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Endothelial and microcirculatory function and dysfunction in sepsis

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SYNOPSIS

The microcirculation is a series of arterioles, capillaries, and venules that performs essential functions of oxygen and nutrient delivery, customized to the unique physiologic needs of the supplied organ. The homeostatic microcirculatory response to infection, which includes barrier hyperpermeability, leukocyte adhesion, and coagulation activation, can become harmful if overactive and/or dysregulated, contributing to the organ failure characteristic of sepsis. In humans, pathologic microcirculatory dysfunction can be directly visualized by intravital microscopy or indirectly measured via detection of circulating biomarkers, such as endothelial glycocalyx fragments. While several treatments have been shown to protect the microcirculation during sepsis, these therapies have not improved patient outcomes when applied indiscriminately. Future outcomes-oriented studies are needed to test the utility of sepsis therapeutics when applied in a manner “personalized” to a patient’s microcirculatory dysfunction.

Keywords

Sepsis; microcirculation; glycocalyx; intravital microscopy; glycosaminoglycans; heparan sulfate

Anatomy and function of the microvasculature

The microcirculation, comprised of < 100 μm-diameter arterioles, capillary beds, and draining venules, performs essential homeostatic functions including oxygen delivery and solute exchange[1]. While this simple construct holds true across all human tissues, there is

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substantial organ specificity of microcirculation structure, reflecting unique functions assigned to different vascular beds. The kidney glomerulus, tasked with plasma ultrafiltration, features afferent and efferent arterioles flanking a capillary network lined with fenestrated endothelium. In contrast, the cerebral and pulmonary vasculature are characterized by tight endothelial barriers (and supporting pericytes), reflecting organ functions that would be threatened by interstitial edema. These organ-specific differences in microvascular function are paralleled by tissue-specific endothelial phenotypes, yielding varied mechanisms of endothelial-leukocyte adhesion (e.g. pulmonary vs. systemic circulations[2]) and organ-specific endothelial glycocalyces[3].

The normal microvascular response to infection

To understand dysfunction of the microcirculation during sepsis, it is necessary to appreciate the appropriate microvascular response to infection. The inflammatory response to infection, as described in the first century AD, consists of *calor* (heat), *rubor* (redness), *dolor* (pain), and *tumor* (swelling)[4]. From a microcirculation standpoint, these responses reflect altered regional blood flow, vascular hyperpermeability, leukocyte recruitment, and coagulation[1]. It is critical to recognize that these physiologic changes are appropriate and effective in the setting of acute infection. The vast majority of viral and bacterial infections are controlled quickly by the host and do not lead to disseminated infection, organ failure, and death. By allowing for the beneficial actions of *calor*, *rubor*, *dolor*, and *tumor*, the microcirculation facilitates local quarantine of pathogens, targeted delivery of soluble anti-infectious agents (e.g. complement, immunoglobulins), and chemotaxis of activated host immune cells.

Leukocyte adhesion

The recruitment of leukocytes to areas of infection is a highly regulated process, consisting (in systemic venules) of active leukocyte rolling, adhesion, activation, aggregation, and transmigration, demonstrating the importance of these processes to tissue homeostasis[5]. In the absence of infection, leukocyte-endothelial interactions are limited, occurring primarily in specialized vascular beds (e.g. lymph node high endothelial venules). There is great heterogeneity across different vascular beds regarding processes of leukocyte extravasation, with rolling being essential for diapedesis from systemic venules but dispensable for extravasation from the pulmonary capillaries[2,6].

Tissue edema

The intense, multi-process regulation of vascular permeability reflects its critical importance in microvascular function[7]. Indeed, the targeted extravasation of antibacterial peptides, antibodies, and complement is beneficial to the host response to infection. However, barrier dysfunction can become pathologic if transvascular fluid flux overwhelms lymphatic drainage or other tissue-specific safeguards against interstitial edema[8].

