



When technical approaches are not enough

BLOOD MANAGEMENT ADVANCES IN CARDIAC SURGERY

Should We Transfuse During Cardiac Surgery?

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Antiplatelet Drugs and Cardiac Surgery

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The Role of Aprotinin in Modulating the Systemic Inflammatory Response

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Neuroprotection = Protecting the Endothelium

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Evaluate significance of platelet activation and function as well as perioperative tissue inflammation during cardiopulmonary bypass
- Assess risk of brain and kidney injury associated with cardiac surgical procedures and evaluate measures to reduce risk
- Review benefits and risks of transfusion therapy and techniques to manage blood
- Describe classes of antiplatelet medications and agents that minimize ischemic tissue injury during surgery

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assigned 1 category 1 continuing education unit to this activity. **Intended audience:** This educational activity is designed for practitioners who care for cardiac surgery patients, including thoracic surgeons, cardiothoracic anesthesiologists, thoracic anesthesiologists, cardiovascular perfusionists, and others who desire to expand their knowledge of the medical and scientific information currently available.

Statement of need: Patients who undergo coronary bypass surgery face significant risks associated with preexisting comorbidities, prior administration of antiplatelet agents, the use of fresh or stored blood products, and other factors. Surgeons need to evaluate factors that may reduce inflammatory factors, develop strategies to protect platelets, and better evaluate the appropriateness of transfusion for each patient.

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Off-label use: This supplement contains discussion of unlabeled/investigational use of drugs, as indicated in the text.

Introduction

Craig Vocelka, CCP

Cardiac surgeons face significant issues in selecting optimal transfusion strategies for their patients. As new data emerge, we must ask ourselves: Are the risks and benefits associated with transfusion clearly elucidated?

This publication addresses critical concerns that face cardiac surgeons and suggests practical strategies to reduce the risk of adverse events. The authors examine the appropriateness of transfusion in light of recent reports demonstrating good outcomes associated with conservative transfusion strategies. In a discussion of the data concerning transfusion, Dr Hill notes that only 1 randomized clinical trial has measured the effect of transfusion on morbidity and mortality, with outcomes that favored avoidance of transfusion.

How applicable are these findings, derived primarily from populations that refuse transfusion on religious grounds, to other cardiac patients? What is the best approach for individuals who may have extensive preoperative morbidity or who may be taking medications that

increase the risks associated with transfusion, specifically the platelet inhibitors, which are widely used today and likely to become more prevalent in their use. Dr Shore-Lesserson focuses her discussion on the challenges associated with antiplatelet medications and suggests strategies to reduce blood loss in these patients.

Dr Murkin reviews the complex inflammatory cascade of events associated with cardiac surgery and its potential effects on cerebral ischemia. The potential effects of pharmacologic agents such as aprotinin on protease-activated receptors are discussed as potentially protective mechanisms. Dr Stump also provides data from recent studies concerning brain injury associated with both cardiac and noncardiac surgery and provides practical strategies to reduce potential injury, including prevention of blood loss, carefully maintaining temperatures, and minimizing manipulation of the aorta.

I hope you will find the material presented herein of great use to you in your efforts to improve outcomes for your patients.

Should We Transfuse During Cardiac Surgery?

Steven E. Hill, MD

Transfusion as a standard of care developed from battlefield experience; however, in other settings, it may increase morbidity and mortality. In studies, healthy adult volunteers have experienced extreme normovolemic hemodilution (hemoglobin [Hb] levels as low as 5 g/dL) and maintained tissue oxygen delivery sufficient to avoid systemic acidosis.^{1,2} However, in a short-term memory study, Hb levels lower than 6 g/dL were associated with increased error rate,³ suggesting that the minimum acceptable Hb level for an adult breathing room air is somewhere between 5 and 6 g/dL.

Effects of preoperative morbidity

In studies of Jehovah's Witness church members, oxygen delivery was inadequate to sustain life when Hb levels declined to less than 3 g/dL.^{4,5} Retrospective database reviews of cardiac surgical patients show that hematocrit (HCT) levels less than 23% correlate inversely to morbidity and mortality in a patient population with significant preexisting disease.⁶⁻⁸ These reports are unadjusted for preoperative HCT or the adverse effects of transfusion (the lowest HCTs had the highest transfusion rates). No randomized, prospective data support transfusion to treat

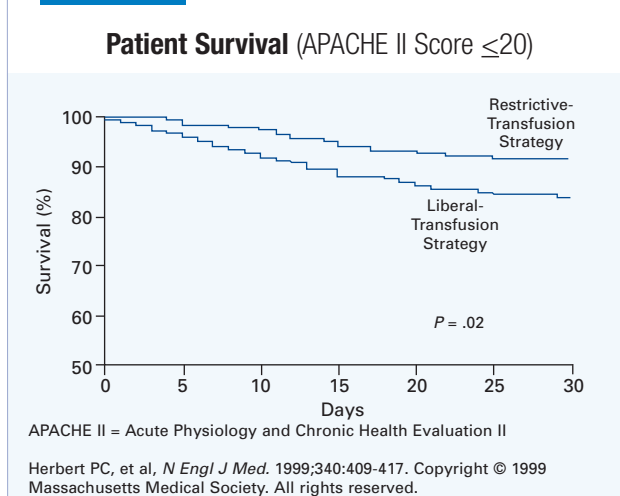
mild-to-moderate anemia in the absence of exsanguination.

