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Monitoring coherence between the macro and microcirculation in septic shock

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Purpose of review
Currently, the treatment of patients with shock is focused on the clinical symptoms of shock. In the early phase, this is usually limited to heart rate, blood pressure, lactate levels and urine output. However, as the ultimate goal of resuscitation is the improvement in microcirculatory perfusion the question is whether these currently used signs of shock and the improvement in these signs actually correspond to the changes in the microcirculation.

Recent findings
Recent studies have shown that during the development of shock the deterioration in the macrocirculatory parameters are followed by the deterioration of microcirculatory perfusion. However, in many cases the restoration of adequate macrocirculatory parameters is frequently not associated with improvement in microcirculatory perfusion. This relates not only to the cause of shock, where there are some differences between different forms of shock, but also to the type of treatment.

Summary
The improvement in macrohemodynamics during the resuscitation is not consistently followed by subsequent changes in the microcirculation. This may result in both over-resuscitation and under-resuscitation leading to increased morbidity and mortality. In this article the principles of coherence and the monitoring of the microcirculation are reviewed.

Keywords
endpoints, hemodynamics, lactate, perfusion, peripheral perfusion, resuscitation, shock

INTRODUCTION

Circulatory dysfunction is a frequent reason for admission to the ICU. The principal role of the circulation is to deliver nutrients (oxygen and fuel) to the organs and remove waste product. This is mainly accomplished by the delivery of red blood cells (RBC) into the microcirculation and the passive diffusion of oxygen from the RBCs to the tissue cells. When requirements are not met, first organ function decreases before ultimately failing. Therefore, the goal in treating circulatory dysfunction is to restore adequate perfusion of the microcirculation. The oxygen content [hemoglobin (Hb) and Hb saturation] are factors that also determine the ultimate amount of oxygen delivered to the organs. However, in this review we will focus on perfusion as the body has limited ability to improve oxygen content acutely. In addition, in response to changes in oxygen demand the first response of the circulatory system is to improve flow. In situations of stress (shock) the system also influences organ blood flow by redirecting flow to more vital organs at the expense of less the perfusion of less vital organs.

The clinical definition of circulatory dysfunction or failure varies and is usually defined by macrohemodynamic parameters like blood pressure (BP), biomarkers in arterial and (central) venous blood and parameters of organ function. Where shock is the worst form of circulatory failure, its definition is not really usable at the bedside [1] so that one has to rely on the same parameters and biomarkers for its recognition. Not only the use of these, sometimes

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KEY POINTS

- During the development of shock microcirculatory perfusion parameters follow the deterioration of macrocirculatory symptoms and parameters of shock (coherence).
- Although in some forms of shock coherence is also present in the resuscitation of shock, especially septic shock represents a state in which coherence is lost.
- As the resuscitation is still mainly focused on macrocirculatory parameters, the loss of coherence may result in both over and under-resuscitation.
- Loss of coherence is associated with increased morbidity and mortality.
- Although loss of coherence between the macrocirculation and peripheral perfusion parameters is also present following initial resuscitation in septic shock, limited research have studied the coherence between the microcirculation and peripheral circulation.

neither specific nor sensitive markers, might result in inadequate treatment of the patient.

For this review, we define hemodynamic coherence as the presence of concordance between changes in the macrocirculation and the microcirculation. We will mainly focus on sepsis as this a very frequent cause of circulatory dysfunction in critically ill patients and has been shown to present a both complex microcirculatory dysfunction and a complex response to its treatment.

METHODS TO MONITOR THE MICROCIRCULATION

The methods available to monitor the microcirculation are numerous but relate to the specific microcirculation of interest. In intact patients this basically means that access to organs is not possible with the exception of patients with an enteral stoma which provides access to gut mucosa. The accessible sites are thus mainly limited to skin and the sublingual area. In different contexts, the mucosa of the rectum and vagina has been used [2,3].

For the skin the methods available have been reviewed extensively earlier [4,5] and will not be discussed here. The sublingual area provides an easy opportunity to visualize a true microcirculatory network. From its first clinically available device, some 20 years ago [6], the technique has been further developed [7], an automated scoring system has become available [8▪] and guidelines for the practical use and interpretation have been published [9▪]. Although other areas can be used to visualize the microcirculation (nailbed, conjunctive, retina) their clinical use is thus far limited.

