Original Article

The Effects of Platelet-Rich-Plasma on Post-Cardiopulmonary Bypass Fibrinolysis

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Winner of the Fellowship Award as the outstanding presentation at the American Society of Extra-Corporeal Technology 31st International Conference, February 26 - March 1, 1993, Dallas, Texas

Keywords: autologous blood, cardiopulmonary bypass, fibrinolysis, plasmapheresis, platelet-rich plasma

ABSTRACT

Postoperative hemorrhage associated with cardiac surgery continues to be a major source of significant patient morbidity. Cardiopulmonary bypass (CPB) induces a number of hemostatic alterations which include platelet defects and coagulation factor imbalances. In addition, the fibrinolytic system is stimulated by CPB, adversely affecting the stability of the fibrin network, leading to early clot dissolution. Various techniques for reducing post-CPB bleeding have been studied, and have included plasmapheresis and the collection of autologous platelet-rich-plasma (PRP). The present study examined the effects of autotransfusing PRP in cardiac surgery patients and the associated effects on fibrinolysis.

Twenty-six patients were diagnosed with fibrinolysis by whole blood elastokinetic monitoring (thrombelastography - TEG). The diagnosis of fibrinolysis was determined from the post-CPB TEG profile when clot dissolution exceeded 50% of the developed clot 30 minutes following protamine administration. Thirteen patients had been treated with PRP and 13 had not (Control - CTR).

There were no differences seen in preoperative or operative parameters between the two groups, nor were there differences in routine laboratory coagulation tests. Total platelet yeild in the PRP group was 1.2 $\pm$ 0.6 X 10^{11}. Patients in the CTR group had a total blood exposure of 39.4 $\pm$ 43.4 units compared to 8.6 $\pm$ 11.2 in the PRP patients ($p<.02$). This study supports the finding that CPB induces a fibrinolytic state, causing significant postoperative hemorrhage, which can be partially ameliorated by the infusion of autologous platelet-rich-plasma.

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INTRODUCTION

Tremendous energies have been spent studying and improving techniques which limit patient exposure to homologous blood products. Despite these efforts, postoperative hemorrhage remains a significant pathophysiological event associated with cardiopulmonary bypass (CPB). (1,2) The major etiological factors implicated in post-CPB bleeding include qualitative and quantitative platelet defects, (3,4) mechanical and physical alterations of clotting factors, (5-7) inadequate surgical hemostasis, and enhanced fibrinolysis. (8-11) Methods studied to reduce alterations in formed and plasmatic elements of blood include improved biocompatibility of synthetic materials of the extracorporeal circuit, (12) evaluation of certain pharmacological agents that reduce platelet surface interactions and inhibit serine proteases, (13,14) increased utilization of autotransfusion and ultrafiltration devices, (15-17) and techniques of autologous plasmapheresis. (18-21) Unfortunately, universal acceptance and incorporation of these techniques into clinical practice is limited, and there remains no panacea which would preclude patients from excessive hemorrhage and homologous blood exposure.

One promising technique that is gaining widespread acceptance as a blood conservation method is perioperative plasmapheresis which produces autologous platelet-rich-plasma (PRP). (18-23) Benefits of PRP include preservation of platelet number and function, (18,19) stabilization of coagulation protein systems, (20,21) and a reduced generation of activated neutrophils. (24) Secondary benefits may be considered logistical and include increased application in patients who might otherwise not be candidates for preoperative donation. PRP may also be used as a preoperative treatment for hypercoagulable patients prone to increased risk of thrombosis. To our knowledge, an examination of the effects PRP has on postoperative fibrinolysis and associated hemorrhage has not been reported. The present study examined the clinical use of autologous PRP in reducing the negative hemostatic effects of CPB, including fibrinolysis.

MATERIALS AND METHODS

The present study examined the operative results of 192 patients who were entered into two separate prospective examinations on autologous PRP. (25,26) In the first study 115 patients were randomly assigned to either a control or treatment group, who had pre-surgical removal of 20% of the patient's circulating plasma volume, and subsequent concentration of a PRP fraction through centrifugation. In the second study (25) 52 patients were randomly assigned to one of three techniques currently utilized to sequester PRP. Data was collected from 25 additional patients who were treated in a similar fashion to those in study one. All cardiac patients were evaluated for inclusion in these combined studies and were excluded only if they met one of the following criteria: ejection fraction less than 35%, critical aortic stenosis with valve area less then 0.7 cm^2, left ventricular end diastolic pressure greater than 20 mmHg, preoperative platelet count less than 150,000, preoperative hematocrit less than 35%, weight less than 50 kg, or left main artery occlusion greater than 50%. All patients were treated with identical operative and postoperative management and were followed from admission to discharge.

