ECRONICON OPEN ACCESS

EC ANAESTHESIA
Review Article

Aspects of Interest in the Systemic Inflammatory Response Syndrome

Carlos de la Paz Estrada*

Second Degree Specialist in Anesthesiology and Resuscitation, Pediatric Teaching Hospital "Eduardo Agramonte Piña", Camagüey, Cuba

***Corresponding Author**: Carlos de la Paz Estrada, Second Degree Specialist in Anesthesiology and Resuscitation, Pediatric Teaching Hospital "Eduardo Agramonte Piña", Camagüey, Cuba.

Received: October 25, 2019; **Published:** March 09, 2020

Abstract

Inflammation can be described as a host reaction against tissue damage or the presence of pathogens. The release of mediators such as histamine, bradykinin and others cause vasodilation and increases tissue permeability, causing inflammation. This inflammation stimulates the nociceptors and produces pain. An important local inflammation can cause an acute phase systemic response. This response is manifested with the release of protein C, complement and others, and is followed by the activation of the cynin system (IL-1, IL-8, TNF) that induces chemotaxis of neutrophils at the site of injury. Some cytokines can induce fever and lymphocytic proliferation, which is typical in the water phase reaction of inflammation. This defensive response sets in motion the phagocytosis mechanisms of invasive pathogens. Inflammation, therefore, is an essential response for the structural repair of tissues damaged by multiple causes. It can also be a harmful reaction for the organism, since an excessive or disorderly response, as occurs in various diseases, can aggravate tissue structural damage; It is currently believed that modulation of this response prevents final tissue damage. As anesthesiologists, we are concerned about the disorderly effects of inflammation in lung damage, in microvascular permeability, in myocardial infarction and reperfusion damage and in acute and chronic pain.

Keywords: *Inflammatory Response Syndrome; Neutrophils; Cytokines*

Introduction

The first descriptions of inflammation date back to 3500 years found in Erbers' papyri. In the first century of our era the Roman physician Cornelius Celsus writes his classic work in which he defines and summarizes inflammation in 4 basic points: pain, heat, blush and tumor [1].

The better knowledge of the mediators of the inflammatory response has resulted in the development of new treatment strategies in order to minimize the adverse effects of microbial agents [2-4].

In 1992 the American College of Physicians of Thorax and the American Society of Critical Medicine published the definition of sepsis; For the first time, the systemic inflammatory response is also defined as an adjunct to the infectious process [5,6].

The inflammatory response is presented as an injurious process of constant progression that, if not controlled, culminates in the development of multiple organ failure syndrome (FOM) and finally in the death of the patient. Currently, it has been possible to identify with certainty the Systemic Inflammatory Response Syndrome (SRIS), despite the unspecific diagnostic criteria; and although it was originally described in the background of an infectious process, it is known that it represents an unspecific response that marks severity and that is closely related to the development of multiorganic failure when the intensity of its presentation is important or when time is not limited of evolution [7-9].

The SRIS is formed by a nonspecific defense mechanism, constituted by a series of nonspecific criteria whose high sensitivity creates difficulties for its proper interpretation. Clinical and laboratory signs of systemic inflammation include changes in body temperature, tachycardia, leukocytosis or disturbance in respiratory rhythm, and can occur in the same way in patients with an underlying infectious process than in problems without an infectious base [10].

After severe trauma, whether major surgery, extensive burn, shock, bacteremia (presence of bacteria in the circulation, demonstrated by culture) or sepsis (bacteremia associated with organic dysfunction, respiratory failure, hypotension or some combination thereof), a series of phenomena with negative nitrogen balance, increase in caloric demand, hyperglycemia, hydroelectrolytic alterations, neuroendocrine changes, hyperthermia and hemodynamic changes are presented. Currently available data indicate that these reactions are part of an integrated system capable of determining the possibility of survival in case of severe trauma [11]. Metabolic and neuroendocrine reactions are part of this syndrome triggered by an organic lesion and that in favorable circumstances, allows the anatomical, functional and individual restoration.

