BRIEF COMMUNICATIONS

FATAL INTRAOPERATIVE PULMONARY THROMBOSIS AFTER GRAFT REPLACEMENT OF AN ANEURYSM OF THE ARCH AND DESCENDING AORTA IN ASSOCIATION WITH DEEP HYPOTHERMIC CIRCULATORY ARREST AND APROTININ THERAPY

John M. Alvarez, FRACS,^a Jacob Goldstein, FRACS,^a J. Mezzatesta, FANZCA,^b B. Flanagan, FANZCA,^b and M. Dodd, FACBS,^c *Melbourne, Australia*

A 69-year-old woman had graft replacement of the distal aortic arch and proximal descending thoracic aorta for a 13 cm atherosclerotic aneurysm. Left ventricular function and coronary artery anatomy were normal, as were results of all preoperative hematologic and coagulation assays.

Heparin administration was 300 units/kg plus 5000 units in the pump prime. Kaolin-based activated clotting time (ACT) was kept above 500 seconds during cardiopulmonary bypass (CPB) and above 750 seconds before circulatory arrest. Protamine was reversed on a 1 mg/100 units heparin ratio (Table I). Aprotinin (Trasylol) was given for a total dose of 6×10^6 kallikrein inactivation units (KIU; 2×10^6 KIU intravenously after anesthetic induction, 2×10^6 KIU in the pump prime, and 0.5×10^6 KIU/hr).

After establishment of CPB, antegrade and retrograde blood cardioplegic arrest together at 18°C, with continuous retrograde cerebral sanguineous perfusion through the superior vena cava during the period of circulatory arrest, were employed. The aneurysm was resected and replaced with a woven polyethylene terephthalate fiber (Dacron) graft; the arch vessels were reimplemented as a Carrel patch.

The patient was weaned from CPB unaided, with normal hemodynamic indexes, effective myocardial contractility, and a dry operative field. Ten minutes later, unheralded right ventricular failure with a normal electrocardiogram occurred. Protamine was discontinued and heparin was readministered to the patient. Despite inotropic support and intraaortic balloon counterpulsation, cardiac function was inadequate. CPB was recommenced, and right ventricular failure frustrated attempts to discontinue CPB. Transesophageal echocardiography revealed no valvular abnormality, with effective biventricular con-

traction in the decompressed heart. The pulmonary artery was opened, yet no evidence of pulmonary embolism was demonstrable. Right ventricular assistance was commenced. Unexplained intermittent inadequate venous return and raised pulmonary pressures hampered effective right ventricular assistance action, and the patient died 70 minutes later.

Postmortem examination revealed extensive deposits of skeinlike, fibrinous material loosely adherent to the walls of the main and segmental pulmonary arteries, right ventricle, and within the venous cannulas. Histologic examination revealed extensive thrombosis within the small pulmonary artery branches. No evidence of thrombosis was detected in other organs.

Aprotinin is highly effective in reducing blood loss after cardiac operations. However, safety concerns, initially raised by the Cleveland Clinic group,¹ remain unanswered. The safety of aprotinin in the setting of aortic reconstruction with deep hypothermic circulatory arrest is currently unclear.

Sundt and associates² from St. Louis and Westaby's group from Oxford³ have reported a detrimental effect of aprotinin in this setting of complex aortic operations with deep hypothermic circulatory arrest. The St. Louis group found a higher operative mortality rate, perioperative myocardial infarction rate, and renal failure rate in the aprotinin group than in a historical case-matched control group (15% vs 0%, 20% vs 0%, and 65% vs 5%, respectively).² The Oxford group reported a greater incidence of bleeding and thrombosis-related deaths associated with aprotinin.³

These reports represent large series by experienced

From the Departments of Cardiothoracic Surgery^a and Anaesthesia,^b Monash Medical Centre, Clayton, Melbourne, and the Victorian Institute of Forensic Medicine,^c Monash University, Melbourne, Australia.

Received for publication August 15, 1997; accepted for publication Sept. 30, 1997.

