What is the Evidence that CPB per-se (versus cardiac surgery and myocardial ischemia-reperfusion) Activates the Inflammatory Response and that this Affects Outcomes?

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Many questions remain in our understanding of inflammation and outcome. Although there is clear evidence that an inflammatory response (of variable intensity) occurs during the course of cardiac surgery, it remains unclear as to the relative contribution of the surgical trauma, ischemia-reperfusion (that occurs when the heart is stopped and reperfused; or other organs are made ischemic), and the specific bypass initiated response due to the interaction between blood and the foreign surfaces of the cardiopulmonary bypass (CPB) apparatus as well as other factors such as endotoxemia [1,2]. Furthermore, the relevance in terms of the clinical significance of the inflammatory response to overall outcomes remains largely an unanswered question.

Considerable heterogeneity exists with respect to the manifestations of the inflammatory response during cardiac surgery [2]. Whereas most patients demonstrate some degree of inflammation, only a subset of patients develop a significant enough systemic inflammatory response syndrome (SIRS) that major organ dysfunction may manifest. Limiting our understanding of the relationships of inflammation to outcome has been an incomplete understanding of the nature of the various components of the inflammatory response, i.e. those which are injurious versus those that are protective, as well as inherent difficulties in accurately measuring these responses. Furthermore, many past studies have been limited by focusing on surrogate endpoints (and other intermediate clinical parameters), as opposed to meaningful, long-term clinical outcomes. Adding to the uncertainty in this field are the inconsistencies in statistical analysis, with most studies reporting only associations (as opposed to causative relationships) in the various statistical reporting that have been outlined.

The direct response to the interaction between the blood and foreign surfaces of the CPB circuit initiates a robust inflammatory reaction. However, even in the absence of CPB, that is, during off-pump cardiac surgery, a significant inflammatory response can be documented. [3] With the emergence of off-pump coronary bypass graft surgery (OPCAB), additional insights into the relative impact of ischemia-reperfusion, surgical trauma, and the effects of the extra-corporeal circulation became apparent, increasing our understanding of the relative contributions of these procedures during cardiac surgery. Theoretically, the operative trauma during off-pump surgery is similar to more conventional CABG and ischemia-reperfusion phenomenon related to aortic cross-clamping should be reduced. In addition, the contact activation between the blood and the foreign surfaces of the bypass circuit should be eliminated during OPCAB surgery. Also to be considered is endotoxemia, which is understudied in the setting of off-pump cardiac surgery, although one could theorize that the hemodynamic compromise and subsequent splanchnic hypoperfusion would have similar levels of endotoxin release as conventional on-pump CABG surgery. Published studies comparing the various inflammatory responses to these two procedures have produced a rather mixed picture. Depending on the inflammatory mediator that is examined, one can draw
quite different conclusions as to the relative contribution of the inflammatory response in these two operative procedures. [3]

Understanding whether cerebral outcome is affected by inflammation has been studied in both experimental and clinical settings. It is not entirely clear whether a specific cerebral inflammatory response occurs as a result of CPB in humans. In the laboratory setting, Hindman et al made the observation in rats that messenger RNA for cyclooxygenase (COX2) was upregulated following CPB suggesting that, on the molecular level, CPB induces an overexpression of this pro-inflammatory gene in the brain. [4] What is not clear was whether this was a primary event (i.e. as a direct result of the pro-inflammatory effects of CPB) or a secondary event as a result of other injurious effects of CPB (such as microembolization etc.) In settings apart from cardiac surgery, inflammation is known to directly injure the brain, [4] but it is also known to result as a response to various cerebral injuries (such as ischemic stroke). [5] Either situation is possible in the case of CPB and continues to be the focus of future research.

