

Randomized Study of Aprotinin and DDAVP to Reduce Postoperative Bleeding After Cardiopulmonary Bypass Surgery

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Background Patients on cardiopulmonary bypass (CPB) have an increased susceptibility to postoperative bleeding. Previous reports using desmopressin acetate (DDAVP) for the prevention of postoperative bleeding have given contradictory results, whereas the protease inhibitor aprotinin has been shown to reduce blood loss after this type of surgery. This randomized study was performed to assess the efficacy of DDAVP versus aprotinin in the prevention of bleeding after CPB.

Methods and Results One hundred nine of 122 eligible patients were randomized to four different groups: Group A (n=28) received aprotinin starting with a bolus of 2×10^6 KIU followed by a continuous infusion of 0.5×10^6 KIU/h until the end of surgery; group B (n=25) received of DDAVP $0.3 \mu\text{g}/\text{kg}$ IV on completion of CPB; group C (n=28) received two doses of DDAVP, the first as in group B and an additional dose 6 hours after surgery; group D (n=28) received no treatment. There was a marked reduction of postoperative blood loss either at 12 hours ($P < .01$) or 72 hours ($P < .02$) in the aprotinin

group compared with all other groups, whereas no significant effect was observed in either of the two DDAVP regimens. A significant reduction in the amount of blood used was observed only in the aprotinin group ($P < .01$). Of the plasma fibrinolytic components assayed, there was a significant reduction of the fibrin degradation product generation in the aprotinin group ($P < .001$), whereas a significant systemic hyperfibrinolysis was observed in both DDAVP-treated groups and the control group. No side effects related to the study drugs were observed in any patient.

Conclusions Aprotinin inhibited fibrinolysis; this correlated with a significant reduction of postoperative blood loss and need for blood replacement after CPB. Neither one nor two doses of DDAVP had a beneficial effect. Aprotinin offers a better alternative than DDAVP in the prevention of bleeding after CPB. (*Circulation*. 1994;90:921-927.)

Key Words • cardiopulmonary bypass • desmopressin acetate • aprotinin • fibrinolysis

Despite the improvement in surgical techniques and extracorporeal circulation, excessive perioperative bleeding continues to complicate cardiopulmonary bypass (CPB) surgery. Patients undergoing CPB often require blood component therapy, reoperation for bleeding control is sometimes necessary, and occasionally life-threatening hemorrhage occurs during the postoperative period.^{1,2}

The majority of patients bleed primarily from the operative site, and the excessive bleeding is related to the surgical damage to blood vessels. In some patients, however, diffuse systemic bleeding suggests an acute acquired hemostatic defect. The basic pathophysiology of altered hemostasis associated with CPB remains confusing because of the complexity of the hemostatic process and the many uncontrolled variables associated with CPB, such as the surgical procedure, type of anesthesia, drug administration, transfused blood products, hypothermia, hemodilution, and the type of oxygenator. The abnormalities most frequently found include heparin and protamin excess, heparin rebound,

low platelet count, low fibrinogen and other coagulation factors, primary fibrinolysis, and disseminated intravascular coagulation.³⁻⁷ However, the major contributor to abnormal hemostasis seems to be the alteration of platelet function resulting from a reversible membrane abnormality.^{8,9}

Research during the past decade has been addressed at reducing postoperative blood loss and transfusion requirements in routine CPB operations. Among the different treatment schedules used, desmopressin acetate (DDAVP) and fibrinolysis inhibitors seem to be the most efficacious in diminishing blood loss after cardiac surgery.

