

Incidence of Hypersensitivity Reactions

Wulf Dietrich, MD

German Heart Center, Munich, Germany

Background. Aprotinin is a naturally occurring serine protease inhibitor derived from bovine lung. In common with all foreign proteins, it possesses antigenic properties and has the possibility of allergic reactions on reexposure.

Methods. Data are presented on the incidence of adverse reactions to aprotinin and the time course of antibody development after initial exposure. Recommendations for reducing the risk and sequelae of these adverse reactions are emphasized and case reports are reviewed.

Results. The incidence rates of aprotinin-related reactions to date (May 1997) at the German Heart Center are 2.7% in the adult population in reexposures (5/183) and 1.2% in the pediatric population (3/254), with an overall incidence of 1.8% (8/437).

Conclusions. With the recommended precautions, reexposure to aprotinin in patients with a high risk of bleeding is justified, and the benefits of aprotinin treatment outweigh the relative risk of a serious allergic reaction.

(Ann Thorac Surg 1998;65:S60-4)

© 1998 by The Society of Thoracic Surgeons

Aproinin, a polybasic polypeptide, is a naturally occurring inhibitor of proteolytic enzymes derived from bovine lungs [1]. As a foreign protein, it possesses antigenic properties, and allergic reactions after reexposure to high-dose aprotinin have been described [2-10]. Aprotinin is especially efficacious in cardiac reoperations [11, 12], which are common in pediatric cardiac surgery. However, the question remains whether the relative risk of an anaphylactic reaction might outweigh the benefit of this drug if given to previously sensitized patients.

This presentation aims to (1) review the incidence of adverse reactions to aprotinin, (2) demonstrate the time course of the development of immunoglobulin G (IgG) and immunoglobulin E (IgE) antibodies against aprotinin, (3) discuss specific case reports, and (4) make recommendations for reducing the risk and sequelae of these adverse reactions.

Adverse Reactions to Aprotinin

German Heart Center Experience

Eleven reports in the literature, from as early as 1983, have described anaphylactic reactions to aprotinin, although most have been in the form of letters and case reports [2-10]. Aprotinin therapy has been in use at the German Heart Center, Munich, for almost 10 years for both adult and pediatric cardiac surgical practice, and this prompted a retrospective investigation of all patients reexposed to the drug at the institution between January 1988 and March 1995 to evaluate the prevalence of adverse reactions [13].

Classification of an Adverse Reaction

An allergic reaction is assumed if at least one of the following symptoms is present within 10 minutes of aprotinin administration: (1) a decrease of systolic blood pressure greater than 20% from baseline, (2) change of heart rate greater than 20% from baseline, (3) an increase of inspiratory pressure greater than 5 cm H₂O, or (4) a skin reaction. Reactions to aprotinin are classified as mild (no intervention), moderate (restoration of circulation within 15 minutes after the event with use of vasopressors), or severe (longer-lasting circulatory depression and instability despite vasopressor therapy).

One problem with this definition is that because aprotinin is administered during the surgical procedure, it is not always possible to be sure that the symptoms observed truly reflect an allergic reaction to aprotinin and are not the result of pathophysiologic changes resulting from other surgical or anesthetic interventions.

Incidence of Aprotinin-Related Adverse Events

More than 6,000 patients undergoing heart operations were treated with high-dose aprotinin in the study period at the German Heart Center, among which were 248 reexposures to aprotinin in 240 patients in 101 operations on adult patients and 147 operations on pediatric patients. Patients up to age 18 years were considered as pediatric patients. Correction of congenital heart lesions and valve replacements were the major surgical procedures in which repeat aprotinin therapy was used (Table 1).

Seven adverse reactions to aprotinin were recorded in the patient charts (Tables 2, 3), of which one was unclear and classified as a "doubtful" reaction to aprotinin (patient 1). Two patients reacted to the test dose of 10,000 KIU (1.4 mg) aprotinin (1 mild, 1 severe; patients 6 and 7) and received no additional aprotinin.

Table 3 also details the time interval between the first administration of aprotinin and reexposure, varying from

Presented at Risk Assessment of Major Perioperative Issues in Pediatric Cardiac Surgery, Washington, DC, May 7, 1997.

Address reprint requests to Dr Dietrich, German Heart Center, Lazarettstr 36, 80636 Munich, Germany.

