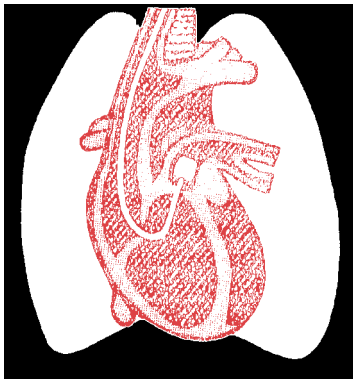




CASE CONFERENCE

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CASE 7—2001

Management During Cardiopulmonary Bypass Of Patients With Presumed Fish Allergy

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Case Presentations*

Case 1. A 74-year-old, 84-kg man having New York Heart Association (NYHA) class III dyspnea and 2 episodes of syncope was diagnosed with severe aortic stenosis with an echocardiographically calculated gradient of 95 mmHg across the aortic valve. Cardiac catheterization confirmed the diagnosis and showed the presence of normal coronary arteries. In the preadmission clinic, the patient was noted to be allergic to fish, which was manifested by generalized rash and wheezing on consumption of food items containing any kind of fish. A skin test was performed to assess the cross-reactivity to protamine. Protamine sulfate was diluted to 0.1 mg/mL, and 0.1 mL of this solution was injected intradermally. A positive reaction occurred in the form of a wheal with dimensions $> 5 \text{ mm} \times 5 \text{ mm}$.

Case 2. A 69-year-old, 79-kg man having NYHA class IV angina was diagnosed with triple-vessel coronary artery disease and symptomatic carotid artery disease. The patient was strongly allergic to fish and eggs, manifesting as generalized rash and bronchospasm on consumption of these food items. Skin testing using intradermal injection of 0.1 mL of diluted protamine was performed. A wheal with dimensions $> 5 \text{ mm} \times 5 \text{ mm}$ was observed, and the test was considered positive. The patient had a right carotid endarterectomy performed under local anesthetic using 100 units/kg of heparin followed by coronary artery bypass graft (CABG) surgery 1 week later.

Cardiopulmonary bypass. Both patients underwent cardiac procedures using a modified strategy. Cardiopulmonary bypass (CPB) was conducted using heparin-bonded bypass equipment and tubing with low systemic heparinization and consequently lower activated coagulation time (ACT). Heparin assay complemented this and helped to achieve target anticoagulation.

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The CPB equipment consisted of a hard shell cardiomy reservoir (Medtronic Europe S.A./V.A., Belgium), soft shell venous reservoir (Medtronic Europe S.A./V.A., Belgium), a woven hollow fiber oxygenator (Maxima Plus PRF & Carmeda bioactive surface, Medtronic Europe S.A./V.A., Belgium), and a 25- μ arterial filter (Medtronic Europe S.A./V.A., Belgium). A centrifugal blood pump (Biomedicus vortex pump, Medtronic Europe S.A./V.A., Belgium) was incorporated into the circuit. All the surfaces in contact with blood were coated with a soluble heparin complex. The circuit was completed with silicon and polyvinylchloride tubing and cannulae coated with heparin. Heparin, 16,000 units, was used in the first patient, whereas the second patient received 14,600 units of heparin, maintaining the ACT between 250 and 350 seconds. The ACT was measured preoperatively, 10 minutes after heparin administration, 10 minutes after the start of CPB, every 25 minutes during CPB, 25 minutes after the culmination of CPB, and 2 hours postoperatively (Fig 1). Simultaneous heparin assays were performed using Heparin Assay Cartridges and Heparin Management System (Hepcon HMS Medtronic Hemotec Europe S.A./V.A., Belgium).

