Microcirculatory dysfunction in critically ill patients: prevalence and significance from a bedside perspective
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This chapter will summarize the main conclusions of the studies described in this thesis in view of recent literature, together with suggestions for future research. Associations between the microcirculation and macrohemodynamics as well as the position of microcirculatory imaging at the bedside will be issues of specific interest.

**EPIDEMIOLOGY OF PERI-OPERATIVE MICROVASCULAR DYSFUNCTION**

Chapter 2 provided the reader with an overview of current literature focusing on microvascular dysfunction in the peri-operative period. The peri-operative period is of specific interest because of the high number of patients being exposed to surgery as well as considerable surgery-related morbidity and mortality [1]. The studies that were discussed in this review highlight the potentially harmful effects of surgery and common peri-operative interventions on the microcirculation. Again, a recurring finding is the absence of a clear association between alterations at the microvascular level and macrohemodynamic parameters. Of note, anesthesia itself appeared to be associated with considerable microvascular alterations [2,3].

Fields of specific interest for future research are the peri-anastomotic microcirculation in gastrointestinal surgery and cardiopulmonary bypass related microcirculatory dysfunction, as these types of surgery affect a large number of patients. In gastrointestinal surgery, studies have mainly applied methods that cannot discriminate capillary perfusion [4-6]. Direct visualization of the peri-anastomotic microcirculation could be of help to detect impaired perfusion as a risk factor for anastomotic dehiscence. In cardiopulmonary bypass, a pulsatile mode is generally associated with less severe microcirculatory dysfunction [7-11]. The association between intra-operative microcirculatory dysfunction and post-operative consequences of pulsatile versus non-pulsatile modes could be further explored, for instance with respect to organ dysfunction. Furthermore, studies could aim to investigate the effects of different resuscitation strategies on microcirculatory dysfunction: as studies do not show unequivocal results with respect to peri-operative microvascular dysfunction, timing as well iatrogenic factors such as peri-operative fluid and hemodynamic management appear to play a significant role. As peri-operative microvascular impairment can be indicative of an increased risk of complications or increased length of ventilation, one would like to incorporate this information in peri-operative management [12-20]. A recent study elegantly evaluated the effect of dopexamine and different post-operative resuscitation strategies on microvascular dysfunction and tissue oxygenation. In patients treated with stroke volume guided fluid therapy combined with a fixed dose of the $\beta_2$-agonist dopexamine, both increased sublingual microvascular flow as well as improved tissue oxygenation was observed, as opposed to patients treated with CVP guided resuscitation. Moreover, acute kidney injury was more frequent in CVP-guided resuscitation as compared to stroke volume guided resuscitation [21].
SETTING OF THE MICROCIRCULATORY SHOCK OCCURRENCE IN ACUTELY ILL PATIENTS (MICROSOAP)

Main project of this thesis was the Microcirculatory Shock Occurrence in Acutely ill Patients (microSOAP). As of now, the microSOAP provides the largest prospectively collected dataset on the prevalence of sublingual microcirculatory alterations in critically ill patients. Data collection would not have been possible without extensive effort of local investigators, specifically with respect to the time consuming medical ethics approval process. Ethics approval processes for the microSOAP varied from extensive reviews to allocation of a waiver of informed consent. This variation in ethics approval is a well-known phenomenon [22,23]. Due to its primarily explorative character in a hitherto underrepresented setting, namely the heterogeneous setting of daily ICU practice, it was not clear beforehand what to expect. Based on previous prospective studies, we successfully aimed for a sample size of around 500 patients. No informed consent was the major reason for exclusion. This could only be partially ascribed to logistic issues, such as unavailability of the next of kin or legal representative. Several participating centers reported that despite the rather non-invasive measurements, a considerable number of patients or their legal representatives preferred not to participate.

Inclusion of 81% of eligible patients was achieved: local investigators excluded 49 patients because of the inability to obtain adequate SDF images, for instance because of recent maxillofacial surgery or injury. Agitation was another common reason for exclusion: 22 patients were unable to cooperate with image acquisition. Only 20 patients had to be excluded due to insufficient image quality. The microSOAP therefore demonstrated the feasibility of application of this demanding imaging technique at a larger scale.

