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# Sepsis-Induced Degradation of Endothelial Glycocalix

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## INTRODUCTION

Sepsis, a systemic host response to microbial infections, is a major cause of death in intensive care units, with mortality rates up to 60%[1,2]. A major pathophysiological process in sepsis is dysregulation of circulation, mainly caused by altered vasomotion, redistribution of organ blood flow, impaired rheology and deformability of red and white blood cells, occlusion of vessels, and loss of endothelial barrier function[3]. This directly induces reduced tissue oxygen supply and causes organ failure[4]. Within this process, the arterial endothelium plays a pivotal role, regulating the vessel resistance and fluid homeostasis between blood and the interstitial space under physiological conditions[5]. Fluid and solute balances between vessels and tissue, either transcellular or paracellular, underlie a fine regulation of the endothelium[6,7]. The active transcellular transport of molecules contributes only little to the vast fluid extravasation during inflammation. It is mainly the passive paracellular transport that is responsible for the major exchange between vessels and tissue, which is also controlled by precise regulation mechanisms[8]. A key function in regulation of these processes is played by the glycocalix. This fine structure decorates the luminal membrane of endothelial cells and was first identified 40 years ago while utilizing special electron microscopic staining techniques[9]. The side branches of the glycocalix consist of negatively charged proteoglycans, glycoproteins, and glycosaminoglycans[10,11,12]. The three core proteins of the proteoglycans found on endothelial cells are the transmembrane syndecan, the basement matrix-associated perlecans, and the membrane-bound glypicans[13,14]. The glycocalix extends luminally from several nanometers to 3 µm, and its dimension is determined by the dynamic balance between biosynthesis, conditions of its microenvironment, such as cation content and concentration, pH, and shear-dependent or enzymatic shedding of its constituent parts[15,16,17,18,19,20,21]. This fragile luminal mesh is responsible for a constant fluid resistance and it interacts with plasma proteins. While binding with its negatively charged heparan sulfate proteoglycans to antithrombin III, it constrains factor Xa-activity and inhibits coagulation[22,23]. It is assumed that the fine structure of the glycocalix is a mechanotransducer that enables the endothelial cells to sense changes in blood flow. In particular, increased shear stress evokes modulation of the vasomotion by the generation of nitric oxide[12,24,25,26]. Furthermore, the three-dimensional glycocalix contributes to the endothelial sieve

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function that is mainly determined by the hyaluronic acid and chondroitin side chains[27,28,29,30]. These negatively charged side chains restrain plasma components as fluid and proteins in the vessel lumen, thus preventing interstitial edema[5,31,32]. Furthermore, the glycocalix is linked to the cortical cytoskeleton of endothelial cells and acts as a transducer for mechanical and chemical stimuli[33,34]. Via this pathway, it influences the activation of cytoskeletal actin filaments, which are linked to the intercellular junction proteins cadherins and integrins[35]. As a response to stimuli onto the glycocalix, it induces retraction and reorganization of the cytosolic actin filaments and of their attached intercellular junctions, hence enhancing endothelium permeability[26,35].

## SEPSIS- AND SURGERY-INDUCED DAMAGE OF GLYCOCALIX

A recent study published in the *Journal of Surgical Research* investigated the deterioration of the vascular glycocalix in patients with sepsis or after major abdominal surgery, and compared these findings with healthy volunteers. Within this clinical study, it has been demonstrated that in patients either with severe sepsis or after major abdominal surgery, the plasma concentrations of glycocalix markers (syndecan-1, heparan sulfate) increased by the same extent. This implies that under both situations, the glycocalix is shed off the endothelium. In sepsis, the glycocalix marker syndecan-1 correlates with concentrations of inflammatory markers (intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1], and mainly with interleukin-6 [IL-6]), which were significantly higher than after abdominal surgery[36]. During sepsis and after abdominal surgery, the plasma leaks out into the interstitial space, and this has great impact on the development of edema and impaired oxygen and nutrient supply to tissues. The deterioration of the endothelial glycocalix is one of the earliest steps within this scenario that triggers the loss of endothelial barrier function[11].

