Oxidative stress and endothelial dysfunction during sepsis

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1. ABSTRACT

Endothelial activation and dysfunction play a key role in the pathogenesis of sepsis. During septic shock, endothelial dysfunction is involved in microcirculation impairment and organ dysfunction. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) have several potentially important effects on endothelial function and are implicated in physiological regulation and disease pathophysiology. The imbalance between the production of ROS and their effective removal by non-enzymatic and enzymatic antioxidants systems could induce endothelial dysfunction with alterations of vascular tone, increases in cell adhesion properties (leukocytes and platelet adhesion), increase in vascular wall permeability and a pro-coagulant state. Increasing evidence supports the idea that the principal cause of EC dysfunction during sepsis is cell injury. ROS and RNS contribute to mitochondrial dysfunction by a range of mechanisms and induce both necrotic and apoptotic cell death. Understanding the mechanisms underlying the generation of ROS and RNS in endothelial cells and the causes of endothelial dysfunction in sepsis may help provide therapeutic strategies to tackle endothelial dysfunction and microcirculatory failure in sepsis.

2. INTRODUCTION

“Shock associated with sepsis is supposedly of relatively infrequent occurrence. Its incidence during recent years should have been further decreased by general use of antibiotics for the prevention and control of surgical infections. Our clinical experience has not supported either of these two contentions.”


This introduction of Altemeier and Cole’s article published in 1956 could also apply today. Despite tremendous fundamental and clinical research, septic shock, one of the leading causes of mortality in Intensive Care Units (ICU), remains an incompletely solved enigma. Characterised by an infection followed by an uncontrolled immune response, septic shock is a syndrome that has greatly different functions at the site of infection and the time course of the disease. Septic shock has been classified by Bone and co-workers in the early nineties as a systemic inflammatory response syndrome complicated with refractory hypotension in presence of proven infection (2). Treatment of septic shock has remained basically
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unchanged over the last 20 years and includes antibiotics, fluid loading, vasoressors and organ support. One of the major evolutions was introduced by EP Rivers et al. in 2001 (3). With the concept of the early goal directed therapy (EGDT), they demonstrated that sepsis is not simply an organ related disease but also is highly dependent upon time and as such one of the keys to successful treatment of a septic shock patient is aggressive and early management in order to prevent organ dysfunction. Several studies have shown that the use of bundles targeting hemodynamic parameters at the very early stage (less than 6 hours) in the management of a patient significantly improves the outcome (4-6).

One of the main goals of these bundles was to monitor hemodynamic states within two hours and to restore a stable hemodynamic state with a targeted mean arterial blood pressure of 65 mmHg, central venous pressure < 12 mm Hg and central venous oxygen saturation > 70% within 6 hours. By using this type of bundle N’Guyen and co-workers decreased mortality rate from 35.2% to 20%. One of the major limitations of these bundles is their implementation feasibility (5). In most of these studies adherence to the bundles didn’t exceed 55% and a more specific and less time dependant treatment is perhaps what is required in the future.

By looking closer at the hemodynamic goals of the bundles it is apparent that the global hemodynamics (mean arterial blood pressure, central venous pressure, central venous oxygen saturation) are being targeted, but sepsis induces also alterations of microcirculation. Altered microcirculatory blood flow is a major pathophysiological feature of severe sepsis and septic shock (7). De Backer et al. showed that microvascular density and microvascular blood flow are both reduced in septic patients compared to healthy volunteers or non-septic ICU patients (8). Moreover, the degree of microvascular impairment has a prognostic value since it worsens in non surviving septic patients compared to those who ultimately overcome their septic episode (9).