Low HCT levels may result from and indicate comorbidities that increase mortality risk. When preoperative morbidity is considered, association between low HCT and adverse outcome disappears.⁹ In a large database study of elderly patients who had acute myocardial infarction, nontransfused patients with low HCT levels had higher 30-day mortality than did transfused patients. They were also half as likely to receive an intervention; their charts were twice as likely to have a "do not resuscitate" order. Transfusion in patients with HCT levels greater than 36% also was associated with increased mortality. Thus, low Hb and HCT levels may be markers of preexisting disease and serve as predictors for increased mortality.¹⁰

In a retrospective analysis of 24,112 patients with acute coronary syndrome,¹¹ transfusion-associated risks remained elevated after controlling for risk factors. Of those transfused within 30 days, 8% subsequently died, compared with 3.08% of nontransfused patients. Heart attacks occurred in 25.16% of transfused patients versus 8.16% of nontransfused patients. Mortality was higher in transfused patients when the HCT level was above 25%.

The association between low Hb and adverse outcomes

FIGURE 1



does not prove that the former causes the latter; transfusion's impact on morbidity and mortality must be measured in randomized clinical trials. Only 1 such trial has been conducted; the outcome favored avoidance of transfusion.¹²

More than 30 observational studies associate allogeneic blood transfusion with up to a 10-fold increase in postoperative infection. Leukocyte depletion may improve outcomes, but evidence is inconclusive.¹³ Immunogenic effects of allogeneic and platelet transfusion are well established.^{14,15}

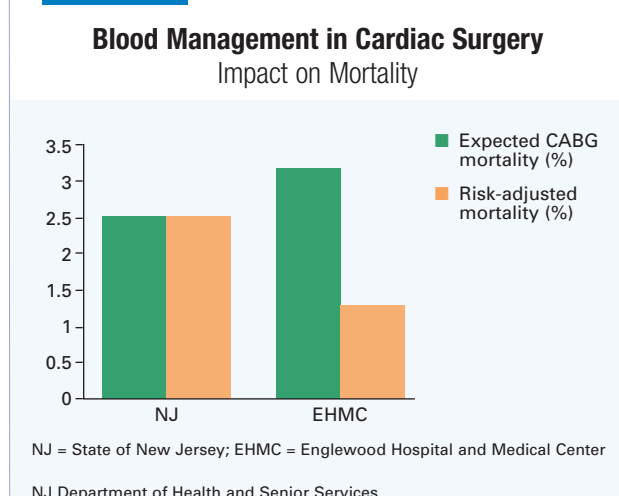
Are these responses part of the etiology of the systemic inflammatory response syndrome and pulmonary injury associated with cardiac surgery? Prolonged storage limits blood product efficacy.¹⁶ Transfusion may not acutely improve oxygen consumption in critically ill patients.¹⁷ It also has also been associated with gut acidosis as measured by gastric tonometry.¹⁸

Liberal versus conservative transfusion

One randomized trial of liberal versus restrictive transfusion therapy¹² showed that restrictive transfusion (maintaining Hb >7 g/dL) had no adverse effect on 30-day survival or organ failure in comparison with a liberal regimen (Hb target level of 10 g/dL to 12 g/dL). When patients were reanalyzed to assess high- and low-risk populations,¹⁹ those with Acute Physiology and Chronic Health Evaluation II scores below 20—indicating the lowest burden of illness—treated with a restrictive transfusion strategy had an increased survival rate ($P = .02$) compared with those treated with a liberal transfusion policy, suggesting that the former group was able to tolerate anemia (FIGURE 1). Transfusion added to risk with no additional benefit.

A prospective, observational European study evaluated anemia in 3534 patients.²⁰ Mortality was 29% for transfused patients versus 14.9% for nontransfused patients. In a matched cohort adjusted for propensity to transfuse, the risk was 22.7% for transfused patients versus 17.1% for nontransfused patients ($P = .02$).

FIGURE 2



Long-term outcomes were evaluated in 1915 patients discharged after primary coronary artery bypass graft (CABG) surgery.²¹ At 5 years, mortality in the transfused patients was double that of the nontransfused group. After correction for comorbidities with a propensity-to-transfuse score, 5-year mortality was 70% higher in the transfused group than in the nontransfused group ($P < .001$). These findings suggest an association of liberal transfusion with poor outcomes.

A practical approach to blood management

One hospital's aggressive blood-management program for cardiac surgery includes preoperative optimization of Hb; intraoperative, acute normovolemic hemodilution; autotransfusion of mediastinal blood within the first 4 postoperative hours; tolerance of anemia; meticulous surgical technique; endovascular vein harvesting; point-of-care coagulation monitoring; and targeted pharmacotherapy with aprotinin to reduce blood loss.²²

In an evaluation of 307 consecutive patients (199 = CABG, 58 = valve, 50 = CABG/valve), transfusion was avoided in 89%.²² Mortality was 3.5% and renal failure, 3% (FIGURE 2).²² The risk-adjusted mortality for the CABG patients was 1.3%, well below the 3.2% expected mortality and the lowest risk-adjusted mortality rate in the state that year (2001).²³ The center's methodologies prevent Hb levels from falling—a key component of success.

Conclusions

A very low Hb level, especially in the presence of comorbidities, is harmful but so is unnecessary transfusion. Outcomes can be improved by preventing low Hb levels and judicious administration of transfusion therapy. We need to change our current culture regarding transfusion. Before we reach for a blood product, we must consider whether the patient really needs it. Most importantly, we need to evaluate the risk that the transfusion will actually harm the patient. ■

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Antiplatelet Drugs and Cardiac Surgery

Linda Shore-Lesserson, MD

Antiplatelet medication regimens complicate the management of cardiac surgery patients. These agents prevent adverse events (AEs) in many patients, but they also exaggerate common hematologic effects of cardiac surgery. Postsurgical inflammation and platelet destruction occur through a cascade of events, described in “The Role of Aprotinin in Modulating the Systemic Inflammatory Response” (see page 6). These effects render platelets dysfunctional and are more pronounced with the use of antiplatelet drugs. The resulting platelet dysfunction is additive and may be synergistic with the platelet defect caused by cardiopulmonary bypass (CPB). The effects of antiplatelet drugs are largely irreversible. Platelet function is not normal until the complement of platelets is generated in 7 to 10 days. What about the patient who requires emergency cardiac surgery? Aprotinin is often used in this setting to prevent activation of platelets, which remain quiescent after cardiac surgery. It also inhibits thrombin's effect on the protease-activated receptor 1 (PAR1), thereby inhibiting PAR1 activation and protecting platelets.