Standard anesthetic techniques were administered to all patients and consisted of premedication with narcotics and amnestic agents. Intraoperative monitoring consisted of a three-lead electrocardiogram, pulse oximeter, capnograph and arterial and pulmonary artery pressure monitoring. The primary anesthetic agent was sufentanyl citrate combined with pancuronium bromide as a muscle relaxant. Systemic anticoagulation was achieved by the administration of 300 IU/kg of beef lung heparin, with activated clotting times (ACT) maintained throughout bypass greater than 480 seconds.

PLASMAPHERESIS PROTOCOL

Patients randomized to the PRP groups had an additional 8.5 French indwelling catheter placed in either the internal or external jugular vein. For each patient, circulating plasma volume was calculated from a hematocrit measured just prior to plasmapheresis, and 20% of that amount was removed by one of three plasmapheresis techniques: 1. dedicated plasma collection system[a], 2. autotransfusion machine A[b], and 3. autotransfusion machine B[c]. The collected product was then stored at 37°C with gentle periodic agitation until reinfusion (within 6 hours of collection). The collected red blood cell fractions were infused to the patient only if the calculated on CPB hematocrit was below 20%. Volume replacement was carried out both prior to and during plasmapheresis with colloids (hetastarch and 5% albumin), and crystalloid (lactated Ringers) solutions, at a rate of 1:1 of total blood volume removed. The PRP product was sampled for platelet count and fibrinogen concentration, and the platelet yield determined from the total PRP volume and platelet count. Infusion of PRP commenced following the administration of protamine (1 mg/100 IU of total infused heparin) and affirmation of total reversal by ACT and concurrent heparin/protamine titration[d].

Moderate hypothermic (28°C) CPB was conducted in all patients with a roller pump arterial drive system[e], membrane oxygenator[f], and closed venous system. Autotransfusion with a cell washing system[b] was employed and ultrafiltration was in-

a Plasma Saver, Haemonetics, Inc. Braintree, MA 02184
b Cell Saver 4 with sequestration set, Haemonetics Inc., Braintree, MA 02184
c Autotrans 1000 with sequestration set, Electromedics Inc., Englewood, CO 80155
d Hepcon HMS, , Medtronic Hemotec, Inc., Englewood, CO 80112
e Shiley Stockert, Sorin, Inc. Irvine, CA 92714
f Sarns Membrane Oxygenator, Sarns 3M Health Care, Ann Arbor, MI 48103

cluded when deemed necessary by the perfusionist. Non-pulsatile perfusion was carried out at cardiac indexes between 1.8 and 2.8 L/min/m^2 maintaining mean arterial pressures between 50 and 80 mmHg. Blood cardioplegia (4:1 blood to crystalloid) was utilized with an initial K^+ concentration of 24-28 mEq/L, with subsequent doses administered at 10-14 mEq/L. ACT measurements were kept above 480 seconds at all times, and were measured at least every 30 minutes while on CPB.

The following transfusion criteria were established for regulating infusion of homologous blood products following CPB: packed red blood cells (PRBC) - patients less than 70 years with hemoglobin levels below 7 gm/dl, and when older than 70, 8 gm/dl*; fresh frozen plasma (FFP) when prothrombin times (PT) were greater than 16 seconds (approximately 50% above baseline values); platelets (PLT) when platelet counts were less then 100,000/ul; and cryoprecipitate (CRYO) when fibrinogen levels were less then 100 mg/dl and inadequate surgical hemostasis ruled out as a cause of bleeding.

Coagulation profiles were performed on admission and included PT, activated partial thromboplastin time (aPTT), template bleeding time (BT), PLT count, and fibrinogen levels. A thrombin time (TT) was performed upon patient entry to the intensive care unit (ICU). Postoperative coagulation screens were performed immediately upon entry into the intensive care unit which routinely occurred within 2 hours of PRP administration.

THROMBELASTOGRAPHY

Whole blood elastokinetic monitoring was performed with the use of a thrombelastograph (TEG),[g] which measures various physical parameters of blood as it changes from a liquid to a gel (coagulum). The overall coagulative status of the patient was assessed via the use of combined discriminant analysis of weighted parameters of the TEG.[g] The following equation for TEG index was calculated using measurable parameters from native (N) and celite (C) activated whole blood TEG profiles:

TEG (N) Index =
-.0227 (R) + 0.0092 (K) + 0.1655 (MA) - 0.0241 (AA) - 5.022

TEG (C) Index =
-.3258(Rc) - 0.1886(Kc) + 0.1224(MAc) + 0.0759(AAc) - 7.792

R = Reaction time, initial time for clot formation
K = Kinetic time, time from initial clot formation to development of clot of specific amplitude
MA = Maximum amplitude, the maximum strength of a clot
Alpha Angle = the rate of clot development
A@60 = Amplitude measured 60 minutes after MA