The microcirculation represents the end stage of the arterial circulation and is comprised of capillaries that have a monolayer of endothelial cells and a basement membrane. The fundamental function of microcirculation is to deliver oxygen to the organ. For this purpose blood flow through the capillaries is controlled by the endothelium. The endothelium is an active tissue that plays a pivotal role in maintaining cardiovascular homeostasis. The endothelium ensures the quality of both the global and microcirculation as it forms an interface between blood and tissues. The human body contains approximately 10^{13} endothelial cells, an area of 4000 to 7000 m² and it’s size is one of the reasons why it must be considered an organ. Physiological functions of EC are: 1/ to control vascular tone and blood flow by regulating the local balance between vasodilators (paracrine release of diffusible vasodilators such as nitric oxide (NO) and prostacyclin and vasoressors such as endothelin-1 (ET-1), 2/ to maintain the fluidity of blood to prevent thrombosis, 3/ to control the exchange of fluid and macromolecules between blood and tissues and 4/ to maintain the local balance between pro-inflammatory and anti-inflammatory mediators. It’s location between blood and tissue makes the endothelium at the forefront when an uncontrolled inflammatory reaction starts spreading during septic shock. Inflammatory compounds like cytokines can activate several cell signalling events within EC and one of the earliest compounds released are reactive oxygen species.

Reactive oxygen species have several potentially important effects on endothelial function and are implicated both in physiological regulation and disease pathophysiology (10-12). During sepsis they play a key role during innate immune response and some of their oxidized by products may have protective effect during acute inflammatory states (13). The effects of ROS on EC are dependent not only on the amount and the sites of production, but also on the processes that degrade or scavenge ROS. The imbalance between the production of ROS and their effective removal by nonenzymatic and enzymatic antioxidants systems could induce endothelial dysfunction with alterations of vascular tone, increases in cell adhesion (leukocytes and platelet adhesion), increases in vascular wall permeability and a pro-coagulant state.

Stimulated endothelial cells also produce NO in order to regulate vascular tone. When the capacity to produce NO is impaired, EC are considered to be dysfunctional. This state occurs in septic shock when endothelial NO synthase (eNOS), subjected to an increase of oxidative stress, is uncoupled. Therefore, the capillaries lose their ability to relax and control blood flow. Once uncoupled, eNOS produces superoxide ions instead of NO and further increasing the oxidative stress within the cell (14). Thus endothelial dysfunction appears to be critical during septic shock, and its occurrence is involved in the impairment of the microcirculation and organ dysfunction.

This review will deal with endothelial dysfunction during septic shock. We will focus on the role of reactive oxygen species and reactive nitrogen species in this dysfunction. We will also review the therapeutic potential of targeting endothelial dysfunction in septic shock.

3. SOURCES OF ROS IN THE ENDOTHELIUM DURING SEPSIS

The endothelium represents both a source and a target for ROS released in the vasculature. During septic shock stimulated inflammatory cells such as neutrophils and macrophages produce large amounts of ROS and RNS (15, 16). This production of ROS and RNS is a crucial mechanism for neutrophils and macrophages to damage or kill microorganisms and contribute to part of the host defence against bacterial spread (16). Oxygen bursts can also cause cell damage, and the endothelium is one of the first targets of ROS. During sepsis, a large number of components (i.e. LPS, endotoxins, pro- and anti-inflammatory cytokine balance, degree of leukocyte activation, oscillatory shear stress etc) and conditions (hypoxia, reperfusion injury etc) may be responsible for
endothelial ROS production (12, 17-19). Three main reactive oxygen molecules are formed within the cells: Superoxide anion (O$_2^-$), hydrogen peroxide (H$_2$O$_2$) and radical hydroxyl (OH$^\cdot$). Under physiological conditions ROS are continuously produced in the cells and play an important role in cell metabolism. When produced, endothelial O$_2^-$ is rapidly transformed by Superoxide dismutase (SOD) into H$_2$O$_2$ which is then transformed by catalase and peroxidase into water. The equilibrium between production and elimination of ROS is crucial for the cell’s survival, and is termed the redox homeostasis. Endothelial O$_2^-$ sources that are implicated in endothelial oxidative stress include mitochondria, xanthine oxidase (XO), uncoupled NO synthases, cytochrome P-450 enzymes and NADPH oxidases. In addition, enzymes such as lipooxygenases may also generate O$_2^-$.

