

Pharmacologic Strategies for Combating the Inflammatory Response

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Abstract: The “systemic inflammatory response” is a multifaceted defensive reaction of the body to surgical trauma and cardiopulmonary bypass (CPB), characterized by systemic activation of fibrinolysis, coagulation, complement, immune cells, platelets, and oxidative pathways, all overlaid onto localized trauma to the grafted vessel or vascular beds susceptible to ischemia/reperfusion. There is going to be no single magic bullet to diminish such a broad host defense response to surgery. The best chance lies with combinatorial—or promiscuous—pharmacotherapy. Combinations of anti-fibrinolytics, anti-coagulants targeted higher up the coagulation cascade, anti-thrombin receptor therapy, improved coated circuits, anti-complement, anti-leukocyte, and antioxidant therapies may blunt sufficient arms of the systemic inflammatory response to be clinically effective. The

alternative is a promiscuous drug like aprotinin, which targets plasmin in the fibrinolytic pathway, kallikrein in the coagulation pathway, thrombin receptors on platelets and endothelium, and leukocytes at the extravasation step. Because of the overriding safety concerns relating to the use of anti-fibrinolytics in cardiothoracic surgery, any future combinatorial or promiscuous pharmacotherapy involving anti-fibrinolytics will require solid underpinning with a known mechanism of action and clinical safety data powered to detect well-defined adverse events (stroke, myocardial injury, renal failure requiring dialysis), preferably in isolation and not as a composite endpoint. **Keywords:** cardiac surgery, anti-inflammatory, antifibrinolytics. *JECT. 2007;39:291–295*

A MULTI-PATHWAY RESPONSE REQUIRES A MULTI-TARGET INTERVENTION

As discussed in the companion article “Why the inflammatory response is important to the cardiac surgical patient,” cardiothoracic surgery with cardiopulmonary bypass (CPB) activates multiple host defense responses against injury and infection. Passage of blood through the extracorporeal circuit activates fibrinolysis, intrinsic coagulation, complement, white cells, platelets, and hemolysis. The term “systemic inflammatory response” does not do justice to the multi-system etiology of the body’s response to surgery, which might be better thought of as a “systemic host response” to surgery. Systemic activation of host defense pathways directly or indirectly account for many clinical symptoms, including excessive bleeding, fever, and massive fluid shifts. Localized complications, like impaired graft patency and end-organ injury, are caused by a more complex composite interaction between systemic and local insults (the main local insult being injury or activation to the vessel wall secondary to perioperative

manipulation of the vein graft or because of ischemia/reperfusion).

When considering the many host defense pathways that make up the “systemic inflammatory response,” it should be clear that effective taming of the inflammatory response is going to take a multi-targeted pharmacologic intervention. Figure 1 below highlights possible drug targets in the systemic inflammatory response.

SURFACE MODIFICATION—MUCH POTENTIAL BUT LITTLE DELIVERY

The most obvious multi-target intervention is to limit contact activation of fibrinolysis, coagulation, complement, and immune cells by surface modification to make the plastic surfaces of the extracorporeal circuit more biocompatible. Circuit coating thus has the greatest potential to limit the genesis of the “inflammatory response,” as opposed to neutralizing effector molecules already generated (1). It must be said that results have been generally disappointing, with the most widespread coating strategy (heparin coating) achieving only modest clinical improvement. The primary target of heparin is thrombin, the most downstream molecule of the intrinsic coagulation cascade.

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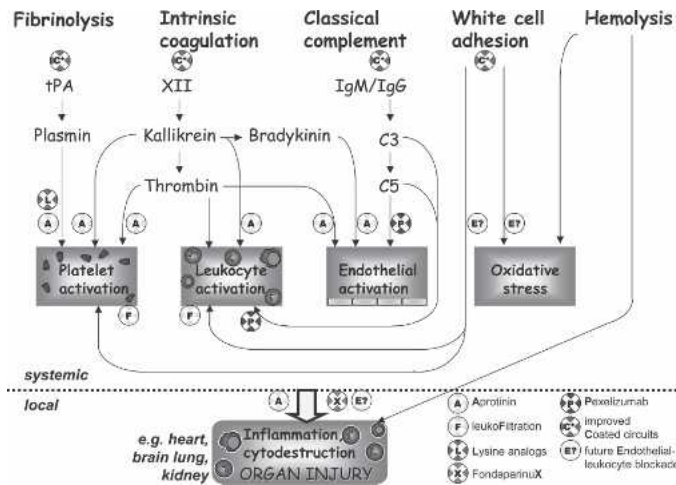


