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Blood Conservation Techniques and Platelet Function in Cardiac Surgery

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Postoperative alterations in platelet function induced by cardiopulmonary bypass (CPB) are of importance. The effect on platelet aggregation of three different techniques for reducing blood consumption was studied in 30 patients undergoing elective aortocoronary bypass grafting from the beginning of anesthesia until the 1st postoperative day. The patients were randomly divided into three groups, in which 1) a cell separator was used during and after CPB; 2) a hemofiltration device was used; and 3) high-dose aprotinin was used in order to reduce the need of homologous blood. A fourth group undergoing neurosurgery procedures served as a control. Platelet aggregation induced by adenosine diphosphate (concentration 0.25, 0.50, 1.0, and 2.0 μM), collagen (4 μl/ml), and epinephrine (25 μM) was determined by the turbidimetric method. Platelet aggregation was not significantly changed in the control group, indicating that the operation itself did not impair platelet function. At the end of the operation (after retransfusion of the salvaged pump blood), the maximum aggregation and maximum gradient of aggregation induced by all three inductors were most reduced (significantly) in the cell-separator patients. On the 1st postoperative day, platelet aggregation in the hemofiltration patients and the patients treated with aprotinin had normalized. Aggregation of patients pretreated with high-dose aprotinin was not different from that of the hemofiltration patients throughout the investigation. Blood loss was significantly highest in the cell-separator group (770 ± 400 ml on the 1st postoperative day) but was not different between the hemofiltration (390 ± 230 ml) and the aprotinin-treated patients (260 ± 160 ml). It can be concluded that the use of the cell separator resulted in the most pronounced deterioration in platelet aggregation. Compared to the use of a hemofiltration device, high-dose aprotinin had no positive effects either on platelet aggregation variables or on blood loss and cannot be recommended in elective, uncomplicated aortocoronary bypass operations. (Key words: Aprotinin. Blood: loss; platelet aggregation; platelet function. Equipment: cell separator. Hemofiltration. Surgery: cardiac. Transfusion: cell saver.)

WITH THE RISK OF TRANSMISSION of viral diseases by transfusion of homologous blood or blood products, any method that lessens the need for blood transfusion is welcome,§ particularly in cardiac surgery, for which large amounts of blood or blood products traditionally are required.[1–5,¶]

Blood conservation techniques have been demonstrated to significantly reduce the need for blood and blood products in cardiac surgery. The methods most frequently used are preoperative autologous blood donation, intraoperative withdrawal of blood, nonsanguineous priming of the heart–lung machine, salvage of blood remaining in the circuit after cardiopulmonary bypass (CPB), autotransfusion of shed mediastinal blood after CPB, and pharmacologic measures, *i.e.*, the use of high-dose aprotinin.[6–9,**,††]

Hemostatic defects associated with CPB are very complex, and the reasons for prolonged and excessive postbypass bleeding are multifactorial.[10] However, deterioration in platelet function certainly seems to be an important factor in impaired coagulation in this situation.[11–13]

This study was designed to investigate the influence on platelet function of three different techniques for reducing homologous blood use in cardiac surgery.

Materials and Methods

PATIENTS AND GROUPING

Thirty male patients undergoing elective aortocoronary bypass grafting were studied. All patients gave informed consent according to the protocol of the Human Ethics Committee of the hospital. Exclusion criteria were previous cardiac surgery, preoperatively impaired myocardial function (left ventricular ejection fraction < 50%; left ventricular end-diastolic pressure > 20 mmHg), preoperative coagulation disorders, and medication with heparin, aspirin, or other cyclooxygenase inhibitors.

Before surgery, patients were prospectively randomized into three groups. In group 1 (n = 10), a cell separator (Cell Saver IV, Hemonetics, Munich, FRG) was to be used

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§ Youngberg JA: Aprotinin and thrombus formation on pulmonary artery catheters: A piece of the coagulation puzzle. J Cardiothorac Anesth 4:155–158, 1990.

¶ Gravlee GP: Blood transfusion and component therapy. In: 1989 Annual Refresher Course Lectures, American Society of Anesthesiologists, pp 164/1-164/7, 1989.

