The Endothelium in Intensive Care

Eric Wiel, MD\textsuperscript{a,b}, Benoît Vallet, MD, PhD\textsuperscript{b}, Hugo ten Cate, MD\textsuperscript{c,*}

\textsuperscript{a}Prehospital Emergency Department, Centre Hospitalier Universitaire de Lille, Avenue Oscar Lambret, F-59037 Lille, France
\textsuperscript{b}Clinique d’Anesthésie-Réanimation chirurgicale II, Hôpital Claude Huriez, CHRU de Lille, rue Michel Polonovski F-59037 Lille, France
\textsuperscript{c}Laboratory for Clinical Thrombosis and Hemostasis, Department of Internal Medicine and Cardiovascular Research Institute Maastricht (CARIM), University of Maastricht, Maastricht, The Netherlands

The endothelium is a single layer of cells that lines the entire vascular tree. It is a highly specialized tissue that forms an organ of almost $10^{13}$ cells and weighs 1 kg. It covers a surface area of about 4,000 to 7,000 m\textsuperscript{2} \cite{1}. The morphological and functional integrity of the endothelial cell layer is important to maintain physiologic processes. In the past, it was considered to be an inert layer separating blood from the underlying tissue; however, it is now well demonstrated that the endothelium is a highly active organ involved in both metabolic and synthetic functions with paracrine, autocrine, and endocrine actions. The endothelium modulates immune responses and vascular cell growth, and regulates the level of hemostatic, inflammatory, and vasoactive agents in the blood. Endothelial cells are involved in the control of vasomotor tone, regulate the flow of nutrient substances, and the trafficking of blood cells maintaining blood fluidity \cite{2}. This regulatory role of the endothelium is achieved through the presence of membrane-bound receptors for several molecules, and through specific junction proteins and receptors governing cell–cell and cell–matrix interactions \cite{3,4}. It has recently been noted that there is a marked heterogeneity in structure, expression patterns, and function caused by a combination of genetic and environmental determinants \cite{5}. Indeed, it has been shown that endothelial cells

\* Corresponding author.
E-mail address: h.tencate@bioch.unimaas.nl (H. ten Cate).
differ in size, shape, thickness, and nuclear orientation from different sites of the vascular system [5]. These endothelial cell phenotypes vary in both space and time, such that cells from different areas of the vascular tree can express heterogeneous patterns with different intracellular signaling pathways generating different responses to the same stimulus [6].

Vascular endothelial cells have a pivotal role in the regulation of thrombosis (antithrombotic effect), in profibrinolysis, platelet adhesion, leukocyte adhesion, vascular tone and blood flow. The endothelium is a key organ in controlling body homeostasis. Endothelial dysfunction or injury with exposure of the subendothelium facilitates leukocyte and platelet adhesion aggravating coagulopathy and favoring impaired perfusion, tissue hypoxia, and subsequent organ dysfunction. The alteration of the endothelium is defined by three distinct situations reported in the literature: endothelial activation and endothelial injury, which can be assessed in vitro, and endothelial dysfunction which can be assessed in vivo in critically ill patients [7].

This review describes first, the main physiologic properties of the endothelium and the concept of heterogeneity, and second, the endothelial activation, injury, and dysfunction, which leads—in association with coagulopathy—to organ failure in critically ill patients.

Physiology of the endothelium

Properties

The endothelium is a metabolically active barrier. It can simultaneously receive messages from the underlying metabolically active tissue and send messages to the underlying tissue or the flowing blood.

The tight junctions between endothelial cells act as protective barriers; for example, the blood-brain barrier protects the central nervous system. These junctions have two properties: the first allows selected paracellular passage of ions, water, and other molecules (gate function); the second allows no passage but maintains cell polarity (fence function) [8]. Beside these paracellular junctions, a transcellular pathway via the caveolae, which are invaginations in the cell membrane, is important in maintaining vascular permeability. Caveolae allows the transport of albumin and other proteins across the endothelium.

The endothelium and smooth muscle cells of arteries and arterioles are coupled both structurally and functionally [4]. It has been demonstrated that conduction along the arteriole is attributable to gap junctions coupling contiguous cells. It may be speculated that sensing involves local depolarization and hyperpolarization of the capillary endothelial cell and that communication is achieved by an electronic transmission via endothelial-smooth muscle cell-to-cell gap junctions. Such gap junctions exist between endothelial cells and smooth muscle cells, and their number increases from first-to-third-order arterioles [4]. This suggests an increasingly important role for endothelial-to-smooth muscle com-
munication in distal (distribution) areas of vascular bed. Electrical coupling of endothelial cells and smooth muscle cells within terminal arterioles would lead to the formation of a myoendothelial regulatory unit [9] with a possible role in metabolic regulation.

