The Turkish Journal of Pediatrics 33: 99-110, 1991

THE EFFECT OF APROTININ (TRASYLOL) ON POSTOPERATIVE BLEEDING IN CYANOTIC CONGENITAL HEART DISEASE*

*Eyüp Hazan MD**, İlhan Paşaoğlu MD ***, Metin Demircin MD***
*A. Yüksel Bozer MD*****

SUMMARY: Hazan E, Paşaoğlu İ, Demircin M, Bozer AY. (Department of Thoracic and Cardiovascular Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). The effect of aprotinin (trasylol) on postoperative bleeding in cyanotic congenital heart disease. Turk J Pediatr 33: 99-110, 1991.

Despite the widespread clinical success in open-heart surgery, bleeding after cardiopulmonary by-pass (CPB) has been a common problem especially in cyanotic congenital heart disease. Recently, there have been reports demonstrating that treatment with high doses of aprotinin reduces postoperative bleeding.

We studied the effect of aprotinin on postoperative bleeding in patients with tetralogy of Fallot who had undergone total correction in the Department of Thoracic and Cardiovascular Surgery of the Hacettepe University Faculty of Medicine, and compared our results with those in the literature.

Ten patients out of 20 in the study were given high doses of aprotinin and were compared with the remaining 10 patients who had not received the drug. Standard anesthesia, perfusion and surgical techniques were used in all operations. The total amount of bleeding in the aprotinin-treated group was found to be 1530 ml, while in the other group it was 4185 ml ($p < 0.05$). The total quantity of blood transfused in the aprotinin-treated patients was 3250 ml while it was 5865 ml in the control group ($p < 0.05$). No significant effect of aprotinin was found on Hb, Hct, PT, aPTT and thrombocyte counts ($p > 0.05$). However, the effect of the drug on bleeding and coagulation time was found to be statistically significant ($p < 0.05$). *Key words: aprotinin, postoperative bleeding, cyanotic congenital heart disease.*

Cardiopulmonary by-pass (CPB) affects all body systems including the hematopoetic system.

It is known that some coagulation defects in congenital cyanotic heart disease may cause massive, lethal bleeding during and after surgery[1-5]. Coagulation defects, especially thrombocytopenia and hypofibrinogenemia are often seen in patients with elevated hematocrit levels[5-8].

* From the Department of Thoracic and Cardiovascular Surgery, Hacettepe University Faculty of Medicine, Ankara.

** Chief Resident in Thoracic and Cardiovascular Surgery, Hacettepe University Faculty of Medicine.

*** Associate Professor of Thoracic and Cardiovascular Surgery, Hacettepe University Faculty of Medicine.

**** Professor of Thoracic and Cardiovascular Surgery, Hacettepe University Faculty of Medicine.

CPB causes a significant reduction in coagulation factors, thrombocytes and blood cells[9,10]. Therefore, CPB leads to massive bleeding requiring transfusion in the cyanotic patient, already at high risk of bleeding. Excessive transfusions may lead to complications and infectious diseases which are transmitted by the blood.

Recently, there have been reports demonstrating that aprotinin, a protease inhibitor, when used in high doses, reduces postoperative bleeding by the inhibition of kallikrein and plasmin[11-14]. In these studies, aprotinin was administered routinely during open-heart surgery, reoperations and to patients with infective endocarditis who were at high risk of bleeding. Our study was designed to determine how aprotinin affects bleeding in cyanotic congenital heart disease and to compare the results with other studies.

Material and Methods

This study was performed on 20 cyanotic patients diagnosed as having tetralogy of Fallot, who were operated on between May-August 1989, at the Department of Thoracic and Cardiovascular Surgery of the Hacettepe University Faculty of Medicine. Total correction was performed in all patients. Ten patients were given aprotinin and were compared with the control group which included the remaining 10 patients who had not been given the drug. Table I shows the mean ages, sexual distribution and mean weights of the patients.

TABLE I: Mean Age, Mean Weight and Male / Female Ratio of Aprotinin - Treated Patients and Control Group

	Mean Age (yrs)	Male / Female	Mean Weight (kg)
Aprotinin	7.5	4 / 6	20
Control	7.1	4 / 6	18

Standard anesthesia, perfusion and surgical techniques were applied in all patients. Aprotinin was administered to the study group using a single protocol.