Mechanisms of action and effects

Certain antiplatelet agents inhibit glycoprotein (GP) IIb/IIIa receptors, responsible for platelet aggregation through various mechanisms of action. Abciximab irreversibly inhibits the GP IIb/IIIa receptor and other platelet receptors.¹ Because its effects are somewhat superior to other agents, it is widely used.

Tirofiban and eptifibatid, also effective agents, inhibit the GP IIb/IIIa receptor and prevent fibrinogen binding. These agents are competitive blockers of the receptor (with half-lives of about 2 hours). When they dissociate from the receptor, it returns to normal, and platelet function returns to baseline. These agents may protect platelets via paralysis or anesthesia of the platelets, preventing platelets from degranulating during CPB. Postprocedure, platelets recover function.¹

Platelets also are protected by using aprotinin or thrombin-inhibiting drugs. Aprotinin also prevents activation of PAR1. New thrombin inhibitors, such as bivalirudin, may also prevent the platelets from activation during bypass and hence preserve their ability to function normally after surgery.²

Various trials show the efficacy of these agents in patients in reducing the rate of cardiac AEs compared with patients administered heparin only, with rates of major bleeding that are not statistically different, and show a statistically insignificantly higher rate of major gastrointestinal bleeding, necessitating reoperation.³⁻⁶

Do all oral platelet medication regimens have similar effects? Clopidogrel, an adenosine diphosphate (ADP)-receptor antagonist, has more localized effects on ADP receptors and does not inhibit platelet function as profoundly as do intravenous agents. It inhibits GP IIb/IIIa upregulation indirectly via ADP-receptor blockade.⁷

Dosage considerations

What is the optimum dose? A randomized double-blind trial evaluated stent recipients who were to have vascular or non-cardiac surgery. The probability of a myocardial AE was lowest in the group receiving clopidogrel as a bolus dose (300 mg) with maintenance dosing (75 mg/d). This group also had the lowest incidence of noncardiac AEs.⁸ An *in vitro* study showed that clopidogrel, 450 mg, inhibits platelet function more effectively than does the 300-mg dose;⁹ in another report, 600 mg inhibited platelet function even better than 300 mg. Outcomes data were not presented.¹⁰

For emergency surgery, how much clopidogrel the patient has received is important so that the risk of bleeding can be assessed. In a 30-day follow-up evaluation of patients who received stents, those who had subacute thrombosis in their stents had much higher levels of platelet reactivity as measured by vasodilator-stimulated phosphoprotein phosphorylation, a flow cytometric assay.¹¹ A 15% or higher nonresponder rate is associated with clopidogrel therapy partly due to genetic alteration of a cytochrome P450 3A4 subgroup.¹² The literature clearly demonstrates that patients who receive clopidogrel within 5 to 7 days of CPB bleed more than other patients.^{10,11,13,14} They likely receive more transfusions. Are transfusions necessary?

In a study of 200 patients, those administered clopidogrel within 7 days of cardiac surgery had more 8- and 24-hour chest-tube drainages than those who did not. They received more donor blood and returned to the operating room with a 7% incidence of reoperation for bleeding. Fewer were weaned from the ventilator within 8 hours. Transfusions provide a plausible explanation for these adverse outcomes.¹³ In a retrospective analysis, clopidogrel recipients were transfused with larger volumes of platelets, packed red blood cells, and cryoprecipitate and had a 9% reoperation rate.¹⁴

How can we prevent bleeding in patients who have received clopidogrel? The Texas Heart Institute transfusion algorithm assessed a prospective cohort of clopidogrel-treated versus untreated patients.¹⁵ Rates of transfusion in this population were compared with historical transfusion rates. Clopidogrel recipients had more transfusions than did nonrecipients, although rates of transfusions overall were lower than historical rates. Although the investigators did not completely eliminate the defect associated with clopidogrel, they were better able to manage transfusions and reduce the transfusion load relative to past experience.

Transfusion algorithms reduce need for transfusions

Aprotinin use has been suggested in these patients; some data suggest that use of aprotinin can successfully reduce blood loss brought on by clopidogrel use. Synthetic agents also may be effective, but, to date, only aprotinin has been studied in this setting.

In an animal model, administration of large doses (5 mg/kg) of clopidogrel was followed by high-dose kallikrein inactivator units (120,000 KIU/kg) of aprotinin. Platelet aggregation was unaffected; however, bleeding time was improved by aprotinin and returned toward normal. Administration of increasing doses of clopidogrel alone prolonged bleeding time by 2 or 3 orders of magnitude.¹⁶ A recent randomized clinical trial evaluated 73 consecutive patients with unstable angina who were administered clopidogrel fewer than 5 days before coronary artery bypass graft (CABG) surgery. Aprotinin, administered to patients undergoing CABG surgery, was shown to decrease postoperative bleeding and the need for transfusions relative to placebo.¹⁷

In our investigations of the effect of aprotinin on platelet aggregation inhibited by clopidogrel, we measured the aggregation response to 5 micromolar ADP.¹⁸ Our data show that a loading dose of clopidogrel reduces platelet aggregation within 24 hours; platelet function recovers by the fifth day after ingestion. Adding aprotinin to the aggregation sample also improves platelet function in a dose-dependent manner, but in our findings, only the 250 KIU/mL dose and the 400 KIU/mL dose were significantly better than baseline. The 50 KIU/mL dose was ineffective.