The endothelium surface is composed of multiple transport systems for glucose and amino acids. The most important is the system \( y^+ \) cationic amino acid transporter, which makes possible the intracellular transport of L-arginine, the substrate for nitric oxide (NO) synthase (NOS) III. The system \( y^+ \) is co-located with NOS on caveolae.

NO is a key mediator involved in the control of vasomotor tone. NO can be released in response to two distinct stimuli: mechanical (shear stress) and humoral (via a receptor-mediated pathway). NO produced by the endothelium maintains the vascular tree vasodilated. The activity of NOS III is regulated by caveolae. The endothelium produces vasoconstrictor substances, such as endothelin (ET)-1 [10]. ET-1 acts on specific receptors (ET\( \_A \)) in vascular smooth muscle cells inducing vasoconstriction, but when stimulating endothelial receptors (ET\( \_B \)), it has either vasodilator or vasoconstrictor effects depending on the blood vessel type [11]. The control of vascular tone is complex and depends on cross-talk between NO, ET, and prostacyclin [12]. In addition to its effect on vasoreactivity, NO produced from endothelial cells inhibits adhesion molecule expression resulting in decreased inflammatory responses. This effect is caused by a stabilization of the inhibitor unit, Ik\( \beta \)B maintaining nuclear factor kappa B (NF\( \kappa \)B) in a non-activated state in the cytoplasm.

The endothelium also regulates blood cell trafficking, which involves adhesion molecules. Endothelial cells can express E-selectin, L-selectin, P-selectin, intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM). Under physiological conditions, platelets and leukocytes do not interact with endothelial cells. These adhesion molecules play a major role in pathophysiological processes.

Because endothelial cells are located at the tissue–blood interface, they have a strategic position in hemostasis. Under basal conditions, the endothelium prevents adhesion of blood cells including leukocytes and platelets and has an anticoagulant and profibrinolytic phenotype. Adhesion and aggregation of platelets is primarily prevented by the secretion of NO and prostacyclin [13]. Heparan sulfates at the endothelial extracellular matrix enhance the inhibitor activity of antithrombin, which is one of the main physiologic inhibitors of coagulation [14]. Under basal conditions, endothelial cells synthesize and express Tissue Factor Pathway Inhibitor (TFPI). TFPI inhibits tissue factor (TF) which is the receptor for factor VII and mediates initiation of the coagulation serine protease cascade. The TF-factor VIIa complex activates factors IX and X, which upon formation of catalytic complexes with cofactors Va and VIIIa on phospholipid surfaces, generates thrombin at ambient levels [15]. TFPI acts primarily upon formation of a quaternary complex consisting of TF, factor Xa, TFPI and phospholipids. A third anticoagulant mechanism consists of the endothelial cell surface receptor thrombomodulin (TM), which binds thrombin. This thrombin-TM complex
activates protein C (PC) initiating the activated PC pathway [16]. The endothelial protein C receptor (EPCR) is involved in this process of activation of PC [17]. Activated PC has to dissociate from EPCR before it binds to protein S, a cofactor of PC. Activated PC and its cofactor protein S proteolytically inactivate activated cofactors V and VIII, which inhibits the rate of thrombin generation. This way, thrombin inhibits its own generation. In addition to these inhibitors of coagulation, fibrinolysis is another important actor in blood coagulation [18]. Fibrinolysis is induced by thrombin through endothelial release of tissue plasminogen activator (tPA) which activity is controlled by plasminogen activator inhibitor (PAI)-1. tPA is constitutively expressed by endothelial cells—the main source of this enzyme—which will only activate plasminogen upon binding to the substrate fibrin [19]. In addition, endothelial cells produce urokinase type plasminogen activator, which may contribute to the profibrinolytic phenotype of these cells. The conversion of plasminogen to plasmin makes possible the degradation of fibrin. There is experimental evidence that this fibrinolytic route protects against excess fibrin formation under physiological conditions (reviewed in [19]). The production and secretion of PAI-1 guarantees that under physiological conditions, fibrinolysis is controlled by inhibiting plasminogen activator activity.

