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Heparin Management Protocol for Cardiopulmonary Bypass Influences Postoperative Heparin Rebound but Not Bleeding

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A group of 63 adult patients undergoing cardiac surgical procedures requiring cardiopulmonary bypass (CPB) were studied to examine the relationship between heparin doses administered and postoperative bleeding. Patients were randomly assigned either to receive heparin 200 U/kg and additional heparin as needed to reach and maintain an activated clotting time (ACT) > 400 s for CPB (group A, n = 30), or to receive heparin 400 U/kg and additional heparin as needed to reach and maintain a whole blood heparin concentration > 4.0 U/ml for CPB (group H, n = 33). Groups were compared for the amount of postoperative bleeding, heparin rebound, homologous transfusion requirements, and standard laboratory coagulation tests. In the last 33 patients studied, additional tests of platelet aggregation and plasma levels of β thromboglobulin (BTG), antithrombin III, and several markers of fibrinolysis were measured and compared by group. The mean heparin dose was 28,000 ± 4,800 U for group A and 57,000 ± 10,700 U for group H ($P < 0.05$ for group A *vs.* group H). At 8 and 24 h postoperatively, mediastinal drainage did not differ significantly between groups (mean 24-h drainage ± SD = 901 ± 414 ml in group A, 1035 ± 501 ml in group H), nor did the incidence of transfusion with homologous blood products. Defining heparin rebound as a >10% increase in ACT, patients in group H had a larger incidence of postoperative heparin rebound (26 of 31 patients [84%] *vs.* 16 of 30 [53%] patients in group A, $P = 0.005$) and of requiring supplemental protamine treatment for heparin rebound (8 patients in group H, 1 patient in group A, $P = 0.01$) in the first 8 h postoperatively. Because heparin rebound was treated with protamine only if excessive bleeding was present, patients in group H had a greater incidence of clinically significant heparin rebound. Overall, the occurrence of heparin rebound did not significantly influence the amount of postoperative blood loss, possibly because its occurrence was aggressively treated whenever bleeding was excessive. Platelet aggregation response to adenosine diphosphate and thrombin did not differ between groups before, during, or after CPB, but collagen-mediated platelet aggregation was significantly more impaired during CPB in group H ($P = 0.01$). Biochemical markers of fibrinolysis suggested ongoing fibrinolysis during and shortly after CPB, but the degree of activation was similar in both groups. Antithrombin III levels were significantly less in group H ($P = 0.03$) during CPB rewarming. In conclusion, the use of smaller *versus* larger doses of heparin for CPB did not significantly influence postoperative blood loss or transfusion requirements, although the larger doses of heparin used in group H increased the incidence of postoperative heparin rebound. (Key words: Anticoagulation: cardiopulmonary bypass. Fibrinolysis: cardiopulmonary bypass. Heparin. Heparin rebound. Monitoring: heparin. Platelet function: cardiopulmonary bypass.)

IN 1975, Bull and colleagues introduced heparin monitoring to cardiac surgery by describing a management protocol based on the use of the activated clotting time (ACT).[1,2] They demonstrated that patients show great variability in both the magnitude and the duration of heparin-induced anticoagulation. After clinical use of their recommended protocol became widespread, however, Culliford *et al.* and others showed that factors other than plasma heparin concentration, principally hypothermia and hemodilution,[3,4] influence the ACT during cardiopulmonary bypass (CPB). Because ACT prolongation during CPB can be partially attributed to these and other factors, some have suggested direct monitoring of blood heparin concentration during CPB.[5,6]

Recent debate has focused on the theoretical merits of measuring ACT *versus* heparin concentration to monitor CPB anticoagulation. In a study comparing the degree of subclinical plasma coagulation (no visible clots) during CPB while using ACT-based or heparin concentration–based anticoagulation monitoring, Gravlee *et al.* found that maintaining higher CPB heparin concentrations better suppressed plasma coagulation but predisposed to increased postoperative blood loss.[7] Since the primary purpose of that study was to assess the importance of subclinical plasma coagulation during CPB, the unexpected difference observed in postoperative blood loss warranted investigation with a larger patient population. If higher heparin concentrations during CPB predispose to excessive postoperative bleeding, then maintaining heparin-in-

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duced anticoagulation within a narrow range of ACT values or heparin concentrations might be clinically important. The present study sought to better define optimal heparin management by comparing ACT-based and heparin concentration-based heparin monitoring in a prospective, randomized investigation of 63 patients. In addition, measurements of antithrombin III (AT III), BTG, platelet function, and fibrinolytic activity were assessed in a subpopulation of 33 patients.

