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Cardiac surgical patients exposed to heparin-bonded circuits develop less postoperative cerebral dysfunction than patients exposed to non-heparin-bonded circuits

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Abstract

A prospective randomized trial was used to study the incidence of cerebral dysfunction in patients undergoing cardiopulmonary bypass (CPB) with heparin-bonded vs non-heparin-bonded circuits. Although the etiology of postoperative cerebral dysfunction is controversial, activation of the systemic inflammatory response may play a role.

After institutional approval and informed written consent, 39 elective coronary artery bypass (CABG) patients were studied. A battery of neuropsychometric tests (NPMTs) was performed preoperatively, and 5 days and 6 weeks postoperatively. Significant change in NPMT performance was defined as a 25% or greater decrease in postoperative performance, compared to baseline. The number of abnormal tests per patient was calculated. Analysis using the Mann-Whitney rank test was performed for the first follow-up.

Patients randomized to heparin-bonded circuits had fewer abnormal NPMTs (>1 abnormal test) on postoperative day 5 (58 vs 70%, n = 19 and 20) than patients randomized to non-heparin-bonded circuits. Patients exposed to heparin-bonded circuits had fewer abnormal tests (>1 abnormal test) at 6 weeks (36 vs 63%, n = 14 and 16).

Results suggested that the attenuation of systemic inflammation by heparin-bonded CPB circuits may lower the incidence of cerebral injury in cardiac surgical patients.

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Introduction

Coronary artery bypass graft (CABG) surgery is one of the most common cardiac surgical procedures performed in the USA. Cardiopulmonary bypass (CPB) is utilized, although many complications have been attributed to the use of CPB, including cerebral injury following this type of surgery. Clinicians recognize the magnitude of the problem of transient or permanent damage resulting from exposure to extracorporeal circulation. The harmful biologic reactions (activation of the coagulation cascade and complement activation) do not occur when normal blood circulates through intact blood vessels lined by endothelial cells. Blood, in contact with the foreign surfaces of artificial materials that comprise the extracorporeal circuit, initiates complement activation, which results in a host of biological reactions that can produce what is known as the 'whole body inflammatory response'.

Successful attenuation of the diffuse inflammatory response related to artificial circulation has been studied in many ways since 1953, when the first successful cardiac procedure was performed.

The use of Carmeda® (Medtronic, Inc., Anaheim, CA, USA) coating has been shown to attenuate the inflammatory response.[1] The neurologic complications associated with CPB are well studied and documented.[2] Cognitive dysfunction is evaluated using a battery of neuropsychometric tests (NPMTs).[3] The incidence of neuropsychometric changes can be as high as 25-30% 1-3 months following cardiac surgery. The etiology of cognitive dysfunction may be the result of cerebral hypoperfusion secondary to inadquate systemic perfusion pressure, or it may be the result of emboli generated from either the surgical site or CPB. The use of a Carmeda®-coated circuit and possible attenuation of neurologic insult from CPB is studied.

Methods

After institutional approval and informed written consent, 39 elective CABG patients were enrolled and randomized to heparin-bonded (Carmeda®) vs non-heparin-bonded CPB circuits. Patients with evidence of preexisting neurologic or psychiatric illness were excluded. The groups were further substratified by age, so that each group had equal numbers of patients of 70 years or older. A battery of NPMTs were performed preoperatively, and 5 days and 6 weeks postoperatively. Significant change in NPMT performance was defined as a 25% or greater decrease in postoperative performance compared to baseline. The number of abnormal tests per patient was calculated. Analysis using the Mann-Whitney test was performed for the first follow-up.

Study circuit design

The circuit comprised polyviny chloride tubing (PVC) coated with Carmeda® covalently bonded heparin through the entire length of the circuit. A Maxima membrane oxygenator, an Intersept cardiotomy reservoir, and a 40 μm Intersept arterial line filter (Medtronic), also coated with heparin, were used. The centrifugal arterial pump was a Medtronic, Biomedicus (Minneapolis, MN, USA). All blood re-introduced to the circuit from the autologous blood salvaging device (Haemonetics, Braintree, MA, USA) was also filtered with a Pall 40 μm blood filter (Pall Biomedical, Glen Cove, NY, USA). The priming solution consisted of 1 liter of Normosol R and 1 liter of Hetastarch, creating a 3% colloid solution. The patient was cannulated with the appropriate-sized arterial cannula (non-coated) and a two-stage venous return canal (non-coated) and placed on bypass at a flow calculated to a cardiac index of 2.4 1/min/m^2. The patients were heparinized with 300 U/kg of porcine heparin and maintained at an activated clotting time > 480 s. During CPB, non-pulsatile flows of 2.4 1/min/m^2 and alpha-stat management of pH during hypothermia to 32°C were used. In some cases, vasoactive

