

The Systemic Inflammatory Response to Cardiac Surgery

Implications for the Anesthesiologist

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THE purpose of this review is to evaluate recent developments in our understanding of the inflammatory response to cardiac surgery. Scientific knowledge in this field is continually expanding, potentially significant advances are regularly reported, and this area constitutes a major interface of clinical and basic scientific research. The review is divided into four major sections. The first section describes the pathophysiology of the inflammatory response to cardiac surgery. Factors that influence the extent of the inflammatory response, including the immunomodulatory effects of drugs commonly administered perioperatively, are discussed in the second section. The third section examines the evidence that the inflammatory response contributes to adverse perioperative events, in particular organ dysfunction, while the final section evaluates potential therapeutic strategies to control this response. The review concludes with a summary of potential future research directions and key deficiencies in our knowledge regarding the inflammatory response to cardiac surgery.

The Systemic Inflammatory Response

Inflammation is the body's response to tissue injury and is a rapid, highly amplified, controlled humoral and cellular response.¹ While the term "sepsis" has classically been utilized to imply a clinical response to infection, a similar response may arise in the absence of infection.² In fact, patients who appear to have sepsis but have

negative microbial cultures have similar morbidity and mortality rates to the respective culture-positive populations.³ This has led to the understanding that this process is a generalized, nonspecific inflammatory response to injury and prompted a diagnostic reclassification of these events into a pathophysiologic continuum by the American College of Chest Physicians-Society of Critical Care Medicine Consensus Conference Committee in 1991 (table 1).²

The term "systemic inflammatory response syndrome" (SIRS) has been proposed to describe the entry point to this continuum, an entity that overlaps with normal postoperative physiology.² SIRS is a nonspecific, generalized inflammatory process, independent of the causative factors, and is of importance for several reasons. It is a sensitive if nonspecific indicator of injury. The classification of severity of SIRS into uncomplicated SIRS, sepsis, severe sepsis, and septic shock based on the existence of documented infection or hypotension has prognostic significance.³ A frequent complication of SIRS is the development of organ dysfunction, including acute lung injury, shock, renal failure, and multiple organ dysfunction syndrome (MODS). Finally, long-term survival in patients developing SIRS may also be adversely affected. This is well documented in the context of sepsis, with the risk of death increased for up to 5 yr after the septic episode.⁴

The Inflammatory Response to Cardiac Surgery

Cardiac surgery provokes a vigorous inflammatory response, which has important clinical implications. In the report from the Society of Thoracic Surgeons National Database, 20% (22,000 patients) of "low-risk" patients developed postoperative complications.⁵ The incidence of MODS following cardiopulmonary bypass (CPB) was 11%, with a mortality rate of 41% in these patients in another study.⁶ Acquired multiple organ dysfunction is the best predictor of mortality in cardiac surgical patients who require prolonged postoperative mechanical ventilation.⁶ Many aspects of a patient's risk of serious

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Table 1. Criteria for Diagnosis of SIRS, Sepsis, and MODS²

SIRS: diagnosis requires presence of two or more of the following: Temperature > 38°C or < 36°C Heart rate > 90 beats/min Respiratory rate > 20 breaths/min or PaCO ₂ < 32 mmHg Leukocytes > 12,000, < 4,000/mm ³ or > 10% immature (band) forms
Sepsis: SIRS with documented infection
Severe sepsis: sepsis associated with organ dysfunction, hypoperfusion or hypotension
Septic shock: sepsis with hypotension despite adequate resuscitation along with the presence of perfusion abnormalities
MODS: a state of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention

SIRS = systemic inflammatory response syndrome; MODS = multiple organ dysfunction syndrome.

perioperative complications are perceived as being relatively fixed (genotype, preoperative health status, surgical difficulty, *etc.*), but the degree to which these may be improved (*e.g.*, hemodynamic optimization using pharmacologic or mechanical support) is still under assessment. The contribution of the inflammatory response to patient outcome is potentially remediable and therefore deserves attention.

Factors influencing incidence, severity, and clinical outcome of the inflammatory response, and in particular the reasons why certain patients develop life-threatening perioperative complications, are currently not well understood. Three separate perspectives contribute to our understanding of the link between the inflammatory response and adverse clinical sequelae. First, the complex interaction of humoral proinflammatory and anti-inflammatory molecules may influence the clinical presentation and course of SIRS, with the balance of proinflammatory and anti-inflammatory cytokines determining the clinical course following cardiac surgery.⁷ Alternatively, changes in the time course, magnitude, or patterns of cytokine release following CPB may contribute to abnormalities in the inflammatory response to cardiac surgery.

Second, a “multiple-hit” scenario may be seen, whereby serious sequelae develop after cardiac surgery as a result of adverse events, such as infection or ongoing organ hypoperfusion.^{1,8} The combination results in the conversion of an inherently self-limiting, tightly controlled homeostatic response to an uncontrolled destructive process resulting in organ dysfunction.^{1,8,9} Potential mechanistic insights into the pathophysiologic basis for multiple hits include the ability of CPB to “prime” neutrophils, causing pulmonary leukosequestration,¹⁰ and enhanced cytotoxin release following a subsequent insult.¹⁰

Third, it has been suggested that there may be a fundamental misconception about the inflammatory re-

sponse. The proinflammatory state, SIRS, may be only one aspect of a multifaceted response. The converse has been termed the compensatory antiinflammatory response syndrome.¹¹ CPB-induced generalized immunosuppression may play an important role in the development of infectious complications.¹² Cumulatively, these responses represent the body’s attempt to reestablish homeostasis and may clinically manifest as predominantly proinflammatory (SIRS), antiinflammatory (compensatory antiinflammatory response syndrome), or an intermediate mixed response.¹¹

Relevance to the Anesthesiologist

As perioperative physicians, anesthesiologists contribute to the management of the patient when adverse sequelae of CPB may pose a significant threat. Anesthesiologists are well positioned to minimize the risk of adverse sequelae resulting from the inflammatory response to CPB by reducing perioperative risk factors. Many drugs administered during the perioperative period, particularly for the purposes of anesthesia and sedation, possess potentially important immunomodulatory effects. Anesthesiologists may be best placed to properly evaluate and eventually implement therapeutic strategies, particularly as many potentially useful therapies seem poised to enter the clinical arena. Finally, a thorough knowledge of all aspects of the inflammatory response to CPB is mandatory if the anesthesiologist is to realize the goal of minimizing perioperative risk.

Pathophysiology of the Inflammatory Response to Cardiac Surgery

Factors That Activate the Inflammatory Response

Nonspecific activators of the inflammatory response include surgical trauma, blood loss or transfusion, and hypothermia. In addition, CPB may specifically activate the inflammatory response *via* at least three distinct mechanisms (fig. 1). One mechanism involves direct “contact activation” of the immune system following exposure of blood to the foreign surfaces of the CPB circuit. A second mechanism involves ischemia-reperfusion injury to the brain,^{13,14} heart,^{14,15} lungs,¹⁶ kidney^{17,18} and liver¹⁹ as a result of aortic cross-clamping. Restoration of perfusion on release of the aortic cross-clamp is associated with activation of key indices of the inflammatory response.^{20,21}

Endotoxemia may indirectly activate the inflammatory cascade. Splanchnic hypoperfusion, a common finding during and following CPB,²² may damage the mucosal barrier, allowing gut translocation of endotoxin.^{23,24} Systemic endotoxin concentrations correlate closely with the degree of cardiovascular dysfunction following CPB,^{25,26} while low preoperative serum immunoglobu-

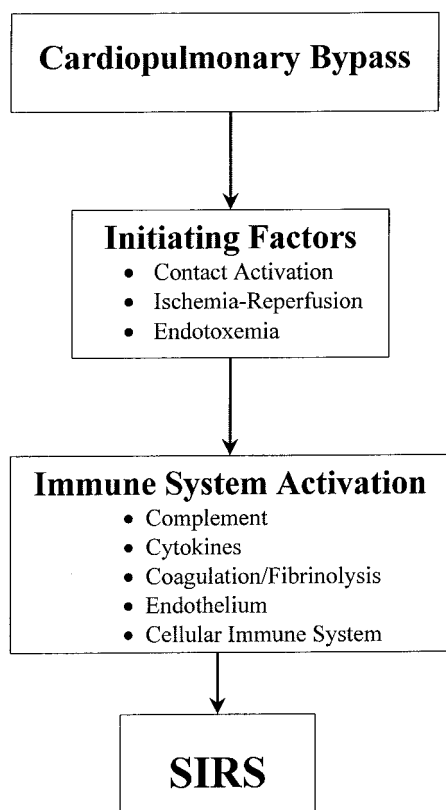


Fig. 1. Schematic diagram of the sequence of events by which cardiopulmonary bypass (CPB) may lead to the development of systemic inflammatory response syndrome (SIRS).

lin M antiendotoxin core antibody concentrations predict poor outcome.²⁷ However, the importance of endotoxin in stimulating the inflammatory response to cardiac surgery remains in doubt, with conflicting evidence regarding the importance of gut translocation.^{26,28} In fact, endotoxin may be a contaminant of fluids, such as cardioplegia and circuit priming fluid, routinely used during CPB.²⁹ The sole study to examine the incidence and time sequence of splanchnic hypoperfusion (as measured by intramucosal pH), gut permeability, and endotoxemia during CPB found no association between mucosal acidosis and either endotoxemia or intestinal permeability.³⁰

Key Components of the Inflammatory Response

The Complement Cascade. Complement is activated during extracorporeal circulation, reperfusion of ischemic tissues, and heparin neutralization with protamine.³¹ Exposure of blood to the foreign surface of the extracorporeal circuit results in direct “contact” activation of the complement cascade, predominantly *via* the alternate pathway (fig. 2).^{20,32,33} The blood-gas interface of the CPB circuit may also play a role in complement activation.³⁴ The formation of heparin-protamine complexes activates the complement cascade mainly *via* the classic (C4a) pathway.^{32,35} In the first 5 days follow-

ing cardiac surgery, a second delayed increase in complement activation products is seen.³⁶ This delayed activation of complement appears to be mediated by C reactive protein in response to heparin-protamine complexes.³⁶

The central role of complement in the inflammatory response to cardiac surgery has been demonstrated by the effects of complement-specific inhibitors. Soluble human complement receptor type 1 attenuates lung and myocardial injury,³⁷ while blockade of C3a formation prevents activation of neutrophils, monocytes and platelets in models of CPB.³⁸ Anti-C5a monoclonal antibodies attenuate CPB-mediated pulmonary,³⁹ myocardial,⁴⁰ mesenteric,⁴¹ and microvascular^{39,40} dysfunction. Specific blockade of the alternative pathway of complement activation by monoclonal antibodies to properdin causes near complete inhibition of C3a and C5b-9 formation and dramatically reduces platelet and neutrophil activation.⁴² Recombinant soluble complement receptor 1,⁴³ C3-binding cyclic synthetic peptide,⁴⁴ and antihuman C5 monoclonal antibody⁴⁵ all prevent up-regulation of adhesion molecules necessary for neutrophils to bind to the CPB circuit and vascular endothelium, a necessary step in the injury process. Finally, increased plasma concentrations of C5b-9, a terminal complex of complement proteins C5 to C9, are seen during CPB (fig. 2). Selective blockade of C5b-9 formation by antihuman C8 monoclonal antibody inhibits platelet but not leukocyte activation in a model of simulated extracorporeal circulation.⁴⁶

The degree of complement activation in patients undergoing CPB has clinical significance. The degree of postoperative pulmonary shunt correlates with activation of the classic pathway by protamine-heparin complexes.⁴⁷ Postoperative levels of C4d-C-reactive protein, a specific marker for C-reactive protein-mediated activation of complement, correlate with the incidence of postoperative arrhythmia following coronary artery bypass graft (CABG).^{35,36} Postoperative C3a concentrations may predict the probability of cardiac, pulmonary, renal, and hemostatic dysfunction⁴⁸ and the likelihood of developing MODS in children.³³ Strategies that improve CPB circuit biocompatibility reduce indices of complement activation and may decrease postoperative morbidity, particularly in high-risk patients.⁴⁹ Anti-C5a antibody, which reduces sC5b-9 formation, significantly reduces myocardial injury, blood loss, and postoperative cognitive deficits in patients undergoing CPB.⁵⁰

The Cytokine Cascade. Cytokines are soluble proteins and polypeptides that act as paracrine messengers of the immune system and are produced by a large variety of cell types, including activated monocytes, tissue macrophages, lymphocytes, and endothelial cells (fig. 3). Individual cytokines may exert either proinflammatory or antiinflammatory effects. Cytokines are essential for immunologic and physiologic homeostasis, and are normally subject to tight homeostatic control, and are

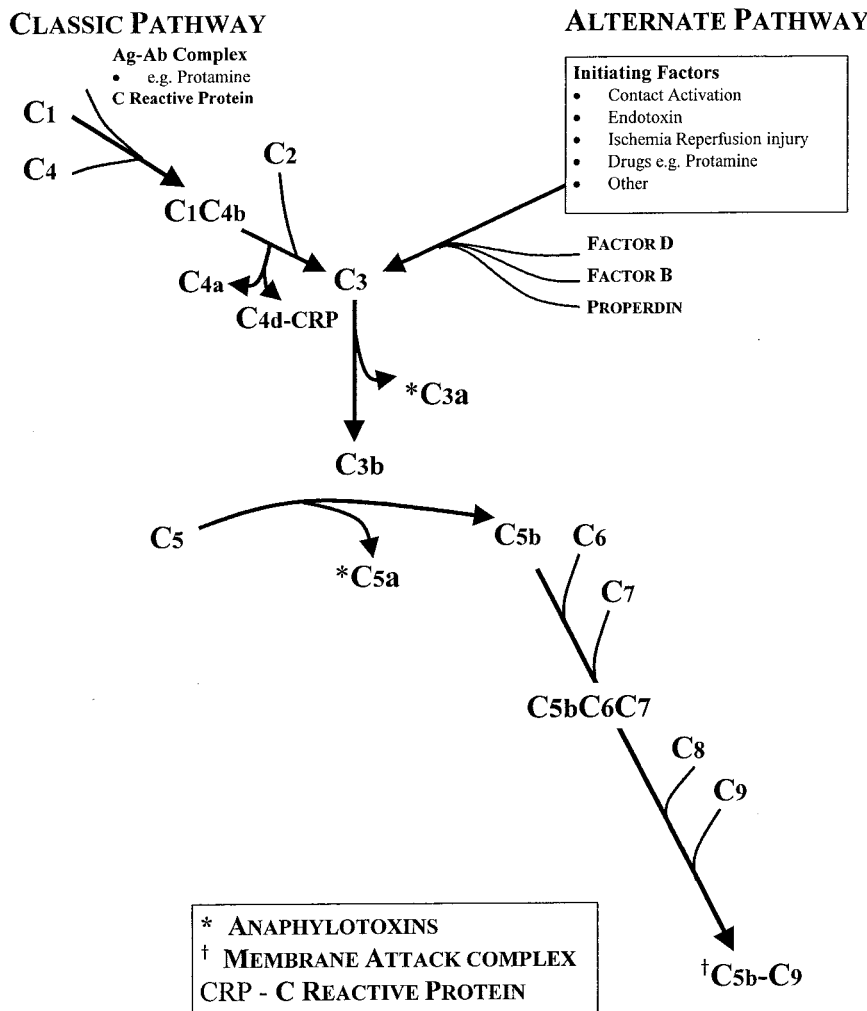


Fig. 2. Schematic diagram of the complement cascade. Two major pathways of complement activation operate in plasma: the classic pathway requires Ag-Ab complexes for activation, while the alternative pathway can be directly activated, e.g., by contact activation endotoxin or ischemia and reperfusion injury. C-reactive protein (CRP) may also activate complement, mainly *via* the classic pathway. Both pathways then proceed through the sequential activation or binding of proteins termed components or factors, resulting in the assembly of a series of components. These assemblies are capable of activating the key component C3. C3a is a potent anaphylatoxin, while C3b activates the final common pathway, leading to the formation of C5a, an anaphylatoxin, and the terminal membrane attack complex. The terminal complex is capable of inserting itself into cell membrane lipid bilayers, allowing passage of water and ions, resulting in cell lysis. C4d-CRP, formed following CRP mediated activation of the cascade, is an index of the contribution of CRP to activation of the complement cascade.

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produced in response to a variety of physiologic and pathologic stimuli.

