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· Minimizing Morbidity of Cardiopulmonary Bypass, Valve and Aortic Surgery



The William K. Edmark Professor of Cardiovascular Surgery

AWARDS

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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. Morbidity is even higher in complex valve and aortic pathologies. Our research efforts are divided into two categories: 1) limit morbidity of cardiopulmonary bypass (CPB), cell salvage and transfusion; and 2) develop alternative therapies for complex aortic and valvular pathologies that do not require CPB.

Minimizing CPB Morbidity

Much of the morbidity of cardiac surgery is related to manipulation of an atherosclerotic aorta (embolization) and artificial perfusion and to the biological response of the body to artificial perfusion and gas exchange through the non-endothelialized CPB circuit. These effects may be compounded by the effects of autologous transfusion. 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 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 with previous reports, the incidence of neurological and persistent neuropsychological deficits following coronary artery bypass grafting (CABG) was markedly reduced to near baseline.

Figure 1 shows a representative scanning electron micrograph at 200-fold magnification of the arterial filter (the last barrier to debris before the blood from the CPB circuit reaches the systemic circulation). 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 compared with conventional non-biocompatible circuits with full anti-coagulation.

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

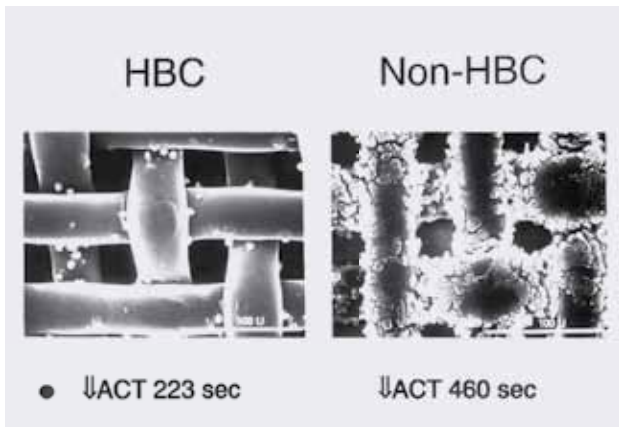


FIGURE 1: Scanning electron micrographs at 200-fold magnification of arterial filter. Lowest activating times (ACT) in seconds are noted. HBC = heparin-bonded circuits. Non-HBC = control non-heparin-bonded circuits.

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 heparin-induced thrombocytopenia thrombosis (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 unfractionated heparin (UFH) is the focus of our future studies.

Our research demonstrates wide differences and individual variability among 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 use a combination of altered equipment, techniques and pharmacological therapy); we hope to develop reliable specific biological assays 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 negatively affect long-term outcomes. As part

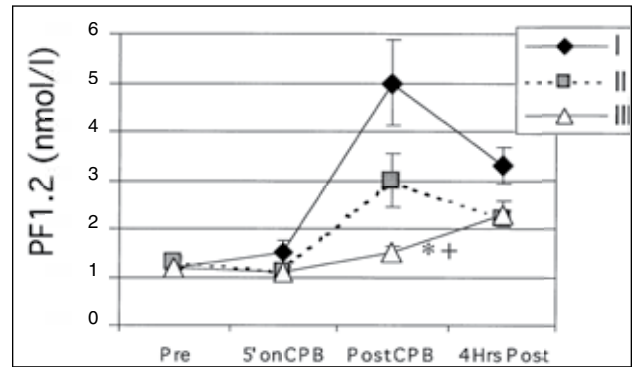


FIGURE 2: PF1.2 for thrombin generation

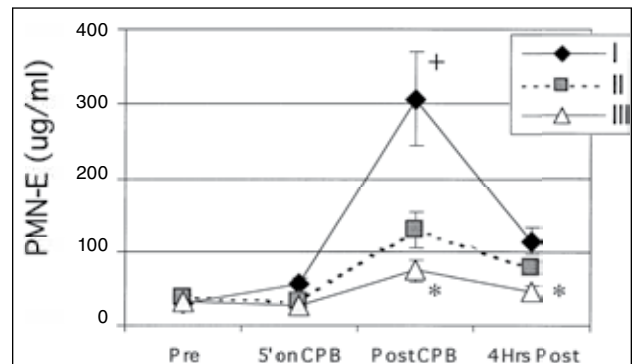


FIGURE 3: PMN-E for elastase

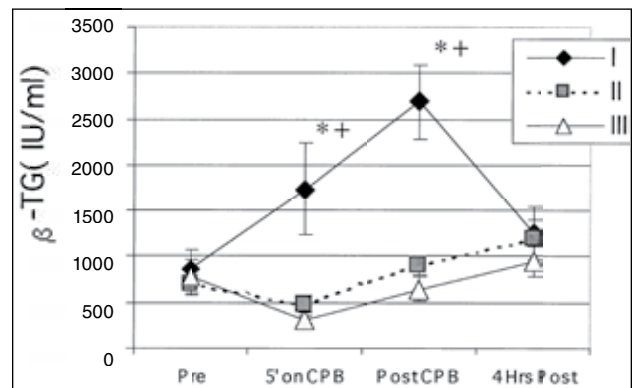


FIGURE 4: beta-Thromboglobulin for platelet activation

of a three-year NIH Specialized Centers of Clinically Orientated Research (SCCOR) grant and in collaboration with Drs. Nelson and Slichter, we are studying these interactions and the effects of the removal of passenger white blood cells from non-autologous blood on clinical and immunological outcomes of patients undergoing cardiac surgery.

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Alternative Therapies (no CPB) for Complex Aortic and Valve Pathologies

Traditional open surgical repair of complex descending thoracic pathologies is associated with significant pulmonary and neurological complications. In collaboration with Drs. Meissner and Starnes from the Division of Vascular Surgery, we are studying the long-term efficacy of innovative techniques (sole and hybrid) using endovascular stenting to minimize morbidity of complex thoracic aortic pathology (dissections and aneurysms) as part of a multi-center national Gore-TAG trial for both thoracic aortic aneurysms and traumatic aortic transections.

Trans-catheter Aortic Valve Therapy

The University of Washington Medical Center has been selected as one of only 25 international sites as part of the international multi-center prospective randomized PARTNER trial to study the safety and efficacy of percutaneous aortic valve therapy using the Edwards SAPIEN valve. This collaboration between Drs. Larry Dean and Mark Reisman from the Division of Cardiology and Drs. Verrier and Aldea from the Division of Cardiothoracic Surgery will offer therapy for symptomatic aortic stenosis to patients who are not candidates for conventional surgery with careful long term follow-up for this evolving percutaneous (trans-femoral) and trans-apical technology.

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