** Bidstrup BP: Blood conservation in cardiac surgery: Can drugs help? Perfusion 3:171–177, 1988.

†† Robblee JA: Blood should be harvested immediately before cardio-pulmonary bypass and infused after protamine reversal to decrease blood loss following cardiopulmonary bypass. J Cardiothorac Anesth 4:519–521, 1990.

during and after CPB (CS patients). In group 2 (n = 10), blood concentration during and after CPB was to be performed by means of a hemofiltration device (HF-80, Fresenius, Bad Homburg, FRG) as previously described[11] (HF patients). In group 3 (n = 10), blood concentration during and after CPB was to be performed with a hemofiltration device, and, in addition, to reduce blood loss, high-dose aprotinin (Trasylol®; Bayer, FRG) was to be given (AP patients) as an infusion of two million units before the operation (loading dose) and then as a continuous infusion of 500,000 units/h until the end of the operation. In addition, two million units of aprotinin were to be added to the priming of the heart–lung machine. Ten additional male patients undergoing neurosurgery operations served as a control (group 4).

Anesthesia and Cardiopulmonary Bypass

Induction and maintenance of anesthesia were comparable for all patients and consisted of weight-related doses of fentanyl (total dose 0.035 mg/kg), midazolam (total dose 0.6 mg/kg), and pancuronium bromide (total dose 0.25 mg/kg). During the operation, the lungs of all patients were mechanically ventilated with a fractional inspired oxygen concentration of 1.0 and zero end-expiratory pressure. Controlled ventilation was maintained during the first 5 h after the end of the operation. CPB was carried out using membrane oxygenators (Sorin 10, Sorin, Torino, Italy) and a nonpulsatile flow of 2.4 $l \cdot min^{-1} \cdot m^{-2}$ throughout the period of bypass.

The circuit was primed with 1,000 ml dextrose solution (5%), 1,000 ml Ringer's solution, 250 ml albumin 5%, and electrolytes (20 mEq potassium and 50 ml sodium 10%). Two million units of aprotinin were added to the priming solution of patients in group 3. The lowest rectal temperature during bypass was 34.1 ± 0.5° C. A two-stage cannula was used for drainage of venous blood (by monoatrial cannulation technique). All fluids (cooling, venting, and suction) were drained into the extracorporeal circuit. One thousand milliliters of ice-cold Bretschneider's cardioplegic solution (which is based on low sodium [15 mM] and the absence of calcium, contains mannitol [20 mM], and is buffered with histidine [180 mM]) was used for myocardial preservation. Within 20 min after the start of CPB, blood in the circuit was concentrated in group 1 by the Cell Saver IV (standardized to two cycles) and in groups 2 and 3 by the hemofiltration device. When necessary, Ringer's solution was added to maintain the filling volume of the circuit. When the hemoglobin concentration was less than 7 g/dl, packed red cells were given.

After separation from CPB, blood remaining in the extracorporeal oxygenation equipment was salvaged by use of the Cell Saver or the hemofiltration device to produce either washed erythrocytes or hemofiltered blood, respectively. Autologous blood was retransfused until the end of the operation. To antagonize heparin effects, protamine sulfate was given after separation from CPB in a 1:1 ratio to the initially administered heparin. All patients were operated upon by the same surgical team, blinded to the grouping.

Measured Parameters and Data Points

Platelet aggregation was measured from arterial blood samples by turbidimetric method[14] using a double-channel APACT-aggregometer (LAbor, Ahrensburg, FRG). Platelet count was adjusted to 150,000 platelets/mm^3 before measurement of aggregation. Aggregation was induced by adenosine diphosphate (ADP; in increasing concentrations, from 0.25 to 2.0 μM), collagen (4 μg/ml), epinephrine (25 μM), and sodium chloride (control). Maximum aggregation was defined as the maximum increase in light transmission after addition of the aggregating agent (read as the percentage increase; see reference 15). Maximum gradient of aggregation was defined as the maximum increase per minute (read as the percentage increase per minute). All measurements were performed in duplicate. Two patients were eliminated because of curve deviation of more than 15% (mean coefficient of variation 9%). Instead of these patients, two other patients chosen randomly were studied.

