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• MINIMIZING MORBIDITY OF CARDIOPULMONARY BYPASS

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Despite advances in traditional techniques, coronary artery bypass graft (CABG) 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 neurologic and neuropsychological function. Alternatives to traditional cardiac surgical methods, including “minimally invasive” techniques, are being developed to limit morbidity associated with conventional CABG.

Many of the complications of CABG are related to the biologic response 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

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

Our results suggest that cardiotomy suction should be eliminated whenever possible and challenge long-held precepts that adverse outcomes possibly associated with thrombin generation, inflammation and platelet activation are inevitable whenever CPB is used.

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. Although these responses are usually short lived and leave no residual deficits, they can lead to long-lasting cardiac, pulmonary, renal and neurologic dysfunction in a subset of patients.

Using recent advances in perfusion technology and research in biomaterial sciences we have developed

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). This comparison demonstrates dramatic reduction (quantified in 60

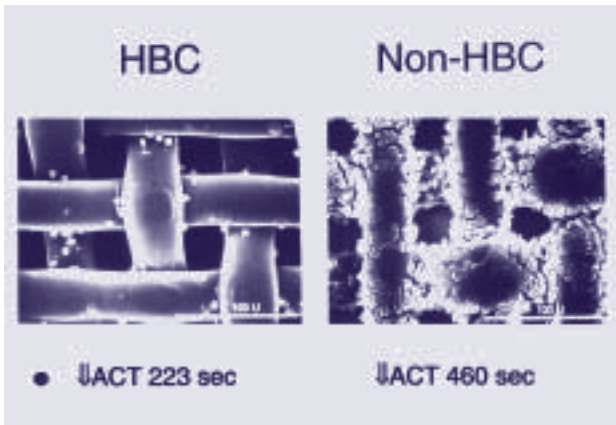


FIGURE 1: Scanning electron micrographs at 200 fold magnification of arterial filter. Lowest activating times (ACT) in seconds are noted. HBC= heparin-bonded circuits. Non-HBC- control non-heparin-bonded circuits.

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 disassociate 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) reinfuses 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 reinfusion. 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 (PFI.2), inflammation (IL-6, IL-8, elastase, complement), platelet function (β -thromboglobulin) and neurological injury (neuron specific enolase, S-100 β) 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

