Assessment of microcirculation in cardiogenic shock

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Purpose of review
Adequate tissue perfusion is of utmost importance to avoid organ failure in patients with cardiogenic shock. Within the recent years, the microcirculation, defined as the perfusion of the smallest vessels, has been identified to play a crucial role. Microcirculatory changes may include capillary flow disturbances as well as changes in the density of perfused vessels. Due to the availability of new technologies to assess the microcirculation, interesting new data came up and it is the purpose of this review to summarize recent studies in the field.

Recent findings
Nowadays, an increasing number of studies confirm parameters of the microcirculation, derived by intravital microscopy, to represent strong outcome predictors in cardiogenic shock. In addition, microcirculation as read-out parameter in innovative clinical studies has meanwhile been accepted as serious endpoint. Treatment strategies such as mechanical assist devices, blood pressure regulating agents or fluids use tissue perfusion and microcirculatory network density as targets in addition to clinical perfusion evaluation and decreasing serum lactate levels.

Summary
The parameter most frequently used to detect tissue malperfusion is serum lactate. Novel, noninvasive methods to quantify microvascular perfusion have the potential to guide treatment in terms of optimizing organ perfusion and oxygenation probably paving the way for an individualized therapy.

Keywords
cardiogenic shock, critically ill, intensive care, intravital microscopy, microcirculation

INTRODUCTION

Cardiogenic shock is a state of low cardiac output (CO) resulting in end-organ hypoperfusion [1,2]. The most frequent cause of cardiogenic shock is acute myocardial infarction with subsequent impairment of left ventricular function. Despite modern treatment algorithms including reperfusion strategies, mortality rates remain critically high. The central dilemma of cardiogenic shock is that the ineffective CO cannot meet the perfusion requirements of organs [3]. This may result in (multi)organ failure, centrally determining patients' prognosis. The recent decade has witnessed a growing knowledge about the central role of the microcirculation in the development of organ failure, especially in shock [4,5]. The purpose of this review is to summarize recent findings evaluating microcirculation in cardiogenic shock and its relevance in clinical practice as well as to shed light on effects of different treatment modalities on the microcirculation in cardiogenic shock.

THE IMPORTANCE OF THE MICROCIRCULATION

The central role of perfusion is delivering oxygen and nutrients to tissues to meet their metabolic demands [6,7]. Insufficient cellular oxygen supply with subsequent tissue hypoxia is a common finding in patients with cardiogenic shock. This initiates the shock cascade, perpetuating the underlying cause and further aggravating organ dysfunction

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KEY POINTS

- A hallmark of cardiogenic shock is the occurrence of organ failure and alterations in the microcirculation play a central role.
- Parameters of the microcirculation such as the density of perfused vessels can predict outcome and are suitable as endpoints in clinical studies in cardiogenic shock.
- New bedside devices have the potential to pave the way for individualized treatment strategies by guiding therapy to aim for optimized organ perfusion and oxygenation.

ultimately escalating to multiorgan failure. Organ tolerance to hypoperfusion varies between tissues but generally might be very low: highest priority is therefore to restore perfusion and resulting oxygenation and circulation. Different treatment protocols targeting toward prespecified surrogate values of hemodynamics and oxygen supply have been shown to improve outcomes [1,8,9]. Of note, this has been made possible by the development of devices enabling real-time monitoring of physiological as well as hemodynamic values. A central milestone in this field was the development of the pulmonary artery catheter by Swan and Ganz [10,11], directly assessing right heart and wedge pressures. This also triggered the development of further invasive estimates of cardiac function and CO [12]. Furthermore, measurements of arterial oxygen content and mixed venous oxygen are frequently used to estimate cardiac performance of critically ill patients, in particular patients with cardiogenic shock. Oxygen delivery and consumption are especially helpful to detect mismatches and guide therapy. Not only the central circulation is of importance, but also peripheral circulation and, in particular, tissue microcirculation play a role. The microcirculation is defined as the perfusion of the smallest vessels with the transition from arteries to arterioles being defined as a vessel diameter below 100 μm [13–15]. This part of the circulation is crucial as nutrients, water, gas, hormons and waste are exchanged. Structurally, the microcirculation consists of arterioles, capillaries and venules. Due to autonomic innervation and local factors released by endothelial cells, the diameter of arteries and arterioles underlie rapid changes. Further down the vascular tree, capillaries have thin walls enabling exchange between blood and surrounding tissues. These capillaries constitute a network with a vessel diameter of around 10 μm without the possibility to be actively regulated [16].