Arterial blood samples were taken as follows:

0. after induction of anesthesia (and in group 3, before aprotinin) (baseline values)
1. 30 min thereafter (and in group 3, after infusion of aprotinin)
2. 20 min after onset of CPB (after hemoconcentration by either the Cell Saver or the hemofiltration technique)
3. after separation from CPB and before the infusion of protamine
4. at the end of the operation (45 min after the end of CPB and after infusion of the blood salvaged from the circuit)
5. 5 h after the end of CPB
6. on the morning of the 1st postoperative day (at this time, all patients were breathing spontaneously and the tracheas were extubated).

Blood samples in the control group (group 4) were taken at time intervals comparable to those of the groups undergoing cardiac surgery.

In addition to platelet aggregation, hemoglobin, hematocrit, number of platelets, and activated clotting time (at the end of operation), blood gas variables, and electrolytes were measured.

Postoperatively, albumin (5%) was infused to maintain stable hemodynamics (when pulmonary capillary wedge

pressure was less than 6 mmHg and cardiac index less than 2.30 $l \cdot min^{-1} \cdot m^{-2}$), and packed red cells were administered when the hemoglobin concentration was less than 9 g/dl. All volume therapy was based upon decisions by anesthesiologists not involved in the study. Blood loss from chest-tube drainage and the use of homologous blood or blood products were documented. Shed mediastinal blood was not retransfused during the postoperative period.

Statistics

All data are expressed as mean values ± standard deviation. One- and two-factor analyses of variance (including multivariate analysis of variance) followed by Scheffe's test were used for statistical interpretation. A P value of < 0.05 was considered statistically significant.

Results

Demographic data as well as data from CPB did not differ among the groups. Blood loss was significantly greater in the CS patients (770 ± 400 ml) than in the HF (390 ± 230 ml) and AP patients (260 ± 160 ml). Use of packed red cells did not differ significantly among the three cardiac surgery groups (table 1). None of the patients received platelets or fresh-frozen-plasma. The greatest amount of additional volume was infused in the CS patients ($P < 0.05$).

Hemodilution (or hematocrit) was comparable in all cardiac surgery patients (fig. 1). Platelet count was similar until the end of CPB. Five hours after the end of CPB, platelet count in the CS patients was lowest (−28%) ($P < 0.05$), whereas it had returned to baseline values in the other two groups (fig. 1).

Changes in platelet aggregation variables are illustrated in figures 2–5. Changes from aggregation parameters after induction of anesthesia to values at the end of the operation are shown in figure 6.

The operative procedure itself did not induce changes in maximum aggregation and maximum gradient of aggregation induced by ADP, collagen, and epinephrine as demonstrated in the control patients. Aggregation with low concentrations of ADP could not always be induced in seven (0.25 μM ADP) and three (0.5 μM ADP) CS patients; this result was significantly different from aggregation in the HF and AP patients. Therefore, only aggregation induced by 1.0 and 2.0 μM ADP is shown in the figures.

At the end of the operation (and after retransfusion of salvaged blood), maximum aggregation and maximum gradient of aggregation induced by both concentrations of ADP was always lowest in the CS patients (fig. 6) ($P < 0.05$). In the later postoperative period, ADP-induced platelet aggregation recovered and returned to baseline values on the 1st postoperative day.

Collagen- and epinephrine-induced aggregation (maximum aggregation and maximum gradient of aggregation) at the end of the operation was also most depressed in the CS patients ($P < 0.05$) (figs. 4–6). Epinephrine-induced maximum aggregation, which was significantly different from the other two groups (fig. 4), did not completely normalize on the 1st postoperative day.