Open source clinical trial software as well as an internet based platform for the exchange of SDF images have greatly facilitated this study. For data collection, a customized open source Open Clinica database was constructed. Open Clinica is one of the most popular software packages in this field. The compliance of Open Clinica software with most recent international legislation on data acquisition in research settings, was key to medical ethics approval for several countries [24,25]. Dedicated software enabled participating centers to identify suitable SDF clips per patient and to send these clips to the study server via the internet. However, as the uploading process proved rather demanding, especially for hospital computer systems, this was a time consuming process with several obstacles. In some instances, SDF images had to be sent to the coordinating study center on a pen drive or DVD by regular mail.

MICROCIRCULATORY ALTERATIONS IN MICROSOAP PATIENTS

The participating centers, 36 ICU’s from all over the world, included a heterogeneous ICU population consisting of 501 patients in whom the sublingual microcirculation was evaluated. At the time of the microSOAP data acquisition, the median [interquartile
length of stay in the ICU prior to study inclusion was 3 [0.9-8] days, which was considerably longer as compared to previous studies in this field. Although an abnormal MFI was not associated with adverse outcome in the overall population, an abnormal MFI did have prognostic significance in a high risk subgroup. This subgroup was identified by the presence of tachycardia (heart rate > 90 beats per minute). Notably, the prognostic significance of an abnormal MFI was independent of arterial lactate levels, thereby underlining the importance of monitoring the microcirculation in critically ill. Moreover, it shows that macrohemodynamic derangement can point towards microvascular dysfunction. The paragraph ‘Microcirculation and macrocirculation: expanding knowledge’ will further elaborate on this issue.

For analysis, it was decided to focus on MFI because of the potential of bedside evaluation, awaiting next generation software that might bring the analysis for other microcirculatory parameters to the bedside [26]. As the prevalence of an abnormal MFI, predefined as a capillary MFI<2.6, was 17% in the microSOAP study population, this was less severe microcirculatory dysfunction than previously observed in single center high mortality subgroups. For comparison, previous studies on sublingual microcirculatory alterations in patients with severe sepsis, septic shock or heart failure have reported mortality rates ranging from 11% to 58% for average APACHE II scores of around 20 [27-34]. After the microSOAP study period several studies have reported a lower prevalence of microcirculatory alterations in lower risk populations, such as non-hypotensive sepsis as well as post-operative patients [35-37]. Moreover, a meta-analysis of De Backer and co-workers suggests that the incidence of severe microcirculatory alterations is decreasing in the last decade [27]. This might coincide with better chances of survival for ICU patients [38,39].

**SIGNIFICANCE OF MILDLY ELEVATED LACTATE LEVELS**

Chapter 5 explored the associations between lactate levels, microcirculatory alterations and outcome in the microSOAP population. These data fit in with recent reports on the prognostic significance of ‘relative hyperlactatemia’, i.e. lactate levels < 2 mmol/L. This study is the first to show that associations between relative hyperlactatemia and adverse outcome are not limited to the early phase of an ICU admission. Furthermore, the association between microcirculatory dysfunction and increases in lactate levels was confirmed. Direct in vivo microscopy can be of help by detecting hypoperfusion at the capillary level. When there are no signs of hypoperfusion at the capillary level in patients with (relative) hyperlactatemia, together with macrohemodynamic parameters in an acceptable range, it is less likely that attempts to increase circulatory support by means of vasoactive drugs or fluid therapy will improve tissue perfusion. Moreover, unnecessary ‘improvement’ of the circulation may even be harmful [40]. However, the question remains what the clinical significance is of a single mildly elevated lactate level for a particular patient and how to respond to it. Most likely, changes in
lactate over time provide more clinically applicable information. Studies in the field of evolution of lactate levels have primarily focused on lactate levels > 2 mmol/L and higher. The microSOAP data suggest that it could be worthwhile to explore this issue for relative hyperlactatemia not limited to early ICU treatment.