Normal range of TEG indices were developed from linear modeling of normal patient TEG profiles as established by the manufacturer,[g] and range from -2.0 to 2.0, representing a mean value ± 2 standard deviations from the mean. Values of -2 and lower represent hypocoagulable states, while values greater then 2 represent hypercoagulable states. The degree of post-CPB fibrinolysis was determined by creating a fibrinolytic index according to the following formula:

$$\text{Fibrinolytic Index} = [1 - (A@60 \div MA)] \times 100$$

Normal fibrinolytic indices have been reported as being 15% or less at 60 minutes.[g]

Concurrent ACT[h] and TEG profiles performed at the following times: Pre-skin incision, post-skin incision, 10 minutes post-protamine, and 30 minutes post-protamine with reinfusion of PRP occurring between these two post-protamine periods.

Parametric data was analyzed using one way and two way analysis of variance. When significant f ratios were reached, additional multiple comparison tests were performed and included either Fisher's least significance difference or Duncan's test. Nonparametric data were analyzed by the Wilcoxon rank sign test. Statistical significance was accepted at the $p<.05$ level. All data are presented as mean ± standard deviation of the mean (SDEV).

RESULTS

There were 26 patients who demonstrated fibrinolysis activity on TEG profiles. These patients were divided into two groups, 13 patients who received PRP and 13 patients who did not (CTR). There were no significant differences between groups in regard to preoperative medication schedules, with the major drug groups being antianginals, antihypertensives and calcium channel blockers. Total PRP volume and platelet yield for the PRP group are shown in Table 2.

The operative and postoperative data are shown in Tables 3 through 6. The administration of colloids, both on CPB and by anesthesia, was greater in the patients who received PRP in order to maintain colloid osmotic pressure close to a predetermined 12 mmHg level. Table 4 lists the results of the coagulation tests for both groups. Post-CPB PT and aPTT were significantly elevated from baseline values in both groups, but did not vary amongst groups. The PRP patients had the highest concentration of preoperative fibrinogen for all groups which also was also evident with higher ICU values.

Homologous blood exposure rates (HBE) are shown in Figure 1. The highest homologous blood transfusion require-

* In the case of incomplete revascularization PRBC were given for a hemoglobin less than 8 gm/dl in all aged patients.

g CTEG 3000 Manual, Haemoscope Corporation, Morton Grove, IL

h Hemochron 801, International Technidyne, Edison, NJ

Table 1
Patient demographic data

Parameter	Fibrinolytic		p Value
	PRP Group	Control Group	
Number	13	13	
Age (years)	63.2±10.6	66.4±7.9	NS
Sex (male/female)	13/0	7/6	.001
BSA (m^2)	2.01±0.2	1.88±0.2	NS
Weight (kg)	84.1±11.1	76.1±12.1	NS
Height (cm)	176.7±6.7	170.6±9.4	NS
Preop Hct (%)	40.8±3.6	39.7±6.3	NS
Preop Plt. Meds. (%)	28	33	NS

All data are mean ± SDEV
BSA=body surface area;Preop Plt. Meds=percent of patients taking preoperative platelet altering medications; NS=non significant

Table 2
Plasmapheresis product for the plasmapheresis group

Parameter	
Platelet Count	183,400 ± 59,000
Fibrinogen Count	272.1 ± 98.2 mg/dl
Total Volume	653 ±100 ml
Platelet Yield	1.2 x 10^{11} platelets

All data are mean ± SDEV

Table 3
Operative data

Parameter	PRP vs.CTR		p Value
	PRP Group	Control Group	
Patient Number	13	13	
Operation			
CABG (graft #)	2.9	2.4	NS
IMA usage (%)	60	58	NS
Valve Replacement (#)	1	4	.05
CABG/Ventricular Aneurysm (#)	0	1	NS
Combined CABG/Valve (#)	1	2	NS
Reoperation	3	1	NS
CPB Time (min)	124.5±52.5	115.3±42.3	NS
Cross Clamp Time (min)	80.0±31.7	84.1±38.2	NS
High CPB ACT (sec)	644.4±105	614.2±109	NS
Low CPB ACT (sec)	424.7±36.1	442.1±47.9	NS
Low CPB Hct (%)	18.7±2.5	19.8±2.8	NS
Low CPB COP (mmHg)	10.8±1.0	10.0±1.5	NS
Prime Albumin (gms)	16.7±12.3	3.6±9.0	.001
Anesthesia Vol. Replacement			
Colloid (ml)	1504±556	1350±391	NS
Crystalloid (ml)	5633±1620	4660±1492	NS

All data are mean ± SDEV
ACT=activated clotting time;CPB-cardiopulmonary bypass; COP=colloid oncotic pressure; CABG=coronary artery bypass grafting; Hct=hematocrit; IMA=internal mammary artery; NS=non significant

