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Physiopathology of Sepsis

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Epidemiology

Infection occurs in 15% to 40% of admissions to the intensive care unit (ICU); mortality ranges from 10% to 80%. The EPIC (European prevalence of infection in intensive care) European study, with 10,038 patients, found that 21% of patients enter intensive care: 65% with pneumonia, 17% with urinary infection, and 12% with bacteremia. The most frequently found germs were the following: enterobacteria (34%), *Staphylococcus aureus* (30%), and *Pseudomonas aeruginosa* (30%). The risk factors observed in the study were the following: prolonged stay, mechanical ventilation, trauma, central venous catheter, and urinary catheter. Only 50% of blood growths were positive in sepsis patients.[1]

The worldwide incidence of sepsis is 1,500 cases per million. Angus et al. report 750,000 cases per year (three in 1,000 persons) in the United States. The average mortality of 30%, equivalent to 250,000 deaths per year, can increase to 60% or more when multiple failure occurs in more than three organs for 3 or more days.[1,3,7] The Atlanta Centers for Disease Control report negative coagulase staphylococcus, *Staphylococcus aureus,* enterococcus, and candida as causes of sepsis.[4]

Definitions

- *Sepsis:* Serious documented infection that causes a systemic inflammatory response syndrome (SIRS).[2]
- *Septic Shock:* Sepsis causing refractory hypotension to an adequate liquid supply, upsetting tissue perfusion and resulting in lactic acidosis, oliguria, and mental alteration.[1]

Sepsis could be secondary to bacteria translocation in the intestine wall with local hypoperfusion. The initial phase of a shock frame and leading to

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progressive multiorgan failure and high mortality. In sepsis, if a systemic inflammatory reaction predominates, the term *SIRS* is used. When the predominating picture is antiinflammatory, the term *CARS* (compensatory antiinflammatory response syndrome) is used, and if there is a balance in response, the term *MARS* (mixed antagonistic response syndrome) is used. The CHAOS nomenclature in sepsis translates to the following defects: cardiac compromise and shock (SIRS), **h**omeostasis (MARS), **a**poptosis and organ dysfunction (SIRS), and **s**uppression of immune system (CARS).

Multiorgan failure should be suspected when the level of lactate is increased in several samples, with the lung being the most commonly affected organ. Adult respiratory distress syndrome (ARDS), with an incidence of 28%, is followed by hepatic failure, renal failure, coagulation and gastrointestinal system problems.[1,2]

Immunologic Response

The first step in host defense depends on cells and molecules that mediate the innate immunity and include neutrophils, macrophages, and naturalkiller cells. These cells act directly on the invading pathogens without compromising the adaptive immune system. The activation of the complement by alternate paths acts also as an innate humoral response; C3b and iC3b opsonize bacteria and facilitate phagocytosis; C3a and C5a stimulate chemotaxis and form the complex membrane attack system (CMAS), producing bacterial lysis. The macrophages arise from the mature monocytes found in the gastrointestinal tract, lung, and Kupffer cells in the liver. The leukocyte wrapped involved in the phagocytosis processes has an immune globulin receptor (Fc) and complement receptor (CR), which is the CD11 – CD18; when they join with C5a, phagocytosis is activated by the macrophage, making it easier if the bacteria is covered with C3b and IgM.

The innate immune system is able to liberate cytokines and to express other stimulating molecules, which in turn activate an adaptive immune response to activate T and B cells. This adaptive immune system is specific and has memory for presented antigens. It is believed that septic shock presents an inadequate increased response to innate immunity.

