

Safety of Repeat Aprotinin Administration for LVAD Recipients Undergoing Cardiac Transplantation

Daniel J. Goldstein, MD, Mehmet C. Oz, MD, Craig R. Smith, MD, Joshua P. Friedlander, BA, Carolyn M. De Rosa, BA, Linda B. Mongero, CCP, and Ellise Delphin, MD

Departments of Surgery and Anesthesiology, College of Physicians & Surgeons, Columbia University, New York, New York

Background. Anecdotal reports of allergic and anaphylactic reactions after aprotinin therapy have raised concern that its repeat use may be associated with substantial morbidity.

Methods. To address this concern, we reviewed our experience with all patients who underwent implantation of a left ventricular assist device and subsequent cardiac transplantation with perioperative use of aprotinin.

Results. Twenty-three patients received full-dose aprotinin during left ventricular assist device implantation and subsequent cardiac transplantation. All patients tolerated primary exposure to aprotinin without complication. One episode of anaphylaxis after secondary exposure was

treated with rapid institution of cardiopulmonary bypass. Although renal dysfunction was observed shortly after cardiac transplantation in 30.4% of patients, the effect was transient and occurred in the presence of cyclosporine. The one perioperative death after secondary exposure was unrelated to bleeding complications. No clinically evident thromboembolic events were documented.

Conclusions. Primary and secondary exposure to aprotinin during operation with cardiopulmonary bypass is associated with limited intraoperative blood use, a low incidence of transient renal dysfunction and anaphylaxis, a rare need of reoperation for bleeding, and no clinical thromboembolic events.

(*Ann Thorac Surg* 1996;61:692-5)

Aprotinin, a polypeptide protease inhibitor with platelet-preserving properties, has received much attention because of its well-established hemostatic effects during cardiopulmonary bypass operations [1-3]. In addition to its salutary blood-preserving properties, aprotinin has recently been shown to reduce the incidence of perioperative mortality and right heart failure in patients undergoing left ventricular assist device (LVAD) implantation [4].

Anecdotal reports of allergic and anaphylactic reactions after aprotinin therapy have raised concern that its repeat use may be associated with substantial morbidity [5, 7]. To address this concern, we reviewed our experience with all Thermo Cardiosystems LVAD recipients who were given aprotinin during device implantation and subsequently underwent cardiac transplantation with perioperative use of aprotinin. The findings of this review constitute the basis of this report.

Material and Methods

At our institution, perioperative full-dose aprotinin is routinely used for all LVAD implantations, cardiac and lung transplantations, and repeat coronary and valve

operations. For first-time exposure, aprotinin is administered as follows: (1) an intravenous test dose of 1.4 mg (10^4 KIU); (2) a loading dose of 280 mg (2×10^6 KIU) infused slowly over 20 to 30 minutes before sternotomy; (3) a pump-prime dose of 280 mg (2×10^6 KIU) added to the priming fluid prior to institution of cardiopulmonary bypass; and (4) a constant infusion of approximately 70 mg/h (5×10^5 KIU/h) until the conclusion of the operation. For repeat exposures, aprotinin is withheld until shortly before the institution of cardiopulmonary bypass. Once the surgeons are ready to cannulate, the test dose is given; if it is uneventful, the loading dose is administered over 3 to 5 minutes, and the constant infusion is begun with the onset of cardiopulmonary bypass.

We identified 23 patients who underwent LVAD implantation and subsequent cardiac transplantation with repeat perioperative administration of aprotinin. The clinical charts, perfusion sheets, and anesthesia records of these patients were reviewed. Demographics, aprotinin dosage and administration, intraoperative blood use, preoperative and postoperative laboratory values, and complications were recorded.

Results

Between January 1991 and June 1995, 53 patients underwent Thermo Cardiosystems LVAD implantation as a bridge to transplantation at our institution of patients, 24 have subsequently had cardiac transplantation. One pa-

Accepted for publication Oct 18, 1995.

Address reprint requests to Dr Goldstein, Department of Surgery, Milstein Hospital, 7th Floor, 7 Garden North, Room 435, 177 Fort Washington Ave, New York, NY 10032.