A number of key regulators well known from evaluating macrocirculation are likewise relevant for microcirculation: CO, regional perfusion differences, vascular resistance as well as the composition of the circulating blood on the capillary level [17▪]. Therefore, microcirculatory disorders in critically ill patients might have different causes. In cardiogenic shock, impaired CO is the driving abnormality. However, alterations of vascular resistance in sepsis and septic shock [18,19] might also contribute to cardiogenic shock: changes in volume composition or pH possibly lead to absolute or relative volume lack [20]. A central consideration is that microcirculation is based on flow in arterioles, capillaries and venules as well as the density of this vascular network [21▪,22]. This microvascular network and its function has been attested a key role in the development and pathophysiology of (multi)organ failure. The central relevance of impaired oxygen transport on capillary level caused by an impaired microflow with consecutive organ failure has been comprehensively shown [23–25]. In consequence, treating physicians assess the microcirculation in clinical practice and use this information to guide management of their patients. This might include biological parameters or scores representing the microcirculation or microcirculation associated organ-disorders. In addition, a direct assessment of the microcirculation with a variety of available devices is possible.

ORGAN MANIFESTATIONS OF MICROCIRCULATORY DISORDERS

Clinical manifestations of altered microcirculation are complex and heterogeneous. In cardiogenic shock, particularly low CO contributes to microcirculatory alterations resulting in impaired flow within perfused vessels but also rarefication of this perfused network [26,27,28▪▪]. However, this can become further accentuated by other parts of the equation: transudation of fluids in the perivascular region increases tissue pressure and alters viscosity within the vessel lumen. Both factors alter microflow in or around organs. Alterations in the microcirculation in cardiogenic shock can become particularly evident in the lungs, kidneys, liver, gastrointestinal tract, brain and the heart itself perpetuating the ongoing cascade into a vicious circle [3,14,29,30]. In the lungs, impaired microcirculation might lead to the recruitment of arteriovenous shunts consequently resulting in atelectasis and hypoxia. In the kidneys, impaired microcirculation clinically manifests as oligo or anuria and an increase in retention parameters. In the liver, altered microcirculation leads to functional disturbances,

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including impaired synthesis of factors crucially involved in the coagulation system. The coagulation cascade as a systemic condition determining hemostasis can be distinctly altered in response to an impaired microcirculation [31,32]. In cardiogenic shock, hypoxic hepatitis occurs in 17% of patients [2,33]. Moreover, the maintenance of a sufficient barrier function is important in the gastrointestinal tract with microcirculatory disorders contributing to its destruction [34]. Further, cerebral malperfusion is of highest prognostic relevance [35], is highly sensitive to changes in oxygen tension [36], and its clinical presentation can range from agitation to somnolence. These organ manifestations need to be monitored by clinicians assessing organ function, as well as scoring systems, which are reviewed elsewhere [1]. In summary, there is no single reliable score in cardiogenic shock summarizing all potential prognostic clinical, laboratory, hemodynamic, imaging and biomarker data. Innovative scores summarizing organ failure data lack validation in larger cardiogenic shock cohorts [37–40]. Therefore, detection of microcirculation abnormalities based on already established organ failure might be too late to achieve the goal of an optimized individualized therapy and 'real time online' tools are necessary.

FROM THE CIRCULATION TO THE MICROCIRCULATION

In clinical practice on the ICU, the most common markers in relation to perfusion and organ function monitored in cardiogenic shock are urine output and as well as SBP, mean and DBP [41]. Furthermore, the mixed venous oxygen saturation is widely used reflecting global oxygen supply-demand balance. By looking deeper into cardiac circulatory performance, CO and cardiac index as well as parameters of pre and afterload are of great importance in that context. But, by assessing these systemic parameters, local mismatches in tissue microcirculation might not be represented adequately. Thus, these parameters do not take into account relevant variations with respect to metabolic activity and especially blood flow volume between distinct organs [42]. Against the background of these considerations, an optimal monitoring system should be able to detect alterations early and reliable and further be easy to use at bedside. Abnormal flow in the assessed regional vascular bed should optimally also correlate with global disturbances reflecting malfunction occurring in other organs. This is of particular importance assessing surrogate parameters in mouth (sublingual region), bladder, muscle or subcutaneous tissue [25,43,44].