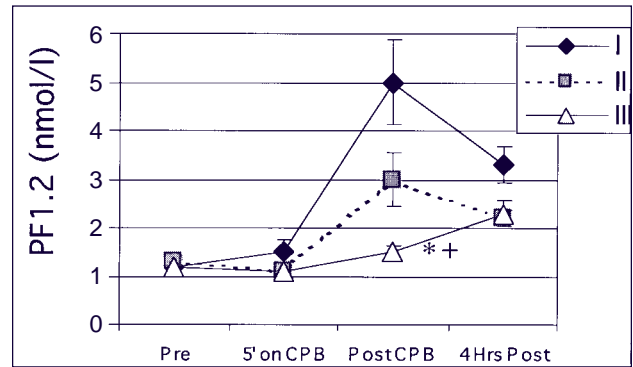


FIGURE 2: PF1.2 for thrombin generation

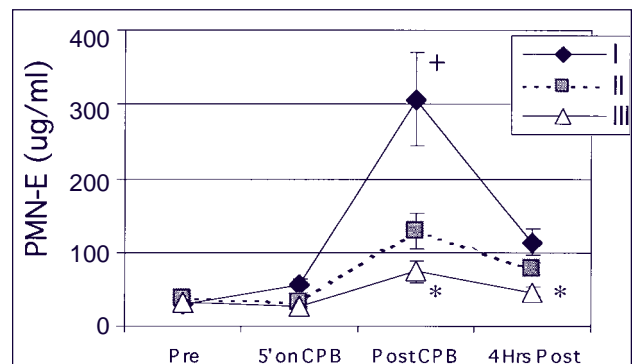


FIGURE 3: PMN-E for elastase

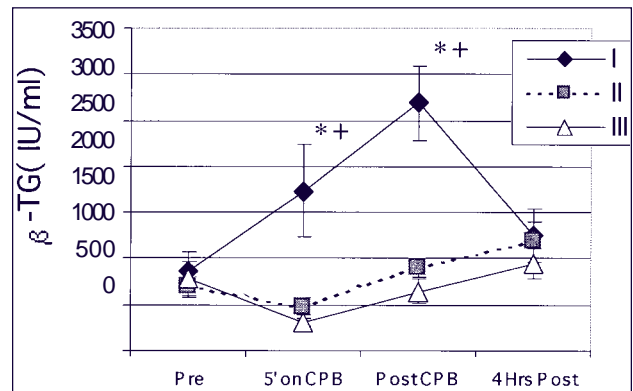


FIGURE 4: β Thromboglobulin for platelet activation

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.

Furthermore, 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 a

very accentuated response to CPB. In collaboration with labs of Drs. Mulligan, Rosengart and Chandler, 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). We hope to develop reliable specific biological essays to predict an individual patient's response to artificial perfusion and direct clinical therapy.

RELATED PUBLICATIONS

1. McKenney PA, Apstein CS, Mendes LA, Connelly GP, Aldea GS, Shemin RJ, Davidoff R. Immediate effect of aortic valve replacement for aortic stenosis on left ventricular diastolic chamber stiffness. *Am J Cardiol*, 1999; 84:914-18.
2. Aldea GS. Heparin-bonded circuits decrease thromboembolic complications in patients undergoing CABG. *Seminars in Cardiothor Vasc Anesth*, 1999; 3(1):9-16.
3. Shapira OM, Xu A, Aldea GS, Vita JA, Shemin RJ, Keaney JF. Enhanced nitric oxide-mediated vascular relaxation in the radial artery compared to internal mammary artery and saphenous vein. *Circ*, 1999; 100(Suppl II):322-27.
4. Shapira OM, Alkon JD, Macron DSF, Keaney JF, Vita JA, Aldea GS, Shemin RJ. Nitroglycerin is preferable to Diltiazem for prevention of coronary bypass conduit spasm – A prospective randomized study. *Ann Thor Surg*, 2000; 70(3):883-9.
5. Aldea GS, Mori H, Hussein WK, Austin RE, Hoffman JIE. Effects of increased pressure inside and outside the ventricles on total and regional myocardial blood flow. *Am J Physiol*, 2000; 279:H2927-38.
6. Slade P, Sanchez P, Townes B, Aldea GS. The use of neurocognitive tests in evaluating the outcome of cardiac surgery: Some methodological considerations. *J Cardiothorac Vasc Anesth*, 2001; 15(1):4-9.
7. Vander Salm TJ, Kip KE, Jones RH, Schaff HV, Shemin RJ, Aldea GS, Detre KM. What constitutes optimal surgical revascularization? Answers from the Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol*, 2002; 39:565-72.
8. Aldea GS, Soltow LO, Chandler WL, Triggs CM, Vocelka CR, Crockett GI, Shin YT, Curtis WE, Verrier ED. Limitation of thrombin generation platelet activation and inflammation by elimination of cardiomy suction in patients undergoing coronary artery bypass grafting treated with heparin-bonded circuits. *J Thorac Cardiovasc Surg*, 2002; Apr 123(4):742-55.
9. Aldea GS, Goss R, Boyle EM et al. Use of off-pump and on-pump CABG strategies in current clinical practice: the Clinical Outcomes Assessment Program of the State of Washington. *J Card Surg*, 2003;18:206-215.
10. Dabal RJ, Goss R, Maynard C and Aldea GS. The effect of left internal mammary artery utilization on short-term outcomes after coronary revascularization. *Ann Thorac Surg*, 2003; 76:464-70.

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