THE IMPORTANCE OF COHERENCE

Where the ultimate goal of resuscitation is to restore microcirculatory perfusion and oxygen exchange, the question is whether the clinically used parameters adequately reflect these processes (Fig. 1) [10]. Perceived adequate macrohemodynamics in the presence of abnormal microcirculatory perfusion has been referred to as microcirculatory shock [11]. In addition, normal peripheral microcirculatory perfusion in patients with septic shock is associated with a significantly lower mortality in the presence of similar macrohemodynamics [12▪]. In both cases, the lack of coherence could represent a different (clinical) phenotype but could also result in either over-resuscitation or under-resuscitation of patients. A relevant clinical example of this could be the use of lactate in the early resuscitation of septic shock as recommended by the Surviving Sepsis Campaign Guidelines [13]. In these, fluid administration is recommended in patients with increased lactate levels as these would mark tissue hypoperfusion with the ultimate goal to normalize lactate levels [13]. Both this assumption and the use of normalization have been seriously questioned as lactate may not (always) indicate tissue hypoperfusion and microcirculatory perfusion may be normal when lactate levels have not normalized yet [14,15] and coherence may be lost [16]. Both conditions could lead to over resuscitation with associated risk of increased morbidity and mortality [17,18].

COHERENCE DURING THE DEVELOPMENT OF CIRCULATORY FAILURE

In acute models of hemorrhagic shock, tamponade, cardiogenic shock and cardiac arrest coherence exists during the development of shock. In other words, during the development of shock, as signaled by the changes in macrocirculatory parameters, also the microcirculation shows abnormal perfusion parameters [19–27]. Although during the development of septic shock, characterized by hypotension and decreased cardiac output (CO), hemodynamic coherence is present [20,28–30]. However, sepsis with preserved macrohemodynamics may still show an abnormal microcirculation [31,32]. In contrast to other organs, the microcirculation of the brain seems to be preserved during the development of septic, cardiogenic and hemorrhagic shock [22,33,34] despite significant macrocirculatory abnormalities.

The study of coherence in human models of shock is limited but in models of hypovolemia in

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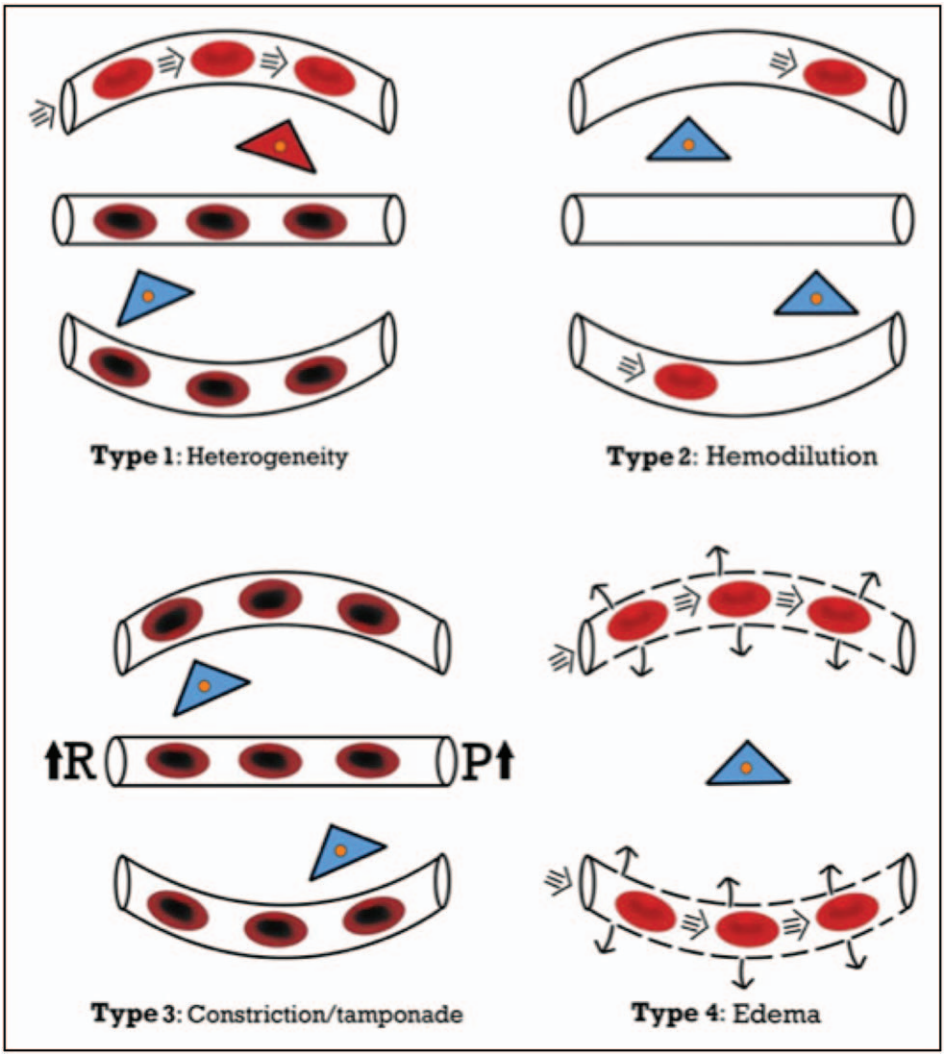