Address for reprints: J. M. Alvarez, FRACS, Department of Cardiothoracic Surgery, Monash Medical Centre, Clayton, 3168 Melbourne, Australia.

J Thorac Cardiovasc Surg 1998;115:723-4

Copyright © 1998 by Mosby, Inc.

0022-5223/98 \$5.00 + 0 12/54/86514

Table I. Case data

Age (yr)	69
Weight (kg)	65
Total dose of heparin (units)	40,000
Total dose of protamine (mg)	400
CPB time (min)	240
Circulatory arrest (min)	76
ACT (sec)	
Before CPB	120
After heparinization	732
Immediately before DHCA	999
Immediately after DHCA	732
After termination of CPB	309

DHCA, Deep hypothermia and circulatory arrest.

operators. Inadvertent underheparinization in these two groups has been proposed as a possible explanation by Smith and associates,⁴ because the diatomaceous earth (Celite)-based ACT used in these two series is spuriously raised in the presence of aprotinin. Westaby and coworkers³ point out that this vital information was not available when aprotinin (Trasylol) was released into the marketplace.

Goldstein and colleagues⁵ recently reported their experience with aprotinin use in this specific group of patients; they found no differences from a historical case-matched control group in operative mortality and perioperative myocardial infarction rates. Renal dysfunction was more common in the aprotinin group (29.2% vs 8.3%), but not significantly so (no *p* value was given). In the series of Goldstein and colleagues,⁵ kaolin-based ACT (aprotinin does not affect this measurement) was kept above 500 seconds and Celite-based ACT was maintained above 750 seconds. Their conclusions are totally at odds with those of Sundt and coworkers² and Westaby and colleagues.³

In our case, kaolin-based ACT was used and kept within accepted guidelines. It is noteworthy that the St. Louis group encountered a similar case of acute right ventricular failure from pulmonary thrombosis or embolism. This case is the only other such complication ever reported with this type of operation. In this case, no evidence of preoperative venous thrombosis was present at autopsy. We firmly believe that this patient was not underheparinized.

Is aprotinin safe? We concur with Westaby and coworkers³ in saying that we do not know. Only a prospective randomized trial will yield the answer. Does it actually produce a benefit? In the series of Goldstein and colleagues,⁵ there was no benefit in terms of total transfusion requirements. Unless aprotinin results in significantly

fewer patients needing blood transfusions and fewer transfusions per patient, differences in volume of drainage and number or type of blood products used are relatively unimportant.

This case strongly implicates aprotinin use in intravascular thrombosis; acute pulmonary thrombosis in this setting is extremely rare. This patient was not underheparinized, nor had she any known coagulation diathesis. Is this so surprising? Put simply, we do not know what aprotinin's physiologic role is, how it works, or how much to give—or even when the best time to give it is. What we do know is that it sure does work; is it surprising when it works too well? To quote Voltaire, “We use drugs about which we know very little in patients in whom we know even less.”

REFERENCES

1. Cosgrove DM 3rd, Heric B, Lytle B, et al. Aprotinin therapy for reoperative myocardial revascularization: a placebo controlled study. *Ann Thorac Surg* 1992;54:1031-8.
2. Sundt TM, Kouchoukos NT, Saffitz JE, Murphy SF, Wareing TH, Stahl DJ. Renal dysfunction and intravascular coagulation with aprotinin and hypothermic circulatory arrest. *Ann Thorac Surg* 1993;55:1418-24.
3. Westaby S, Forni A, Dunning J, et al. Aprotinin and bleeding in profoundly hypothermic perfusion. *Eur J Cardiothorac Surg* 1994;8:82-6.
4. Smith CR, Mongero LB, DeRosa CM, Michler RE, Oz MC. Safety of aprotinin ion profound hypothermia and circulatory arrest. *Ann Thorac Surg* 1994;58:603-8.
5. Goldstein DJ, DeRosa CM, Mongero LB, et al. Safety and efficacy of aprotinin under conditions of deep hypothermia and circulatory arrest. *J Thorac Cardiovasc Surg* 1995;110:1615-22.