A separate role of major importance in endothelial physiology is probably played by the cellular protease activated receptors (PARs). These receptors are widely distributed among different cell types, but PAR-1 and PAR-2 are present on endothelial cells [20,21]. Here, these receptors are linked to cell signaling functions, which modulate endothelium-dependent relaxation and contraction, angiogenesis, vascular permeability and expression of P-selectin, ICAM and VCAM upon stimulation. The principle of activation is the cleavage and exposure of a tethered ligand which induces cell signaling. Phosphorylation of cellular proteins turns down the expression of the receptor, thus maintaining a regulated level of activity. Thrombin, trypsin, and activated protein C are major agonists of PAR-1 on endothelial cells [20,21]. PAR-2 is mainly activated by factors Xa and VIIa (in competition with binding to TF), which also drives cell signaling functions [22].

In conjunction with coagulation, the endothelium expresses an angiogenic factor, vascular endothelial growth factor, which is responsible for angiogenesis defined as the formation of new blood vessels from pre-existing endothelium [23]. It has an important role in pathophysiologic condition by contributing to the inflammatory response and interacting with TF in controlling angiogenesis [24].

**Endothelium heterogeneity**

The endothelium has several functions in a multitude of physiologic processes from transport of amino acid and other molecules to the regulation of vasomotor tone, and from the trafficking of blood cells maintaining blood fluidity to angiogenesis. All these actions are probably regulated in space and time. Indeed,
between different segments of the vascular tree and from one moment in time to the next in the same segment, the endothelium phenotype may change in its structure and function. This defines the endothelial cell heterogeneity or vascular diversity [5].

Experimental studies performed in various species of animals have demonstrated differences in structural determinants of endothelium derived from different sites of the vascular system. For example, in rats, endothelium from the pulmonary artery is larger than endothelium from the aorta, which is thicker than endothelium in capillaries and veins [25]. In rabbits, endothelium is larger in the vena cava than in the aorta [26]. Differences have been found in endothelial cell junctions in arterioles when compared with capillaries and venules. In arterioles, tight junctions form a continuous network surrounding gap or communicating junctions; whereas, capillaries have no communicating junctions, and venules have the least organized junctions [5].

Expression of transcription factors and signaling pathways may differ from a subset of endothelial cells to another, resulting in large differences in responses to a specific stimulus. This structural heterogeneity has consequences on endothelium function, especially on regulation of vasomotor tone. As an example, several experimental studies have demonstrated site-specific actions of NO. Most of these studies showed a higher activity of the NO pathway in the arterial tree, but differences in the animal models used are important to consider. In the mouse, a higher expression of NOS III protein and mRNA in heart and lung compared with liver has been demonstrated [27]. In a rat model of increased blood flow, NOS III levels are higher in the aorta compared with pulmonary arteries; however, in a model of hypoxia it is the opposite [28,29]. In the same way, hemostatic properties change from one vascular bed to another. An illustrative example of vascular bed heterogeneity was based on observed differences in the expression of the vWF promoter [30]. In addition, TFPI is found preferentially in the microcirculation, TM is presumably not expressed in brain endothelial cells and other organ-specific differences in expression of TM, EPCR, PAI-1, and tPA have been observed [31–33]. The endothelium heterogeneity is, at least in part, genetically predetermined, but the environment plays an important role (for a review, see [5]). As yet, the functional consequences of this heterogeneity are largely unknown, but could explain why the endothelial response to pathophysiological stimuli may vary in space and time, of which the vascular bed-specific changes in the hemostatic balance may be a prominent example [34].

**Endothelium in infection and inflammation**

Altered endothelial properties have been extensively described in the literature with different, and partly overlapping, meanings. The most commonly used three descriptors deserve further discussion because of their clinical relevance. They
are defined in this article, which describes why altered endothelial properties may be critically involved in organ failure within the context of sepsis.

**Endothelial activation**

Endothelial activation refers to a change in endothelium phenotype. It is defined by an increased expression or release of endothelial adhesion and procoagulant molecules. Quiescent endothelium has an anticoagulant, antiadhesive, and vasodilatory phenotype, but activated endothelium expresses a procoagulant, proadhesive, and vasoconstricting phenotype [19]. Expression of adhesion molecules leads to adhesion of monocytes and leukocytes to endothelial cells facilitating their migration into tissues. Cytokines such as interleukin (IL)-8, IL-1 and tumor necrosis factor (TNF)-alpha, regulate the surface adhesion, adhesion avidity, and surface modulation of these molecules. Migration is divided into three steps. The first consists of leukocytes rolling into the proximity of activating signals exhibited by endothelial cells in the direction of flow; this involves the selectin family. The second step allows leukocyte arrest and adhesion strengthening and involves receptors from the integrin family and immunoglobulin-like receptors. The third step consists of migration of activated leukocytes to the borders of endothelial cells, and interaction with ICAMs, endothelial cell leukocyte adhesion molecules, platelet endothelial cell adhesion molecule, or VCAM [35].