Thirty thousand U/kg aprotinin was infused in 20-30 min at the start of anesthesia. After this initial dose, it was infused at 100,000 U/hr until the end of anesthesia. Five hundred thousand units of aprotinin was added for every liter of blood that was perfused through the patient, and 1,000,000 units of aprotinin was added to the priming volume of the oxygenator.

Patients with coagulation disorders and a history of allergy were not included in the study.

Prior to aortic cannulation, 3 mg/kg heparin was administered to the patients. Activated clotting time (ACT) was then maintained at > 400 sec. Heparin was neutralized with protamine sulphate after perfusion was completed.

Cold K^+ cardioplegia, topical cooling and systemic hypothermia at 28 °C was performed in all patients.

The following studies were carried out on the blood samples obtained from the patients.

1– Hb and Hct values (preoperative; 24 hours postoperative, one week postoperative.
2– The thrombocyte count (just after induction; 10 minutes after sternotomy, at the end of CPB; 10 minutes after the initiation of protamine at the end of surgery, 24 hours postoperative.
3– Bleeding time (Preoperative, 90 minutes postoperative).
4– Coagulation time (Preoperative, 90 minutes postoperative).
5– Prothrombin time (Preoperative, 90 minutes postoperative).
6– Activated partial thromboplastin time (preoperative, 90 minutes postoperative).
7– Amount of postoperative bleeding.
8– Quantity of blood transfused postoperatively.

Results

The patients had no problems following surgery. None of the patients had to undergo reoperation due to postoperative massive bleeding. Coagulation parameters, thrombocyte counts, bleeding and coagulation times of all patients were found to be normal preoperatively. Laboratory findings of the study group and the control group are shown in Tables II and III.

1– Hb and Hct values:

Preoperative Hb and Hct vaules of the study and control groups were almost similar. Twenty-four hours after the operation, the Hb values were found to be decreased similarly in both groups. Hb values continued to decline at a slower rate up to the seventh postoperative day. There was no significant difference between the study and control groups (Fig. 1).

2– Thrombocyte count:

In both groups, the thrombocyte counts began to fall during sternotomy and became more significant during CPB. Although this decline seemed to be

TABLE II: Laboratory Findings of Patients in the Aprotinin-Treated Group

No	Hb (g/dl)	Hct (%)	Bleeding time (min)	Coagulation time (min)	PT (sec)	aPTT (sec)	Blood loss (ml)	Blood transfusion (ml)
	pre-operative / 7 days post-operative		pre-operative / 90 minutes post-operative					
1	14.0 / 14.1	40 / 40	4 / 5	5.5 / 6	15 / 16	38 / 40	150	100
2	16.7 / 14.6	56 / 44	4 / 4.5	6 / 7	15 / 16	38 / 42	50	50
3	15.9 / 15.8	50 / 50	4.5 / 5	6 / 7	15 / 16	37 / 38	280	200
4	18.4 / 19.5	55 / 58	3 / 4	4.5 / 5	14 / 15	35 / 38	50	100
5	14.3 / 13.4	48 / 40	4 / 6	5 / 8	14 / 15	38 / 42	200	300
6	17.5 / 16.3	53 / 48	3.5 / 4.5	5 / 6	14 / 15	42 / 48	180	600
7	14.7 / 13.8	44 / 40	3 / 3.5	5.5 / 6	14 / 15	43 / 46	100	750
8	17.8 / 14.5	54 / 46	3 / 4	4.5 / 6	13 / 14	42 / 42	200	450
9	14.6 / 16.0	42 / 48	3.5 / 7	3 / 4.5	18 / 22	68 / 63	100	250
10	21.0 / 18.0	67 / 54	4 / 5.5	5.5 / 7	13 / 13	42 / 42	220	450