The CPB circuit was primed with 2 L of heparinized Hartmann solution using 2000 units of heparin. CPB was conducted with a flow rate of 2.4 L/min/m² at 34°C. Warm blood cardioplegia was used antegradely and intermittently. Aortic valve replacement was done using Carbomedics Top Hat valve (Sulzer Carbomedics Inc) in the first patient. The aortic cross-clamp time was 63 minutes, and the CPB time was 81 minutes. The second patient had triple CABG surgery using the left internal mammary artery to left anterior descending artery and saphenous vein grafts to an obtuse marginal branch of the circumflex artery, and the posterior descending artery. The aortic cross-clamp time was 48 minutes with a CPB time of 85 minutes. Both patients were successfully weaned off CPB without any difficulty. After decannulation, extensive surgical hemostasis was performed. Protamine was not used, but 4 units of fresh frozen plasma were transfused in both patients. CPB was conducted without any problem, and no thrombus deposition was detected in the entire circuit throughout the procedure, including the gas exchange device. The oxygenator surface was subjected to scanning electron microscopy, which confirmed that its surface was clean (Figs 2 and 3). The intraoperative

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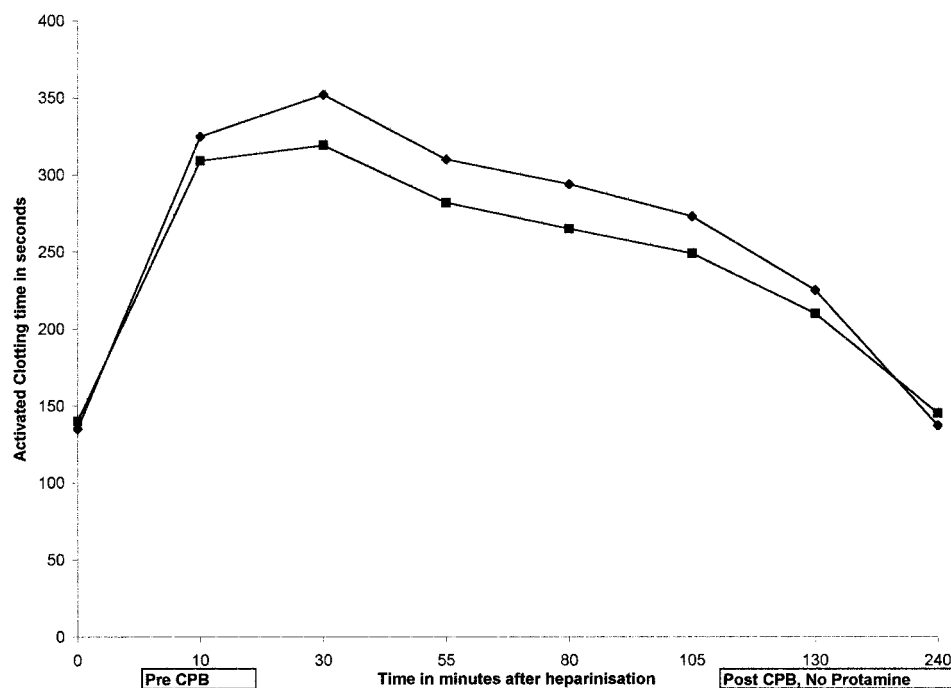


Fig 1. Activated coagulation times in the 2 patients at varying intervals. Abbreviation: CPB, cardiopulmonary bypass. —◆—, Patient no. 1; —■—, Patient no. 2.

blood loss was estimated to be 650 mL in the first patient and 575 mL in the second patient. The total drainage from the mediastinal tubes was 450 mL in the first patient and 525 mL in the second patient during the 24-hour period. Two units of homologous blood were transfused in both patients (Table 1).