- ies after cardiac operations. *J Thorac Cardiovasc Surg* 1997; 114:676-8.
15. Scheule AM, Jurmann MJ, Wendel HP, et al. Anaphylactic shock after aprotinin reexposure: time course of aprotinin-specific antibodies. *Ann Thorac Surg* 1997;63:242-4.
 16. Dietrich W, Spannagl M, Jochum M. Influence of high-dose

- aprotinin treatment on blood loss and coagulation patterns in patients undergoing myocardial revascularization. *Anesthesiology* 1990;73:1119-26.
17. Levy JH. Antibody formation after drug administration during cardiac surgery: parameters for aprotinin use. *J Heart Lung Transplant* 1993;12:S26-33.

DISCUSSION

DR PAUL YOST (Seal Beach, CA): How soon do the antibodies develop? If a patient requires extensive reoperation within 24 to 72 hours of initial exposure and administration of aprotinin, can you give the drug a second time?

DR DIETRICH: Within 24 hours, yes, you can do it. But after 2 or 5 days, it might be dangerous, and after 1 week I would not do so.

DR HAMISH MUNRO (Ann Arbor, MI): I have a comment and a question. We had a case of repeated exposure within a week in which the test dose was negative and approximately 5 minutes after starting the loading dose we saw a clear anaphylactic reaction that was, under your criteria, moderate in nature. So test doses are not always foolproof.

The question is, do you give just one dose of the H₁ and H₂ blockers, or, as is recommended by some people for latex-allergic patients, give it up to 12 hours before in repeated doses?

DR DIETRICH: It would be ideal to give it twice, but we do not have the time before operation. I agree with you, the test dose is not secure, and it might be that the reaction to aprotinin is delayed. That means you wait 5 or 10 minutes and you feel secure, but then the reaction occurs.

DR JERROLD H. LEVY (Atlanta, GA): I have a couple of comments. I am very familiar with the anaphylaxis literature, so it is sort of strange for me to recommend H₁ and H₂ blockers, because that is going to prevent the hemodynamic response to the test dose. The other point is that true full-blown anaphylaxis is a complex, multimediator event, so we tend to think that there is a benefit of giving H₁ and H₂ blockers. This comes from a lot of German literature on colloid volume expanders as well as from the American literature on contrast media. These are nonimmunologic events. So although this prophylaxis is recommended, although it is not a bad idea, it should be emphasized that there is a downside.

All the data regarding latex allergies are really untenable, because pretreatment in true anaphylaxis does not exist. I have cases in which 2 g of methylprednisolone were given and in 4 hours acute life-threatening pulmonary vasoconstriction and right heart failure occurred. I think this is important to note, because we get lulled into a sense of security that pretreating has beneficial effects.

DR DIETRICH: I have a question for you, Dr Levy. Would you recommend steroids in these cases? I did not do so, but . . .

DR LEVY: There are no data that steroids are going to be effective.

DR DIETRICH: Or that they are not harmful.

DR LEVY: Exactly. They may have a beneficial effect, but the point is that you can pretreat and still see life-threatening anaphylaxis and cardiovascular collapse. The other important and interesting thing is that everybody gets immunoglobulin G

antibodies. In Michael Weiss's study published in the *New England Journal of Medicine* in 1989, which looked at protamine reaction, immunoglobulin G antibodies were shown to be really not predictive in anaphylaxis. There are so many different broad subsets of immunoglobulin G antibody. But immunoglobulin E tends to be pretty predictive. Did you look at immunoglobulin E antibodies in your immunologic evaluation of your patient series?

DR DIETRICH: Yes, we did, but there have been no immunoglobulin E-positive tests before adverse reactions so far. On the other hand, it is much more difficult to measure immunoglobulin E antibodies than immunoglobulin G antibodies. That is a problem.

DR ROBERT F. CONIFF (West Haven, CT): I just want to make a few comments relative to our American experience. First of all, because this drug has only been available in the United States for a few years, the incidence of reexposures has been very low, so the incidence of allergic or anaphylactic-type reactions has also been extremely low. In contrast, in Europe, where the drug has been available and used for a wide variety of indications for somewhat more than 30 years, we did measure antibodies in several of our large multicenter clinical trials. Our experience was very similar to what Dr Dietrich reported: we found generally between 50% and 60% of patients who received aprotinin for the first time seroconverted to positive. We also found that it was very, very difficult, particularly in those patients who had high immunoglobulin G antibody titers, to sort out the immunoglobulin E antibodies. I would say that we have only had one fatality from anaphylaxis in the United States. That was a patient who had been in one of our control trials, who then 3 months later had a repeat procedure. The surgeon gave that patient steroids and antihistamines before doing the skin test. The skin test result was negative, but about 10 minutes into the loading dose the patient crashed, and could not be resuscitated. So again, the skin test can be negative, but it also brings up the issue of whether pretreating them may modify the skin test reactivity, as Dr Levy just mentioned.