Procoagulant activation of endothelial cells has been extensively studied in vitro, using cultured human endothelial cells. In general, a range of pro-inflammatory stimuli, including endotoxin, II-1, II-6 and TNF-alpha, have been implicated in the induction of TF as well as the downregulation of anticoagulant molecules antithrombin and TM [19,36]. Activation of endothelial cells may occur during mild stages of inflammation such as mimicked by low dose endotoxin infusion in humans and primates. In these models, endotoxin (2–4 ng/kg iv dose) elicits a pro-inflammatory response characterized by clinical changes in temperature and blood pressure. In blood from such individuals and animals, II-6 and other cytokines rapidly increase and this phase is associated with a procoagulant reaction consisting of generation of thrombin and tPA, rapidly followed by a rise in PAI-1 offsetting fibrinolysis [37–39]. The procoagulant response is entirely TF dependent, but the contribution of endothelial TF is uncertain [40]. More likely, the rapid generation and exposure of TF on mononuclear cells [41] is the dominant source of TF. All these changes do not result in irreversible damage to the organism and likely the response of the endothelium is also reversible in nature.

**Endothelial injury and associated altered coagulation and fibrinolysis**

Endothelial injury describes a state in which (1) microscopically visible endothelial cells shape change or injury, as well as defects in the continuity of
endothelial lining, or (2) elevated soluble markers of endothelial injury can be identified [42]. Anatomical damage to the endothelium during endotoxic shock has been assessed in several studies. Endotoxin injected as a single bolus has been demonstrated to be a non-mechanical technique for removing endothelium [43]. As early as 15 min after endotoxin injection, cellular injuries are apparent, with nuclear vacuolization, cytoplasmic swelling and protrusion, cytoplasmic fragmentation, and various degrees of detachment of the endothelium from its underlying layer [44,45]. Proinflammatory cytokines increase permeability of the endothelial cells, and this is manifested approximately 6 hours after inflammation is triggered and becomes maximal over 12–24 hours as the combination of cytokines exert potentiating effects [46]. Endothelial disruption causes inflammatory fluid and cells to shift from the flowing blood into the interstitial space. These stages have been further established in the baboon models in studies by Fletcher Taylor and colleagues. Several experiments in models for sepsis showed that a first phase lasting about 6 hours (after live *Escherichia coli* infusion) is characterized by rapid thrombin generation, and that rises in endothelial cell markers (soluble TM) and soluble fibrin occur more pronounced during the second phase of approximately 24–48 hours (reviewed in [39]). However, with increasing doses of *E. coli* these two phases merge into one more dramatic response characterized by clotting, endothelial cell damage and neutrophil activation (elastase secretion), all contributing to disseminated intravascular coagulation [47].

In general, endothelial injury can be identified by elevated soluble markers, such as plasma TM, ICAM-1, E-selectin and von Willebrand factor (vWF) and its propeptide [48–50]. It has been demonstrated that the half-life of mature vWF and that of its propeptide differ fourfold to fivefold [51]. The molar ratio of the propeptide to mature vWF can serve as a tool with which to assess the extent of endothelial cell injury and to distinguish between acute and chronic disease [52]. In acute sepsis, both vWF and propeptide are elevated several fold, whereas in patients with diabetes mellitus propeptide levels are slightly elevated and vWF levels are elevated two- to threefold. High plasma levels of TM, ICAM-1, and vWF were found in several inflammatory diseases, sepsis, and acute lung injury with nonpulmonary sepsis. It has been demonstrated that endothelial injury is sustained over time. In an endotoxic rabbit model, we demonstrated that endothelium denudation is present at the level of the abdominal aorta as early as several hours following injury and persisted for at least 5 days afterward [44]. After 21 days, we observed a total recovery of the endothelial surface. The de-endothelialized surface accounted for approximately 25% of the total surface. This was associated with coagulation activation marked by maximal monocyte TF expression at 5 days, coinciding with maximal endothelial injury. This may ultimately lead to the development of DIC and multorgan failure.