Figure 1. Potential molecular targets in the host response to CPB. Two multi-targeting interventions are shown: aprotinin, a broad acting serine protease inhibitor, and “improved” coated circuits (“improved” because present coating strategies do not efficiently abrogate contact activation). An exciting area for future research is to examine novel pharmacologic agents targeted against the endothelial–leukocyte adhesion cascade; some 30+ such agents, mostly at preclinical–phase II stage, have been developed for use in a host of unrelated inflammatory conditions but may exhibit efficacy in the setting of CPB, possibly in synergy with other mono-targeting drugs such as the complement C5 inhibitor pexelizumab, leukofiltration, or antioxidants.

Ideally, one would want to interdict higher up the cascade, by targeting factor XIIa, IXa, or tissue factor in the extrinsic pathway (2,3). Indeed, whatever beneficial effects heparin coating achieves may be caused by its subsidiary targeting of factor IXa activation of Xa (4). There is some evidence that specifically targeting factor IXa may be highly efficacious (5). A systemic review of circuit coating strategies from an evidence-based perspective concluded that circuit coating merited a disappointing Class II, Level B rating as a means to curb the systemic inflammatory response (6). Clearly, much research remains to be done in order for circuit modification to realize its proper potential as a way to limit contact activation across a broad front in the host response to surgery.

APROTININ: PROMISCUOUS WONDER DRUG OR NEPHROTOXIC MENACE?

As the only FDA-approved compound to limit transfusion requirement in cardiothoracic surgery, aprotinin has been subjected to intensive scrutiny, both for its efficacy and safety. Anti-inflammatory effects have been recognized, which are not seen with other anti-fibrinolytic agents (the lysine analogs tranexamic acid and ϵ -aminocaproic acid); thus, it is likely that those additional benefits stem from mechanistic actions unrelated to hemostatic targeting of plasmin.

Because aprotinin is a broad-based serine protease inhibitor, it can inhibit a number of potential targets in the

host response to surgery (as shown in Figure 1): plasmin, kallikrein, and thrombin receptor protease-activated receptor 1 (PAR1), which is activated by proteolytic cleavage with a serine protease. The actions of aprotinin on the platelet thrombin receptor are discussed in greater detail in a companion article. (7). Although the mechanism of PAR1 targeting is beyond the scope of this article, it is important to remember that thrombin triggers pro-inflammatory pathways in leukocytes and endothelial cells and that aprotinin is therefore likely to mediate anti-inflammatory effects by targeting PAR1 (8). We were able to show this principle in endothelial cells in vitro, in which thrombin-induced calcium fluxes, intracellular signaling, transcription factor upregulation, and interleukin-6 production, were all inhibited by aprotinin (9). A component of aprotinin’s anti-inflammatory action is therefore likely to be through PAR1 inhibition on endothelium. Whether aprotinin can exert similar anti-inflammatory effects on leukocytes through PAR1 remains unknown.

Research in the early 1990s showed that aprotinin could inhibit contact activation of platelets and neutrophils in the extracorporeal circuit through targeting of kallikrein (10). Because the inhibition constant (K_i) for kallikrein is much weaker than for plasmin, protection from kallikrein requires a clinical high dose (Hammersmith dose), consisting of 2×10^6 kallikrein inhibitory units (KIUs) in the pump prime, 2×10^6 KIU loading, followed by 0.5×10^6 KIU/h infused intravenously during bypass (11). Animal and in vitro studies have shown that protection from edema and cerebral metabolites leading to stroke was observed at a high dose, through inhibition of bradykinin generation (12). Clinically, a large body of studies support the notion that aprotinin is stroke protective.