TABLE III: Laboratory Findings of Patients in the Control-Group

No	Hb (g/dl)	Hct (%)	Bleeding time (min)	Coagulation time (min)	PT (sec)	aPTT (sec)	Blood loss (ml)	Blood transfusion (ml)
	pre-operative / 7 days post-operative		pre-operative / 90 minutes post-operative					
1	15.2 / 14.1	51 / 44	4 / 6.5	5 / 9	14 / 16	42 / 48	575	140
2	16.3 / 17.3	54 / 50	4 / 6	5.5 / 8	13 / 14	46 / 48	180	230
3	21.8 / 18.8	62 / 52	4 / 7	5 / 7.5	13 / 15	46 / 48	190	800
4	14.7 / 11.4	47 / 35	3.5 / 6.5	5.5 / 8	13 / 17	46 / 52	350	745
5	15.1 / 14.8	46 / 40	4 / 6.5	5 / 8	13 / 16	40 / 48	350	1150
6	22.2 / 17.3	68 / 52	4 / 7	5.5 / 7.5	14 / 16	42 / 43	470	500
7	14.2 / 14.0	46 / 40	4 / 6.5	5.5 / 8.5	14 / 16	37 / 42	400	600
8	13.8 / 16.5	43.8 / 49	2.5 / 4.5	4 / 8.5	15 / 17	42 / 48	290	500
9	21.2 / 20.5	65 / 61	5 / 7.5	4 / 6.5	13 / 14	46 / 48	630	500
10	16.0 / 13.0	48 / 38	4.5 / 7	5 / 7.5	14 / 15	46 / 48	350	700

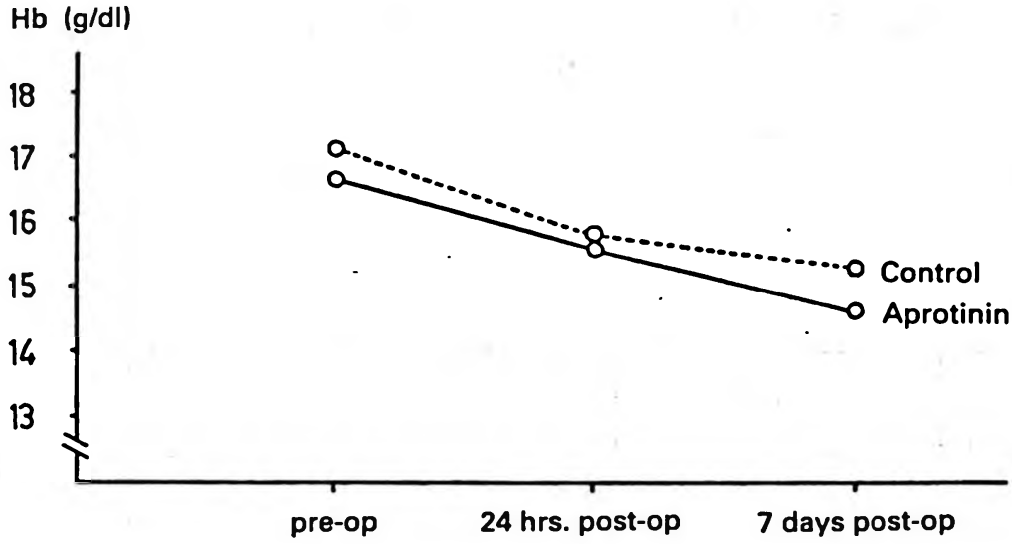

Fig. 1: Hemoglobin variations of aprotinin-treated patients and control group

evidenced more in the control group, there was no significant difference found between the two groups ($p > 0.05$) (Fig. 2).

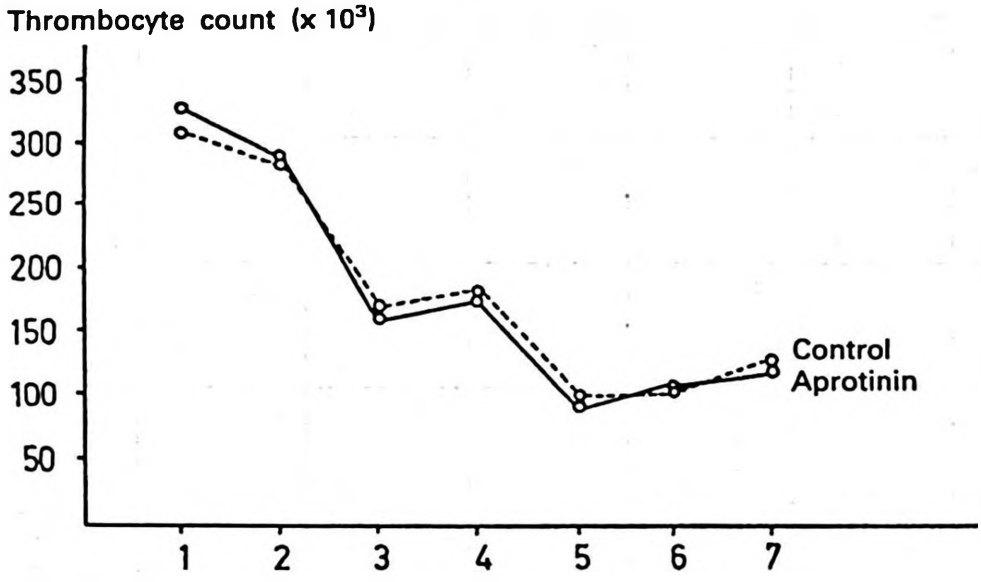

Fig. 2: Thrombocyte counts of aprotinin-treated patients and control group.