DR DIETRICH: You mentioned the skin test. Our results were also very disappointing: all the patients have been negative up to now. So I think there is no predictive value of a skin test. I do not know why; it should be a very sensitive method, should it not, Dr Levy? Skin testing is recommended by all the immunologists.

DR LEVY: Skin testing, as you point out, is not predictive. The other important thing is that one of the reasons why we give the loading dose of aprotinin over 20 to 30 minutes is because it is like vancomycin, like morphine, and like curare: it is a nonimmunologic histamine releaser. So you have to give it to attenuate the histamine-releasing effects. If you do decide to skin test, you have to dilute it out, or you will get false positives. But there have been no studies really looking at it.

Table 1. Types of Operations Using Repeat Aprotinin

Operation	Adults	Pediatrics
Coronary artery bypass grafting	20	0
Valve re-replacement	63	18
Conduit or shunt	4	44
Heart transplantation	3	0
Correction of congenital defects	10	84
Miscellaneous	1	1
Total	101	147

Reprinted with permission from Dietrich W, Spath P, Ebell A, et al. Prevalence of anaphylactic reactions to aprotinin: analysis of two hundred forty-eight reexposures to aprotinin in heart operations. *J Thorac Cardiovasc Surg* 1997;113:194-201.

22 days up to 19 years. Figure 1 displays this time dependency of adverse reactions to aprotinin reexposure in relation to the percentage of patients who were reexposed. This graph includes additional data collected after the published study was concluded in March 1995 and details eight adverse events from a total of 437 reexposed patients. Approximately 50% of patients were reexposed to aprotinin within 200 days of the initial exposure, and 80% within 1,000 days. All but one of the severe adverse reactions occurred within the first 200 days, the exception being in 1 patient who had received the first exposure to aprotinin 2 years before the adverse event.

Unpublished data on the current incidence rates of aprotinin-related reactions to date (May 1997) at the German Heart Center are 2.7% in the adult population in reexposures (5/183) and 1.2% in the pediatric population (3/254), with an overall incidence of 1.8% (8/437). This number differs from those of other reports: Schulze and associates [7] reported a prevalence of 5.8% for allergic reactions after aprotinin reexposure, Diefenbach and associates [5] a frequency of 6%, and Ceriana and colleagues [3] 1 patient in 200 reexposures. This difference may be explained by incomplete data collection either because of missed reexposures without sequelae or overlooked mild reactions to aprotinin. Of note, in the current series of patients there was a wide variation in the severity of the symptoms of the adverse events, and it was not always unequivocally possible to relate hemodynamic instability to a reaction to aprotinin.

Antibody Development Against Aprotinin

Weipert and colleagues [14] demonstrated that IgG antibodies to aprotinin develop within 6 weeks after operation in 47% of patients (17/36), with a further 19% of patients (7/36) with questionable antibody development. By 48 months, 39% of all patients (14/36) still showed measurable levels of IgG against aprotinin. Figure 2 shows that 8 of the 17 antibody-positive patients in the initial postoperative period still showed measurable levels of IgG at 48 months, whereas the remainder had undetectable or questionable levels [14]. Of interest were 6 patients who had questionable or negative antibody titers initially but became positive when tested 48 months later. The probable explanation for this is that testing was

performed in these patients within 7 days of the exposure to aprotinin. This was probably insufficient time for IgG antibodies against aprotinin to develop.

The formation of IgE antibodies against aprotinin, which are mainly responsible for the immediate-type allergic reaction, also has been described [5]. If the hypersensitivity reactions to aprotinin are antibody-mediated, the assessment of drug-specific antibodies before treatment may identify patients at risk. However, a clinically useful, reliable, and predictive test system does not yet exist.