DDAVP is a synthetic analogue of the neurohypophyseal nonapeptide arginine vasopressin. It is known that this hormone causes the appearance of larger von Willebrand factor (vWF) multimers in addition to increased concentrations of vWF and factor VIII; thus, a role for DDAVP has been indicated in patients with mild hemophilia or von Willebrand's disease.¹⁰ DDAVP has also been shown to shorten the bleeding time in other conditions, including uremia, chronic liver disease, and aspirin ingestion.¹¹⁻¹³ Finally, although DDAVP has been shown to be effective in reducing bleeding after orthopedic¹⁴ and cardiac surgery,¹⁵ the beneficial effect in CPB remains unclear.^{16,17}

Aprotinin is a serine protease inhibitor with inhibitory effects on human plasmin, trypsin, and kallikrein that has been shown to reduce postoperative blood loss

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and the need for blood transfusion in cardiac surgery through an inhibition of fibrinolysis mechanisms.^{18,19} As already mentioned, alterations in platelet surface membrane receptors have been described during extracorporeal circulation,^{9,20} and it appears that aprotinin also preserves platelet function.¹⁹

Previous studies have reported some adverse effects attributable to the use of both DDAVP and aprotinin, especially in patients undergoing revascularization procedures, since they may increase the risk of graft thrombosis.^{21,22}

We therefore undertook a randomized clinical study to compare the effectiveness of aprotinin versus DDAVP in reducing postoperative blood loss in patients undergoing cardiac surgery with extracorporeal circulation.

Methods

Study Population

To be eligible for recruitment, patients had to satisfy the following inclusion criteria: age >18 years and valvular or coronary disease. Patients were excluded for the following reasons: emergency surgery, known hemostatic defect, hepatic and renal insufficiency, previous exposure to the study drugs, and use of other techniques of blood saving. Patients receiving nonsteroidal anti-inflammatory drugs or aspirin before surgery were not excluded, because a large percentage of patients undergoing routine CPB at our institution are on these medications up to the time of surgery.

Heparin was administered at an initial dose of 300 U/kg to maintain the activated clotting time >400 seconds (Hemochrom Internationaltechnique). CPB was instituted with a two-stage right atrial and ascending aortic cannula. A roller pump maintained nonpulsatile flow between 2.0 and 2.4 L·min⁻¹·m⁻². Moderate systemic hypothermia (25°C) was maintained during aortic occlusion. After discontinuation of CPB, heparin was reversed with protamine sulfate (1.5:1) by slow intravenous infusion.

Study Design

The protocol was approved by our hospital's Clinical Assays Committee. After informed consent was obtained, a prospective randomized trial involving 122 patients was begun. Of the total number of patients admitted to the study, 13 (4 in the placebo group and 9 in the treatment groups) were excluded from subsequent analysis because they did not complete the study. The remaining 109 patients were assigned to one of the following groups.

Group A patients (n=28) received aprotinin (Trasylo) supplied by Bayer in bottles containing 70 mg aprotinin (500 000 kallikrein inactivator units, KIU) in 50 mL 0.9% saline solution without further additives or preservative substances. Patients in this group received a bolus infusion of 2×10⁶ KIU within 30 minutes after induction of anesthesia followed by a continuous infusion of 0.5×10⁶ KIU/h until the patient left the operating room and an additional bolus of 2×10⁶ KIU aprotinin in the pump prime by replacement of crystalloid solution.

Group B patients (n=25) received DDAVP, 0.3 µg/kg body wt (supplied by Ferring Pharmaceuticals) in a 50-mL saline solution over a period of 20 minutes, given intravenously on completion of CPB and immediately after administration of protamine.

Group C patients (n=28) received two doses of DDAVP, 0.3 µg/mL, the first as in group B and an additional dose 6 hours after surgery.

Group D patients (n=28) did not receive aprotinin or DDAVP and were considered a control group.

Blood Sampling

Blood samples were obtained before operation, at the end of bypass, and 90 minutes and 24 hours after surgery. Venous blood was drawn in Vacutainer tubes (Becton Dickinson) containing 0.129 mol/L sodium citrate in a 9:1 proportion. Platelet-poor plasma was prepared by centrifugation at 1500g for 20 minutes and snap-frozen in aliquots at -70°C until used. For measurements of hemoglobin and hematocrit, blood was mixed with EDTA.