Proinflammatory cytokines play a pivotal role in stimulating the inflammatory process, with plasma concentrations of specific cytokines, such as interleukin-1 β (IL-1 β) and interleukin-6 (IL-6), predictive of outcome in certain critically ill patient subgroups (table 2).⁵¹ Tumor necrosis factor α (TNF- α) and IL-1 β are elevated early following cardiac surgery, with IL-6 and IL-8 peaking later.^{52,53} While a direct cause-and-effect relation has not been demonstrated, elevations of proinflammatory cytokines have been strongly associated with adverse outcome following cardiac surgery. Patients who develop SIRS demonstrate significant elevations in cytokine concentrations compared to patients with an uncomplicated course following cardiac surgery.⁵⁴ Within the subgroup of cardiac surgical patients who develop SIRS, nonsurvivors had dramatically higher IL-8 and IL-18 concentrations compared to survivors.⁵⁴ In addition, serum concentrations of IL-6 correlate with mortality following pediatric cardiac surgery.⁵⁵

The proinflammatory cytokine response to cardiac surgery is balanced by a phased antiinflammatory cytokine

response, with soluble cytokine receptors, cytokine receptor antagonists, and antiinflammatory cytokines also produced in large quantities (table 3).⁵² Key antiinflammatory cytokines include interleukin-10 (IL-10), interleukin-1 receptor antagonist (IL-1ra), TNF soluble receptors 1 and 2 (TNFsr 1 and 2), and transforming growth factor β . IL-10 is a potent inhibitor of the production of TNF- α , IL-1 β , IL-6, and IL-8.⁵⁶ While the specific role of other antiinflammatory mediators remains undefined, it has been suggested the clinical prognosis following CPB may depend on the balance between proinflammatory and antiinflammatory cytokines.⁷

Nitric Oxide. Nitric oxide (NO) is a ubiquitous biologic mediator that acts as a physiologic regulator and can be responsible for tissue damage. Physiologic regulatory functions include endothelial-mediated vasodilation in both the systemic and pulmonary circulations, potentially significant immunomodulatory functions, as well as protean roles in nociception, memory, and erectile function.⁵⁷ NO may have several protective roles in the inflammatory response. NO-induced vasodilation may prevent accumulation of injurious mediators at the endothelium (fig. 3). NO may scavenge free radicals and

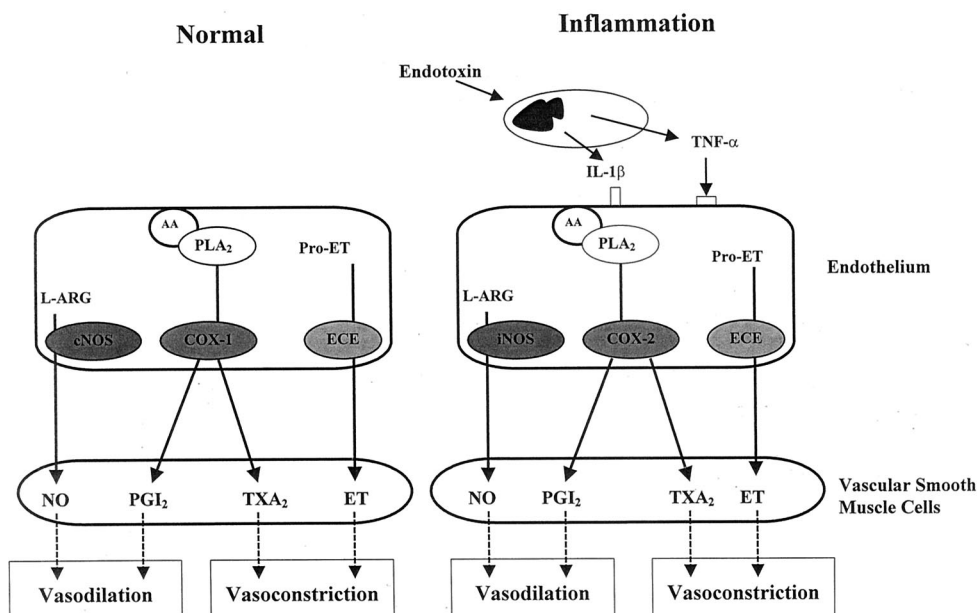


Fig. 3. This schematic diagram depicts the role of the endothelium in the regulation of vascular tone and illustrates important early events known to occur in systemic inflammatory response syndrome (SIRS) at the level of the endothelium. The endothelium regulates local vascular tone and adapts organ blood flow to metabolic needs, by altering the balance of 4 key mediators: nitric oxide (NO), prostacyclin (PGI₂), thromboxane (TXA₂), and endothelin (ET). Endotoxin (lipopolysaccharide [LPS]) binds to macrophages to release cytokines, which bind to and activate the endothelium. This increases production of these vasoactive agents, in particular NO, by up-regulating the inducible form of NO synthase (iNOS). This alters the dynamic balance of these 4 vasoactive agents over time and appears to play a central role in the hemodynamic sequelae of SIRS. cNOS = constitutive form of NOS; COX-1 = cyclooxygenase 1; COX-2 = cyclooxygenase 2; PLA₂ = phospholipase 2; AA = arachidonic acid; L-ARG = L-arginine; pro-ET = proendothelin; ECE = endothelin-converting enzyme.

prevent up-regulation of neutrophil CD11/CD18 adhesion molecules.⁵⁸ Supplementation of cardioplegia and perfusate with an NO precursor (arginine) or NO donor (SPM-5185) has beneficial effects on postreperfusion neutrophil accumulation, endothelial function, and myocardial performance following experimental myocardial ischemia,⁵⁹ possibly by inhibiting neutrophil adherence and cytotoxicity. The release of NO during CPB appears to be dependent on the type of bypass flow, with attenuation of basal NO release during nonpulsatile flow leading to end-organ functional capillary closure as a result of diminished vessel wall shear stress.^{60,61} This release of NO is considered to be physiologic, produced by endothelial constitutive NO synthase (cNOS),^{60,62} and its release appears to be a function of both the frequency and amplitude of the pulsatile flow.⁶³

The role of NO in the inflammatory response is complex, however, and NO has several potentially deleterious actions. Cytokine-induced decrements of myocardial function appear to be related to increases in myocardial inducible NO synthase (iNOS),⁶⁴ which is up-regulated by CPB.⁶⁵ Prevention of myocardial iNOS up-regulation may reduce hemodynamic instability post-CPB,⁶⁵ while NOS inhibition can reverse refractory hypotension in established shock. NO is a highly reactive free radical and combines with a variety of molecules *in vivo*. While the free radical scavenging role of NO is generally protective,⁶⁶ NO may combine with the free radical super-

oxide to form peroxynitrite, a more reactive and injurious free radical.^{66,67} Finally, NO appears to be a powerful direct cellular toxin, inactivating enzymes involved in glycolysis, the Krebs cycle, and the electron transport chain⁶⁷ and reducing intracellular adenosine triphosphate and antioxidant concentrations, hence predisposing to cell death.

The timing, source, and quantities of NO produced may be the key to dissecting these apparently paradoxical roles. NO is produced constitutively in small (picomolar) quantities by cNOS isoforms, such as the vascular endothelial isoform (ecNOS). ecNOS plays a pivotal role in the physiologic regulation of basal vascular tone, blood flow capillary integrity, and leukocyte and platelet adhesiveness to the endothelium.⁵⁷ The activity of ecNOS appears to be inhibited in the earliest phases of the inflammatory response, allowing both unopposed vasoconstrictive influences and increased leukocyte and platelet adhesion to the endothelium. However, within 4–8 h, iNOS is produced in a wide variety of tissues, including vascular smooth muscle, hepatocytes, and Kupffer cells,^{67,68} and produces NO at much higher (nanomolar) quantities. Cytokines, particularly IL-1β, play a pivotal role in the process of NO-induced inflammatory dilatation.⁶⁹ The proinflammatory response, once fully developed, represents a high-output NO state.⁶⁷ In fact, exhaled NO following initiation of CPB

Table 2. Key Proinflammatory Cytokines in the Immune Response to Cardiac Surgery

Cytokine	Source	Functions	In Cardiac Surgery
TNF- α	Macrophages Monocytes Natural killer cells T cells and B cells Mast cells Endothelial cells	Primary mediator in inflammatory response Provokes pathophysiologic effects of SIRS Proinflammatory cytokine release Neutrophil release (from bone marrow) and activation Macrophage/monocyte differentiation and activation Activates coagulation/complement cascades Endothelial adhesion molecule synthesis Acute phase protein production Endogenous pyrogen	Elevated early following cardiac surgery ^{52,53}
IL-1 β	Macrophages Monocytes Endothelial cells	Primary mediator in inflammatory response Initiation of cell mediated immune response Activation of T cells and macrophages iNOS expression; prostaglandin production Inhibition of lipoprotein lipase Procoagulant activity Release of proinflammatory cytokines Endothelial adhesion molecule synthesis Acute phase protein production Endogenous pyrogen	Elevated early following cardiac surgery ^{52,53} May predict outcome in certain critically ill patient subgroups ⁵¹
IL-6	Macrophages Type 2 helper cells	Key later role in inflammatory cascade Activation of lymphocytes Differentiation of B cells and antibody production T-cell activation and differentiation Acute phase protein production Endogenous pyrogen	Elevated later following cardiac surgery ^{52,53} Myocardial depressant ⁶⁴ Serum concentrations may correlate with mortality following pediatric cardiac surgery ⁵⁵ May predict outcome in from critically illness ⁵¹
IL-8	Macrophages T cells Endothelial cells	Key later role in inflammatory cascade Chemotaxis of neutrophils, basophils, and T cells Regulates neutrophil activity, including neutrophil chemotaxis, the neutrophil respiratory burst, transendothelial neutrophil migration, and neutrophil dependent plasma leak	Elevated later following cardiac surgery ^{52,53,402} Important role suggested in regulating neutrophil inflammatory response to cardiac surgery. ⁴²⁷ Negative correlation between IL-8 and postoperative cardiac index. ⁴⁰²

TNF- α = tumor necrosis factor α ; IL = interleukin; SIRS = systemic inflammatory response syndrome; iNOS = inducible nitric oxide synthase.

may represent an index of severity of the inflammatory response,⁷⁰ although this has been disputed.⁷¹

Coagulation-Fibrinolytic Cascades. The coagulation-fibrinolytic cascades and the inflammatory response, while in many respects separate processes, are closely interconnected, with activation of coagulation a key component of the acute inflammatory response and *vice versa*. In this context, inflammation and coagulation should perhaps be considered different facets of the same host response to injury.

The coagulation system has traditionally been divided (for conceptual and practical purposes) into the intrinsic and extrinsic pathways, both of which lead to a final common pathway, and result, *via* thrombin generation, in the formation of an insoluble fibrin clot. Activation of coagulation after CPB had been thought to be predominantly due to activation of the intrinsic pathway *via* the contact system. In this paradigm, plasma factor XII was pivotal to this process, becoming adsorbed and activated on contact with the CPB circuit. However, patients with congenital deficiency of factor XII still generate throm-

bin following CPB.⁷² This suggests that the extrinsic pathway, which requires expression and activation of tissue factor, perhaps in response to inflammatory stimuli and oxidative or shear stress, may also be involved.⁷³

Hemostasis is mediated by a balance of procoagulant and anticoagulant forces, which normally coexist in a delicate balance. The coagulation cascade consists of inactive circulating precursors, which are sequentially activated *via* enzymatic cleavage, yielding an active serine protease that hydrolyses the next factor in the cascade. Thrombin, the end product, catalyzes the formation of insoluble fibrin from fibrinogen, which form the strands that bind the platelet plug. This process is normally controlled and limited to discrete sites of injury by modulators, including plasminogen activators, thrombomodulin, proteins C and S, and serine protease inhibitors such as antithrombin III.⁷⁴ The fibrinolytic cascade, activated during coagulation, results in the formation of plasmin, which splits fibrinogen and fibrin, remodelling the formed clot and later removing the thrombus when the endothelium heals.

Table 3. Key Antiinflammatory Cytokines in the Immune Response to Cardiac Surgery

Cytokine	Source	Functions	In Cardiac Surgery
IL-10	Macrophages	Feedback role in limiting inflammatory response Potent inhibitor of TNF- α , IL-1 β , IL-6, and IL-8 production/release Down-regulates monocyte HLA-DR expression	Elevated early following cardiac surgery ^{7,428} May attenuate neutrophil activation during CPB ⁷ Increased production post-CPB in steroid-treated patients ^{402,404} Liver potential source during CPB ⁴⁰³
TGF- β	Macrophages ^{7,429} Lymphocytes ⁴²⁹ Platelets ⁴²⁹	Down-regulates proinflammatory cytokine production Attenuates lymphocyte activation May have direct cardioprotective action ⁴³⁰ Stimulator of extracellular matrix synthesis ⁴²⁸	Elevated early following cardiac surgery ^{7,428} Attenuates lymphocytic response to cardiac surgery ⁴²⁸ TGF- β expression in cardiac allografts associated with impaired graft function and limited survival ⁴²⁹
IL-1ra	Shed hydrophilic extracellular portion of receptor containing ligand binding site	Specific antagonist to IL-1 β Possible role in limiting inflammatory response by binding circulating IL-1 β	Elevated early following cardiac surgery ⁷ Increased production post-CPB in steroid treated patients ⁴⁰²
TNFsr 1 and 2	Shed hydrophilic extracellular portion of receptor containing ligand binding site	Specific antagonist to TNF- α Possible role in limiting inflammatory response by binding circulating TNF- α	Elevated later following cardiac surgery ⁷

IL = interleukin; TNF- α = tumor necrosis factor α ; HLA = human leukocyte antigen; CPB = cardiopulmonary bypass; TGF- β = transforming growth factor β ; IL-1ra = interleukin 1 receptor antagonist; TNFsr = tumor necrosis factor soluble receptor.

Several specific points regarding the complex interrelation between coagulation and inflammation, in the context of CPB, deserve attention. The endothelium is intricately involved in both processes (see Endothelium). Proinflammatory cytokines play a key role in initiating the coagulation process locally at sites of inflammation, by activation of the endothelium, induction of the expression of tissue factor, eliciting the expression of leukocyte adhesion molecules on the intravascular cell surfaces, and stimulating production of platelet-activating factors.^{75,76} This, combined with down-regulation of thrombomodulin expression and of the fibrinolytic and protein C anticoagulant pathways, alters the balance between procoagulant and anticoagulant activities, resulting in a markedly procoagulant state.^{75,76}

The coagulation system in turn impacts on the inflammatory response. Platelet activation at sites of tissue injury results in the release of multiple mediators that alter tissue integrity. Several key coagulation proteins, such as thrombin and factor Xa, have proinflammatory properties. Thrombin, formed following activation of the coagulation cascade, stimulates several cell chemotaxins and mitogens, which are responsible for the spreading of the lesion and the tissue repair process.^{75,76}

Heparin and protamine, which are used to modulate coagulation in almost all patients undergoing cardiac surgery, may have important immunomodulatory effects.^{32,77} Heparin appears to possess important anti-inflammatory effects.⁷⁷ Protamine neutralization of heparin may result in multiple cardiovascular effects, including increased pulmonary artery pressures and decreased systolic and diastolic blood pressure, myocardial

oxygen consumption, cardiac output, heart rate, and systemic vascular resistance.⁷⁸ Although protamine by itself has adverse effects, the heparin-protamine complex is particularly deleterious. The heparin-protamine interaction activates the inflammatory response by several mechanisms, including complement activation, histamine release, thromboxane and nitric oxide production, and antibody formation.⁷⁸ The release of thromboxane may result in severe pulmonary hypertension.⁷⁸ In a minority of patients, severe anaphylactoid reactions may result from the heparin-protamine interaction.

The balance of procoagulants and anticoagulants is profoundly disturbed in CPB patients. Activation of procoagulants such as thrombin mandates administration of anticoagulant drugs prior to CPB to prevent blood from clotting instantly on contact with the extracorporeal circuit. In addition, the stimulation of fibrinolysis during CPB appears to contribute to the postoperative coagulopathy commonly seen in these patients.⁷⁹ Widespread vascular injury following CPB may result in uncontrolled platelet activation, thrombin generation, and disseminated intravascular coagulation.⁸⁰ The resulting widespread fibrin deposition in the microvasculature may occlude microcirculatory flow and cause end-organ damage, which may progress to MODS and death.⁸⁰

The Endothelium. The vascular endothelium is a dynamic participant in cellular and organ function rather than a static barrier, as was once believed. It is intimately involved in a variety of physiologic and pathologic processes and has emerged as the central focus of many of the biologic events that affect the perioperative course

of the cardiac surgical patient. The endothelium controls vascular tone and permeability, regulates coagulation and thrombosis, and directs the passage of leukocytes into areas of inflammation, through the expression of surface proteins and secretion of soluble mediators.

The inflammatory response to CPB is characterized by a state of widespread endothelial activation and diffuse endothelial dysfunction.⁷⁰ Inflammatory mediators, including TNF- α and IL-1 β , bind to specific receptors on the endothelium, initiating diverse signal transduction pathways, which in turn activate a specific set of genes within the nucleus of the endothelial cell, termed activation genes. The transcription factor NF- κ B plays a pivotal role in the signal transduction process. When activated, it dissociates from the cytosolic inhibitory protein I κ B, translocates to the endothelial cell nucleus, binds with specific DNA sequences, and alters the conformation of the basal transcriptional apparatus, resulting in the transcription of the activation genes.⁸¹ This process results in the translation of proteins, including adhesion molecules (*e.g.*, E-selectin, intercellular adhesion molecule-1) and cytokines (*e.g.*, IL-8), required for endothelial cell activation, a process that takes approximately 4 h and peaks at 8–24 h depending on the gene.⁷³

The activated endothelial cell plays a pivotal role in linking the inflammatory and coagulation systems, by expressing proteins central to the activation of coagulation and inflammation.^{73,76} Endothelial cell adhesion molecule expression mediates the interaction between the neutrophil and the endothelial cell (see The Cellular Immune Response), resulting in neutrophil adhesion, activation, and degranulation. This further damages the endothelium, causing diffuse capillary leak and edema formation.^{73,82} Endothelial injury results in the expression of tissue factor, augmented by IL-1 β and TNF- α , which activates the extrinsic pathway of coagulation⁷⁶ and may result in disseminated intravascular coagulation.⁷⁵ In addition, protein C, a key inhibitory regulator of hemostasis, is antagonized in inflammatory states, most probably by TNF- α , further shifting the balance toward a procoagulant state.⁷⁶

Vascular endothelium plays a central role in the pathogenesis of microcirculatory derangement following CPB. Endothelial regulation of local vascular tone (fig. 3) is mediated *via* a variety of endothelium-derived relaxing and contracting factors such as NO, prostacyclin, endothelium-derived hyperpolarizing factor, endothelin, and thromboxane A₂.⁸³ The increase in pulmonary vascular resistance following CPB is attributed to reduced NO release from dysfunctional pulmonary endothelium⁷⁰ and is reversed by NO supplementation.⁸⁴

A complex interplay between impaired endothelial function, inflammation, and atherosclerosis in the pathogenesis of adverse cardiovascular events.^{85,86} Alterations in NO generation appear to underpin these interrelationships.⁸⁶ Of particular concern, the inflammatory

response to cardiac surgery may increase the risk of a postoperative cardiac event. Proinflammatory cytokines and endotoxin can impair endothelium-dependent dilatation, and the endothelium may lose its ability to respond to circulating hormones or autacoids.^{69,86} Studies of forearm vasoregulation demonstrate that IL-1 β , TNF- α , and endotoxin^{87,88} cause prolonged but reversible impairment of endothelial relaxation, termed “endothelial stunning.”^{88,89} Proinflammatory cytokines inhibit production of NO and a vasodilator antiplatelet prostanoïd.⁸⁷ Loss of the vasodilator and antithrombotic effects of NO may alter myocardial perfusion⁸⁸ and expose preexisting atheroma to unopposed vasospastic and prothrombotic influences.⁸⁶ This may explain the association between an acute inflammatory episode and a transient increase in the risk of a cardiovascular event.⁸⁹

In addition, endothelial dysfunction may limit the long-term success of cardiac surgery, particularly CABG, by contributing to the development of narrowing at graft anastomotic sites as a result of medial hyperplasia⁸⁵ and by accelerating the progression of atherosclerosis. Abnormalities of endothelium-dependent vasodilation, including paradoxical vasoconstrictor responses to, *e.g.*, exercise, are often observed in the earliest stages of coronary artery disease.⁸⁵ Long-term follow-up clinical studies demonstrate that this is associated with an increased rate of cardiovascular events.⁹⁰ Endothelial dysfunction activates the inflammatory response, recruiting leukocytes and platelets to the arterial wall, which may initiate the formation of atherosclerotic plaque.^{85,89} This process is particularly likely at sites of disturbed blood flow such as occur at graft anastomoses⁹¹ and is markedly potentiated by the presence of hypercholesterolemia. Endothelial dysfunction in hypercholesterolemic patients is in large part due to a reduced bioavailability of NO.⁹² In this regard, statins, which lower cholesterol, have been demonstrated to rapidly restore endothelial function, in part by directly up-regulating eNOS.⁸⁵ This restoration of endothelial function results in improved myocardial perfusion, reduced myocardial ischemia, and reversal of atherosclerosis.⁸⁵