Materials and Methods

Patient Selection and Clinical Management

Sixty-three adults undergoing cardiac surgical procedures requiring CPB were studied. Preoperative testing included coagulation screening for prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count. Any adult requiring CPB was considered eligible unless any of the following exclusions applied:

1. abnormal blood coagulation by clinical history or by preoperative laboratory screening;
2. recent therapy with drugs that might affect blood coagulation during cardiac surgery, such as streptokinase, warfarin, or heparin. Patients taking aspirin received Ivy (template) bleeding times preoperatively and were included only if the Ivy bleeding time was less than 8 min;
3. repeat operative cardiac procedure;
4. once enrolled in the study, patients were excluded if postoperative mediastinal bleeding required surgical reexploration and the surgeon found surgically correctable bleeding sites.

Patients were premedicated with lorazepam, morphine sulfate, and their usual cardiac medications, and were anesthetized using high-dose opioids (fentanyl or sufentanil) supplemented with benzodiazepines and nondepolarizing muscle relaxants. CPB was conducted with a hollow-fiber membrane oxygenator (Sarns 3M, Ann Arbor, MI) and systemic hypothermia to 25–29° C. The extracorporeal circuit was primed with 1300 ml lactated Ringer's solution, 250 ml 5% albumin in normal saline solution, 12.5 g mannitol, and 10,000 USP units (U) of bovine lung heparin (Upjohn, Kalamazoo, MI). Perfusion flow rates were adjusted to maintain a mixed venous oxygen saturation greater than 70% and mean arterial pressures between 40 and 80 mmHg. Separation from CPB was accomplished after patients were rewarmed to a rectal temperature exceeding 36° C. Immediately before induction of anesthesia and several times during and after the procedure, blood samples were drawn for coagulation studies. Blood samples were obtained *via* an indwelling arterial catheter after withdrawal of 10 ml blood to clear the sampling dead space, which was approximately 1 ml.

Experimental Protocol

Patients were randomly assigned to one of two groups: group A comprised 30 patients who received an initial heparin dose of 200 U/kg and additional heparin as required to reach and maintain an ACT (Hemochron, International Technidyne, Inc., Edison, NJ) level > 400 s for CPB. Group H included 33 patients who received an initial heparin dose of 400 U/kg and additional heparin as required to reach and maintain a whole blood heparin concentration (Hepcon, HemoTec, Inc., Englewood, CO) greater than 4.0 U/ml for CPB. Both ACT and heparin concentrations were measured 5 min following heparin bolus administration and every 30 min during CPB. Protamine doses were determined by measuring blood heparin concentration and applying an algorithm based on an estimate of blood volume derived from the patient's height and weight (HemoTec, Inc.).[8] Before sampling arterial blood for any post-CPB coagulation studies, complete heparin neutralization by protamine was confirmed by measuring ACT and heparin concentration. Heparin was considered neutralized once the ACT had returned to the baseline level measured after surgical incision and the heparin concentration was less than 0.2 U/ml whole blood.

Intraoperative blood loss was assessed by measuring suction drainage into a canister from the time protamine neutralization was confirmed until the sternum was closed. After sternal closure, mediastinal blood loss *via* the indwelling tubes was drained by suction and quantified for the duration of the intraoperative period as well as hourly for the first 24 h after arrival in the intensive care unit. Heparin rebound was diagnosed if ACT increased to more than 10% above the value obtained after heparin neutralization in the operating room.[9] Once diagnosed, heparin rebound was assessed by measuring an ACT upon arrival in the intensive care unit and then every 2 h for the first 8 h. Heparin rebound was treated with 25–50-mg increments of protamine only if mediastinal drainage was judged excessive (usually $> 2\ ml \cdot kg^{-1} \cdot h^{-1}$) by the surgical house officer, who was blinded to the patient's group assignment.