Coagulation

Microvascular coagulation is important to the host response to infection. Endothelial damage and inflammatory cytokines lead to a pro-coagulant state in the microvasculature, allowing for the development of microthrombi[9,10]. This response functions to isolate infection and

prevent dissemination. Murine studies have shown that anticoagulants facilitate bacterial spread after peritonitis, leading to worsened sepsis outcomes[11]. The failures of activated protein C, antithrombin III, and tissue factor antagonists to improve sepsis outcomes perhaps reflect homoeostatic effects of microvascular coagulation[12–14].

These and other microcirculatory responses are adaptive and often successful in localizing and eliminating infectious insults[15–17]. However, in extreme cases of overwhelming infection, these processes may contribute to the overall morbidity and mortality of sepsis (Figure 1).

Evidence of microvascular dysfunction during sepsis

Oxygen delivery (DO_2) is a function of both cardiac output and blood oxygen content. As early sepsis is characterized by a low systemic vascular resistance/high-cardiac output state, DO_2 is typically elevated in sepsis. Indeed, the kidney, brain, and heart all experience augmented blood flow during sepsis[19]. Despite this increased bulk delivery of oxygen, tissue hypoxia persists in sepsis and contributes to septic organ injury[1]. This suggests that the defect of sepsis is not a loss of macrovascular blood supply, but rather a loss of microvascular function. Indeed, therapeutic attempts to augment macrocirculatory oxygen delivery by increasing cardiac output or hemoglobin have failed to improve outcomes in sepsis[20–24].

This suspected microvascular defect in sepsis has been extensively investigated using animal models[25], identifying critical pathogenic roles of endothelial barrier dysfunction[26,27], inappropriate leukocyte adhesion[28], platelet activation[29], activation of microvascular coagulation[9], and aberrant control of vascular tone[30]. These changes broadly mediate injury across numerous organ systems of relevance to sepsis outcomes, including the lung[31], kidney[32], and brain[33]. Importantly, there is no discrete, readily-apparent inflection point at which beneficial microvascular responses to infection change to pathologic contributors to sepsis. Sepsis may arise from numerous microcirculatory changes, including activation of anti-infection responses in vascular beds where no pathogens exist, or a magnitude of anti-infection response that outstrips what is necessary for microbial clearance. This complexity warrants a deeper understanding of the precise changes occurring within an individual during sepsis, potentially allowing for personalization of sepsis therapeutics.

Measuring septic microvascular dysfunction in humans

Detecting and characterizing microvascular dysfunction in humans is technically challenging, given difficulties in the direct measurement of clinically-relevant vascular beds. Systemic, circulating biomarkers of tissue ischemia (e.g. central venous oxygenation, lactate) are not sensitive to microcirculatory defects, given the potential for “functional shunting” in which venular PO_2 exceeds capillary PO_2[1]. Furthermore, the value of therapeutically targeting these markers is uncertain, given recent negative studies of early goal-directed therapy[22–24]. As recently reviewed elsewhere[27,34], numerous promising biomarkers for capillary endothelial dysfunction (e.g. angiopoietins, glycocalyx fragments) have been identified in septic shock. These biomarkers, however, often are not easily

measured point-of-care and have yet to be validated as clinically-relevant treatment endpoints.

An alternative approach to rapidly measuring microcirculatory function is direct imaging of microvessels using intravital microscopy[35]. While nail fold or episcleral vessels can be visualized at the bedside[35], these vascular beds yield little quantitative data regarding microvascular function without the use of large microscopy systems. However, the development of microscopy techniques such as orthogonal phase spectrometry (OPS) or sidestream darkfield imaging (SDF) has led to increasing enthusiasm for the bedside imaging of the sublingual microvasculature. OPS and SDF imaging can clearly identify RBCs, due to the absorptive effects of hemoglobin. As such, these techniques can identify RBC-perfused vessels (Figure 2); a lack of visualized sublingual vessels serves as evidence of absent or impaired RBC flow[36].

This visualized loss of sublingual microvascular RBC perfusion can be quantified via several techniques, either at point-of-care[37] or during later review of recorded images. Loss of RBC flow yields a heterogeneous loss of vascular density apparent on OPS and SDF imaging, particularly involving small (< 20 μm) microvessels. This microvascular drop-out can be quantified by using several different validated approaches, including the De Backer score (which employs a stereological-like approach in which vessel density is calculated from intersections with overlying gridlines) or the microvascular flow index (a semiquantitative score determined from the average of qualitative assessments across four visual field quadrants, Figure 2)[36,38].