The generation of antibodies to protein antigens depends on the T-helper cells (Th) and on the native independent B cells of the thymus (Ti). Antigen Ti-1 cells may induce proliferation of B cells and secrete antibody in absence of a specific antigen joined to the surface in a more rapid way. Cell Ti-2 antigen significantly increases the production of antibodies of B cells because it stimulates Th cells through cytokines. IgM and IgG are induced by antigen Ti-2. In summary, the T cells (adaptive immunity) require that signals be activated to proliferate and to produce cytokines. By joining an unknown antigen or by joining to the CD14 receptor or to the B7.1 protein, which are glucoproteins expressed in presenter cells of antigen, such as macrophages and neutrophils, the CD4T activated cells

are programmed to secrete pro-inflammatory substances and anti-inflammatory substances called cytokines. The T-helper type 1 (Th1) produces TNF, interferon, and interleukin 2 (IL-2) with inflammatory properties. The T-helper type 2 cells 2 (Th2) produce IL-4 and IL-10 with anti-inflammatory properties; in addition, they are involved in the production of adaptive immunity. The factors determine whether the response of CD4T cells is their action on Th1 or Th2 is not known, but it is believed that they could influence the type of pathogen, the size of the microbial inoculums, and the location of infection The mononuclear cells of burn or trauma patients had diminished levels of cytokines by Th1 but increased levels for Th2.[5]

Activation of polymorphonuclear (PMN) neutrophils such as the first cells participant in inflammation varies among individuals depending upon the insult. Adams et al. show that sepsis patients present marked diminishing receptor response of PMN subtype II to the chemokine (quemoquina) IL-8.[9]

The defensins are a family of cation antimicrobial peptides of 3 to 4 MW, secreted by phagocyte cells such as the protein bacterial permeability increasers (BPI) of 50 MW.

The lipopolysaccharide binding protein (LBP) of 65 MW is of acute phase. This facilitates the transference of the lipopolysaccharide to the CD14, to promote the synthesis of the cytokines, and it acts as an opsonin.

There are three receptors for the A lipid portion of lipopolysaccharide: the CD14, the sweeper SR, and the integration integrin B2 of leukocyte(CD11-CD18), which are present in monocytes and macrophages. These receptors initiate cellular signs but need transmembrane proteins to transmit the signals. The toll-like receptors (TLR), have an extracelular domain rich in leucine and a cytoplasm tail homologous to the receptor of IL-1. This TLR sends the transmission signal activating the gene nuclear kB (NF-kB), a transcription factor, which phosphorizes and degrades the IkB inhibitor in order to activate the NF-kB. This system a transcriptional regulation in pro-inflammatory genes, which again encode intercelular adhesion molecules, cytokines. Right now, there are about 10 TLRs; nowadays, the more studied are TLR2 and TLR4. TLR4 is the favorite of the lipopolysaccharides of Gram-negative and TLR2 of lipoteichoic acid of the Gram positive. The TLR4 also increases production of B7.1, coestimulator molecule involved in the antigen presentation. The cytokines, product of this process, stimulate cells T and B of the adaptive system, producing the tumor necrosis factor (TNF) and immunoglobulins. TLRs are the principal inductors of innate immunity detecting critical pattern recognizing molecules that alert the host to the presence of a microbial pathogen. The TLR2 has a strong expression pattern in the mononuclear peripheral blood cells. TLR3 mRNA is expressed in lung, muscle, heart, brain, and intestinal cells. TLR4 is expressed in lymphocytes, spleen, and heart. TLR5 mRNA is detectable in blood periphery monocytes and leukocytes. TLR6 is expressed in the spleen, thymus, ovary, and lung.

Microbial mediators induce inflammation by acting on host receptors described as follows: lipopolysaccharide (LBP-CD14-TLR4), peptideglycan

(CD14-TLR2), lipoid acid (lipoteichoic (CD14-TLR2), microbial DNA (TLR9), bacteria pili (TLR5), and double-chain RNA virus TLR3). These microbial mediators in turn come from the following germs: LPS and A lipid (gram-negative bacteria), lipoid acid (lipoteichoic acid) (gram-positive bacteria), protein F of respiratory syncytial virus, and heat shock protein 60 (other ligators). TLR2 and TLR4 require adaptive protein MYD88 as transducer of signals in order to express MHC molecules class II and costimulatory molecule B.7 that is found in antigen presenter cells, finally activating the T cells.[8]

The migration inhibitor factor (MIF) is secreted by lymphocytes sensitized by antigen, pituitary gland, cerebral cells, kidney, lung, prostate, and macrophages. The macrophage produces MIF and at the same time is its target of the same. The lipopolysaccharides, TNF and interferon (INF) activate the macrophage to produce MIF that is in charge of promoting inflammation stimulating eicosanoid production and TNF. The MIF stimulates the cytosolic phospholipase A2, which induces liberation of arachidonic acid and of leukotriene.

