EDITORIAL VIEWS

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Inflammatory Cascade

A Final Common Pathway for Perioperative Injury?

Traumatic wounds, bee stings, and bacterial, viral, and parasitic infections all produce early phase reactants that lead to the efficient recruitment of targeted inflammatory cells to the affected site. Millions of years of evolution have produced dozens of molecules, primarily cytokines and growth factors, that precisely control the immune system response. The first of these early alert proteins to be discovered were the three interferons—α, β, and γ. Subsequently, during the past 2 decades, numerous proteins have been cloned and sequenced and their products used to define their precise function(s). These secreted protein mediators include cytokines (to date, interleukin (IL)-1-16), growth factors such as transforming growth factor-β, and chemokines such as macrophage inflammatory protein-1 α, β, and RANTES. Isolating the individual components of this complex communication network has enhanced our understanding of the inflammatory response and its role in acute disease. Recent findings even suggest important implications for high-risk patients undergoing surgery, particularly when subjected to postischemic reperfusion, as exemplified by a cardiopulmonary bypass (CPB) model.[1]

An Inflammatory Cascade Paradigm—The CPB Model

Cardiopulmonary bypass represents a unique medical condition that induces a systemic inflammatory response for which the human immune system has not yet evolved a specific response. Consequently, when confronted with the multiple insults of CPB, the magnitude of the immune system response is exaggerated, confusing, and complex. For example, the postbypass period is characterized by large fluid shifts, temperature changes, coagulation disturbances, and increased concentrations of catecholamines and stress hormones.[2,3]‡ An exaggerated inflammatory response to reperfusion may be largely responsible for systemic vasodilation during rewarming, fever, postoperative bleeding, and reperfusion injury to the heart, brain, kidney, and gut, leading to either permanent organ injury or transient dysfunction.[1,4]

How might we envision the role of the inflammatory response, given this complicated sequence of events? Based on *in vitro* and *in vivo* studies, we can suggest a paradigm describing the interactive steps that likely take place during the postischemic inflammatory state after CPB. Figure 1 is one schematic representation. In this model, neutrophil-endothelial cell adhesion is central to postischemic reperfusion.[5] Initially, oxygen free radicals are released from endothelial cells in reperfused organs, such as the heart and lung, leading to alterations in endothelial cells that promote early neutrophil targeting, activation of neutrophils in transit through these organs, local activation of serum complement, and induction of cytokine synthesis. Initial neutrophil attachment to the endothelium results in translocation of P-selection from intracellular vesicles to the cell membrane and initiation of platelet activating factor synthesis. These changes lead to more neutrophil adhesion, neutrophil activation, and neutrophil adhesion protein (CD11/CD18 integrin) expression *via* endothelial membrane-bound platelet activating factor.[6] Proinflammatory cytokines such as IL-1β and TNFα, and chemokines such as IL-8, are newly synthesized, largely within endothelial cells, in reperfused organs within hours, and induce increased expression of adhesion molecules on endothelial cells and other tissue-specific cells (*e.g.,* myocytes, pulmonary alveolar lining cells, glomerular or renal tubular epithelium).[7] In turn, this results in tighter neutrophil attachment *via* intercellular adhesion molecule-1, transmigration of neutrophils into the interstitial space, and release of large amounts of free radicals.

Nitric oxide produced by endothelial cell nitric oxide synthase or other nitric oxide synthase isoforms may exert important controls over many of these processes by inducing vasodilation, regulating leukocyte recruitment, scavenging endothelial-generated oxygen radi-

