Pathogenesis of CPB-induced SIRS

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INTRODUCTION

Cardiopulmonary bypass (CPB) has often been compared to the pathophysiologic changes occurring in sepsis or systemic inflammatory response syndrome (SIRS). The definitions for SIRS is classically considered to be related to sepsis, shock, and multiple organ dysfunction syndrome (MODS).1 The idea behind defining SIRS was to define a clinical response to a nonspecific insult of either infectious or noninfectious origin. SIRS for sepsis is defined as 2 or more of the following variables: 1) fever of more than 38°C or less than 36°C; 2) heart rate of more than 90 beats per minute; 3) respiratory rate of more than 20 breaths per minute or a PaCO2 level of less than 32 mm Hg; and abnormal white blood cell count (>12,000/µL or < 4,000/µL or >10% bands). However, this definition is not useful for understanding CPB induced SIRS, which is nonspecific and can be caused by multiple factors including inflammation, trauma, infection, or a combination of several insults as seen after cardiac surgery and CPB.2 However, both of these syndromes share similar inflammatory and mediator pathways that result in MODS.

The inflammatory response to CPB represents pathophysiologic changes, like SIRS, that can range from mild organ dysfunction to multisystem organ failure. The clinical manifestations can be quite variable and include coagulopathy, pulmonary dysfunction, and multigorgan system failure.3,4 These diverse injuries are a consequence of multiple inflammatory cells and mediators as seen in SIRS including neutrophil activation and liberation of multiple inflammatory pathways including complement, kinins, kallikrein, cytokines, and others.3,5,6 Plasmin and kallikrein amplify the inflammatory response by activating components of the contact activation system and other inflammatory pathways. This may also be important for traumatic injury as antifibrinolytic therapies are increasing being used to manage these patients as well as for CPB.7

INFLAMMATION/COAGULATION INTERACTIONS

Activation of coagulation is also closely linked to inflammatory responses via a complex network of both humoral and cellular components including proteases of the clotting and fibrinolytic cascades.8 Hemostatic initiation, contact activation, tissue factor expression, and other pathways amplify inflammatory responses to collectively produce end-organ damage as part of host defense mechanisms. Thrombin is activated as a central element of a both local but also a systemic response to inflammation. Thrombin can amplify inflammation induced by other stimuli, either through ischemia (consequent upon thrombosis), indirectly through generation of downstream mediators such as activated protein C, or directly via signals through protease activated receptors (PAR).9 Thrombin is an important constituent of immunity, able to amplify and modify responses to invading pathogens or tissue damage.9

Several of the key coagulation components and their products have proinflammatory effects including thrombin and factor Xa. Thrombin also has direct chemoattractant activity for polymorphonuclear leukocytes, monocytes, and is a potent activator of mast cells. Factor Xa also interacts with receptors on mast cells to cause degranulation through a variety of different
mechanisms including receptor activation. Activation of monocytes and macrophages release of interleukin-1, tumor necrosis factor, and other chemotactic factors that recruit additional leukocytes into the lesion.

HEMOSTATIC ACTIVATION DURING CPB

CPB and surgical injury create hemostatic activation by multiple mechanisms. Surgery induced tissue injury with large vessel bleeding as well as microvascular bleeding can occur. Patients often have acquired defects that may be complicated by the surgical insult, or coagulation abnormalities that occur due to preexisting antiplatelet or anticoagulant use or massive blood loss. Major coagulation abnormalities occur perioperatively in our patients and are often influenced by multiple factors including the type of surgery, CPB and time, as well as dilutional changes, cellular and clotting factor activation/sequestration, tissue factor and thrombin generation, and contact activation.10,11

Increased tissue plasminogen activator (tPA) and kallikrein mediated plasmin generation have multiple effects on hemostatic proteins and platelets.4 Strategies continue to evolve to reduce this activation including limiting cardiotomy suction, increasing circuit biocompatibility, antithrombin supplementation, and antifibrinolytic use as recently reviewed by Sniecinski and Chandler.4 Because of the variability of SIRS and complex causes, multimodal approaches to reduce hemostatic/inflammatory activation associated with CPB are warranted as recently described.4

Hemostatic activation occurs during CPB despite standard therapies including heparin and maintenance of adequate ACTs. Hemostatic changes are complex and have been previously described. One interesting target is the acquired antithrombin (AT) deficiency in the perioperative cardiac surgical period may be related to the preoperative use of heparin, the effects of hemodilution, and/or CPB-related consumption. AT levels as low as 20%-30% activity, which are similar to levels observed with heterozygous hereditary deficiency or DIC are commonly seen during CPB.12 Because the data in DIC suggests AT may potentially reduce inflammation and/or end-organ dysfunction13, we over the years expanded this consideration to cardiac surgical patients and have investigated whether AT represents an important therapeutic intervention that alone, or in conjunction with other therapies, may further reduce the inflammatory sequelae.12,14,15

INFLAMMATORY CELLS

Vascular cells and polymorphonuclear leukocytes as part of their complex host immunosurveillance properties can initiate and amplify coagulation via multiple, receptor-mediated processes. Leukocytes also have the ability to generate thrombin as part of their role in modulating inflammatory responses. The inflammatory response induced by Factor Xa included prominent perivascular accumulation of activated and partially degranulated mast cells.16 Although the neutrophils play central roles in acute inflammation, findings have also identified a direct role of clotting and fibrinolytic proteases in intracellular signal transduction and modulation of inflammatory cell responses.