1. Induction.
2. Ten minutes after sternotomy.
3. Tenth minute of CPB.
4. End of CPB.
5. Ten minutes after protamine.
6. End of operation.
7. Postoperative 24th hour.

3– Bleeding and coagulation times:

Preoperative bleeding and coagulation times of the patients were normal. Postoperative values were significantly different in the study and control groups. Bleeding and coagulation times in the control group were prolonged significantly, however, this prolongation was very little in the aprotinin treated group. The difference between the two groups was statistically significant ($p < 0.05$) (Fig. 3).

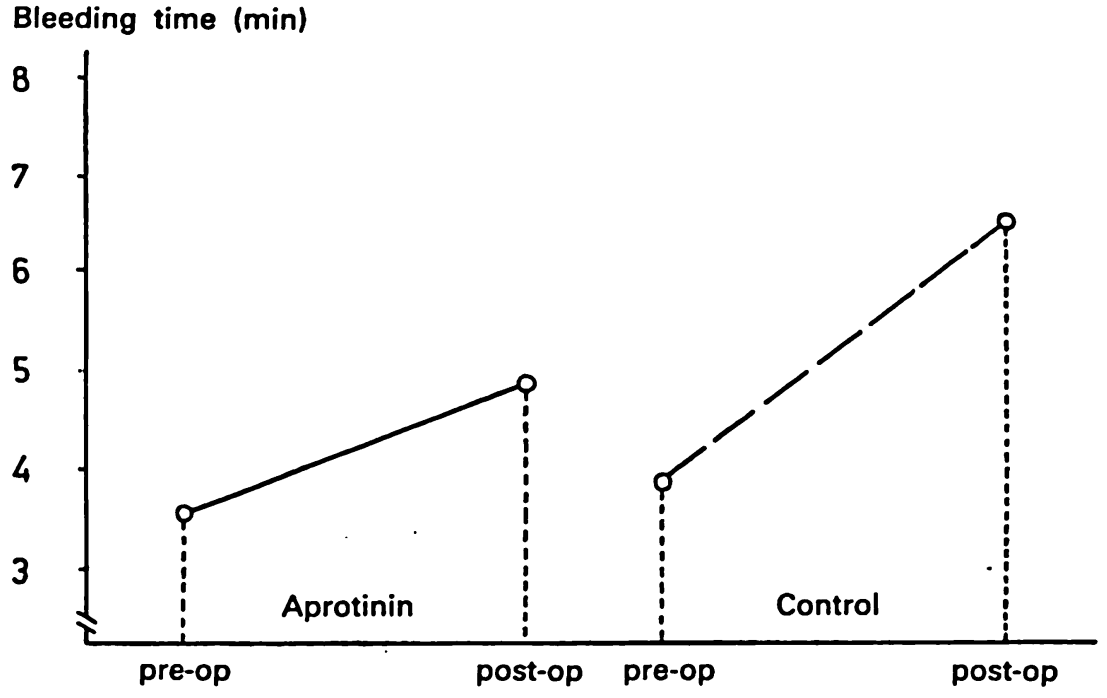

Fig. 3: Bleeding time (min) preoperatively and 90 minutes postoperatively

4– PT and aPTT values:

Preoperative PT and aPTT values of the two groups were not different. Ninety minutes after surgery, the prolongation of these values in the control group was greater than that in the study group, but it was not statistically significant ($p > 0.05$) (Table IV).

TABLE IV: Prothrombin Times (sec) Preoperatively and 90 Minutes Postoperatively

	Pre – op	Post – op
Aprotinin	14.5	15.7
Control	13.6	15.6

5– The amount of postoperative bleeding and quantity of blood transfused:

The amount of postoperative bleeding in the study and control groups seemed to be different. The bleeding from the sternal edge and medulla was significantly very little during the operation of the aprotinin-treated patients. The quantity of blood transfused in the two groups was also different, and was found to be statistically significant ($p < 0.05$) (Fig. 4).