The Cellular Immune Response. The process of neutrophil-endothelial adhesion is an essential component of the inflammatory response leading to widespread endothelial damage and is now well understood, involving distinct phases of primary and secondary adhesion (fig. 4).⁸² In the noninflamed state the leukocyte travels at around 1,000 μ m/s, along with the erythrocytes, in the center of the postcapillary venule. In the first phase, primary adhesion, the freely moving neutrophil is converted to the “rolling” state, in which it tumbles slowly (around 30 μ m/s) along the endothelium.⁸² This is mediated by the expression of a family of adhesion molecules known as selectins. P- and E-selectin are expressed on the endothelium, and L-selectin is expressed on the neutrophils. These are involved in the

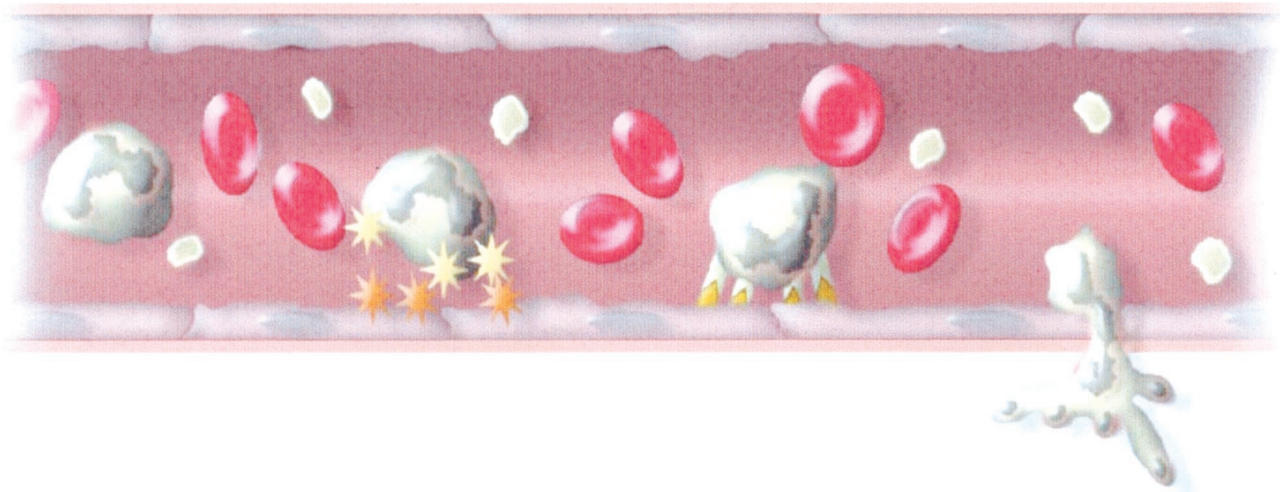


Fig. 4. This schematic diagram illustrates the neutrophil–endothelium interaction. Each neutrophil illustrates a key event, as it proceeds from left to right along the capillary. Briefly, neutrophils become tightly adherent to the endothelium in a 3-stage process. In the first stage, the freely moving neutrophil is converted to the “rolling” state, in which it moves slowly along the endothelium. The neutrophil loosely interacts with the endothelium *via* the expression of selectins on both the neutrophil and endothelial cell membranes. In the second stage, the expression of integrins on neutrophil and endothelium results in a tighter binding to the capillary wall. In the third stage, the neutrophil becomes tightly adherent to the endothelium and transmigrates out of the circulation, triggering activation and degranulation and further endothelial injury.

formation of loose bonds between the endothelium and the neutrophil, which slows down the passage of the leukocyte along the blood vessel wall. C5a, released on activation of the complement cascade following contact with the extracorporeal circulation, is a potent stimulant of P-selectin expression.⁹³ P-selectin is stored preformed in cytoplasmic vacuoles (the Weibel Palade Bodies) and rapidly reaches the plasma membrane by exocytosis after endothelial cell activation.⁹⁴ This may underlie the sudden leukosequestration in the pulmonary circulation, which occurs following initiation of CPB.⁹³ This process of primary adhesion is later maintained by E-selectin, which must be produced *de novo* by the activated endothelium.⁷³

Secondary or tight adhesion of the neutrophil to the endothelium requires the action of the integrin family of cell surface receptor molecules. These macromolecules consist of two different protein chains (α and β) that are noncovalently associated and are expressed on the cell surface. One subfamily of integrins, which share the same β chain (CD18), is expressed only on leukocytes. CD11a/CD18 and CD11b/CD18 are expressed abundantly by neutrophils, the former at relatively constant concentrations, while expression of the latter is greatly enhanced by cytokines, such as IL-8 and C5a.^{73,82,95} The activated integrins bind to adhesive molecules expressed on the endothelial surface, in particular, intercellular adhesion molecule-1. CD11a/CD18 may also bind to a related adhesion molecule, intercellular adhesion molecule-2, and CD11b/CD18 may adhere to elements of the extracellular matrix, such as fibrinogen.⁸² The neutrophil becomes tightly adherent to the endothelium, flattens out, and eventually transmigrates out of the circ-

ulation.^{82,96} Adherence *via* CD11b/CD18 appears to prime the neutrophil to degranulate and undergo the respiratory burst.⁸² The primed neutrophils release cytotoxic proteases, such as elastase and myeloperoxidase, and reactive oxygen species,^{96,97} resulting in damage to the vascular endothelium and surrounding tissues. This complex process of coordination of the function of adhesive molecules and regulation of the migration of neutrophils is modulated by chemokines, in particular, platelet activating factor, IL-8, and C5a.^{82,98} Therefore, in the absence of secondary insults, such as shock or infection, endothelial cells return to their resting state and lose their adhesive properties following return of cytokine and C5a concentrations to normal. This limits the inflammatory response in most patients undergoing cardiac surgery.⁷³

The cellular immune system is central to the inflammatory response following cardiac surgery. Increased spontaneous activation of both granulocytes and macrophages is observed following CPB.⁹⁹ Hyperstimulation of naïve monocytes and granulocytes occurs following exposure to plasma from CPB patients.¹⁰⁰ CPB activates monocytes and macrophages *via* increased monocyte chemoattractant factor production,¹⁰¹ and up-regulation of macrophage adhesion molecule expression and cytokine production.¹⁰² Increased concentrations of leukocyte adhesion molecules (selectins and integrins) have been demonstrated following CPB.⁹⁵ During CPB, the neutrophils are primed for enhanced free radical generation, as evidenced by an enhanced oxidative burst response seen up to 24 h after CPB⁹⁷ and demonstration of the release of intracellular lysosomal granular contents post-CPB.⁹⁶ Elevated circulating neutrophil counts and

increased neutrophil aggregability, superoxide generation, and elastase release occur up to 24 h after surgery,¹⁰³ with impaired oxidative function at 48 h postoperatively.¹⁰⁴ This suggests a biphasic abnormality with potential early tissue cytotoxicity followed later by neutrophil dysfunction. In addition, reticuloendothelial Kupffer cells demonstrate greatly increased phagosomes following CPB,¹⁰⁵ which may cause a relative "overuse" type of impairment of phagocytic activity.^{105,106}

The clinical importance of leukocytes in the inflammatory response to CPB is underscored by several findings. Pulmonary neutrophil sequestration has been demonstrated following CPB and is associated with evidence of severe histologic lung injury.^{107,108} Inhibition of neutrophil CD11/CD18 expression¹⁰⁹ or function¹¹⁰ improves myocardial function following cardiac surgery. Blockade of neutrophil adhesion¹¹¹ decreases pulmonary injury after CPB. Finally, strategies that deplete circulating leukocytes can attenuate organ injury and may improve patient outcome following CPB (see Therapeutic Strategies).¹¹²

Factors Influencing the Extent of the Inflammatory Response to Cardiac Surgery

Preoperative Factors

Preexisting disorders may influence the inflammatory response to cardiac surgery. Disordered cytokine balance may be a pathophysiologic feature of ischemic heart disease.¹¹³ Patients with preoperative left ventricular dysfunction undergoing CPB appear to have a greater degree of proinflammatory cytokine release, which is associated with impaired hemodynamics and a higher incidence of perioperative complications.¹¹⁴ CPB appears to cause greater oxidative stress in patients with diabetes, and there are qualitative differences in the inflammatory response in diabetic patients.¹¹⁵ Poorly controlled diabetes impairs the inflammatory response.¹¹⁶

The perioperative course of proinflammatory and antiinflammatory cytokine release in adult patients undergoing CABG does not differ with age.¹¹⁷

Perioperative Hemodynamic Factors

Perioperative hemodynamic instability predicts morbidity and mortality following CPB,¹¹⁸⁻¹²⁰ with low cardiac output syndrome the most common event leading to patient death.¹²¹ Strong clinical and experimental evidence links postoperative splanchnic hypoperfusion to the development of complications such as acute respiratory distress syndrome.¹⁶ Experimental splanchnic ischemia-reperfusion induces lung recruitment and sequestration of neutrophils,¹²² increased pulmonary iNOS expression,¹²³ and free radical injury.¹²⁴ Cytokines, particularly TNF- α , also appear central to this process.^{125,126} In addition, translocation of toxins and microbial flora

may occur following ischemic compromise of the integrity of the mucosal barrier.

Gastric mucosal pH, as measured by gastric tonometry, provides an index of splanchnic perfusion.¹²⁷ Gastric mucosal acidosis indicates inadequate oxygenation of splanchnic tissue and is common following weaning from CPB, even in the absence of gross hemodynamic instability.¹²⁸ It is a highly sensitive predictor for complications,¹²⁹ independent of clinical risk stratification, even during uneventful cardiac surgery with low expected mortality.¹³⁰ Therapeutic strategies to maintain hemodynamic stability and minimize postoperative splanchnic ischemia may reduce postoperative complications.

Anesthetic Techniques

Thoracic Epidural Anesthesia. Thoracic epidural anesthesia combined with general anesthesia for CABG decreased the perioperative stress response, as measured by plasma epinephrine, and may decrease postoperative myocardial and pulmonary injury.¹³¹ However, thoracic epidural anesthesia does not significantly alter the cytokine response to CPB.¹³²

Lung Management during Cardiopulmonary Bypass. Apnea during CPB may lead to activation of lysosomal enzymes in the pulmonary circulation, which in turn are correlated with the degree of postoperative acute lung injury (ALI).¹³³ This may be attenuated by a vital capacity maneuver performed before termination of the bypass¹³⁴; however, continuous positive airway pressure applied during CPB appears ineffective.¹³⁵

Anesthetic Agents and Adjuvant Drugs

Many of the drugs used to produce anesthesia and maintain postoperative sedation and analgesia possess immunomodulatory effects (table 4). The clinical implications of such effects, particularly in the context of CPB, remain unknown, with most data in this area to date confined to *in vitro* experiments. Nevertheless, developments in this emerging field are worthy of consideration in the light of their future therapeutic potential.

Propofol may enhance the antiinflammatory response to surgery by several mechanisms. Propofol may preserve hepatosplanchnic blood flow during CPB, thereby aiding maintenance of the mucosal barrier.¹³⁶ It alters the balance between proinflammatory and antiinflammatory cytokines, increasing production of the antiinflammatory cytokine IL-10 and IL-1ra,¹³⁷ while decreasing neutrophil IL-8 secretion,¹³⁸ and scavenges reactive oxygen species.¹³⁹ Low concentrations of propofol reduce neutrophil uptake in the coronary circulation following myocardial ischemia and reperfusion.¹⁴⁰ However, this effect is abolished at higher propofol concentrations; this may be due to the propofol solvent Intralipid (Kabi Pharmacia, Uppsala, Sweden).¹⁴⁰ Propofol impairs several aspects of monocyte and neutrophil function, including the respiratory burst,^{141,142} polarization,¹⁴³ che-

Table 4. Antiinflammatory Effects of Anesthetic Drugs Used during Cardiac Surgery

Agent	Antiinflammatory Effects	In Cardiac Surgery
Propofol	Enhances production of IL-10 ¹³⁷ Enhances production of IL-1ra ¹³⁷ Decreases neutrophil IL-8 secretion ¹³⁸ Scavenger of oxygen-derived free radicals ¹³⁹ Impairs neutrophil respiratory burst ^{141,142} Impairs neutrophil polarization ¹⁴³ Impairs neutrophil chemotaxis ¹⁴⁴⁻¹⁴⁶ Impairs neutrophil phagocytosis ¹⁴¹ Impairs neutrophil oxygen radical generation ¹⁴⁷ Inhibits monocyte oxidative burst and phagocytosis ¹⁴¹	
Sodium thiopental	Inhibits neutrophil polarization, chemotaxis, and adherence ¹⁴⁴⁻¹⁴⁶ Inhibits neutrophil phagocytosis and killing ^{141,144-146} Inhibits the neutrophil respiratory burst ¹⁴² Inhibits the monocyte respiratory burst ¹⁴¹ Inhibits monocyte phagocytosis ¹⁴¹ Inhibits <i>E. coli</i> clearance ¹⁴¹	
Ketamine	Suppresses IL-6 concentrations ¹⁴⁹ Decreases <i>E. coli</i> clearance ¹⁴¹ Decreases neutrophil phagocytosis ¹⁴¹ Decreases monocyte phagocytosis ¹⁴¹	Suppresses the increase of serum IL-6 concentrations, both during and following CPB ¹⁴⁹
Methohexitone	Inhibits respiratory burst of neutrophils ^{142,148}	
Morphine	Inhibits the activity of lymphocytes, granulocytes, and macrophages ¹⁵² Suppresses the antibody response ¹⁵³ Inhibits lymphocyte proliferation in response to T- and B-cell mitogens ¹⁵⁰ Inhibits natural killer cell cytotoxicity ¹⁵⁰ Inhibits the production of IL-2 and interferon γ ¹⁵⁰ Increases the secretion of antiinflammatory substances, such as CRH, ACTH, and glucocorticoids ⁴³¹	
Fentanyl	Increases concentrations of IL-1ra ¹⁵⁵	Increased CD11b ⁵² Reduced lymphocyte HLA-DR expression ⁵² Attenuated the increase in monocyte HLA-DR expression ⁵²
Midazolam	Decreases extracellular IL-8 accumulation ¹³⁸	
Volatile anesthetic agents	Decreases release of IL-1 β , TNF- α ¹⁵⁶ Decreases alveolar macrophage phagocytosis and microbicidal function ¹⁵⁷ Protect against myocardial free radical injury ¹⁵⁸⁻¹⁶⁰	

IL = interleukin; IL-1ra = interleukin 1 receptor antagonist; CPB = cardiopulmonary bypass; CRH = corticotrophin-releasing hormone; ACTH = adrenocorticotrophin hormone; TNF- α = tumor necrosis factor α .

motaxis,¹⁴⁴⁻¹⁴⁶ phagocytosis,¹⁴¹ and oxygen radical generation.¹⁴⁷ Certain immunomodulatory effects of propofol, such as suppression of respiratory burst of neutrophils by propofol, may be caused by the solvent Intralipid,¹⁴⁸ while other actions, such as its ability to scavenge free radicals, appears to be a property of propofol itself.¹³⁷

Sodium thiopental impairs the neutrophil respiratory burst,¹⁴² polarization, chemotaxis, adherence, phagocytosis and killing,¹⁴⁴⁻¹⁴⁶ and coronary uptake of neutrophils following myocardial ischemia and reperfusion.¹⁴⁰ At therapeutic concentrations, thiopental also inhibits the monocyte respiratory burst.¹⁴¹ In high concentrations thiopental affects *Escherichia coli* clearance *in vitro* and neutrophil and monocyte phagocytosis.¹⁴¹ The effect of thiopental on the respiratory burst of neutrophils appears less pronounced compared to propofol.¹⁴⁸

Ketamine attenuates the increase of serum IL-6 concentrations during and following CPB¹⁴⁹ and reduces coronary uptake of neutrophils following myocardial ischemia and reperfusion.¹⁴⁰ Ketamine affects *E. coli* clearance and neutrophil and monocyte phagocytosis *in vitro*, although only in high concentrations.¹⁴¹ Methohexitone has only minimal effects on the respiratory burst of neutrophils *in vitro*.^{142,148}

Opioids have multiple effects on the immune system, mediated indirectly *via* the central nervous system or through direct interactions with the cellular immune system.^{150,151} While the precise cellular mechanisms underlying the immunomodulatory effects of opioids are largely unknown, emerging evidence indicates that opioids share many properties with cytokines.^{151,152} Ultrahigh affinity novel δ , μ , and κ opioid receptors have been demonstrated on inflammatory

cells.¹⁵¹ Granulocytes contain both opioid peptide selective δ 2 receptors (which stimulate chemotaxis) and opiate alkaloid-selective, opioid peptide-insensitive receptors (which inhibit cytokine-induced activation and chemotaxis).¹⁵¹

Morphine down-regulates the activity of lymphocytes, granulocytes, and macrophages, and suppresses the antibody response.¹⁵³ Microinjection of morphine into the lateral ventricle of the rat induces pronounced, dose-dependent reductions in lymphocyte proliferation to T- and B-cell mitogens, natural killer cell cytotoxicity, and the production of IL-2 and interferon- γ .¹⁵⁰ Morphine also increases the secretion of CRH, ACTH, and glucocorticoids, *i.e.*, substances with inhibitory effects on the immune system. Certain immunomodulatory actions of morphine, including NO release and inhibition of cell adhesion, appear to be mediated specifically *via* the μ 3 receptor.¹⁵⁴

Fentanyl increases concentrations of IL-1ra in *in vitro* monocyte cultures.¹⁵⁵ In an isolated blood primed CPB circuit, fentanyl increased CD11b, augmented the reduction in lymphocyte HLA-DR expression, and attenuated the increase seen in monocyte HLA-DR expression.⁵² However, fentanyl, unlike morphine, appears to lack the ability to bind to the μ 3 receptor, diminishing its ability to down-regulate the inflammatory response to CPB.¹⁵⁴

Midazolam, the best studied benzodiazepine, has little influence on host defense mechanisms. Midazolam decreases neutrophil IL-8 secretion in response to lipopolysaccharide but does not alter IL-8 production.¹³⁸ Midazolam reduces postischemic uptake of neutrophils in the coronary circulation following myocardial ischemia and reperfusion.¹⁴⁰ Midazolam, at clinically relevant concentrations *in vitro*, does not attenuate neutrophil polarization¹⁴³ and has minimal effects on the neutrophil respiratory burst,¹⁴⁸ neutrophil phagocytosis,¹⁴⁸ and clearance of *E. coli*.¹⁴⁸

Sevoflurane, isoflurane, and enflurane decrease proinflammatory cytokine (IL-1 β , TNF- α) release by human peripheral mononuclear cells *in vitro*.¹⁵⁶ Isoflurane decreases alveolar macrophage phagocytosis and microbicidal function to a greater extent compared with propofol.¹⁵⁷ Halothane, isoflurane, and enflurane attenuate free radical-mediated myocardial injury.^{158,159} Isoflurane and halothane (but not sevoflurane) appear to attenuate hydroxyl radical production in the ischemic rat heart.¹⁶⁰ Sevoflurane and isoflurane and halothane reduce neutrophil¹⁶¹ and platelet^{162,163} uptake in the coronary circulation and preserve cardiac function following myocardial ischemia and reperfusion.¹⁶²⁻¹⁶⁴ This effect is mediated at least in part *via* reduced neutrophil expression of the adhesion molecule CD11b.¹⁶⁴

Clonidine appears to exert antiinflammatory actions in such diverse areas as acute pain models,¹⁶⁵ in extrinsic asthma,¹⁶⁶ and angiotensin-converting enzyme inhibitor-induced inflammation.¹⁶⁷ It appears that the antiinflammatory action of clonidine is a property of α ₂ adre-

noceptor activation.¹⁶⁸ Furthermore, α ₂ adrenoceptor agonists may regulate cytokine production *via* stimulation of α ₂ receptors on macrophages to augment TNF- α release in response to endotoxin.¹⁶⁹ While use of clonidine during CABG does not appear to influence the perioperative stress response,¹³¹ its immunomodulatory effects in the context of CPB remain to be characterized.

