highest mortality rate (80%) at day 30.<sup>[9]</sup> Therefore, dynamic CPC-IIIb reflects patients who require immediate attention and focuses on how to restore Macro, and those who might have a high risk of circulatory collapse. Moreover, some life-saving interventions warrant implementation, depending on the pathophysiologic condition (eg, emergency surgery to control bleeding for hemorrhagic shock, pericardial drainage, antibiotic adjustment for sepsis, and mechanical support for cardiac shock).

### Dynamic CPC-II

Dynamic CPC-II (moderate coupling) indicates an acceptable tissue perfusion response (the improvement of tissue perfusion >15% over baseline or an increased absolute value above the lower end of the standard deviation (SD) of the healthy population) to the improvement of the Macro. Dynamic CPC-II indicates that the current therapeutic intervention might be corrected and maintained with careful monitoring. A 5% variation of clinical parameters might be within the range of physiological variation. More than a 15% variation of a parameter might warrant a physician's attention considering that a 15% increase of cardiac output or oxygen consumption has clinical relevance.<sup>[47]</sup> Moreover, variation below the 2SD for blood pressure of health population has been used as a diagnostic standard of

**Table 2: The degree scale of dynamic circulation-perfusion coupling.**

Items	Timepoint at baseline	Timepoint after early resuscitation	Degree scale of dynamic CPC	Clinical relevance
Global circulation Tissue perfusion	Abnormal Abnormal	Normal Normal	Dynamic CPC-IIIa, robust coupling	Successful resuscitation of Macro, Micro, and cell, and therapy that need to shift to deresuscitation
Global circulation Tissue perfusion	Abnormal Abnormal	Abnormal Abnormal	Dynamic CPC-IIIb, robust coupling	Unsuccessful resuscitation of Macro, and continually focus on how to correct global circulation
Global circulation Tissue perfusion	Abnormal Abnormal	Normal Significant improvement (>15% or 2 SD of healthy population) over baseline	Dynamic CPC-II, moderate coupling	Maintain current treatment, and dynamically evaluate the ongoing tissue perfusion with caution
Global circulation Tissue perfusion	Abnormal Abnormal	Normal Mild improvement over baseline (<15% or 2 SD)	Dynamic CPC-I, mild coupling	Optimize treatment, and exclude other potential factors contributing to poor tissue perfusion
Global circulation Tissue perfusion	Abnormal Abnormal	Normal Worsened	Dynamic CPC-0, uncoupled	Current treatment might be ineffective for perfusion, and therapeutic direction is required to adjust

CPC: Circulation-perfusion coupling; Macro: Macrocirculation; Micro: Microcirculation; SD: Standard deviation.