## VASCULAR PERMEABILITY

The importance of the glycocalix has been underestimated for a long time, however, during the past years, it became apparent that this structure plays a major role in regulating circulatory fluid homeostasis and vessel integrity[4,5]. During sepsis and abdominal surgery, the glycocalix is disintegrated and its components can be quantified within the plasma, reflecting peripheral endothelial cell injury[36]. However, an earlier study provided evidence that in patients with septic shock, the plasma concentrations of glycosaminoglycans increase and are highest in nonsurvivors compared to survivors[37]. Consequently, the confirmation of glycocalix components within the plasma can be used to diagnose the severity of septic processes, because they provide evidence of endothelial barrier damage and impairment of microcirculation. Within the plasma, the separated heparan sulfate compounds contribute to the recruitment of leukocytes, acting as a chemotactical positive feedback mechanism by leading leukocytes to the site of inflammation[38,39]. Beside sepsis and surgical trauma, the glycocalix is also degraded during ischemia/reperfusion after vascular surgery, and hyperglycemia leads to damage of the glycocalix in diabetes type 1. All these pathophysiological processes are accompanied by increased vascular permeability, by opening paracellular pathways and the interruption of intercellular junctions. This impairment of the endothelial barrier can be evoked by inflammatory mediators such as tumor necrosis factor alpha (TNF-α), bradykinin, thrombin, vascular endothelial growth factor (VEGF), and histamine acting directly on endothelial cells[40,41,42,43]. Increased paracellular permeability is also induced by damage of the glycocalix during inflammation, since this structure contributes to the fluid balance in tissues[44,45,46,47]. Additionally, it has been shown that the integrity of the glycocalix is impaired by TNF-α or lipopolysaccharide (LPS); both inflammatory mediators reduce the thickness of the glycocalix, hence, extravasation of fluid and solutes are triggered[28,48,49]. During inflammation, the glycocalix also acts as a receptor for cytokines that leads to a rearrangement of syndecans to clusters within the luminal endothelial cell membrane[50]. Mainly, the syndecans integrate extracellular signals by their

association to cytosolic effectors, such as the actin filaments[51]. In a following step, actin filaments change their order to stress fiber formation and intercellular junctions become more permeable, allowing fluid extravasation[50]. Consequently, the glycocalix contributes to the modulation of endothelial barrier function during (patho-)physiological conditions via different pathways.

## COMPARISON OF SEPSIS- AND SURGERY-INDUCED GLYCOCALIX DEGRADATION

The study of Steppan et al.[36] compared changes in the glycocalix in patients suffering from sepsis with patients after abdominal surgery and with healthy individuals. The aim was to provide evidence that sepsis and abdominal surgery cause significant flaking of the endothelial glycocalix. The study compared a total of 150 individuals, including 104 patients with severe sepsis, 28 patients after abdominal surgery, and 18 healthy volunteers. In the sepsis group, the 28-day mortality after diagnosis was 47%; the initial site of infection was either the lung (58.7%), genitourinary tract (11.6%), gastrointestinal tract (3.8%), surgical site (6.7%), or other (10.6%). Blood samples were either taken at the time point of diagnosis, or briefly after surgery, 6, 24, and 48 h later, whereas blood samples from healthy volunteers were taken once. The plasma concentrations of glycocalix components, such heparan sulfate, syndecan-1, IL-6, ICAM-1, and VCAM-1, were quantified by applying enzyme-linked immunosorbent assays (ELISA). The study found significantly higher concentrations of IL-6, ICAM-1, and VCAM-1 in patients with severe sepsis than in surgical patients or in healthy people. In surgical patients, the inflammatory marker IL-6 was significantly increased compared to healthy individuals, whereas ICAM-1 and VCAM-1 showed no difference between both groups. In the sepsis and surgical groups, the concentrations of glycocalix markers syndecan-1 and heparin sulfate were significantly higher than in the control group. In surgical patients, the heparan sulfate levels were higher than in the sepsis group; on the other hand, syndecan-1 was more elevated in the sepsis group than in the surgical group. There was no difference of these two markers between patients who survived or patients who died during sepsis. The levels of IL-6 correlated with levels of VCAM-1, ICAM-1, syndecan-1, and lactate. Both sepsis and abdominal surgery cause flaking of the glycocalix, which is in line with findings that both cause vascular leaking. However, the damage of the glycocalix in sepsis is more substantial, which is reflected by the increased levels of the cell membrane molecule syndecan-1 levels. However, the syndecan residues that are shed function as important signal molecules during the subsequent inflammation cascade. In murine sepsis studies, syndecan-1 shedding is associated with removal of tissue-bound CXC chemokines and this further facilitates resolution of neutrophilic inflammation[52]. So syndecan-1 may play a pivotal role during sepsis by regulating the host response. This is supported by findings in mice where thermal injuries cleave syndecan-1 and this allows the spreading of *Pseudomonas aeruginosa* assumed by enhanced vascular permeability. Furthermore, syndecan-1 null mice are less susceptible to systemic *Pseudomonas* infections. They show lower mortality rates and significantly lower levels of proinflammatory cytokines[53]. On the contrary, syndecan-1 shedding protects from Gram-positive toxic shock; it inhibits amplification and dysregulation of the host inflammatory response[54]. So shedding of the glycocalix contributes to increased vascular permeability, by a reduced sieve function, and by rearranging cytoskeletal proteins and altering intercellular junctions.

