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- Minimizing Morbidity of Cardiopulmonary Bypass



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Despite advances in traditional techniques, coronary artery bypass graft cardiac surgery is associated with a mortality rate of 1-4%, as well as a 1-4% incidence of perioperative myocardial infarction (MI) and stroke, or changes in neurological and neuropsychological function. Alternatives to traditional cardiac surgical methods, including “minimally invasive” techniques, are being developed to limit morbidity associated with conventional cardiac surgery. Although much effort has been focused on smaller alternative incisions to median sternotomy, much of the morbidity of cardiac surgery is related to manipulation of an atherosclerotic aorta (embolization) and artificial perfusion and to the biological response

they can lead to long-lasting cardiac, pulmonary, renal and neurological dysfunction in a subset of patients with limited reserve.

Using recent advances in perfusion technology and research in biomaterial sciences we have developed specific surgical techniques that have resulted in the routine application of more biocompatible circuits, such as heparin-bonded cardiopulmonary bypass circuits with alternatives to full anticoagulation protocol. In the laboratory, these techniques have been demonstrated to blunt the inflammatory response to CPB and promote hemostasis.

Clinically, the use of these circuits and techniques reduced the need for homologous transfusion

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*These different approaches result in markedly different effects on inflammation and thrombin generation during artificial perfusion.*

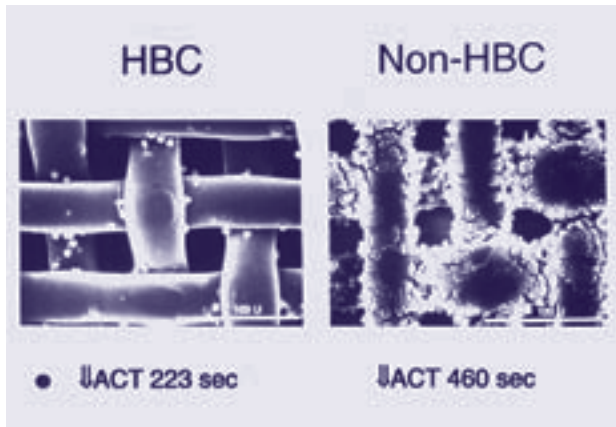
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of the body to artificial perfusion and gas exchange through the non-endothelialized cardiopulmonary bypass (CPB) circuit.

Within seconds of CPB, formed and unformed blood elements come into contact with the large surface area of the CPB circuit. Despite anticoagulation with heparin, this interaction results in extensive activation of platelets, neutrophils, complement, cytokines and the fibrinolytic system, producing a complex and intense “inflammatory” response. Furthermore, response to CPB is very heterogeneous and varies tremendously between patients, with some patients manifesting marked inflammatory changes and other little or none. Although these responses are usually short lived and leave no residual deficits,

and decreased neutrophil and complement activation, resulting in a reduction in thromboembolic complications, myocardial and pulmonary dysfunction, postoperative morbidity, and cost. The use of heparin-bonded circuits also has resulted in a dramatic decrease in the incidence of perioperative MI to less than 1%, neurological deficits to less than 1%, and pulmonary complications to 1.5%. Compared to previous reports, the incidence of neurological and persistent neuropsychological deficits following CABG were markedly reduced to near baseline.

Figure 1 shows a representative scanning EM at 200-fold magnification of the arterial filter (the last barrier to debris before the blood from the CPB circuit reaches the systemic circulation).

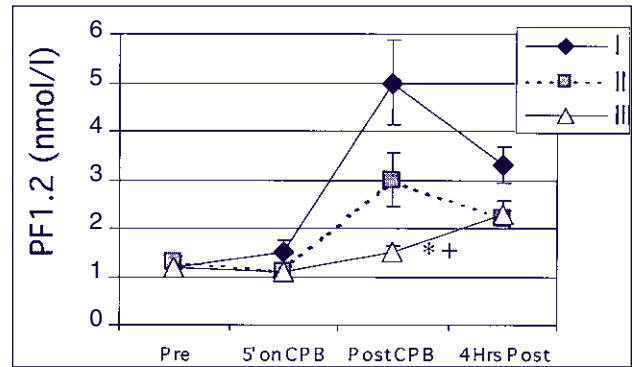


**FIGURE 1:** Scanning electron micrographs at 200 fold magnification of arterial filter. Lowest activating times (ACT) in seconds are noted. HBC= heparin-bonded circuits. Non-HBC- control non-heparin-bonded circuits.