Increasing evidence supports the idea that ROS generated from mitochondria significantly contribute to EC dysfunction. The mitochondrial respiratory chain can be a major source of O$_2^-$ (10, 19, 20). During the oxidative phosphorylation, up to 1–4% of O$_2$ may be incompletely reduced in the mitochondrial respiratory chain, resulting in O$_2^-$ formation, mainly at complex I (NADH coenzyme Q reductase) and complex III (ubiquinol Cyt c reductase) of the mitochondrial respiratory chain (19). Increased mitochondrial O$_2^-$ generation appears to be particularly prominent in situations of metabolic perturbation. For example, hyperglycemia, hypoxia, and ischemia/reperfusion induce O$_2^-$ production. Moreover, pro-inflammatory cytokines (ie. tumour necrosis factor (TNF-α)) may directly induce mitochondrial O$_2^-$ production (21).

As ROS are highly toxic components, their production is tightly controlled by enzymatic and non-enzymatic antioxidant components (22). The effects of ROS generated within EC are dependent on the amount of ROS generated and on the capability of antioxidant systems to control this ROS production. The deleterious effects of ROS can be modulated by enzymatic and non-enzymatic antioxidant systems that can either specifically inhibit ROS formation or facilitate ROS conversion into inactive components. Antioxidant systems comprise non-enzymatic molecules and specific antioxidant enzymes (23). Non-enzymatic antioxidants in EC include uric acid, ascorbic acid (vitamin C), α-tocopherol (vitamin E), and glutathione (GSH) (24, 25). Glutathione is the major thiol antioxidant in EC, serving as a substrate for glutathione peroxidase to eliminate lipid hydroperoxides and H$_2$O$_2$, whereby it becomes converted to GSH disulfide (GSSG). Normally, GSSG is maintained at levels <1% of total GSH. Enzymatic antioxidants in EC include SOD, catalase, the thioredoxin system, glutathione peroxidase, and heme oxygenase (Figure 1) (26). During septic shock SOD activity doesn’t appear to be compromised. In fact, when
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Figure 2. Mechanisms of nitric peroxide-mediated cell death. Nitric peroxide directly oxidizes DNA, lipid membranes and proteins leading to direct damages of the cell. It can also inhibit mitochondrial respiration leading to a decrease of cell metabolism and apoptosis.

EC are exposed to plasma from septic shock patients SOD activity remains unchanged despite increases of ROS production (27). On the other hand, a significant decrease of H₂O₂ antioxidant defences is observed (28). These results may indicate that antioxidant therapy needs to target specific ROS to be efficient.

4. NO PARADOX IN SEPTIC SHOCK

NO is a well-known vasodilator that can be synthesised by eNOS, inducible Nitric Oxide Synthase (iNOS) or neuronal Nitric Oxide Synthase (nNOS). During septic shock an increase of NO availability has been described and attributed to the increase in iNOS activity within the smooth muscle cells of the artery or nNOS activity (29). Released into the bloodstream and bound to haemoglobin, NO could potentially spread throughout the whole organism. This has been found to be partially responsible for the uncontrolled hypotensive state often occurring during septic shock. The underlying cause of the activation of iNOS remains unclear and its deleterious effect remains to be clearly demonstrated. Indeed, several studies have tried to inhibit iNOS activity in animal models of septic shock without much success. The activation of iNOS has been described just hours after the initiation of shock and could last for more than 48 hours (30). Thus, bioavailable NO can combine with O₂⁻ to form peroxynitrite (ONOO⁻). ONOO⁻ is a highly unstable RNS that can lead to major cell damage (Figure 2). Unlike ROS, ONOO⁻ can induce cell damage far away from its site of production. More recently it has been reported that nNOS seem to play a crucial role in the impairment of hemodynamic parameters in a sheep model of septic shock (31, 32). Inhibition of nNOS may have beneficial effect but these results remain controversial (33, 34).