Table 4
Perioperative coagulation parameters

Parameter	Preop	Postop	p Value		
			vs. preop	vs. CTR preop	vs. CTR postop
PRP Group					
Prothrombin Time (sec)	12.2±0.7	14.9±1.0	.001	NS	NS
A. Part. Thrombplast. Time (sec)	30.3±13.2	36.7±5.2	.009	NS	NS
Thrombin Time (sec)	——	35.8±26.1	——	NS	NS
Bleeding Time (sec)	5.0±1.6	——	——	NS	——
Fibrinogen (mg/dl)	510.9±205.7	197.5±74.4	.0001	.005	.05
Platelets (thousands)	230.7±72.3	108.1±33.7	.0001	NS	NS
Calcium (mg/dl)	——	7.0±0.9	——	——	——
Control Group					
Prothrombin Time (sec)	12.0±0.5	15.3±2.1	.001		
A. Part. Thrombplast. Time (sec)	29.6±7.3	41.5±12.8	.001		
Thrombin Time (sec)	——	36.4±27.3	——		
Bleeding Time (secs)	5.2±1.9	——	——		
Fibrinogen (mg/dl)	383.2±121.1	169.2±57.2	.0001		
Platelets (thousands)	235.7±68.9	119.6±44.4	.0001		
Calcium (mg/dl)	——	7.0±.0.5	——		

All data are mean ± SDEV
Part. Thromplast=activated partial thromboplastin; PRP=platelet-rich plasma; Postop=postoperative; Preop=preoperative

Table 5
Postoperative data

Parameter	Fibrinolytic		p Value
	PRP Group	Control Group	
Total Postop CT Drainage (ml)	1431±677	1162±581	NS
Total Ventilatior Time (hrs)	17.8±4.4	35.3±28.5	.01
Total ICU Time (hrs)	57.1±39.9	61.9±33.6	NS
Discharge Hematocrit (%)	31.5±5.2	29.8±4.8	NS
Total Hospital Stay (days)	11.3±8.6	12.3±5.3	NS

All data are mean ± SDEV
CT Drain=chest tube drainage; PRP=platelet-rich plasma; Postop=postoperative

ments were seen in the CTR group. Patients in this group had significantly greater PRBC, FFP, PLT and CRYO transfusion requirements than patients in the PRP and NON-FIB groups (Figures 2 and 3).

TEG results are summarized in Table 6 and shown in Figures 4 and 5. Pre-skin incision TEG indices in all groups trended towards hypercoagulable which corresponded well with previous results. (25,26) Ten minutes following protamine administration both groups displayed significantly decreased coagulability by the TEG index. In both the CTR and PRP groups the TEG index had increased toward baseline values although these levels were not fully reached. The CTR group, however, remained significantly depressed at 30 minutes post protamine indicating a continued coagulopathy. Following heparin reversal the TEG data demonstrated increased fibrinolytic activity in all groups with the most significant findings evident in the PRP and CTR groups. Figure 5 shows the effects of infusing PRP on reducing the FIB Index in the PRP group, with only a slight decrease in FIB Index seen in the CTR group. There were no patients in the PRP group who had hyperfibrinolytic TEG profiles following PRP administration, while only 37% of CTR patients had similar TEG parameters.

Table 6
Thrombelastograph data

Parameter	Control		PRP	
	Pre-Skin Inc.	Post Skin Inc.	Pre-Skin Inc.	Post Skin Inc.
R Time (min)	16.3±10.5	13.3±6.7	14.3±7.2	13.4±3.9
K Time (min)	7.1±6.6	6.0±4.8	6.3±4.7	5.4±2.9
MA (mm)	56.7±8.9	60.0±10.6	63.8±5.3	61.0±10.1
A @ 60 (mm)	53.1±11.1	53.5±8.9	57.3±3.5	54.6±9.3
Alpha Angle (deg)	46.8±17.7	46.0±20.4	47.8±16.8	47.1±15.6

Parameter	Control		PRP	
	10′ Post Prot	30′ Post Prot.	10′ Post Prot	30′ Post Prot.
R Time (min)	10.8±5.3	10.3±4.7	18.8±9.4	23.5±9.1
K Time (min)	6.7±6.1	4.0±24	13.9±17.1	16.6±11.8
MA (mm)	31.3±15.3	51.5±9.3	30.7±15.7	35.1±12.3
A @ 60 (mm)	8.7±10.8	46.0±9.1	9.67±11.1	17.4±18.1
Alpha Angle (deg)	41.1±19.6	50.3±14.3	29.3±20.2	20.8±13.9

All data are mean ± SDEV
Inc=incision; NS=not significant; Postop=postoperative; Pre-Skin Inc=pre skin incision; Prot=protamine; PRP=platelet rich plasma;TEG=thrombelastograph