medications such as phenylephrine or isoflurane were administered during CPB to maintain the mean arterial pressure between 55 and 70 mmHg. Myocardial protection was facilitated with antegrade and retrograde cardioplegia delivery using 4-6°C solution consisting of a ratio of 4:1 blood to crystalloid. Blood temperature was never taken above 37.5°C during the rewarming phase of the procedure. Air was evacuated using the mechanical technique of Trendelenberg positioning, and ascending aortic venting. In many cases, the adequacy of these procedures was assessed using transesophageal echocardiography.

Neuropsychometric tests

The neurological 'Mini-Mental Status' test was used for orientation, memory, attention, calculation, general knowledge, and language. The Rietan Trail-Making test was used to measure visual, conceptual, and visiomotor tracking. The Repetitive Tapping test was used to measure manual dexterity. The Buschke Verbal Selective Reminding test was used to measure retention, storage, and retrieval. Finally, the Grooved Pegboard test was used as another measure of manual dexterity. These tests were selected for their ease of administration, reliability and patient acceptance, and capacity to examine different cognitive domains.

Results

Patients randomized to heparin-bonded circuits had fewer abnormal NPMTs (>1 abnormal test) on postoperative day 5 (58 vs 70%, $n = 19$ and 20) than patients randomized to non-heparin-bonded circuits. Patients exposed to heparin-bonded circuits had fewer abnormal tests (>1 abnormal test) at 6 weeks (36 vs 63%, $n = 14$ and 16).

Discussion

The clinical need addressed by coating the blood-contact surfaces of the extracorporeal circuit is to imitate the biocompatible properties of the vascular endothelium that lines the circulatory system of the human body. The deleterious effects of extracorporeal circulation, some of which continue to manifest themselves for years after surgery, have been disregarded because of the necessity of use for life-saving procedures.

These biological reactions include whole defensive systems such as coagulation, fibrinolytic, complement, kallikrein and kinin systems. These systems involve activation and consumption of platelets, activation of leukocytes and destruction of red blood cells, anaphylactic reaction, oxygen free radicals, and endotoxins, among others. Furthermore, these systems can crossactivate each other. Eventually these interactions affect the heart, lungs, kidneys, brain, and other organs to cause the 'whole body inflammatory response', or 'postperfusion syndrome'.

Normally these systems initiate hemostasis to maintain vessel integrity, stimulate fibrinolysis, attack foreign bodies, activate the immune system, and perform other roles to maintain the balance between these systems. Once the blood is exposed to large areas of a foreign surface, the normal state is disrupted and these defense mechanisms are activated. These detrimental effects are caused not by what the foreign surface does to the blood, but rather what it does not do to the blood, which is to mimic the endothelium. The concept to bond artificial blood-contact surfaces with heparin was conceived as a way of bridging the inert with the living.[4]

The method of Carmeda® BioActive surface coating is this type of endpoint-attached heparin. This method mimics the orientation of heparan sulfate on the plasma membrane of natural endothelial cells. Heparan sulfate is a heparin-like proteoglycan that helps bestow thromboresistant properties to endothelial cells.

By arranging heparin molecules and preserving active sites, endpoint-attached heparin is able to interact with blood. Heparin binds to the ATIII molecule, a normal physiological inhibitor of the coagulation cascade, at an active available site. This induces a conformational change in ATIII that increases its affinity by at least 1000 times. Thrombin (factor IIa), as a representative coagulation factor, binds to ATIII, forming a harmless inactive complex, which prevents thrombin from activating fibrinogen and eventually forming fibrin and organized thrombi. These inactive complexes, known as thrombin-antithrombin III or TATs, are released from the imobilized heparin and swept away from the site by flowing blood. The immobilized heparin molecules serve as catalysts for this reaction, are not consumed and are available to repeat this cycle.