While consensus statements have detailed standardized approaches to the quantification of intravital measures of microvascular function[36], there remain several practical challenges to the wide-spread implementation of these approaches. A major concern is the risk of visual artifacts (e.g. capillary dropout) produced from undue pressure of the microscope objective on the sublingual microvessels[36,39]. Even when excluding video clips that have such artifacts, only 30.8% of SDF recordings were found to be of excellent technical quality[39]. Despite these concerns, a recently-published international study (“microSOAP”) performed across 56 ICUs performed SDF sublingual microvascular measurements in 501 patients, with low variation in MFI (2%) and De Backer scoring (7%)[40].

An additional concern regarding the sublingual microcirculation is the relevance of this vascular bed during sepsis, particularly given divergent responses of the sublingual microvasculature from vascular beds more proximal to the site of a sepsis-inducing infection (e.g. the submucosa of an intestinal ostomy during abdominal sepsis)[41]. However, convergent findings from multiple groups have linked sublingual microvascular alterations with clinical outcomes in sepsis, providing reassurance for the relevance of these measurements. Using OPS imaging of the sublingual microvasculature, De Backer and colleagues compared 10 healthy volunteers, 16 patients prior to cardiac surgery, 5 non-septic ICU patients, and 50 patients with sepsis/septic shock[42]. Patients with sepsis had significant loss (or intermittent interruption) of RBC perfusion in small (< 20 μm) sublingual microvessels. Perfusion was highly variable in patients with sepsis, and vessel perfusion was lower in non-survivors. Interestingly, these changes were independent of measures of

macrovascular function, including mean arterial pressure and need for vasopressor medications. Further studies demonstrated that septic shock survivors tended to have rapid (albeit incomplete) correction of early microvascular dysfunction, as opposed to persistent abnormalities in patients who ultimately died[43]. Indeed, an increase in small vessel perfusion of > 7.8% in the first 24 hours of sepsis was 82% specific for survival[43]. In the microSOAP study, 17% of mixed ICU patients (septic and non-septic) demonstrated abnormal sublingual microvascular function; in the subgroup of patients with tachycardia, this dysfunction predicted hospital mortality[40]. These studies as well as others[44–46] support the feasibility (and reproducibility) of bedside measures of sublingual microvascular function and their relevance to sepsis outcomes.

As with any observational human approach, it is difficult to prove that observed changes in microvascular dysfunction during sepsis are causal to, as opposed to a consequence of, organ dysfunction. For example, it is possible that loss of microvascular flow is in fact an appropriate response to decreased tissue metabolic demand. Sepsis-induced suppression of mitochondrial oxidative phosphorylation would be expected to decrease cellular oxygen demand, triggering a reactive decrease in microvascular flow and vascular density. This phenomenon, however, is not supported by available experimental data. During sepsis, extravascular tissue CO_2 partial pressures (a measure of cellular respiration quantifiable by sublingual capnometery) increase as microvascular flow decreases, suggesting that tissue metabolic activity outstrips microvascular blood supply[47].

Pathogenesis of microvascular dysfunction during sepsis

Given the potential causal importance of microvascular dysfunction during sepsis, the pathogenic mechanisms underlying these changes are attractive therapeutic targets. Likely contributors to these changes include pathophysiologic events typically implicated in septic organ injury, including aberrant vascular tone, inappropriate barrier dysfunction (and consequent tissue edema), inappropriate leukocyte adhesion (and inflammation), and activation of microvascular coagulation[1]. These pathophysiologic events can yield a signature appearance on intravital microscopy, with extraluminal (tissue edema, vasoconstriction) and intraluminal (coagulation, leukocyte adhesion) events conspiring to produce a loss of visualized RBC flow. Loss of RBC flow has physiologic consequence, leading to tissue hypoxia in the setting of tissue injury-amplified metabolic demands. While loss of microvascular flow can be compensated by increased flow through other vessels, this compensation can produce a “functional shunt”, in which the high velocity of flow through patent collateral microvessels decreases the capillary dwell time of RBCs, diminishing oxygen diffusion and potentially leading to additional hypoxia surrounding perfused microvessels[19].