DISCUSSION†

Protamine is a polycationic peptide isolated from sperm-rich gonads of male salmon. It neutralizes heparin through a polycationic-polyanionic reaction. This reversal of heparin helps to minimize blood loss and consequently reduce the use of blood and blood products. Protamine is also associated with a variety of major adverse reactions.¹ These have been categorized into 3 types. A type 1 reaction is hypotension resulting from rapid administration of intravenous protamine, which could prove fatal if uncorrected, especially in the presence of reduced afterload.^{2,3} This reaction is presumed to occur as a result of vasodilation or the myocardial depressant effect of protamine and usually responds to rapid volume replacement.^{4,5} A type 2 reaction is an anaphylactic or anaphylactoid reaction manifested by hypotension, compensatory tachycardia, and development of bronchospasm and pulmonary edema. This type of response is mediated by immunoglobulins and results in production of histamine, leukotrienes, kinins, and other mediators.⁶ Patients with previous cardiac catheterization or cardiac or vascular procedures as well as insulin-dependent diabetics, vasectomized men, and patients allergic to fish are particularly at risk of developing such reactions.^{7,8} A type 3 reaction is pulmonary hypertension and bronchoconstriction with eventual systemic hypotension. This reaction may be due to complement

activation and release of mediators, such as thromboxane, in the lungs.⁹

The incidence of adverse reactions varies from 0.06% to 27% depending on the propensity to develop such reactions, and some of these could be fatal. Diabetic patients receiving insulin-containing protamine have a 30- to 50-fold increased risk of life-threatening reactions when given intravenous protamine.^{10,11}

Individuals allergic to fish may have serum antibodies directed against protamine. Commercial protamine preparations may be contaminated with fish proteins, to which patients allergic to fish may react. Knape et al⁷ and Caplan and Berkman¹² described their experience of anaphylactic reactions after protamine infusion in patients with fish allergy. The patients discussed in the present report had potentially serious allergic reactions on consumption of fish. Suspecting cross-reactivity with protamine, these patients were subjected to skin test by the allergist with diluted intradermal protamine. There are few reports regarding use of skin testing for identifying patients who could have immediate adverse reactions to protamine. Nevertheless, reports of positive intradermal skin tests to protamine using 1 ng/mL to 1 mg/mL after clinical hypersensitivity reaction have been used as evidence for an anaphylactic phenomenon.^{13,14} Positive skin test may be beneficial in predicting an adverse reaction but a negative reaction does not rule out this possibility. Enzyme-linked immunosorbent assay (ELISA) and C3a and C4a levels can be of some value, but the authors did not use these because the skin test was suggestive. The positive skin test in these patients prompted the authors to look for an alternative strategy for performing cardiac surgery.

The search for alternatives to protamine led to the incorporation of various strategies involving pharmacologic or physical agents. There are reports of performing cardiac operations

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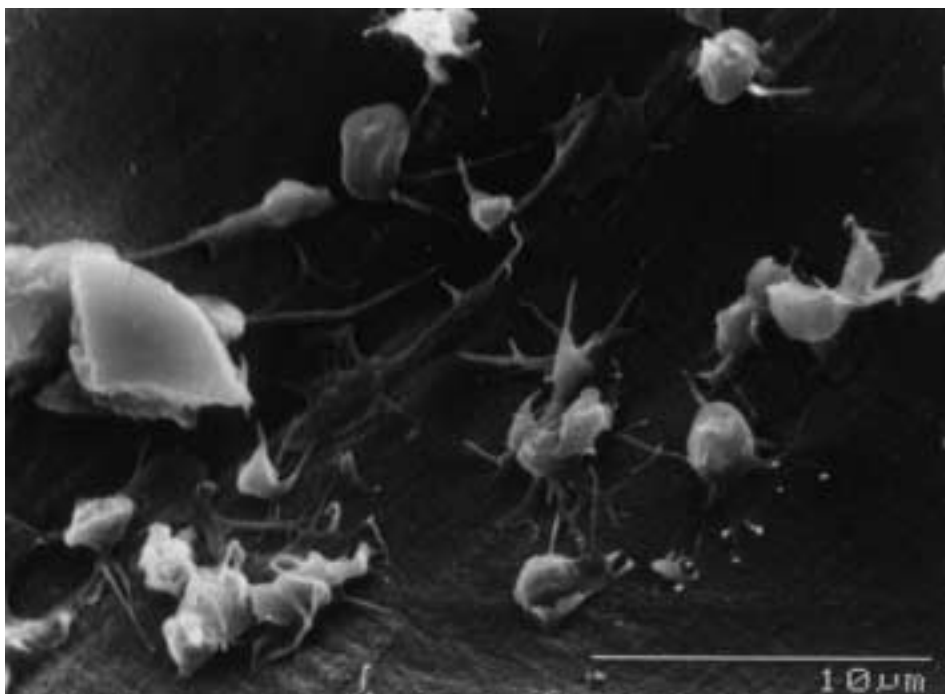