Interestingly, the increase of iNOS activity is followed by a decrease of eNOS activity and expression (35). This finding may have a major impact in future clinical studies. As NO is mainly produced by EC in the microcirculation, the decrease of its production during septic shock may be involved in the impairment of the microcirculation blood flow. The mechanism underlying the decrease of NO production in EC is could be due to the uncoupling of the eNOS. This occurs when the essential NOS cofactor, tetrahydrobiopterin (BH₄), is oxidized. eNOS is a homodimeric complex that includes enzymatic sites with reductase and oxidase activity. NO formation is the result of two successive reactions. The first consists of molecular oxygen formation that hydroxylates guanidino-nitrogenated L-arginine and forms N⁵-hydroxy-L-arginine. The second reaction consists of N⁵-hydroxy-L-arginine oxidation and leads to NO and L-citrulline formation. The cofactor BH₄ is necessary for both reactions. When BH₄ levels are reduced or absent, NOS can become “uncoupled,” leading to the generation of O₂⁻. Thus uncoupled eNOS is responsible of an increase in oxidative stress (36-38). In addition to increased catabolism
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or degradation, another reason for BH4 depletion may be its reduced synthesis. NOS uncoupling results in a loss of endothelial vasodilation due to decreases in NO production and an increase in oxidative stress. ROS therefore play a pivotal role in vasomotor disturbances observed in septic shock.

5. MECHANISMS OF ENDOTHELIAL DYSFUNCTION DURING SEPSIS

Our group has tested the capacity of plasma from patients with septic shock as a whole to induce ROS production in naïve human umbilical vein endothelial cells (HUVEC) (27). For this study, we used a fluorescence technique that is widely used by our group and others to quantify ROS production in HUVEC (20, 21, 39). We found that plasma from patients treated for septic shock induces ROS formation in naïve HUVEC, and that the extent of ROS production was higher in non-survivors than in survivors and furthermore, this correlated with criteria of the severity of septic shock such as SOFA score and SAPS II (27). Therefore, these experiments revealed the ability of the plasma to induce ROS production independently of any direct effect of sepsis mediated by circulating cells on the EC. This could be of clinical relevance because during septic shock, infection and inflammatory response are initially spatially limited. Subsequently however, a systemic inflammatory response and organ dysfunction at a distance from the initial infection site can occur, events for which EC activation is a key element.

Increasing evidence supports the idea that the principal cause of EC dysfunction during sepsis is cell injury (12, 18, 40). It is essential to understand the difference between EC dysfunction and EC activation. Activated EC respond by the acquisition of a new endothelial function, which is going to be beneficial for the host. A dysfunctional EC reflects the failure of the EC to adequately perform a homeostatic function. Significant injury leads to EC shedding and release of membrane vesicles known as exosomes or microparticles with an increased thrombotic propensity.

ROS cytotoxicity is always due to the association of two phenomena i.e. an increase in ROS production and a decrease in antioxidants defences. We have also reported that ROS cytotoxicity induced by plasma from septic shock patients is dependent upon the rapid decrease (4 hours) of intracellular GSH levels in HUVEC (28). GSH levels are one of the critical determinants of EC damage during septic shock. Neither O$_2^-$ nor NO is particularly toxic in vivo because O$_2^-$ is rapidly removed by SOD and NO is removed by its rapid diffusion into red blood cells where it is converted to nitrate by the reaction with oxyhemoglobin. However, when NO is in the high nanomolar range, NO may compete with SOD and react with O$_2^-$ to generate ONOO$^-$ (O$_2^-$ reacts with NO at a significantly faster rate than SOD, k = 6.7 x 10$^9$ mol$L^{-1}.s^{-1}$). Under pro-inflammatory conditions, simultaneous production of O$_2^-$ and NO can be upregulated to increase production 1,000-fold, which will increase the formation of ONOO$^-$ by a 1 million-fold (40). Thus, even modest increases in the production of O$_2^-$ and NO will increase the formation of ONOO$^-$ and this reaction ultimately leads to a decrease in NO availability. A large body of evidence supports a key role of ONOO$^-$ in cell cytotoxicity (40, 41). The half-life of ONOO$^-$ is short (10 – 20 ms), but sufficient to cross biological membranes. Thus, ONOO$^-$ diffuses and reacts within one to two cell diameters. In comparison, OH$^-$ is so reactive that it reacts within a very short diffusion distance (= less than the diameter of a protein). Once formed, ONOO$^-$ causes cell injury by oxidizing biological molecules. In addition, it can yield hydroxyl radical and nitrogen dioxide (NO2$^-$). Through these reactions, ONOO$^-$ in activated macrophages and in EC damages proteins, lipid and DNA. Moreover, ONOO$^-$ can react with most of the components of the electron transport chain including complexes I and III (Figure 2) (40-42).