Case Reports

Case 1

A 13-year-old female patient had pulmonary atresia (patient 4, Table 3). Three years before the operation in which reaction to aprotinin occurred, a right ventricle-pulmonary artery conduit had been placed. During that operation she had received 1.4×10^6 KIU (196 mg) aprotinin. Most recently the patient underwent replacement of the calcified conduit. Before skin incision the patient received 50,000 KIU (7 mg) aprotinin as a test dose without adverse reaction. Ten minutes later, infusion of 1.3×10^6 KIU (182 mg) aprotinin over 10 minutes was begun. Five minutes later, the systolic blood pressure dropped from 110 to 60 mm Hg. Despite massive inotropic support the mean arterial pressure remained between 30 and 40 mm Hg. Operation was started immediately, and commencement of cardiopulmonary bypass (CPB) was possible after 45 minutes of preparation. The patient was cooled to a core temperature of 16.9°C, and the conduit replacement was done with the use of deep hypothermic circulatory arrest lasting 57 minutes. Total CPB time was 153 minutes. After termination of CPB, circulation recovered slowly with inotropic support. The postoperative course was uneventful. This case was classified as a severe reaction to aprotinin.

Case 2

A 66-year-old male patient had mitral regurgitation (patient 6, Table 3). He had had a previous mitral valve replacement 120 days before undergoing the operation in which a reaction to aprotinin occurred. The most recent operation was done for repair of a leakage on the mitral valve and aortic valve replacement to correct aortic valve

Table 2. Distribution and Severity of Adverse Reactions to Aprotinin^a

Group	n	Reactions				Total
		Doubtful	Mild	Moderate	Severe	
Adult	101	1	2	...	1	4
Pediatric	147	...	...	1	2	3
Total	248	1	2	1	3	7

^a Explanation of severity score is given in text.

Reprinted with permission from Dietrich W, Spath P, Ebell A, et al. Prevalence of anaphylactic reactions to aprotinin: analysis of two hundred forty-eight reexposures to aprotinin in heart operations. *J Thorac Cardiovasc Surg* 1997;113:194-201.

Table 3. Adverse Reactions to Aprotinin

Patient No.	Age (y)	Operation	Time Interval	Test Dose	H ₁ /H ₂ Blockers ^a	Steroids	Reaction
1	71	VR	193 days	No	Yes	No	Doubtful
2	82	VR	127 days	No	Yes	No	Severe
3	5	Congenital	29 days	No	Yes	Yes	Moderate
4	13	Congenital	1,106 days	Yes	No	Yes	Severe
5	20	Congenital	19 years	Yes	No	No	Mild
6	66	VR	120 days	Yes	Yes	No	Mild
7	7	Congenital	22 days	Yes	Yes	Yes	Severe

^a Given before the test dose.

VR = valve replacement.

Reprinted with permission from Dietrich W, Spath P, Ebell A, et al. Prevalence of anaphylactic reactions to aprotinin: analysis of two hundred forty-eight reexposures to aprotinin in heart operations. J Thorac Cardiovasc Surg 1997;113:194-201.

insufficiency. During the previous uneventful operation he had received 6×10^6 KIU (840 mg) aprotinin. In the most recent operation, after standard induction of anesthesia, H₁/H₂ blocker was given. During skin incision a test dose of 10,000 KIU (1.4 mg) aprotinin was given. Shortly after, a skin flush developed, but the patient's condition remained hemodynamically stable. No further aprotinin was given and the operation was continued routinely. Perfusion pressure during CPB was remarkably low. This case was classified as a mild reaction to aprotinin. Despite this very mild reaction, IgG antibody titers in this patient obtained 6 weeks after an uneventful recovery were in excess of 2,000 times normal.

Case 3

A 7-year-old boy with a body weight of 19 kg had pulmonary atresia and ventricular septal defect (patient 7, Table 3). Other complex lesions rendered primary correction of the defect impossible. In his first year of life, an aortopulmonary shunt was placed. The shunt was renewed 4 years before the most recent operation. During that operation the patient received a total of 80,000 KIU aprotinin. In a third operation 3 weeks before the most recent operation, a replacement of the aortopulmonary shunt was done. During this operation 1.5×10^6 KIU (210 mg) aprotinin was given after H₁/H₂ blockade and

8 mg dexamethasone. The patient tolerated this reexposure to aprotinin without sequelae. Oxygen saturation remained poor after operation. Therefore a new shunt revision was scheduled 3 weeks later. H₁/H₂ blockade was given before this most recent operation. Thirty minutes after the start of the operation a test dose of 10,000 KIU (1.4 mg) aprotinin was injected. Immediately the systolic blood pressure dropped from 100 to 70 mm Hg. The heart rate increased from 100 to 180 beats/min. Venous cannulation for CPB was difficult because of severe bleeding from the site of cannulation. Despite 50 μ g of epinephrine, the blood pressure remained 80/40 mm Hg. Blood loss at this time was severe. Twenty minutes after aprotinin injection CPB was begun. After termination of CPB, inotropic support with norepinephrine and dopamine was required. The postoperative period was uneventful. This incident was classified as a severe reaction to aprotinin.