Surgical Factors

Proinflammatory cytokine concentrations in patients undergoing heart transplantation are greater than in CABG patients.¹² Possible explanations include the fact that these patients have severe ventricular dysfunction, a condition known to increase cytokine concentrations after cardiac surgery,¹¹⁴ or to the longer ischemia time required to perform this procedure.¹² The later course of cytokine concentrations after heart transplantation may be further influenced by immunosuppressive therapy.¹² Patients undergoing valve surgery appear to have similar immunologic response profiles to CABG patients.¹⁷⁰ In general, indices of inflammation appear to correlate with overall severity of illness rather than specific surgical procedure.¹⁷¹

Extracorporeal Perfusion Factors

The composition of the priming solution, cardioplegia, presence of pulsatile or nonpulsatile perfusion, type of oxygenator and pump, type of extracorporeal circuit, and temperature during CPB are all important factors influencing the inflammatory response. In an isolated circuit, CPB duration correlated with IL-8 concentrations and neutrophil adhesion molecule expression.⁵² The release of inflammatory mediators appears to be temperature dependent, with warm CPB associated with an increased inflammatory response compared to hypothermic CPB.^{172,173} However, there is evidence to suggest that hypothermic CPB may simply delay cytokine release and neutrophil activation, and that tepid CPB, in which the core temperature is simply allowed to drift to 32–34°C, may most effectively attenuate the inflammatory response.^{173,174} Warm blood cardioplegia reduces the inflammatory response as compared to cold crystalloid cardioplegia.¹⁷⁵ Heparin-coated CPB circuits reduce complement and proinflammatory cytokine release.¹⁷⁶ The type of CPB prime, *i.e.*, colloid (gelofusine) *versus* crystalloid, does not appear to influence cytokine release.¹⁷⁷ Membrane oxygenators may result in less activation of the inflammatory system and improve postoperative cardiac, respiratory, and renal function.¹⁷⁸ However, a later study demonstrated no sustained advantage over bubble oxygenators in terms of inflammatory activation or postoperative respiratory function.¹⁷⁹ In pediatric patients undergoing CPB, use of centrifugal pumps may result in less activation of the inflammatory response¹⁸⁰; however, another study demonstrated no advantage over conventional roller pumps.¹⁸¹ In adult

CPB patients, centrifugal pumps may induce a greater inflammatory response than roller pumps.¹⁸² Pulsatile CPB flow is associated with less endotoxemia,²³ lower cytokine and endothelin-1 concentrations,^{23,183} and increased NO production.^{60,62}

Shear Stress. During normal circulation within the vasculature, blood is exposed to various physical or mechanical forces. This is termed “shear stress” and may have a physiologic function, such as releasing NO from the endothelium.⁶⁰ However, excessive shear stress may develop during CPB as a result of large pressure changes across the CPB circuit, causing damage to blood constituents and activating the inflammatory response. Shear stress appears to be especially pronounced along the arterial cannula.¹⁸⁴ Shear stress decreases erythrocyte deformability and increases hemolysis.¹⁸⁵ Leukocyte adhesiveness is increased, and mechanical disruption, with neutrophil degranulation and release of cytotoxic products, may be seen at high levels of shear stress.¹⁸⁶ Excess shear stress also increases platelet activation¹⁸⁷ and may contribute to endothelial injury.¹⁸⁸ Strategies that minimize shear stress, by decreasing the pressure decrease across the CPB circuit, such as the use of hollow fiber membrane oxygenators, reduce leukocyte activation.¹⁸⁹

Transfusion

Allogeneic Transfusion. An estimated 20% of allogeneic blood transfusions in the United States are associated with cardiac surgery.¹⁹⁰ The immunomodulatory effects of allogeneic transfusion in cardiac surgical patients are increasingly recognized. Allogeneic blood transfusions appear to exacerbate the proinflammatory response to cardiac surgery. Intraoperative packed erythrocyte transfusions directly increase the concentrations of inflammatory mediators and indirectly stimulate the inflammatory response.¹⁹¹ This may explain, in part, the greater morbidity in patients who receive intraoperative allogeneic packed cells.¹⁹¹ In addition, transfusion-associated graft-versus-host disease is a recognized complication of fresh nonirradiated homologous whole blood.¹⁹²

Allogeneic erythrocytes are usually given to augment systemic oxygen delivery. However, a controlled clinical trial failed to demonstrate a beneficial effect of erythrocyte transfusion on systemic oxygen uptake in critically ill patients with sepsis. In fact, patients receiving old transfused erythrocytes developed evidence of splanchnic ischemia. The investigators postulated that the poorly deformable transfused erythrocytes cause microcirculatory occlusion and tissue ischemia in some organs.¹⁹³ These concerns have been further highlighted by a recent large multicenter study of critically ill intensive care unit (ICU) patients that demonstrated that a restrictive strategy of erythrocyte transfusion improved mortality in the less severely ill patients and overall was

at least as effective as and possibly superior to a liberal transfusion strategy.¹⁹⁴

Autotransfusion. Autotransfusion of shed blood from the thoracic cavities during and following CPB is a common clinical practice used to reduce the need for allogeneic blood transfusion.^{195,196} However, concerns exist regarding the efficacy and safety of autotransfusion. Extensive clotting and fibrinolysis have been demonstrated in blood from the thoracic cavities during CPB.¹⁹⁶ Studies to date on the efficacy of autotransfusion in reducing allogeneic blood transfusion have yielded conflicting results. One recent randomized clinical trial demonstrated that autotransfusion reduced allogeneic transfusion requirements but led to increased postoperative bleeding.¹⁹⁷ Conversely, in another randomized controlled trial, autotransfusion of blood suctioned from the thoracic cavity during the surgical procedure increased circulating concentrations of thrombin-antithrombin III complex, tissue-type plasminogen activator, fibrin degradation products, and free plasma hemoglobin. Autotransfusion impaired hemostasis, resulting in increased postoperative blood loss and similar if not increased consumption of blood products when compared to patients who were not autotransfused.¹⁹⁶ A metaanalysis of randomized trials assessing the effectiveness of cell salvage to minimize perioperative allogeneic blood transfusion in cardiac surgical patients concluded that it was only of marginal benefit.¹⁹⁸ Of further concern, the potential exists for autotransfused blood to stimulate the inflammatory response. Shed mediastinal blood contains a high proportion of activated leukocytes with a significantly increased production of TNF- α and IL-6 seen in *in vitro* studies.¹⁹⁵ However, in one study, while shed mediastinal blood did contain high concentrations of IL-6 and activated leukocytes, autotransfusion in the postoperative period did not cause measurable elevations in cytokines.¹⁹⁵

Postoperative Factors

Continuous Renal Replacement Therapies. Continuous renal replacement therapies such as hemofiltration appear to remove both mediators, including TNF- α and IL-1 β , and their inhibitors, such as TNFsr1, TNFsr2, and IL-1ra, from the plasma of patients with SIRS.¹⁹⁹ This offers the possibility that these therapies may alter the course of SIRS in critically ill patients. However, the use of continuous renal replacement therapy in the absence of conventional indications for dialytic support remains unproven. No significant survival advantage has been demonstrated for critically ill patients with SIRS-MODS when treated with continuous renal replacement therapy as an adjunct to conventional therapy.²⁰⁰

Mechanical Ventilation. Ventilatory strategies involving stretch of unrecruited lung units (*i.e.*, high tidal volume, low positive end-expiratory pressure), appear to cause—or potentiate—ALI.²⁰¹ Furthermore, such injury

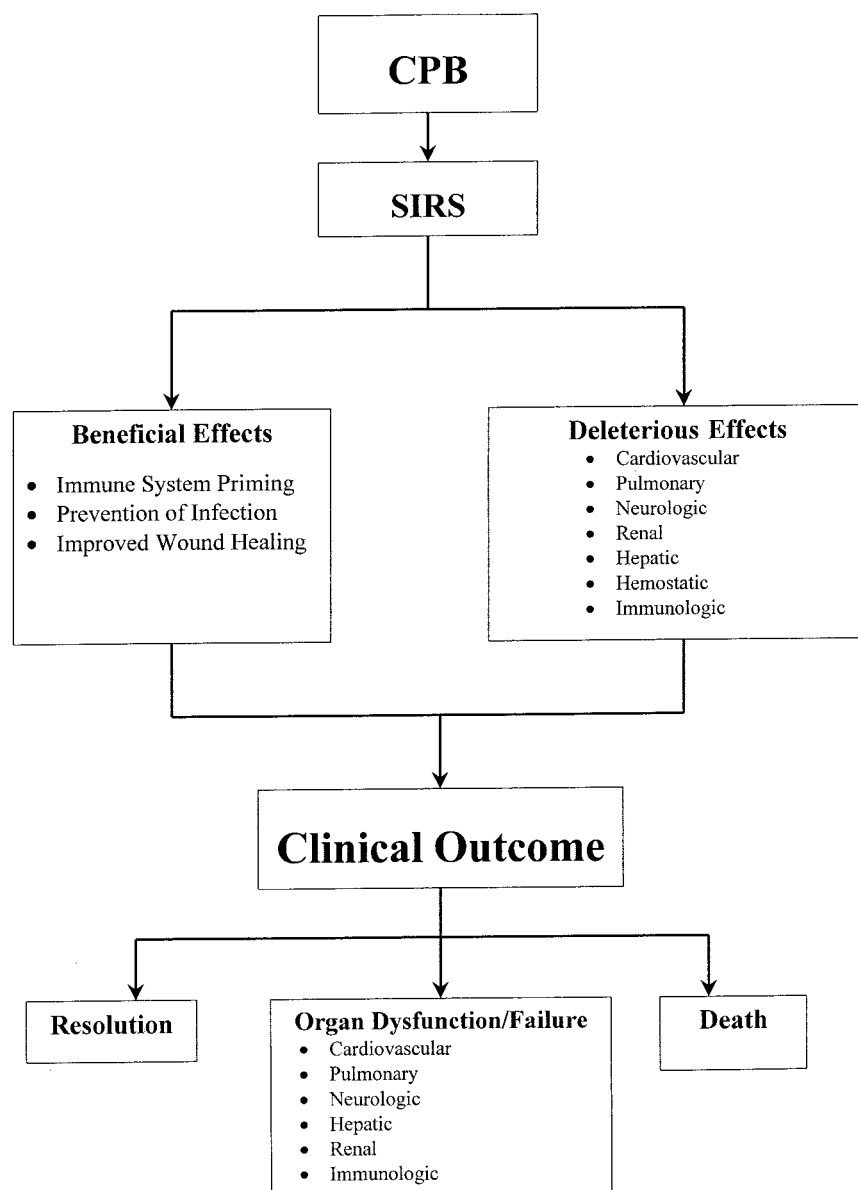


Fig. 5. Schematic diagram of the balance between beneficial and adverse effects and the resultant clinical sequelae of the inflammatory response following cardiac surgery.

may contribute to the inflammatory response by several mechanisms, such as facilitating translocation of intrapulmonary bacteria across the alveolar capillary barrier,²⁰² accumulation of intrapulmonary cytokines,²⁰³ and release of cytokines into the systemic circulation.²⁰⁴ The role of ventilatory strategies in the inflammatory response following CPB is not yet known. However, in patients with acute respiratory distress syndrome, ventilation strategies that minimize overdistention and recruitment-derecruitment of the lung attenuate the inflammatory response.²⁰⁵

Clinical Implications of the Inflammatory Response to Cardiac Surgery

Potential Beneficial Effects

A controlled, self-limiting inflammatory response to cardiac surgery has important beneficial effects such

as immune system priming, which may aid in preventing perioperative infection and promoting wound healing (fig. 5). CPB priming of neutrophils may be beneficial in preparing the host to mount a robust response to the physiologic stresses of the perioperative period. In this context, experimental pretreatment with inhaled endotoxin induces pulmonary leukocyte recruitment, which protects against subsequent bacterial lung infections.²⁰⁶ Gut translocation of endotoxin in minute amounts may be a physiologically important phenomenon to boost the reticuloendothelial system, especially Kupffer cells.²⁰⁷ $\text{TNF-}\alpha$ and $\text{IL-1}\beta$ have been shown to be necessary for wound healing,²⁰⁸ and $\text{TNF-}\alpha$ may even function to down-regulate certain aspects of the inflammatory response.²⁰⁹ Finally, $\text{IL-1}\beta$ pretreatment may reduce the severity of ischemia and reperfusion injury.²¹⁰

Potential Adverse Effects

An uncontrolled inflammatory response appears to play a significant role in the morbidity or mortality observed in patients undergoing CPB (fig. 5). The inflammatory response contributes to the pathogenesis of acute pulmonary, cardiovascular, neurologic, splanchnic, hematologic, and immune system dysfunction following cardiac surgery. In addition, although less well documented, there is evidence to suggest that the inflammatory response contributes to the pathogenesis of subacute sequelae, such as postoperative fever,²¹¹⁻²¹⁵ postcardiotomy pericarditis,^{211,216} and pleural effusions after CPB.²¹⁷

Pulmonary. Acute lung injury, defined as the triad of hypoxemia ($\text{PaO}_2/\text{FiO}_2 \geq 300$), bilateral pulmonary infiltrates, and normal pulmonary capillary wedge pressure,²¹⁸ is a serious and poorly understood complication following cardiac surgery. The risk^{219,220} and severity²²¹ of ALI has been consistently linked to duration of CPB. Other issues related to CPB, such as the type of oxygenator used, may also contribute to the risk of ALI.^{178,222} Severe ALI following CPB, while relatively uncommon (1-3%),^{220,223} has been associated with a 50% mortality.²²⁰ Lesser degrees of lung injury, such as reduced oxygenation index, increased \dot{V}/\dot{Q} mismatch, decreased lung compliance, are seen in up to 12% of patients.^{96,219} Pulmonary injury is detectable even following uncomplicated CPB using sensitive measures of ALI, such as protein accumulation index and bronchoalveolar lavage neutrophil and myeloperoxidase concentrations.²²¹ Early pulmonary dysfunction after cardiac surgery increases morbidity, including renal, neurologic, and infectious complications, duration of mechanical ventilation, ICU and hospital stays, and risk of mortality.²¹⁹

The inflammatory response has deleterious effects on the pulmonary circulation^{107,108,224} and the lung parenchyma.¹⁰⁷ Several lines of evidence implicate the inflammatory response in the pathogenesis of postoperative pulmonary dysfunction. Histologic evidence demonstrates that CPB can cause profound pulmonary endothelial, epithelial, and interstitial damage.^{107,225} Up to 50% of circulating neutrophils are sequestered in pulmonary capillaries during rewarming, with subsequent degranulation contributing to pulmonary vascular endothelial damage.¹⁰⁸ Postoperative elevations of granulocyte elastase, an index of neutrophil lysosomal degranulation, correlate with deteriorations in the oxygenation index, alveolar-arterial gradient, and intrapulmonary shunt.^{96,226} Increases in pulmonary vascular permeability following CPB correlate with markers of lipid peroxidation and a reduction of plasma antioxidants, both indicators of an oxygen-radical-induced injury process.²²⁴

Strategies that attenuate the inflammatory response may reduce post-CPB ALI. While serum and alveolar proinflammatory mediator concentrations correlate with post-CPB pulmonary dysfunction,^{55,226} mechanical me-

diator removal may decrease lung injury.^{56,227} Leukocyte depletion during CPB,²²⁸ or blockade of neutrophil adhesion,^{111,229} attenuates postoperative lung dysfunction. Finally, inhibition of complement activation results in significant reduction of post-CPB ALI.²³⁰

Cardiovascular. Major perioperative cardiovascular complications (cardiac death, myocardial infarction, heart failure) occur in at least 10% of CABG patients.²³¹ The Multicenter Study of Perioperative Ischemia Research Group, in a multicenter study involving 566 patients after CABG, found that up to 25% fulfilled either electrocardiogram (*i.e.*, presence of Q waves), CK-MB fraction, or autopsy criteria for myocardial infarction.²³² Nearly 10% of patients had a Q-wave infarct, while 20.5% fulfilled CK-MB criteria for myocardial infarction.²³²

The inflammatory response may be involved in the pathogenesis of post-CPB cardiovascular dysfunction. Increased hemodynamic instability during cardiac surgery may result from systemic spillover of proinflammatory cytokines, such as IL-6.¹⁴⁹ Furthermore, there appears to be a clear link between CPB-induced inflammatory mediators and postbypass myocardial stunning, ischemia, and dysfunction, and β -adrenergic desensitization.^{233,234} TNF- α , IL-1 β , and IL-6 have been implicated in cardiac myocyte refractoriness to adrenergic stimulation following CPB.²³⁴ Myocardial performance in elderly patients after CPB is suppressed by TNF- α ,²⁵ while anti-TNF antibodies reverse the myocardial depression seen in sepsis.²³⁵ Left ventricular wall motion abnormalities and myocardial ischemic episodes after CPB correlate with IL-6 or IL-8 concentrations.²³³