Peroxynitrite may reach mitochondria either from extramitochondrial compartments or may be directly produced within the mitochondria. Indeed, mitochondria can produce both NO, by the activity of a Ca$^{2+}$-sensitive mitochondrial NOS (mtNOS) and superoxide, due to the natural leak of electron from the mitochondrial respiratory chain (40). Peroxynitrite may mediate apoptosis by permeabilization of their outer membrane. Mitochondrial outer membrane permeabilization allows the efflux of various proapoptotic signaling molecules, which promote cell death or by a phenomenon termed mitochondrial permeability transition (MPT). MPT describes the permeabilization of the inner mitochondrial membrane. The permeability of transition pore causes the dissipation of mitochondrial membrane potential, this resulting in cessation of electron transfer and ATP production. Furthermore ONOO$^-$ nitrates and inhibits Mn-SOD preventing the breakdown of locally produced superoxide, which further fuels the formation of ONOO$^-$. Peroxynitrite may induce DNA damages with activation of the DNA repair enzyme PARP-1 (Figure 2). Upon severe DNA injury, over activation of PARP-1 depletes the cellular stores of NAD$, an essential cofactor of the glycolytic pathway, the tricarboxylic acid cycle, and the mitochondrial electron transport chain. As a result, the loss of NAD$^+$ leads to a marked decrease in the cellular pools of ATP, resulting in cellular dysfunction and cell death (“suicide hypothesis” after irreversible DNA injury). Whereas apoptosis is a typical consequence of low to moderate concentrations of peroxynitrite, exposure of cells to higher concentrations has been associated with necrosis.

Overproduction of O$_2^-$ leads also to an excess of H$_2$O$_2$ production. Our findings seem to indicate that H$_2$O$_2$ is the main ROS involved in endothelial dysfunction during sepsis. We have shown that SOD activity was not impaired in red blood cells and in endothelial cells. But peroxidase activity and glutathione levels were significantly decreased in both cells during septic shock (27, 28). These results suggest H$_2$O$_2$ as the leading ROS involved in the damages of EC during septic shock. Despite his own toxic effects H$_2$O$_2$ might induce hydroxyl radical formation by the Fenton reaction (H$_2$O$_2$ + Fe$^{3+}$ $\Rightarrow$ OH$^-$.OH$^+$ + Fe$^{2+}$) or Haber-Weiss cycle (H$_2$O$_2$ + O$_2^-$. $\Rightarrow$ OH$^-$.OH$^+$ + O$_2$) when in the presence of oxidized transition metals like copper or
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Figure 3. Sequence of endothelial dysfunction induced by ROS and RNS during septic shock. The cascade involved in ROS induced EC damages during septic shock: Activation of NADPH oxidase, Xanthine oxidase, Complex I and III of the mitochondria, Cytochrome P450, by inflammatory compounds or ischemia reperfusion, lead to an overproduction of $\text{O}_2^-$. NO compete with SOD and leads to production of ONOO$^-$ by using $\text{O}_2^-$ and ONOO$^-$$^-$ uncoupled e-NOS therefore producing $\text{O}_2^-$-4$^-$ activly transformed by SOD leads to overproduction of H$_2$O$_2$. 5- Decrease of glutathione pathway antioxidant defences leads to an increase of H$_2$O$_2$. 6- H$_2$O$_2$ and O$_2^-$ accumulation trigger Fenton reaction. 7- Overproduction of ROS and RNS impair mitochondrial function and induce cell damages leading to cell death.

iron (43, 44). The OH$^-$ radical is one of the most unstable and therefore toxic ROS. This may be key information for clinical trials trying to target oxidative stress during sepsis. Targeting any antioxidant defences might not be relevant. It seems more relevant to focus on specific defence such as glutathione or glutathione peroxidase.