The loading dose of aprotinin (two million units) did not change any of the measured platelet aggregation variables (figs. 2–5). In the later course of the investigation,

TABLE 1. Demographic Data and Data from the Perioperative Period

	CS	HF	Aprotinin	Control
Age (yr)	60.4 ± 7.1	62.4 ± 8.6	62.7 ± 7.8	46.6 ± 16.2
Weight (kg)	76.2 ± 10.1	80.1 ± 11.1	74.8 ± 11.1	80.2 ± 15.2
LVEF (%)	70.4 ± 4.0	71.1 ± 5.5	70.2 ± 4.4	—
LVEDP (mmHg)	12.2 ± 1.9	13.4 ± 3.3	14.1 ± 2.2	—
CPB (min)	76.2 ± 11.1	72.2 ± 9.9	75.3 ± 14.1	—
Ischemia (min)	49.5 ± 12.1	44.4 ± 10.1	45.4 ± 9.8	—
Fluid balance during CPB (ml)	500 ± 250	150 ± 300	130 ± 430	—
Blood loss (ml)				
5 h after CPB	370 ± 200	180 ± 110	110 ± 80	30 ± 20
Until 1st postoperative day	770 ± 400*	390 ± 230	260 ± 160	100 ± 30
Packed red cells (patients/units)	2/2	0/0	1/2	0/0
Volume infusion (ml)				
5 h after CPB	650 ± 80*	250 ± 50	300 ± 70	—
Until 1st postoperative day	800 ± 120*	300 ± 80	350 ± 90	—

Data are means ± SD.
CPB = cardiopulmonary bypass; LVEF = left ventricular ejection fraction; LVEDP = left ventricular enddiastolic pressure. Ischemia: period of aortic cross-clamping.
* $P < 0.05$ compared to the other cardiac surgery patients.

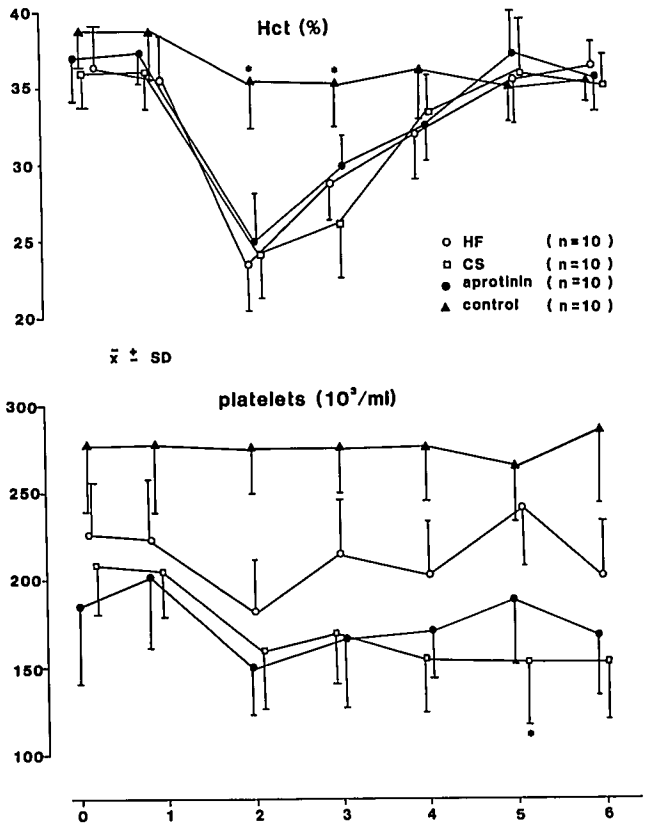

FIG. 1. Changes in hematocrit (Hct) and platelet count. 0 = After induction of anesthesia (before infusion of aprotinin, *i.e.*, baseline values); 1 = 30 min thereafter (after aprotinin in group 3); 2 = 20 min after start of CPB; 3 = after separation from CPB; 4 = end of operation; 5 = 5 h after end of CPB; 6 = the morning of the first postoperative day.

values for ADP-, collagen-, and epinephrine-induced platelet aggregation in the AP patients were similar to those for the HF patients.

Activated clotting time, blood gas parameters, and electrolytes were without differences among the groups throughout the investigation period.