Alterations in NO homeostasis may play an important role in the pathogenesis of cardiovascular events following cardiac surgery. The human myocardium constitutively produces NO *via* cNOS, and this is regulated by the contractile state of the heart,²³⁶ possibly by a β -adrenergic signaling pathway.²³⁷ This constitutively produced NO has important cardioprotective effects, including regulation of vascular tone (fig. 3), myocardial contractility,^{238,239} coagulation,²⁴⁰ and pulmonary endothelial function.⁸⁴ However, up-regulation of iNOS by proinflammatory cytokines following CPB may greatly increase myocardial NO production.²⁴¹ In this context, NO may have deleterious effects and contribute to postoperative myocardial dysfunction, particularly myocardial stunning.²⁴¹ IL-1 β up-regulates iNOS-mediated NO production²⁴² and has been demonstrated to depress myocardial contractility through a NO-dependent mechanism.⁶⁴ Mechanisms underlying NO-mediated myocardial dysfunction may include inhibition of mitochondrial activity,²⁴³ induction of adrenergic refractoriness,²³⁴ increased platelet adhesiveness,²⁴⁰ and peroxynitrite-induced cellular damage.⁶⁶

Neurologic. Neurologic complications increase perioperative morbidity following cardiac surgery, resulting in longer hospitalization, and may increase mortality up

to 10-fold.¹³ Focal cerebral deficits, such as transient ischemic attacks and stroke, occur in 1–3% of patients, while less severe clinical abnormalities, such as seizures, are observed in 5–10%.^{244,245} Postoperative neurologic dysfunction, including cognitive dysfunction and disability, unrelated to focal injury, is seen in 69% of patients immediately postoperatively and persists for at least 1 month in 36%.²⁴⁶ Patients with the apolipoprotein E- ϵ 4 allele²⁴⁷ or previous neurologic injury²⁴⁸ may be predisposed to neurologic complications after CPB. In the largest series to date, the mortality rate was 29% in patients with adverse cerebral complications.²⁴⁵

The inflammatory response plays a pivotal role in the pathogenesis of post-CPB neurologic injury. The role of endothelial dysfunction and the endothelial-neutrophil interaction in neurologic injury after CPB is well documented. Loss of cerebrovascular endothelial-mediated vasodilation may contribute to the pathogenesis of postoperative perfusion deficits.²⁴⁹ NO formed by up-regulation of neuronal NOS, *e.g.*, in response to glutamate, has been implicated as a potent neurotoxin in animal models of post-CPB neurologic injury.^{250,251}

Strategies that attenuate the inflammatory response may decrease neurologic injury. Experimental blockade of selectin adhesion molecules reduces cerebral injury in an animal model.²⁵² Aprotinin, a serine protease inhibitor with important hemostatic and antiinflammatory properties, decreases the incidence of stroke after CPB.²⁵³ Finally, heparin coating of CPB circuits, which improves its biocompatibility, thereby reducing contact activation of the inflammatory response, may reduce the incidence of neurologic dysfunction in humans.²⁵⁴

Renal. Perioperative renal dysfunction occurs in 7–13% of patients, with 1–1.5% requiring some form of dialytic therapy.^{18,255} Renal insufficiency following cardiac surgery increases ICU and hospital stay and greatly increases mortality (27% *vs.* 0.9%).¹⁸ The mortality rate for patients requiring postoperative dialysis ranges from 28–64%.^{18,255} The incidence of renal dysfunction is directly related to the duration of CPB.¹⁸

The role of the inflammatory response in the pathogenesis of renal dysfunction continues to be defined. Renal ischemic-reperfusion injury combined with the inflammatory response to CPB may be important causes of renal dysfunction after CPB. Hypoperfusion of the superficial renal cortex has been demonstrated during the rewarming phase of CPB in an animal model.²⁵⁶ The inflammatory response may exacerbate renal hypoperfusion, both indirectly as a result of hemodynamic instability, and directly *via* renal arteriolar vasoconstriction and altered intrarenal distribution of perfusion due to alterations in catecholamines and NO concentrations. TNF- α released during CPB induces glomerular fibrin deposition, cellular infiltration, renal cell apoptosis, and vasoconstriction, leading to a reduction in the glomerular filtration rate.¹⁷ Furthermore, anti-TNF- α strategies

have been proposed to reduce renal insufficiency after CPB.¹⁷

Hepatic. Hepatic dysfunction following CPB is common, with up to 47% of patients developing at least transient postoperative dysfunction.²⁵⁷ Postoperative hepatic dysfunction is related to the duration of CPB and may greatly increase mortality.²⁵⁸

The mechanism of hepatic injury after CPB and the role of the inflammatory response is not well characterized. Nevertheless, there is some evidence that the inflammatory response to CPB may play a role in hepatic injury. Hepatic ischemia-reperfusion injury may result from hepatic venous congestion during weaning from CPB.¹⁹ High concentrations of C3a and C4a have been associated with post-CPB liver dysfunction in humans.²⁵⁷ During hypothermic bypass, portal concentrations of endothelin-1, a potent vasoconstrictor, have been associated with decreased hepatic blood flow and post-CPB liver dysfunction in an animal model.²⁵⁹ In patients following CPB, hepatic perfusion may be decreased for up to 24 h.²² Finally, there is increasing evidence that cytokines TNF- α and IL-6 may contribute to the pathogenesis of hepatocellular dysfunction.²⁶⁰

Hemostatic. Cardiopulmonary bypass-induced hemostatic defects may contribute significantly to perioperative morbidity. Potential mechanisms include direct contact activation of the coagulation and fibrinolytic cascades by the bypass circuit, platelet dysfunction, and capillary leak due to endothelial damage. The inflammatory response may be central to the development of these hemostatic defects. The amount of postoperative blood loss has been correlated with degree of activation of the complement cascade.²⁶¹ Mechanical removal of cytokines, such as by hemofiltration, has been associated with a reduction in postoperative blood loss following cardiac surgery.⁵⁶

Cardiopulmonary bypass-associated impairment of platelet function may be cytokine mediated.²⁶² Endotoxin and IL-1 β stimulate the release of von Willebrand factor from the vascular endothelium, which may promote activation and localization of platelets and enhance thrombogenicity at inflammatory foci.²⁶³ Platelet activation during CPB may contribute, through IL-1 β release, to endothelial cell activation.²⁶² Preoperative harvest of platelet-rich plasma with reinfusion following CPB may result in significantly less pulmonary dysfunction and shorter ICU stays, in addition to improved hemostatic function.²⁶⁴ In addition, nonsurgical postoperative bleeding is correlated with both leukocyte count and the percentage change in leukocyte count over the course of CPB.²⁶⁵ Finally, CPB with more biocompatible circuits may decrease platelet activation, fibrinolysis, and thrombin generation and increase platelet preservation.²⁶⁶

Immunosuppression. Cardiopulmonary bypass-associated immunosuppression may play an important role in the development of postoperative infectious compli-

cations. Immunosuppression may result from a predominance of antiinflammatory cytokine production.⁷ Cell-mediated immunity is also altered with decreases in CD3+ T-lymphocyte and CD4+ T-helper cell counts,²⁶⁷ increases in CD8+ suppressor-cytotoxic T cells and monocyte counts,²⁶⁸ decreased lymphocyte responsiveness to mitogens, and suppression of the T-helper cell-induced cell-mediated inflammatory response after CPB.^{267,269} Pretreatment with indomethacin and thymopentin, which stimulates activation and differentiation of the T-lymphocytes, appears to restore certain aspects of this response.²⁶⁹ IL-10 may play a role in postoperative immunosuppression, with IL-10 gene expression correlating with decreased monocyte HLA-DR antigen expression in a study of patients undergoing major abdominal surgery.²⁷⁰ These alterations in the inflammatory response highlight the need to consider both the potential beneficial and adverse aspects of this response and further underline the clinical benefit of a balanced, controlled inflammatory response to CPB.

Therapeutic Strategies to Modulate the Inflammatory Response

The development of strategies to control the inflammatory response following cardiac surgery is currently the focus of considerable research efforts. Diverse techniques, including maintenance of hemodynamic stability, minimization of exposure to CPB circuitry, and pharmacologic and immunomodulatory agents have been examined in clinical studies. Table 5 summarizes the findings of recent randomized clinical trials in this field.

Risk Stratification

Accurate risk stratification would permit selective delivery of potentially useful therapies to those patients who might be expected to derive most benefit. Clinical risk assessment has taken the form of complex multivariate modelling.^{271,272} An approach that combines assessment of "fixed" baseline risk together with "dynamic" event-related risk related to adverse perioperative events probably holds most promise (fig. 6). In this regard, several key indices of the inflammatory response appear to predict postoperative morbidity following cardiac surgery and may help to further stratify patient risk. In the preoperative phase, elevation of C-reactive protein concentrations predicts a greater likelihood of septic complications and need for catecholamine therapy, longer duration of respiratory support, and increased duration of ICU stay,²⁷³ while low preoperative immunoglobulin M antiendotoxin core antibody concentrations independently predict poor postoperative outcome.²⁷ Postoperatively, early elevations in serum soluble TNF receptor-p55 concentrations in high-risk cardiac surgical patients

predicts increased mortality.²⁷⁴ Finally, the characterization of particular genotypes, such as apolipoprotein E- ϵ 4 allele,²⁴⁷ which predicts risk of post-CPB neurologic injury, is a novel approach that holds promise.

Novel Cardiac Surgical Techniques

Off-pump Coronary Artery Bypass Grafting. Concerns regarding complications and cost surrounding the use of CPB has led to renewed interest in off-pump coronary artery bypass grafting (OPCAB) techniques. Extensive observational data suggest a relation between poor outcome and the use of (1) aortic cross-clamping and concomitant global ischemia and reperfusion injury and (2) extracorporeal circulation. Avoidance of aortic cross-clamping and CPB may decrease the inflammatory response and improve postoperative organ function and patient outcome, particularly in high-risk patients.

Off-pump coronary artery bypass grafting does reduce the elaboration of key mediators of the systemic inflammatory response. OPCAB decreases concentrations of cytokines such as TNF- α ,^{275,276} IL-6,²⁷⁷ IL-8,²⁷⁶⁻²⁸⁰ IL-10,^{279,280} and TNFsr1 and 2.^{277,280} OPCAB attenuates the cellular inflammatory response, decreasing neutrophil and monocyte counts,²⁷⁸ neutrophil elastase,^{276,278,281} and E-selectin²⁷⁶ concentrations. Indices of complement activation, such as C3a^{276,281} and C5a,²⁸⁰ are decreased. In addition, OPCAB attenuates other indices, including platelet β -thromboglobulin²⁸¹ and procalcitonin.²⁸² Finally, OPCAB decreases reactive oxygen species-induced injury.²⁷⁶

The clinical trials reported to date suggest that OPCAB may attenuate indices of postoperative organ dysfunction but does not eliminate SIRS following cardiac surgery (table 5).^{276,278,281,283,284} Initial clinical experience with selected patients suggests reduced cardiovascular,^{275,279} pulmonary,²⁷⁵ neurologic,²⁸⁵ and hemostatic²⁷⁵ dysfunction, with decreased morbidity and shorter ICU and hospital stay.²⁷⁵ One retrospective study comparing elderly patients undergoing OPCAB to matched conventional controls indicated that OPCAB decreased postoperative cardiovascular complications and expedited ICU and hospital discharge.²⁸⁶ However, these trials were small, with enrollment restricted to low-risk patients, often with specific single or double vessel coronary lesions. There are no reported randomized trials of OPCAB in high-risk patients. A retrospective comparison of the first 55 patients who underwent OPCAB at Duke University Medical Center to a larger cohort who underwent conventional CABG failed to demonstrate a reduction in renal risk.²⁸⁷ Therefore, the short-term benefits of OPCAB remain to be convincingly demonstrated.

Minimally Invasive Cardiac Surgery. Advances in minimally invasive surgery in other areas, such as laparoscopic and thoracoscopic procedures, have prompted interest in approaches that avoid full median sternotomy.²⁸⁸ Minimally invasive cardiac surgery techniques

Table 5. Recent (post-1995) Randomized Controlled Clinical Trials and Meta-analyses of Interventions to Attenuate the Inflammatory Response to Cardiac Surgery, Which Incorporate Assessment of Clinically Relevant Endpoints

Study	Intervention (n per group)	Main Results
Novel CABG techniques		
Ascione <i>et al.</i> , ²⁸³ 2000	CABG with CPB (30) <i>versus</i> off-pump CABG (30) in low-risk patients	Off-pump CABG group had shorter intubation time and length of ICU and hospital stay, lower incidence of postoperative total and pulmonary infection, and lower blood loss and transfusion requirements.
Cox <i>et al.</i> , ²⁸⁴ 2000	CABG with CPB (26) <i>versus</i> off-pump CABG (26) in low-risk patients	Off-pump group had decreased total postoperative respiratory complications [combined chest infection, pneumothorax, lung collapse] and reduced postoperative blood loss. No intergroup difference in degree of pulmonary dysfunction, as assessed by alveolar-arterial oxygen gradient.
Matata <i>et al.</i> , ²⁷⁶ 2000	CABG with CPB (10) <i>versus</i> off-pump CABG (10) in low-risk patients with single or double vessel disease	Off-pump CABG group had shorter duration of mechanical ventilation, less postoperative blood loss, less postoperative fever. No intergroup difference in length of hospital stay.
Richter <i>et al.</i> , ²⁹¹ 2000	CABG with full CPB (15) <i>versus</i> CABG (15) using lungs as oxygenator in low-risk patients	Lung oxygenator group had decreased pulmonary [PaO ₂ , A-ao ₂ gradient, intrapulmonary shunt, respiratory index, duration of endotracheal intubation] and hemostatic [postoperative blood loss, allogenic blood transfusion] dysfunction.
Ascione <i>et al.</i> , ²⁷⁸ 1999	CABG with CPB (25) <i>versus</i> off-pump CABG (25) in low-risk patients	Off-pump CABG group had improved maintenance of renal function [creatinine clearance; urinary microalbumin/creatinine ratio; N-acetyl glucosaminidase activity]; decreased blood loss; decreased blood, platelet, and plasma transfusion; decreased ICU and hospital stay.
Gu <i>et al.</i> , ²⁸¹ 1998	CABG with CPB (31) <i>versus</i> off-pump CABG (31) in low-risk patients with isolated LAD stenosis	Off-pump group had shorter duration of surgical procedure, less blood, shorter ventilatory support, and a shorter postoperative hospital stay.
Thoracic epidural anesthesia		
Loick <i>et al.</i> , ¹³¹ 1999	Thoracic epidural anesthesia (25) <i>versus</i> clonidine (24) <i>versus</i> control [no intervention] (21) in low-risk CABG patients	Thoracic epidural anesthesia group had decreased myocardial injury [lower troponin T]; decreased myocardial ischemia [ST-segment changes]; decreased stress response [plasma epinephrine]; and decreased pulmonary injury [decreased duration of tracheal intubation].
CPB temperature		
Ohata <i>et al.</i> , ¹⁷⁴ 1997	CPB at 34°C (10) <i>versus</i> CPB at 34°C (8) in low-risk CABG patients	Tepid CPB [34°C] group had decreased pulmonary injury [lower respiratory index; decreased duration of tracheal intubation].
Heparin-coated circuits		
Belboul <i>et al.</i> , ²⁹⁵ 2000	HCCs (20) <i>versus</i> conventional circuits (19) in low-risk CABG patients	HCC group had decreased myocardial injury [CK-MB concentrations]; decreased plasma hemoglobin. No intergroup difference in postoperative blood loss, duration of mechanical ventilation, ICU or hospital stay.
Grossi <i>et al.</i> , ⁴³² 2000	HCCs (11) <i>versus</i> conventional circuits (12) in pediatric patients	HCC group had improved pulmonary [lower postoperative peak airway pressure] and coagulation [prothrombin time] function.
Ranucci <i>et al.</i> , ⁴⁹ 1999	Durafllo II HCCs (442) <i>versus</i> conventional circuits (444) in medium- to high-risk patients	HCC group had shorter length of ICU and hospital stay, lower rate of postoperative morbidity or death. No intergroup difference in duration of mechanical ventilation. Subgroup analysis showed less renal dysfunction in diabetic patients, and less lung dysfunction in patients with COPD or post-mitral valve procedure.

(continues)

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; ICU = intensive care unit; PaO₂ = arterial oxygen tension; A-ao₂ gradient = alveolar-arterial gradient for oxygen; LAD = left anterior descending artery; HCC = heparin-coated circuit; CK-MB = creatine kinase myocardial isozyme; COPD = chronic obstructive pulmonary disease; IABP = intraaortic balloon pump; pHi = gastric intramucosal pH; SvO₂ = mixed venous oxygen saturation; CO = cardiac output; GIT = gastrointestinal tract; AVR = aortic valve replacement; MVR = mitral valve replacement; CI = cardiac index; LVEF = left ventricular ejection fraction; HR = heart rate; MAP = mean arterial pressure; Hb = hemoglobin; PCWP = pulmonary capillary wedge pressure; CNS = central nervous system; MI = myocardial infarction; APACHE = Acute Physiology and Chronic Health Evaluation; NAC = N-acetyl cysteine; SVRI = Systemic Vascular Resistance Index; PIP = peak inspiratory pressure; IL = interleukin.