We hypothesize that aprotinin exerts a nonspecific benefit to platelet function. In a patient who has received clopidogrel prior to cardiac surgery, use of aprotinin during surgery may minimize the hemostatic abnormalities. Aprotinin may be useful as a tool to manage patients who require cardiac surgery soon after the administration of clopidogrel.¹⁸

Discontinuation of antiplatelet therapy to decrease the risk of bleeding is not a benign intervention. In a group of patients at Methodist Hospital in Houston, TX, who required noncardiac surgery within 6 weeks of stent implantation, mortality was 20%. Of the 8 patients who died, 6 died within 1 or 2 days of stent placement. Most had stopped their aspirin and ticlopidine regimens. The most frequent cause of death was myocardial infarction (not a bleed).¹⁹

In a case series of 4 patients reported by McFadden,²⁰ each patient continued dual antiplatelet therapy for at least the minimum time period recommended by their physician and the stent manufacturer. When single antiplatelet therapy (aspirin) was stopped, in anticipation of major surgery, each patient suffered a large myocardial infarction due to stent thrombosis.

Conclusion

Lifelong treatment with aspirin and, often, clopidogrel is a reality for an increasing number of patients. Thus, we need strategies to provide good medical care and outcomes for cardiac surgery patients. One strategy is to identify nonresponders to treatment, requiring a bedside and user-friendly

ly point-of-care measure of platelet function. Another is to use pharmacologic agents to counter the antithrombotic drugs during cardiac surgery, thereby providing better and more rational care to emergency cardiac surgical patients exposed to platelet therapeutic drugs. ■

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The Role of Aprotinin in Modulating the Systemic Inflammatory Response

John M. Murkin, MD, FRCPC

Clinicians who manage patients at risk for postoperative ischemic or cerebral ischemic events seek to implement strategies to detect and reduce cerebral injury. A key concept is that perioperative stroke represents a progressively evolving event. For at least 24 hours, localized and systemic inflammatory processes, hyperthermia, hyperglycemia, etc, may aggravate tissue injury. Increasingly, inflammation is seen to be of fundamental importance in the genesis of disease states including major vascular events. The physiologic environment during which an ischemic perioperative injury occurs is important in the cascade of events; these include activation and amplification of direct and indirect mediators of vascular endothelial permeability and vasoreactivity, chemotaxis with influx of activated leukocytes and generalized white blood cell (WBC) endothelial transmigration, localized thrombin generation and accumulation, activation by thrombin of specific receptor subtypes, protease-activated receptors (PARs), perivascular tissue factor expression, and generation of inflammatory cytokines and vasomediators.

Chronic inflammation, with accumulations of perivascular WBCs, has been implicated in the development of systemic atherosclerosis. Acute or chronic exacerbation of inflammatory processes can progress to unstable atherosclerotic plaques with localized thrombus formation

and vascular occlusion, manifested as an ischemic event. The CAPRIE trial (aspirin versus clopidogrel), with more than 18,000 patients, evaluated the temporal relation of ischemic endpoints to major vascular events.¹ In the week before the vascular event, most patients had a substantial increase in WBC count or elevations in inflammatory markers including C-reactive protein (CRP).

Additionally, CRP is a nonspecific but sensitive measure of a patient's overall inflammatory status and risk for atherogenesis that has been linked to acute ischemic events. Acute infection is an associated trigger factor: An inflammatory process (eg, cold or flu) may secondarily precipitate an acute vascular event, potentially via nonspecific WBC activation. Also, genetic factors appear to independently increase susceptibility to cerebral ischemic events.²

In cardiac surgery, instrumentation and exposure of the blood to nonendothelialized surfaces associated with cardiopulmonary bypass (CPB) incite and amplify inflammatory processes.³ So, however, do skin incision and sternotomy, blood transfusion, readministration of shed blood, and other factors. Surgical stress, therefore, initiates inflammatory pathways, as does administration of protamine, a polycationic protein that abruptly changes pH.⁴ High-dose heparin, in contrast, has been associated with anti-inflammatory properties and may decrease neurologic

impairment after cerebral air embolism.^{5,6} It also is associated with generation of bradykinin from kallikrein, key enzymes associated with increased vascular permeability and WBC chemotaxis.^{7,8} Bradykinin plays a significant role in altering tissue permeability and mediating vasogenic edema during ischemic brain injury. In the animal model, tissue injury and brain edema were reduced by suppression of bradykinin through administration of either aprotinin or another nonspecific antiprotease, soybean trypsin inhibitor. Cerebral tissues also showed less lactate accumulation, edema formation, and greater adenosine triphosphate preservation after aprotinin administration.⁸

Thrombin and PAR interaction

Thrombin-activated PARs are widely distributed on various tissues, including platelets and also throughout the vascular endothelium in all organs. They are part of the system whereby thrombin acts beneficently to initiate local tissue healing after trauma.^{9,10} During bypass, increased levels of circulating thrombin lead to activation of platelet protease-activated receptors 1 (PAR1) with associated morphologic deterioration and subsequent aggregation and clumping of platelets, primarily a thrombin/platelet-PAR1 interaction specifically inhibited with clinical concentrations of aprotinin, as shown *in vitro* by Poullis et al.¹¹