Results from antibody measurements subsequently revealed that at the time of the second operation, neither IgG nor IgE antibodies were present. However, within 7 days, a grade III high titer of IgG was detected, and at the time of the third operation, when the reaction to the test

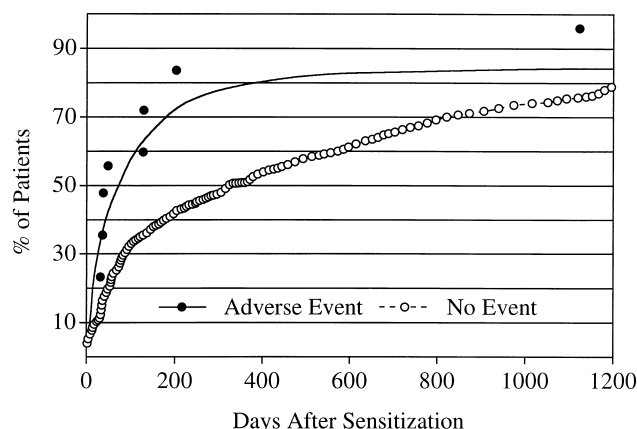


Fig 1. Adverse reactions to aprotinin reexposure.

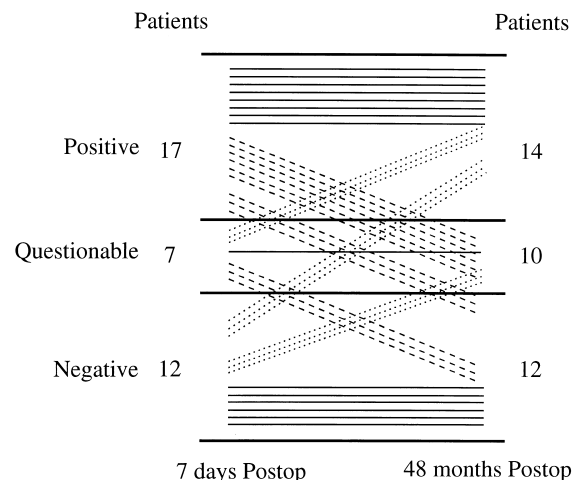


Fig 2. Detection of immunoglobulin G antibodies 7 days and 4 years after initial exposure to aprotinin. (Data taken from reference 14.)

dose occurred, levels of both IgG and IgE were elevated. Neither antibody was detectable 6 months after the reaction.

The time course of antibody development is described in a recent report by Scheule and colleagues [15]. A 75-year-old woman required rereplacement of her mitral valve 3 months after the unsuccessful first operation. Preoperatively, tests were positive for both IgG and IgE antibodies. Aprotinin was administered during the skin incision and a severe anaphylactic reaction occurred after infusion of 150,000 KIU (21 mg). Five minutes after the reaction, the levels of IgG had decreased and IgE was undetectable. Further measurements made 3 hours after bypass and during the first postoperative day were negative for both antibodies. However, IgG levels were markedly elevated again by 14 days postoperatively. This consumption of antibody during an anaphylactic response may explain why some investigators do not detect high antibody titers in the immediate period after the reaction.

Recommendations to Reduce Adverse Reactions

The following procedures are recommended to reduce the risk and severity of adverse reactions to aprotinin: (1) Give a test dose of 10,000 KIU (1.4 mg) aprotinin in all patients who will receive aprotinin treatment (not restricted to reexposures), (2) delay the first bolus injection of aprotinin until the surgeon is ready to commence CPB, (3) use H₁/H₂ blockade in known or possible reexposures, and (4) avoid reexposure within the first 6 months after the last exposure.

Test Dose of Aprotinin

A test dose of aprotinin of 10,000 KIU (1.4 mg) should be administered 10 minutes before the loading dose. It is advisable to delay priming the heart-lung machine with aprotinin until after the test dose is given in case a reaction to the test dose results in a mandatory exchange of the bypass circuit. The test dose must also be given if only the oxygenator is primed with aprotinin (prime-only protocols). The test does not prevent allergic reactions; adverse events do occur after a test dose.