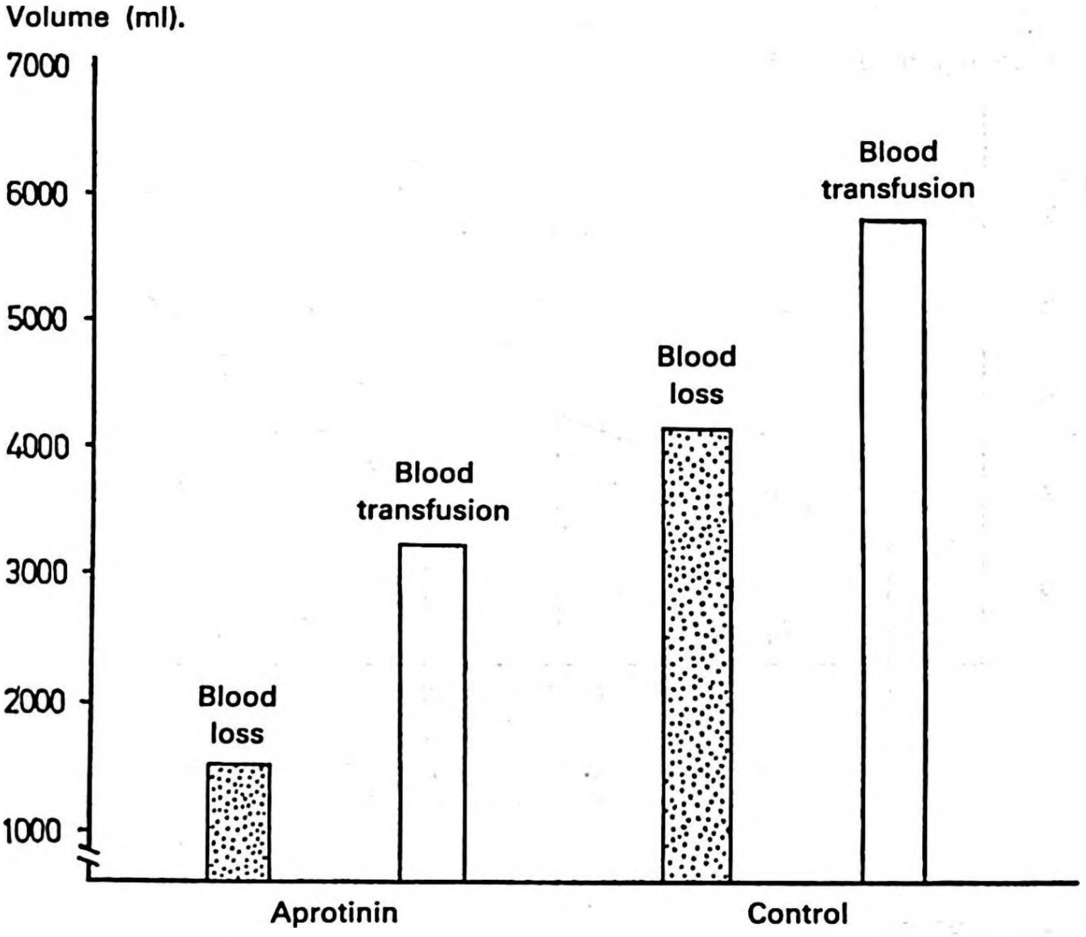

Fig. 4: Postoperative blood loss and need for blood transfusion were significantly decreased in the aprotinin-treated patients

Total body weights, total amount of bleeding, and total quantity of blood transfused were determined, and a blood loss of 7.5 ml/kg and 23 ml/kg was found in the study and control groups, respectively. The volume of blood transfused was 15.8 ml/kg in the study group and 32.5 ml/kg in the control group.

Discussion

Postoperative bleeding and the maintenance of hemostasis is occasionally a troublesome problem in open-heart surgery, especially in patients with cyanotic congenital heart disease, since some coagulation defects are present preoperatively[1-6, 15]

For several years aprotinin has been used to reduce bleeding. In 1963, Tice and associates[16]treated their patients with aprotinin for bleeding due to hyperfibrinolysis. Subsequently, aprotinin continued to be used for treatment purposes and not as a prophylactic[17-19]. Later, when hyperfibrinolysis was observed in the CPB apparatus, it was realized that aprotinin was not effective when given after by-pass[20]. In 1978, Philipp[21] suggested that if the levels of aprotinin are adequate, inhibition of plasmin and kallikrein can be achieved.