**TREATMENT OF MICROCIRCULATORY ABNORMALITIES**

As discussed in the introduction of this thesis, effects of vasoactive drugs on microcirculatory perfusion are not unequivocal. Chapter 7 describes the results of an open label pilot study on the effects of intravenous ketanserin on the microcirculation. Besides vasodilation, this drug may influence microvascular derangements by favorably modifying thrombocyte aggregation and cytokine profiles. The approach described in this chapter was characterized by 1) solely including patients with markedly altered microcirculation after fulfillment of a strict resuscitation protocol; 2) its dose finding character. By including patients with a persisting small vessel MFI ≤ 2.5 it was ensured that it would be possible to visualize improvement of microvascular perfusion at the bedside [26]. Moreover, the results would not be clouded by patients in whom microcirculatory perfusion was more or less normalized. This combination of bedside MFI assessment and a dose finding schedule turned out to be feasible. However, a major limitation of this study is its open label design. The rapid microcirculatory improvement (for most patients within 60 minutes) makes it tempting to conclude that the improvements in MFI were ketanserin-induced. Several studies describe improvement of MFI towards a value of 3; however, this is described over a time course of several days rather than hours [30,41]. This, as well as an improved microcirculation during ketanserin administration, can also be interpreted as regression to the mean: the natural tendency of values to tend to regress to the ‘true’ mean [42]. Regression to the mean might also have played a role in previously published open label studies. Especially studies describing an amelioration of microcirculatory perfusion and diffusion that is inversely correlated to baseline values, could essentially describe regression to the mean instead of an influence of the study protocol on microvascular perfusion [43 -46]. Values at both extremes of a dataset will tend to regress to mean: patients with an extremely altered microcirculation are likely to show less microcirculatory derangement at a follow up measurement. Therefore, regression to the mean can be erroneously interpreted as a treatment effect. Major pitfall in these studies is the lack of a placebo group, as a comparison with a placebo group can unmask the confounding effect of regression to the mean. Interestingly, out of the studies with a control group, only studies on levosimendan and activated protein C showed beneficial effects on microcirculatory dysfunction [47,48]. Placebo controlled studies on nitroglycerin and dobutamine in septic patients failed to show any effects, as opposed to open label studies on these drugs [30,49 -51].
MICROCIRCULATION AND MACROCIRCULATION: EXPANDING KNOWLEDGE

As discussed in the introduction of this thesis, the associations between macrohemodynamic parameters and microcirculatory dysfunction are relatively loose. Nevertheless, several studies describe associations between micro- and macrohemodynamics in the early phase of disease. Both the microSOAP as well as chapter 6 on elevated central venous pressure and microcirculatory dysfunction show that it could be worthwhile to zoom in on the microcirculation from a macrohemodynamic perspective.

Among other well-known variables that are associated with mortality, tachycardia (heart rate > 90 beats per minute) was independently associated with adverse outcome in microSOAP patients. The association between tachycardia as one of the signs of sympathetic (over)stimulation and an increased risk of death is widely known [52-58]. Interestingly, the presence or absence of tachycardia in microSOAP patients did not seem to be a factor in determining whether a patient was considered adequately resuscitated. This is even more intriguing in view of recent studies on reducing heart rate in critically ill [59-62]. Moreover, in microSOAP patients with tachycardia, a MFI < 2.6 was associated with higher hospital mortality as compared to a MFI ≥2.6, independent of arterial lactate levels. As tachycardia can be seen as an expression of the sympathetic response to disease, the inability to preserve microcirculatory perfusion could be interpreted as a sign of the inability to cope with critical illness-induced stress. Because heart rate is continuously monitored in most critically ill patients and is a well-known predictor of adverse outcome, this macrohemodynamic parameter could serve as a convenient starting point for detecting prognostic important microcirculatory dysfunction. Of specific interest in this respect is a recent study describing the effects of reducing sympathetic stress by esmolol administration. In patients with septic shock, intravenous esmolol was titrated to achieve a heart rate between 80 and 94 beats per minute after initial stabilization. Sublingual microcirculation was not impaired by this strategy [63].