The criteria for administering blood products and for the treatment of excessive bleeding and clinical coagulopathy were standardized. Red blood cells or whole blood was administered for hematocrits less than 25% following reinfusion of the washed, hemoconcentrated residual contents of the oxygenator circuit and shed blood from the surgical field. If a clinically significant coagulopathy was considered present by the amount of oozing from the surgical field, heparin rebound was assessed by measuring ACT and heparin concentration. Once heparin rebound was either excluded or treated, a blood sample for determination of platelet count, PT, APTT, and plasma fibrinogen and fibrin degradation products was obtained,

after which desmopressin (1-desamino-8-D-arginine vasopressin) 0.3 μg/kg was administered intravenously. If coagulopathy persisted after desmopressin, either a single-donor platelet pheresis or 6–12 units of pooled platelet concentrates were administered. If coagulopathy persisted and results of the coagulation studies were not yet available, fresh frozen plasma (2–4 units) was administered. If laboratory results had returned, components were administered guided by laboratory coagulation abnormalities. This protocol was also applied in the postoperative period, except that coagulopathy was then diagnosed by mediastinal drainage exceeding 2 $ml \cdot kg^{-1} \cdot h^{-1}$.

Coagulation Testing

The ACT method used 2 ml of celite-activated blood placed in a Hemochron 400 or 800 device (International Technidyne, Inc.). Heparin concentration was measured by automated protamine titration (HemoTec, Inc.). PT and APTT samples were collected in citrated tubes and centrifuged for plasma separation, and the tests were performed on an MLA Electra 700 (Medical Laboratory Automation, Pleasantville, NY) automated photooptical clot detector (normal PT 11.0–13.4 s, normal APTT 24–31 s). Plasma fibrinogen was assayed by clottable protein present in a diluted plasma sample to which excess thrombin (Dade Diagnostics, Inc., Miami, FL) was added, producing a normal plasma fibrinogen range of 180–363 mg/dl. Fibrin degradation products were measured on serum by latex agglutination using particles coated with antibodies to fibrinogen and fibrin degradation products (normal concentration 0–8 μg/ml, with higher values quantified by serial dilutions). Platelet counts were performed on EDTA-anticoagulated samples with a Coulter Counter S-plus (Coulter Electronics, Hialeah, FL) and confirmed by phase-contrast microscopy.

To define the mechanism of any possible bleeding outcome differences between groups, platelet aggregation was measured in response to adenosine diphosphate (ADP) concentrations of 2, 5, and 10 μM; thrombin 1 unit/ml; and collagen concentrations of 2, 5, and 10 μg/ml in the last 33 patients studied (15 patients in group A, 18 patients in group H). These tests were performed on citrated samples from which platelet-rich plasma was obtained by centrifugation and then tested on a luminescence aggregometer (Chrono-Log Corp., Havertown, PA) at 37° C while stirred at 1,100 rpm. Normal values for percent aggregation were 50–60% for ADP 10 μM, 60–80% for thrombin 1 unit/ml, and 50–70% for collagen 10 μg/ml.

Assays were also performed for plasmin (total free protease), α-2-antiplasmin, plasminogen, and AT III, on the last 33 patients studied. Fibrinolytic components were assayed using enzyme-linked fibrinolytic techniques previously described (Elcatech, Inc., Winston-Salem, NC).[10] AT III was measured by a modification of the enzyme-linked coagulation assay (Elcatech, Inc., Winston-Salem, NC).[11] The normal activity ranges for AT III, α-2 antiplasmin, and plasminogen are 80–120%, and plasmin is normally undetectable in plasma. BTG was also measured by radioimmunoassay (Amersham/Searle, Inc., Arlington Heights, IL). The normal range for BTG is 0–25 ng/ml on plasma anticoagulated with citrate.