The role of peri-ischemic thrombin generation, also mediated in part through PAR activation, is increasingly implicated in the pathogenesis of ischemic cerebral injury.¹² During cerebral ischemia, a cascade of events occurs, including impairment of blood brain barrier (BBB) integrity; capillary endothelial disturbances, including WBC-receptor expression and a deterioration in inter-cellular junctions; localized cytokine release and further chemotaxis with influx of WBCs into areas of damaged tissue. Significant increases in thrombin generation by ischemic tissue, with subsequent activation of various PAR subtypes, lead to release of glutamate and other excitotoxins and result in metabolic instability, failure of cellular ion pumps, and, ultimately, to overwhelming calcium influx and cell death.¹³

Cerebral endothelial PAR1s are activated in the presence of cerebral ischemia via massive localized release of thrombin, demonstrated indirectly in acute stroke patients: In such patients, platelets are exhausted and refractory to PAR stimulation.¹⁴ PAR1-deficient mice (or mice in which a specific PAR1 antagonist, BMS-200261, was administered) demonstrate a much greater tolerance to ischemia/reperfusion injury.¹⁵ This offers a potential therapeutic intervention in the management of clinical stroke via pharmacologic PAR1 blockade. Clinically relevant dosages of aprotinin, but not lysine-analogue antifibrinolytics, have been shown to specifically inhibit thrombin activation of endothelial PARs, according to personal communication from Landis.

On intravital microscopy of rat mesentery, aprotinin-treated animals have shown a substantial reduction in perivascular tissue accumulation of WBCs after administration of a WBC chemoattractant, N-formyl-methyl-leucyl-phenylalanine.¹⁶ This may represent a PAR-mediated mechanism if WBC transmigration and cellular tight junction integrity are thrombin responsive. Ischemia/reperfusion models have clearly shown improvement in histologic grading and functional recovery with inhibited WBCs, platelet plugging, and tissue infiltration.¹⁷

Aprotinin and inflammation

Royston et al demonstrated the influence of high-dose aprotinin to significantly decrease bleeding and transfusion requirements in a high-risk group of cardiac surgical patients.¹⁸ This study was among the first to consistently demonstrate pharmacologic suppression of bleeding. Less well appreciated is that this finding was almost incidental: The study goal was to evaluate anti-inflammatory aspects of aprotinin with a dosage designed to inhibit a variety of inflammatory mediators. The Hammersmith ('full-dose aprotinin') regimen achieves a plasma concentration of aprotinin of about 200 kallikrein inactivator units (KIU)/mL or 4.3 $\mu\text{mol/L}$, well within the inhibitory range of plasmin. Patients have less bleeding as a result of the antifibrinolytic effect; however, in a dose-related fashion, this regimen also suppresses other inflammatory mediators including trypsin and kallikrein. It demonstrates measurable activity against leukocyte elastase *in vitro*.¹⁹

Aprotinin and potential reduction of stroke

It might seem that decreased bleeding may accompany an increase in stroke and thrombotic risks. What is the risk of stroke with administration of aprotinin? In a preclosure study, a significant reduction in bleeding and transfusion requirements occurred in aspirin-treated coronary artery bypass graft (CABG) recipients; however, the stroke rate—while not significantly different—was considerably lower in the aprotinin group in absolute terms.²⁰

Subsequent, better-powered studies have confirmed this observation.²¹⁻²⁵ In a multicenter dose-ranging study, a significantly lower stroke rate was associated with aprotinin administration compared with placebo therapy in high-risk cardiac surgical patients.²¹ Subsequently, a meta-analysis of all then-current North American randomized, placebo-controlled trials evaluating aprotinin efficacy found that a significant decrease in stroke was associated with full-dose aprotinin administration.²² Retrospective analysis of a high-risk group of elderly CPB patients with evidence of cerebrovascular disease and significant ascending aortic atheroma²³ showed an overall clinical stroke rate 16% higher in patients who did not receive aprotinin versus no strokes in patients who received full-dose aprotinin. Although retrospective

and relatively underpowered, this finding may again reflect a salutary anti-inflammatory effect of aprotinin.

A recent meta-analysis of 35 randomized trials using full-dose aprotinin showed that aprotinin is highly efficacious to reduce blood transfusions; no evidence for increased thrombotic complications was seen.²⁴ These data also demonstrated a reduced risk of stroke and a tendency for reduced incidence of atrial fibrillation in patients treated with aprotinin.

Still, the question must be asked: How is a serine protease inactivator associated with stroke reduction? Part of this may result from a primary decrease in overall transfusion and, specifically, in reduced platelet transfusions.²⁵ There may well be more: We hypothesize that this outcome represents a multifactorial anti-inflammatory effect of aprotinin involving suppression of WBC chemotaxis and transmigration, decreased bradykinin and vasogenic edema, reduction in proinflammatory cytokines, and, increasingly, the suppression of thrombin-mediated PAR activation in ischemic brain tissue appears to be a highly important mechanism.²⁶

Conclusions

The actions of aprotinin on inflammatory processes are complex and take effect via multiple pathways. This broad spectrum anti-inflammatory effect suggests new therapeutic avenues for which aprotinin may be especially beneficial either alone or in combination with other, more selective cerebroprotectants. As has been demonstrated, cerebral ischemic processes involve inflammatory mediators acting via a multitude of pathways. Potentially, a nonspecific serine protease inactivator such as aprotinin may prove effective in reducing risk of clinical stroke in the perioperative period. ■

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Neuroprotection = Protecting the Endothelium

David A. Stump, PhD

Coronary revascularization and valve repair/replacement have been linked to postoperative brain injury, although such injuries often result from lipid microembolization and are associated with many interventions.¹