Although we still await a prospective randomized clinical trial with stroke as a primary outcome, meta-analyses of studies measuring stroke as a secondary outcome, and studies into neurocognitive impairment, suggest that aprotinin has neuroprotective properties, especially when used at a high dose and in high-risk patients (13–15). A possible mechanism contributing to neuroprotection is by blocking leukocytes from infiltrating into organs (16). This principle was first shown in animal and in vitro work from our group, showing that leukocyte extravasation in response to localized chemotactic stimuli was inhibited by high-dose aprotinin (17,18). Similar findings have since been reported in animal models of ischemia/reperfusion and, most recently, a large animal model of CPB (19,20).

Safety of aprotinin has been the dominant issue in cardiac surgery in 2006/2007. Unfortunately, the highest scientific standards have not always been in evidence during the debate, either by the researchers raising the safety concerns or by the drug’s manufacturer, leaving clinicians in a state of limbo. Bayer Pharmaceutical was roundly condemned for withholding safety data from the FDA

hearing into aprotinin in September 2006, and it is hard to know what to make of three observational studies from the Ischemia Research and Education Foundation, which triggered the safety concerns, the first two of which concluded that aprotinin use was linked to renal failure and death (21,22). The third (using the same database as the first two studies) did not find aprotinin as a predictor of renal dysfunction/failure (23).

Prospectively collected safety data from randomized placebo controlled trials has not revealed any increased risk of renal failure leading to dialysis. This includes data from three recent meta-analyses, one of which was an evidence-based review from the Cochrane Collaboration (14,24,25). It should be noted, however, that renal function was not a primary outcome measure in any of the prospective randomized trials carried out to date, and we are thus still working in a certain vacuum of knowledge. A transient rise in serum creatinine levels (not leading to dialysis) has been shown in cardiac surgical patients receiving high-dose aprotinin (25,26). A possible drop in perfusion pressure has been postulated as a theoretical model to explain transient renal dysfunction with aprotinin in patients already receiving angiotensin-converting enzyme (ACE) inhibitors and there is scope for studying this hypothesis in greater depth (27). A good editorial discussing the controversies and safety issues surrounding aprotinin has been published recently in accompaniment to an excellent meta-analysis into the efficacy and safety of the anti-fibrinolytics (25,28). That timely meta-analysis found that none of the anti-fibrinolytics were linked to increased risk of mortality, renal failure, myocardial injury, or stroke in cardiac surgery. Only high-dose aprotinin reduced the risk of re-exploration, but it led to a transient rise in serum creatinine not linked to subsequent dialysis-dependent renal failure. The field is now eagerly awaiting the results of the BART trial (Blood Conservation Using Anti-fibrinolytics: Randomized Trial in High-Risk Cardiac Surgery), the first head-to-head randomized placebo controlled trial into the efficacy and safety of aprotinin, tranexamic acid, and ϵ -aminocaproic acid. This non-industry-funded trial should have sample sizes large enough to determine adverse drug effects (if any) on rare events such as death from massive hemorrhage, stroke, non-troponin myocardial injuries, and renal failure requiring dialysis—results are expected toward the end of the year.

In light of published and company-held observational datasets, the FDA issued new guidelines in December 2006 recommending that aprotinin use should be limited to patients “who are at an increased risk for blood loss and blood transfusion” in the setting of coronary artery bypass graft surgery with CPB. Furthermore, to address safety concerns regarding hypersensitivity reactions to this bovine protein, the FDA now contraindicates “administra-

tion of Trasylol to any patient with a known or suspected prior exposure to Trasylol or other aprotinin-containing products within the previous 12 months.” The new FDA guidelines make sense and effectively reinforce existing trends for aprotinin use, which is generally reserved for higher-risk patients, such as those receiving anti-platelet medication (29).

COMBINATIONS OF MONO-TARGETING DRUGS: A WAY FOR THE FUTURE?

Instead of a multi-targeted intervention (such as an improved form of circuit coating or promiscuous protease inhibition), an alternative approach to blocking the many arms of the host response to surgery would be to administer a combination of mono-targeting drugs. This would counter the narrow focus of mono-targeted agents, which have not been able to deliver the anticipated clinical benefits. An example of such a drug is the complement C5 inhibitor Pexelizumab, which despite elegant preclinical research and development work, failed to meet its primary endpoint in phase III clinical trials (30–32). Because Pexelizumab blocks a pathway not specifically targeted by other pharmacologic interventions, it would be interesting to see this compound used in combination with other agents, such as inhibitors of leukocyte diapedesis.