Chapter 6, Elevated central venous pressure is associated with impairment of microcirculatory blood flow in sepsis: a hypothesis generating post hoc analysis, provides a downstream approach to microcirculatory perfusion. Specifically, this study was intended to focus on the difference between microcirculatory perfusion pressure and systemic perfusion pressure. As systemic perfusion pressure is classically defined as the difference between mean arterial pressure and central venous pressure, this definition does not take the pressure drop at terminal arterioles into account. Because of this pressure drop, the actual microcirculatory perfusion pressure is the pressure gradient between post-arteriolar and venular pressure (fig. 1) [64,65]. Increased venular pressure could therefore serve as an outflow obstruction for the microcirculation. The hypothesis generating finding of an association between a CVP > 12 mmHg and impaired microcirculatory perfusion could invite researchers to observe the microcirculation from this downstream perspective. Interestingly, Den Uil et al. observed an inverse association between CVP and PVD in early phase cardiogenic shock as well as in heart failure treated with nitroglycerin [33,66]. In addition, it is of interest that microcirculatory flow was impaired in CVP guided peri-
operative management [21]. Moreover, increases in central venous pressure are associated with renal dysfunction, irrespective of cardiac index [67 -69]. Microcirculatory outflow obstruction may therefore be one of the mechanisms underlying the detrimental effects of increased venous pressure.

Concluding, at the bedside both tachycardia and increased CVP can point towards microcirculatory dysfunction from a macrohemodynamic perspective. A prospective analysis of the course of macrohemodynamic parameters and microcirculatory perfusion could further elucidate these issues. However, limited macrohemodynamic monitoring in the microSOAP patients precluded an extensive evaluation of associations between the microcirculation and the macrocirculation. Although blood pressure and heart rate were available for all patients, cardiac index was available for only 6.2% of patients; S(c)vO\textsubscript{2} for 20%. Of note, this was not due to a lack of availability of these techniques at the participating institutions: pulmonary artery catheters, continuous S(c)vO\textsubscript{2} monitoring and/or pulse contour analysis were available in over two thirds of ICU’s at the time of microSOAP participation (2011). The optimal approach to monitoring, how to respond to ‘abnormal’ values and the implications with respect to outcome, are subject to ongoing debate (e.g. [70 -77]). Since a recent study on early goal directed sepsis therapy (the ProCESS-trial) showed no significant differences in outcome between two goal directed treatment strategies and non protocolized standard care, this issue becomes even more complicated [78].

![Figure 1](image.png)

**Figure 1.** Schematic representation of microcirculatory perfusion pressure. Increases in central venous pressure (CVP) decrease the perfusion pressure (ΔP) of the microcirculation. This leads to impairment of microcirculatory perfusion.
FUTURE PERSPECTIVES ON THE MICROCIRCULATION IN CRITICALLY ILL: SUGGESTIONS ON ITS ROLE FROM A BEDSIDE PERSPECTIVE

In an ideal world, direct in vivo microscopy could be become incorporated in daily resuscitation practice in order to provide detailed information on tissue perfusion. Taking the studies described in this thesis as a starting point, a priori chances of detecting microcirculatory alterations will be highest in 1) patients with arterial lactate levels > 1.5 mmol/L; 2) in the early phase of ICU stay (< 24 hours) and 3) possibly, in association with elevated central venous pressure. A crucial finding in the microSOAP database was the independent prognostic significance of a capillary MFI<2.6 in patients with tachycardia as this was independent of arterial lactate level. This highlights the importance of microcirculatory perfusion as a factor that has to be taken into account at the bedside and could fit in with, as suggested by Dünser and co-authors [79], a tailored approach to organ perfusion with the potential to avoid macrohemodynamic overstimulation that might not benefit the patient.

As is known that persisting microcirculatory alterations are associated with an unfavorable clinical course, a sensible approach could be to screen for microcirculatory alterations in patients who remain tachycardic or have (slightly) elevated lactate levels after conventional macrohemodynamic resuscitation. In patients with persisting microcirculatory alterations, first step would be to critically review the ‘conventional’ resuscitation process: is the resuscitation process performed according to plan? Is there room for fine tuning? A second step could be to evaluate the effect of changes in therapy on microcirculatory perfusion, as the ultimate goal is to enhance tissue perfusion. As a study by Pranskunas et al. demonstrated, microcirculatory perfusion improved in patients with clinical signs of impaired organ perfusion and a baseline MFI < 2.6, but not in patients with a higher baseline MFI. As this was independent of the systemic hemodynamic response, monitoring the microcirculation proved to be of added value. As described in chapter 7, bedside assessment of MFI together to evaluate the effect of administration of a vasoactive drug is feasible. In this, frequent reassessment is key.

