Systemic Inflammatory Response Syndrome (S.I.R.S.) after Cardiac Surgery

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The number of publications dealing with organic responses to injuries produced by the widest range of causal agents and their consequences on the organism is increasing. The idea of the aforetime named "surgical stress" as just a many-sided defense mechanism in response to the aggression implied by the surgical act has also increased.

Inflammation is the body’s response to tissue injuries. It involves a fast, highly enlarged and response-controlled both humoral and cellular process [1]. Its only purpose is reestablishing the homeostasis present before such injury. The term "sepsis", coined in the Infectology field, defines the organism’s clinical response to infection [2]. Such response may appear in the absence of infection [2]. What is more, it is known that a patient with sepsis and negative cultures has identical mortality to a patient with positive cultures [3].

The conclusion drawn from these facts is that this inflammation is a non-specific and generalized response to injury regardless of its nature. In 1991, a diagnostic definition of "source" was achieved as well as the definition of some clinical stages as listed on Table 1 [2]. Scientific knowledge has been accomplishing a continuous expansion in the understanding of the physiopathological facts involved.

SIRS is, therefore, a non-specific generalized inflammatory process independent of the causal factor. Its classification, as listed on Table 1, has prognostic importance [3]. Its presence may lead to multiorganic failure (MODS) and, even if overcome, survival is compromised in periods as long as 5 years [4]. Cardiac surgery causes SIRS and that is considered to be a physiological response to this act [2]. It could then be wondered which factors are determining that an out of control, in itself physiological process may develop complications endangering the patient’s life. Nowadays, the answer known is not satisfactory.

An appropriate starting point would be to take into account two basic factors:
- SIRS could be just one part of the integral process where opposed forces are opposed by a compensatory anti-inflammatory response syndrome (CARS) [5]. Predominance of one or an intermediate response would determine the clinical course [5]. All this could be caused by a complex interaction between pro-inflammatory and anti-inflammatory factors, probably some polypeptides called cytokines, not only in their quantitative values but also their temporal kinetics [6].

- Cardiac surgery with CPB generates some already known facts: neutrophil activation [7], cytokine
The following paragraphs will try to clarify, in view of evidence, why this river useful for irrigation becomes deadly when it overflows and causes floods.

There is plenty of evidence showing that cardiac surgery provokes an organic response like the SIRS definitions listed above. It has also already been described that such process constitutes a physiological response to surgery [2]. It is difficult to estimate its prevalence (100%?) due to lack of a more precise clinical definition. In a study published in 1995 MODS prevalence resulted in 11% and its mortality reached 41% [9]. A detailed sequence of facts after CPB is shown in Figure 1.

![Figure 1](image.png)

The second is called the ischemia-reperfusion phenomenon involving brain [10,11], heart [11,12], kidney [13,14] and liver [15] as a result of aortic clamp and the use of a non-pulsatile device. The normal flow reinstatement is associated with indications of inflammatory response [16,17].

The third mechanism, and maybe the most controversial one, is splanchnic hypoperfusion which may damage the intestinal mucosa allowing endotoxin translocation [18,19]. Some existing data oppose these statements [20,21,22]. Once this mechanism is triggered, a storm of facts in multiple organic systems unfolds. The complement is activated by the "contact" mechanism, the ischemia-reperfusion phenomenon of several organs and the heparin neutralization by protamine [23]. This activation is done in both ways (classic and alternative) [16,24,25,26].

There is a second activation five days later triggered by CRP [27]. Clinically, the activation of the complement is expressed through the increase of intrapulmonary shunt [28], arrhythmias [26], cardiac contractility depression, renal function impairment and homeostasis deficit [29]. Several experimental studies have shown this by selectively blocking these mechanisms [31,32,33,34,35,36].

As stated on Figure 1, cytokines play an important role. There is a closely monitored response to injury with release of these products both with pro and anti-inflammatory properties. This release takes place in several sites in the organism and its presence is necessary to reestablish homeostasis. High levels of Interleukin (IL) 1b and 6 as well as the Tumor Necrosis Factor-a (TNFa) are constants takes place in several sites in the organism and its presence is necessary to reestablish homeostasis. Unlike the previous ones, the increased amount of IL-8 y 18 does [39]. The presence of anti-inflammatory cytokines is less known but it may seem that the balance between both types of these substances is the patient's evolution determining factor [6]. Maybe nitric oxide (NO) is the paradigmatic mechanism of this complex answer. Under normal conditions, the endothelium produces small quantities (micromolars) of this molecule by the action of nitric oxide synthetase via non-constitutive NO. Its effect controls vascular tone, capillary flow and prevents leukocyte and platelet adhesiveness to the endothelium [39]. After CPB, it occurs during a first instance of these properties, with opposed forces prevailing. An excessive release (nanomolar) begins 4-6 hours after surgery from a great amount of tissues [40,41]. Thus, an excessive vasodilatation of variable degree occurs whose highest expression is distributive shock [42]. Coagulation and fibrinolysis cascades are closely interconnected to SIRS since they can mutually activate. CPB conditions the activation of both coagulation pathways [43,44]: intrinsic from factor XII and extrinsic from tissue factor. In case this does not occur, fibrinolysis is activated producing plasmin which separates fibrinogen and fibrina. Thus removal of previously formed clots occurs. Once the coagulation system is activated, it would be altered via platelet activation. Also, thrombin and factor Xa have pro-inflammatory properties. Thrombin stimulates chemotaxis and mitogenesis aiming to contribute with repairing [45,46].