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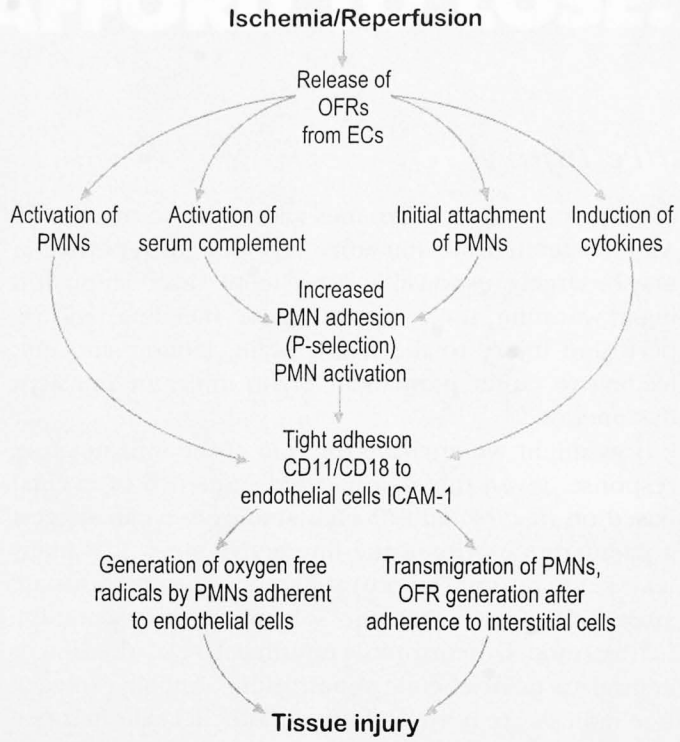

Fig. 1. A schematic representation of interactive components of the immune response that likely occur during the postischemic inflammatory state after CPB. EC = endothelial cells; OFR = oxygen free radicals.

cals, and preventing upregulation of neutrophil CD11/CD18. However, nitric oxide production is impaired after ischemia/reperfusion, and inhibitory controls over leukocyte migration, oxygen radicals, and neutrophil adherence are mitigated.

Therefore, there are a number of potentially serious immunologic consequences associated with cardiac surgery that may lead to adverse clinical events, including: 1) the CPB circuit itself is immunogenic and induces activation of complement, platelets, and neutrophils, as well as release of proinflammatory cytokines; 2) reperfusion of ischemic organs after CPB initiates a complex interaction between these same inflammatory components, which may lead to exaggerated local, organ-based, inflammatory responses in lung, heart, kidney, brain, and gut; and 3) rewarming may further induce systemic neutrophil adhesion, sequestration, and degranulation.

Clinical Investigation of the Perioperative Inflammatory Response

Clearly, the clinical implication of the perioperative inflammatory response may be enormous and, therefore, warrants serious investigation. Four stages of this investigatory process can be postulated. The first stage, which consists of observational studies, has been addressed during the past decade, and has demonstrated complement activation and cytokine/chemokine release, as well as increased concentrations of neutrophils, endotoxin, and elastases, during and after CPB.[8–12] Although these descriptive results are of interest, the critical challenge for investigators is to establish the true significance of these findings by determining whether a relation between these inflammatory markers and adverse clinical outcome exists, and, if it does, whether this relation is associative or causal (the second stage of investigation). If, in fact, the second stage studies find that no relations exist, then one questions the rationale for further substantive research. However, if an associative relation can be discerned (or even perhaps a causal relation), then there is potential for discovering therapeutic agents that may mitigate the CPB inflammatory response (the third stage of investigation). Finally, if these investigations yield such agents, and if these are proven safe, then pursuit of large-scale outcome trials (the fourth stage of investigation) is warranted, to establish the efficacy and cost-effectiveness of these novel therapeutic agents.

Currently, it appears that we are at the second stage of investigation of CPB-induced inflammatory response, and preliminary studies have been encouraging, because they suggest a relation between CPB-induced mediators and both early and late hemodynamic effects, as well as more important surrogates of injury, such as myocardial ischemia and dysfunction.[4] Also, these investigators postulate that the early effects are mediated through regulation of nitric oxide homeostasis, and the later effects by alteration of the vascular endothelium. These findings are important, but are limited because only surrogates of outcome have been investigated, and not adverse outcome itself.