In order to facilitate implementation of microcirculatory imaging at the bedside, several issues need to be addressed: doctor’s mindset, feasibility of SDF imaging and analysis at the bedside, heterogeneity in microcirculatory perfusion and - most important- therapeutic approaches and prognostic consequences.

Doctor’s mindset
Changing the doctor’s mindset to a primarily perfusion based approach is challenging. For instance, current Surviving Sepsis Campaign (SSC) guidelines advocate a resuscitation strategy that is primarily pressure based. An individualized approach to SSC-guided fluid administration incorporating echocardiographic evaluation of volume status showed that in 30% of patients physicians refrained from fluid administration when the decision to administer fluids was based on a combination of echocardiographic evaluation and SCC-guidelines as compared to SCC-guidelines alone [80,81]. Moreover, as discussed in the previous paragraph, macrohemodynamic
monitoring providing information other than blood pressure and heart rate appears to be rather limited in daily ICU practice. This limits flow and perfusion based resuscitation. In our ICU, introduction of a fluid responsiveness protocol based on a passive leg raise test was associated with a compliance of only 56%, despite adequate training [82]. Interestingly, a recent study on blood pressure targets in septic shock patients showed similar signs of non-compliance [83]. Aim of this study was to compare MAP targets of 65-70 mmHg and 80-85 mmHg. No patients in the low pressure target group had a MAP < 70 mmHg: since all patients received vasopressor support, physicians apparently failed to decrease vasopressor load, despite its well-known adverse effects [84]. Extensive and regular feedback has shown to improve protocol adherence when introducing new resuscitation strategies [85].

**Easy application of in vivo microscopy at the bedside**

At the present moment, bedside application of SDF is limited because of both equipment specifications and analysis procedures. Although bedside assessment of MFI is validated, parameters of vessel density and PPV still require time consuming offline analysis. Despite availability of an image acquisition stabilizer, current SDF cameras require a considerable learning period [86,87]. It is expected that next generation light weight in vivo microscopy cameras as well as improved analysis software will lead to easier application of in vivo microscopy at the bedside [88]. Both a higher resolution and a higher frame rate can enhance imaging of for instance leukocyte rolling and glycocalyx degradation. Moreover, the next generation device has a quantitative focusing mechanism enabling determination of patient-specific focus depths [89]. Advances in analysis software will enable fast and reliable assessment of vessel densities at the bedside. Furthermore, attempts could be made to incorporate emission of light with different wave lengths in the absorption spectrum of hemoglobin. This would allow for quantification of capillary oxyhemoglobin and deoxyhemoglobin. These kind of advances in direct in vivo microscopy would help to further unravel mechanisms that contribute to microcirculatory dysfunction as well as extend the possibilities of monitoring treatment effects at the bedside.

**Spatial heterogeneity and heterogeneity over time**

Heterogeneity within and between organs as well as over time is a factor of potential major influence. Specifically, the timing as well as the extent of the insult, such as infection or myocardial infarction, cannot be determined as precise as in animal experiments. Therefore, this has the potential of being an important confounder. However, sublingual alterations have been associated with adverse outcome in several distinct clinical settings, including a high risk subgroup of microSOAP patients. Because of the convenience of the sublingual region, it appears reasonable to proceed with this focus on the sublingual microcirculation. Nevertheless, one needs to stay aware of the presence and potential significance of heterogeneity. Future studies focusing on the course of microcirculatory alterations could shed more light on interindividual variations over time.
Will treatment of microvascular alterations lead to better outcomes for individual patients?