In the clinical setting, although there is no direct evidence that inflammation causes cardiac surgery-associated adverse cerebral outcome, there is some compelling indirect evidence. For example, Mathew and colleagues demonstrated a relationship between poor cognitive outcome and an impaired immune response to circulating endotoxin that inevitably translocates from the gut into the bloodstream due to alterations in splanchnic blood flow during CPB. [6] It is known that having a low antibody response to circulating endotoxin is associated with an over-stimulated inflammatory response. [7] Thus, demonstrating the relationship between low endotoxin antibodies and poor cognitive outcome may be mediated by an augmented inflammatory response. Further insights into inflammation and outcome have come from recent genetic studies. In a study of 2140 patients examining 26 different SNPs, an association between genes related to the inflammatory response (CRP and IL6) and an increased risk of stroke after cardiac surgery was demonstrated. The presence of the minor alleles of CRP, IL-6 had a three-fold increase in the risk of stroke after cardiac surgery. [8] Interestingly, there was no single (or combination) of prothrombotic genes associated with stroke suggesting that inflammatory mechanisms supersede thrombotic in post-op patients at risk of a stroke. If inflammation appears to be important to stroke, genetic linkages have also been found with more subtle neurologic injury such as cognitive dysfunction. [9] In a similar study to the previously mentioned stroke trial, more than 30 genes were probed to examine not only a relationship between a certain gene combination and adverse outcome but a biologically plausible mechanism based on work related to platelet activation after cardiac surgery. In this most recent and intriguing study outlining the impact of genetics on outcome after cardiac surgery, 513 patients were extensively genotyped and had cognitive testing after cardiac surgery. A link between the presence of 2 SNPs a CRP and P-selectin (CRP1059G4/C and SELP1087G/A) and a reduction in cognitive deficit was found. The incidence of cognitive deficit was 16.7% in carriers of the minor alleles of both these genes compared to 42.9% of the patients possessing these major alleles representing an absolute risk reduction of 20% in the CRP allele patients and 50% in the SELP allele patients. What was unique about this study was the fact that it was the closest link that has been found towards a mechanism-based genetic effect where these polymorphisms were associated with reductions with both CRP and platelet activation, respectively, suggesting a diminution of the perioperative inflammatory and prothrombotic states may be beneficial with respect to reducing the cognitive deficits which continue to be experienced after cardiac surgery. [9]

As previously stated, evidence linking inflammation to specific end-organ outcome is scarce, but indirect evidence does suggest individual organ-specific relationships. With respect to cardiac outcome, atrial fibrillation (AF) that occurs in 20-50% of postoperative patients [10-13],
has been linked to an inflammatory response in other settings, such as myocarditis [14]. In the setting of cardiac surgery, Lo et al [15] have found a relationship between increases in preoperative C-reactive protein (CRP) levels and the subsequent development of post-cardiac surgery AF. Further evidence suggests a dose-dependent effect of inflammation on AF. Indeed, a study by Gaudino et al [16] demonstrated that genetic polymorphisms that predisposed to higher postoperative levels of interleukin-6 (IL-6) were more prevalent in those who subsequently went on to develop AF postoperatively. A further link has been found with respect to the upregulation of monocyte adhesion and receptor, CD11b. [17] Acute elevations in these inflammatory mediators appear to be linked, (although only demonstrating association, not specific causation) with acute AF. Chronic elevations in inflammatory mediators have also been linked to postoperative AF with the cardiac surgery population. Mandal found that those with elevations in preoperative levels of auto-antibodies directed towards heat shock protein 65 (HSP-65) were also more likely to develop AF postoperatively. With HSP-65 being one of the chaperone proteins that several cell types, including monocytes, express on their surface after stressful stimuli, Mandal et al hypothesized that with the stress of cardiac surgery and the subsequent HSP upregulation, patients with higher preoperative titres of anti-HSP65 autoantibodies would be more predisposed to an intensified inflammatory response in the atrial tissues, leading to a higher incidence of AF.

**Renal outcome** has also been found to have an inflammatory component. Rinder et al [2] have demonstrated that there is a relationship between cellular activation and acute postoperative renal injury after cardiac surgery. Specifically, they examined neutrophil adhesion receptor CD11b together with evidence for higher circulating polymorphonucleocytes (PMNs). This link between inflammation and adverse renal outcomes after cardiac surgery is also parallel to the link between other inflammatory settings, such as sepsis-induced renal dysfunction, again adding weight to the evidence linking inflammation overall to renal injury.

**Pulmonary injury** after cardiac surgery was the focus of early studies. Soon after the advent of modern cardiac surgery [18], a link between systemic inflammation and lung injury has been demonstrated. Tomasdottir [19] for example, demonstrated that a specific gene polymorphism for TNFβ and the combination of TNFβ and apo-lipoprotein ε4 was associated with elevated plasma levels of TNF-alpha and IL-6. Furthermore, these pro-inflammatory mediators were correlated with postoperative pulmonary dysfunction, as manifest by prolongation of patient intubation. These particular links are arguably less robust than other organ dysfunction; however, they are still present.

Unquestionably, there are multiple studies that show an association between inflammation and adverse outcome, although it has been difficult to demonstrate direct causation. As a result, many important clinical outcomes have only been demonstrated to have an indirect relationship to inflammation. That said, there is important, meaningful data which has outlined various inflammatory responses to adverse clinical outcomes. No single piece of information will solve the complex puzzle of inflammation and outcome. It is the individual pieces, of sometimes unrelated information, that put together will make meaningful contributions to the ultimate solution.

**References**

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