FIGURE 1. Microcirculatory changes in lost hemodynamic coherence. Different microcirculatory changes characterize the mechanisms associated with the loss of hemodynamic coherence resulting in a decreased delivery of oxygen to the cells. Type 1: Heterogenous perfusion of the microcirculation as seen in sepsis. Some capillaries have no flow where others have normal or increased flow resulting in scanted oxygen delivery to some cells. Type 2: Loss of hematocrit in the microcirculation as seen in hemodilution. The result in not only reduced delivery of oxygen but also increased diffusion distance between the red blood cells and the tissue cells. Type 3: Stasis in the microcirculation induced by altered systemic variables. Increased arterial resistance (R), increased venous pressure (P) resulting in a tamponade of the microcirculation. Type 4: Development of tissue edema (e.g. due to capillary leak) resulting in increased diffusion distance between the normally perfusion capillaries and the tissue cells. Red: well oxygenated red blood cells and tissue cells. Dark red/black: red blood cells with decreased oxygen saturation. Blue: tissue cells with reduced oxygenation. From [10].

healthy volunteers, hemodynamic coherence is also present during the progression of circulatory abnormalities. In a model of simulated hypovolemia Bartels *et al.* [35] showed that lower body negative pressure resulted in decreased CO (while BP was maintained) coinciding with abnormal sublingual microcirculatory perfusion. In human models of sepsis, the (macrohemodynamic) characteristics mimic the ones seen in patients presenting with sepsis [36–39]. In a volunteer study, Draisma *et al.* [38] showed that a bolus of endotoxin in healthy volunteers resulted in a decrease in mean arterial pressure and an increase in heart rate (HR) characteristic of clinical sepsis. The bolus of endotoxin was also associated with a decrease in vascular reactivity and a decrease in microcirculatory perfusion, both being restored 4 h after the bolus [38].

With the exception of the brain microcirculation, we can thus assume that in the early phase of severe macrocirculatory dysfunction the microcirculation is compromised. It is conceivable that microcirculatory perfusion abnormalities may

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develop before macrocirculatory hemodynamic changes are prominent. This could especially be the case during a tamponade of the microcirculation by increased central venous pressure (CVP). A clue to this was the finding by Vellinga *et al.* [40] that patients with increased CVP showed an impaired sublingual microcirculation. In patients with sepsis [41] and cardiac failure [42], CVP has been shown to be an independent risk factor for acute kidney injury despite adequate macrocirculatory parameters. However, all of these findings were postresuscitation and thus, other than keeping CVP as low as possible during resuscitation of shock, general recommendations cannot be made from this [43]. It is clinically not feasible to monitor sublingual microcirculatory perfusion in all patients at risk while having normal macrocirculatory parameters although monitoring by ICU nurses of the sublingual microcirculation using a simplified scoring system has been shown to be feasible [44]. In addition, the benefit of intervening to restore microcirculatory abnormalities in patients with adequate macrocirculatory parameters has not been shown, this clearly has a sound rationale and represents a research challenge. Overall, the assumption that the microcirculation is compromised in patients with developing abnormal macrocirculatory parameters in a relevant context seems valid.

COHERENCE IN THE TREATMENT PHASE: EXPERIMENTAL DATA

The main clinically relevant phase of the presence or absence of hemodynamic coherence is the resuscitation phase. As argued earlier, the absence of coherence in this phase may have significant effects on the adequacy of resuscitation as it may result in both over-resuscitation and under-resuscitation. It is clear from experimental models in many different pathophysiologic conditions, including sepsis, that resuscitation on global hemodynamic parameters frequently fails to restore microcirculatory perfusion and oxygenation [25,28,45–47]. The effects in different microcirculatory systems or even within one microcirculatory system may however not be similar [30,48]. There may be few exceptions possibly related to the specific hemodynamic compromise or that may reflect differences in individual responses. In a model of tamponade, van Genderen *et al.* [20] showed that removing the pericardial fluid resulted in a rapid restoration of both macrocirculatory and microcirculatory perfusion parameters. This was very different in the model of septic shock these researchers studied, where restoration of baseline macrohemodynamics did not restore the microcirculation, only resuscitation to a hyperdynamic state restored the microcirculation. However, as there were no control animals in their study, the effect of time could not be ruled out [20]. Although some (experimental) treatments have shown to be more effective in restoring microcirculatory perfusion and oxygen exchange than the use of fluids only [46,49,50] the type of fluids may not be an unimportant aspect of restoring microcirculatory perfusion as well [51,52]. However, a detailed discussion about this is beyond the scope of this publication.