On the other hand, both heparin and protamine and, specially, the complex made up by both have an outstanding role in this response. The former has anti-inflammatory properties [47]. The latter, and especially the combination, significantly increases the inflammatory response [48] leading to cardiac output and peripheral resistances reduction as well as triggering the increase of complement and thrombexane and NO production [48]. Then, the usual balance between anti and pro-coagulatory factors is altered after CPB. Extensive fibrin deposition in microvasculature can obstruct it and cause tissue damage which may eventually provoke MODS [49]. Alterations after CPB are clearly seen on the endothelium. Its dysfunction, generated by this process, leads to vascular tone alterations, permeability and deregulation, as stated before the coagulation phenomena, and allows leukocyte recruitment to the inflammation sites [50]. Its mechanism works by cytokine union leading to a complex genetic modification which changes its important homeostatic role [44,51].

Finally, immune system response generates through leukocyte adhesion to endothelium, activation of
those leukocytes and endothelium dysfunction [52]. Such mechanism is achieved through loss of leukocyte circulation speed leading to leukocyte migration and adhesion via selectines, a phenomenon known as "rolling stone" [52]. This allows leukocyte migration through the vessel wall after activating the complement cascade. At the same time, selectines (P and E) are activated by CPB. This well-known phenomenon has a particular meaning in pulmonary condition. In the absence of other stimuli (shock, infection). Recovery of the ones of endothelial cells to normal is fast. This would limit organ damage [44].

Organic response to surgery is complex and hard to sum up in a few lines, as can be concluded from this short and maybe complicated summary. It is also evident that the available information related to the mechanisms is still incomplete.

Which are the clinical factors conditioning and predicting its occurrence?

So far, only pre-surgical hemodynamic instability and a not controlled DBT have proven to be predicting factors to SIRS occurrence [53,54].

There is no conclusive evidence up to date showing that anesthetic factors, perfusion techniques, surgical type and technique or post-surgical management significantly modify this response. Even though some communicated data have shown encouraging results in studies done with a few patients, its usefulness has not been proven in large outcome trials. Clinical course of SIRS is shown in Figure 2.

The phenomenon occurs after CPB and its evolution depends on the balance between the beneficial and deleterious phenomena already described. In the following paragraphs, each organ individual affection is briefly detailed conforming the so-called clinical features of each patient. The final result ranges from post-surgical without complications (most usual) and MODS occurrence followed in 50% of cases of death. Complications of this phenomenon at the pulmonary level are interstitial edema and normal capillary pressure causing variable degrees of affection which can reach, in the most serious cases, to pulmonary injury or eventual distress. Its occurrence is not frequent (1 to 3 %) but its mortality is high. The most frequent cardiovascular system affection is hemodynamic instability, either by vasoplegia or low output [56,57,58]. Such conditions affect at least 40% of the patients, with variable degrees of severity. Arrhythmias, as detailed in physiopathology, have been linked to SIRS. From the neurological standpoint, surgery with CPB causes strokes up to 3% of the patients, as well as 69% of cognitive deficiencies and 36% continue until one month after the act [59]. A certain degree of liver dysfunction is observed around 13% but only 1.5% require some dialysis procedure [14,60]. Mortality of these later is high (27%) [14]. Its occurrence is closely related to CPB time. Liver dysfunction is over 45% and rapidly changed [61]. Its prevalence is also related to CPB time. Homeostasis is temporarily compromised and the amount of blood loss through draining tubes is closely related to complement activation [62]. In our facility, hematoc loss in the first hours is on average 420c and reoperation rate was 1.5%. Lastly, surgery provokes immunodepression compromising both ways (cellular and humoral) as a result of anti-inflammatory cytokine activation [6].

There are other complications on top of he ones described, even though its prevalence is lower. Even though it’s a long list, most of the abovementioned complications usually lack enough severity to endanger the patient’s life and recovery is fast and, most of the time, spontaneous. Up to now, there is no specific treatment allowing modulation of inflammatory response to make it proportionate to the injury and accomplish beneficial effects. Given the complexity and extent of the resources used in the following chart, modified by Laffey et al., the current strategy reported in the literature is summed up. (Table 2)
Some of the elements mentioned there are just the result of basic research without practical application for the time being. On the other hand, given the current situation of our country, some of them seem to be science fiction. Obviously, the usual vital support measurements of some organs and/or systems are added to these facts.

Conclusions

SIRS is a usual physiological response to the injury caused by surgery. Its effect is beneficial up to a certain extent after which it starts generating harmful effects determining alterations of organs and systems and their variable degree failure. In the most severe cases, it leads to MODS and its, already stated, very high mortality. Understanding the totality of these phenomena and their interconnection is still incomplete. But even more important is the lack of knowledge of why the phenomenon loss of modulation occurs, transforming it in deleterious. In the future, we may be able to understand these elements allowing us to reach an appropriate understanding of the physiopathology and its subsequent classification in clinical features. Then, we would have obtained rational foundations for its prevention and treatment.

Bibliography


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