Statistical Analysis

The study was designed as a two-stage trial to assess differences in blood loss in patients randomly assigned to lower or higher doses of heparin for CPB. Assuming standard deviations comparable to those previously reported,[7] 25 patients were needed in each group (13 first stage, 12 second stage) to ensure 90% power for detecting a one standard deviation (SD) difference in 24-h blood loss at the 5% two-sided level of significance. This design minimized the average of the expected sample sizes under the null and alternative hypotheses. Because the actual sample sizes exceeded this projection, the actual power for detecting the specified difference was 95%. The first statistical analysis of our primary outcome (24-h blood loss) occurred after completing 30 patients. At that point, 24-h blood loss was higher in group H and approached statistical significance ($P = 0.13$). The null hypothesis could neither be accepted nor rejected, so the second stage (33 patients) was initiated. The studies of platelet aggregation and fibrinolytic activity were added to the second stage. Before performing statistical analysis, plasma levels of plasminogen, plasmin, α-2 antiplasmin, and AT III were adjusted for hematocrit fraction. Platelet aggregation studies and BTG levels were adjusted for platelet count before statistical analysis.

Differences between groups in pretreatment characteristics were assessed using Fisher exact tests for categorical data and Wilcoxon rank-sum tests for continuous data. Analysis of covariance was used to assess group differences in 8- and 24-h blood loss. Changes over time in individual parameters were assessed by repeated-measures analysis of variance (ANOVA). When the time effect was significant ($P < 0.05$), individual intragroup comparisons with the preinduction levels were performed with linear contrasts using the pooled estimate of the mean squared error, with $P < 0.05$ considered significant. Regression analysis (Spearman's rank correlation) was performed to determine if any biochemical markers or laboratory tests were significantly associated with postoperative blood loss. The two groups were combined for this latter analysis.

Results

Two patients in group H were excluded from statistical analysis because surgical bleeding was discovered at mediastinal reexploration, leaving 31 patients in group H

and 30 patients in group A. Table 1 shows demographic characteristics of the two patient groups. None of the differences was statistically significant except those directly related to the study design (mean CPB ACT heparin concentration, total heparin dose, and protamine dose). Table 2 compares the amount of blood loss, homologous transfusion requirements, and the results of traditional coagulation screening tests by group. Between laboratory confirmation of heparin neutralization and sternal closure, intraoperative blood loss collected by suction was always less than 50 ml, so this quantity was not subjected to statistical analysis. Differences in chest drainage and in homologous blood product administration were not significant. Group H had significantly longer PT and APTT after heparin neutralization. Twenty-four hours after surgery, the PT and APTT were normal in group H, leaving no significant difference in coagulation studies between the groups. Aside from this, the only change in these parameters occurring during the first postoperative day was that fibrinogen levels increased to a mean of approximately 340 mg/dl in both groups.

Figure 1 shows the platelet functional parameters and plasma BTG levels over time for each group. Platelet aggregation in response to adenosine diphosphate was often below normal before anesthetic induction, although platelet responses to thrombin and collagen were normal at that time. Over the course of surgery and the first postoperative day, ADP-induced aggregation changed little and never differed significantly from the preinduction values in either group. Thrombin-induced platelet aggregation was obliterated in both groups during anticoagulation for CPB but returned to normal after protamine was given. Collagen-induced platelet aggregation was more impaired in group H than in group A during CPB, with this difference reaching significance during rewarming. After protamine, collagen-induced platelet aggregation was less impaired in both groups, and returned to normal 24 h after surgery. BTG levels increased from slightly to markedly elevated in both groups, peaking during CPB rewarming and after protamine. During CPB rewarming, group H had significantly higher BTG levels than did group A. Figure 1 also plots platelet counts over time; these did not differ between groups at any measurement interval.

Figure 2 plots markers of the fibrinolytic pathway over time by group. Plasmin levels were increased during CPB rewarming and following protamine but were otherwise barely detectable and did not differ between groups. Plasminogen levels decreased significantly at the onset of CPB even after correcting for hemodilution, remained at approximately the same reduced level at all subsequent sampling times, and did not differ between groups. α-2 Antiplasmin levels decreased progressively over the course of surgery, reaching significance (after adjusting for hemodilution) only after protamine, but did not differ between groups. AT III levels are shown in figure 3. These diminished with the onset of CPB and remained low for the remainder of the 24-h period. During CPB rewarming, AT III levels were significantly lower in group H than in group A.