There is a group of bacteria-like group A streptococci that produces exotoxin, and *Staphylococcus aureus,* which produces enterotoxin. Together they belong to the group called *superantigens*. They stimulate $CD4^+$ - $CD8^+$ T cells through the receptor of T cell and without the colaboration of the major complex of class histocompatibility, causing an aberrant proliferation of specific T cells in massive form. These superantigens produce the toxic shock syndrome. They are soluble proteins of 230 amino acids. The superantigens interacting with T cells liberate cytokines. The Gram-positive bacteria now produce 50% of the cases of severe sepsis and septic shock.[1,4,6]

The cytokines known as pro-inflammatory are described as follows:

- *Tumoral Necrosis Factor:* This is divided into TNFα and TNFβ. TNFα is produced by monocytes and macrophages, and TNFβ, by T cells. Tumor necrosis factor is a protein of 17 MW. It originates in cells of the lung, pancreas, heart, kidney, and uterus. It generates SIRS, fever, hemodynamic instability, leukopenia, increased hepatic enzyme, coagulopathy, and chemotaxis. It induces acute phase proteins, muscular gluconeogenesis; it activates monocytes, macrophages, neutrophils, and finally apoptosis They present two types of receptors of 55 MW and of 75 MW, whose union initiates the transmembrane signalization process with induction of transcription NF-kβ factor. They have 1 to 2 hours of maximum peak and return to nondetectable levels within 4 hours. The serum levels of TNFcorrelate with severity and poor prognosis in sepsis.

- *Interleukin 1:* Interleukin 1 is a protein whose molecular weight is of 17. It has two forms, IL-1α and IL-1β. Its actions are similar to those of TNF but its effect is less potent. It has I and II receptors and a soluble antagonist of receptor IL-1ra that is produced by the same cells that produce IL-1. It

induces transduction signals activating the molecular transcription factor AP-1 and NF-kβ. Its high serum levels also correlate with high mortality.

- *Interleukin 6:* Interleukin 6 is a protein of 22 to 29 MW produced by monocytes, macrophages, endothelial cells, astrocytes, fibroblasts, and B and T lymphocytes. It handles the acute phase response. Its receptor is soluble and it transports to the IL-6 to be joined to the signal transductor SP130. It is a marker of systemic inflammation and is liberated by TNF and IL-1. It stimulates production of reactive C protein in the liver. Serum levels of IL-6 are also related to the diagnosis of septic shock.

- *Interleukin 8:* This is a peptide of 10 MW acting as chemotatico for neutrophils. It is produced by monocytes activated by lipopolysaccharide. It belongs to the chemokine family and is produced by endothelial cells, T lymphocytes, and monocytes. It liberates lyzosomic enzymes and superregulates complement receptors. It is liberated by the stimulus of TNFα and IL-1. It causes SDRA and its levels are correlated with mortality and sepsis.

- *Interleukin 10:* This is a protein of 35 MW, produced by Th1 cells, B cells, monocytes, and macrophages. It suppresses production of interferon by Th2 and natural killer cells and suppresses the cytokine production by the monocites (TNF, IL-1, IL-6, IL-8). It increases production of IL-1ra. It is considered the perfect anti-inflammatory cytokine. Its high levels correlate with severe sepsis, septic shock, and the severity index of APACHE II.

- *Other anti-inflammatory cytokines:* These include the soluble receptors of TNF (TNFR1 and TNFR2) that limit their activity and the soluble antagonist of receptor IL-1ra that limits the activity of IL-1. It also includes IL-12, the inhibiting protein of monocytes 1α and 1β, the stimulator factor of colonies of granulocytes and macrophages and nitric oxide.

