REVIEW ARTICLE

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Sepsis After Cardiac Surgery: From Pathophysiology to Management

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CARDIAC SURGERY PROVOKES a systemic response.[1] Surgical trauma, shear stress, and the contact of blood with large artificial surfaces within the cardiopulmonary bypass (CPB) circuit, and the internal drainage system for recovery and reinfusion of blood contribute to the induction of a systemic response.[2,3] The initial systemic inflammatory response may lead to immunosuppression, whereby the patient becomes more susceptible to nosocomial infection and the development of sepsis.[4–7] Furthermore, ischemia followed by reperfusion in cardiac surgery may increase endothelial permeability and result in the release of endotoxin from the intestine.[8–10] In this case, the systemic response is not fueled by the pathogen itself, but by toxins produced by the pathogen. Endotoxin, or lipopolysaccharide (LPS), is present in large quantity in the human intestine, but when it enters the circulation, it induces a systemic response, which may lead to organ damage.[10,11]

The systemic inflammatory response syndrome (SIRS) previously was defined as 2 or more abnormalities in body temperature, heart rate, respiration, or white blood cell count, whereas sepsis was defined as 2 or more SIRS criteria plus suspected or documented infection.[12] However, SIRS and its progression to sepsis are biologically very complex, and controversies still exist both in the understanding of its pathophysiology and the definition of the disease, its diagnosis, and its treatment.[13–16] The pathophysiology of sepsis involves a complex interplay among several molecular pathways, pro-inflammatory and inflammatory responses, release of cytokines, activation of the coagulation cascade, the complement system, and cellular components of inflammation.[17]

Although a lot of effort has been put into developing drugs that could modulate the immunologic response in sepsis, this approach so far has failed to show any consistent and significant clinical benefit in large clinical trials, and there currently are no drugs available that specifically target sepsis.[18,19] Evidence-based guidelines have been published with the aim of improving outcome by standardizing the diagnosis and treatment of sepsis.[20] Early diagnosis, aggressive fluid resuscitation, adequate antibiotic therapy, source control, and organ support are the key elements of sepsis management.[20,21] However, although the guidelines may have improved the management of sepsis in the general population, they do not provide guidance to specific patient populations, other than adult and pediatric patients. Cardiac surgery patients, whose cases are complicated, represent a particularly challenging patient population. Because the patient's condition already is compromised, obtaining hemodynamic stability and adequate tissue perfusion during the progression of sepsis in this patient cohort can be difficult.

The diagnosis of sepsis currently relies mainly on the recognition of clinical manifestations, and these can be very subtle and difficult to recognize in the cardiac surgery patient because they easily are confused with common postoperative complications.[21] Furthermore, patients undergoing cardiac surgery increasingly are becoming older, present with multiple comorbidities, and require more complex and prolonged cardiac procedures. Elderly patients often have impaired immunity due to immunosenescence, putting this patient population at increased risk of developing sepsis.[22,23] Immunosuppression is a risk factor for cardiac transplant recipients, and patients requiring more intensive immunosuppressive therapy due to rejection are at increased risk of severe infection.[24]

The occurrence of sepsis after cardiac surgery is a rare event, with a reported prevalence between 0.39% and 2.5%.[25–28] However, patients who do develop severe sepsis after cardiac surgery experience a high mortality, varying from 65% to 79%.[25,26] They also require prolonged mechanical ventilation and intensive care unit and hospital length of stay.[28–30] In this review, the authors discuss the pathophysiology and management of sepsis, from preventative to postoperative strategies, in adult patients who undergo cardiac surgery.

LITERATURE REVIEW METHODS

A preliminary PubMed search for English language, narrative review articles on the subject "management of sepsis after cardiac surgery" revealed that, despite increasing knowledge of sepsis in recent years, there is a scarcity of publications dealing specifically with cardiac surgery patients. The authors then rigorously searched PubMed for studies on the topic of sepsis and septic shock in patients undergoing cardiac surgery. Inclusion criteria were English language articles published between January 1990 and June 2015, identified by using

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1053-0770/2601-0001$36.00/0
http://dx.doi.org/10.1053/j.jvca.2015.11.009
Key words: sepsis, septic shock, cardiac surgery, postoperative complications, sepsis management

combinations of the keywords "sepsis," "septic shock," "sepsis management," "postoperative complications," and "cardiac surgery." Articles on studies of pediatric patients were excluded. The reference lists of the selected articles were scanned for additional relevant reports. Articles were excluded if they were not pertinent to the focus of the study.

PATHOPHYSIOLOGY OF SEPSIS IN CARDIAC SURGERY PATIENTS

Cardiac surgery provokes a systemic response, both directly and indirectly. Direct contact activation of the immune system is caused by surgical trauma, shear stress, and contact of blood with large artificial surfaces within the extracorporeal circulation circuit, and the internal drainage system for recovery and reinfusion of blood.[1,2] In the normal host response to injury or infection, initiation of the inflammatory response with release of cytokines serves to maintain homeostasis. Until recently, it was believed that organ damage in sepsis was caused by a hyperinflammatory response, a so-called "cytokine storm," in which pro-inflammatory cytokines are dominant in the initial phase of sepsis, followed by a phase in which anti-inflammatory cytokines are dominant.[31] However, more recent studies have demonstrated that both pro-inflammatory and anti-inflammatory processes take place concomitantly.[32,33] This has led to the theory that immunosuppression is the main cause of organ damage in sepsis.[6,7] Immunosuppression makes the patient more prone to infection by opportunistic pathogens, which is supported by a number of studies showing that unresolved opportunistic infections are prevalent in patients with late-stage sepsis.[34,35] In relation to cardiac surgery, common types of infection may be ventilator-associated respiratory infections, catheter-associated bloodstream infections, urinary infections, and surgical-site infections.[29,36]