Fig 2. Scanning electron micrograph (10 μm) of the oxygenator surface after using heparin-bonded circuit. Surfaces are smooth with no or minimal platelet adhesions or fibrin deposits.

with omission of protamine after CPB, but such an approach is usually associated with excessive blood loss and increased use of blood and blood products.¹⁵ There are anecdotal reports of 2 patients allergic to protamine who were managed with steroid-antihistamine pretreatment.¹⁶ Three pharmacologic alternatives have been explored—hexamethridine, platelet factor 4, and heparinase—with varied results. The heparin removal device is

a useful tool to extract heparin after culmination of CPB. The device uses an extracorporeal plasmapheresis filter containing a special resin that binds and immobilizes heparin from circulating heparinized blood. It is a physical process that was found to be effective in animal experiments and is undergoing phase 1 clinical trial.¹⁷ Use of this device would avoid the use of protamine.

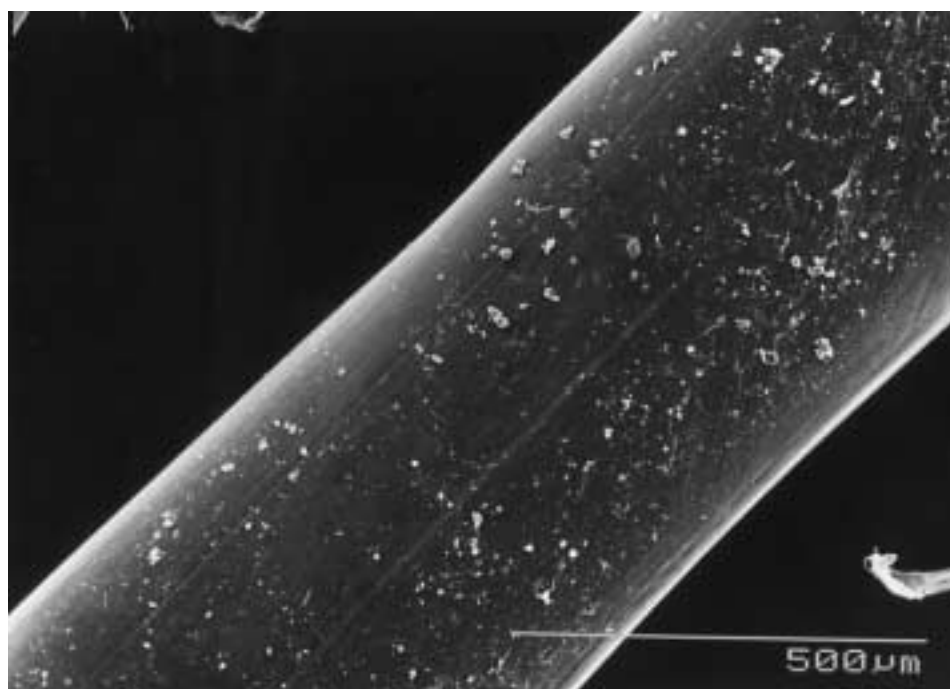


Fig 3. Scanning electron micrograph (500 μm) of the oxygenator surface after using non-heparin-bonded circuit and heparinization with 300 mg/kg of heparin. Platelet adhesions and fibrin deposits are present.

Table 1. Perioperative Details

Characteristics	Patient No. 1	Patient No. 2
Heparin (units)	16,000	14,600
ACT on CPB (maximum) (sec)	350	319
ACT on CPB (minimum) (sec)	258	249
Aortic cross-clamp time (min)	63	48
CPB duration (min)	81	85
Intraoperative blood loss (mL)	650	575
Postoperative chest drainage (24 h) (mL)	450	525

Abbreviations: ACT, activated coagulation time; CPB, cardiopulmonary bypass.