Delay First Bolus Injection

For patients known to have been previously exposed to aprotinin, it is recommended that both the test and loading doses of aprotinin be delayed until the surgeon is ready to immediately institute CPB. Hemostatic activation during the time before CPB is not comparable with the activation that occurs during CPB and the influence of aprotinin in this period, if any, is minimal [16]. On the other hand, CPB may be lifesaving in the face of circulatory collapse caused by anaphylaxis. Especially in repeat operations the interval between skin incision and the start of CPB can be prolonged because of difficult dissection.

H₁/H₂ Blockade in Known or Possible Reexposures

To date, H₁/H₂ blockade (clemastine, 0.03 mg/kg; cimetidine, 5 mg/kg) is used in all patients reexposed to

aprotinin at the German Heart Center. Aprotinin, like other polypeptides, has been implicated as a histamine releaser from mast cells [17]. For aprotinin reexposure, H₁/H₂ blockade, though not yet proved effective in a controlled study, is recommended.

Avoid Reexposure Within First 6 Months After First Exposure

A remarkable time-dependent risk of anaphylactic reactions exists. The incidence of reactions was higher in patients with a reexposure interval less than 200 days [13]. In this time period, aprotinin reexposure must be avoided. If reexposure appears unavoidable, one must proceed using all precautions. Most reports of adverse events describe a short time interval of 22 days to 2 months between the first and second aprotinin exposure.

With these precautions a reexposure to aprotinin in patients with a high risk of bleeding is justified, and the benefits of aprotinin treatment outweigh the relative risk of a serious allergic reaction.

References

1. Fritz H, Wunderer G. Biochemistry and applications of aprotinin, the kallikrein inhibitor from bovine organs. *Arzneimittelforschung* 1983;33:479-94.
2. Böhler H, Bach A, Fleischer F, et al. Adverse haemodynamic effect of high-dose aprotinin in a paediatric cardiac surgical patient. *Anaesthesia* 1995;45:853-4.
3. Ceriana P, Maurelli M, Locatelli A, et al. Anaphylactic reaction to aprotinin [Letter]. *J Cardiothorac Vasc Anesth* 1995;9:477-84.
4. Dawachter P, Mouton O, Masson O, et al. Anaphylactic reaction to aprotinin during cardiac surgery [Letter]. *Anaesthesia* 1993;48:1110-1.
5. Diefenbach C, Abel M, Limpers B, et al. Fatal anaphylactic shock after aprotinin reexposure in cardiac surgery. *Anesth Analg* 1995;80:830-1.
6. Freeman JG, Turner GA, Venables CW, et al. Serial use of aprotinin and incidence of allergic reactions. *Curr Med Res Opin* 1983;8:559-61.
7. Schulze K, Graeter T, Schaps D, et al. Severe anaphylactic shock due to repeated application of aprotinin in patients following intrathoracic aortic replacement. *Eur J Cardiothorac Surg* 1993;7:495-6.
8. Schuler TM, Frosch PJ, Arza D, et al. Allergie vom Soforttyp: anaphylaktische Reaktion auf Aprotinin. *München Med Wochenschr* 1987;129:816-7.
9. Yanagihara Y, Shida T. Immunological studies on patients who received aprotinin therapy. *Jpn J Allergol* 1985;34:899-904.
10. Wuthrich B, Schmid P, Schmid ER, et al. IgE-mediated anaphylactic reaction to aprotinin during anaesthesia [Letter]. *Lancet* 1992;340:173-4.
11. Cosgrove DM III, Heric B, Lytle BW, et al. Aprotinin therapy for reoperative myocardial revascularization: a placebo-controlled study. *Ann Thorac Surg* 1992;54:1031-8.
12. Levy JH, Pifarre R, Schaff HV, et al. A multicenter, double-blind, placebo-controlled trial of aprotinin for reducing blood loss and the requirement for donor-blood transfusion in patients undergoing repeat coronary artery bypass grafting. *Circulation* 1995;92:2236-44.
13. Dietrich W, Spath P, Ebell A, et al. Prevalence of anaphylactic reactions to aprotinin: analysis of two hundred forty-eight reexposures to aprotinin in heart operations. *J Thorac Cardiovasc Surg* 1997;113:194-201.
14. Weipert J, Meisner H, Jochum M, Dietrich W. Long-time follow-up of aprotinin-specific immunoglobulin G antibody