As numerous pathophysiologic events contribute to microvascular dysfunction during sepsis, it is unlikely that targeting a discrete contributor to vascular injury would have broad beneficial effects on patient outcomes in sepsis. As such, there has been great effort invested in identifying, and subsequently targeting, unifying mechanisms upstream of endothelial barrier dysfunction, inflammation, and microthrombosis. Particularly intense attention has been dedicated to the immunopathogenesis of sepsis, a broad topic ranging from the initial

infection-associated release of pathogen-associated molecular patterns, consequent induction of pattern receptor (e.g. toll-like) signaling, downstream induction of inflammatory cytokine production ("cytokine storm"), leukocyte recruitment, and tissue damage with release of immune-amplifying damage-associated molecular patterns[48]. These events coincide with induction/augmentation of coagulation pathway signaling[48]. These proinflammatory pathways, however, have largely failed to identify clinically-effective immunotherapies for sepsis[49–51]. While these failures may be largely the consequence of practical challenges in therapeutically interrupting hyperacute events driving sepsis onset, it may also reflect our incomplete understanding of the complex immunologic events surrounding sepsis. Indeed, recent efforts have highlighted the pathologic significance of anti-inflammatory signaling in severe sepsis and septic shock[52].

These limitations of the classic "cytokine storm" theory as a unifying mechanism of microcirculatory dysfunction have raised the need to identify novel pathophysiologic pathways of organ dysfunction (and microcirculatory failure) in sepsis. De Backer and colleagues demonstrated that septic sublingual microcirculatory heterogeneity can be completely corrected by the topical administration of vasodilators (e.g. acetylcholine)[42,53]. This rapid reversibility suggests that septic microvascular failure may arise largely from pathologic involvement of processes associated with the dynamic regulation of vascular tone. Accordingly, nitric oxide (NO) has been the intense focus of research as a mediator of sepsis and septic organ injury. Unfortunately, NO signaling is highly complex, with context-specific functions that can be both homeostatic and pathologic[54–56]. Human studies of NO-targeted microvascular therapeutics have accordingly been disappointing[57,58], potentially reflecting broad, nonspecific effects of NO manipulation[59]. These challenges (and opportunities) of NO-based therapies have been reviewed in detail elsewhere[60].

The limitations of systemic, NO-targeted therapeutic approaches in sepsis have raised interest in other, more specific manipulations of vascular tone. While many pathways are currently the focus of intense investigation, this review will focus upon one particularly-promising therapeutic target—the endothelial glycocalyx.

Endothelial glycocalyx and the septic microcirculation

The endothelial glycocalyx is a layer of glycosaminoglycans (GAGs) and associated proteoglycans lining the vascular lumen (Figure 3)[61]. First described by as a 20 nm-thick "endocapillary layer" in 1966, the glycocalyx was long thought to be a structure of trifling significance[62]. This underappreciation of glycocalyx structure/significance likely reflected glycocalyx aberrance *in vitro*[63] as well as its frequent degradation during tissue fixation[64]. With the advent and optimization of intravital microscopy, it is now apparent that *in vivo*, negatively-charged glycocalyx GAGs sequester water, forming a massive (0.5 – 11 μm) endothelial surface layer (ESL) with measurable rigidity[61,65,66]. The ESL has several homeostatic functions, including maintenance of the endothelial barrier to fluid and protein[67] as well as regulation of leukocyte-endothelial adhesion[5]. The ESL also serves as a mechanotransducer of shear stress: in the presence of sufficient shear, the ESL-replete endothelium activates endothelial NO synthase, leading to vasodilation and accommodation of increased flow[68]. Experimental ESL degradation induces edema[67], inappropriate

leukocyte adhesion[69], and loss of microvascular autoregulation[68]. Accordingly, degradation of the ESL in animal models increased microvascular heterogeneity, with some vessels becoming occluded to RBC flow and others becoming hyperemic[70,71].