Discussion

Quantitative (thrombocytopenia) and qualitative (thrombocytopathy) alterations in platelets during CPB result most likely from an interaction between the platelets and the synthetic surfaces of the extracorporeal oxygenation equipment.[13] Hemodilution is the major factor for the decrease in platelet count, but the decrease is greater than would be expected by hemodilution alone.‡‡ The contact between blood and the synthetic surfaces of CPB equipment produces adverse platelet alterations that lead to decreased adhesiveness, reduced membrane binding of fibrinogen, α granule release, and a reduced response *in vitro* to ADP and collagen.[11,16-18] Therefore, loss of platelet function seems to be the most important injury to the hemostatic system in patients undergoing CPB procedures.[19]

Like several others,[20,21] we found reduced aggregation in all patients undergoing CPB. Friedenberg *et al.*[22] also demonstrated abnormalities in aggregation with all three inductors—epinephrine, collagen, and ADP—in patients undergoing CPB: the second phase of platelet aggregation with epinephrine was abolished; the response to collagen was delayed and attenuated; and the response to ADP was attenuated and showed early dysaggregation. After termination of CPB, the number of platelets increased, most likely because of the hemoconcentration in this period but also because of a release of platelet pools in the lungs and bone marrow.[23] Platelet function follows a similar pattern of change, but it appears to recover more rapidly than does the platelet count.[23]

The purpose of this study was to investigate how efforts

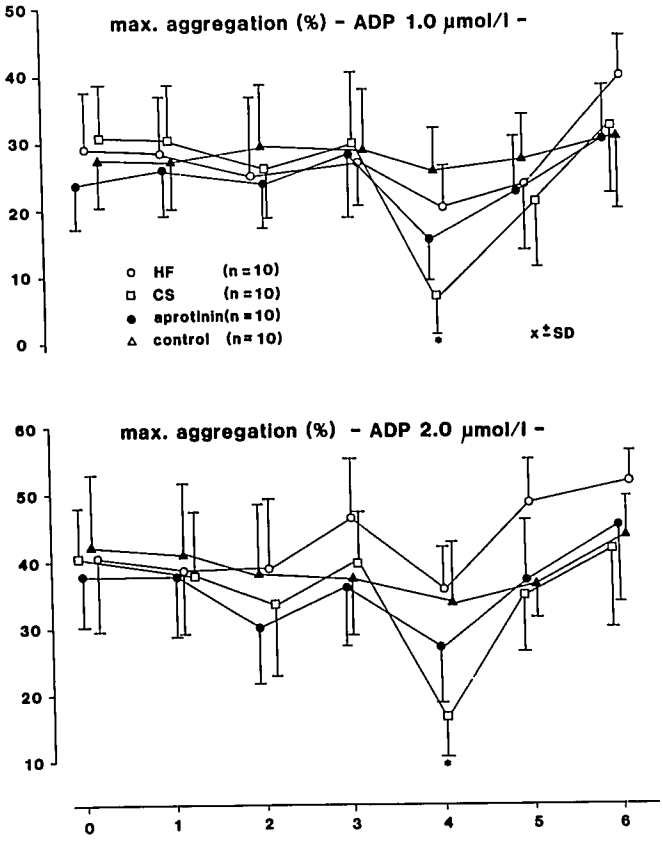

FIG. 2. Changes in maximum platelet aggregation induced by adenosine triphosphate (1.0 and 2.0 μM ADP). (For identification of data points, see legend to fig. 1.) *$P < 0.05$ compared to the other cardiac surgery patients.

‡‡ Demeyere R: Coagulation in cardiac surgery. Current Opinion in Anesthesiology 3:77-85, 1990.