There is also some evidence that endpoint-attached heparin also inhibits factor XII at the initiation of the coagulation cascade. Heparin binds factor XII and inhibits its conversion to activated factor XIIa. Inhibition of the coagulation cascade at its beginning may have a more profound effect on thrombus formation than inhibiting factors toward the end of the cascade because of the amplifying effect of the cascade. Inhibiting factor XII immediately would be more effective in the prevention of thrombosis than inhibiting thrombin (factor II) after the amplifying effect has increased its concentration. As factor XII activates other enzymatic systems such as the kallikrein and fibrinolytic system, there would now be inhibition of these defensive systems with inhibition of factor XII.

The complement system is a cascade of at least 20 different plasma proteins, much like the coagulation system. Complement has a central function within the body's defenses against non-self. It is involved in regulation of other effector systems such as neutrophils, and also has direct cytotoxic activity of its own. Like the coagulation system, it has two pathways activated by different stimuli, but they unite to a common effector system. The classical pathway is stimulated by antibody, whereas the alternative pathway is the main system involved in the response to extracorporeal circulation. Carmeda® is a well-known inhibitor of C3-convertase, which catalyzes the formation of C3a and C3b from C3. Also, C3b adsorption to the uncoated extracorporeal circuit makes complement unavailable for breakdown by its circulating inhibitors. Heparin coating interferes with C3b binding to the circuit and renders this protein more available to systemic inactivators. By complement inhibition, heparin-coated circuits decrease the propensity for white blood cell activation and degranulation. *In vitro* studies have documented a decrease in the complement cascade intermediate C3b, using the Carmeda-coated circuits. After 1 h in a heparin-coated system, the increase in terminal complement complex (TCC) returned to baseline, whereas in a control system, TCC was still increasing at this time-point.[5]

In vivo studies also indicate that leukocyte activation and generation of complement cascade activation products are significantly blunted. Animal studies using Carmeda-coated circuits have shown decreases in C3 split products and decreased bleeding and an improvement in pulmonary dynamics, evidenced by a reduced alveolar-arterial oxygen tension gradient, decreased pulmonary vascular resistance, and increased static lung compliance.[6]

The use of heparin-coated circuitry has also been shown to attenuate the release of tumor necrosis factor and neutrophil-derived proteins that modulate lipopolysaccharide effects that may mitigate the inflammatory response to CPB. However, the use of these circuits resulted in attenuated upregulation of the adhesion molecules CR1, CR3, and CR4 and less downregulation of L-selectin. Further enhancements in biocompatibility include less leukocyte activation and preserved platelet function. Studies in humans showed decreases in the levels of enzymes that mark leukocyte activation, a possible reduction in the whole-body inflammatory response similar to that seen with leukocyte-depletion techniques.

Heparin coating of the extracorporeal circuit may also further inhibit the thrombin formation that is still present during CPB, despite very high levels of systemic anticoagulation with heparin. Less generation of thrombin will result in diminished activation of the fibrinolytic system during CPB, less platelet activation (because thrombin is a platelet activator), and thus less bleeding. Although markers of thrombin generation decrease during heparin-coated CPB, these markers increase in all patients after the administration of protamine. Although thrombin generation still occurs, differences in blood loss and transfusion requirements using heparin-coated circuits have predominantly been shown when a reduced dose of heparin is used.[7] It becomes more obvious that the Carmeda BioActive surface should ultimately help to reduce the whole body inflammatory response.

The endothelial injury after CPB is similar to the concept of endothelial cell activation. In response to inflammatory signals, such as cytokines and complement activation, endothelial cells are converted to an activated state, resulting in profound changes in gene expression and cellular function. In the response to injury, endothelial cell activation is beneficial in recruiting neutrophils and promoting coagulation to limit the local spread of infection. This is the first wave of complement-mediated neutrophil adhesion. Secondly, the cytokine levels increase in direct response to the length of the procedure, stimulating more endothelial activation. Signals are transmitted through the cell wall to signal transduction pathways that translocate to the nucleus to turn on a specific set of genes, known as the activation genes. These genes are transcribed as a result of endothelial cell activation. In the patient undergoign bypass operation, the most significant are the genes that encode for E-selectin, intracellular adhesion molecule (ICAM), interleukin-8, and tissue factor.

Summary

Techniques designed to attenuate neutrophil-endothelial cell interaction, also known as ‘whole body inflammatory response’, will have the most important impact to the patient. Heparin coating is commercially available for use and is proven to decrease complement activation, which seems to increase the biocompatabilty of the circuit. The extent to which imitation of endothelial-like properties has been achieved by heparin coating thus far contributes towards improving patient outcomes, saving lives, and perhaps allowing treatment where treatment was not previously possible.

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