Mast cells are key cells of type I hypersensitivity reactions, however, their ubiquitous distribution throughout perivascular spaces makes their “pharmacopoeia” of mediators available to a spectrum of cell types including vascular endothelial cells, inflammatory cells, and vascular smooth muscle. Mast cells have been suggested to play important roles in a series of inflammatory and proliferative disorders. The release of mast cell mediators by multiple stimuli
may play a pivotal role in host defense. Mast cell-derived mediators can produce multiple proinflammatory effects. Histamine enhances both fibroblast proliferation and collagen synthesis; tryptase and chymase can digest multiple cellular components, and cytokines such as tumor necrosis factor, IL-4, and growth factors have effects on multiple cell types.\textsuperscript{17,18}

**BLEEDING, TRANSFUSION, AND CARDIAC SURGERY**

Transfusional therapies are also thought to contribute to inflammatory responses in cardiac surgery. Observational studies suggest that RBC transfusion, especially older blood, increases adverse responses, and multiorgan failure due to multiple mechanisms, and is the basis of the current NHLBI sponsored RECESS study. Other transfused factors including platelets and FFP may also contribute to adverse outcomes although again many of these studies are observational in nature where higher risk patients also receive transfusions.

**ROLE OF COMPLEMENT ACTIVATION AND THERAPEUTIC APPROACHES**

One of the major inflammatory pathways for CPB induced inflammatory responses, and due to ischemia and reperfusion injury is complement activation. This pathway contributes to systemic and cardiac injury via two products of C5 cleavage: C5a, a potent anaphylatoxin, and C5b-9, the membrane attack complex that causes cell lysis. Pexelizumab is a monoclonal antibody fragment that binds to the C5 component of complement with high affinity inhibiting complement activation and acute inflammatory reactions.

We reported a previous study (PRIMO CABG) that pexelizumab treatment was associated with a statistically significant reduction in myocardial infarction (MI) or death (11.5% vs. 14% for placebo, P = .030) 30 days after surgery in 3099 patients who had CABG surgery with or without valve surgery.\textsuperscript{19} However, the difference between groups did not reach statistical significance for the primary composite endpoint of death or MI through 30 days for patients undergoing CABG surgery without valve replacement (n = 2746).\textsuperscript{19} Enrollment in the PRIMO CABG trial required the presence on one or more predefined patient risk factors including female gender, recent or multiple MIs, urgent surgery, repeat CABG surgery, a history of diabetes mellitus, and advanced age.\textsuperscript{7–9} These risk factors have been demonstrated to predict increased morbidity and mortality following CABG, and are becoming increasingly prevalent in an aging patient population and more selective referral since the introduction of coronary stenting.\textsuperscript{20} Post hoc analysis in the PRIMO CABG trial suggested that pexelizumab was effective, compared to placebo, in patients with 2 or more of these predefined risk factors, and the effect was directly related to increasing risk.\textsuperscript{21} In addition, there was a parallel reduction in perioperative MI in pexelizumab-treated patients that suggested a biological mechanism for the associated mortality reduction. This association was further suggested by protective effects of pexelizumab in surgery patients undergoing prolonged aortic cross clamp time (>90 minutes).\textsuperscript{22} A second trial of pexelizumab was evaluated in patients who had two or more predefined preoperative risk factors of 4254 patients undergoing CABG with or without valve surgery at 249 hospitals in North America and Western Europe from June 2004 to July 2005. The primary composite endpoint was death or MI within 30 days of randomization. The PRIMO CABG II trial did not meet its pre-specified primary end points of death or MI at 30 days, or secondary endpoints of death at 30 days, or the development of new or worsening CHF. However, in a combined analysis of both PRIMO CABG I and II pivotal trials (N=7353), death at 30 days was significantly reduced for the highest risk subset (N = 2156, pexelizumab 5.7% vs. placebo 8.1%,
Furthermore, this mortality reduction persisted through the 180 day follow up period (pexelizumab 11.1% vs. placebo 14.4%, P=.036)23

SUMMARY

Complex interactions exist between inflammation and coagulation following activation of thrombosis. Recent discoveries understanding molecular basis of this both crosstalk and amplification have been examined. Because of the complex variables, cellular and humoral cascades involved, and because of the phenomenal humoral amplification that occurs in any injury process, understanding the pivotal role of any one mediator is still unclear. However, the ability under physiologic conditions to preserve the pro and anti-inflammatory process when damaged and the importance of autoregulation via purified and recombinant proteins are still being explored as potential therapeutic applications. The study of inflammation cannot be limited to the influence of single mediators, or inflammatory cells but needs to include the complex influences of a broad spectrum of pathways that are initiated concomitantly or in a cascade. The role of specific mediators and their potential antagonists plays a never-ending role in our potential to block and decrease inflammatory injury, coagulation, and ultimately improve patients outcomes.24

REFERENCES