Can we assess brain function as an outcome measure? Varied etiologic factors can result in identical symptoms. Similar levels of damage have different outcomes for individuals. Acute and remote symptoms evolve with time. Consequences of significant brain swelling (confu-

TABLE 1

Diffusion MRI Lesions: New Infarcts After CPB

Wake Forest (OPCAB 2/15 [13%])*	4/11 (36%)
Wurzburg [†]	9/26 (26%)
Kuopio [‡]	8/38 (21%)
Hopkins [§]	4/13 (31%)

MRI = magnetic resonance imaging; CPB = cardiopulmonary bypass; OPCAB = off-pump coronary artery bypass
^{*}Baker MD, et al: *Ann Thorac Surg.* 2002;73:S367
[†]Bendszuz M, et al: *Arch Neurol.* 2002;59:1090-1095
[‡]Vanninen R, et al: *Arch Neurol.* 1998;55:618-627
[§]Wityk RJ, et al: *Arch Neurol.* 2001;58:571-576

TABLE 2

Neurobehavioral Outcomes in High-Risk CABG Patients

	MULTICLAMP	SINGLE-CLAMP	OPCAB
1 week	60% (25/42)	60% (44/74)	67% (33/47)
1 month	51% (25/49)	32% (27/85)	39% (20/51)
6 months*	57% (24/42)	29% (22/74)	32% (13/42)*

* No aprotinin
 Six-month comparisons (chi square): $P = .007$, all groups; $P = .035$, OPCAB vs multiclamp; $P = .005$, multiclamp vs single clamp
 CABG = coronary artery bypass graft; OPCAB = off-pump coronary artery bypass

sion, stupor) may be apparent postsurgery; loss of brain mass (dementia) may be obvious only after a year or more.^{2,3}

Magnetic resonance imaging (MRI)-based studies suggest that roughly 1 in 4 patients have a new cortical lesion after a coronary artery bypass graft (CABG) (TABLE 1). The event rate may be higher: MRI is insensitive to small lesions; very ill patients were not evaluated. Interestingly, the percentage of patients with new MRI lesions is similar to the proportion of patients with neurobehavioral deficits at 6 months.

Most neuroprotective efforts⁴⁻¹¹ start with the premise that ischemia results from insufficient O₂ delivery (from compromised global cerebral blood flow [CBF]) or particulate embolus artery occlusion. However, gaseous emboli seldom cause a radiologically apparent lesion: The embolus “sticks and slips,” never stopping long enough for an infarction to develop.¹²

Microemboli passing through the vascular bed disrupt the endothelium and initiate the inflammatory cascade, with lost brain mass as damaged neurons die. This may be why patients demonstrate acute symptoms that abate over weeks; however, a year later, performance is reduced compared with that of patients without short-term deficits.^{13,14}

Thus, neuroprotection should be described as preventing injury and, secondarily, ameliorating or blunting the effects of entities responsible for damage at time of injury.

Specific causes of brain damage

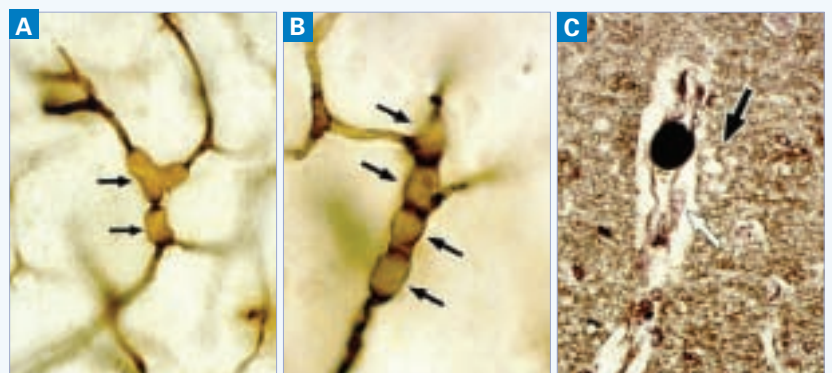
Recently, our group showed a direct relation between the number of ultrasonically detectable emboli in the carotid artery and the use of specific

aortic cross clamps.¹⁵ Increased aortic manipulation also was linked with neurobehavioral dysfunction 6 months post-CABG (TABLE 2).¹⁶

Smaller lipid and gaseous microemboli, seldom occurring in isolation, also cause transient occlusions in smaller vessels. These may not be evident by ultrasound: When many microemboli are present, they may appear as the background. A greater reflectivity may be observed. In histologies from patients who do not survive cardiopulmonary bypass (CPB) or orthopedic procedures, millions of 15 to 70 micron lipid microemboli (FIGURE 1) are trapped in the small arterioles of the brain.^{17,18} Over time, they may migrate through the vascular bed;¹⁹ extrusion of gaseous and lipid microemboli initiates a cascade of events that can result in significant brain swelling. Importantly, emboli are not necessarily “pushed” through the vascular system. The differential between arterial and venous pressure “pulls” an embolus by deforming the surface and shredding a

FIGURE 1

High Magnification Photomicrograph of SCADs From Patients Dying After CPB

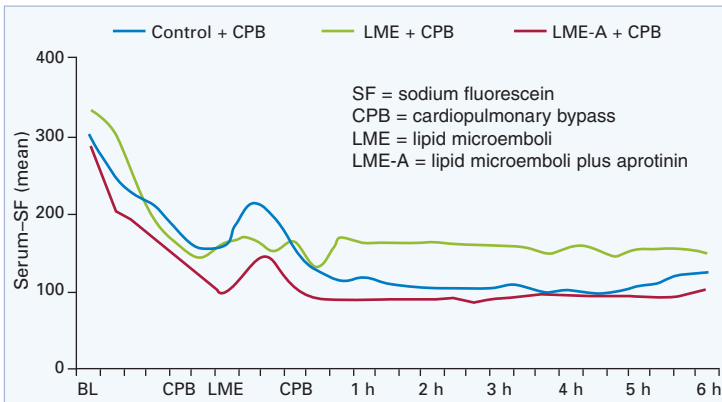


Original magnification x50. (a) and (b) SCADs at bifurcation points (arrows) in 100-mm-thick celloidin sections with AP microvascular staining. (c) SCAD stained black with osmium indicates that it is lipid. Swollen astrocytic end-feet (white arrow) vacuolization in the adjacent neuropil (black arrow) indicate tissue injury. This is a paraffin-embedded, 5-mm-thick osmium-fixed section.