The heparin-bonded surfaces in the CPB circuit have been shown to be more biocompatible and less thrombogenic. Since initial use in early 1990, heparin-coated circuits have been widely accepted in clinical practice, and their efficacy has been shown in many clinical studies.¹⁸ In the early stages, the CPB equipment was only partially heparinized, and there was a reluctance to significantly reduce the dose of heparin. As the technology advanced, completely heparin-bonded equipment became available, which helped to reduce the dose of heparin for the conduct of CPB. The safety of conducting CPB using heparin-coated bypass circuit and low systemic heparinization has been well shown in many studies. Some anesthesiologists and surgeons have safely conducted CPB with a 30% to 70% reduction in the dose of heparin using the heparin-coated equipment, maintaining the ACT between 250 and 450 seconds.^{19,20} Von Segesser et al²¹ conducted a prospective, randomized trial with low versus full systemic heparinization using heparin-bonded CPB circuits. These studies showed that the reduced heparinization results in decreased blood loss and transfusion requirements. The entire circuits, including the oxygenators, were shown to be free of thrombi, and the procedures were performed safely and efficaciously with the added advantage of using less protamine for heparin reversal. The concern about increased thrombogenicity has been addressed by Ovrum et al.¹⁹ The levels of PFI.2, TAT complex, and β -thromboglobulin increased during CPB conducted with standard as well as low systemic heparinization, indicating that thrombin is formed steadily during CPB, even with an ACT of > 480 seconds. The extensive elevation in the level of thrombogenic markers 2 hours after the end of operation indicate, however, that the degree of thrombin generation during CPB remained within acceptable limits in patients with low systemic heparinization. Investigators also showed that the findings of major thrombin formation are comparable to those of others using CPB with ordinary uncoated circuits as well as to findings of investigators using heparin-coated CPB circuits and full systemic heparinization.²² More importantly, there were no clinical findings indicating harmful thrombogenicity. Von Segesser et al²¹ highlighted the ways to approach some of the difficult problems associated with conduct of CPB using low systemic heparinization.

Encouraged by these studies, the authors decided to use the heparin-coated bypass equipment with low-dose heparinization to avoid using protamine in the 2 patients who were allergic to fish. All efforts were directed toward reducing the blood loss.

The centrifugal pump was incorporated into the CPB circuit because it minimizes trauma to blood components and further reduces the coagulation disturbance.²³ The additional use of the heparin management system and Hepcon cartridges helped to achieve target anticoagulation and to minimize the heparin dose.²⁴ The blood loss was reasonable in both cases, whereas the requirement of blood and blood products was not excessive. Fresh frozen plasma was transfused prophylactically after the culmination of CPB.

Administration of protamine to susceptible individuals can lead to fatal anaphylactic reaction. Cross-reactivity of protamine with patients allergic to fish is a recognized phenomenon. Protamine was avoided in these 2 patients during CPB using a heparin-bonded circuit and low systemic heparinization. It is reasonable to avoid potentially life-threatening reactions in susceptible patients using the above-described strategy.

COMMENTARY NO. 1†

The true vertebrate fish salmon provides medicinal protamine. Although several case reports^{7,12,25,26} link anaphylaxis after exposure to protamine with human allergy to true vertebrate fish (eg, salmon, mackerel, pike), no compelling data do so for allergy to shellfish (eg, lobster, clams, and crabs) or other sea dwellers, such as octopus or squid.^{1,27} For this reason, careful clinicians elicit a detailed history from patients with a *fish allergy*. Because atopic individuals in general are more prone to additional allergies,²⁸ allergy limited to shellfish does not ensure benign administration of protamine or any other drug.

