Innate immune inflammatory response to danger: when, how, and why does a friend become a foe?

Filippo Crea* and Luigi M. Biasucci

Institute of Cardiology, Universita Catolica del Santo Cuore, L.go Vito 1, 00168 Rome, Italy

Online publish-ahead-of-print 23 February 2012

This editorial refers to ‘Systemic inflammatory response syndrome predicts increased mortality in patients after transcatheter aortic valve implantation’†, by J.-M. Sinning et al., on page 1459

The immune response induced by non-infectious agents is called systemic inflammatory response syndrome (SIRS), while an infection-induced systemic immune response is called sepsis. The host inflammatory response in SIRS and in sepsis is similar and may lead to multiple organ dysfunction syndrome (MODS), which may progress to multiple organ failure syndrome (MOFS) and ultimately to death (Figure 1). Anything causing tissue stress or damage is recognized as a danger by the immune system. Pathogen-associated molecular patterns (PAMPs), being exogenous molecules derived from microorganisms, can activate immune cells. Besides PAMPs, endogenous alarmins can also activate immune-competent cells. Alarmins are molecules released by stressed or damaged tissues and include DNA, RNA, adenosine, heat shock proteins, and urate crystals. PAMPs and alarmins are inducers recognized by pattern recognition receptors which are present both on the surface (Toll-like receptors) and in the cytosol (NOD-like receptors) of immune cells. The activation of pattern recognition receptors triggers the production of inflammatory mediators and effectors which may alter the function of tissues and organs. Mediators and effectors of systemic inflammation include cytokines and chemokines, reactive oxygen and nitrogen species, plasma cascades (complement system, coagulation system, fibrinolytic system, and kallicrein–kinin system), and acute phase proteins. Of note, activation of immune cells can also unleash an anti-inflammatory response characterized by the release of anti-inflammatory cytokines and activation of the neuroendocrine system. This anti-inflammatory response can eventually become prevalent, leading to the compensatory anti-inflammatory response syndrome (CARS), characterized by immune anergy, associated with a high risk of severe infections and death. Importantly, the sympathetic, parasympathetic, and peripheral nervous system as well as the hypothalamic–pituitary–adrenocortical axis, the hypothalamic–pituitary–gonadal axis, and the hypothalamic–pituitary–thyroid axis are involved in signaling between the central nervous system and the immune system. Furthermore, the initial inflammation activates afferent signals to the nucleus tractus solitarius in the brain with subsequent activation of vagus efferent activity which inhibits cytokine synthesis through acetylcholine receptors on macrophages. Of note, many immune cells have receptors binding to neuropeptides, neurotransmitters, and neurohormones, and in some cases immune cells produce and secrete neural mediators.

Systemic inflammatory response syndrome typically occurs in seriously ill patients admitted to the intensive care unit, in particular in patients with trauma, extensive surgery, heat stroke, pancreatitis, respiratory distress syndrome, and burns. The differential diagnosis between SIRS and sepsis, because of the overlapping pathogenic mechanisms, is not always straightforward, in particular when the search for infectious agents is difficult or produces ambiguous results. Among biomarkers, procalcitonin (PCT) appears particularly useful as its levels are much more elevated in sepsis (typically >10 ng/mL) than in SIRS (typically <2 ng/mL). PCT is the precursor for the hormone calcitonin. While calcitonin is found in the thyroid C cells and in pulmonary endocrine cells only, all tissues throughout the body have the potential to elaborate PCT. Sepsis is characterized by a ubiquitous expression of PCT in nearly all tissues in an ongoing unregulated constitutive fashion. It has been postulated that this sepsis-related increased transcription of the gene coding for PCT is mediated by activation of the gene promoter by microbial products such as endotoxins.

Sinning et al. have now investigated, for the first time, the prevalence of SIRS among 152 patients undergoing transcatheter aortic valve implantation (TAVI) and the impact of SIRS on outcome. TAVI is gaining growing interest as an alternative to surgery in high-risk patients. Indeed, the PARTNER trial initially...
showed that in patients with severe aortic stenosis who were not suitable candidates for surgery, TAVI, as compared with standard therapy, significantly reduced the rates of death from any cause, the composite endpoint of death from any cause or repeat hospitalization, and cardiac symptoms, despite the higher incidence of major strokes and major vascular events. In a more recent
study, the PARTNER trial investigators showed that in high-risk patients with severe aortic stenosis, transcatheater and surgical procedures for aortic valve replacement were associated with similar rates of survival at 1 year, although there were important differences in periprocedural risks. In the study by Sinning et al., the diagnosis of SIRS was based on accepted clinical criteria. The authors found that 61 out of 152 (40%) patients undergoing TAVI developed SIRS; the latter was associated with a significant elevation of interleukin (IL)-6 and IL-8 levels peaking at 24 h, of C-reactive protein levels peaking at 72 h, and of PCT levels peaking at 48 h. Of note, the average peak level of PCT (<0.2 ng/mL) was far lower than that observed in sepsis. In contrast, in patients who did not develop SIRS, PCT was not measurable, while the other inflammatory biomarkers showed some increase. The small increase of PCT in patients with SIRS might be related to visceral hypoperfusion, associated with increased permeability and passage of endotoxin in the blood.