Source: Dickson M. Moody. Supported by NS 20616.

FIGURE 2

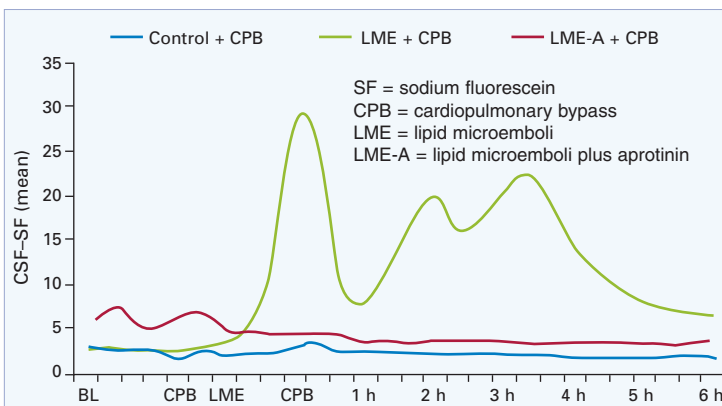
Impact of Aprotinin on Serum-SF in Dogs During CPB



Source: DA Stump. Supported by NS 20616.

FIGURE 3

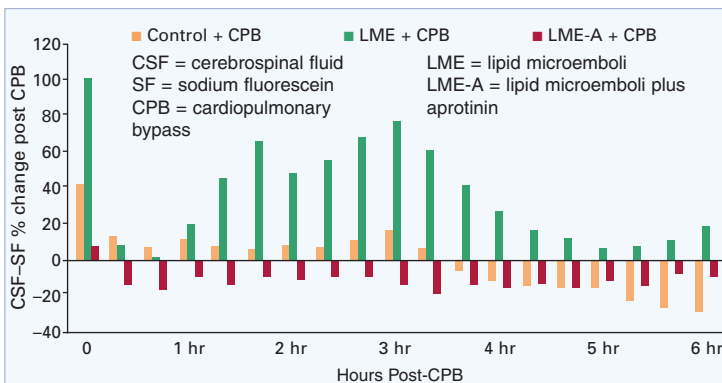
Impact of Aprotinin on Serum-SF in Dogs Post-CPB



Source: DA Stump. Supported by NS 20616.

FIGURE 4

Change in CSF-SF in Dogs Undergoing CPB in the Post-lipid Microembolization Period



Source: DA Stump. Supported by NS 20616.

deformable embolus into smaller microemboli that eventually travel to the venous system²⁰ where they may reconstitute into larger emboli and pass through the system again.

Trauma associated with microemboli

The passage of air/lipid microemboli in the cerebral circulation causes endothelial activation, initiating adherence of neutrophils and leukocyte migration.²¹ Could aprotinin protect the cerebral microvasculature and reduce blood-brain barrier (BBB) permeability related to similar embolic events that occur during CPB?

Studies of anesthetized dogs suggest this is the case. One group received 0.8% sodium fluorescein (SF) intravenously (bolus/infusion) over 10 hours as serum (jugular); cerebrospinal fluid (CSF) samples (cisterna magna) were collected at 20-minute intervals. The control group (n = 6) had no further intervention. After 3 hours of SF infusion, the lipid microemboli (LME) group (n = 6) received lipid-laden blood (18 cc triolein + 350 cc blood, well-agitated with air) via the left ventricle of the heart, simulating the return of cardiotomy-suctioned blood. The LME plus aprotinin (LME-A) group (n = 5) was pretreated with an aprotinin bolus (4 mg/kg) followed by continuous infusion (1 mg/kg/h) prior to a like-timed LME infusion. Sampling continued for 6 hours after LME infusion.

Serum-SF levels, similar in all groups, reached a steady state by the end of the sham CPB period. Aprotinin-treated and non-embolized control groups showed slight leakage of SF into the CSF via the meninges and choroid plexus; otherwise the CSF remained SF-free. The LME group demonstrated BBB disruption within 2 hours of lipid microembolization.

These differences are more apparent after calculating the CSF-SF percent change post-lipid microembolization. The LME group's CSF-SF levels rose above 50% within 2 hours and persisted 35% to 50% thereafter. The LME-A group did not increase until nearly 3 hours after lipid microembolization by 20%. In the control group, individual CSF-SF values demonstrated an inconsistent BBB response. Conversely, aprotinin demonstrated a significant reduction in CSF-SF variability within the

LME-A group indicating protection of the cerebral endothelium.

CPB embolization model

In a similar series, dogs had 90 minutes of CPB, including 30 minutes of hypothermia at 28°C. The control group (n = 4) had no further intervention. The LME group (n = 5) received lipid-laden blood (50 cc triolein + 450 cc blood) from the CPB circuit that simulated the return of suctioned shed blood during cardiac surgery. The LME-A group (n = 6) was pretreated with an aprotinin bolus (4 mg/kg) followed by continuous infusion (1 mg/kg/h) prior to a like-timed triolein/blood infusion during CPB. Serum-SF levels stabilized at similar levels in all groups after the CPB period; however, during CPB, serum-SF increased transiently, possibly related to profound hemodilution and temperature changes (FIGURE 2). Aprotinin-treated dogs had a minor rise in CSF-SF. The LME group demonstrated a rapid but transient BBB disruption following lipid microembolization during CPB, which then rose 2 to 3 hours post-CPB (FIGURE 3).