Criteria	Values
Heart rate	More than 90 beats per minute
Breathing frequency	More than 20 breaths per minute or less than 32 mmHg of CO_2 in an arterial gasometry
Temperature	More than 38º or less than 36º
Leukocytosis	Leukocytosis of more than 12,000/mm^3 or leukopenia less than 4000/mm^3 or more than 10% of bands

Table 1: *Diagnostic criteria for systemic inflammatory response syndrome.*

Development and Discussion

Physiopathology

The endothelium is the main organ of shock in the SRIS, its initial condition causes a series of events that not only maintain the inflammatory process but multiply it [12-15].

The decisive pathophysiological event for triggering SRIS is tissue injury; This can be mechanical, caloric, due to cellular lesions caused by hypoxia-reperfusion and free radicals. Infection and endotoxemia cause a cascade of both local and systemic response.

This type of event prepares the release of cytokines. Kappa-Beta (FN-kB) nuclear factor activation in sepsis is mediated by the action on pro-inflammatory cytokine membrane receptors synthesized by activated macrophages, free radicals (ischemia-reperfusion), viruses, bacterial proteins, lipopolysaccharides and T lymphocytes Once the pro-inflammatory membrane receptors are stimulated, they activate different cytoplasmic proteinases that phosphorylate and degrade the inhibitor of the Nuclear Factor-kB alpha (iFN-kB alpha). Once free, the heterodimer that forms the FN-kB is translocated to the nucleus where it joins the promoter region of the genes that mediate the synthesis of the different cytokines and molecules involved in SRIS [16].

In this phase the synthesis of proinflammatory cytokines conditions a positive regulatory loop that perpetuates the activation of cytoplasmic proteinases and thus the activity of FN-KB.

Free radicals cause a cascade of intracellular events resulting in the release of FN-kB from the inhibitory factor. This allows its translocation in the nucleus where FN-kB binds to DNA facilitating the process of transcription of genes involved in inflammation. FN-kB controls the production of acute phase mediators such as tumor necrosis factor (FNT) IL 2, IL 2 receptors, which activate FN-kB by amplifying the cascade.

Other transcriptional factors such as activator protein 1, serum protein 1, nuclear factor and IL-6, enhance the action of FN-kB and amplify the synthesis of interleukins 1, 6 and 8, the tumor necrosis factor (FNT) and nitric oxide synthetase, through a positive feedback effect.

Activated FN-kB is also a transcription factor for the synthesis of its inhibitor: the iFN-kB alpha, an extremely important event since it constitutes the negative self-regulating loop to block the molecular cascade that perpetuates the synthesis of SRIS mediators and promotes appearance of the compensatory anti-inflammatory response [17].

When the systemic anti-inflammatory response begins, the host's adaptive capacity will depend on the urgency of the onset of SRIS, the severity of the response, the onset of the compensatory anti-inflammatory response and the final organic capacity for adaptation.

IL 8 has a strong chemotactic action for neutrophils that causes an over-regulation of adhesion molecules and stimulates their degranulation with the release of proteolytic enzymes. IL6 is responsible for the coordination of the acute phase response which consists of fever, tachycardia, leukocytosis, alteration in vascular permeability, and increased production of acute phase proteins.

The degree of volumetric resuscitation that is done in the first hours, the presence of infectious processes, non-viable tissue, and bacterial translocation [18] are involved in the severity of the process.

In addition to all the inflammatory mediators described, a series of angiogenic growth factors have also been discovered whose function is essential in the inflammatory response. Of the different types so far characterized, angiopoietin 1 and 2 (ang 1 and 2) are the best known of their function.

Ang 1 has elementary anti-inflammatory functions, inhibits the function of FN-KB, also reduces endothelial permeability in response to the inflammatory process, decreases the expression of adhesion molecules of endothelial cells, thereby restricting adhesion and leukocyte transmigration. Through the endothelium Ang 2 has the opposite effects and promotes the maintenance and multiplication of the inflammatory process.