The diapedesis step remains a highly attractive pharmacologic target to limit inflammatory organ injury after CPB. The lack of attention in this area seems puzzling, because it is well established that leukocyte entry and release of cytotoxic mediators represent key stages in organ injury, especially in the context of localized ischemia/reperfusion (16,33,34). A veritable raft of some 30+ novel pharmacologic agents have been developed for blockade of adhesion molecules and chemoattractant receptors involved in the extravasation process; these are at various phases of clinical trial development for treating inflammatory conditions such as inflammatory bowel disease, rheumatoid arthritis, vasculitis, sepsis, atherosclerosis, and more (35,36). It would be most interesting to develop such agents as anti-inflammatory agents for use in surgery with CPB, but to the best of my knowledge, this approach has not yet been attempted. One note of caution when considering using such anti-adhesion molecule therapies is that they have been linked to pro-inflammatory side effects (37,38). Small molecular weight antagonists may avoid the serious side effects of antibody therapies, and it is sobering to consider the failed stroke trial of enlimomab, an anti-intercellular adhesion molecule (ICAM)-1 antibody treatment (39). However, the potential efficacy of targeting the leukocyte-endothelial adhesion pathway has been shown by the “part-time” leukocyte inhibitory effects of the anti-coagulant, fondaparinux. A pentasaccharide motif from fondaparinux not

related to its anti-coagulant properties inhibited leukocyte adhesion and inflammatory injury in a model of kidney ischemia/reperfusion injury (40).

It is disappointing that dedicated agents specifically invented to target the leukocyte transendothelial migration step in other fields have not thus far been tested in the context of cardiothoracic surgery with CPB. Instead, it has been left to part-time inhibitors, such as aprotinin and fondaparinux, to show the principle that such inhibition could exert powerful protection on the systemic inflammatory response.

A useful strategy to complement almost any other form of intervention is leukofiltration (41). Although this does little to prevent inflammatory activation from occurring in the first place, it prevents the most activated (and adhesive) leukocytes and platelets from re-entering the patient circulation.

Further study is also needed into circuit design with a view to curbing the hydrodynamic shear forces exerted on erythrocytes as they pass through the extracorporeal circuit. Hemolysis is an ongoing problem of extracorporeal perfusion, despite being recognized as a concern since the 1970s (42). Recent work has shown that free hemoglobin, once it is released from the protective environment of the red corpuscle, harbors a uniquely bioavailable heme iron moiety that is potently pro-oxidant and is linked to renal failure (43–45). In cardiac surgery, genetic traits associated with impaired scavenging of free hemoglobin are linked to a raft of vascular and perioperative complications in diabetic patients (46–48). An oxidative burst caused by hemolysis occurs at the time of cross-clamp release, contemporaneous with the main burst of microbubble generation, long before systemic cytokines are raised in the circulation (49,50). It is highly likely that modifications to the circuit or cardiotomy suction devices to curb the extent of hemolysis would simultaneously curb microbubble formation (51,52). Antioxidant therapy could also be considered during CPB, especially if used in combination with other anti-inflammatory interventions (53).

CONCLUSIONS

Pharmacologic strategies to curb the systemic inflammatory response to surgery have evolved in large part from existing agents used to control bleeding and coagulation (e.g., aprotinin and heparin coating of circuits). Very few dedicated anti-inflammatory agents have been developed specifically to combat the inflammatory response and, where they have, their therapeutic target may have been too narrow to blunt the multi-system etiology of the systemic inflammatory response. An inescapable truth would seem to be that a multi-system disorder such as the host response to CPB requires a multi-targeted intervention, either through the use multi-targeted intervention

(e.g., serine protease inhibition or improved circuit coating) or a combination of mono-targeting interventions (e.g., anti-fibrinolytic, anti-coagulant, anti-complement, anti-leukocyte, anti-cytokine, and antioxidant treatments). Safety issues related to the use of anti-fibrinolytics in cardiac surgery dictate that clinical trials in future be adequately powered to detect clearly defined adverse events, such as stroke, myocardial injury, and acute renal failure requiring dialysis.

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