EVALUATION OF THE MICROCIRCULATION: INDIRECT METHODS

In clinical practice, an established method to indirectly assess microcirculation is evaluating serum lactate levels and its changes [26,45]. This laboratory value is established as clinical standard in treatment protocols of cardiogenic shock patients. However, there are limitations: For example, liver metabolism alterations possibly influence lactate levels [46]. However, lactate levels above 2 mmol/l are considered to stratify critically ill patients at risk for unfavorable outcomes reflecting inadequate oxygen levels in single or various organs [47,48,49▪]. Serial lactate measurements allow the calculation of lactate clearance with possible additional information whether the patient responds to treatment [50–52]. Details of the relevance of serum lactate in patients with cardiogenic shock are reviewed in a separate review article in this issue of the journal. In summary, hyperlactatemia is a sensitive but nonspecific marker of global tissue hypoxia. There are numerous other (bio-)markers of tissue hypoxia in cardiogenic shock, such as tissue-specific microparticles released from activated cells. Nevertheless, these markers have not reached clinical practice until now [53,54]. Further modalities (Table 1) with possible information on microcirculation include contrast echocardiography or contrast-enhanced ultrasound and (contrast enhanced) MRI. However, MRI technology is not available for patients in cardiogenic shock due to logistic reasons. Oxygen in tissues is evaluated by oxygen and CO_2 tonometry: electrodes are inserted with catheter systems or by endoscopic application systems to measure aerobic or anaerobic metabolism [55]. Of note, pharmacological therapy, alimentation or symphatico-adrenergic changes alter pCO_2 and this must be taken into account. On the contrary, meaningful clinical data are lacking using these devices [30,56]. Another method that can noninvasively assess the microcirculation is laser-Doppler technology [16,57]. Recently, Hernandez *et al.* [58▪▪] evaluated capillary refill time, which comes at no costs and assesses peripheral perfusion in critically ill patients: compared with lactate concentration it was noninferior.

EVALUATION OF THE MICROCIRCULATION: DIRECT METHODS

Methods directly visualizing the microcirculation contributed to further knowledge and understanding of the microcirculation [4,28▪▪,29,44]. These developments were triggered by older technologies such as nail-fold video capillaroscopy being highly dependent on body temperature and catecholamine

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Table 1. Selected modalities to investigate the microcirculation in cardiogenic shock

Assessment of the microcirculation	Advantages	Disadvantages
Indirect methods		
Blood pressure	Monitored in every CS patient, no costs	Questionable correlation to organ perfusion
Central venous pressure	Available in most patients	Only one of various variants determining organ microcirculation
Capillary refill	Easy available, no costs	Influenced by extremity perfusion, interobserver and intraobserver variability
Mottling score	Easy available and reproducible	Comparable low correlation to organ microcirculation
Serum lactate	Easy available	Influenced by other parameters and conditions, not on-line with delayed response
Various serum parameters	Sensitive and specific markers available for different organs in research contexts	Not available within a reasonable time frame
(Contrast) Ultrasound/ Echocardiography	Good organ resolution	Moderate correlation to organ failure
(Contrast) MRI	Good organ resolution	Not applicable in CS patients
Gas tomography	Reflects organ metabolism	Direct or indirect organ access necessary, low correlation to organ failure
Direct methods		
Capillaroscopy (nail-fold)	Good reproducibility under standardized conditions	Limited availability, low correlation to organ perfusion, dependent on body temperature
Intravitalmicroscopy [SDF (imaging), IDF (imaging)]	Good reproducibility, good correlation to organ failure, outcome prediction validated, on-line available	Limited availability

CS, cardiogenic shock; IDF, incident dark-field; SDF, sidestream dark-field.

use [59–61]. The central step for further improvement was the development of intravital microscopy systems: Different systems and their application have been reviewed recently elsewhere [28▪▪].

Using these methods, direct in-vivo visualization of the microcirculation on a mucosa became available at bedside. Assessment of microflow as well as density of the vascular network can be described noninvasively and real-time with subsequent (semi)quantification [4,29,44]. The basic principle is that polarized green light gets depolarized by erythrocytes (hemoglobin) serving as optical contrast agent. An example is given in Fig. 1. This method has been used in several hundred clinical studies including numerous studies in cardiogenic shock [23,24,62–67]. Especially, the density of the perfused vascular network is of certain interest due to its high prognostic relevance [68]. For instance, it has been shown that online microcirculatory assessment correlates with future lactate levels in patients with cardiogenic shock [26]. Further recent developments include advancements in the software analysis, new imaging technique such as incident dark field imaging. Next steps will include further improved image resolution with analysis of vessel-compartments such the glycocalyx [27,69,70] and large, prospective clinical studies [71]. In the near future, publication of a microcirculation substudy of the CULPRIT-SHOCK study in cardiogenic shock [72] is expected.