Table 5. (continued)

Study	Intervention (n per group)	Main Results
Shimamoto <i>et al.</i> , ²⁹⁹ 2000	Group A (10), HCC with silicone-coated oxygenator; group B (11), whole HCC; group C (11), conventional circuit; in low-risk patients	Group A: A-ao ₂ gradients and respiratory index better than control. Group B: A-ao ₂ gradient was better than control. Duration of intubation and the length of ICU stay shorter in groups A and B than in group C. Silicone-coated oxygenator superior to heparin-coated oxygenator.
Wan <i>et al.</i> , ³⁰⁰ 1999	Durafluo II HCCs (14) <i>versus</i> conventional circuits (15) in patients undergoing heart or heart-lung transplants	HCC group had less myocardial injury [cardiac troponin I]. No intergroup difference in postoperative blood loss and transfusion, duration of mechanical ventilation, length of ICU stay, or mortality.
Videm <i>et al.</i> , ²⁹⁸ 1999	Durafluo II HCCs (81) <i>versus</i> conventional circuits (75) in high-risk patients	No intergroup difference in postoperative blood loss, duration of mechanical ventilation, organ dysfunction, infection or reoperation rates, or mortality.
Wildevuur <i>et al.</i> , ²⁹⁷ 1997	Durafluo II HCCs (398) <i>versus</i> conventional circuits (407) in low-risk CABG patients	Wide variability among study centers. No intergroup difference in postoperative: blood loss, transfusion requirements; myocardial infarction; neurologic, respiratory, renal or hepatic dysfunction; ICU stay; morbidity or mortality. On analysis of subgroups with higher morbidity, HCC was beneficial in females [lower blood product use, earlier tracheal extubation, fewer arrhythmias] and patients with long aortic cross-clamp time [shorter ICU stay; trend to less IAPB use].
Jansen <i>et al.</i> , ²⁵⁴ 1996	HCCs (51) <i>versus</i> conventional circuits (51) with aprotinin prime in low-risk patients receiving aspirin	HCC group had shorter ICU stay and lower overall risk for adverse events [combined incidence cardiac, coagulation, respiratory, neurologic dysfunction]. No intergroup difference in postoperative blood loss, transfusion requirements, vasoactive medication support, or duration of endotracheal intubation.
Selective digestive decontamination		
Nathens <i>et al.</i> , ³⁰⁸ 1999	Meta-analysis of SDD, subanalysis of SDD in low-risk cardiac surgical patients	SDD in cardiac surgical patients reduced incidence of infection but did not alter mortality in a group of patients with low baseline mortality rate.
Martinez-Pellus <i>et al.</i> , ²³ 1997	SDD (50) <i>versus</i> control (50) in low-risk patients	SDD group had attenuation of the decrease in gastric pH _i . No change in rate of fever, respiratory or coagulation dysfunction, sepsis-like syndrome, or duration of ICU stay.
Hemodynamic optimization		
Pölonen <i>et al.</i> , ³²¹ 2000	Hemodynamic goal-directed therapy (196) [maintain Svo ₂ > 70%; lactate ≤ 2.0 mm] <i>versus</i> conventional therapy (197)	Similar intergroup length of ICU stay. Median hospital stay was shorter and incidence of organ dysfunction was lower in the protocol group. Trend to reduced mortality in protocol group.
Christenson <i>et al.</i> , ³²⁷ 1999	Preoperative IAPB (30) <i>versus</i> conventional therapy (30) in high-risk CABG patients, preoperative IAPB subgroups: 2 h (10), 12 h (10), and 24 h (10) prior to aortic cross-clamp	Preoperative IABP group had lower incidence of postoperative low CO; shorter intubation time and length of ICU and hospital stay. Trend toward lower mortality in IABP group. There were no differences between the IABP subgroups, with 2 h counterpulsation equally effective. The overall IABP complication rate was 8.3%.
Mollhoff <i>et al.</i> , ²⁴ 1999	Milrinone [30 μg/kg bolus; 0.5 μg · kg ⁻¹ · min ⁻¹] (11) <i>versus</i> placebo (11) in low-risk CABG patients	Milrinone attenuated the decrease in splanchnic oxygenation [gastric pH _i] and preserved gut barrier function [hepatic venous endotoxin] but had no effect on renal function [creatinine clearance].
Berendes <i>et al.</i> , ³²⁵ 1997	Dopexamine 0.5 (10), 1.0 (10), or 2 μg · kg ⁻¹ · min ⁻¹ (10) <i>versus</i> placebo (14) in low-risk CABG patients	Dopexamine preserved renal function [creatinine clearance]; but had no effect on splanchnic oxygenation [gastric pH _i , hepatic venous oxygen saturation] or pulmonary function [shunt fraction].
Loick <i>et al.</i> , ⁴³³ 1997	Enoximone [0.2-mg/kg bolus; 5 μg · kg ⁻¹ · min ⁻¹] (10) <i>versus</i> placebo (11) in low-risk CABG patients	Enoximone preserved gut barrier function [hepatic venous endotoxin] but had no effect on splanchnic oxygenation [gastric pH _i].
Sinclair <i>et al.</i> , ³²⁶ 1997	Dopexamine [2.0 μg · kg ⁻¹ · min ⁻¹] (14) <i>versus</i> dopamine [2.5 μg · kg ⁻¹ · min ⁻¹] (16) in low-risk CPB patients	Dopexamine reduced GIT permeability <i>versus</i> dopamine following CPB. No intergroup difference in pH _i .

(continues)

Table 5. (continued)

Study	Intervention (n per group)	Main Results
Mythen <i>et al.</i> , ³¹⁸ 1995	Perioperative plasma volume expansion protocol (30) <i>versus</i> conventional therapy (30) in low-risk patients [CABG, AVR, MVR]	Plasma volume expansion with colloid reduced the incidence of splanchnic dysoxia [gastric pH], reduced ICU and hospital stay, and decreased major complication rate [single or multiple organ dysfunction].
Parviainen <i>et al.</i> , ⁴³⁴ 1995	Dobutamine [3.5–5.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$] (11) <i>versus</i> placebo (11) in postoperative CABG patients with $\text{CI} > 2 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$	Dobutamine decreased splanchnic oxygenation [gastric pH].
Hemofiltration Boga <i>et al.</i> , ³³⁵ 2000	Modified hemofiltration (20) <i>versus</i> control [no intervention] (20) in low-risk adults for CABG	In the hemofiltered group cardiac output, cardiac index, and systemic vascular resistance values were significantly greater in the early postoperative period only. Hemofiltered group required less allogeneic blood postoperatively. No mortality or organ dysfunction in either group.
Bando <i>et al.</i> , ³³¹ 1998	Dilutional ultrafiltration during CPB and venovenous modified ultrafiltration after CPB (50) <i>versus</i> control group (50) [conventional ultrafiltration] during CPB in pediatric patients with complex congenital heart disease	Overall, modified ultrafiltration attenuated pulmonary [reduced duration of ventilatory support] and coagulation [decreased blood and coagulation factor transfusion] dysfunction, and decreased ICU stay. Preoperative pulmonary hypertension: modified ultrafiltration reduced postoperative pulmonary arterial pressure, attenuated pulmonary [PaO_2 , reduced duration of ventilatory support] coagulation [decreased postoperative blood loss and blood and coagulation factor transfusion] dysfunction; led to earlier chest tube removal; and decreased ICU stay. Neonates: Modified ultrafiltration attenuated pulmonary [reduced duration ventilatory support] and coagulation [decreased coagulation factor transfusion] dysfunction; and decreased ICU stay. Prolonged CPB: Modified ultrafiltration attenuated pulmonary [reduced duration ventilatory support] and coagulation [decreased blood and coagulation factor transfusion] dysfunction; and decreased ICU stay.
Bando <i>et al.</i> , ³³⁰ 1998	Dilutional and modified ultrafiltration (12) <i>versus</i> conventional ultrafiltration (12) in pediatric patients with pulmonary hypertension at end of CPB	Dilutional and modified ultrafiltration group decreased pulmonary [PaO_2 , duration of ventilatory support] and coagulation [less requirements for platelets and fresh frozen plasma] dysfunction; decreased pulmonary/systemic pressure ratio; and tended toward less pulmonary hypertensive crises.
Davies <i>et al.</i> , ³³³ 1998	Modified ultrafiltration (MUF) (11) <i>versus</i> control [no intervention] (10) in infants at end of CPB	Modified ultrafiltration improved intrinsic left ventricular systolic function, improved diastolic compliance, increased blood pressure, and decreased inotrope use in the early postoperative period. However, no intergroup difference in mortality, duration of ventilatory support, or ICU stay.
Babka <i>et al.</i> , ³³⁴ 1997	Conventional ultrafiltration (30) <i>versus</i> control [no intervention] (30) in adults for CABG	No intergroup difference in postoperative blood loss, blood transfusion requirements, length of hospital stay, or patient cost.
Journois <i>et al.</i> , ⁵⁶ 1996	High volume, zero balanced hemofiltration (10) <i>versus</i> standard hemofiltration (10) in pediatric patients at end of CPB	High volume, zero balanced hemofiltration decreased pulmonary (decreased A-a gradient and time to extubation) and coagulation (decreased postoperative blood loss) dysfunction and incidence of pyrexia.
Leukocyte depletion Roth <i>et al.</i> , ¹¹² 2000	Leukocyte depletion of blood cardioplegia (17) <i>versus</i> control [dummy filters] (15) in adult CABG patients with left ventricular dysfunction	Leukocyte depletion of blood cardioplegia attenuated myocardial injury [troponin T concentrations] and improved early myocardial function [LVEF; use of inotropes]; no effect on postoperative hemodynamics [HR, MAP, CI].
Baksaas <i>et al.</i> , ³⁴² 1999	Leucocyte depletion (20) <i>versus</i> control [standard arterial line filter] (20) following release of aortic cross-clamp in low-risk elective CABG patients	Leukocyte depletion following cross-clamp release did not decrease pulmonary [duration of mechanical ventilation] or hemostatic [mediastinal drainage; postoperative Hb; autologous blood retransfused] dysfunction.
Gu <i>et al.</i> , ³³⁷ 1999	Leukocyte depletion (20) after rewarming, through the venous bypass circuit <i>versus</i> control (20) in adult patients for CABG/heart valve or combined operations	Feasibility study with no significant intergroup difference in clinical parameters. Trend to attenuation of pulmonary dysfunction [postoperative PaO_2 , duration of endotracheal intubation] and reduced hospital stay.

(continues)

Table 5. (continued)

Study	Intervention (n per group)	Main Results
van de Watering <i>et al.</i> , ³⁴⁶ 1998	Freshly leukocyte-depleted (305) <i>versus</i> stored leukocyte-depleted (303) <i>versus</i> non-leukocyte-depleted (306) transfused blood in adult patients for CABG/heart valve or combined operations	Leukodepletion of transfused blood significantly reduced the overall 60-day mortality; dramatic reduction in death from MODS; reduced postoperative infection rate in patients who received more than 3 units of blood.
Hurst <i>et al.</i> , ³⁴¹ 1997	Neutrophil-specific (11) <i>versus</i> standard blood filter (13) during CPB for adult elective open heart valve surgery	No significant intergroup difference in clinical parameters, including respiratory [Pao ₂ , lung function tests] or cardiovascular [CI, LVEF, hemodynamic variables, use of inotropes] dysfunction, or in duration of ICU or hospital stay.
Gu <i>et al.</i> , ²²⁸ 1996	Leukocyte depletion (20) of residual heart-lung machine blood at the end of CPB <i>versus</i> control [no intervention] (10)	Leukocyte depletion improved postoperative lung gas exchange. No intergroup difference in pulmonary hemodynamics, postoperative blood loss, or duration of intubation, ICU, or hospital stay.
Morioka <i>et al.</i> , ³³⁹ 1996	Leukocyte and platelet depletion (21) from start of surgery to 60 min after aortic clamp release <i>versus</i> control [no intervention] (21) in adult patients for CABG or heart valve surgery	Leukocyte and platelet depletion attenuated postoperative respiratory dysfunction [A-a gradient; respiratory index]. Most benefit on subgroup analysis in patients with lower preoperative Po ₂ and long CPB time.
Sawa <i>et al.</i> , ³⁴⁴ 1996	Leukocyte-depleted terminal blood cardioplegia (10) <i>versus</i> terminal blood cardioplegia (10) <i>versus</i> whole blood cardioplegia (10) in patients with left ventricular hypertrophy undergoing heart valve surgery	Leukodepletion of terminal blood cardioplegia decreased myocardial injury [histologic indices; CK-MB concentrations] and improved cardiac function [less inotropic support]; no effect on postoperative hemodynamics [CI; PCWP].
Johnson <i>et al.</i> , ³³⁸ 1995	Leukocyte-specific (16) <i>versus</i> standard blood filter (16) in adult CABG patients	Leukocyte depletion resulted in transient (< 24 h) improvements in pulmonary [intrapulmonary shunt] and cardiovascular [MAP] function.
Plateletpheresis Christenson <i>et al.</i> , ²⁶⁴ 1996	Preoperative platelet-rich plasma harvest with reinfusion after CPB (20) <i>versus</i> control [no harvest] (20) in patients undergoing CPB for repeat CABG	Plateletpheresis attenuated pulmonary dysfunction [improved gas exchange; decreased duration of mechanical ventilation]; decreased ICU stay; improved hemostatic function [decreased blood loss; decreased blood transfusions].
Aprotinin Rahman <i>et al.</i> , ³⁶⁰ 2000	Pump prime aprotinin [2 million units] (10) <i>versus</i> saline (10) in low-risk patients undergoing CPB for CABG	Aprotinin attenuated lung injury [A-ao ₂ gradient; lung neutrophil accumulation] following CPB.
Gott <i>et al.</i> , ³⁵⁵ 1998	Standard [roller pump, membrane oxygenator, methylprednisolone] therapy (112) <i>versus</i> aprotinin, [standard plus aprotinin] (109) <i>versus</i> leukocyte depletion, [standard plus leukocyte filtration] (112) <i>versus</i> biocompatible [heparin-bonded circuitry, centrifugal pumping with surface modification] (67)	No significant intergroup difference in morbidity [CNS, cardiac, pulmonary, renal, hematologic, infection], transfusion requirements, or mortality. Multivariate analysis: In low-risk patients, leukocyte filtration reduced length of hospital stay and cost. In high-risk patients, aprotinin reduced length of hospital stay and cost.
Lemmer <i>et al.</i> , ³⁵⁶ 1996	High dose (173) <i>versus</i> low dose (180) <i>versus</i> pump prime-only (173) doses of aprotinin <i>versus</i> placebo (178) in low-risk CABG patients	Aprotinin reduced bleeding and transfusion requirements. No between-group differences in mortality or the incidences of renal failure, strokes, or definite myocardial infarctions. Pump prime-only dose was associated with a small increased incidence of MI.
Levy <i>et al.</i> , ²⁵³ 1995	High-dose aprotinin (61) <i>versus</i> low-dose aprotinin (60) <i>versus</i> pump prime aprotinin (68) <i>versus</i> placebo (65) in patients for repeat CABG	High- and low-dose aprotinin reduced need for blood and blood product transfusion, and reduced incidence of stroke. No intergroup difference in rate of MI, cardiovascular complications renal dysfunction, or mortality.
Wendel <i>et al.</i> , ³⁵⁴ 1995	High-dose aprotinin (20) <i>versus</i> placebo (20)	Aprotinin decreased postoperative myocardial injury [troponin T concentrations].
Pentoxifylline Hoffmann <i>et al.</i> , ³⁷⁰ 1998	Pentoxifylline (15) <i>versus</i> placebo (25) in high-risk patients [APACHE score ≥ 19 on first postoperative day] after major cardiovascular surgery (> 90% cardiac)	Pentoxifylline decreased duration of mechanical ventilation, decreased the incidence of renal dysfunction and need for hemofiltration/dialysis and length of ICU stay. There was no intergroup difference in duration of hospital stay or mortality.

(continues)

Table 5. (continued)

Study	Intervention (n per group)	Main Results
Kleinschmidt <i>et al.</i> , ³⁷² 1997	Intraoperative pentoxifylline (15) <i>versus</i> γ -hydroxybutyrate (15) <i>versus</i> placebo (15) in low-risk CABG patients	No intergroup difference in renal glomerular or tubular function up to 24 h postoperatively.
Antioxidant vitamins		
Westhuyzen <i>et al.</i> , ¹⁵ 1997	Preoperative vitamin C plus E (38) <i>versus</i> placebo (38) in low-risk CABG patients	No intergroup difference in myocardial injury [CK-MB concentrations, thallium 201 uptake, electrocardiography].
Sisto <i>et al.</i> , ³⁸⁴ 1995	I: preoperative regimen vitamins C and E plus allopurinol (20) <i>versus</i> control (25) in stable CABG patients; II: shorter preoperative regimen vitamins C and E plus allopurinol (17) <i>versus</i> control (19) in unstable CABG patients	I: Preoperative supplementation resulted in decreased cardiovascular dysfunction [fewer ischemic events] in stable patients. II: Preoperative supplementation resulted in decreased cardiovascular dysfunction [fewer ischemic events; fewer arrhythmias; less dopamine support] and less myocardial injury [less CK-MB release] in unstable patients.
N-acetyl cysteine		
De Backer <i>et al.</i> , ³⁸⁶ 1996	Preoperative NAC (10) <i>versus</i> placebo (8) in low-risk CABG patients	NAC attenuated postoperative lung dysfunction [Pao ₂ /Fio ₂ ratio].
Allopurinol		
Coetzee <i>et al.</i> , ³⁹² 1996	Preoperative allopurinol (29) <i>versus</i> placebo (23) in low-risk CABG patients	No intergroup difference in left ventricular stroke work index or need for vasoactive drugs. No deaths in either group.
Castelli <i>et al.</i> , ³⁹⁰ 1995	Pre-CPB allopurinol (18) <i>versus</i> placebo (15) in low-risk CABG patients	Allopurinol attenuated early postoperative cardiac dysfunction [cardiac output, left ventricular stroke work] and reduced myocardial injury [CK-MB concentrations]. No intergroup difference in perioperative MI, inotropic support, or mortality.
Steroids		
Tassani <i>et al.</i> , ⁴⁰⁴ 1999	Methylprednisolone (26) <i>versus</i> placebo (26) before CPB in CABG patients	Methylprednisolone attenuated indices of pulmonary [PO ₂ ; lung compliance; A-a gradient], cardiac [HR, MAP, CI, SVRI], coagulation [postoperative blood loss], and renal [urine output] dysfunction. No intergroup difference in duration of endotracheal intubation, or in duration of ICU or hospital stay.
Wan <i>et al.</i> , ³⁹⁹ 1999	Methylprednisolone (10) <i>versus</i> placebo (10) before CPB in CABG patients	Methylprednisolone reduced inferior vena cava endotoxin concentrations during and after CPB. No intergroup difference in pulmonary [length of ventilatory support], cardiac [CK-MB], coagulation [postoperative blood loss] indices, or in length of ICU stay.
Yilmaz <i>et al.</i> , ⁴⁰⁷ 1999	Low-dose methylprednisolone (10) <i>versus</i> placebo (10) into the pump prime solution in low-risk CABG patients	Pump prime methylprednisolone attenuated myocardial injury [CK-MB concentrations]; however, no difference in postoperative LV ejection fraction. No intergroup difference in duration of mechanical ventilation, ICU or hospital stay, morbidity, or mortality.
Hill <i>et al.</i> , ⁴⁰⁶ 1995	Methylprednisolone (16) <i>versus</i> placebo (11) before CPB in low-risk CABG patients	No intergroup difference in reported indices of pulmonary [A-aO ₂ gradient, PIP] or cardiac [pulmonary artery pressure, CI] dysfunction.
Kawamura <i>et al.</i> , ⁴⁰⁵ 1995	Methylprednisolone (16) <i>versus</i> placebo (11) before CPB plus pre-declamping of aorta in low-risk CABG patients	Methylprednisolone attenuated early postoperative cardiac dysfunction [CI, PCWP]. No intergroup difference in myocardial injury [CK-MB concentrations] or catecholamine requirements. Negative correlation between IL-8 and CI.
Antimediator therapies		
Fitch <i>et al.</i> , ⁵⁰ 1999	Humanized anti-C5 antibody administered before CPB, phase 1 [n = 3 + 1 placebo] received increasing doses of anti-C5 [0.2, 0.5, 1, 2 mg/kg]; phase 2 [n = 6] received placebo, 1.0 or 2.0 mg/kg	Dose-dependent reduction in myocardial [CK-MB] injury, and in CNS [cognitive deficits] and coagulation [postoperative blood loss] dysfunction.

