mented with regional cerebral perfusion may provide better cerebral protection than more conventional techniques.

Although the data presented by Pigula, Siewers, and Nemoto are suggestive of adequate cerebral protection, we still believe that core cooling to 18°C is the principal component of our cerebral protection strategy. Further study is warranted to ascertain the relative merits of regional cerebral perfusion versus hypothermia for cerebral protection during aortic arch reconstruction in the neonate.

Christopher A. Caldarone, MD

Douglas M. Behrendt, MD

Division of Cardiovascular Surgery

Children's Hospital of Iowa

200 Hawkins Dr

Iowa City, IA 52242-1083

REFERENCE

1. Pigula FA, Siewers RD, Nemoto EM. Regional perfusion of the brain during neonatal aortic arch reconstruction. *J Thorac Cardiovasc Surg* 1999;117:1023-4.

12/8/101415

Drug therapy before coronary artery operations

To the Editor:

We were greatly interested by the results of the IMAGE trial,¹ which suggests European patients are more susceptible than US patients to aprotinin-induced vein graft occlusion. This has prompted us to inquire whether our patients have a European or US response to aprotinin.

We have used aprotinin in varying doses for patients undergoing redo operations or for those with recent aspirin ingestion. Table I describes our mortality rate in consecutive patients undergoing coronary artery bypass grafting with or without other procedures between 1993 and 1998; a dose-dependent increase in mortality is evident. However, the indications for aprotinin are also very important risk factors for perioperative mortality. Thus it may not be too surprising that patients given aprotinin have a higher mortality rate. To clarify this, we have further analyzed our data to take risk factors for mortality into account.

The patients and model have been described in detail elsewhere.² Logistic regression was performed with in-hospital mortality from any cause as the dependent factor and 22 independent factors: age, sex, urgency of the operation, history of cardiac surgery, concurrent cardiac or cardiovascular procedures, left ventricular function, recent myocardial infarct, left main coronary artery stenosis, chronic airways disease, cerebrovascular disease, diabetes, hypertension, and other risk factors including preoperative cardioactive drug use. Stepwise regression was not used.

In this model we found the relative risk of mortality attributable to aprotinin to be 1.34 per million units of aprotinin with 95% confidence intervals of 1.1 to 1.7 ($P = .01$ for relative risk = 1). This indicates a risk-adjusted association between aprotinin and in-hospital mortality.

In the jargon of evidence-based medicine, our data are

Table I. Dose of aprotinin, number of patients, and in-hospital mortality rate for 1593 consecutive patients undergoing coronary artery operations

Dose of aprotinin (10 ⁶ KIU)	n	Mortality rate (%)
0	839	1.8
<1	248	3.2
1-1.9	191	3.1
2-2.9	201	6.5
3-3.9	62	9.7
≥4	52	11.5

“class III evidence” and should not be considered conclusive. However, taken in conjunction with the IMAGE trial results, our data support the hypothesis that in some circumstances aprotinin may have a deleterious effect on patients undergoing coronary artery operations.

We do not understand why aprotinin appears to have adverse effects in some surgical units and not others. We use balanced salt solutions for vein distention, maintain kaolin-activated clotting times above 600 seconds, and never administer our blood cardioplegic solution through vein grafts. Until it becomes clear why the adverse effects of aprotinin appear to be site specific, we would suggest that aprotinin should be used with caution in coronary artery operations.

William M. Weightman, MB, ChB

M. A. J. Newman, MD

Departments of Anesthesia and Cardiac Surgery

Sir Charles Gairdner Hospital

Verdun St

Nedlands 6009, Australia

REFERENCES

1. Alderman EL, Levy JH, Rich JB, Nili M, Vidne B, Schaff H, et al. Analyses of coronary graft patency after aprotinin use: results from the International Multicenter Aprotinin Graft Patency Experience (IMAGE) trial. *J Thorac Cardiovasc Surg* 1998;116:716-30.
2. Weightman WM, Gibbs NM, Sheminant MR, Whitford EG, Mahon BD, Newman MAJ. Drug therapy before coronary artery surgery: nitrates are independent predictors of mortality and beta adrenergic blockers predict survival. *Anesth Analg* 1999;88:286-91.

12/8/101197

Reply to the Editor:

The letter by Weightman and Newman suggests a dose-dependant mortality for aprotinin doses ranging from 0 to ≥4,000,000 KIU (see their Table I). In the IMAGE study (*J Thorac Cardiovasc Surg* 1998;116:716-30), the average dose in aprotinin-treated patients was 5,550,000 KIU ($n = 436$). This total includes the 2,000,000 KIU loading dose, 2,000,000 KIU into the cardiopulmonary bypass circuit prime, plus 1,570,000 KIU by continuous infusion at a prescribed rate of 500,000 KIU per hour. IMAGE study results showed that this administration regimen for aprotinin had no effect on mortality (placebo, 1.6%; aprotinin, 1.4%). In the

IMAGE study, 7 hospital deaths occurred in 434 placebo-treated patients (1.6%). This is similar to the 1.8% hospital mortality reported for non-aprotinin treated patients by Weightman and Newman. However, aprotinin-treated patients in the IMAGE study had a substantially lower hospital mortality than those patients treated with a comparable dose ($\geq 4,000,000$ KIU) in Weightman and Newman's letter: 1.4% compared with 11.5%.