DISCUSSION

Alterations in the hemostatic mechanism in patients undergoing cardiac surgery are dependent upon a multitude of events and conditions which profoundly affect clot formation and stabilization. Normal hemostasis is represented by a summarization of interactions between platelet surfaces and coagulation proteins. The trauma associated with surgery exposes significant quantities of subendothelial surfaces to blood, activating various protein systems, which have as their underlying goal the reduction of hemorrhage. Both cellular and plasmatic components of blood become involved in an thrombophilic process to reduce the flow of blood from cut vessels. Platelets are activated to adhere to subendothelial collagen, and concurrently, release vasoactive substances, such as thromboxane A_2, which cause vessel constriction. Coagulation proteins are activated leading to the generation of thrombin and the formation of fibrin. (6)

In addition, the conduct of CPB leads to physical changes in all coagulation components. Hemodilution and hypothermia cause both quantitative and qualitative reductions in hemostatic capacity. More importantly, however, is the contribution of physical and mechanical alterations of formed and plasmatic elements of blood associated with contact activation with synthetic surfaces. These interactions adversely affect platelet morphology and function, and stimulate various protein systems involved in fibrin clot stabilization. (3-5) In addition, proteolytic enzymes are stimulated that affect clot stabilization, leading to an early resolution of thrombus, re-establishing free flow of blood. The primary components of this fibrinolytic pathway are plasminogen and plasmin.

Plasmin, derived from a circulating precursor zymogen called plasminogen, is a proteolytic enzyme which binds with the substrate fibrin, resulting in the solubilization of the clot. The normal function of the fibrinolytic system is to regulate the generation of fibrin, serving as a control system that maintains a patent vascular system. During cardiac surgery tissue plasminogen activator (t-PA), produced by the endothelium, serves as an extrinsic source of circulating plasminogen activator. (27) Circulating levels of tPA increase to approximately 150% above baseline value during cardiac surgery, (7) and activate plasminogen at the site of fibrin formation. Therefore, t-PA does not induce widespread generalized systemic fibrinolysis, but instead, facilitates clot dissolution at localized sites. Activated plasmin has broad specificity and generates polypeptide end products, which are denoted fibrin degradation products (Figure 7). Plasmin will also digest other coagulation proteins such as fibrinogen and factor VIII. Cardiopulmonary bypass has been shown to generate increased circulating plasmin, combined with a reduction in plasminogen, which leads to hyperfibrinolysis and the potential for postoperative bleeding. (8-11) The general response is an imbalance between activators and inhibitors of the fibrinolytic system. Excessive stimulation of serine proteases through extracorporeal circulation has been well established, and

Figure 1
Total homologous blood exposure in all fibrinolytic patients

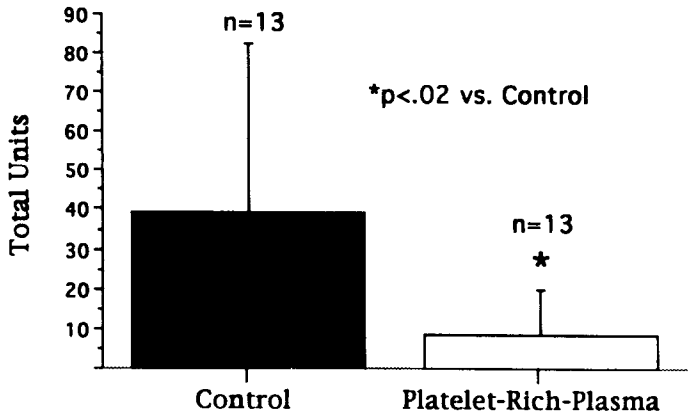


Figure 2
Packed red blood cells and fresh frozen plasma transfusion in fibrinolytic patients