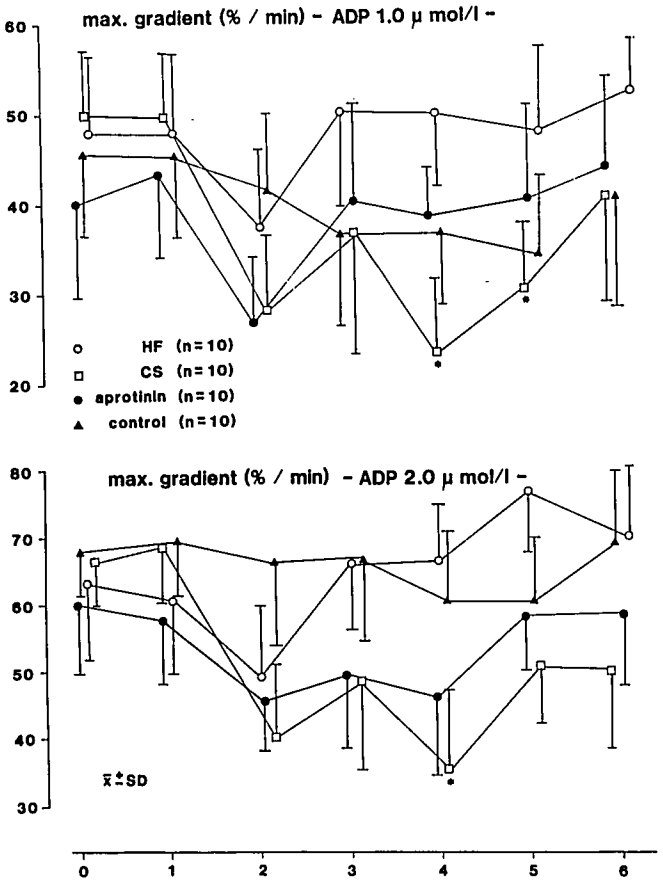

FIG. 3. Changes in maximum gradient of platelet aggregation induced by adenosine triphosphate (1.0 and 2.0 µM ADP). (For identification of data points, see legend to fig. 1.) *$P < 0.05$ compared to the other cardiac surgery patients.

to reduce homologous blood consumption influence platelet function. Induction of anesthesia by fentanyl, pancuronium bromide, and midazolam did not impair platelet function, as shown by several preliminary tests. Also, the surgical trauma itself did not cause a reduction in platelet aggregation, as demonstrated by our control patients, who were undergoing noncardiac operations.

One of the major findings of our study was that platelet aggregation differed significantly in the cardiac surgery patients. Platelet aggregation was diminished most markedly at the end of the operation in patients in whom a Cell Saver was used. Aggregation in the CS patients was reduced absolutely with respect to all inductors: there was deterioration in maximum aggregation and maximum gradient of aggregation with ADP, epinephrine, and collagen. Moreover, in these patients, sensitivity to induced aggregation also was reduced, at 0.25 and 0.5 µM ADP induction. The reason for these effects on platelet function may be the additional trauma through the recovery and centrifuge phases of CS salvage. In contrast to the CS group, aggregation in the HF patients was less reduced, and platelet function returned to normal within the first several postoperative hours and reached baseline values on the 1st postoperative day.

The degree of platelet destruction, adhesion, and decrease of aggregation has been suggested to be reduced by the use of pharmacologic agents, including aprotinin.[9,24] One of the major effects of aprotinin seems to be a direct or indirect protection of the platelets at the molecular level: aprotinin seems to preserve membrane-bound glycoprotein receptors, which are of central importance for platelet aggregation.[24] Royston *et al.*[9] suggest that the protection of platelet function is the most important aspect of aprotinin in this situation. However, with regard to platelet aggregation variables, in our study, patients receiving high-dose aprotinin plus hemofiltration were not different from those patients in whom only hemofiltration was used. Blood loss and the need for homologous blood also were without difference between these two groups. These results suggest that it is not necessary to use high-dose aprotinin in patients undergoing elective, uncomplicated aortocoronary bypass operations.