Procedures

Hematocrit and hemoglobin were determined by routine analysis with a Coulter S Plus II. Plasminogen and α₂-antiplasmin were determined by amidolytic assays (Coatest Plasminogen and Coatest Antiplasmin, Kabi Diagnostica). Plasminogen activator inhibitor type 1 (PAI-1) activity was measured with chromogenic substrates as previously described.²³ Tissue-type plasminogen activator (TPA) antigen was measured with a commercially available ELISA assay (TintElize t-PA, Biopool). Fibrin degradation products (FbDP) were assayed by use of a specific monoclonal antibody as described by Nieuwenhuizen²⁴ (Fibrinostika FbDP, Organon Teknika). Data presented in the figures and used in the statistical calculations are values measured on plasma samples corrected for hemodilution, as assessed by the difference between each hematocrit with respect to its own baseline value.

The postoperative blood loss in the first 72 hours was determined by measuring the drainage losses. Red cell transfusions within the first 72 hours were also measured. Blood pressure and urine output in the first 24 hours were recorded.

Investigators and laboratory personnel were blinded to treatment or control groups.

Statistical Analysis

Results are expressed as mean±SD. Student's *t* test was used to compare mean values, and Student's *t* test for paired observations was used to compare the mean values of the same variable at different times. Statistical analysis for group comparisons was performed with a two-way ANOVA. Differences were considered to be significant when *P*<.05.

Results

One hundred twenty-two patients who consented to participate in this trial were randomized into four different groups, and 109 completed the study. The baseline characteristics, the main diagnoses, and types of surgery are listed in Table 1. There were no significant differences with regard to any of the characteristics analyzed among the four group of patients. Only one patient in the control group had a previous intrathoracic operation, compared with the greater number of patients in the treated groups. However, no significant differences could be demonstrated.

All patients had normal coagulation parameters, platelet counts, and hemoglobin levels before surgery.

Blood Loss and Transfusion Requirements

As shown in Table 2 and Fig 1, there was a marked reduction (*P*<.01) of postoperative blood loss during the first 12 hours in the group treated with aprotinin (137.9±70.6 mL/m²) compared with groups B (278.7±164.1 mL/m²), C (208.8±111.7 mL/m²), and D (214.5±120.8 mL/m²), with no differences between groups B and C and the control group. The total postoperative blood loss at 72 hours was also reduced (*P*<.02) in the aprotinin group (358.5±156.3 mL/m²) compared with groups B (551.8±324.1 mL/m²), C (498.5±235.6 mL/m²), and D (438.7±228.1 mL/m²).

TABLE 1. Characteristics of the Patients Studied

	Group A (n=28)	Group B (n=25)	Group C (n=28)	Group D (n=28)
Age, y	58.9±10.0	56.6±8.8	57.3±7.6	56.3±10.1
Sex, M/F	16/12	14/11	20/8	22/6
Body surface, m ²	1.7±0.2	1.7±0.1	1.8±0.2	1.8±0.1
Type of surgery				
Coronary	13	12	16	14
Valvular	14	12	11	14
Mixed	1	1	1	0
Reintervention	4	4	6	1
Duration of extracorporeal circulation, min	127.3±45.4	122.4±34.4	131.6±39.3	121.3±36.2

Values are mean±SD.

There was also a significant reduction in the amounts of bank blood used in the aprotinin group, either in the first 12 hours ($P<.02$) or at 72 hours after surgery ($P<.01$) (Table 2). The total blood transfused was 366.1 ± 331.9 mL/m² in group A, which was significantly less than in groups B (740.4 ± 416.3 mL/m²), C (662.8 ± 380.7 mL/m²), and D (678.1 ± 462.2 mL/m²), without differences in the two DDAVP-treated groups compared with the control group.

Hemoglobin Levels

The preoperative hemoglobin levels were similar in all groups. At 24 hours after surgery, the levels in all groups fell a similar amount (Fig 2).