Endothelial glycocalyx/ESL integrity is therefore highly relevant to septic organ injury and microvascular dysfunction. In experimental models of polymicrobial sepsis, GAG degradation occurred within the pulmonary and renal vascular beds, contributing to both lung edema/inflammation[8,28] as well as loss of glomerular filtration[72]. In a rat model of endotoxemia, loss of intestinal capillary density occurred in association with mesenteric ESL degradation[73]. In humans, several techniques exist for the detection and quantification of glycocalyx degradation in critically-ill patients (Table 1). Loss of glycocalyx/ESL integrity was apparent within the sublingual microcirculation after endotoxin administration to healthy volunteers, coincident with loss of capillary density[74]. Patients with sepsis demonstrate elevated circulating ESL degradation products, including proteoglycans[75–77] as well as GAGs heparan sulfate, hyaluronic acid, and chondroitin sulfate[75,78–83]. Accordingly, glycocalyx/ESL degradation is predictive of clinical outcomes in critical illness[78,79]. The development of rapid, point-of-care assays for glycocalyx breakdown products (Table 1) may allow for microvascular “personalization” of sepsis treatment, identifying patients who may benefit the most from vascular-protective therapies.

Therapeutic targeting of the microcirculation in sepsis

The ability to directly visualize the sublingual microvasculature in human subjects has allowed for hypothesis-generating human studies identifying treatments that, by virtue of rescuing the dysfunctional microvasculature, could serve as clinically-effective treatments for sepsis[89]. Such microcirculation-protective therapies, however, have largely failed to improve patient outcomes when broadly applied across large, multicenter trials (Table 2).

The failure of activated protein C as a treatment for sepsis is particularly disappointing, not only due to the promising microcirculation-protective effects observed in animal models and preliminary human studies[90], but also due to the initial success of drotrecogin alfa as reported in the seminal PROWESS[91] study. Ultimately, the futility of drotrecogin alfa was demonstrated in the ADDRESS[92] and PROWESS-SHOCK[12] studies, paralleling negative studies of other anticoagulants such as antithrombin III[14] and tissue factor antagonists[13]. However, a recent meta-analysis suggested a mortality decrease with heparin treatment during sepsis (OR 0.88)[111], although this analysis is derived largely from a single study of low-dose heparin for venous thromboembolism prophylaxis (a dosing regimen of uncertain relevance to the septic microcirculation) in patients receiving activated protein C[112]. Interestingly, low-dose heparin administration had been previously implicated as detrimental in sepsis studies of antithrombin III[14] and tissue factor antagonists[13]. This complexity may reflect the varied biologic effects of heparin, including the ability of this highly-sulfated GAG to inhibit selectins[113], influence growth factor signaling[114], and inhibit enzymes implicated in endothelial glycocalyx degradation (i.e. heparanase)[28]. Indeed, many anticoagulants (including activated protein C and antithrombin) have multiple biologic effects; the failure of these agents to improve sepsis outcomes therefore cannot be viewed as

a direct repudiation of the pathophysiological importance of tissue thrombosis to organ injury.

Novel microcirculation-protective therapies

The general failures of microcirculation-targeted therapies to improve patient outcomes highlights a need to identify new therapeutic targets in sepsis. Given the known benefit of early antibiotics in sepsis, studies of the impact of antibiotic administration on microcirculatory function would be instructive as to potential new therapeutic targets[115]. "Sheddases" implicated in septic glycocalyx degradation may be targeted[116], including the use of doxycycline[69] or sphingosine-1-phosphate[117] to inhibit matrix metalloproteinases responsible for proteoglycan shedding. Alternatively, coagulant or non-anticoagulant variants of heparin can be employed to block heparanase, a heparan sulfate-degrading endoglucuronidase responsible for septic endothelial glycocalyx degradation and lung and kidney injury[28,72]. Furthermore, interventions aimed at promoting glycocalyx reconstitution may hasten a return of microvascular homeostasis. Rosuvastatin improved glycocalyx reconstitution in patients with familial hyperlipidemia[118]; however, a randomized trial of statins failed to show benefit as a sepsis therapeutic[119]