Other inflammation mediators in sepsis are the free radicals of oxygen and the platelet activator factor (PAF). This amplifies the liberation of early inflammatory mediators such as TNFand late susbtances such as thromboxane A2 (TxA2) and leukotriene B4.[1,6,7]

Many lymphocytes and epithelial cells are in the gastrointestinal system and die by apoptosis during sepsis with a potential mechanism such as endogenous glucocorticoids induced by stress. The apoptic cells induce anergy and secretion of anti-inflammatory cytokines that deteriorate the immune response. Necrotic cells produce immune stimulation and increase the antimicrobial defense. Apoptosis can also induce loss of cells of the adaptive immune system, such as B cells and the dendritic follicular cells diminishing production of antibodies, the activation of macrophages, and the presenta-

tion of antigens, respectively. Munford and Pugin indicate that normal corporal stress responds with an anti-inflammatory mechanism.[10] Heidecke et al. showed initial immunosuppression as a response to sepsis. This would come into controversy with the traditional initial response of SIRS exposed up to now.[5]

Immunologic Sequence in Sepsis

Septic shock is the result of an interaction between the invader (the microorganism and its products) and the host, liberating factors in response to the invasion (cytokines and other mediators) in an excessive way that causes (MODS) (multiple organic dysfuntion systemic) and death. The initiation of the inflammatory response in sepsis is originated by the endotoxin lipopolysaccharide of the Gram negative with TLR4 and by the peptidoglycan or lipoteic acid of the Gram-positive fungus, parasites, and virus with TLR2. The lipopolysaccharide joins to a plasmatic transporting protein (LPB) and is deposited in the receptor of the macrophage membrane CD14. This complex announces through the receptor TLR4 and TLR2, the transducting signal that generates the following sequence. The joining of the liganders causes dimerization of the receptor with compromise of IL-1RAP (accessory protein) in the intracellular portion of the receptors, forming a complex of MYD88 and IRAK (kinase associated with the receptor IL-1). This phosphorizes TRAF6 (factor 6 associated to the receptor TNF), which in turn activates I-kβ kinase (inhibitor subunit k), leaving free the expression of NF-kβ to translocate the cell nucleus initiating the transcription of assembling genes of cytokines such as TNF, IL-1, IL-8.[8] These mediators attract more macrophages and monocytes and the cycle becomes self-perpetuating and grows.

The LPB could join to soluble receptors CD14 of the serum, promoting the joining of the lipopolysaccharide to the endothelial cells via TLR. In the same way anti-inflammatory cytokines are being liberated, such as IL-4, IL-6, IL-10, factor of transforming growth (TGFβ-), TNFR and IL-1ra, which goes to block or attenuate the production of TNFα and IL-1. Recently, an intestinal vasoactive peptide has been discovered and a pituitary polypeptide that by activating adenylcyclase acts like anti-inflammatory proteins suppressing production of IL-6.[9]

The mediators already produced by the mechanisms described earlier (IL-1, IL-2, IL-6, IL-8. TNF, PAF), together with endorphins, eicosanoids, nitric oxide, protein of high-mobility group 1 (HMG-1), and MIF, will have cardiovascular, renal, pulmonary, hepatic, nervous system, and coagulative effects. These effects will cause myocardial dysfunction and hypotension, acute renal failure, acute hepatic failure, SDRA, and coagulopathy. In septic shock, the most clinically relevant expression of sepsis, it will also show poor blood flow, causing failure of microcirculation, and increased permeability. All the preceding result in interstitial edema with liquid in the third space

decreasing the intravascular volume (hypovolemia) and increasing intercapillary distance with presence of a disorder in the oxigenation of the cells called disoxy, dysfunction of cells, MODS, and death.[2,6,7]