Fibrinolytic System

Table 3 shows the preoperative, intraoperative, and postoperative evolution of the different fibrinolysis parameters analyzed in the control group. In patients who did not receive any treatment, we observed a significant decrease of plasminogen and α_2 -antiplasmin ($P<.001$) and a marked increase of TPA antigen, PAI-1, and FbDP ($P<.001$) intraoperatively compared with the baseline value. Whereas plasminogen and α_2 -antiplasmin showed a tendency to recover in the sample taken 90 minutes after operation with normalization on postoperative day 1, the TPA, PAI-1, and FbDP concentrations remained significantly elevated after surgery ($P<.01$).

There were no significant differences among the three treatment groups with regard to plasminogen and PAI-1 concentrations in relation to values observed in the control group (data not shown). TPA antigen (Fig 2) was slightly elevated in both DDAVP-treated groups

only in the sample taken 90 minutes after surgery, with differences in relation to the corresponding levels in groups A or D ($P<.05$). Whereas the intraoperative and postoperative levels of α_2 -antiplasmin did not change significantly in the aprotinin group with respect to the preoperative value, a reduction similar to that in the control group was observed in both DDAVP-treated groups. α_2 -Antiplasmin levels recovered in all groups in the sample taken 24 hours after surgery (Fig 2). A significant reduction of FbDP generation could be demonstrated in patients receiving aprotinin in the samples obtained at the end of bypass and immediately after surgery ($P<.001$), but no differences in this parameter were observed in both DDAVP-treated groups in relation to the control group (Fig 2).

No correlations between the different fibrinolysis parameters analyzed and either the blood loss or transfusion requirements could be demonstrated.

Side Effects

Neither DDAVP nor aprotinin provoked complications with regard to blood pressure or urinary output. No thrombosis, deaths, or severe complications occurred intraoperatively or during the first 10 postoperative days in any patients included in the study.

Discussion

The use of CPB for cardiac surgery is performed routinely in western countries and is generally regarded as safe, although these patients are at considerable risk of postoperative bleeding requiring blood transfusion and reoperation in approximately 3% of cases. It is well known that cardiac surgery with CPB results in large alterations in hemostasis and platelet function, so there

TABLE 2. Results of the Study

	Group A	Group B	Group C	Group D
Blood loss, mL/m ²				
0-12 h	137.9±70.6*	278.7±164.1	208.8±111.7	214.5±120.8
Total, 0-72 h	358.5±156.3†	551.8±324.1	498.5±235.6	438.7±228.1
Red cell transfusions, mL/m ²				
0-12 h	164.5±197.5†	366.9±233.6	238.1±258.6	340.9±324.3
Total, 0-72 h	366.1±331.9*	740.4±416.3	662.8±380.7	678.1±462.2

* $P<.01$ and † $P<.02$ aprotinin in relation to all other groups.

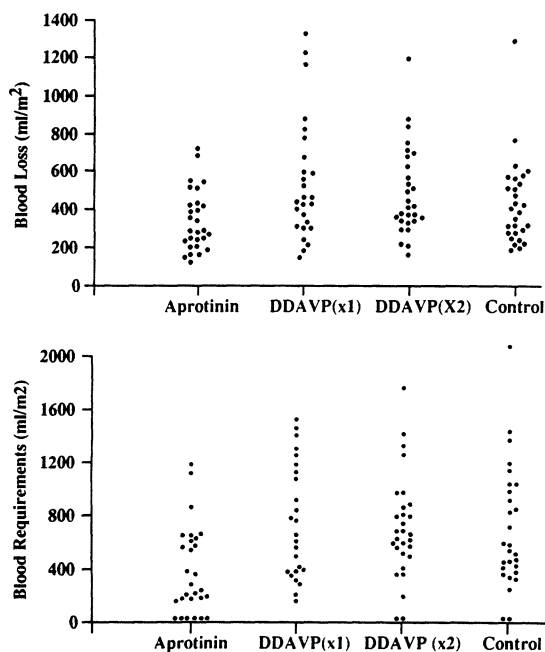


FIG 1. Scatterplots showing individual distribution of blood loss (top) and red cell transfusions (bottom) in the treated groups and in the control group. DDAVP indicates desmopressin acetate.