While the general failure of microcirculation-protective interventions to improve clinical outcomes may reflect a lack of novel therapeutic targets, a more compelling explanation might lie in the indiscriminant administration of microcirculation-protective therapies in multicenter trials. Microvascular-protective treatments might only benefit patients who demonstrate baseline abnormalities of microvascular function[89]. Ideally, future studies will pursue such microvasculature-targeted, "personalized" approaches to sepsis resuscitation. This assessment of baseline microvascular status could be based upon bedside intravital microscopy (with its accompanying technical limitations) or systemic markers of endothelial damage (with their accompanying logistic concerns as point-of-care tests). The promise of such personalized approaches to infection treatment has been demonstrated in recent studies of pneumonia, in which a benefit of adjunctive corticosteroids existed largely in patients with baseline evidence of systemic inflammation[120,121].

Summary

The microcirculation is a promising therapeutic target in sepsis. While several techniques allow for the detection of microcirculation dysfunction in humans (including intravital imaging and measures of glycocalyx degradation), these approaches have yet to guide sepsis therapeutics in a manner that demonstrably (in phase III studies) improves patient outcomes. Validating, multicenter patient outcome-focused studies of interventions titrated to improving microcirculation function are needed to create new treatment paradigms in sepsis.

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KEY POINTS

- Microcirculatory functions critical for the homeostatic control of infection can become dysregulated and harmful during sepsis.
- Microcirculation dysfunction may arise in part from septic degradation of the endothelial glycocalyx, a substantial, glycosaminoglycan-rich layer lining the vascular lumen.
- The microcirculation can be measured at the bedside, either directly via intravital microscopy or indirectly via circulating measures of vascular damage. Such evidence of microcirculatory dysfunction is predictive of sepsis outcomes.
- Additional human studies are needed to determine if sepsis treatments, when titrated to improvement of microvascular function, improve patient outcomes.

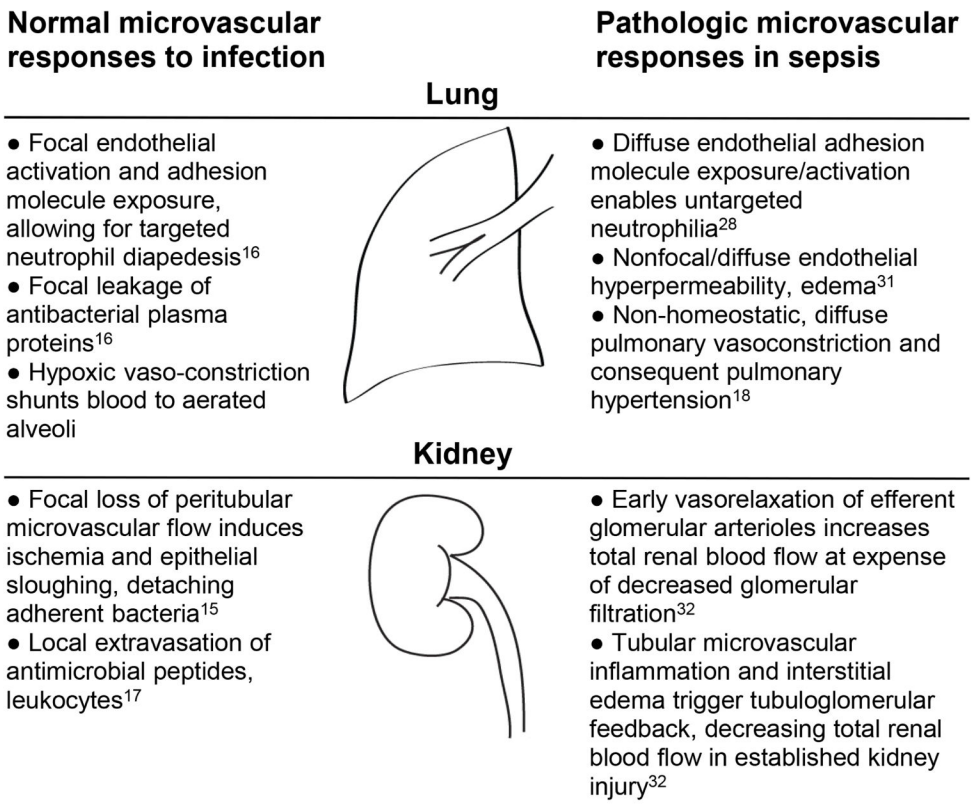

Figure 1.