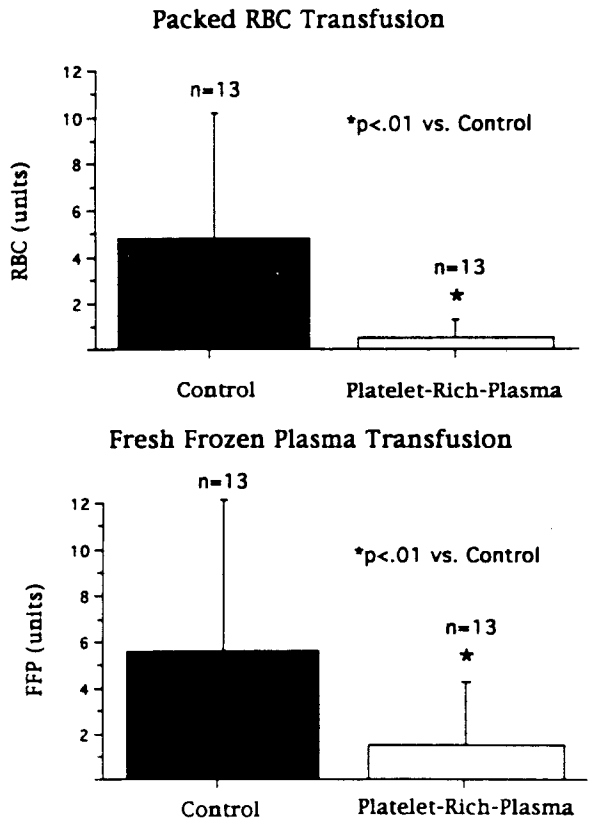
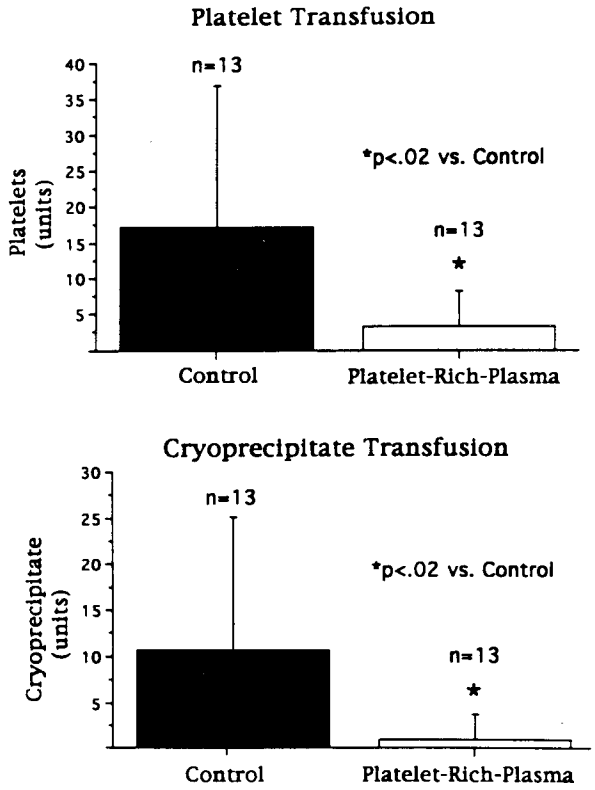


Figure 3
Platelet and cryoprecipitate transfusion in fibrinolytic patients



methods of pharmacologic manipulation of these activated proteins is the subject of intense research. (13,14)

An associated disorder of the hemostatic mechanism, often confused with primary fibrinolysis induced through plasmin activation, is disseminated intravascular coagulation (DIC). The process of DIC is poorly understood, but it is known that there is a depletion in coagulation factors (factors V, VIII, prothrombin, and fibrinogen) and platelets. During DIC, the fibrinolytic system is also activated (secondary fibrinolysis) resulting in the production of breakdown products of fibrin, including FDP, D-dimers and soluble fibrin monomers, which are products of thrombin generated complexes. (7) DIC is rarely encountered during cardiac surgery, while primary fibrinolysis is more common.

Both epsilon-aminocaproic acid (EACA) and tranexamic acid have been shown to be effective antifibrinolytic agents in treating bleeding following CPB. (28,29) In one study, post-CPB infusion of EACA reduced postoperative bleeding and homologous transfusion by 30%. (30) In a recent study, postoperative chest tube drainage was significantly reduced in patients given high doses of tranexamic acid. (28) An important consideration

Figure 4
Thrombelastograph index in control (n=13) and platelet-rich plasma (PRP) patients. Post-Prot=Post-protamine