CLINICAL DATA

Several studies in patients with sepsis and septic shock have shown a lack of coherence between the macrocirculation and microcirculation when treating the patient or following optimization of macrohemodynamics [53–59]. Similar findings have been shown in patients with cardiac failure, cardiogenic shock and hemorrhagic shock [56,60–62]. When there is a lack of coherence following initial resuscitation, some of these studies have shown that recovery of the microcirculation may take a much longer time. In many of these studies, the lack of coherence and prolonged recovery time of the microcirculation has been associated with mortality. Persistent macrohemodynamic abnormalities in combination with microcirculatory abnormalities may impose an even more increased risk of mortality [63].

The relevance of different microcirculations, limited by the scarce availability of these in patients, is unknown. In a study in patient with sepsis two studies reported on the coherence of the intestinal microcirculation [64,65]. Both studies showed the absence of coherence between intestinal microcirculation the sublingual microcirculation and the macrohemodynamics. In the study by Boerma *et al.* [64], it was shown that recovery of coherence between the sublingual and intestinal sites was restored after several days.

The use of vasoactive agents to resuscitate the microcirculation has been reviewed earlier [66] and is outside of the scope of this article. The use of beta blocker therapy has gained new interest as both experimental and clinical studies have shown positive effects on microcirculatory perfusion [50,67,68]. As in these studies beta blockers were titrated to HR, the recent finding of the additional effect on mortality of increased HR in patients with abnormal microcirculatory perfusion [63] should encourage additional research in this context.

CONCLUSION

From the previous the following clinical consequences could be drawn. In patients with abnormal macrohemodynamics it is very likely that microcirculatory

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parameters of perfusion are impaired as well. Although in some clinical contexts the improvement of the macrohemodynamics may coincide with improvements in microcirculatory perfusion, restoration of microcirculatory perfusion by aiming to restore macrocirculatory parameters, especially in patients with severe sepsis and septic shock, is unlikely. If anything, restoration of microcirculatory perfusion may take much more time. The clinical relevance is that the absence of coherence, and thus rapid restoration of microcirculatory perfusion is associated with increased mortality in the majority of studies and clinical contexts. Where specific vasoactive drugs and specific resuscitation fluids have been shown to favor improvements in microcirculatory perfusion both the clinical protocol on how to use these and the subsequent effect on patient outcome has hardly been studied.

Therefore, the ultimate conclusion of this article is a call to design studies that evaluate the early resuscitation of the microcirculation together or following restoration of macrohemodynamics.

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Conflicts of interest

J.B.: none. C.I.: Received honoraria and independent research grants from Fresenius-Kabi, Bad Homburg, Germany; La Jolla Pharmaceutical Co., La Jolla, CA, USA and Cytosorbents Monmouth, NJ, USA. C.I. has developed SDF imaging, which is a hand-held video microscope, and is listed as the inventor on related patents commercialized by MicroVision Medical (MVM) under a license from the Academic Medical Center (AMC). He receives no royalties or benefits from this license. Braedius Medical, a company owned by a relative of C.I., has developed and designed a handheld microscope called CytoCam-IDF imaging. C.I. has no financial relationship with Braedius Medical of any sort, that is, never owned shares, or received consultancy or speaker fees from Braedius Medical. The MicroTools software for automatic analysis of microcirculation images is being developed by Matthias Hilty (MH) with support from Active Medical BV of which C.I. and MPH are shareholders. Active Medical runs an internet site called microcirculationacademy.org which offers educational courses and services related to clinical microcirculation and provides more information regarding MicroTools.

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- ■■ of outstanding interest

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The clinical application of assessing the sublingual microcirculation at the bedside and also in clinical research has been limited by the labor intensive way of grading the state of the microcirculation. The computer program discussed in this article might chance these barriers by rapidly analyzing the recording a providing a detailed description of the state of the microcirculation.

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