The Current Study

In the current issue of ANESTHESIOLOGY, Journois and colleagues[13] focus our attention on the potential role of inflammatory mediators modulating specific clinical end-points, including postoperative pulmonary oxygen exchange, bleeding, and body temperature fluctuations after bypass. The results of this preliminary study suggest beneficial effects of high-volume, zero-fluid balance ultrafiltration (z-BUF) during the rewarming period of CPB in children. The use of z-BUF was associated with

reduced perioperative blood loss, time to extubation, and postoperative alveolar-arterial oxygen gradient, and suggest potential association between these events and reduction in plasma levels of proinflammatory mediators. Immediately after z-BUF, TNFα, C3a, and myeloperoxidase, a surrogate marker for neutrophil degranulation, were reduced; and, at 24 h, plasma levels of proinflammatory cytokines IL-1β and IL-6, the neutrophil chemoattractant IL-8, neutrophil counts, and myeloperoxidase levels also were decreased. Although this is a preliminary study in which an association is suggested, and although there are a number of limitations in this study's design, the findings are suggestive and potentially important.

Journois *et al.*'s[13] finding of a significant reduction in time to extubation and postoperative alveolar-arterial oxygen gradient suggests diminished post-CPB pulmonary injury. Postoperative blood loss may have resulted from multiple factors, such as a direct or indirect effect on platelet function, a reduction in capillary leak typically induced by proinflammatory cytokines and complement, or inhibition in cytokine-induced coagulopathy and fibrinolysis. Inhibition of sustained and increased levels of cytokines may have blunted the typical central actions of cytokines that produce fever.[14]

However, three factors are important to consider:

1. A direct cause-and-effect relation between the measured inflammatory mediators and improvements in clinical endpoints cannot be proven;
2. Whether the broad removal of multiple inflammatory mediators is necessary for clinical benefit is unclear. Significant reductions in post-CPB pulmonary injury were demonstrated previously experimentally either with pharmacologic inhibition of complement[15] or the use of a complement-deficient model.[9] In addition, in previous studies, researchers suggested that mechanical removal of neutrophils alone may confer protection from postischemic injury.[10]
3. Neutrophils, cytokines, and other inflammatory mediators are necessary for wound healing and, because CPB is known to induce a state of immunosuppression, the indiscriminate removal of inflammatory mediators may be detrimental. For example, proinflammatory cytokines may play a beneficial role in preconditioning of ischemic tissues,[16] and may confer protection from ischemic injury in certain patients.

An additional intriguing finding by Journois and colleagues is the elimination of IL-10 in the immediate post-CPB period. Interleukin-10 is a potent antiinflammatory cytokine that inhibits the release of TNFα and IL-8 by activated macrophages and neutrophils, which are induced during and after CPB.[11,12] Accordingly, as Journois and colleagues acknowledge, the elimination of, or reduction in, cytokine levels may not *a priori* lead to desired antiinflammatory effects.

Conclusions

The data presented by Journois *et al.* suggest that the cumulative effect of mechanically removing inflammatory mediators during CPB by their ultrafiltration method may be clinically beneficial in pediatric cardiac surgery patients, and warrants further study. Understanding the inflammatory cascade during and after CPB will be important in forming the basis for new therapies and in designing rational clinical trials to definitively test the safety and efficacy of hemofiltration in the setting of CPB. If larger controlled studies confirm and expand on the beneficial clinical effects of hemofiltration, and continue to demonstrate that hemofiltration is safe, a positive impact on postcardiac surgical morbidity and mortality may result. From a cautionary perspective, it is important to note that modulation of the human immune response has always been difficult, and often dangerous. Therefore, future clinical trials likely will need to focus on a relatively homogeneous clinical population and contain rigorous measures of safety, before multicenter trials in the broad population are undertaken. Perhaps, though, cardiac surgery offers both a unique window into the workings of immune system and a unique opportunity to modulate it. Because the human immune system has only dealt with CPB for less than two generations, we may be able to create a more perfect balance between appropriate wound healing and a systemic immune response gone awry.

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