Attention to detail in testing patients with a history of true fish allergy facilitates their care. When injected intradermally as for skin testing, undiluted protamine elicits a wheal-and-flare reaction in every subject. What dilution would avoid these false-positive results? Fisher²⁹ recommended 1 μ g/mL, a 10,000-fold dilution of the commercially available 10-mg/mL product. Horrow et al³⁰ showed false-positive rates of 31% and 13% with final concentrations of 10 μ g/mL and 1 μ g/mL. Intradermal injection correctly performed uses 0.01 to 0.02 mL of test solution and measures induration of skin, as detected by palpation, rather than appearance. A single, widest diameter of at least 8 mm persisting for 30 minutes denotes a positive response.³⁰ Interested clinicians can find more information about skin testing by consulting Fisher's³¹ article or a trusted specialist in allergy.

Because skin tests, even properly performed, yield many false-positive results, they afford limited utility. In contrast to skin tests, serum-based laboratory tests (radioallergosorbent test, ELISA) involve no exposure of the subject to potentially harmful antigen, but these tests require batched processing, incur special laboratory fees, and may feature intrinsic limitations in terms of false-positive results³⁰ and false-negative results.

The availability of alternatives to protamine would obviate the need for testing. This case report shows that total omission of heparin neutralization can succeed with a combination of meticulous attention to hemostasis, administration of fresh fro-

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zen plasma, heparin-bonded bypass circuitry, and reduced systemic heparin administration. Clinicians and patients want more elegant, less expensive, less risky options, however. Many pharmaceutical alternatives to protamine are currently in development, including recombinant platelet factor 4, heparinase-I (Neutralase, IBEX, Montréal, Québec), transgenic lactoferrin, designer polycation molecules, and Heparrest (Commonwealth Biotechnologies, Richmond, VA). Recombinant human platelet factor 4 neutralizes heparin by polycation-polyanion interactions.³² Heparinase 1, currently in phase III clinical testing, enzymatically cleaves heparin into small saccharide chains.³³ Human lactoferrin binds heparin in polycation-polyanion fashion. Production of large amounts in transgenic cow's milk may provide sufficient material for heparin neutralization. Designer polycation molecules promise retention of neutralization efficacy with removal of toxicity.³⁴ The drug development process will determine which, if any, of these agents emerge as safe and effective and which will fail, as did hexadimethrine (effective but causes renal failure), methylene blue (ineffective and causes pulmonary hypertension), and platelet concentrates (ineffective and carry a large allogenic transfusion exposure). This process, although costly and imperfect, provides clinicians and patients with reasonable assurance of safety and efficacy. It is hoped that this process will produce an alternative soon.

COMMENTARY NO. 25

The 2 cases presented took a novel approach to CPB. There are many different strategies for accomplishing CPB without the use of protamine. Because these 2 cases were *successful*, it should not be concluded that this is the *best* way to approach the problem. One scenario is to complete CPB in the usual manner and simply let the heparin be metabolized and cleared. The *best* dosage of heparin for CPB is not known. Each institution uses its own dosing, acceptable heparin level, or ACT. At some institutions, target ACTs of 350 seconds have been maintained, whereas others choose 450 or 500 seconds.³⁶⁻³⁷ In a study in which the ACT target was 350 seconds, the chest tube bleeding, consumption of fibrinogen, and platelets were normal.³⁵ Other studies have argued, however, that increased ACT targets of 750 seconds may decrease the formation of thrombin and preserve platelet function after surgery.^{38,39} Not only does controversy continue with regard to the *best* heparin level for CPB, but also low heparin levels have been used as an excuse for graft thrombosis in one controversial study of aprotinin.⁴⁰ That study had ACT and heparin levels in excess of the work by Metz and Keats³⁵ that showed no increased risk from low heparin. Confusing as it is, some heparin is needed to keep the CPB circuit and oxygenator from coagulating.