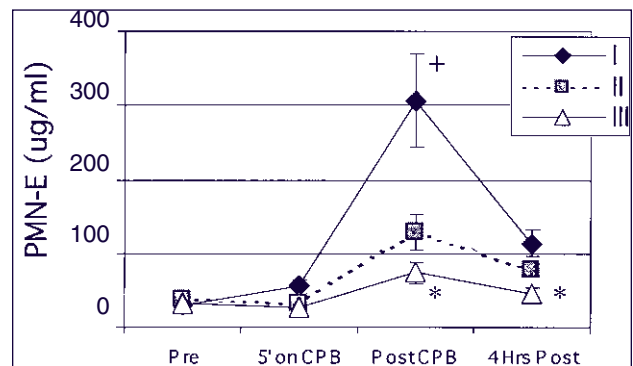
This comparison demonstrates dramatic reduction (quantified in 60 patients to be >80% reduction) in debris and inflammation resulting from the use of biocompatible heparin-bonded circuits with reduced anticoagulation protocol (HBC) compared with conventional non-biocompatible circuits with full anti-coagulation.

We are involved in several ongoing clinical investigations to study ways to dissociate the contribution of biocompatible circuits from the specific surgical techniques (the effects of cardiomy suction vs. use of cell saver technology) on markers of hemostasis, inflammation, neurological and neuropsychological deficits. Although both result in blood conservation, one (cardiotomy suction) re-infuses blood directly from the surgical field into the arterial side of the CPB machine. Cell saver technology, though not perfect, washes the cells prior to intravenous re-infusion. These different approaches result in markedly different effects on inflammation and thrombin generation during artificial perfusion. This research may lead to changes in both the design and application of this technology.

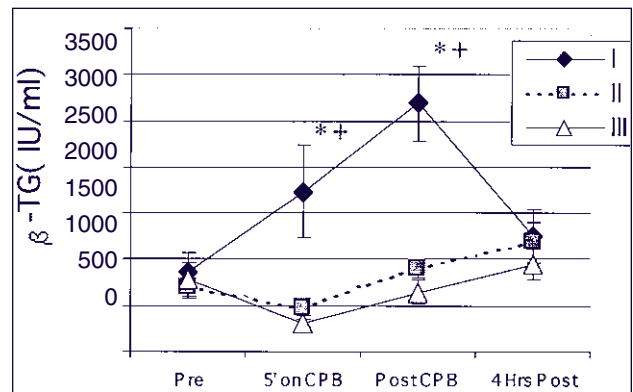
Heparin bonded circuits (HBC) have been proven to be effective in several research groups, including our own, in preserving platelet function and decreasing inflammation during CPB. However, markers of thrombin generation (PF1.2), inflammation (IL-6, IL-8, elastase, complement), platelet function ( $\beta$ -thromboglobulin) and neurological injury (neuron specific enolase, S-100b) are all nearly completely blunted when HBC are used and cardiomy suction is eliminated during CPB. Our results suggest that cardiomy suction should be eliminated whenever possible. Our results challenge



**FIGURE 2:** PF1.2 for thrombin generation.



**FIGURE 3:** PMN-E for elastase.



**FIGURE 4:**  $\beta$ -Thromboglobulin for platelet activation.

long held precepts that adverse outcomes possibly associated with thrombin generation, inflammation and platelet activation are inevitable whenever CPB is used (Figures 2-4).

We continue to investigate novel targeted pharmacological interventions as well as further biomaterial modifications of the perfusion surface to further attenuate platelet, neutrophil, and complement activation, and cytokine release.

With the increasing incidence and awareness of HIT(T) we have evaluated alternatives to heparin

anticoagulation using the short acting direct thrombin inhibitor Bivalirudin and have demonstrated safety and efficacy. The significance of post CPB HIT antibody conversion on long-term outcomes and the importance of limiting ubiquitous uncontrolled use of UFH is the focus of our future studies.

Finally, we are becoming more aware of differences and individual variability between individual patients in expressing such responses to CPB with some patients having a minimal response and others having very accentuated responses to CPB. We are trying to determine ways to identify individual

biological susceptibility prior to surgery so we can alter surgical technique (either avoid CPB altogether or used a combination of altered equipment, techniques and pharmacological therapy) and hope to develop reliable specific biological essays to predict an individual patient's response to artificial perfusion and direct clinical therapy. We also recognize that both CPB and transfusion may change patients' immunity and immunization and perhaps affect long term outcomes. We will study these interactions in collaborations with Drs. Nelson and Slichter in a three year NIH SCCOR-sponsored study.

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