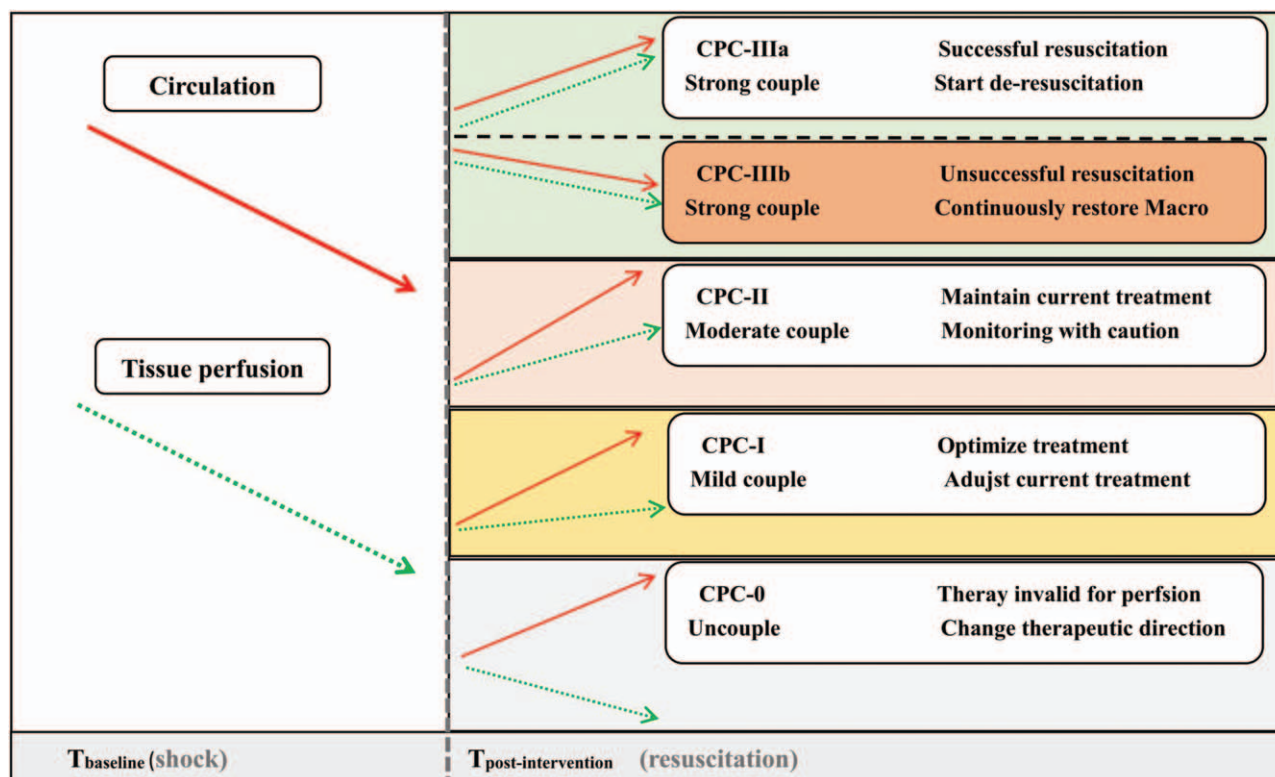


Figure 3: Schematic diagram of the degree scale of dynamic circulation-perfusion coupling (CPC).

hypotension in septic shock.<sup>[48]</sup> Therefore, we believe that a cutoff value of 15% or 2 SD of the expected perfusion parameter might be reasonable and relevant in clinical practice. Additionally, the time interval is an important factor to determine the dynamic CPC degree. A study showed a different threshold value of the lactate clearance rate related to outcome at different time intervals in critically ill patients.<sup>[49]</sup> Further study is required to define precise cutoff values for different expected perfusion targets during the preset time period. Here, we suggest a dynamic CPC evaluation frequency of 3 to 6 h for typical circulatory shock resuscitation, with an increased frequency of 1 to 2 h for critical conditions. Lastly, the response time and kinetics of expected tissue perfusion targets should be considered in the evaluation of dynamic CPC.

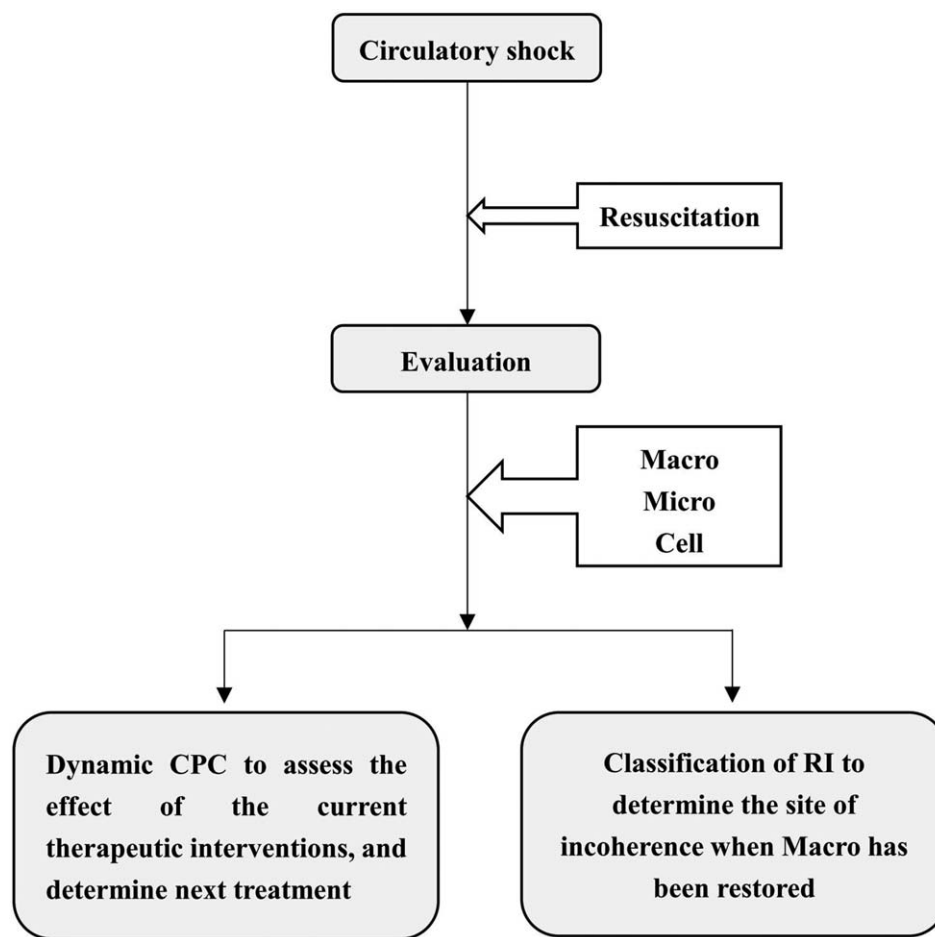
#### Dynamic CPC-I (mild coupling)