may be utilized in the presence or absence of CPB. The surgical incision may affect the inflammatory response generated, with reduced complement activation following limited anterolateral thoracotomy as opposed to median sternotomy,²⁸⁹ although this is disputed.²⁸⁰ One nonrandomized study of patients undergoing mitral valve surgery *via* limited right anterolateral thoracotomy

and port access suggested that this group resumed work or normal activity earlier than comparable patients undergoing conventional median sternotomy.²⁹⁰ However, the efficacy of minimally invasive cardiac surgery remains to be clearly demonstrated. At present, operating times are considerably longer with minimal access techniques.²⁹⁰

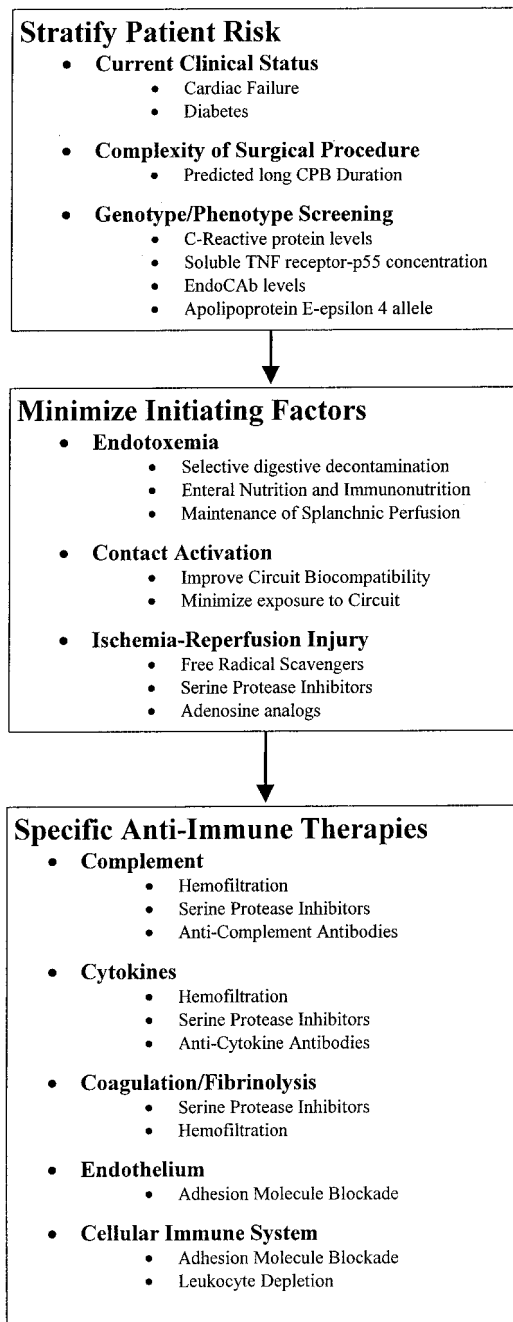


Fig. 6. Schematic diagram of potentially useful strategies and therapies that may allow the clinician to control and modulate the inflammatory response to cardiac surgery.

Drew-Anderson Technique. An intermediate, less invasive approach may be to use the patient's own lungs as an oxygenator *via* bilateral extracorporeal circulation. This technique, introduced by Drew and Anderson, allows good surgical access yet avoids the need for an artificial oxygenator. A recent randomized clinical trial, focusing on this method as a means of attenuating the inflammatory response, reported decreased concentrations of IL-6 and IL-8 and an attenuation of postoperative hemostatic and pulmonary dysfunction (table 5).²⁹¹

Summary. Since aortic cross-clamping and CPB were universally used for all forms of cardiac surgery, their relative role in the pathogenesis of postoperative complications has been unclear. OPCAB will help to delineate the intrinsic effects of bypass on the inflammatory response to cardiac surgery. OPCAB and minimally invasive cardiac surgery have demonstrated encouraging short-term benefits in the small-scale clinical studies of low-risk patients carried out to date, but clinical studies have not been carried out in the high-risk groups most likely to benefit. Finally, concerns regarding the quality of graft anastomoses achieved with OPCAB or minimal access techniques remain to be addressed.

Strategies to Improve Biocompatibility of the Extracorporeal Circuit

Improving the biocompatibility of the CPB circuit in order to reduce contact activation of the immune system, particularly the complement cascade, may be a useful strategy to limit the inflammatory response. Potential approaches include use of more biocompatible materials in the circuit or modifications of the surface of the circuit by coating with compounds that are less immunogenic.

Heparin-coated Circuits. Heparin-coated CPB circuits (HCCs) enhance biocompatibility, reduce contact activation, and may decrease postoperative cardiovascular, respiratory, hemostatic, and neurologic dysfunction.²⁵⁴ The method by which the circuit is coated and the type of heparin used may have implications for its effects on the coagulation and complement systems. The Duraflo II HCC, which uses ionically bonded unfractionated heparin (Duraflo II surface; Baxter Healthcare Corp., Irvine, CA), reduces kallikrein and complement activation⁴⁹ but is less effective in attenuating coagulation or fibrinolysis.²⁹² The Carmeda Bioactive Surface system (CBAS; Medtronic Inc., Minneapolis, MN) uses end-attached covalently bonded heparin that has been fragmented by treatment with nitric acid. The Carmeda circuit appears superior to the Duraflo II in reducing complement,²⁹³ neutrophil²⁹⁴ activation, and endothelin-1 concentrations.²⁹⁴

Clinical studies to date suggest that the beneficial effects of HCCs are confined to high-risk patients (table 5). In low-risk patients, HCCs decrease neutrophil activation,²⁹⁵ decrease myocardial injury,²⁹⁵ and reduce complement activation.²⁹⁶ The largest study to date in low-risk patients revealed no overall clinical benefit,²⁹⁷ although subgroup analysis suggested that women and patients with prolonged aortic cross-clamp times may benefit from HCC.²⁹⁷ Duraflo II HCCs decreased the duration of ventilatory support and ICU stay and reduced the incidence of poor outcome (death or prolonged ICU stay) in a large study of high-risk patients.⁴⁹ However, a similar but smaller study failed to confirm these benefits.²⁹⁸ The benefits of HCC-based technology may be

more apparent in patients with preexisting organ dysfunction.⁴⁹ Outcome may be enhanced when Duraflow HCCs are combined with the use of silicone-coated oxygenators.²⁹⁹ HCC may attenuate the proinflammatory response more markedly and may have greater myocardial protective effects where perfusion times are prolonged, especially in heart and heart-lung transplantation.³⁰⁰

Other Strategies. Other strategies to improve biocompatibility having therapeutic potential include coating of circuitry with phosphatidylcholine,³⁰¹ silicone,³⁰² synthetic proteins³⁰³ and polymers,³⁰⁴ or surface-modifying additives.^{305,306} Decreasing oxygenator surface area may also decrease activation of the inflammatory response.³⁰⁷

Strategies to Reduce Endotoxemia

Selective Digestive Decontamination. Selective digestive decontamination (SDD) is a technique to reduce the gut content of enterobacteria. This is achieved by preoperative administration of oral nonabsorbable antibiotics such as polymyxin E, tobramycin, and amphotericin B, and has been demonstrated to reduce plasma concentrations of endotoxin, TNF- α , and IL-6 in patients undergoing CPB.²³ A recent metaanalysis of SDD suggests that it reduces rates of postoperative infection, but not mortality, in patients undergoing cardiac surgery.³⁰⁸ Since mortality reduction with SDD in critically ill patients appears to be related to baseline mortality risk,³⁰⁹ trials of SDD in cardiac surgery thus far contain too many low-risk patients, resulting in inadequate study power. SDD may prove worthwhile in high-risk cardiac surgical patients,³⁰⁸ but since its use raises both practical issues (notably the logistics of performing it) and theoretical concerns (changes in bacterial flora, emergence of resistance), its adoption is unlikely pending further studies.

Enteral Nutrition and Immunonutrition. Hypoalbuminemia and low body mass index independently predict increased morbidity and mortality after cardiac operations.³¹⁰ In an early study, well-nourished patients undergoing valve surgery had a much shorter hospital stay compared to those with preoperative malnutrition.³¹¹ Laboratory evidence in animals suggests that protein-calorie malnutrition decreases left ventricular function³¹² and that myocardial glycogen concentration correlates with left ventricular function following CPB.³¹³

The beneficial role of early institution of enteral nutrition, particularly "immunonutrition," which contains supplements such as arginine, purine nucleotides, and ω -3 fatty acids, which are considered to enhance immune function, has been established in other groups of postoperative and critically ill patients. In critically ill patients, immunonutrition reduced the duration of ICU and hospital stay, infectious complications, duration of SIRS, and mechanical ventilation compared to patients receiving conventional nutrition.³¹⁴ In patients for elec-

tive gastrointestinal surgery, preoperative and postoperative immunonutrition has beneficial effects on immune function, complication rate, and duration of hospital stay.^{315,316} The use of glutamine supplementation may improve survival of patients with organ failure who require parenteral nutrition.³¹⁷

There is no information available concerning the effect of nutritional support in patients undergoing cardiac surgery who have a complicated postoperative course.

Strategies to Maintain Hemodynamic Stability and Organ Perfusion

Perioperative hemodynamic instability, especially post-CPB low cardiac output syndrome, is a marker for later adverse outcome and death. Splanchnic perfusion abnormalities, as measured by tonometrically derived intramucosal pH and Pco₂, strongly predict postoperative morbidity in cardiac surgical patients.¹³⁰ Covert hypovolemia may exacerbate splanchnic hypoperfusion during and after CPB, and this may be treatable by increasing intravascular volume. Other therapeutic options include pharmacologic and mechanical circulatory support.

Optimization of intravascular volume status may be beneficial even in apparently stable patients.³¹⁸ In low-risk cardiac surgical patients, intraoperative intravascular volume expansion with the objective of maximizing stroke volume resulted in improved gastric intramucosal pH values, less hemodynamic interventions, lower complication rates, and shorter ICU and hospital stay.³¹⁸ Furthermore, low intraoperative filling pressures and high pressor usage may contribute to increased gut permeability and endotoxemia.³¹⁹ Excessive hemodilution during CPB may play a role in the pathogenesis of post-CPB low cardiac output syndrome. In a multicenter observational study, excessively low hematocrit values during CPB independently predicted in-hospital mortality, need for intraaortic balloon pump usage, and return to bypass following failed separation.³²⁰

There are no outcome-based data to support the routine use of pharmacologic interventions to maximize splanchnic perfusion in patients undergoing cardiac surgery. However, patients failing to meet preset hemodynamic goals may benefit from such measures. In a recent randomized trial in which early postoperative cardiovascular function was optimized, using preload augmentation and dobutamine to normalize mixed venous oxygen saturation values and lactate concentration, optimized patients had reduced length of hospital stay and reduced organ dysfunction at the time of discharge compared with patients receiving standard care.³²¹ Pharmacologic interventions to maximize splanchnic perfusion may attenuate the inflammatory response. Immune cells contain type IV and type III phosphodiesterase,³²² and phosphodiesterase inhibitors appear to directly limit inflammatory activation and organ dysfunction in sepsis models.^{322,323} Milrinone attenuates the reduction in gas-

tric intramucosal pH, reduces both venous and hepatic endotoxin concentrations, and may decrease postoperative IL-6 concentrations in healthy patients undergoing cardiac surgery,²⁴ although this has been disputed.³²⁴ Dopexamine attenuates the postoperative increase in IL-6 concentrations³²⁵ and reduces gastrointestinal permeability,³²⁶ but does not improve splanchnic perfusion (as measured by intramucosal pH) or decrease plasma endotoxin concentrations,³²⁵ following CPB.

The elective use of mechanical circulatory support, such as preoperative intraaortic balloon pump, in selected high-risk patients, especially the elderly^{327,328} and those with severe left ventricular dysfunction,³²⁹ may reduce the incidence of postoperative low cardiac output syndrome, mortality, and ICU stay without significant increases in morbidity or cost.

Filtration Techniques

Hemofiltration. Hemofiltration is a process that uses ultrafiltration, *i.e.*, the processes of convection, osmosis under a hydrostatic pressure gradient, to remove fluid and low-molecular-weight substances from plasma. Initially introduced to treat patients with renal failure and to correct accumulation of extravascular water following CPB, hemofiltration appears to exert beneficial anti-inflammatory effects, particularly in pediatric patients.⁵⁶ Hemofiltration may remove proinflammatory mediators, with reductions in postoperative TNF- α , IL-1, IL-6, IL-8, C3a, and myeloperoxidase concentrations.^{56,227,330} This technique improves hemodynamic stability²²⁷ and early postoperative oxygenation,^{56,227,331} and reduces postoperative blood loss^{56,227,331} and duration of mechanical ventilation^{227,331} in pediatric cardiac surgery. Hemofiltration may reduce pulmonary hypertension after congenital heart surgery, possibly by facilitating removal of endothelin-1.³³⁰ Modified hemofiltration³³² after CPB improves intrinsic left ventricular systolic function and diastolic compliance, increases blood pressure, and decreases inotropic drug use in the early postoperative period in infants.³³³

Hemofiltration appears to be less effective in adults, with no decrease observed in postoperative blood loss, average bank blood transfused, postoperative weight gain, length of stay, or overall patient costs.^{334,335} Hemofiltration in adults undergoing CPB is less effective in removing proinflammatory cytokines than in pediatric patients,^{335,336} perhaps explaining its apparent lack of efficacy in this population.

Leukocyte Depletion. Leukocytes play a central role in the inflammatory response to cardiac surgery. Leukocyte depletion during cardiac surgery, by means of leukocyte-specific filters, decreases circulating leukocyte^{228,337,338} and platelet concentrations³³⁹ and attenuates indices of oxidative stress³⁴⁰ and inflammation.³³⁷ There is increasing evidence that leukocyte depletion may attenuate pulmonary and myocardial injury following CPB. Benefit appears

most consistent in patients with risk factors such as left ventricular dysfunction, urgent surgery, or long CPB time. Leukodepletion has been shown to improve postoperative respiratory function in CPB patients,^{338,339} particularly in patients with a low preoperative oxygenation capacity or long CPB time.³³⁹ In addition, leukocyte depletion of the residual heart-lung machine blood, which contains high quantities of activated leukocytes, prior to retransfusion, improved lung function in patients undergoing elective CABG.²²⁸ Leukodepletion during CPB, combined with leukodepletion of transfused blood, decreased indices of myocardial cell injury in patients undergoing urgent CABG for unstable angina.³⁴⁰ Conversely, in low-risk patients, depletion of activated neutrophils during CPB did not confer clinical benefit.³⁴¹ Limiting leukocyte depletion to the "reperfusion phase" of CPB (following aortic unclamping) does not appear to confer any clinical benefit in CABG patients.³⁴²

Leukocyte depletion of blood cardioplegia alone attenuated myocardial cell injury and improved early myocardial function in patients with left ventricular dysfunction undergoing CABG with CPB.^{112,343} Leukodepletion of terminal blood cardioplegia, (*i.e.*, blood cardioplegia administered for 10 min immediately prior to aortic unclamping as an adjunct to crystalloid cardioplegia) decreased myocardial injury and improved cardiac function in patients with left ventricular hypertrophy undergoing valve surgery.³⁴⁴

The immunomodulatory effects of leukocytes in allogeneic blood has focused attention on the potential benefits of leukodepleting stored blood.³⁴⁵ A large-scale clinical trial conducted in CPB patients demonstrated that leukocyte depletion of transfused blood significantly reduced the overall 60-day mortality.³⁴⁶ The difference in mortality was predominantly due to a dramatic reduction in noncardiac causes of death, particularly multiorgan failure.³⁴⁶ In addition, leukodepletion reduced the postoperative infection rate in patients who received more than 3 units of blood.³⁴⁶

Agents That May Suppress the Inflammatory Response

Serine Protease Inhibitors. Many effector proteins of the cytokine, complement, and hemostatic cascades are serine proteases, *i.e.*, when activated they catalyze the next step in the cascade by hydrolyzing and activating further proteins, a process termed "cascade amplification." Control processes that limit inflammation to the sites of injury and reduce systemic inflammation include serine protease inhibitors. Aprotinin is the best known and studied of these inhibitors.

Aprotinin. Aprotinin, a complex polypeptide and nonspecific serine protease inhibitor, has clearly been demonstrated to prevent excessive blood loss during cardiac surgery.³⁴⁷ In addition, aprotinin has multiple actions that may suppress the inflammatory response,

particularly at higher dosages. Antiinflammatory effects include attenuation of platelet activation, maintenance of platelet function,³⁴⁸ decreased complement activation,³⁴⁸ inhibition of kallikrein production,³⁴⁸ decreased release of TNF- α ,³⁴⁹ IL-6, and IL-8,³⁵⁰ inhibition of endogenous cytokine-induced iNOS induction,³⁵¹ decreased CPB-induced leukocyte activation,^{348,352} and inhibition of up-regulation of monocyte and granulocyte adhesion molecules.^{95,353}

In clinical studies, high-dose aprotinin reduces postbypass myocardial ischemia and myocyte damage³⁵⁴ and length of hospital stay in high-risk patients.³⁵⁵ However, a pump-prime-only dose of aprotinin may increase the risk of postoperative myocardial infarction.³⁵⁶ Levy *et al.* found no such increase in the incidence of perioperative myocardial infarction in patients undergoing repeat CABG.²⁵³ Concerns over graft patency following aprotinin therapy have been reduced by the IMAGE trial, which found no difference in early (10-day) patency rates for internal mammary artery grafts³⁵⁷ or for saphenous vein grafts after controlling for confounding factors.³⁵⁸

Aprotinin may reduce pulmonary and cerebral injury following CPB. Aprotinin decreases experimental CPB-induced and cytokine-induced bronchial inflammation³⁵⁹ and was demonstrated to attenuate lung reperfusion injury following CPB in one small clinical study.³⁶⁰ An early report of use of aprotinin in high-risk cardiac surgery patients indicated an incidence of fatal stroke of 0.5%, compared to rates of 2-3% in contemporary studies that did not use aprotinin.^{361,362} A multicenter trial of repeat CABG patients found that the incidence of stroke was reduced with high- or low-dose aprotinin.²⁵³ Lemmer *et al.* failed to show a significant decrease in the incidence of stroke with three different dosage regimens in their large-scale multicenter study.³⁵⁶ However, a pooled analysis of six trials, including the aforementioned trials, found that high-dose aprotinin significantly reduced the incidence of stroke.³⁶³ Initial concerns over the potential for adverse effects of aprotinin on renal function appear unfounded.³⁵⁶

No single study of aprotinin has clearly demonstrated improved patient outcome to date.^{253,356} However, a recent metaanalysis reported that aprotinin reduces surgical blood loss, allogeneic blood transfusion, and the need for rethoracotomy, and decreases perioperative mortality almost twofold, with no increase in the risk of myocardial infarction.³⁴⁷ These data provides strong support for the use of aprotinin in patients undergoing cardiac surgery.