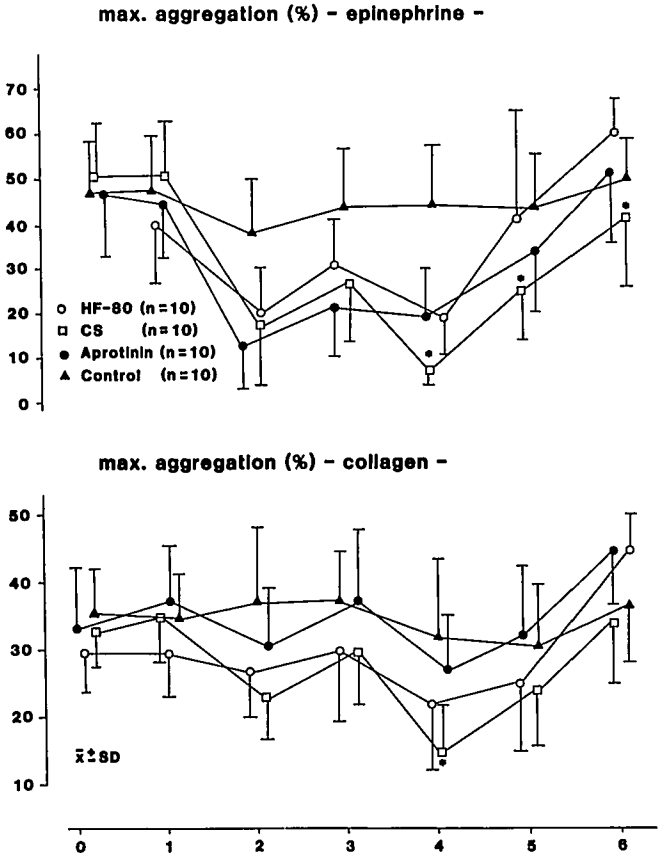

FIG. 4. Changes in maximum platelet aggregation induced by collagen and epinephrine. (For identification of data points, see legend to fig. 1.) *$P < 0.05$ compared to the other cardiac surgery patients.

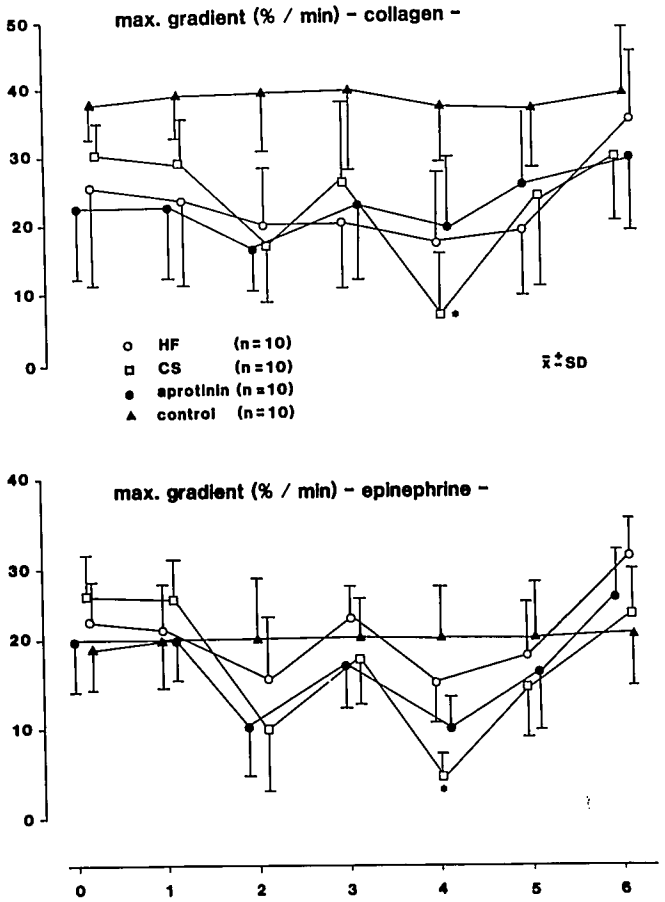

FIG. 5. Changes in maximum gradient of platelet aggregation induced by collagen and epinephrine. (For identification of data points, see legend to fig. 1.) *$P < 0.05$ compared to the other cardiac surgery patients.

Moreover, since the risks associated with the use of aprotinin have not been fully elucidated,§§ high-dose aprotinin should be limited to repeat operations and other complicated procedures with prolonged CPB times.