The sequence that can be drawn to detail the cascade involved in ROS EC damages during septic shock is summed up in Figure 3.

6. MICROcircULATION: THE THERAPEUTIC TARGET OF THE NEXT DECADE

Increased interest for microcirculation during the last decade has led to the development of new tools to directly evaluate the microcirculation. One of the major obstacle is to assess the microcirculation within the human body. Sublingual microcirculation has been assessed with Orthogonal Polarized Spectral and is correlated to severity of patients (9, 45). It has also enabled investigators to make therapeutic tests. Dubin and coworkers have shown that improving the macrocirculation with NOREPINEPHRINE doesn’t change the microcirculation state (46). But when using DOBUTAMINE De Backer and coworkers observed an increase of the microcirculation blood flow even before macro hemodynamic changes (47). Recently Trzcinski et al demonstrated that EGDT improved microcirculation and decreased organ dysfunction (7). Changes in microcirculation were positively correlated to decrease of organ dysfunction. In another study Spronk et al targeted specifically e-NOS uncoupling in resuscitated septic shock patients by nitroglycerine infusion. They showed a positive effect on microcirculation although this finding was not
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substantiated by a larger clinical trial in septic shock patient but failed to demonstrate any difference (48,49).

In our perfused endothelial cell model we have demonstrated that glutathione supplementation significantly decreases ROS production and endothelial cell death when cell were exposed to plasma from septic shock patients (28). Therefore antioxidant therapy may also have a positive effect on endothelial cell dysfunction during septic shock.

Combining antioxidant therapy and NO supplementation may be the successful key to treat endothelial dysfunction. Meziani et al. used in a rodent septic shock model Human Serum Albumin (HSA). Albumin has well known antioxidant effect mainly because of its thiol group. Animals resuscitated with HSA showed a significant decrease of ROS and RNS production (17). This was associated to a better vascular reactivity. Taken all together these findings strongly confirm the hypothesis that microcirculation is impaired during septic shock and that treating EC dysfunction may be a key element during septic shock resuscitation.

The question that still remains is when and how to modulate oxidative stress during septic shock to enable a better prognosis. The choice of the drug may be crucial. A promising therapeutic for the next decade might be the use of endothelial progenitor cells (EPC). These progenitors are released in the circulation in order to allow endothelium repairing and angiogenesis. Recently Rafat et al. showed that endothelial progenitor cells were significantly increased in septic shock (50). This increase was significantly higher in survivors than in non-survivors. Abou-Saleh et al. demonstrated in a model of acute vessel induced injury that EPC inhibit platelet activation, aggregation, and adhesion to collagen, and thrombus formation, predominantly via upregulation of cyclooxygenase-2 and secretion of prostacyclin (51). This may also be one of a track to follow in the near future.

7. CONCLUSION

Endothelial cells activation and dysfunction play a role in the pathogenesis of sepsis. They are one of the first targets of systemic inflammation due to septic shock. Vasomotor tone modifications, leukocyte and platelet adhesion, capillary leak, and procoagulant state lead to a global decrease and heterogeneity in capillary perfusion as well as a decrease in tissue oxygen extraction capacities. Endothelium dysfunction is involved in microcirculation impairment and organ dysfunction. Reactive oxygen species and RNS have several potentially important effects on endothelial function and are implicated both in physiological regulation and disease pathophysiology. During sepsis, the endothelium becomes both a target and a source of ROS and RNS. Exogenous sources of ROS and RNS are mainly phagocytes. Understanding the mechanisms underlying the generation of ROS and RNS in endothelial cells and the causes of endothelial dysfunction in sepsis may help therapeutic strategies to tackle endothelial dysfunction and microcirculatory failure in sepsis. However, even if some studies show encouraging results by antagonizing reactive oxygen species, none of them have clearly demonstrated absolute benefit for antioxidant strategies. It is one of the most important therapeutic challenges to be investigated in the near future.

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