Weightman and Newman report that of 754 patients receiving aprotinin, 93% received less than 4,000,000 KIU of aprotinin (see their Table I). Their reporting of the total dose makes unclear the administration regimen (ie, pump only, half dose, or full dose, as in the IMAGE study) and timing (from the beginning of the operation, as recommended, or, perhaps, after loss of hemostasis). Furthermore, and with the exception of pump-only administration, aprotinin is typically administered as a constant infusion per hour. In the simplest scenario (no pump or loading dose), any differences in the amount of aprotinin administered would result wholly from the length of the operation.

The variables that separated European from US patients in the IMAGE study were primarily related to adverse angiographic characteristics of the recipient vessels in addition to female sex, older age, prior aspirin use, and abnormal left ventricular ejection fraction. The only predictor variables in the IMAGE study for which there are data in Weightman and Newman's patient population (Anesth Analg 1999;88:286-91) are age, sex, and aspirin use. Their patients were older than those in the IMAGE study (63.8 years compared with 61.6 years at US sites and 62.0 years at Danish and Israeli sites), had a higher proportion of women (20.5% compared with 9.4% at US sites and 14.3% at Danish and Israeli sites), and a higher proportion of aspirin users (58.8% compared with 42.8% at US sites and 26.1% at Danish and Israeli sites). In the IMAGE study, aspirin use was associated with a lower risk of graft occlusion, whereas the other 2 variables, sex and age, were consistent with patients having a higher risk for vein graft occlusion. Comparative data on Weightman and Newman's patient characteristics are too limited to determine whether responses are more similar to those observed in our European or US patient populations. It is also unclear whether Weightman and Newman's data are prospective or retrospective.

These differences suggest that patients in Weightman and Newman's population—and particularly those receiving aprotinin—had a more adverse patient profile than either US or European patients in the IMAGE study or there were other technical differences in the surgical procedures. Thus inferences should not be made from a nonrandomized study, particularly one with apparent treatment biases.

Edwin L. Alderman, MD
For the IMAGE Investigators
Division of Cardiovascular Medicine
Stanford University School of Medicine
Falk Cardiovascular Research Center
CV-261, 300 Pasteur Dr
Stanford CA 94305-5406
12/8/101196

Abciximab (ReoPro) removal with a hemoconcentrator during cardiopulmonary bypass

To the Editor:

The problem of performing emergency cardiac surgery on patients who have been recently treated with abciximab (ReoPro, Eli Lilly and Company, Indianapolis, Ind) as addressed by Poullis and associates¹ is indeed of considerable interest to surgeons. The in vitro experiment they described, however, may have limited applicability to the clinical situation of operating on a patient who has been recently treated with abciximab. In their method, abciximab was added to a solution of saline and then subjected to hemoconcentration during circulation in an in vitro cardiopulmonary bypass circuit. However, platelets were not included in the test solution. This protocol is quite different from the situation of a patient who has been recently treated with abciximab and who does have platelets.

Poullis and associates state that the purpose of hemofiltration is to remove free abciximab so that subsequently administered donor platelets will have the role of providing hemostasis rather than "primarily absorbing free antibody." This hypothesis, however, is not consistent with the pharmacodynamic profile of abciximab.

When abciximab is administered, the drug rapidly binds to the platelet glycoprotein IIb/IIIa receptors and results in severe inhibition of platelet aggregation and prolongation of the bleeding time.^{2,3} The binding of abciximab to the platelets is noncompetitive and the dissociation rate from platelets is slow. Excess non-bound abciximab is rapidly cleared, and within 30 minutes of abciximab administration less than 4% of the administered dose is present within the serum as free antibody.⁴ Thus essentially no abciximab is available for removal by hemofiltration. Likewise, when donor platelets are transfused, no free abciximab is present to be "absorbed." When platelets are transfused there is, however, redistribution of abciximab from native (bound) platelet receptors to transfused (unbound) platelet receptors, resulting in an overall reduction in the percentage of bound receptors. When this overall percentage of blocked receptors falls below approximately 80%, the bleeding time and hemostasis return toward normal. This is the rationale for transfusing platelets to reverse the effect of abciximab.^{3,4}

Potential methods to reduce the bleeding diathesis in patients requiring surgery while under the effect of abciximab are welcome to surgeons who have to deal with this problem. At present, however, platelet administration to dilute the abciximab blockade of the platelet glycoprotein IIb/IIIa receptors would appear to be the antidote of choice. My colleagues and I⁵ recently reported experience with 12 patients who required emergency coronary artery bypass grafting shortly after abciximab treatment. The routine transfusion of 1 apheresis platelet unit (volume equal to 6 random donor platelets but acquired from a single donor) after reversal of heparin effect by protamine, with addition-