Homeostatic vs. pathologic (septic) pulmonary, renal microvascular responses to infection

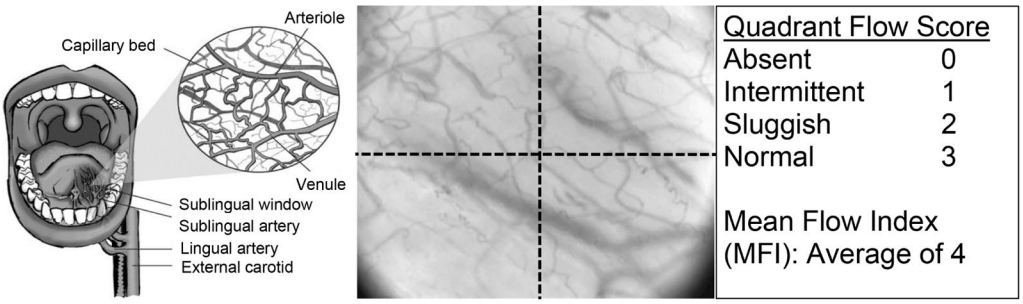

Figure 2.

Semiquantitative assessment of sublingual microvascular flow. Intravital microscopy can access the sublingual miscrovasculature (OPS image, middle). Semiquanitative measurements of flow in each quadrant of image yields an average mean flow (MFI); at least 5 images should be measured.

Adapted from Klijn E, Den Uil CA, Bakker J, Ince C. The heterogeneity of the microcirculation in critical illness. *Clinics in Chest Medicine.* 2008;29(4):643–654; with permission.

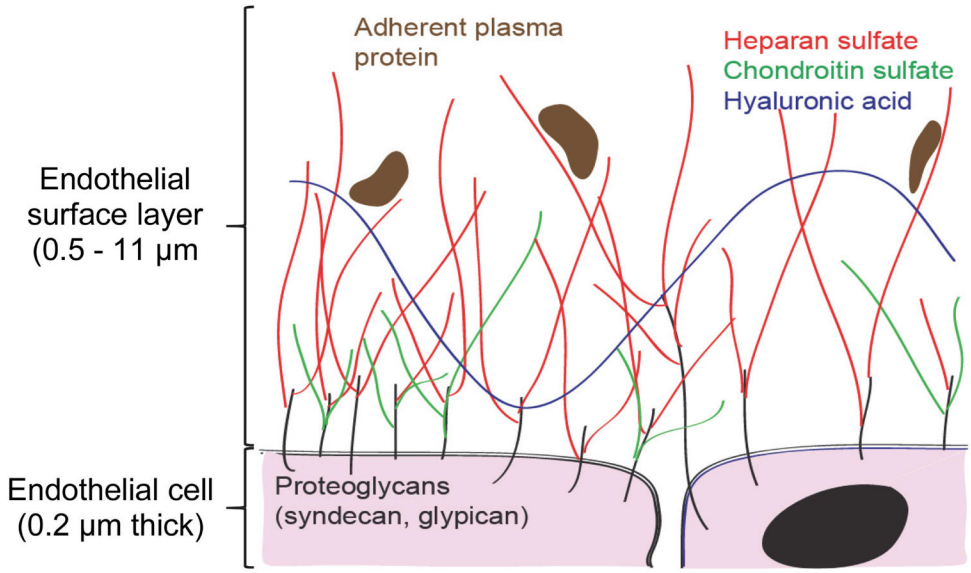

Figure 3.
The Endothelial Glycocalyx

Table 1

Measurement of endothelial glycocalyx/ESL degradation in humans.