As extensively discussed, studies on microcirculatory resuscitation do not show unequivocal results. The etiology of microcirculatory alterations can differ between diseases, therefore it is likely that illness specific approaches will be needed. In this, timing of an intervention might be crucial. Preferably, underlying mechanisms will be thoroughly studied in an experimental setting before a promicrocirculatory strategy is tested in patients. Moreover, adequate selection of eligible patients is key to a proper evaluation in a clinical setting. However, until potentially effective strategies have been studied in larger populations, it remains unknown whether therapy-induced amelioration of microcirculatory alterations will benefit the individual patient. For instance, activated protein C is reported to have beneficial effects on microcirculatory alterations in sepsis, whereas it is withdrawn from the market because of a lack of mortality reduction [90 -93]. Moreover, it is possible that microcirculatory alterations are part of a potentially adaptive and protective mechanism [94].

SUGGESTIONS ON FUTURE RESEARCH

It is clear that microcirculatory alterations can be an indication of an unfavorable clinical course, both in high mortality critically ill subgroups as well as in a heterogeneous ICU population. As the microSOAP was a point prevalence study, future research could aim to explore the incidence as well as the course of microcirculatory alterations in a similar context. Specifically, a setting with comprehensive macrohemodynamic monitoring would facilitate exploration of associations between macrohemodynamic and microhemodynamic parameters. Although the microSOAP provides the largest dataset this far, comparatively small numbers per subgroup might have clouded differences in microcirculation between subgroups. Therefore, aiming for a large number of inclusions for a particular admission group would facilitate extrapolation of the findings. Hopefully, that will enable refinement of the prognostic implications of microcirculatory alterations in daily practice. With respect to evaluating the effects of increased venous pressure, the association with resistance to venous return could be studied. Recently, it was described how to estimate mean systemic filling pressure at the bedside by measurements of cardiac output and central venous pressure during inspiratory holds with varying pressure levels. Resistance to venous return can subsequently be calculated as the slope of the curve describing the relationship between cardiac output and central venous pressure [95].

Although it is crucial to have a clear framework of microcirculatory dysfunction and its prognostic significance, even more important is knowledge on how attenuation of microvascular alterations could influence outcome. Extensive knowledge on the etiology of microcirculatory alterations can indicate potentially effective strategies. Experimental studies can be of help: as the timing as well as the extent of an insult (induction of endotoxemia, hypoxia) is well-controlled, it allows for observation of the microcirculation with as little as confounding factors as possible. Moreover, as monitoring
of microcirculatory and mitochondrial PO$_2$ is limited to research settings at the present moment, it could allow for evaluation of beneficial effects of a particular therapy on oxygenation at the level of the microcirculation.

Before conclusions on the prognostic effect of treatment of microcirculatory dysfunction can be made, pro-microcirculatory strategies that are effective in a clinical setting will have to be identified. As the ‘magic bullet’ for treatment of microcirculatory alterations is yet to be found, this is still a hope for the future. A placebo controlled setting would allow for correcting for confounders as best as possible. However, this is not feasible for every study. Future research could aim to explore the clinical effects of pro-microcirculatory strategies that are directed at vasodilation, coagulation modification or glycocalyx integrity that have been proven effective in an experimental setting. As the study on ketanserin administration (chapter 7) showed, it is feasible to incorporate a dose finding protocol with bedside evaluation of microcirculatory response. Similar methods could be incorporated in future studies, as it will help to answer the question of finding the appropriate dose of a particular drug for the individual patient. Furthermore, direct in vivo microscopy could be used to map effects of conventional therapies. As it is expected that next generation acquisition hardware and analysis software will allow for easier image acquisition and bedside automated analysis of both flow and vessel densities, effects of fluid therapy with respect to vessel density as a measure of diffusion distance and edema formation could be monitored. An interesting example in this respect is an animal study on fluid management based on sublingual PCO$_2$-values, demonstrating that less volume is required to achieve microcirculatory perfusion goals, as compared to a conventional blood pressure goal [96]. However, direct in vivo microscopy would allow for visualization of resuscitation effects at the level of the capillaries. Similarly, the effects of decreasing vasopressor load could be observed.

On top of that, research could be designed to map local microcirculatory responses, such as peri-anastomotic microcirculation and peri-operative renal perfusion. In this, incorporation of direct in vivo microscopy in laparoscopy devices as well as combinations with other techniques such as laser speckle would be of great help [97].

Hopefully, future research will shed more light on effective pro-microcirculatory strategies and provide insight on the prognostic effects of microcirculatory guided resuscitation.
REFERENCES