The finding that blood loss was greatest in patients in whom the Cell Saver was used is in accordance with a previous study.[8] Because of the complexity of coagulation cascade we did not attempt to correlate platelet aggregation variables with bleeding. Aprotinin did not reduce blood loss significantly in comparison with patients in whom only a hemofiltration device was used. Use of packed red cells was without difference among the three groups, perhaps because of the small number of patients studied. Moreover, we tolerated reduced hemoglobin values and did not use homologous blood unless hemoglobin concentration decreased to less than 9 g/dl.

§§ Böhrer H, Fleischer F, Lang J, Vahl C: Early formation of thrombi on pulmonary artery catheters in cardiac surgical patients receiving high dose aprotinin. J Cardiothorac Anesth 4:222–225, 1990.

Comparison with other studies investigating platelet aggregation is difficult because of differences in the study conditions and protocols: different patient gender ratios, different cardiac surgery procedures, different prime solutions and oxygenators, routine use of blood products in the postbypass period (*i.e.*, fresh frozen plasma and platelets), varying periods of CPB, and the absence of blood conservation devices may explain the varying results. The patients in our study were very homogeneous (only men, of comparable ages), and the cardiac surgical procedures were standardized with comparable techniques (surgeons) and CPB times. Therefore, although the number of patients in this study was small, influences on platelet function other than the different blood conservation techniques can be excluded.

It can be concluded that our attempts to reduce blood consumption in cardiac surgery were associated with different effects on platelet function. 1) Hemofiltration impaired platelet function significantly less than did the Cell Saver technique. 2) The use of high-dose aprotinin in

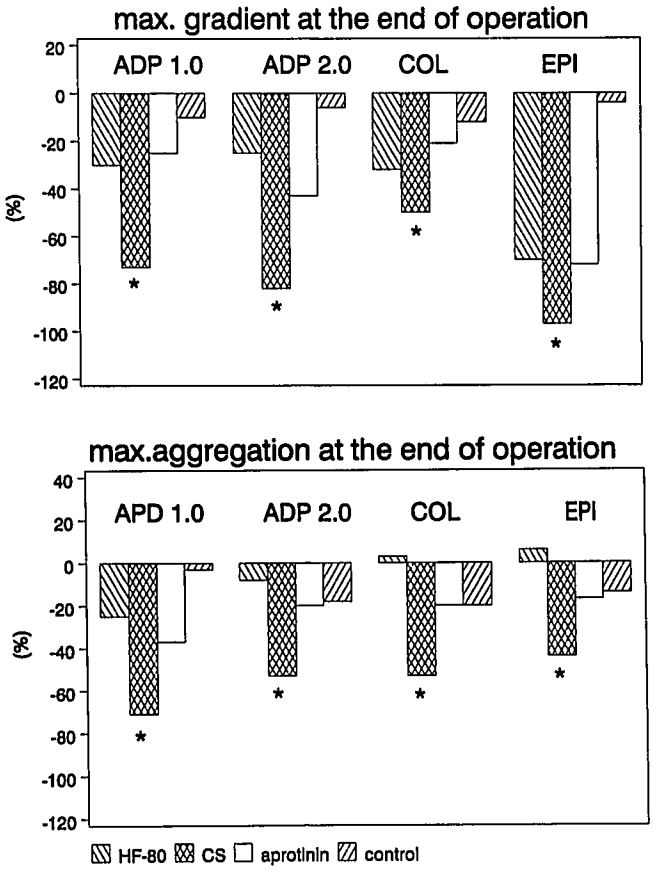

FIG. 6. Changes (percent) of maximum platelet aggregation and maximum gradient of platelet aggregation induced by ADP (1.0 and 2.0 μM), collagen (CO), and epinephrine (EPI) from baseline values to the end of operation (after retransfusion of salvaged pump blood). *$P < 0.05$ compared to the other cardiac surgery patients.

addition to the Cell Saver was without positive effect on platelet aggregation or postoperative bleeding and therefore cannot be recommended for preservation of platelet function in uncomplicated cardiac surgery procedures.

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