Heparin has far-reaching biochemical and pharmacologic consequences that are underappreciated by anesthesiologists and surgeons.⁴¹⁻⁴⁴ The reader is referred elsewhere to examine the detrimental effects of heparin alone.⁴¹ It may be that heparin sets up the coagulopathy of CPB in many ways. It is known that

heparin activates platelets and forces them to express the vital glycoprotein binding sites that are destroyed or inactivated by CPB.⁴² Research in coagulation and CPB has always used heparin until heparin-bound circuits were available. No one ever thought of separating these two before and investigating them as independent contributors to the CPB coagulopathy. Heparin allergy or heparin-induced thrombocytopenia was considered a rare event. Some new work and sensitive ELISAs show, however, that most patients undergoing CPB have IgG to heparin.⁴⁵⁻⁴⁸ Not everyone undergoes heparin thrombocytopenia, but there must be implications in routine CPB when platelet factor 4 immunoglobulins are bound to platelet surfaces. It is hoped that someday with heparin-bonded circuits these properties can be investigated scientifically with systemic heparin present or absent.

Protamine in conjunction with heparin already bound to the surface of platelets is particularly bad for platelet function.⁴⁹ Platelet counts decrease dramatically within minutes of protamine infusion.^{50,51} This decrease does not occur with protamine infusions alone. Protamine alone (without heparin or CPB) does not cause the severity of pulmonary vasoconstriction, thromboxane release, and platelet dysfunction seen with routine CPB. Protamine was avoided in these 2 patients because of the fear of an anaphylactic reaction. That seems reasonable, and the patients bled no more than routine patients.

There is confusion regarding the effects of heparin-bonded circuits and the coagulopathy of CPB. CPB affects platelet functions and inhibits or destroys platelet glycoprotein sites. Platelet count alone has been shown to be higher after CPB with heparin-coated systems.⁵² In one study in which heparin coating was used with and without aprotinin therapy, the heparin-coated systems had a higher platelet count at 60 and 90 minutes.⁵² Platelet factor IV, a marker of platelet activation, was lowest in groups of patients who had heparin-bound circuits.³² In a heterogeneous group of patients, the heparin-coated systems showed reduced platelet adhesion to the CPB circuit.⁵³ With a new heparin-coated system, in a bovine model using low heparin (ACT, 180 seconds), the platelet count decreased only to 76% of baseline in the heparin-coated group and 57% in the control group at the end of 6 hours of CPB.⁵⁴ In another *in vitro* study, circuits were incubated with whole blood in the presence of high-dose and low-dose heparin.⁵⁵ The heparin-coated circuits showed lower platelet adhesion.⁵⁵ Sixty patients undergoing CABG surgery who had full heparin dosages had higher platelet counts than patients with heparin-coated circuits.⁵⁶

The fibrinolytic system has been widely implicated in bleeding after CPB.⁵⁷ The interaction of the fibrinolytic system and platelet function is complex, and elevation of tissue plasminogen activator has effect on the glycoproteins.⁵⁸ Previous work showed that there is a variability in fibrinolytic response to the CPB machine.⁵⁹ In a study of full-dose heparin CPB at normothermia with and without heparin-coated circuits, it was shown that levels of tissue plasminogen activator activity and antigen were lower with heparin-coated circuits.⁶⁰ There was a subgroup of about

30% of patients who had a massive release of tissue plasminogen activator, but only in the control group.

Other investigators have not confirmed decreased fibrinolytic activation. Wagner et al¹⁸ and others showed that D-dimer levels were not changed by the use of heparin-coated systems until after reperfusion and protamine.⁶¹⁻⁶⁴ D-Dimer is the end product of formed fibrin destruction, and during CPB that should be low. The authors of these studies, some of which were retrospective, did not measure tissue plasminogen activator activity.