The calculated CSF-SF percent change postlipid microembolization demonstrates the differences between groups (FIGURE 4). The control group's CSF-SF did not surpass 17% during the post-CPB period. The LME group's CSF-SF levels rose 100% at the end of CPB, then diminished to nearly zero within an hour before elevating 40% to 75% during the 1- to 4-hour post-CPB period. The aprotinin-treated LME-A group was elevated 7% at the end of CPB then remained above 0% throughout the remainder of the 6-hour post-CPB period.

Unexpectedly, blood appeared in the CSF frequently in dogs undergoing CPB. Only control and LME-A non-CPB dogs had consistently clear CSF (FIGURE 5).

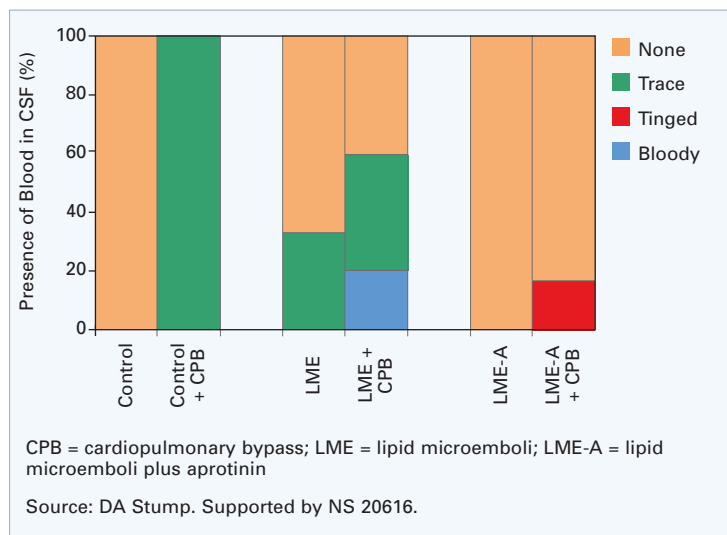
Conclusions

Protecting the brain during cardiac surgery can best be attained by preventing injury. Our data suggest that pump use—more than the circuit itself—affects outcomes. Three areas of neuroprotection are:

- **Blood management:** Prevent blood loss and minimize the return of cardiotomy suction blood. Purge the arterial filter to the venous reservoir instead of the cardiotomy suction reservoir.
- **Temperature management:** Carefully monitor arterial inflow temperatures so as to never exceed 37.5°C.
- **Minimizing the manipulation of the aorta:** Use epi-aortic scanning to avoid fragile areas of the arch and use of a gentle single-cross clamp.

FIGURE 5

Presence of Blood in CSF in Dogs Undergoing CPB



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CME Exam and Evaluation

CME EXAM

To receive CME accreditation, circle the correct response, complete the program evaluation and registration form, and then submit this form to Medical Education Resources. Certificates will be mailed to the address you list below. Please allow 3 weeks for processing.

- Randomized, prospective data support transfusion to treat mild to moderate anemia not due to exsanguination.**
 - True
 - False
- In a retrospective analysis of patients with acute coronary syndrome, the following outcomes were reported within 30 days of transfusion:**
 - 10% of those transfused died, compared with 6.08% of nontransfused patients.
 - 4% of those transfused died, compared with 12.08% of nontransfused patients.
 - 8% of those transfused died, compared with 3.08% of nontransfused patients.
 - 8% of those transfused died, compared with 6.08% of nontransfused patients.
- One randomized trial of liberal versus restrictive transfusion therapy showed that restrictive transfusion (maintaining Hb > 7 g/dL) had the following effects in comparison with liberal transfusion strategies:**
 - Increased mortality
 - Increased organ failure
 - Had no adverse effect on 30-day survival or organ failure
 - Increased mortality in patients with the lowest burden of illness
- Following discontinuation of chronic oral antiplatelet therapy, platelet function is not normal until the normal complement of platelets is generated in how many days?**
 - 3 to 6 days
 - 7 to 10 days
 - 10 to 14 days
 - 2 to 5 days
- Which agents protect platelets from activation during coronary artery bypass graft surgery and increase their ability to function normally after surgery?**
 - Aprotinin
 - Bivalirudin
 - Aprotinin and bivalirudin
 - None of the above
- Clopidogrel has more localized effects on ADP receptors and does not inhibit platelet function as profoundly as do intravenous agents.**
 - True
 - False
- What is the nonresponder rate associated with clopidogrel therapy?**
 - 10%
 - 15%
 - 20%
 - 25%
- In a study of 200 patients, those administered clopidogrel:**
 - Had more 8- and 24-hour chest tube drainages than those who did not
 - Received more donor blood than those who did not
 - Returned to the operating room because of bleeding
 - All of the above
- Aprotinin has been show to decrease postoperative bleeding brought on by use of clopidogrel in patients undergoing coronary artery bypass graft surgery.**
 - True
 - False

PROGRAM EVALUATION

- The program objectives were met
 STRONGLY DISAGREE DISAGREE AGREE STRONGLY AGREE
- The program content was useful and relevant
 STRONGLY DISAGREE DISAGREE AGREE STRONGLY AGREE
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- The program will change the way I practice
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- The authors demonstrated expertise in the topic
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