In the study of Sinning et al., major vascular complications and the number of pacing runs, likely to be associated to severe hypotension, were independent predictors of SIRS. These findings suggest that tissue hypoxia, caused by hypotension, was the likely cause of tissue damage, followed by the release of alarms triggering the activation of immune cells. Notably, SIRS was an independent predictor of 1-year mortality.

The two major strengths of this study are the following: (i) the demonstration that the prevalence of SIRS among patients undergoing TAVI is considerably high and comparable with that observed following major cardiac or vascular surgery, and (ii) the identification of predictors of SIRS.

The major weakness is lack of new information on the mechanisms of SIRS. Nevertheless, the data accurately reported in this study can generate new interesting questions. For instance, it is quite intriguing that Kaplan–Meier curves showing the survival of patients with SIRS vs. those without SIRS kept diverging over time; accordingly only one-third of patients with SIRS died within the first month. It is certainly possible that early SIRS-related damage might have had a ‘tethering’ effect, contributing to late mortality excess. More probably, the progressive divergence of survival curves might be caused by a persistent hyper-reactivity of the immune system, characterized by an enhanced pro-inflammatory activity not counterbalanced by an appropriate anti-inflammatory response, as observed in asthma. Persistent hyper-reactivity of the immune system has also been observed in patients with acute coronary syndromes. Indeed, we have previously demonstrated that peripheral blood mononuclear cells and with increased mortality in patients with recent history of unstable angina.

At the other extreme, SIRS-associated late mortality in the study by Sinning et al. might be related to CARS. As noted above, a late complication of SIRS is a state of immune anergy associated with increased susceptibility to severe infections and death (Figure 1). In conclusion, while an appropriate immune response plays a pivotal role in the survival of mankind, the immune system, in seriously ill patients, can become a foe when it hyper-reacts to exogenous or endogenous triggers. The molecular mechanisms responsible for the transition from SIRS to MODS and MOFS are still largely speculative. An emerging concept is the association between nitric oxide overproduction, antioxidant depletion, decreased ATP concentrations, and mitochondrial dysfunction. The demonstration of decreased ATP levels in muscle biopsies from septic patients who did not survive, in contrast to maintained or elevated ATP levels in those who survived, supports this association. Elevated tissue oxygen tensions have also been reported in septic patients. These pieces of evidence have led to the hypothesis that organ failure might be due to a cellular inability to use oxygen rather than to hypoxia (Figure 1).

What about treatment of SIRS? It should be strongly emphasized that the concept of modulation of the inflammatory response in critical illness is extremely complex, as documented by the disappointing results of studies aiming to modulate specific mediators in the complex orchestra of systemic inflammation. Essential factors involved in the response include the type of challenge, the genetic predisposition of the host, the intensity of the inflammatory response, and eventually the response of affected organs. Interfering with such a complex system is still a huge challenge. As suggested by the elegant study by Sinning et al., the best approach, at the current time, is prevention. The identification of predictors of SIRS in patients undergoing TAVI opens the way to prospective randomized studies testing whether approaches aiming at reducing periods of severe hypotension can reduce the incidence of SIRS and, ultimately, improve the outcome of TAVI.

Conflict of interest: none declared.

References
A 25-year-old female was admitted with chest distress, and a chest X-ray showed a giant heart (Panel A). A transthoracic echocardiogram showed a huge coronary artery aneurysm (CAA) and a fistula between the aneurysm and the right atrium (Panel B, the arrow points to fistula; see Supplementary material online, Videos S1 and S2). A computed tomographic scan demonstrated the CAA (14.4 cm × 12.0 cm in size), arising from the left circumflex coronary artery, compressing the right and left atria (Panels C and D; see Supplementary material online, Videos S3 and S4).

During surgery, the root of the aneurysm was ligated between the aorta and the base of the aneurysm. After the proximal aneurysm wall was cut open, the orifice of the aneurysm was further closed with a 4-0 prolene suture. And the fistulous communication was also closed (Panel E, the left arrow points to the root of the aneurysm and the right arrow points to the orifice of the aneurysm; see Supplementary material online, Videos S5–S9). The patient tolerated the procedure well and was discharged in 7 days.

Coronary artery aneurysm is caused mainly by atherosclerosis, congenital Kawasaki disease, post-percutaneous transluminal coronary angioplasty, and endocarditis. Most aneurysms originate from the proximal part of the right coronary artery. The symptoms are subclinical, according to the size and location of the aneurysm. Huge aneurysms usually compress the vicinal vessels, atriums, and ventricles, causing chest distress. For the symptomatic patients and the asymptomatic patients whose haemodynamics are affected by the CAA, surgery is curative. Normally, coronary artery bypass grafting (CABG) is needed. Fortunately, in this case, no coronary artery arose from the aneurysm and the heart blood supply was not affected without CABG.

Panels A–E. LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery; RA, right atrium; RV, right ventricle.

Supplementary material is available at European Heart Journal online.