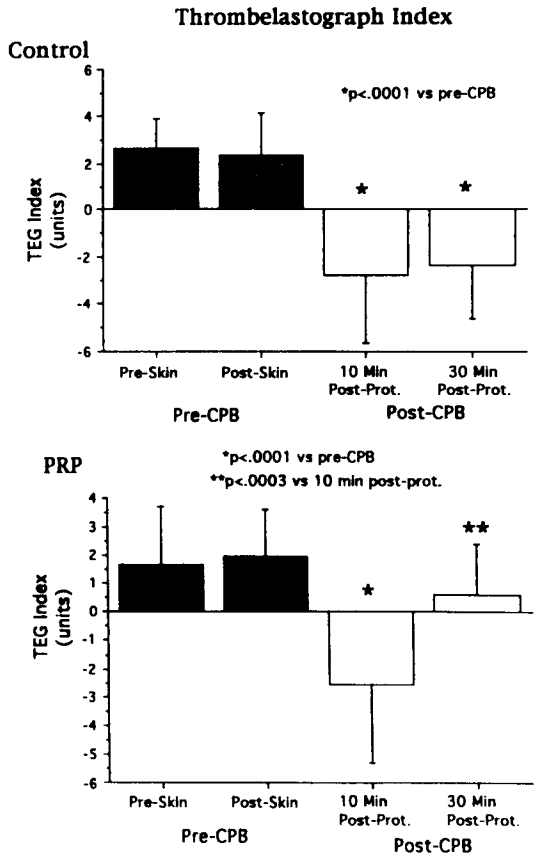
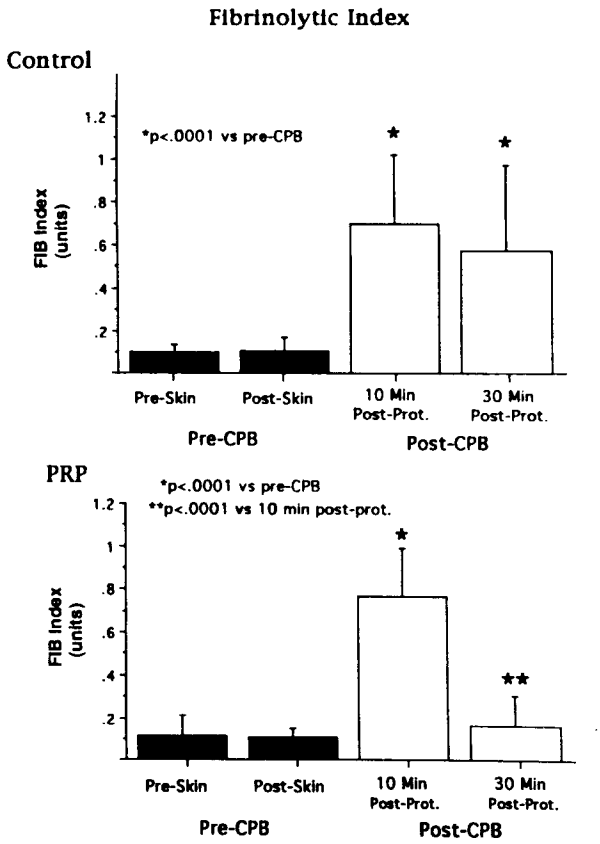


Figure 5
Fibrinolytic index in control (n=13) and platelet-rich plasma (PRP) patients. Post-Prot=post-protamine

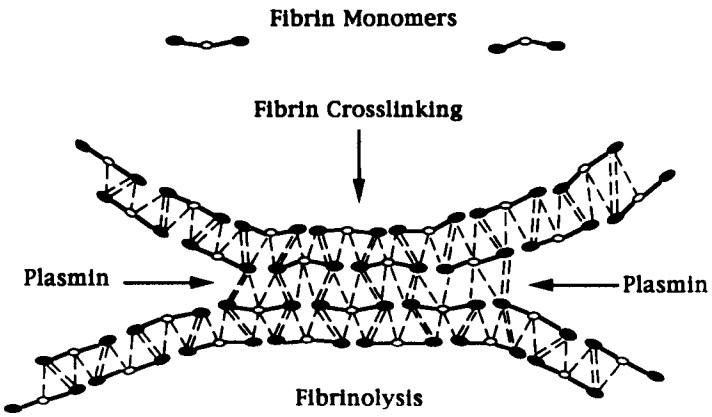


when using antifibrinolytic agents following CPB is the increased risk of thrombosis. (9,31) During DIC the secondary fibrinolysis that occurs may reduce the risk of thromboembolic events associated with hypercoagulable states. Although not proven, cardiac patients who are at an increased risk of developing excessive clot postoperatively should probably not be administered antifibrinolytic agents prophylactically. In the present study, no patients in the PRP group were administered any antifibrinolytic agent until the effects of PRP could be ascertained. Aprotinin is a potent antifibrinolytic agent because of its high binding affinity for plasmin, and stabilizes platelet function following CPB. (32,33) Aprotinin has been shown to protect the natural inhibitor alpha-2-antiplasmin from excessive reduction during CPB. (32)

The main circulating inhibitor of free plasmin is a protein called alpha-2-antiplasmin, while additional naturally occurring inhibitors include alpha-2-macroglobulin and alpha-1-antitrypsin. Reduced circulating concentrations of these substances is evident during CPB, and may predispose patients to increased fibrinolytic risk. (7,32) The reduction in alpha-2-antiplasmin measured at the termination of CPB has been shown to vary among studies, with reductions of 64% of standard, (32) 38%, (31) and by 42%(7) all reported. Physiologic inhibition of fibrinolysis is also modulated by the activity of certain proteins called plasminogen activator inhibitors (PAI). These function by competitively inhibiting plasminogen, reducing the generation of plasmin. In the present study, patients receiving the autologous PRP product had reduced fibrinolytic activity, which leads to the postulation of these endogenous substances in the plasma fraction.