## CLINICAL ASPECTS

The degradation of the glycocalix during sepsis and major abdominal surgery has a great impact on fluid balance and the development of edema. However, so far, there exist no methods to evaluate endothelial dysfunction and vascular leakage during sepsis and during the postoperative period; therefore, diagnosis of fluid distribution during these scenarios is very difficult[55]. The findings of Steppan et al.[36] that the glycocalix is damaged during major abdominal surgery and sepsis can explain the large fluid shifts into

the interstitial space. It has been estimated that during major surgery, a fluid shift of 3–6 l occurs; beyond that in septic patients, an extracellular overload of 10 l has been demonstrated after 2 days of treatment[56,57,58,59,60]. This overinfusion ought to be avoided, since it further worsens oxygen supply of tissues and organs[4]. Still, there exists no routine bedside method to quantify interstitial edema, blood volume, or extracellular fluid compartments. Anyway, it is important to maintain hemodynamic stability during sepsis and after abdominal surgery. Currently, the hydration conditions have to be appropriately maintained by sufficient fluid supply. Applied crystalloid solutions, omitting any osmotic forces, do not remain intraluminally even in the presence of an intact glycocalix and physiological vascular permeability. These solutions are distributed over the entire extracellular space, which consists of interstitial (80%) and intravascular (20%) compartments[31,32]. This provides reason for the observation that administered crystalloid boluses stabilize only insufficiently impaired perioperative hemodynamics[31]. To achieve stable hemodynamics in sepsis, the administration of 4–6 l of crystalloid solutions or 1.5–3 l of colloidal solutions are required[61]. Colloidal solutions remain almost completely intravascular and can enhance cardiac preload in situations with an intact endothelial barrier[31]. However, during impaired endothelial barrier function, colloidal solutions also distribute into the interstitial space and can aggravate edema[62]. Furthermore, colloidal solutions, such as pentastarch, with higher substitution grades can provoke kidney injury and impair patient outcome in sepsis[63]. To avoid iatrogenic overinfusion, the fluid administration should be adjusted to specific hemodynamic parameters, as it has been suggested in clinical studies to achieve adequate circulatory functions[1,64]. The fluid therapy should not be monitored by heart rate, blood pressure, or cardiac filling pressures, such as central venous pressure or pulmonary capillary wedge pressure, only. Instead, dynamic parameters, such as stroke volume, cardiac index, capillary perfusion, and urine production, should be taken into account for monitoring fluid therapy[1,65,66,67]. Nevertheless, the endothelial barrier is deteriorated during sepsis and major abdominal surgery, but colloidal solutions can rapidly stabilize cardiocirculatory dynamics. This should be a fluid-saving therapy without impairing further edema, tissue oxygenation, and endothelial function. Therefore, monitoring glycocalix compounds in the bloodstream may be employed for longer periods in order to determine further endothelial barrier damage or amelioration of endothelial function.

## CONCLUSION

The glycocalix is shed during inflammation and nonspecifically after surgery, explaining capillary leaking. Future studies should focus on how the glycocalix is degraded in sepsis and after abdominal surgery. This understanding will be pivotal in order to develop therapeutic strategies to preserve the glycocalix and, consequently, this will possibly reduce vascular leaking, with its fateful impact on organ functions, and improve the outcome of patients after abdominal surgery and sepsis.

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