In summary, some patients will never develop sepsis, others will develop it but will recover from it, and some will develop sepsis plus multiorganic dysfunction syndrome (MODS) and die from it. The probability of occurrence of each one of these possibilities depends upon the existence of biologic variations in individual response to a given stimulus. These variations include positive and negative interactions among CD14, TLRs, MIF, TNFα, FAS, CD11b, DNA polymorphism for genes, eicosanoid, polymorph DNA paragenes, eicosanoid, free radicals, and antioxidants. Some persons have simple genetic alterations of par base (simple nucleotide polymorphism nucleotide) in genes that control the response of the host to microorganisms. A specific genetic polymorphism could be present of TNF in its promoting region with the consequent hypersecretion TNFα correlating with the sepsis development. It is also present to polymorphism in receptors of IL-1 and TLR, determining a concentration of inflammatory and antiinflammatory cytokines marking in the individual a hyperinflammatory response or hypoimmune to infection. The polymorphism is useful for identifying patients with high risk for developing sepsis and (MODS) during an infection, and there is a correlation between mortality and genetic polymorphism for TNFα and TNFβ.[5,9] Gillon et al. showed individual variation in the major complex of class II histocompatibility expressed in monocytes, which expresses the integrin in the neutrophils wall CD11b-CD18 to adhere to PMN in the endothelium.[9] In patients with septic shock and death, HLA-DR decreased and did not recover normal levels. The major complex of antigen histocompatibility type II (MHC-II) expressed at the surface of antigen-presenting cells has been found to be diminished in monocytes of critical patients, predisposing them to infection and sepsis. The same occurs with the decrease in the expression of human HLA-DR, which presents an inverse relation to severity of sepsis, demon strating that in septic shock a severe endocytosis of HLA-DR exists, possibly mediated by IL-10. Thus, this diminishes its expression at the surface of the monocytes.[10] Several interleukins, MIF, and the eicosanoids express HLA-DR.[2]

Abnormalities of Coagulation and Sepsis

The bacterial endotoxins and exotoxins, the cytokines (TNF, IL-1, IL-6), and PAF expose tissue factor (TF) on the surface of the endothelial cell. This activates the extrinsic pathway of coagulation by the complex activated tissue factor VII (TF-VIIa). This increases and frees thrombin, transforming the fibrinogen in fibrin and increasing deposits of fibrin in microcirculation with formation of vascular microthrombosis. The VIIa factor El factor VIIa in turn can activate the intrinsic path by acting through factor IX.[13] It presents deple-

tion of coagulation factors and a decrease in the platelet account and intravascular disseminated coagulation (ICD) as a result of the septic pro-coagulant stage. However results presented in the ibuprofen study in sepsis found an incidence of only 10% for ICD in septic patients.[13]

Other coagulative dysfunctions also were caused by such mechanisms as deficiency in fibrinolysis resulting from an increase in the plasminogen inhibitor activator of the tissue (PAI-1) and of the inhibitor of fibrinolysis activated by the thrombin. As a reflection of coagulation activation the antithrombin (coagulation antagonist) and the Xa factor are diminished in sepsis due to an increase in its consumption, decrease in its hepatic production, and increase in degradation by PMN; its low concentrations are associated with greater mortality. The C protein is activated by the complex thrombin-thrombomodulin in endothelium and is facilitated by cofactors and VIIa. In sepsis the C protein (PCA) is diminished by an increase in its consumption and by deficiency in its activation due to lack of regulation of the thrombomodulin in the vascular endothelium. The C protein inhibits generation of thrombin, joins the thrombin with the thrombomodulin through the endothelium protein C receptor (EPCR), increases fibrinolysis, and depletes PAI-1. The tissue factor inhibitor (TFPI) is a direct inhibitor of factor Xa and retrofeeds with the complex TF-VIIa; it is produced in the endothelial cell. We should remember that thrombin is pro-inflammatory because it expresses selectin, increasing the formation of PAF, and it activates cytokines together with factors VII and. Treatment with PCA, antithrombin III, and TFPI is effective to block coagulation at various levels, and for its anti-inflammatory properties.[3,4,12] Protein C also increases fibrinolysis, neutralizing PAI-1, and it carries out its anti-inflammatory effect through the inhibition in production of TNF and the translocation of NF-kin monocytes with the corresponding decrease in production of cytokines.[13]