Table 3 shows the incidence of heparin rebound by group, the incidence of heparin rebound requiring treat-

TABLE 1. Selected Descriptive Statistics

	Group A (n = 30)	Group H (n = 31)
Age (yr)	60 ± 11	58 ± 14
Weight (kg)	79 ± 18	77 ± 16
Sex (% male)	81	67
Operation (number of procedures)		
CABG	23	24
Valve repair or replacement	4	5
CABG plus valve, LV aneurysm, or AICD	3	1
Interruption of bundle of Kent		1
Chronic medications (% taking)		
Calcium blocker	68	73
Nitrates	74	57
β-adrenergic blocker	42	40
Duration of CPB (min)	108 ± 41	121 ± 37
Baseline ACT (s)	135 ± 14	134 ± 14
Mean CPB ACT (s)	499 ± 58	748 ± 193*
Mean CPB heparin concentration (U/ml)	3.2 ± 0.3	4.3 ± 0.3*
Total heparin dose (U × 10^2)	280 ± 48	570 ± 107*
Protamine dose (mg)†	193 ± 55	256 ± 61*

Mean ± SD where appropriate.

CABG = coronary artery bypass grafts; LV = left ventricular; AICD = automated implantable converter/defibrillator; CPB = cardiopulmonary bypass; ACT = activated clotting time; U = USP units.

* $P < 0.05$, compared to group A.

† Excludes protamine administered postoperatively for heparin rebound.

TABLE 2. Hematologic Comparisons Following CPB

	Group A (n = 30)	Group H (n = 31)	P
8-h chest drainage (ml)	511 ± 230	573 ± 322	0.75
24-h chest drainage (ml)	901 ± 414	1035 ± 501	0.24
Homologous RBCs or WB given*	13	16	0.45
Homologous platelets or FFP given*	4	8	0.21
PT (s)	14.5 ± 0.9	15.2 ± 1.3	0.02
APTT (s)	29.8 ± 5.0	43.6 ± 31.2	0.0002
ACT (s)	129 ± 13	131 ± 25	0.87
Fibrinogen (mg/dl)	185 ± 48	192 ± 73	0.62
Platelet count (×$10^3/\mu$l)	145 ± 56	143 ± 33	0.82
Median FDP titer†	8–32	8–32	0.71

Mean ± SD where appropriate. Laboratory values were taken immediately after laboratory confirmation of heparin neutralization following CPB. PT = prothrombin time; APTT = activated partial thromboplastin time; ACT = activated clotting time; FDP = fibrin degradation products.

* Number of patients receiving product.

† 8–32 represents positive latex agglutination in the 1/8–1/32 dilution range.