At the molecular level, the immune response is initiated when pattern recognition receptors on the surface of host immune cells recognize pathogen-associated molecular patterns, such as LPS, and danger-associated molecular patterns, which are released in response to inflammatory stress, such as surgical trauma or cardiopulmonary bypass.[37,38] Toll-like receptors play a central role in the inflammatory response because they control numerous downstream pathways (Fig 1).[39] The inflammatory response is interconnected closely with the coagulation cascade and the fibrinolytic system. Thrombin generation may lead to the deposition of fibrin and disseminated intravascular coagulation, an independent predictor of organ failure and mortality.[40,41] Also, the complement system is involved in the inflammatory response and is activated by multiple mechanisms during cardiac surgery. Endotoxin activates complement through the alternative pathway, causing the release of proteases and oxygen free radicals, which are believed to lead to endothelial injury. Tissue hypoperfusion and hypotension play a key role in organ dysfunction and the progression to multiple organ dysfunction syndrome.

DIAGNOSIS AND EARLY IDENTIFICATION OF SEPSIS IN CARDIAC SURGERY

Currently, sepsis is defined as the suspected or documented presence of infection together with systemic manifestations of

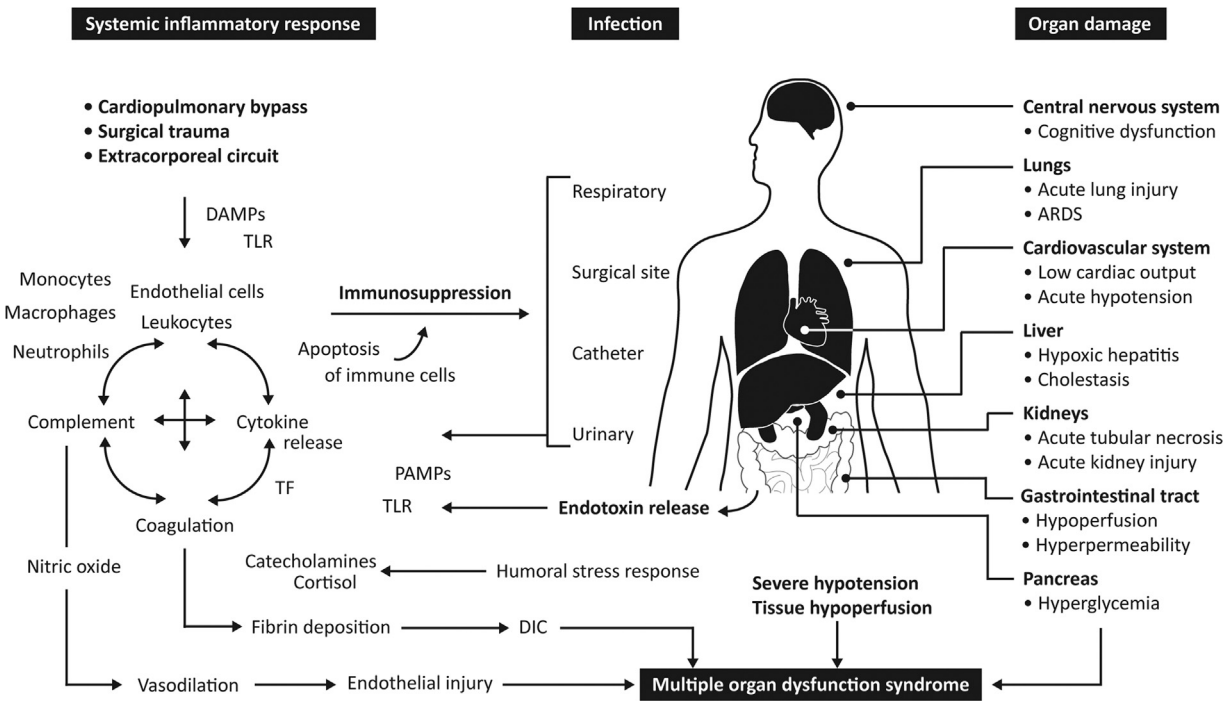

Fig 1. Pathogenesis of sepsis after cardiac surgery. Cardiac surgery induces a systemic response. Ischemia followed by reperfusion may lead to endotoxin release due to increased intestinal permeability. The initial systemic response leads to activation of endothelial cells and subsequent cytokine release. Activation of tissue factor leads to coagulation and fibrin deposition. Complement is activated in relation to cardiac surgery and may lead to the release of reactive oxygen species, such as nitric oxide, and this may lead to vasodilation and endothelial injury. Tissue hypoperfusion is a major cause of organ damage. DAMPs, danger-associated molecular patterns; TLR, toll-like receptors; TF, tissue factor; PAMP, pathogen-associated molecular patterns; DIC, disseminated intravascular coagulation; ARDS, acute respiratory distress syndrome.