

Alteration of Haemostasis during Sepsis: A Complex Multifactorial Pathological Action

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Abstract

The alteration of haemostasis during bacterial infection and sepsis are well known. Several mechanisms have been described in last decades and may lead toward disseminated intravascular coagulation. Here we report most common mechanisms that may be treated from a clinical point of view during a bacterial sepsis.

Keywords: Haemostasis; Sepsis; Endotoxin

Background

Alterations of haemostasis during bacterial sepsis are a well-known complication [1]; pathophysiological mechanisms are multiple and different, leading to a progressive consumption of fibrinogen and thereafter inducing disseminated intravascular coagulation (DIC) and multiorgan failure (MOF) until irreversible septic shock [2].

From a clinical point of view all these pathophysiological processes may be characterized by disseminated microthrombosis and bleeding due to progressive fibrin deposition and consumption inducing multiorgan and distrectual ischaemia and necrosis [3]. Most common damaged organs are liver, kidney, lung, brain. The toxic bacterial action starts after hypersensitivity to the bacterial wall and its components as Lipopolysaccharide (LPS) and other bacterial proteins [4]. Here we report best known pathophysiological mechanisms inducing alteration of haemostasis during bacterial sepsis.

Basic scientific principles

The medical literature offers several items that are periodically updated by scientific improvements in particular in the pathophysiology of clotting abnormalities during sepsis. Usually we can summarize these updates in two different points: bacterial role and host role.

Bacterial agents can be found in the bacterial wall, in particular in gram negative bacteria. The presence of different bacterial components as LPS and porins may induce clotting abnormalities. All these components can be found inside the bilayer of bacterial membrane [4,5].

The procoagulant action of these molecules can be exerted in different ways. The hyperactivation of monocytes during infection may release several substances as tissue factor (TF) and interleukin-1 that may extend their actions to other inflammatory cells [6] so inducing a complex cell-interleukin and cell-protein and protein-protein interactions. These mechanisms are focused to escape the bacterial growth and the bacterial proliferation.

The role of host is also due to its adequate production of interleukins and inflammatory proteins and to inflammatory cells migration that may be associated to alteration of haemostasis [7]. The most common alterations of haemostasis secondary to sepsis, in fact, may be related to increased production of thrombin, that is also associated to decreased action of clotting inhibitors and to decreased fibrinolytic power.

The impaired and decreased action of natural clotting inhibitors as protein C in fact has a double way association with increased

thrombin generation and with decreased fibrinolytic system. The continuous pro-inflammatory state due to infection, in fact, is also associated to a progressive impaired liver function, in particular on the synthesis of clotting proteins as antithrombin and protein C, and to a decreased endothelial function, in particular to a decreased release of thrombomodulin, natural heparinoids and tissue factor pathway inhibitor (TFPI). This step is very dangerous because it has been demonstrated in experimental models that a reduction of TFPI less than 30% is associated to strong prothrombotic state and to spontaneous DIC in clotting *in vitro* [8].

So, in this way the reduction of available thrombomodulin exerts an indirect reduced function of protein C and furthermore a reduced availability of heparinoids reduce the function of antithrombin.

Bacterial toxins and porins

Several mechanisms are involved in this process but the clotting system acts mainly toward bacterial LPS and bacterial porins. Bacterial porins are a family of protein that is able to activate the human thrombin by a direct action as demonstrated *in vitro* in several experimental models. Moreover in several models this direct activation of thrombin by bacterial porins is fast and strong if compared to that induced by other molecules [5].

On the other hand also LPS, that acts as bacterial endotoxin, is able to increase the activity of the clotting system by extrinsic pathway [4]. The LPS can act inducing an increased exposure and release of tissue factor (TF, i.e., clotting factor III) by monocytes so inducing the activation of factor VII (i.e., factor VIIa) [9] that goes to activate factor X to factor Xa. Factor Xa is able to increase the activation of thrombin so inducing the permanent increased production of fibrin. The only system that may counteract this hyperactivation is the system based on TFPI that is produced mainly by endothelial cells.

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Yet, the system of TFPI usually is unable to control the hyperactivation of clotting system also because the amplification of the host response by monocytes as previously underlined; the role of monocytes in fact is to expand the reaction by the release of several type of cytokines as IL-1 and tumor necrosis factor (TNF) [10].

Hyperproduction of thrombin

Bacteria and their toxic products are fought not only by immune system and immune cells but also by the clotting system [11] in particular by clotting proteases as thrombin and fibrinolytic proteins as plasmin.

The increased release of proteases by the host, in fact, is a specific action of proinflammatory cells as leukocytes. Antibacterial proteases are unselective so they may induce also the activation of other proteases as proteins of the complement system and of haemostatic system as thrombin and plasmin. So the hyperactivation of clotting system during infections has as basic function the function to fight the bacterial proliferation. Thrombin and plasmin act as proteases that damage proteins present in the bacterial wall in order to limit damages induced by the infection [12].

So, the hyperproduction of thrombin may be summarized in three different ways: the hyperactivation due the release of TF by LPS, the direct activation induced by bacterial porins, the hyperactivation due to the protease-protease inflammatory network.

Decreased clotting inhibitors activity

We already underlined the decreased action of thrombomodulin (i.e., CD 141). Yet, this reduction leads to a decreased activation of protein C, but the remaining part of activated protein C suffers of the increased consumption due to the increased production of thrombin. So, these combined mechanisms may be considered a first degree of decreased availability and action of clotting inhibitors during sepsis [13].

On the other hand the constant interleukin productions induced by proinflammatory cells induces a reduced activity of the liver that produces a less quantity of all proteins in particular of antithrombin. This reduced synthesis of antithrombin by the liver is associated again to a reduced inhibition of thrombin.

Moreover also the release of TFPI is decreased by endothelial cells because the proinflammatory state and this may contribute again to a reduced inhibition of factor VII and TF. This topic is really relevant because in experimental models in vitro a 30% of reduction of TFPI is able to induce DIC spontaneously [8].

Hypofibrinolysis

Hypofibrinolysis is mainly due endothelial dysfunction induced by infection. Endothelial activities in fact change after the release of proinflammatory cytokines by proinflammatory cells: these changes lead also to a change in the release of endothelial proteins. We already underlined that the release of endothelial TFPI is reduced during these phases of infection and this change is also associated to a change in the release of proteins involved in the fibrinolytic system: the release of plasminogen activator inhibitor type 1 (PAI-1) is increased while the release of tissue plasminogen activator is decreased (tPA), so inducing an impairment of fibrinolytic balance with a trend toward hypofibrinolysis.

Moreover, the release of thrombomodulin by monocytes makes a change and this change is associated also to the increased production

of thrombin. Furthermore, the decreased action of thrombomodulin induces not only a reduced action of protein C as we previously described, but also an inhibition of fibrinolysis by cleaving thrombin-activatable fibrinolysis inhibitor (TAFI) [14].

So, according to all described changes during infection or sepsis, the hypofibrinolysis is strongly increased and this condition increases prothrombotic state driving toward DIC in its final stage.

Conclusions

There are always several mechanisms involved in the human response against bacteria: spontaneous immunity, induced immunity, immunoglobulins, proteases' systems as complement system, clotting system and fibrinolytic system. However in each system we note that prothrombotic state go on stronger than others and for this reason we may only underline that during sepsis we are more prone to develop thrombotic complications and to be defended by other clinical manifestations as haemorrhagic complications.

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