The benefits of autologous PRP include the following: reduction in patient exposure to homologous blood products, (18,20,22) reduction in the logistical steps involved in autologous predonation through blood banks, increase in the patient population not otherwise suitable for predonation, preservation of platelets and protein fractions from exposure to the extracorporeal circuit during cardiopulmonary bypass, and reduction in activation of polymorphonuclear neutrophils and post-CPB pul-

Figure 6
Fibrin formation and breakdown (fibrinolysis) with production of fibrin degradation products



monary dysfunction. (20,24) Boldt has shown that plasmapheresis reduces the circulating levels of pulmonary elastase, a proteolytic enzyme released by polymorphonuclear neutrophils, (34) which has been implicated as a pathogen associated with post-CPB pulmonary dysfunction. (35)

Centrifugation of whole blood collected during plasmapheresis results in the concentration of formed elements in fractions according to density. Although a small quantity of platelets remain in the heavier red cell layer, the majority are retained in the plasma layer, and have been examined and quantified in many PRP studies. The remaining plasma is also rich in circulating proteins and in two previous studies fibrinogen levels have ranged from 189 to 260 mg/dl. (25,26) These levels represented approximately 65% of preoperative fibrinogen concentrations prior to CPB. Although we did not measure specific factors in the PRP product it may be inferred that other circulating proteins would also be retained in similar ratios to fibrinogen. In another study we have shown that during CPB, reductions in endogenous antifibrinolytic agents routinely occurs most likely as an effect of hemodilution and activation. By removing these compounds, such as alpha-2-antiplasmin and alpha-2-macroglobulin, they are spared extracorporeal exposure and exert immediate antifibrinolytic activity upon reinfusion. Both alpha-2-antiplasmin and alpha-2-macroglobulin are primary inactivators of circulating plasmin, and may have participated in the observed antifibrinolytic effects of PRP.

In the present study, routine coagulation tests were nonspecific in identifying bleeding coagulopathies resulting from CPB. The ACT time is insensitive to most fibrinolytic conditions and can not be used as an fibrinolytic marker. Degradation products of fibrinogen/fibrin (FDP), and of fibrin (D-dimers) have been used to assess fibrinolysis following CPB. (31,32) However, these indicators are routinely elevated during and after CPB, and therefore, must be interpreted carefully as fibrinolytic indicators.

The thrombelastograph is a elastokinetic measuring device that reflects the ex-vivo hemostatic mechanism, and is an excellent prognostic tool for identifying platelet function, coagulation protein interactions leading to fibrin formation, and clot resolution. The TEG has been identified as an effective means of detecting post-CPB bleeding resulting from hyperfibrinolysis and DIC. (8,10,36,37) Previous studies have shown the TEG to be an effective tool in identifying the perioperative benefits of reinfusing autologous PRP. (25,26) All measured TEG parameters improved following PRP infusion, and these changes were substantially greater than the initial reduction in coagulation status seen by phelobotimizing a significant volume prior to surgery.

The incidence of coagulopathies associated with CPB is estimated at approximately 3%, (1,2) while the diagnosis of active fibrinolysis varies among centers. (8-11) In the present study 13.5% of the 192 patients demonstrated hyperfibrinolysis with significant postoperative hemorrhage. The TEG detects low levels of plasmin activity and produces a characteristic fibrinolytic profile. The level of fibrinolytic activity detected by the TEG may not always reflect clinically significant bleeding. In the present study, the infusion of blood products, other than red blood cells, did not correlate with the TEG profile information in 13 of 26 hyperfibrinolytic patients (50%). Nevertheless, the fibrinolytic TEG data was prognostic in identifying the cause of excessive hemorrhage, identified through open-chest observation of bleeding, or through chest tube drainage. When significant bleeding did not occur, the TEG information was still useful in alerting the clinicians to the potential for developing a bleeding coagulopathy as a result of rising plasmin concentrations. In no case did the TEG fail to identify an induced coagulopathy following cardiopulmonary bypass, which has also been confirmed by others. (38,39) The diagnosis of false-positive TEG parameters, where TEG parameters predicted a coagulopathy while clinically significant bleeding was not observed, has been identified in approximately 1 of 5 cases. (38,39) Possible reasons for false-positive diagnoses may include sensitivity of the TEG to extremely low levels of heparin (possibly from contaminated sampling), variation between studies in identifying postoperative bleeding, and the complex nature of the body's hemostatic ability.

In conclusion, the present study demonstrates a previously not described benefit of plasmapheresis with the production of autologous platelet-rich-plasma. When platelet-rich-plasma was reinfused to patients diagnosed with fibrinolysis through thrombelastography, there was a significant reduction in homologous blood exposure. Although this study did not identify specific plasmatic factors associated with the bleeding diathesis, the rapid restoration of thrombelastograph profiles to preoperative levels implicates that platelet-rich-plasma contains endogenous

antifibrinolytic products that have clinically significant benefits.

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