The expression of Ang 2 is overregulated after exposure to proinflammatory factors and hypoxia. The most important function of ang 2 in the physiology of sepsis is to maintain inflammation and promote capillary leakage.

Metabolic changes found in patients with systemic inflammatory response translate the changes occurred in protein synthesis; there is a redistribution of nutrients with the intention of facing the harmful process; There is also an increase in gluconeogenesis, proteolysis, lipolysis and lactic acid production in order to keep the defense lines active which maintains a sustained change in metabolic pathways. Micronutrients also undergo significant changes in their metabolism, especially those involved in oxide-reduction processes.

The antioxidant capacity is drastically diminished against a sustained and excessive production of free radicals, both derived from oxygen and nitric oxide. Oxidative stress contributes to the development of the systemic inflammatory response syndrome; Free radicals not only produce direct cell injury by peroxidation of lipids in cell membranes but also increase the production of proinflammatory cytokines. On the other hand, oxidative stress contributes to the early development of liver dysfunction by lowering local glutathione levels, which favors liver damage by free radicals.

These problems are a direct consequence of an initial and sustained activation of the innate immune system which causes and maintains oxidative stress; this maintains the inflammatory process thus constituting a key pathophysiological factor that causes the syndrome and finally multiple organ failure (FOM) [19].

FOM is the main complication of severe sepsis and septic shock. Although the massive systemic inflammatory response marks its appearance, it does not always remit when the inflammatory process is controlled.

So, they have now been involved in the process of sequential organic failure as a result of the systemic inflammatory response to the processes of organ-regional apoptosis.

Statins have a protective action of the endothelium, but this action depends not only on the decrease in lipid levels but also has an anti-inflammatory mechanism mediated by NO. The cardioprotective effects of statins are explained by the increase in the expression of the constitutive nitric oxide synthetase (eNOS) which therefore causes greater NO synthesis activity that modulates the inflammatory process. These anti-inflammatory effects caused by statins at the level of endothelial protection favor the development of a compensatory phase in the inflammatory state.

Evolution of the systems inflammatory response syndrome

The prevalence of SRIS is very high, affecting one third of all hospitalized patients, more than half of the patients admitted to the ICU and more than 80% in surgical and trauma ICUs. Approximately one third of patients with SRIS have or develop sepsis and the risk of having documented infection or sepsis increases with the number of SRIS criteria present.

Several studies confirm the hypothesis of a hierarchical progression of patients with sepsis through the stages proposed in the consensus conference so that the transition to the next stage implies a progression in organ dysfunction and an increase in the frequency of microbiological documentation. of infection and mortality.

Authors who studied the dynamics of sepsis progression following a Markov model observed that more than half of the patients in a given stage have remained at least one day in the previous stage, which is an opportunity to allocate assistance resources adequate early and effective therapeutic measures [20].

The first phase in the development of the inflammatory response is a pro-inflammatory response, followed by an anti-inflammatory response that compensates for the first; However, some patients maintain a sustained proinflammatory phase, or the evolution to an anti-inflammatory response is marked (immunopalysis). After severe trauma or severe sepsis there is a decrease in progressive immune function accompanied by a sustained systemic inflammatory response which leads to multiorgan failure and death.

The initial endothelial dysfunction causes alterations in the oxide-reduction balance due to the presence of free radicals; the release of active cytokines to neutrophils with release of proteolytic enzymes; All this maintains endothelial dysfunction.

Hemodynamic changes in the SRIS are found in a hyperdynamic patient. Vascular resistance is low and cardiac output remains high. This happens in an attempt to maintain normal systemic perfusion but when there are open capillary beds without metabolic needs that justify it, there is a significant amount of cardiac output that is poorly used [21].

The hemodynamic response can be divided into three stages.

Phase 1

There is an increase in systemic and pulmonary vascular resistance mediated by cyclooxygenase when thromboxanes are synthesized; This initial vasoconstriction response is not of the same magnitude throughout the economy.

