Systemic Inflammatory Stress Response During Cardiac Surgery

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The response of the body to the traumatic insult of a surgical procedure has been a topic of interest for many years. The direct traumatic injury of surgery initiates a chain of physiological events via the endocrine, metabolic, cardiovascular, and immune systems. Furthermore, the unregulated stress response can lead to systemic inflammatory response syndrome (SIRS) with organ dysfunction, although an obliterated response would predispose the body to infection and the failure of the recovery process. Cuthbertson identified the response as a distinctly biphasic "ebb" and "flow" process. A period of reduced metabolic activity, which lasts for 2-3 days (ebb phase), is initially observed and is followed by a more prolonged catabolic and hyper-metabolic phase (flow), which lasts for over a week depending on the recovery process (Figure).

Patients with surgical injuries exhibit alterations in hemodynamic, metabolic, and immune responses that are largely orchestrated by endogenous mediators; these mediators are referred to as cytokines. Cytokines regulate the function of the activated cells in order to maintain total body homeostasis. These active biological autocoids are produced by diverse cell types at the site of injury and by systemic immune cells. Cytokine interaction with specific cellular receptors results in the activation of intracellular signaling pathways and, subsequently, in the regulation of gene transcription. Through this mechanism, cytokines contribute to immune cell activity, differentiation, proliferation, and survival. Furthermore, cytokines can also regulate the production and activity of other cytokines, which may either augment or attenuate the inflammatory response. Amplified and prolonged surgical stress may exaggerate the systemic inflammatory response, contributing to increased perioperative morbidity and mortality.

During cardiac surgery involving a cardio-pulmonary bypass (CPB), a systemic inflammatory response is triggered due to the combination of surgical trauma, activation of blood components in the extracorporeal circuit, ischemia/reperfusion injury, aortic-cross clamping, hypothermia, and endotoxin release. There is then an increase in the circulating levels of the tumor necrosis factor-alpha; interleukins 1, 6, and 8; and several other cytokines. Steroids attenuate the inflammatory response to cardiac surgery and CPB, and they are reported to improve the quality of recovery scores, reduce the incidence of atrial fibrillation and bleeding, decrease the length of hospitalization, and improve hemodynamic stability. However, two randomized controlled trials found no differences in the mortality or major morbidity in high-risk patients who received intraoperative steroids.

The postoperative cognitive dysfunction seen after cardiac surgery has also been shown to be a result of the surgical inflammatory response and the CPB circuit. Inflammatory mediators in the brain may influence learning and memory directly as well as indirectly by inhibiting intra-neuronal signaling pathways. Pro-inflammatory cytokines can inhibit brain-derived neurotrophic factor signaling via the activation of p38 mitogen-activated protein kinase and nuclear factor κB, resulting in reduced neurogenesis and neuronal plasticity.

Minimizing surgical trauma is an expectation of patients and seems to provide the benefit of accelerated physical recovery. Advances in patient evaluation, instrumentation, and operative techniques have allowed surgeons to perform a wide variety of complex operations through smaller incisions and, in some cases, without CPB. Minimally invasive techniques have been applied to a wide range of cardiac procedures. Furthermore, numerous reports have demonstrated the feasibility, safety, and efficacy of minimally invasive cardiac surgery and have supported its integration into clinical practice. The roster of less invasive surgical approaches includes minimally invasive direct coronary artery bypass (CAB), minimally invasive multivessel coronary surgery through a small thoracotomy, endoscopic atraumatic CAB, totally endoscopic CAB, and hybrid coronary revascularization. There has been a move towards reducing the use of CPB through an off-pump (OPCAB) approach and increasing the use of novel technological or robotic assistance. Advances with most of these techniques require massive monetary and time investments so much so that their application becomes limited to a few select centers. Significant learning curves, extensive experience, and specialized equipment are required to implement these techniques.

In Japan, isolated coronary artery bypass grafting
Immune Activation

Moderate Immune Suppression

↑ Adrenaline
↑ Noradrenaline
↑ Glucagon
↑ Pro-inflammatory Cytokines
   IL-1, TNF-α, IL-6, IL-8
↑ NK cell activity
↑ Leucocytosis
↑ Adhesion molecules

↓ Cortisol
↓ Insulin
↓ Anti-inflammatory Cytokines
   IL-10, IL-1ra
↓ Monocyte MHC II
↓ NK cell activity
↓ Lymphocyte activity

1 2 3 Days

Figure. Surgery instigates a number of responses from the specific and non-specific immune systems, which are both pro- and anti-inflammatory. If the anti-inflammatory response is greater, the immune system will be suppressed, and the risks of sepsis will be elevated. In most cases, pro-inflammatory activation predominates throughout the first 36 hours, followed by moderate immune suppression over the next few days. IL indicates interleukin; TNF, tumor necrosis factor; MHC, major histocompatibility complex; and NK, natural killer.

(CABG) was performed in 14,454 cases; among those cases, off-pump CABG was intended in 9,006 cases (62.3%) with a success rate of 98.3%. The operative and hospital mortality rates associated with primary elective CABG procedures in 12,335 cases were 0.8% and 1.3%, respectively. More than 30% of patients had less than two-vessel disease; however, 99.7% of them underwent median sternotomy. CABG continues to be performed primarily through a median sternotomy. This is due to several factors that make CABG more complicated when performed through small incisions, including the technical demands of delicate vascular dissection and suturing; the difficulty of exposing multiple areas of the heart, internal mammary arteries, and aorta; and prolonged operating times.

To overcome the limitations of technical demands and specialized equipment, Su, et al. applied easy-to-perform minimally invasive bypass graft surgery on triple-vessel diseases. They combined the off-pump coronary artery bypass approach with lower distal mini-sternotomy for multivessel coronary revascularization (TM-OPCAB). TM-OPCAB improved the patients’ periods of time on ventilation, post-operative in-hospital stays, and blood transfusion rates compared to standard off-pump coronary artery bypass surgery, which includes the conventional full-length sternotomy. After an average of 35 months of follow-up, the overall survival rate and the percentage of patients freed from major adverse cardiac and cerebrovascular events were similar between both groups. The researchers reported that patients with triple-vessel diseases will benefit from Su’s surgical technique, which requires less resources.

Thanks to improvements in patient preparation for surgery and anesthetic and surgical techniques during operation, the risks and morbidity associated with surgical procedures have steadily decreased in recent decades. The key pathogenic factor in postoperative morbidity, excluding the failures of surgical and anesthetic techniques, is the surgical stress response with subsequent increased demands on organ function. "Enhanced recovery after surgery," or "fast-track surgery," is a multimodal, evidence-based pathway devised to optimize the perioperative care of surgical patients. Compelling evidence has demonstrated that bundles of evidence-based best practices, delivered by a multidisciplinary team throughout the operative process, lead to an earlier return to preoperative physiologic functions after surgery compared to traditional methods. Enhanced recovery after surgery (ERAS) programs have been shown to reduce the component parts of the surgical stress response, such as insulin resistance and the resulting catabolic state. In addition, with a reduced stress response comes a faster recovery time, which improves both morbidity and short-term and long-term mortality. The process of implementing ERAS involves a team of surgeons, anesthetists, an ERAS coordinator (often a nurse or a physician assistant), and staff from units that care for the surgical patient. No single intervention to modulate the stress response demonstrated a significant difference; rather, multiple approaches were required to suppress systemic inflammatory responses. Therefore, both surgical practitioners and other medical specialists involved in the management of patients should be familiar with the factors that contribute to the development and amplification of the surgical stress response.

Disclosures

Conflicts of interest: The authors have no conflicts of in-
terest to declare.

References