Table 1. Summary of Demographic Data

Patient No.	Age (y)	Sex	Cause of Cardiomyopathy	Duration of LVAD Support (d)
1	64	M	Idiopathic	98
2	53	M	Ischemic	48
3	50	M	Idiopathic	179
4	59	M	Ischemic	225
5	54	M	Ischemic	80
6	57	M	Ischemic	154
7	51	M	Ischemic	185
8	61	F	Idiopathic	103
9	52	F	Myocarditis	134
10	32	M	Idiopathic	118
11	47	M	Ischemic	99
12	59	M	Ischemic	53
13	48	M	Ischemic	49
14	63	M	Ischemic	31
15	45	M	Ischemic	65
16	51	F	Ischemic	45
17	62	M	Ischemic	100
18	42	M	Idiopathic	75
19	47	M	Idiopathic	54
20	62	M	Idiopathic	40
21	58	M	Ischemic	135
22	48	M	Ischemic	48
23	46	M	HOCM	24

HOCM = hypertrophic obstructive cardiomyopathy; LVAD = left ventricular assist device.

tient, the first LVAD recipient, did not receive aprotinin at the time of LVAD implantation and therefore was excluded from the analysis. The demographic profile of the remaining cohort of 23 patients is shown in Table 1. Nineteen of these patients underwent placement of the Thermo Cardiosystems 1000 IP pneumatic device (Thermo Cardiosystems, Woburn, MA) and 4 patients, the Thermo Cardiosystems 1200 VE electric device. All LVAD implantations and explantations for transplantation were performed by one of us (M.C.O.).

There were 20 men and 3 women with an average age of 53 ± 8 years ($\pm$ the standard deviation). The most common underlying cause of end-stage heart failure was ischemic cardiomyopathy. Mean duration of LVAD support ranged from 24 to 225 days with a mean of 93 ± 54 days ($\pm$ the standard deviation).

Primary Aprotinin Exposure

During LVAD implantation, no allergic or anaphylactic reactions were observed. All patients tolerated high-dose aprotinin well, and no histamine receptor blocker or steroid prophylaxis was used. At the time of initiation of aprotinin infusion, 17 patients (74%) were receiving α -agonist support. On average, patients required 2.3 ± 0.4 units of exogenous packed red blood cells, 5.4 ± 1 units of platelets, 3.8 ± 0.7 units of fresh frozen plasma, and 1 ± 1 unit of cryoprecipitate. Eight patients (35%) did not require any packed red blood cell transfusion (Fig 1).

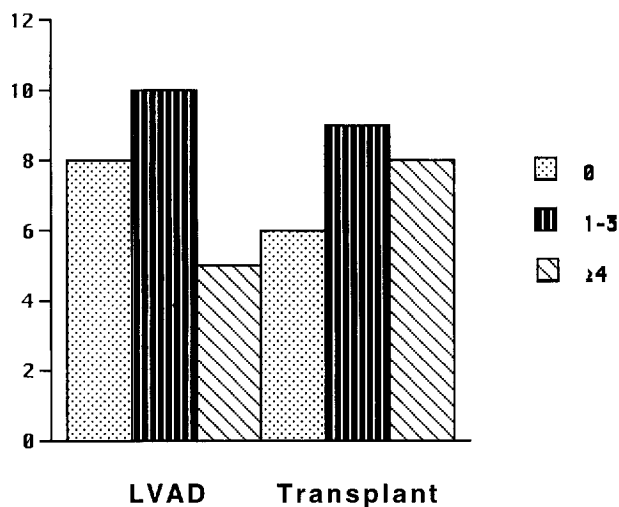


Fig 1. Distribution of intraoperative use of exogenous packed red blood cell (units) during left ventricular assist device (LVAD) implantation and cardiac transplantation in the presence of full-dose aprotinin.

Postoperative 24-hour chest tube output averaged $1,441 \pm 264$ mL ($\pm$ the standard error of the mean).

Comparison of renal function test results obtained preoperatively and on postoperative day 1 is provided in Table 2. There was no significant difference between preoperative and early postoperative renal function in regard to blood urea nitrogen and serum creatinine values ($p = 0.73$ and $p = 0.40$, respectively). Renal dysfunction, defined as an elevation of 50% or higher in baseline serum creatinine value, was seen in 2 (10%) of 20 patients for whom preoperative and postoperative renal function test results were available. The dysfunction was transient and resolved within 2 weeks in both instances. Only 2 patients (8.7%) required temporary postoperative dialysis (continuous arteriovenous or venovenous hemodialysis) for management of volume overload.