The splanchnic bed responds in a more intense way which causes organ-regional ischemia, generation of free radicals and favors bacterial translocation (one of the most important factors in maintaining the systemic inflammatory process). In this phase the myocardial depressor factor is released.

Phase 2

It is characterized by an increase in endothelial permeability especially at the level of the pulmonary bed; there are no major hemodynamic changes; This phase is basically mediated by tumor necrosis factor alpha (TNF-alpha), IL-6 and platelet activating factor (FAP).

Phase 3

Short circuits are greatly increased, hypoxic pulmonary vasoconstriction intensifies (in an attempt to limit wasted pulmonary circulation), there is evidence of myocardial dysfunction. The synthesis of nitric oxide (NO) is maintained by means of the eNOS in phase 1 and 2 but in the third phase, when there is an evident hyperdynamic state, the production of NO is carried out by means of inducible nitric oxide synthetase (iNOS).

Evolutionary phases of the increase in endothelial permeability

The increase in vascular permeability that constitutes another of the fundamental findings of the SRIS can be divided into three phases.

Phase 1

It is characterized by the increase in hydrostatic pressure, which increases the lymphatic flow of a protein-poor liquid; This increase in hydrostatic pressure is basically due to the initial vasoconstriction state.

Phase 2

The lymphatic flow remains high but now the fluid has a higher concentration of proteins; the increase in endothelial permeability begins, especially at the level of the pulmonary bed, the capillary leak syndrome develops as such. Endothelial cells actively participate in this phase by producing pro-inflammatory substances, release cytokines, produce free radicals, ischemia-reperfusion damage and the expression of adhesion molecules is increased; All this perpetuates the endothelial lesion.

Phase 3

The increase in endothelial filtration coincides with a state of blood stasis and an increase in hydrostatic pressure, this as a consequence of the vasodilation observed by the decrease in peripheral vascular resistance; It is possible in this phase the participation of atrial natriuretic factor and endothelin. The permeability alterations observed in the SRIS are not only due to endothelial problems: the epithelial surfaces, especially at the bronchial and intestinal level, have an important participation manifested by the presence of bacterial translocation at these sites.

Hyperglycemia as a causant of endothelial injury

Hyperglycemia by itself cannot cause a systemic inflammatory response but intensifies the response to external factors such as endotoxins. This observation leads us to suspect a critical level of glycemia necessary to initiate oxide-reduction problems with the consequent generation of free radicals [22,23]. However, insulin levels play a fundamental role; It has been shown that insulin levels of less than 45u have a limited impact on oxidative stress independent of the glycemic figure. But when there is hyperglycemia and hyperinsulinemia, the inflammation criteria are present. On the other hand, these inflammatory effects are limited when, despite hyperinsulinemia, the blood glucose levels are almost normal (below 150 mg). Maintaining an adequate level of glycemia by administering insulin according to requirements presents clinical advantages as well as limiting hepatic oxidative stress [24,25].

Conclusion

Inflammation plays an important role in anesthesiology in a variety of circumstances, and in all of them, proper control of it becomes an essential goal for proper patient management while in our care during the entire perioperative period, especially for Postoperative pain control.

Bibliography

1. Brun-Buisson C. "The epidemiology of the systemic inflammatory response". *Intensive Care Medicine* 26.1 (2000): S64-S74.

2. Shapiro NI., *et al*. "The association of sepsis syndrome and organ dysfunction with mortality in emergency department patients with suspected infection". *Annals of Emergency Medicine* 48.5 (2006): 583-590.

3. Bernard GR., *et al*. "Efficacy and safety of recombinant human activated protein C for severe sepsis". *New England Journal of Medicine* 344.10 (2001): 699-709.

4. Rivers E., *et al*. "Early goal-directed therapy in the treatment of severe sepsis and septic shock". *New England Journal of Medicine* 345.19 (2001): 1368-1377.

5. Shapiro NI., *et al*. "Mortality in Emergency Department Sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule". *Critical Care Medicine* 31.3 (2003): 670-675.