Pentoxifylline. Pentoxifylline is a nonspecific phosphodiesterase inhibitor with diverse antiinflammatory effects, many of which may be mediated by inhibition of phosphodiesterase IV.³⁶⁴ These include attenuation of TNF- α release in sepsis,^{365,366} decreased endotoxin and cytokine activation of neutrophils,³⁶⁷ reduction of indi-

ces of endothelial injury and permeability,³⁶⁸ decreased pulmonary leukocyte sequestration,³⁶⁹ and attenuation of increases in pulmonary vascular resistance.³⁶⁹ Clinical studies to date have been limited. In one study, pentoxifylline decreased the duration of ventilation and hemofiltration and the incidence of MODS when administered postoperatively to selected high-risk cardiac surgical patients³⁷⁰ and may be of therapeutic benefit in human sepsis.³⁷¹ However, pentoxifylline treatment did not improve postoperative renal³⁷² or pulmonary³⁷³ function in other small clinical studies. Most recently, in elderly cardiac surgical patients, pentoxifylline attenuated the increase in neutrophil elastase, C-reactive protein, and proinflammatory cytokines (IL-6, IL-8, and IL-10). These patients also had reduced requirements for vasoactive medication and a shorter time to tracheal extubation.³⁷⁴ In a parallel study, the same investigators reported improved splanchnic perfusion and hepatic-renal function with pentoxifylline.³⁷⁵

Free Radical Scavengers and Antioxidants. Generation of reactive oxygen species (ROS) (hydrogen peroxide and the superoxide and hydroxyl radicals) occurs upon reperfusion following bypass,³⁷⁶ and these may be important contributors to tissue injury. Leukocytes activated during bypass may also release substantial amounts of cytotoxic ROS.^{96,97} When present in equimolar concentrations, superoxide and NO may combine form peroxynitrite, a more reactive and injurious free radical.^{66,67} Myocardial antioxidant enzymes, including glutathione reductase, superoxide dismutase, and catalase, are activated in proportion to the degree of myocardial ischemia and reperfusion injury.³⁷⁷ Host antioxidants become depleted after CPB,^{378,379} presumably as a result of consumption by free radicals. When ROS production exceeds host defense scavenging capacity, cellular injury results.^{376,380} There is an inverse correlation between preoperative total plasma antioxidant status and lipid peroxidation, the latter of which is directly correlated with indices of myocardial cellular injury.³⁷⁹ Furthermore, post-CPB coronary endothelial dysfunction appears to be partially mediated by ROS.³⁸¹ Free radical scavengers, such as enzymatic scavengers, antioxidants, and iron chelators, may be potentially useful therapeutic adjuncts to control the deleterious effects of the inflammatory response.

High-dose vitamin C (ascorbic acid) has been demonstrated to effectively scavenge free radicals, decreasing cell membrane lipid peroxidation^{376,382} and indices of myocardial injury, and improving hemodynamics with a shorter ICU and hospital stay.³⁸² Vitamin E (α -tocopherol) reduces plasma concentrations of hydrogen peroxide, a marker of free radical concentrations,³⁸³ and decreases cell membrane lipid peroxidation³⁷⁶ following CPB. Preoperative supplementation with a combination of ascorbic acid, α -tocopherol, and allopurinol reduced cardiovascular dysfunction in both stable and unstable

patients undergoing CABG. Unstable CABG patients sustained less myocardial injury and a decreased incidence of perioperative myocardial infarction.³⁸⁴ A more recent trial of combined α -tocopherol and ascorbic acid supplementation in CABG surgery revealed no detectable decrease in myocardial injury.¹⁵

High-dose *N*-acetylcysteine before or during bypass appears to act as a free radical scavenger³⁸⁵ and reduces the neutrophil oxidative burst response³⁸⁵ and elastase activity.³⁸⁶ In an early interventional trial in patients with established acute lung injury, *N*-acetylcysteine was shown to improve oxygenation and lung mechanics, although no impact on progression to acute respiratory distress syndrome was noted.³⁸⁷

Allopurinol is an inhibitor of the enzyme xanthine oxidase, a pivotal generator of free radicals during reperfusion injury. Allopurinol may decrease myocardial formation of cytotoxic free radicals,^{380,388} lower markers of myocardial cellular injury,³⁸⁹ and improve recovery of myocardial function following CPB.^{390,391} However, other studies have demonstrated no improvement in either myocardial function³⁹² or myocardial cellular injury with allopurinol use,^{388,393} casting doubt on its therapeutic potential.

Pretreatment of patients with mannitol reduces myocardial formation of cytotoxic free radicals after CPB in humans.³⁸⁰ Other free radical scavengers—antioxidants that appear from animal studies to possess therapeutic potential include methionine, reduced glutathione, dimethylthiourea, mercaptopropionyl glycine, superoxide dismutase, catalase, and desferrioxamine.^{381,394–397}

Immunomodulation

The Corticosteroid Controversy. The use of corticosteroids in the context of CPB continues to be controversial because of their potential risks. Past negative experience, particularly with the use of corticosteroids in septic shock,³⁹⁸ has served to emphasize the need for caution when considering corticosteroid use, even in noninfective inflammatory conditions, where their potent antiinflammatory actions might be expected to be beneficial. However, there have been significant advances in our understanding of the molecular mechanisms by which corticosteroids might blunt the inflammatory response to cardiac surgery.

Corticosteroid pretreatment may blunt the inflammatory response in humans by several distinct mechanisms. Administration of glucocorticoids prior to CPB may attenuate endotoxin release³⁹⁹ and complement activation.^{400,401} Methylprednisolone lowers post-CPB concentrations of the proinflammatory cytokines TNF- α ,³⁴⁹ IL-6, and IL-8,⁴⁰² and increases concentrations of the anti-inflammatory cytokines IL-10 and IL-1ra,⁴⁰² but not IL-4.⁴⁰³ Corticosteroids also attenuate post-CPB leukocyte activation,²⁰ neutrophil adhesion molecule up-regulation,³⁴⁹ and pulmonary neutrophil sequestration.⁴⁰¹

Prebypass administration of methylprednisolone in aprotinin-treated patients improves early postoperative indices of pulmonary, cardiovascular, hemostatic, and renal function.⁴⁰⁴ Glucocorticoid pretreatment may improve cardiac performance⁴⁰⁵ and reduce evidence of bronchial inflammation following CPB.⁴⁰⁶ Low-dose methylprednisolone in the pump prime solution appears to attenuate myocardial cell damage.⁴⁰⁷ Dexamethasone^{213,214} and methylprednisolone^{212,215} decrease the incidence of postoperative fever. In animal studies, corticosteroid pretreatment improved several indices of lung injury, including pulmonary compliance, alveolar-arterial gradient, pulmonary vascular resistance, and extracellular fluid accumulation.⁴⁰⁸ However, the ability of corticosteroid pretreatment to attenuate post-CPB pulmonary inflammation,⁴⁰⁹ endotoxemia,⁴⁰⁰ and complement activation is disputed.^{20,410}

The clinical implications of corticosteroid use are not yet fully elucidated, and clear benefit is not yet demonstrated. The dosage, formulation, and timing of administration of corticosteroids may be critical, and differences in dosage regimens may explain conflicting results. Preoperative combined with prebypass administration may be superior to prebypass administration alone.⁴⁰⁸ It is premature to advocate the use of corticosteroids in the absence of proven outcome benefit, determination of optimal dosage regimens, and characterization of harmful effects, *e.g.*, immunosuppression, which may result from their use.

Cyclooxygenase Inhibitors. Aspirin, the prototype nonsteroidal antiinflammatory drug (NSAID), is widely used in cardiac surgical patients for the purposes of pain relief and antiplatelet activity. However, the potential for NSAID's inhibitors to attenuate the inflammatory response to cardiac surgery has not been widely evaluated in clinical trials. Traditional NSAIDs, such as indomethacin, inhibit both the constitutive cyclooxygenase 1 (COX-1) as well as COX-2, the inducible isoform activated by inflammatory stimuli. Nonspecific COX inhibition attenuates the increase in pulmonary vascular resistance and ALI⁴¹¹ and reverses pulmonary microvascular dysfunction⁴¹² in CPB models. One older clinical study of indomethacin demonstrated that it decreased the duration of postoperative fever, chest pain, malaise, and myalgias following CPB.²¹¹ However, inhibition of COX-1 appears to increase free radical-generated isoprostane formation, which aggravates postischemic myocardial dysfunction.^{413,414}

Specific COX-2 inhibitors exhibit considerable potential to attenuate the inflammatory response following cardiac surgery. COX-2 has been implicated in the pathogenesis of adverse events after cardiac surgery.^{415,416} COX-2 is up-regulated following CPB,⁴¹⁵ in multiple tissues, including the brain,⁴¹⁶ while COX-2 products, particularly thromboxanes⁴¹⁷ and vasoconstrictor prostaglandins, are increased.⁴¹² COX-2 up-

regulation following experimental CPB may contribute to postoperative coronary vasospasm⁴¹⁵ and increased pulmonary vascular resistance.⁴¹⁸ In addition, myocardial COX-2 is up-regulated during cardiac allograft rejection⁴¹⁹ and myocardial infarction⁴²⁰ and contributes to endotoxin-induced myocardial depression.⁴²¹ Inhibition of COX-2 attenuates the myocardial inflammatory response during cardiac allograft rejection,⁴¹⁹ reduces endothelial dysfunction following myocardial ischemia and reperfusion,⁴²² and improves cardiac function in experimental myocardial infarction.⁴²⁰ In addition, COX-2 inhibition decreases endotoxin-induced myocardial depression⁴²¹ and lung ischemia and reperfusion injury.⁴²³ However, the clinical efficacy of specific COX-2 inhibitors in attenuating the inflammatory response to cardiac surgery remains to be determined.

Complement-directed Therapies. Therapies that utilize endogenous soluble complement inhibitors may be a suitable approach to reduce contact activation and thereby control the inflammatory response. A recent two-stage randomized clinical trial of a monoclonal antibody specific for human C5 demonstrated its efficacy and safety in patients undergoing CPB.⁵⁰ The generation of activated complement mediators and leukocyte adhesion molecule formation was inhibited in a dose-dependent manner. Furthermore, C5 inhibition resulted in a dose-dependent reduction in myocardial injury, postoperative cognitive deficits, and coagulation dysfunction. These data suggest that C5 inhibition may represent a promising therapeutic modality for preventing complement-mediated inflammation and tissue injury in patients undergoing CPB.⁵⁰ Compstatin, a recently discovered peptide inhibitor of complement, may have the potential to prevent complement activation during and after cardiac surgery. In preliminary primate studies, compstatin completely inhibited *in vivo* heparin-protamine-induced complement activation without adverse effects.³¹

Other promising strategies include the C1 inhibitor, recombinant soluble inhibitor-1, monoclonal antibodies to C3 and C5a, and strategies that attenuate complement receptor 3-mediated adhesion of inflammatory cells to the vascular endothelium. Utilization of membrane-bound complement regulators may also be feasible by means of transfection techniques.⁴²⁴

Antimediator Therapies. Direct antimediator therapies that focus upon the endotoxin molecule itself and the proinflammatory cytokine cascade following CPB offer new approaches. However, the complex pathway observed in patients with SIRS does not appear to readily respond to antimediator therapy. Multicenter clinical trials blocking endotoxin and proinflammatory mediators such as IL-1 or TNF- α conducted in SIRS patients have shown no benefit in reducing mortality secondary to sepsis. Reasons for the relative failure of immunomodulatory therapies to date may include the timing of

intervention, the heterogeneous nature of the inflammatory response, and the reciprocating and redundant nature of the proinflammatory cascades. High circulating concentrations of antiinflammatory mediators, such as the cytokine antagonists IL-1ra, TNFsr1, and TNFsr2, may also limit the efficacy of therapies that aim to augment natural defenses against endotoxin or the proinflammatory cytokines.⁴²⁵

The experience with antimediator therapy in sepsis suggests a need for caution in considering the application of these therapies to control the inflammatory response to CPB. Nevertheless, antimediator therapies may be worthy of investigation for two reasons. These therapies may enhance our understanding of the inflammatory process following CPB. Their administration prior to bypass, in order to modulate the inflammatory pathways at their earliest stages, might constitute a more successful approach than that used in other clinical scenarios, such as in sepsis, where the inflammatory response may be already well developed before antimediator therapy is possible.

Therapies to Attenuate Endothelial Injury. Current evidence suggests that therapeutic efforts in patients with SIRS should include modulation of endothelial cell function. Better definition of the molecular mechanisms of endothelial cell activation may facilitate development of therapies that allow selective inhibition of vascular endothelial activation. Adhesion molecule blockade may prevent neutrophil adherence during the first 24 h after CPB, thereby preventing the neutrophils from mediating widespread organ damage. In this regard, blockade of endothelial and neutrophil selectin adhesion molecules results in marked attenuation of cerebral injury in an animal model of CPB and deep hypothermic circulatory arrest.²⁵² Inhibition of neutrophil adhesion markedly reduced pulmonary injury in a porcine model of CPB.²²⁹ However, there may be limits to this approach because adhesion molecule blockade increases susceptibility to infection.⁴²⁶ Finally, methods to prevent nuclear localization of the transcriptional activator NF- κ B in order to prevent endothelial cell activation are also being studied in animal models.⁹⁸

Future Research Directions

The development of organ dysfunction following CPB remains an indicator of poor outcome despite advances in resuscitation, drug, and adjunctive therapies. Organ support therapies, *e.g.*, mechanical ventilation, can sustain life but may impair both local and remote organ function, *e.g.*, ventilator-associated lung injury.²⁰¹ A better understanding of the inflammatory response to cardiac surgery may be the key to development of successful strategies to minimize patient morbidity. With some exceptions, such as recent data on HCCs and inhibition

of complement activity, the link between the inflammatory response and adverse clinical sequelae, while persuasive, is currently associative rather than causative. A primary research priority must be to establish direct causal links between (and mechanistic insights into) the inflammatory response to surgery or CPB and clinical outcome. Therapeutic interventions cannot be justified in the absence of clear cause-and-effect relations.

There remains a need to document clear clinical benefits from interventions designed to modify the inflammatory response. Modulation of the human inflammatory response has always been difficult, primarily as a result of our incomplete understanding of this response, and may lead to unexpected sequelae. The complexity of the inflammatory response is a significant obstacle to identification of the mechanism(s) by which alteration of a particular aspect of the response may affect clinical outcome. Indiscriminate inhibition-prevention of the inflammatory response to CPB may have detrimental effects, such as loss of appropriate wound healing and defenses against infection. Certain proinflammatory cytokines, such as IL-1 β ²¹⁰ and even endotoxin,²⁰⁶ appear to have poorly understood protective effects. In this regard, IL-1 β pretreatment protects against subsequent myocardial ischemia and reperfusion injury.²¹⁰ The emphasis of future strategies must therefore be on the control of, rather than the simple inhibition of, the inflammatory response to CPB.

Further research is required to determine why certain patients appear to be at increased risk of clinically important bypass-induced injury. Monitoring tools such as gastric tonometry and other indicators of systemic organ hypoperfusion in CPB patients have provided physiologic insights, but their role in therapy remains to be clarified. Preoperative or early perioperative identification of patients most likely to develop adverse clinical sequelae from SIRS would allow focusing of investigative, preventive, and therapeutic maneuvers, and should be a research priority.

The heterogeneity of the patient population undergoing CPB is well illustrated by the finding of a near 20-fold difference in mortality (1.8% *vs.* 34.3%) for first time elective *versus* high-risk reoperative coronary artery bypass procedures.⁵ Many studies of therapeutic interventions have been carried out in relatively low-risk patients, in whom the risk of adverse postoperative events might be expected to be minimal. It is possible that beneficial effects of these therapeutic strategies may be diluted by studies that include low-risk patients. Therefore, future investigations of interventions to control the inflammatory response to CPB may be best focused on patients at high risk of postoperative organ dysfunction. Future studies should utilize direct clinical indicators of organ injury as outcome measures rather than simply measurement of mediator concentrations as surrogates of injury. Many of the previously conducted clinical trials

do not contain adequate patient numbers to detect meaningful differences in outcome. There is a clear need for large-scale clinical trials of more promising strategies such as selective gut decontamination, maintenance of splanchnic perfusion, drug therapies including corticosteroid pretreatment, aprotinin, acadesine, and adjunctive measures, such as hemofiltration, and use of biocompatible materials in the extracorporeal circuit. These trials, restricted to patients at significant risk of perioperative morbidity, may have to be completed using multiple centers. Finally, more investigation is needed to determine the efficacy and safety of off-pump cardiac surgery, and new methods for myocardial protection in this context need to be developed.

Conclusions

Cardiac surgery evokes a generalized inflammatory response in all patients, with serious clinical consequences in a minority, despite advances in pharmacology, perfusion technology, cardiovascular monitoring, and anesthetic and surgical technique. This is most clearly evident with regard to postoperative pulmonary and cardiovascular dysfunction. The etiology of these events is probably a composite of unstable peribypass hemodynamics, global myocardial ischemia, suboptimal organ perfusion during CPB, and immune events related to exposure to extracorporeal circulation *per se*. A balanced, controlled inflammatory response is potentially beneficial, aiding host defenses against infection and facilitating wound healing, but loss of control of the inflammatory response may herald the onset of SIRS and single or multiple organ dysfunction.

The complex interaction of key proinflammatory and antiinflammatory components of the inflammatory response, the significance of alterations in the magnitude or time course of release, and their relation to the clinical sequelae seen following CPB remain to be fully elucidated. Further work to establish direct causal links between the inflammatory response to CPB and organ dysfunction may lead to mechanistic insights and in turn stimulate the development of successful preventive and therapeutic strategies. The increasing use of minimally invasive surgical techniques such as OPCAB will contribute to these insights, particularly the relative roles of CPB and peribypass events. The link between interventions and clinical benefit is gradually being established for several strategies, including improved circuit biocompatibility, maintenance of splanchnic perfusion, hemofiltration (in the pediatric population), aprotinin, and corticosteroid therapy. The need to better characterize and focus therapeutic interventions on the patient at risk of MODS following CPB is imperative.

The goal of modulation of the perioperative inflammatory response is to attenuate its deleterious effects while

preserving the ability of the patient to mount an appropriate defense to the physiologic trespasses of the perioperative period. Although knowledge is growing about the role of altered immune function, the role of immunomodulatory therapies will remain investigational (especially in view of the failures of these therapies in recent sepsis trials) until the initiating events in postoperative SIRS become clearer.

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