Reoperation for bleeding was necessary in only 1 patient (4.3%), whose postoperative course was complicated by coagulopathy, hypotension, and development of right-sided circulatory failure requiring temporary right ventricular assist device support [8]. Until the time of

Table 2. Renal Function Test Results Before and After Left Ventricular Assist Device Implantation and Cardiac Transplantation^a

Variable	LVAD Implantation		Transplantation	
	Preoperative	POD 1	Preoperative	POD 1
BUN (mg/dL)	40 ± 8	40 ± 6	17 ± 1	26 ± 2^b
Serum creatinine (mg/dL)	1.9 ± 0.2	2 ± 0.2	1.1 ± 0.04	1.6 ± 0.2^b

^a Data are shown as the mean $\pm$ the standard deviation. ^b Significance: $p < 0.05$ versus preoperative value.

BUN = blood urea nitrogen; LVAD = left ventricular assist device; POD = postoperative day.

transplantation, none of the patients received systemic anticoagulation. No perioperative or postoperative cerebrovascular accidents or other clinically evident thromboembolic events were observed.

Secondary Aprotinin Exposure

At the time of cardiac transplantation (secondary exposure), all patients received 500 mg of Solu-Medrol (methylprednisolone sodium succinate) (The Upjohn Co, Kalamazoo, MI) before or shortly after induction of general anesthesia but before initiation of aprotinin infusion. Oral cyclosporine (range, 0 to 2 mg on the basis of preoperative creatinine clearance) was also administered preoperatively according to the institutional cardiac transplant protocol. None of the patients received prophylactic histamine blockers. Only 8.7% of patients were receiving α -agonist support at the time aprotinin infusion was begun. No adverse reactions to the aprotinin test dose were observed. However, 1 patient became hypotensive shortly after administration of the aprotinin loading dose and required emergent institution of cardiopulmonary bypass and pressor agent support. Simultaneous with the aprotinin loading dose, this patient was receiving intravenous vancomycin (Eli Lilly and Company, Indianapolis, IN) and aztreonam (E. R. Squibb & Sons, Princeton, NJ).

During cardiac transplantation, the mean number of packed red blood cell units transfused was 3.6 ± 1.2 per patient. Use of other blood products paralleled that seen during LVAD implantation (5.6 ± 1 units of platelets, 3.1 ± 1 units of fresh frozen plasma, and no cryoprecipitate). Only 1 patient (4.3%) did not require any blood products whatsoever.

In regard to renal dysfunction, a significant rise in both blood urea nitrogen and serum creatinine levels was noted by postoperative day 1 (see Table 2). Perioperative renal dysfunction occurred in 7 (30.4%) of the transplant recipients. No patient required permanent dialytic therapy. The same patient in whom a postoperative coagulopathy developed during LVAD implantation manifested the same clinical scenario after transplantation. He was treated in similar fashion by reoperation and temporary right ventricular assist device support.

Only one perioperative death (postoperative day 5) occurred, and it was due to sepsis after transplantation. The three late deaths at 1 month, 3 months, and 4 months after transplantation were due to respiratory arrest, donor heart failure, and severe rejection, respectively. The remaining 19 patients are alive and well at a mean follow-up of 14.4 ± 2.6 months (range, 2 to 42 months).

Comment

Aprotinin, a serine protease inhibitor isolated from bovine lung, has been shown to improve hemostasis after cardiopulmonary bypass. Although its effectiveness is hardly questioned, the safety profile of this drug has been the subject of occasional reports in the literature. These data, however, mainly comprise anecdotal cases in which hypersensitivity and anaphylactic reactions oc-

curred after primary [9, 10] or secondary [5-7] exposure to the drug. Schulze and associates [7] described 1 patient in whom an anaphylactic reaction developed on repeat exposure to aprotinin, but they did not elaborate on the 47 patients who presumably underwent uncomplicated repeat aprotinin infusion. A previously reported series [11] evaluating the safety of repeat aprotinin therapy described the use of the drug for inoperable gastric cancer. The authors of that study concluded that repeated dosing of aprotinin could be considered safer provided patients received an intradermal challenge before each dose.

In view of the scarce available data, the objective of the present study was to investigate the safety of reexposure to aprotinin in the clinical setting in which the drug is most commonly used today, namely, operations requiring cardiopulmonary bypass. Because of the risk of bleeding and bleeding-related complications inherent to LVAD implantation and cardiac transplantation, we routinely administer perioperative full-dose aprotinin. Further, the decreased use of exogenous blood during LVAD implantation reduces sensitization of the recipient to blood cell antigens, and in this era of organ donor shortage, this can be critical. Our extensive experience with LVAD support as a bridge to transplantation provides a unique population of homogeneous patients in whom the safety of aprotinin readministration can be assessed.