Dynamic CPC-I (mild coupling) reflects a perfusion improvement (ie, a range of improved tissue perfusion of 0%–15%/0–2 SD over baseline) that is not significant but has not become worse. We suggest that dynamic CPC should be reevaluated with caution after 1 to 2 h. If the expected perfusion targets improve and reach the level of dynamic CPC-II, the current treatment might continue, with careful monitoring. However, if the expected perfusion targets do not change or perhaps worsen, the therapeutic direction should be changed. Moreover, other unchecked factors that result in persistent impaired microcirculatory perfusion should be suspected, such as new-onset sepsis, an occult infection source, profound ischemia-reperfusion injury, or an undetermined etiology of the circulatory shock.

#### Dynamic CPC-0 (uncoupled)

Dynamic CPC-0 (uncoupled) indicates no effect of the improved Macro on tissue perfusion. Importantly, tissue perfusion further deteriorates. Compared with dynamic CPC-I patients, dynamic CPC-0 patients are always more critically ill and require alterations to the current therapeutic direction and a determination of the potential origin (eg, optimize Micro, reassess and retreat the etiology of the circulatory shock). Moreover, the interactive levels of RI should be determined in the dynamic CPC-0 condition.

The dynamic CPC degree is suggested to evaluate the dynamic relationship between the Macro and tissue perfusion in the procedure of resuscitation, and the RI classification is suggested to determine where coherence is lost. It is necessary to evaluate the combined effect of colloids on Macro and Micro for correctly interpret the role of colloids in the shock resuscitation.<sup>[50]</sup> The first expected aim of the recovery of the Macro is the Micro, and the expected aim of the improved Micro is improved cellular oxygen metabolism. In theory, stepwise targets should be proposed to interpret the dynamic CPC. However, the relationship between the Micro and cellular oxygen metabolism is difficult to quantitatively analyze, and impaired Micro always accompanies poor cellular oxygen metabolism in clinical practice. Thus, it might be difficult in clinical practice to divide tissue perfusion into microcirculatory perfusion and cellular oxygen metabolism using a dynamic CPC degree scale. Recent studies supported the P(v-a)CO<sub>2</sub> might be a potential indicator of sublingual microcirculation.<sup>[51]</sup> Furthermore,



**Figure 4:** A conceptual protocol of the use of dynamic circulation-perfusion coupling (CPC) and resuscitation coherence loss. RI: Resuscitation incoherence.

studies indicated that perfusion-related variables exhibited different normalization rates in septic shock survivors.<sup>[52,53]</sup> Here, we emphasize using serial and dynamic parameters in multimodal monitoring strategies for the abovementioned three domain (Macro, Micro, and cell) parameters to assess the loss of coherence and dynamic CPC.<sup>[54]</sup> We believe that the concepts of resuscitation coherence and dynamic CPC may provide meaningful information to assess the effect of shock resuscitation and determine further therapeutic directions. In summary, a conceptual protocol of the use of dynamic CPC and RI is shown in Figure 4.

### Conclusions

The concepts of resuscitation coherence and dynamic CPC may provide meaningful information to interpret shock resuscitation. These clinical findings should be considered for the management of circulatory shock. Moreover, these concepts require further study for validation in clinical practice.

### Funding

This work was supported by a grant from the Fundamental Research Funds for the Central Universities (No. 3332018010).

### Conflicts of interest

None.

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**How to cite this article:** He HW, Long Y, Liu DW, Ince C. Resuscitation incoherence and dynamic circulation-perfusion coupling in circulatory shock. *Chin Med J* 2019;132:1218–1227. doi: 10.1097/CM9.0000000000000221