6. Shapiro NI., *et al*. "Serum lactate as a predictor of mortality in emergency department patients with infection". *Critical Care Medicine* 45.5 (2005): 524-528.

7. Jaimes F., *et al*. "Comparison between logistic regression and neural networks to predict death in patients with suspected sepsis in the emergency department". *Critical Care* 9.2 (2005): R150-R156.

8. Nguyen HB., *et al*. "Early lactate clearance is associated with improved outcome in severe sepsis and septic shock". *Critical Care Medicine* 32.8 (2004): 1637-1642.

9. Carrillo ER. "Modulación genética de la respuesta inflamatoria sistémica en sepsis". *Revista de la Asociación Mexicana de Medicina Crítica y Terapia Intensiva* 15.3 (2001): 92-95.

10. Talan DA. "Dear SIRS: It's time to return to sepsis as we have known it". *Annals of Emergency Medicine* 48.5 (2006): 591-592.

11. Lemieux C., *et al*. "Angiopoietins can directly activate endothelial cells and neutrophils to promote proinflammatory responses". *Blood* 105.4 (2005): 1523-1530.

12. Kim I., *et al*. "Angiopoietin-1 reduces VEGF-stimulated leukocyte adhesion to endothelial cells by reducing ICAM-1, VCAM-1, and E-selectin expression". *Circulation Research* 89.6 (2001): 477-479.

13. Orfanos SE. "Angiopoietin-2 is increased in severe sepsis: Correlation with inflammatory mediators". *Critical Care Medicine* 35.1 (2007): 199-206.

14. Berger MM. "Antioxidant supplementation in sepsis and systemic inflammatory response syndrome". *Critical Care Medicine* 35.9 (2007): S584-S590.

15. Crimi E., *et al*. "The role of oxidative stress in adult critical care". *Free Radical Biology and Medicine* 40.3 (2006): 398-406.

16. Padeh S. "Auto-inflammatory fever syndromes". *Rheumatic Disease Clinics of North America* 33.3 (2007): 585-623.

17. Werdan K. "Immunoglobulin G treatment of postcardiac surgery patients with score-identified severe systemic inflammatory response syndrome. The ESSICS study". *Critical Care Medicine* 36.3 (2008): 716-723.

18. Pei-Ra L. "Acute effects of hyperglycemia and hyperinsulinemia on hepatic oxidative stress and the systemic inflammatory response in rats". *Critical Care Medicine* 35.2 (2007): 555-560.

19. Dong Z., *et al*. "Procalcitonin for the differential diagnosis of infectious and non-infectious systemic inflammatory response syndrome after cardiac operation". *Chinese* 26.7 (2014): 478-479.

20. Bauer ME., *et al*. "Maternal Physiologic Parameters in Relationship to Systemic Inflammatory Response Syndrome Criteria: A Systematic Review and Meta-analysis". *Obstetrics and Gynecology* 124.3 (2014): 535-541.

21. Chen L., *et al*. "Analysis for risk factors of systemic inflammatory response syndrome after one-phase treatment for apyrexic calculous pyonephrosis by percutaneous nephrolithotomy". *Beijing Da Xue Xue Bao* 46.4 (2014): 566-569.

22. Talebi-Taher M., *et al*. "Serum Inflammatory Markers in the Elderly: Are They Useful in Differentiating Sepsis from SIRS?" *Acta Medica Iranica* 52.6 (2014): 438-442.

23. Lindvig KP., *et al*. "How do bacteraemic patients present to the emergency department and what is the diagnostic validity of the clinical parameters temperature, C-reactive protein and systemic inflammatory response syndrome?" *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 22.1 (2014): 39.

24. Semler MW and Wheeler AP. "Systemic inflammatory response syndrome after cardiac surgery: time for a change". *Chest* 145.6 (2014): 1181-1182.

25. Serrano-Berrones MA and Centeno-Durán G. "Systemic inflammatory response syndrome in the obstetric patient. Case report". *Ginecologia y Obstetricia de Mexico* 82.4 (2014): 257-260.

Volume 6 Issue 4 March 2020