Assay	Human studies	Advantages	Disadvantages
Detection of circulating glycocalyx fragments			
DMMB/Alcian Blue	• Plasma GAGs (via Alcian blue binding) increased in septic shock, correlated with mortality.[75] • Urinary, plasma GAGs increased in pediatric meningococcemia.[83] • Modified DMMB assay feasible in trauma patients.[84]	Rapid, inexpensive colorimetric assay	Only detects sulfated glycosaminoglycans (cannot detect hyaluronic acid)
ELISA/Latex Agglutination Assay	• Plasma hyaluronan increased in endotoxin-treated volunteers[74], patients with septic shock.[79,82] • Plasma heparan sulfate increased in septic shock[79]. • Plasma syndecan-1 shedding increased in sepsis patients.[75,81]	Quantitative measure of proteoglycans, glycosaminoglycans	Insufficient rapidity to date for bedside use; uncertain specificity of antibody binding to glycosaminoglycans
Mass spectrometry	• Elevated heparan sulfate in patients with severe sepsis[78] • Chondroitin sulfate unchanged in severe sepsis.[78–79]	High sensitivity; allows detection of sulfation signatures, potentially identifying tissue source	Expensive, impractical for rapid bedside use
Thromboelastography (TEG)	• Trauma patients with TEG evidence of circulating sulfated heparan sulfate fragments had higher plasma syndecan-1, injury severity.[85]	Rapid, inexpensive measurement of circulating heparan sulfate fragments with anticoagulant ability	Detection limited to highly-sulfated heparan pentasaccharides (or larger)
Measurement of whole-body glycocalyx volume			
Tracer dilution technique[86]	• In healthy volunteers, total body glycocalyx volume correlated with sublingual intravital imaging.[86]	Can measure whole-body endothelial surface layer volume based upon differences in tracer volumes of distribution	Technical assumptions controversial[87]
Intravital microscopy			
Sublingual sidestream dark field (SDF) imaging	• Loss of sublingual glycocalyx thickness in endotoxin-treated volunteers[74], ICU patients.[88]	Rapid, point-of-care assay. Allows for simultaneous measurements of microvascular function.	Concerns regarding relevance of imaged vascular bed and interobserver variability; need for specialized training

Table 2

Microcirculation-protective therapies and outcomes in clinical trials of sepsis.

Intervention	Microcirculation benefit	Benefit as sepsis therapeutic
Anticoagulants		
Activated Protein C	• 4-hour improvement in capillary perfusion; improvement did not persist after drug cessation[90].	Initial benefit[91] unable to be reproduced in confirmatory studies[12,92].
Vasoactive medications		
Vasopressors	• Mixed benefit of norepinephrine, with studies showing either microvascular benefit of increasing MAP from 65 to 85 mm Hg[93] or no change[94].	Targeting MAP of 80 – 85 mm Hg equivalent to MAP of 65 mm Hg to 70 mm Hg in septic shock[95].
Inotropic agents	• Dobutamine (added to patients receiving dopamine ± norepinephrine) improves perfused capillary density[53].	No benefit from early goal directed therapy studies which included dobutamine therapy[22–24]. No benefit and potential harm from supranormal oxygen delivery in established sepsis[96].
Anti-inflammatory therapy		
Corticosteroids	• Stress dose (50 mg) hydrocortisone improved sublingual microvascular function within 4 h; perfused capillary density remained improved at 24 h[97].	High dose steroids without benefit[98,99] and potential harm[100]. Stress dose steroids without benefit[101].
Hemofiltration (endotoxin removal)	• Improved De Backer score during hemofiltration sessions; benefit lost after filtration[102]. • MFI improvement during 12 h hemofiltration, persistent for 6 hours after session[103].	Potential early mortality benefit of two hemofiltration sessions after surgery for intra-abdominal infection; benefit lost at 30 days[104].
Fluid therapy		
Early goal-directed therapy	• Fluid bolus administration early (< 24 h) in sepsis improves microvascular function; no such benefit later (72 h) in sepsis[105]	No benefit from early goal-directed therapy in sepsis[22–24]. This may reflect efficacy/ implementation of very early fluid resuscitation (i.e. prior to study enrollment).
Colloids	• Hydroxyethyl starch more effective than saline at improving sublingual MFI in septic patients[106]. Albumin equivalent to crystalloid[105].	While albumin may be beneficial in septic shock (based on post-hoc subgroup analyses[107]), hydroxyethyl starch is associated with harm[108–110].