Microcirculation and Sepsis

Abnormalities of microcirculation in sepsis precede the initiation of (MODS). Distributive abnormalities in blood flow and in vascular volume, changes in capacitance venous tone, panendothelial activation with leukocyte adherence, and increase in vascular permeability due to contraction of endothelial cells activated by histamine, bradyquinins, endotoxin, cytokines, endothelin-1, and free radicals of O_2 (ROS) occur, with damage to the endothelial cell and loss of polarity of the same.

Endothelial permeability increases in colon circulation, liver, heart, and kidneys, which are initially presented in the venular capillary. Low levels of AMPc increase microvascular permeability due to changes in the conformation of the endothelial cytoskeleton. Activation of coagulation with excessive transendothelial escape of liquid to the interstice and formation of interstitial edema that compresses capillaries are present. Swelling of endothelial cells and leukocyte tampons, platelets and nondeformable red glob-

ules produces capillary obstruction, which together with loss of reactive hyperemia and reduced capillary density causes tissue hypoxia and dysfunction in O_2 extraction. De Backer et al. show that there is a reduction in about 40% of capillary density, in severe sepsis.[10] Intense vasoconstriction is present in the intestinal circulation, and vasodilatation occurs in hepatic circulation. Constriction occurs in the large arterioles, as does dilatation in the smaller ones with decreased systemic vascular resistance (SVR).

There are regional differences in behavior of microcirculation and in blood flow in different organs during sepsis:

- *Skeletal muscle:* Long arterioles are contracted (A1-A2), and the smaller ones are dilated (A3-A4) with no change in venous diameter with decrease in the pressor response

- *Short intestine:* Vallet et al. showed redistribution of blood flow away from the mucous membrane toward the muscle and serous cape with defect of mucosal O_2, decrease in arteriole diameter of the mucosal hairiness (A3-A4), and 50% decrease in flow. Capillary density at the hairinesses of the intestinal mucosa now is diminished, which generates a 40% increase in intercapillary area. Besides this phenomenon there is an increase of the intestinal permeaabilitywith translocation of bacterias or endotoxins through the inatestinal wall generating MODS.[11]

- *Mesenteric circulation:* It presents transitory but severe hypertension, with an increase in resistance to flow in the liver, decrease in mesenteric blood flow with low regulation of nitric oxide constitutive synthetase, high regulation of inducible nitric oxide in mesenteric arteries, and a 50% increase in extraction of O_2. As an odd datum, the jejunum maintains its flow while it falls in the stomach and colon. According to the study of Hildebrand et al., the flow in the liver could decrease by 50%, while the pancreas is the most hypoperfused organ in the early phase of septic shock.[16]

- *Renal circulation:* Hypoperfusion episodes and selective renal vasoconstriction with loss of autoregulation in cortex microcirculation flow and decrease in renal plasma flow are present.

- *Coronary circulation:* Vasodilation is present with overperfusion related to supraregulation of inducible oxide nitric synthetase (iONS) in vascular muscle and by bradykinin and deterioration of the receptors 1 and 2 adrenergic function.

In summary, there are regional differences in vascular reactivity and microcirculatory flow that result in lack of correlation between the regional and systemic flow in sepsis, presenting early bad distribution in blood flow with organic ischemia in form of patches. The hypoflow of the pancreas, liver, and colon could develop organic dysfunction in other organs far away from the aerea os hypoperfusion .[13-18,21]

Role of Nitric Oxide in Sepsis

In sepsis there is an overproduction of nitric oxide (NO); it is associated with severity of the disease, renal insufficiency, and MODS. The endotoxins and cytokines (-IFN, TNF, IL-1, PAF) increase their production alone or in synergism.