Our results indicate that full-dose aprotinin can safely be used in repeat fashion for patients undergoing a second operation requiring cardiopulmonary bypass. The effectiveness of aprotinin in this study cannot be evaluated because no control (or untreated) group was studied concurrently. However, the requirements for intraoperative blood product use are similar to those reported elsewhere [12].

Primary exposure to aprotinin was associated with no anaphylactic episodes, a low incidence of transient renal dysfunction, a low need of reoperation, and no clinically evident thromboembolic events. During secondary exposure, one episode of hypotension (after initiation of a loading dose) possibly related to aprotinin use occurred. It was easily managed by immediate institution of cardiopulmonary bypass and α -agonist support. It is certainly possible that other hypersensitivity or anaphylactic reactions were averted by the preoperative high-dose steroids routinely administered to all our transplant recipients. A significant elevation in renal function test results was noted after transplantation. Renal dysfunction was idiosyncratic in that a preoperative elevated creatinine level was not predictive of subsequent renal dysfunction. It is very possible that the renal dysfunction observed in the cardiac allograft recipients may be partly or entirely due to the coadministration of cyclosporine.

Despite the theoretic possibility of induction of a hypercoagulable state in the presence of an antifibrinolytic agent, no perioperative clinical thromboembolic events were observed during initial or secondary aprotinin administration.

We conclude that repeat administration of aprotinin

for patients undergoing LVAD implantation and subsequent heart transplantation is associated with a low incidence of anaphylaxis and renal dysfunction. Further, no thromboembolic episodes were observed. Our current practice of withholding the aprotinin loading dose during secondary exposure until the surgeons are ready to cannulate appears warranted. Our anecdotal experience does not suggest that this practice diminishes the hemostatic efficacy of aprotinin.

References

1. Bidstrup BP, Royston D, Sapsford RN, Taylor KM, Cosgrove DM. Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin. *J Thorac Cardiovasc Surg* 1989;97:364-72.
2. Van Oeveren W, Jansen NJG, Bidstrup BP, et al. Effects of aprotinin on hemostatic mechanisms during cardiopulmonary bypass. *Ann Thorac Surg* 1987;44:640-5.
3. Fraedrich G, Weber C, Bernard C, Hettwer A, Schlosser V. Reduction of blood transfusion requirement in open heart surgery by administration of high doses of aprotinin—preliminary results. *Thorac Cardiovasc Surg* 1989;37:89-91.
4. Goldstein DJ, Seldomridge JA, Chen JM, et al. Use of aprotinin in LVAD recipients reduces blood loss, blood use, and perioperative mortality. *Ann Thorac Surg* 1995;59:1063-8.
5. Dewachter P, Mouton C, Masson, Gueant JL, Haberer JP. Anaphylactic reaction to aprotinin during cardiac surgery. *Anaesthesia* 1993;48:1110-1.
6. Diefenbach C, Abel M, Limpers B, et al. Fatal anaphylactic shock after aprotinin reexposure in cardiac surgery. *Anesth Analg* 1995;80:830-1.
7. Schulze K, Graeter T, Schaps D, Hausen B. Severe anaphylactic shock due to repeated application of aprotinin in patients following intrathoracic aortic replacement. *Eur J Cardio-thorac Surg* 1993;7:495-6.
8. Chen JM, Levin HR, Catanese KA, et al. Use of a pulsatile right ventricular assist device and continuous arteriovenous hemodialysis in a 57 year old man with a pulsatile left ventricular assist device. *J Heart Lung Transplant* 1995;14:186-91.
9. Bauer J, Futterman S, Dreiling DA. Anaphylactic shock secondary to initial Trasylol administration. *Am J Gastroenterol* 1971;56:542-4.
10. Bohrer H, Bach A, Fleischer F, Lang J. Adverse haemodynamic effects of high dose aprotinin in a pediatric cardiac surgical patient. *Anaesthesia* 1990;45:853-4.
11. Freeman JG, Turner GA, Venables CW, Latner AL. Serial use of aprotinin and incidence of allergic reactions. *Curr Med Res Opin* 1983;8:559-61.
12. Havel M, Owen AN, Simon P, et al. Decreasing use of donated blood and reduction of bleeding after orthotopic heart transplantation by use of aprotinin. *J Heart Lung Transplant* 1992;11:348-9.