As discussed elsewhere in this issue, exposure of endothelium to inflammatory or septic stimuli results in a procoagulant behavior associated with blunted profibrinolytic properties due to decreased release of tPA and increased release of
PAI-1. During sepsis, the procoagulant activity of TF increases with transcriptional upregulation of its expression on monocytes and endothelial cells; whereas, levels of endothelium anticoagulant membrane components decrease, with internalization of TM and neutrophil elastase mediated cleavage, and release of soluble TM into the bloodstream [53].

Uninhibited activation of coagulation associated with impaired fibrinolysis, known as the DIC syndrome [54] results in fibrin deposition, tissue ischemia, and tissue necrosis. In the critically ill patient, the syndrome is associated with increased risk for death. Conversely, inhibition of coagulation is expected to prevent organ dysfunction. Unfortunately, major clinical trials with three different therapeutic agents (TFPI, antithrombin, and activated PC) have yielded limited benefit; only activated PC had a modest effect in reducing the mortality rate [55].

Although endothelial cells probably have an important role in DIC, other cells including neutrophils, platelets, and monocytes are involved in this complex syndrome. We assessed the impact of endothelial injury and monocyte activation on coagulation disorders in the rabbit endotoxic shock model. We tested L-arginine, the substrate for the NOS III, and perindopril, an angiotensin-converting enzyme inhibitor, for their demonstrated ability to treat endothelial injury. L-arginine and perindopril could prevent septic shock-associated deterioration in endothelium-dependent relaxation [56,57]. However, this protective effect was not associated with any reduction in TF expression on monocytes, suggesting that these abnormalities are not strictly linked. In another study, we tested an anti-glycoprotein IIb/IIIa, which attenuated endotoxin-induced monocyte TF expression through decreased platelet activation [58]. We found a marked reduction in endothelial injury and increased endothelium-derived relaxation. Those findings suggest that monocyte activation and TF expression may be important in sepsis-associated injuries, and that coagulation activation may contribute to endothelial cell injury during sepsis.

Endothelial injury, in turn, exacerbates sepsis-induced coagulation abnormalities. Endothelium release of NO and prostacyclin is impaired during sepsis resulting in leukocyte and platelet aggregation and aggravation of coagulopathy. Localized coagulation activation associated with innate immune response serves to protect against injury, but when generalized intravascular coagulation induced by generalized inflammatory process develops, it is detrimental to the host leading to widespread fibrin deposition and impaired tissue perfusion.

Two other features potentially reflecting endothelial cell damage deserve attention. First, circulating endothelial cells have been observed in different conditions associated with systemic inflammation including sepsis [52] and sickle cell disease [59]. These circulating cells express active TF suggesting that these cells contribute to the procoagulant nature of blood in those patients. However, the origin and quantitative clinical significance of these cells has not been established. Second, endothelial cells, like other cells from the blood compartment, may generate microparticles, which may be potent contributors to the procoagulant milieu in a variety of disorders including sepsis. The generation of
microparticles may be a reflection of apoptosis; the result is phospholipid cell remnants rich in phosphatidylserine, which provides a catalytic surface for procoagulant reactions supporting thrombin generation [36,60].

**Endothelial dysfunction**

Endothelial dysfunction refers to a decreased endothelium-dependent vascular relaxation or NO release, and decreased expression or activity of endothelial NOS III. It has been shown that the relaxing response of in vitro isolated vascular rings to acetylcholine is dependent on the presence and integrity of endothelial cells [61]. Altered endothelium-dependent relaxation in response to acetylcholine has been demonstrated in sepsis [44,56–58]. This may be explained by morphological injury, but other explanations exist such as alteration in endothelial cell receptors, modified signal transduction pathways (acetylcholine receptor-NOS III coupling), altered function or density of the NOS III, changes in pathways that lead to release of NO, or changes in mechanisms participating in degradation of NO. As for endothelial activation, endothelial dysfunction is dependent in its nature and extent on the location within the vascular tree.