The constitutive nitric oxide synthetase (cONS) has a biphasic response with early increment and late reduction. The NO deteriorates cardiac contraction through GMPc, inhibiting the use of O_2 by the mitochondrion and inducing myocardial ischemia through loss of coronary autoregulation. The cONS produces early fall of vascular tone, but it could maintain the flow of some vascular beds. The NO limits and may maintain the renal blood flow. The iONS appear in late phases of sepsis. The NO might react with the superoxide anion and might form peoxintrites, oxidative molecules that according to Wang et al. determine the microvascular protein escape.[10] They deteriorate mitochondrial respiration and activate the poly-ADP ribose result in decreased, in electron transportation, and in the generation of ATP (cytopathic hypoxia). The iONS may compensate for the decrease in cONS. A blocking of NO could have deleterious effects, such as decreased bactericide activity, loss of ROS scavenger, decrease of modulation of active coagulation, and increase in demand for O_2.[19,20]

Physiopathology of Vasodilator Shock

The hypotension of septic shock is the result of failure of vascular smooth musculature towards vasoconstriction with poor response to vasopressors. As producer mechanisms the following could be given:

- *Adenosine:* This is a nucleotide of purine liberated by endothelial cells and myocytes in the presence of a metabolic stress. A rapid depletion of intracellular ATP leads to an accumulation of AMP, which produces adenosine when dephosphorylation occurs. The adenosine is a strong vasodilator generated from the ischemia-reperfusion phenomenon. It acts on interstitial purinergic receptors, causing relaxation of smooth vascular muscle and activation of the Gi (inhibitory protein G) which depresses myocardial contraction. Adenosine could maintain the hepatic-splenetic, gastric, and pancreatic flow, which helps to protect them. It could generate ROS by action of the xanthine-oxidase, and by inhibiting T cells, acting as an immune-suppressor. The adenosine increases its synthesis by means of tissue hypoxia and adrenergic stimulus by increment of AMPc. Its high plasma concentration correlates with higher mortality in septic shock.[12]
- *Activation of channels K^+-ATP:* It is secondarily produced from a decrease in ATP cellular; increase in hydrogen ion and cellular lactates; and increment of atrial natriuretic peptide, calcitonin, and adenosine. All these events are characteristic of septic shock. The NO can also activate these channels by GMPc.

- *Increase in NO synthesis:* The increase in NO synthesis relates especially to iONS in cells of the smooth vascular muscle, endothelium, and macrophages. This increment is caused by overexpression generated by cytokines and adenosine. The vasodilation of NO is effected by activation of phosphatase of the light chain of myosin and by activation of the K^+-ATP channels in the plasmatic membrane of the smooth vascular muscular cell. These channels are open by hyperpolarization of the membrane in direct form, or in secondary form by the activation of a kinase protein depending on GMPc. Takakura et al. describe that the union of the NO with the superoxide anion, when producing the peroxinitrite inactivates the adrenergic 1 receptors.[9]

- *Decrease of vasopressin:* Vasopressin decreases in concentration by diminishing its storage in the presence of a profound and sustained baroreflex stimulus The vasopressin directly inactivates K^+-ATP channels in the smooth vascular muscle, blocks the GMPc, and diminishes the synthesis of the iONS.[22] Bucher et al. report down-regulation of the vasopressin receptors V (1A) promoted by IL-1B, TNFa, and g interferon. Zaloga proposes as one of the explanations of vasodilation the term of "syndrome of adrenal deficiency in sepsis," by a resistance to corticotropin and reduced adrenal synthesis of glucocorticoids.[9]

Myocardial Dysfunction in Sepsis and Septic Shock

Dysfunction of the cardiovascular system is present in 40% of the patients with sepsis, and its presence increases mortality from 30% or 40% to 70%. Studies by Clowes and Nishiyima show that the increase in cardiac index (CI) in sepsis correlates with a better survival as well as a hyperdynamic stage. MacLean is the first to report cardiac failure in the septic patient. Later on, Calvin et al. found an increment in filling pressures of the left ventricle (LV) with an increase in telediastolic volume and decrease in ejection fraction (EF) in this population. Parker et al. find more survival time in patients with increase in telediastolic volumes in the LV and with EF returning to normal between the seventh and tenth days after the septic picture. After the onset of sepsis Jafri et al. confirm diastolic dysfunction of the LV.