has been great interest in improving postoperative hemostasis by use of drugs that prevent alterations in those systems.²

This randomized study convincingly shows that aprotinin is a useful drug in reducing postoperative blood loss as well as the need for blood transfusion in patients undergoing CPB surgery, whereas neither one nor two doses of DDAVP were able to significantly reduce either blood loss or transfusion requirements.

The hemostatic properties of DDAVP in patients undergoing open-heart surgery with CPB were first studied by Czer et al²⁵ in a prospective nonrandomized clinical study. Patients treated with DDAVP required significantly less transfusion of blood products. Moreover, DDAVP infusion shortened the bleeding time and significantly increased factor VIII and vWF levels. Salzman et al¹⁵ performed a double-blind prospective trial in which patients were randomized to DDAVP or placebo. The DDAVP-treated patients showed a significant reduction in intraoperative and postoperative blood loss and lower red cell transfusion requirements. In these patients, higher vWF:Ag levels than those in the placebo group were observed 90 minutes after infusion. In the light of these results, it seemed that the beneficial effect of DDAVP in CPB was probably related to an elevation of vWF in plasma. In another study, however, the effectiveness of DDAVP in reducing blood loss could not be related to the increase of large vWF multimers.²⁶

In a randomized trial comparing DDAVP versus placebo, we could not confirm that DDAVP reduces the total blood loss and transfusion requirements, although it was observed to significantly reduce intraoperative blood loss.¹⁶ These results were later confirmed by Hackmann et al.²⁷ Furthermore, four additional studies did not find significant improvement in postoperative blood loss,²⁸⁻³¹ and one report shows that the total

postoperative blood loss and the red cell transfusion rates were significantly higher in the DDAVP group than in the control group, which could be related to the DDAVP-induced TPA release from endothelial cells and subsequent fibrinolysis.³²

Since, as suggested by our findings, the administration of DDAVP was effective only in reducing intraoperative bleeding, we decided to administer a second dose 6 hours after surgery to establish whether it could also improve the postoperative blood loss. The results of the present study clearly indicate that a second dose of DDAVP given after surgery does not reduce postoperative bleeding. It could be speculated that a tachyphylaxis phenomenon could hamper the possible benefit of DDAVP, but it is unlikely that later administration could be more effective.³³ There is evidence that the administration of DDAVP may be useful in reducing hemorrhage in patients at high risk, such as those undergoing valve replacement combined with coronary artery bypass graft surgery or in those with aspirin-related bleeding after bypass, or even in patients with severe platelet dysfunction and excessive mediastinal bleeding after termination of CPB.^{34,35} However, the majority of patients who undergo cardiac surgery without complications will have only moderate blood loss, and in these cases DDAVP does not appear to offer any advantages beyond those of conventional techniques to reduce the use of blood products. Thus, DDAVP could be administered to patients who are at particular risk of bleeding but not routinely to all patients undergoing CPB surgery.^{17,36}

Aprotinin has been used in patients having cardiac surgery since the 1960s on the basis of a reduction of the hyperfibrinolytic state observed during open-heart operations.^{37,38} These reports indicated that relatively low doses of aprotinin significantly reduced fibrinolytic activity but had no effect on postoperative bleeding. More recent data suggested that high-dose aprotinin might reduce bleeding after cardiac surgery not only by inhibiting fibrinolysis but also by preserving platelet function.^{18,19,39-42} These results have clearly been confirmed in the present study, in which a high-dose aprotinin regimen significantly diminished the blood loss and transfusion requirements compared with either the control group or the two DDAVP-treated groups.