The hemostatic defect associated with CPB is very complex[22-24]. It is known that a transient and occasionally severe defect in platelet function occurs[25-28].

Recent studies have evaluated the effects of other drugs on blood loss after CPB. The administration of desmopressin acetate[29] and dipyridamole[30] resulted in significant reductions in blood loss, but neither drug can eliminate the need for blood transfusion. Prostacyclin was also investigated for this purpose, but its routine use was not suggested[31]. Aminocaproic acid, a synthetic antifibrinolytic drug, reduced blood loss slightly, but a difference in the quantity of blood required for transfusion was not reported[32].

Many studies have reported the efficacy of aprotinin either in routine open-heart surgery or in patients who were at high risk of bleeding because of reoperation or infective endocarditis[11-14].

In this study, aprotinin was used to treat patients with cyanotic heart disease, and its effect was demonstrated in regard to the amount of bleeding and the quantity of blood transfused either during the total correction operation or during the postoperative follow-up period.

With the increase in information regarding the risks inherent in blood transfusions, studies for reducing the amount of bleeding have progressed and auto-transfusion systems have appeared[11].

While at present, the transmission of the human immunodeficiency virus (HIV) is estimated to be of low probability, the same cannot be said of hepatitis B and hepatitis non-A non-B[33, 34].

Mismatched blood transfusions cause acute renal insufficiency or pyrogenic reactions due to an incompatibility of ABO or a subgroup. Moreover, the citrate, which is used as an anticoagulant in bank blood, binds the calcium ions of plasma and causes hypocalcemic tetany and coagulation defects since the ionized calcium is necessary for normal coagulation[35].

This study demonstrated that treatment with high doses of aprotinin reduced postoperative blood loss in cyanotic congenital heart disease, thus decreasing the need for bank blood and transfusion. On a search of the literature, we were unable to find another study illustrating the effect of aprotinin on postoperative bleeding in cyanotic congenital heart disease.

REFERENCES

1. Eernisse JG, Brand A, Repelaer van Driel OJ, et al. Prevention of bleeding tendency after open-heart surgery for Tetralogy of Fallot. *Scand J Thorac Cardiovasc Surg* 11:105, 1977.
2. Ekert H, Gilchrist GS, Stanton R, et al. Hemostasis in cyanotic congenital heart disease. *J Pediatr* 76:221, 1970.
3. Kontras SB, Sirak HD, Newton WA Jr. Hematologic abnormalities in children with congenital heart disease. *JAMA* 195:611, 1966.
4. Naiman JL. Clotting and bleeding in cyanotic congenital heart disease. *J Pediatr* 76:333, 1970.
5. Wedemeyer AL, Edson JR, Krivit W. Coagulation in cyanotic congenital heart disease. *Am J Dis Child* 124:656, 1972.
6. Goldschmidt B. Platelet functions in children with congenital heart disease. *Acta Paediatr Scand* 63:271, 1974.
7. Komp DM, Sparrow AW. Polycythemia in cyanotic heart disease-a study of altered coagulation. *J Pediatr* 76:231, 1970.
8. Gross S, Keefer V, Liebman J. The platelets in cyanotic congenital heart disease. *Pediatrics* 42:651, 1968.
9. Bozer AY. *Ekstrakorporeal Dolaşım ve Hipotermi.* Ankara: Hacettepe University Press, 1973, pp 61-69.
10. Faust RJ, Cucchiara RF, Messick JM Jr. Hemostasis and coagulation. In Tarhan S (ed). *Cardiovascular Anesthesia and Postoperative Care.* Chicago: Year Bk Med, 1982, pp 403-413.
11. Bidstrup BP, Royston D, Sapsford RN, Taylor KM. Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin (Trasylol). *J Thorac Cardiovasc Surg* 97:364, 1989.
12. Van Oeveren W, Eijsman L, Roozendaal KJ, Wildevuur CR. Platelet preservation by aprotinin during cardiopulmonary bypass [letter]. *Lancet* 1:644, 1988.
13. Van Oeveren W, Jansen NJ, Bidstrup BP, et al. Effects of aprotinin on hemostatic mechanisms during cardiopulmonary bypass. *Ann Thorac Surg* 44:640, 1987.
14. Royston D, Bidstrup BP, Taylor KM, Sapsford RN. Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. *Lancet* 2:1289, 1987.
15. Brodsky I. Coagulation abnormalities in cyanotic heart disease. *J Pediatr* 77:918, 1970.
16. Tice DA, Reed GE, Clauss RH, et al. Hemorrhage due to fibrinolysis occurring with open-heart operations. *J Thorac Cardiovasc Surg* 46:673, 1963.
17. Gans H, Castaneda AR, Subramanian V, et al. Problem in hemostasis during open heart surgery. IX. Changes observed in the plasminogen-plasmin system and their significance for therapy. *Ann Surg* 166:980, 1967.
18. Tice DA, Worth MH Jr. Cellular damage associated with extracorporeal perfusion: plasminogen activation and lysosomal enzyme activity. *Surgery* 63:669, 1968.
19. Tice DA, Worth MH Jr, Clauss RH, Reed GH. The inhibition of trasylol of fibrinolytic activity associated with cardiovascular operations. *Surg Gynecol Obstet* 119:71, 1964.
20. Köstering H, Kirchhoff PG, Völker P. et al. Untersuchungen der Blutgerinnungs-veränderungen während und nach Operationen mit Hilfe der Herz-Lungen-Maschine. *Thoraxchirurgie* 21:534, 1973.
21. Phillipp E. Calculation and hypothetical considerations on the inhibition of plasmin and plasma kallikrein by Trasylol. In Davidson JF. Rowan RM, Samama MM (eds). *Progress in Chemical Fibrinolysis and Thrombolysis* Vol 3. New York: Raven, 1978, pp 291-295.