The septic patient presents a bad response to ventricular work to a charge of a given volume, moving the curve of Frank-Starling to the right and down, as was shown by Weisel et al. and Rackow et al. Septic shock relates to a decrease in systemic vascular resistance (SVR) Groenveld et al. propose that the peripheral vascular failure is a greater determinant of mortality in septic shock. Aximi and Vincent show favorable results with CF, less than 106 beats/minute.[24-25]

The persistence of the hyperdynamic stage and the incapacity of LV to be dilated because of myocardial edema with decrease in complacency and deficient response to inotropics are markers of a bad prognosis. The best index of

systolic function or of contractibility is the slope at the end of systole of the volume-pressure curve. This slope moves downward in septic shock. The cardiac output (CO), however, is kept high, notwithstanding the myocardial depression caused by systemic vasodilation (decrease in post-load) and resulting from the dilatation of LV (increase in preload). It is suggested that the optimum wedge pressure of pulmonary artery during sepsis is located between 12 and 16 mmHg. The survivors of sepsis show acute ventricular dilation of LV and decrease in FE, whereas the nonsurvivors have normal cardiac volumes and normal EF.[26] The dysfunction described is reversible in survivors returning to a normal function between day 7 and day 10.

Pulmonary hypertension induced by severe sepsis could generate dilatation of the right ventricle (RV), diminishing its EF and occasioning a fall in final diastolic volume of the LV and of CO. A dysfunction of the LV could generate dysfunction of the RV due to a decrease in coronary perfusion pressure of the RV that is performed both in systole and in diastole in a way that does not depend on the increase in pulmonary pressure, according to the report of Dhainaut et al. and Schneider et al. They have demonstrated abnormal distensibility of the RV during septic shock.[24]

The myocardial dysfunction could produce disoxia due to insufficient tissue supply of O_2 over an above-normal range, because the high CO is insufficient to supply the high demand of O_2 during sepsis and septic shock.[25]

Cardiac Dysfunction Mechanisms

Microcirculatory abnormalities of myocardial perfusion are evident, notwithstanding the increase in coronary flow. TNFα, IL-1B, IL-8, and C3a are myocardial depressors by synergic action more than by individual action. They also super regulate adhesion proteins in the coronary endothelium with leukocyte entrapping and production of ROS with damage to the endocardium and distortion of the relation between the supply and consumption of myocardial O_2.

Chung and et al. observed that TNF affects production of AMPc with deterioration of the adenylcyclase and catecholamine response. The TNF induces apoptosis of the cardiac myocytos; it produces its effects by activation of iONS. The NO depresses the myocardium, due to suppression of the current of calcium-L channels in response to stimulation by catecholamines and stimulate inhibitory G proteins in adrenergic β receptors. Gauthier et al. show that NO and GMPc activate adrenergic receptors β3 with a negative inotropic effect by inhibitory G proteins.

GMPc could activate phosphodiesterases degrading the AMPc, and that reduces the response of the myofilament to calcium A study by Bishop-Bailey et al. shows that the eicosanoids depress the myocardium through the stimulus of the cyclooxygenase enzyme–2 in cells of the smooth vascular muscle (prostacyclin and thromboxane). Finally, Turner et al. found an increase in troponin I in septic shock, with high values in nonsurvivors and a peak between the second, third, and fourth days of the septic picture.[25]

In summary, sepsis produces myocardial depression not only through a depressing factor, as was previously believed, but through the synergist action of various pro-inflammatory and inflammatory factors. It should be recovered in a period of no more than 10 days in order to increase the survival time of the patients if it is accompanied by a decrease in EF and by a final diastolic dilatation of the ventricles as compensatory mechanisms.

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