It has been shown that a brief exposure to endotoxin is responsible for an impaired endothelium-dependent relaxation for many days, even after recovery from the acute insult: this process is known as endothelial stunning. Vasodilation in tissues with high metabolic rates competes with sympathetic vasoconstrictor

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**Fig. 1.** Alterations of endothelial cell functions play an important role in multiple organ failure (MOF). This may occur through capillary occlusion and altered perfusion with secondary indirect inflammation or through direct induced inflammation after activation of immunity and coagulation.
tone, adjusting the balance between local tissue oxygen supply to the demanded level. Because endothelial cells are in direct contact with blood, they are effective sensors. In a study investigating the role of the endothelium in regulating the balance between oxygen demand and supply within an individual organ (in an in vivo model of endothelial stripping in the dog hind limb), a severe limitation in the increase in oxygen extraction capabilities during ischemia has been found, suggesting that vascular endothelium plays an important role in matching oxygen supply to demand [62].

An intra-organ defect in blood flow related to abnormal vasoreactivity, cell adhesion, and coagulopathy may account for impaired organ oxygen regulation and function. During sepsis, the inflammatory response alters circulatory homeostasis, vasomotor tone, and the distribution of blood flow among and within organs [63].

Interestingly, it has been demonstrated that endotoxin, mimicking sepsis which is characterized by impaired tissue perfusion (Fig. 1) and abnormal oxygen extraction [64], reduces intercellular communication in in-vitro and in-vivo systems comparably in a reversible and tyrosine kinase-dependent manner [65]. The authors suggest that sepsis is associated with abnormal interendothelial cell coupling and a reduction in the arteriolar conducted response.

**Endothelium in ICU patients**

In healthy volunteers, even brief exposure to endotoxin or certain cytokines impairs endothelium-dependent relaxation for many days (endothelial stunning) [66,67]. After recovery from the acute insult, the endothelium may remain dysfunctional (stunned) for a long period of time before full recovery occurs. Hingorani et al, [68] also demonstrated that a mild inflammatory response such as that generated by *Salmonella typhi* vaccine is associated with temporary, but profound, dysfunction of the arterial endothelium in both resistance and conduit vessels to both physical and pharmacological dilator stimuli. Nevière et al, [69] have shown that reactive hyperemia is attenuated in critically ill patients with septic shock despite normal or elevated whole body oxygen delivery. In an experimental study in dogs, an ablated reactive hyperemia was associated with endotoxemia-induced impaired oxygen extraction at the level of the gastrointestinal tract [70]. Proposed mechanisms to explain blunted hyperemia in septic patients might include impaired vascular reactivity or microvascular obstruction that limits the number of recruitable capillaries. In critically ill patients with sepsis, it has been observed that decreased reactive hyperemia coexists with increased leukocyte adhesion and increased release of surrogate markers of endothelial injury [71,72].

Thus, assessment of reactive hyperemia might be used in the future to evaluate the effects of treatments aimed at restoring endothelial function and tissue perfusion, such as coagulation modulators or leukocyte adhesion antagonists [73].
Summary

Endothelium is an organ system allowing whole body homeostasis. Endothelial cells are very sensitive to the environment and play a key role in cell and nutrient trafficking, vasomotor tone, maintenance of blood fluidity, and modulation of coagulation. Quiescent endothelium has anticoagulant and profibrinolytic properties; however, it becomes procoagulant and antifibrinolytic when activated by exposure to inflammatory stimuli. The response of endothelial cells to such inflammatory stimuli is complex because of phenotypic variation in both space and time. Indeed, endothelial cells from different areas of the vascular tree can express heterogeneous patterns with different intracellular signaling pathways generating different responses to the same stimulus. Moreover this may be observed in the same area of the vascular tree. Systemic inflammation, such as observed during sepsis, profoundly alters the endothelial cell phenotype causing activation, dysfunction, and cell damage depending on the strength and duration of the stimulus. These processes have been mimicked in different animal and human models of sepsis, and during the past decades our understanding of the pathophysiological mechanisms has rapidly advanced. In spite of this progress in knowledge, options for specific therapeutic modulation of endothelial cell properties are lacking. However, several promising tools have become available including angiotensin converting enzyme inhibitors and statins in patients with diabetes, atherosclerosis and immune disorders, but with the potential to generate tools for patients with sepsis. Specific modulators include L-arginine, which as a substrate for NO, is expected to be tested in patients with sepsis [74], and specific anticoagulants, including activated protein C, are promising with regard to improvement of survival [55]. In the latter case, the main clinical action may be prevention of fibrin formation, although on the basis of experimental evidence, anti-inflammatory or anti-apoptotic actions of this agent have been postulated. It is evident that major efforts are still needed to understand the therapeutic potential of endothelial modulation to reduced morbidity and mortality caused by sepsis and other life threatening syndromes.

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References