Work regarding inflammatory indicators has been more confusing. Complement levels were studied extensively in 15 patients undergoing CABG surgery who had full-dose heparin with heparin-coated circuits and 14 patients as a control group.⁶⁵ The C3bc and the terminal complement complex were reduced in the heparin-coated group. Many intermediary complement complexes did not show differences (C4bc, Bb, and C5a-des Arg). The complement inhibitory complex, C1rs-C1, was increased in the heparin-coated group but had no direct correlation to the levels of final complement complex. Several studies in pediatric patients appear to confirm that data.⁶⁶⁻⁶⁸ Levels of C3a and terminal complement complex as well as interleukin-6 (IL-6) were lower when heparin-coated circuits were employed.⁶⁶⁻⁶⁸ In contrast, a study with the use of heparin-coated circuits in patients having thoracic aortic operations with decreased systemic heparinization showed no difference in complement levels.⁶⁹ A study in which occult myocardial damage after CABG surgery was reduced showed no difference in complement levels; however, other inflammatory markers were decreased.⁷⁰

The levels of interleukins have positive and negative reports. Blood samples activated to stimulate leukocyte release of interleukins showed that IL-6 and IL-10 were less in the group that had undergone heparin-coated CPB.⁷¹ In pediatric patients, some studies show a 5-fold smaller increase in IL-6 production with heparin coating.⁶⁶ By contrast, 200 patients underwent CABG surgery and were randomized in both CPB circuits and without aprotinin. Tumor necrosis factor- α , IL-6, IL-8, myeloperoxidase, and elastase levels were measured with no intergroup differences.⁷² Another study using low-dose aprotinin and a similar protocol found that patients with the heparin-coated system had lower IL-6 and IL-8 production, but tumor necrosis factor- α was not different.⁷³

As all the research is weighed, it seems there is support for the reduction of inflammatory mediators, better platelet activity (number, function, and preservation), and perhaps decreased fibrinolytic activation. Mediators and platelet numbers do not always equate to improved outcomes. A meta-analysis of 26

studies concluded that there were significant benefits to the use of heparin-coated CPB circuits.⁷⁴ The literature supported decreases in blood loss after surgery, decreased time in the intensive care unit, decreased C3a production at the end of CPB, decreased time to extubation, improved platelet count, and decreased lactoferrin. The literature did not support a decrease in overall red cell transfusion, thrombin-antithrombin complex generation, and many other hemocoagulation indices.⁷⁴ The pros and cons are constantly undergoing debate.^{75,76} Not only are outcomes important, but also the elusive goal of cost-effectiveness is brought in as a major argument.⁷⁶

Why is the literature yet unclear? Some of the confusion is related to how cardiovascular hematology and inflammation research is conducted. Variability is the evolutionary rule in biologic systems. Most cardiac anesthesia research describes the *normal* or mean response to CPB, whereas focus needs to be on the outliers and bizarre reactors. Many heparin-coated circuit research studies have been performed with small numbers. One study noted no change in the mean levels of bleeding; however, they found no severe bleeding.⁷⁷ The genetic variabilities are now being appreciated from the cardiology literature.⁷⁸

The research in heparin-coated CPB circuits has used at least 3 or 4 different types of coatings. It should be expected that differences exist even within each coating because heparin from different batches is bound to the surface of the CPB circuits. Each of the studies mentioned here may have used a different circuit, heparin coating technology, and batch, and some studies may have incomplete coverage of heparin circuits (suction catheters or connectors not heparin coated). Few if any standardized the heparin batch that they used in their own study. Transfusion criteria almost never were mentioned. Transfusion of allogenic blood products carries large quantities of complement and interleukins.⁷⁹ Platelet concentrates are filled with activated white cells and myeloperoxidase as well as neutrophil elastase. The literature is unclear, and the techniques for the studies are so widely varied that it is sometimes difficult to scientifically compare. One researcher suggested that heparin-coated circuits may be effective only when turbulent states exist within the system.⁸⁰ Some commented that they believe reducing the systemic heparin dosage in conjunction with the use of heparin-coated systems is ill advised or dangerous. The literature as reported here does not bear that out, however.

Research shows decreased hematologic and inflammatory activation as compared with routine circuits or heparin-bonded circuits. There has never been any suggestion that these circuits increase hematologic destruction or inflammation. The use of a heparin-bonded circuit as a method to decrease heparin use and to avoid protamine administration is well grounded.

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