22. Bachmann F, McKenna R, Cole ER, Najafi H. The hemostatic mechanism after open-heart surgery. I. Studies on plasma coagulation factors and fibrinolysis in 512 patients after extracorporeal circulation. *J Thorac Cardiovasc Surg* 70:76, 1975.

23. Bick RL. Hemostasis defects associated with cardiac surgery, prosthetic devices, and other extracorporeal circuits. *Semin Thromb Hemost* 11:249, 1985.

24. Mammen EF, Koets MH, Washington BC, et al. Hemostasis changes during cardiopulmonary bypass surgery. *Semin Thromb Hemost* 11:281, 1985.

25. Harker LA. Bleeding after cardiopulmonary bypass. *N Engl J Med* 314:1446, 1986.

26. Harker LA, Malpass TW, Branson HE, et al. Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: acquired transient platelet dysfunction associated with selective α-granule release. *Blood* 56:824, 1980.

27. Martin JF, Daniel TD, Trowbridge EA. Acute and chronic changes in platelet volume and count after cardiopulmonary bypass induced thrombocytopenia in man. *Thromb Haemost* 57:55, 1987.

28. Mohr R, Golan M, Martinowitz U, et al. Effect of cardiac operation on platelets. *J Thorac Cardiovasc Surg* 92:434, 1986.

29. Salzmann EW, Weinstein MJ, Weintraub RM, et al. Treatment with desmopressin acetate to reduce blood loss after cardiac surgery: a double-blind randomized trial. *N Engl J Med* 314:1402, 1986.

30. Teoh KH, Christakis GT, Weisel RD, et al. Blood conservation with membrane oxygenators and dipyridamole. *Ann Thorac Surg* 44:40, 1987.

31. Fish KJ, Sarnquist FH, van Steennis C, et al. A prospective randomized study of the effects of prostacyclin on platelets and blood loss during coronary bypass operations. *J Thorac Cardiovasc Surg* 91:436, 1986.

32. Vander Salm TJ, Ansell JE, Okike ON, et al. The role of epsilonaminocaproic acid in reducing bleeding after cardiac operation: a double-blind randomized study. *J Thorac Cardiovasc Surg* 95:538, 1988.

33. Ward JW, Holmberg SD, Allen JR, et al. Transmission of human immunodeficiency virus (HIV) by blood transfusions screened as negative for HIV antibody. *N Engl J Med* 318:473, 1988.

34. Zuck TF. Transfusion-transmitted AIDS reassessed. *N Engl J Med* 318:511, 1988.

35. Guyton AC. *Textbook of Medical Physiology* (6th ed). Philadelphia: WB Saunders Co, 1981, pp 99-111.