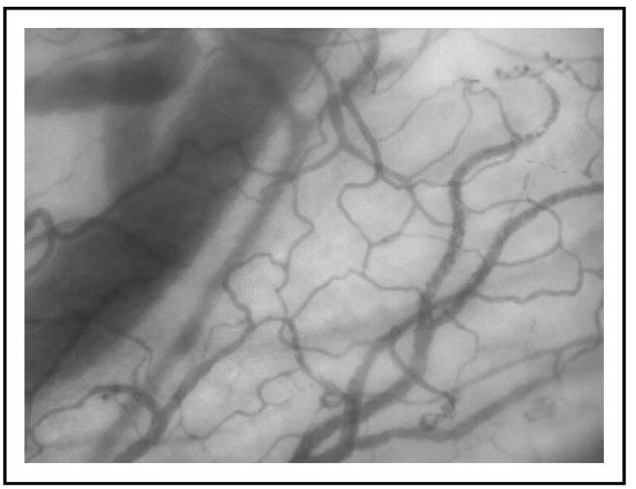


FIGURE 1. Representative visualization of the sublingual microcirculation using sidestream darkfield intravital microscopy.

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CARDIOGENIC SHOCK AND ITS TREATMENT: FINDINGS ON THE MICROCIRCULATORY LEVEL

As described, cardiogenic shock with low CO is characterized by impaired microvascular perfusion [23,73,74]. Its assessment might guide treatment and influence clinical decision-making in critically ill ICU patients and cardiogenic shock patients. The aim is to restore microperfusion reflected by decreasing lactate levels. It has been demonstrated that especially the smallest capillaries are affected in cardiogenic shock [68], the vessel category with the highest prognostic relevance [68]. Initial studies convincingly demonstrated that the microcirculation can be assessed in serial measurements during ongoing therapy [63,74–76]. Most studies in the setting of cardiogenic shock investigated the treatment consequences of assist devices, a powerful modality to improve CO and perfusion [46,73,75,77–79]. The first randomized study investigating the microcirculation in cardiogenic shock was published in 2015 revealing no acute (5 min stop of intra-aortic balloon pump (IABP) support) or chronic (randomized into the IABP versus control group) IABP treatment effect. Outcome could be predicted using microcirculatory parameters. Recently, Yeh *et al.* [80▪] also used early microcirculatory parameters to predict outcome during extracorporeal membrane oxygenation (ECMO), such as perfused small vessel density. Also, sublingual measurements of the microcirculation have been used to guide weaning from ECMO in cardiogenic shock and were found to be specific and sensitive weaning parameters compared with echocardiographic assessment [81]. However, comparability of studies investigating ECMO use in cardiogenic shock regarding the microcirculation is limited due to huge differences in patient populations and microcirculation assessment strategies [82].

Another randomized study was published recently by Fuernau *et al.* [83▪▪], whereas hypothermia is an established treatment modality following cardiopulmonary resuscitation [35], it might also affect organ oxygen consumption. However, in this recent study, hypothermia did not improve macrocirculation or microcirculation. A component of individualized therapy in cardiogenic shock is a differentiated catecholamine therapy with a fundamental meaning of the cautious and fine-tuned combination of inotropic substances and vasopressors. The most frequent substances recommended in guidelines are dobutamine as inotropic agent and the vasopressor norepinephrine [1,84]. Although perfusion pressure is mandatory, norepinephrine negatively affects the microcirculation due to its strong vasoconstrictive effects [26,85]. Of note, the target blood pressure in cardiogenic shock remains unknown but small cohorts might indicate that increasing mean arterial pressure fairly above 60 mmHg does not improve microcirculation [86,87]. However, inotropy might positively influence the microcirculation in patients with cardiogenic shock in nonrandomized studies. Furthermore, an improvement in the microcirculation in patients with cardiogenic shock can be achieved using nitrate administration [88,89] and this might also be applicable for other compounds. It seems reasonable to use the microcirculation in addition to hemodynamic parameters to guide diagnostic and therapeutic considerations [24,90].

CONCLUSION

Alterations in the microcirculation are a pathophysiological hallmark in cardiogenic shock and a central feature of organ failure. This essentially determines the prognosis of cardiogenic shock patients. The widely accepted and most frequently used parameter to detect tissue malperfusion is serum lactate. However, noninvasive methods to quantify microvascular perfusion currently gain more and more attention and are increasingly used. These technologies might pave the way for individualized treatment strategies by guiding therapy with focus on optimizing organ perfusion and oxygenation.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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