Although it has been suggested that both DDAVP and antifibrinolytic drugs may cause premature saphenous vein graft occlusion, several prospective studies reported no increase in the frequency of occlusion.^{27,39,43} Two recent reviews evaluating the incidence of thrombotic events in controlled trials of DDAVP in cardiac surgery also indicate that DDAVP does not increase the incidence of thrombosis.^{44,45} In our study, there were no incidences of suspected acute graft thrombosis in either of the treated groups, although no patients in either group underwent angiography to demonstrate patent bypass grafts. Very recently, however, Cosgrove et al⁴⁶ reported a significant incidence of graft thrombi in postmortem examinations of patients receiving aprotinin who died during the study. The evidence of vein graft thrombosis raises the question of a hypercoagulable state that may adversely influence patient outcome. Other complications with the use of aprotinin include allergic reactions, renal toxicity, and heparin resistance.⁴⁷ We observed no significant allergic complica-

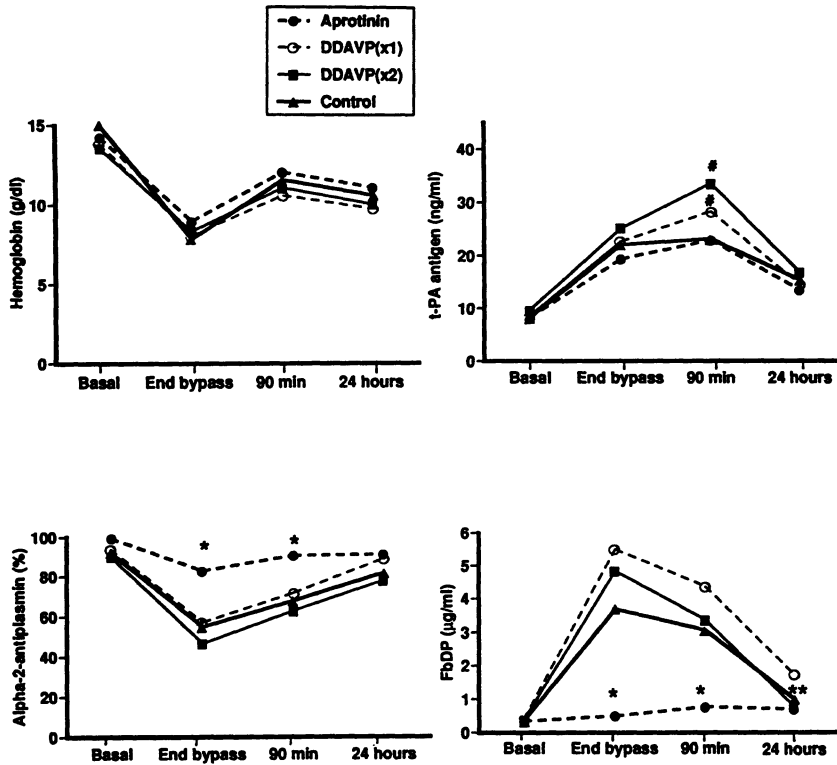


Fig 2. Graphs showing mean hemoglobin, tissue-type plasminogen activator (t-PA), α_2 -antiplasmin, and fibrin degradation product (FbDP) concentration in blood samples obtained before operation, at the end of bypass, and 90 minutes and 24 hours after surgery in aprotinin, one dose of desmopressin acetate (DDAVP), two doses of DDAVP, and control groups. * $P < .001$ aprotinin compared with all other groups; ** $P < .05$ aprotinin compared with one dose DDAVP; # $P < .05$ both DDAVP-treated groups compared with aprotinin and control groups.

tions or drug interactions in our study. In an attempt to document whether the beneficial effect of aprotinin in reducing bleeding would be related to an inhibition of fibrinolysis, we compared the changes observed in different fibrinolysis parameters measured preoperatively, intraoperatively, and postoperatively in the placebo group and in the treated groups. Hyperfibrinolysis during and after CPB is well documented in the literature⁴⁸⁻⁵⁰ and was also found in the present study, as demonstrated by a significant decrease of plasminogen and α_2 -antiplasmin and an increase of TPA and FbDP observed in the control group. Whether this hyperfibrinolytic state is a primary event or secondary to the activation of the coagulation system is not completely understood,⁵¹ but the clinical significance of hyperfibrinolysis for the amount of postoperative blood loss is well shown by laboratory data and the results of therapeutic intervention studies.

Neither of the two DDAVP regimens significantly improved the intraoperative and postoperative fibrinolysis alterations observed in the control group, but they induced a slight increase of TPA concentrations. It has

been shown that DDAVP induces a rapid release of TPA from its endothelial cell storage sites with a subsequent fall in PAI-1 activity, which was thought to be due to the formation of TPA/inhibitor complexes.⁵² The lack of differences in the DDAVP-treated patients compared with the control group might be due to the transient effect of the drug reaching a peak 20 minutes after intravenous delivery and thus not detected in the sample obtained at the end of bypass. Aprotinin inhibited excessive fibrinolysis by preventing the plasminogen and α_2 -antiplasmin consumption and FbDP generation. Whereas the observed changes in α_2 -antiplasmin might be an artifact in relation to the chromogenic assay, it seems clear that aprotinin treatment resulted in a reduction of intraoperative and postoperative hyperfibrinolysis as assessed by the decrease of FbDP levels.

Other studies have used a similar schedule to maintain a constant intraoperative plasma aprotinin concentration of approximately 4 $\mu\text{mol/L}$. This concentration has been reported to inhibit plasmin in vitro, to prevent platelet activation and aggregation, and to block the loss of platelet membrane glycoprotein Ib during CPB.^{41,42,53,54} It has

TABLE 3. Values of Fibrinolysis Parameters Studied in the Control Group

	Preoperative	End of Bypass	90 min	24 h
Plasminogen, %	91.7±15.5	78.2±20.4*	82.5±23.5†	92.6±27.8
α_2 -antiplasmin, %	92.2±12.4	55.1±21.4*	67.5±20.7*	81.3±19.3†
TPA antigen, ng/mL	7.9±5.5	22.1±10.9*	23.0±6.7*	15.4±9.1†
PAI-1, U/mL	9.6±8.4	24.3±21.7†	34.4±16.9*	26.8±17.3†
FbDP, $\mu\text{g/mL}$	0.3±0.2	3.7±2.5*	3.1±1.9*	0.9±0.7†

TPA indicates tissue-type plasminogen activator; PAI-1, plasminogen activator inhibitor; and FbDP, fibrin degradation products. Values are mean±SD. * $P < .001$ and † $P < .01$ with respect to the preoperative value.

been hypothesized that aprotinin reduces blood loss after CPB by stabilizing the platelet membrane by means of its antifibrinolytic effects. However, it is not clear whether these effects of aprotinin on normalizing hemostatic function might be exclusively related to inhibition of plasmin or inhibition of other coagulation cascade serine proteases.⁵⁵

Other lysine-analogue antifibrinolytic preparations such as ϵ -aminocaproic acid and tranexamic acid also appear safe in decreasing blood loss and transfusion requirements after cardiac surgery.^{56,57} Interestingly, Horrow et al⁵⁸ investigated the separate and combined hemostatic effects of tranexamic acid and DDAVP during cardiac surgery. DDAVP exerted no hemostatic effect with or without prior administration of antifibrinolytic drug.

In summary, aprotinin inhibited fibrinolysis, and that correlated with a significant reduction of postoperative blood loss and need for blood replacement after CPB. Although DDAVP may be effective in reducing hemorrhage in patients at high risk, our results clearly indicate that in the majority of patients, the protease inhibitor aprotinin offers a better alternative than DDAVP in the prevention of bleeding after cardiopulmonary bypass surgery.

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