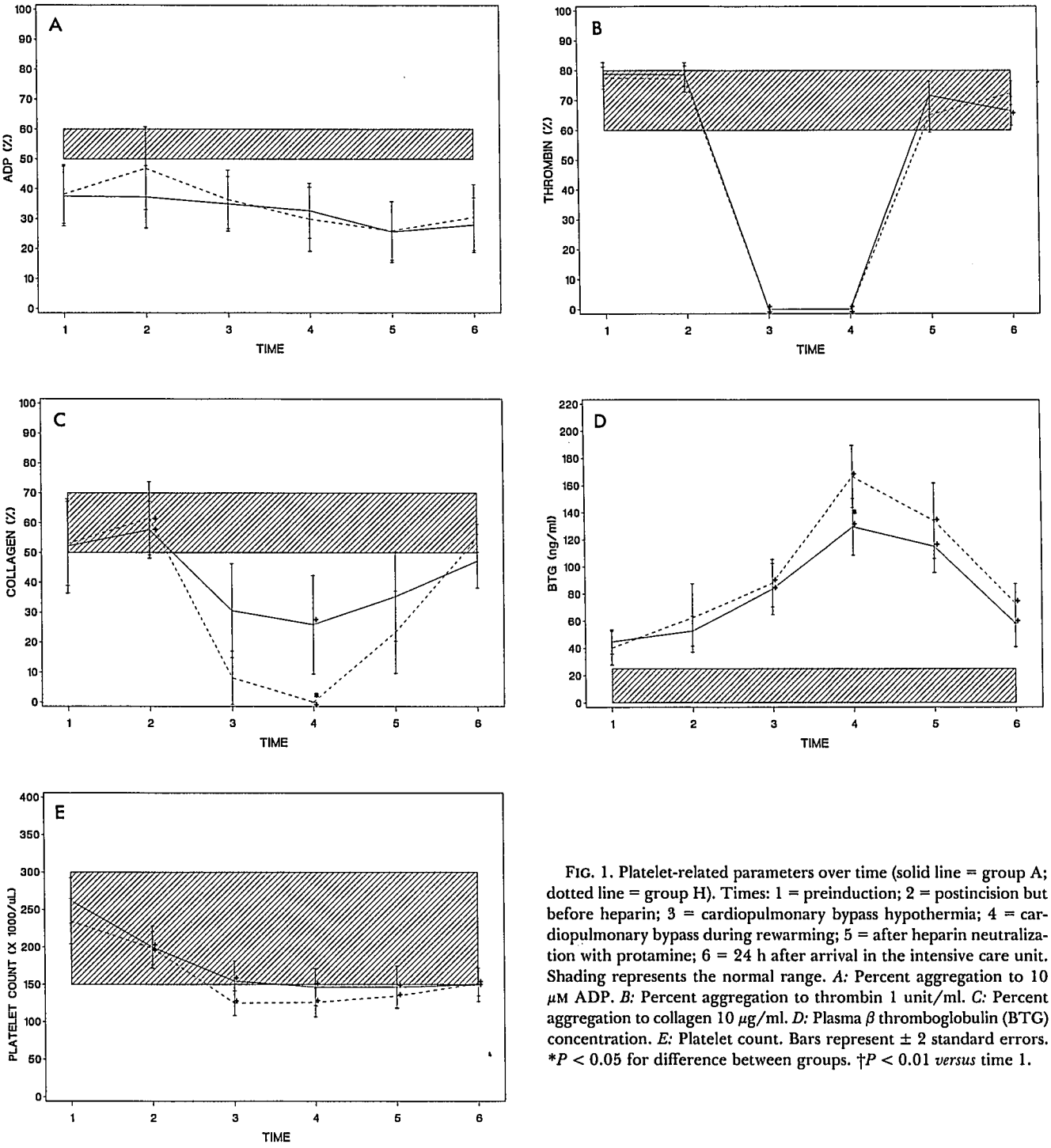

FIG. 1. Platelet-related parameters over time (solid line = group A; dotted line = group H). Times: 1 = preinduction; 2 = postincision but before heparin; 3 = cardiopulmonary bypass hypothermia; 4 = cardiopulmonary bypass during rewarming; 5 = after heparin neutralization with protamine; 6 = 24 h after arrival in the intensive care unit. Shading represents the normal range. *A:* Percent aggregation to 10 μM ADP. *B:* Percent aggregation to thrombin 1 unit/ml. *C:* Percent aggregation to collagen 10 μg/ml. *D:* Plasma β thromboglobulin (BTG) concentration. *E:* Platelet count. Bars represent ± 2 standard errors. *$P < 0.05$ for difference between groups. †$P < 0.01$ *versus* time 1.

ment with additional protamine, and the 24-h blood loss in patients who experienced heparin rebound. Although heparin rebound occurred more frequently in group H ($P = 0.005$), this did not influence postoperative mediastinal drainage. However, heparin rebound required postoperative increments of protamine in 1 of 30 patients in group A and in 8 of 31 patients in group H ($P = 0.01$). This treatment may have influenced 24-h blood loss in group H, because the mediastinal drainage rate almost always decreased following the supplemental protamine dose. Postoperative ACT values did not differ significantly between groups A and H at any measurement interval.

None of the parameters reported in table 2 or in figures 1–3 correlated significantly with 24-h mediastinal drain-

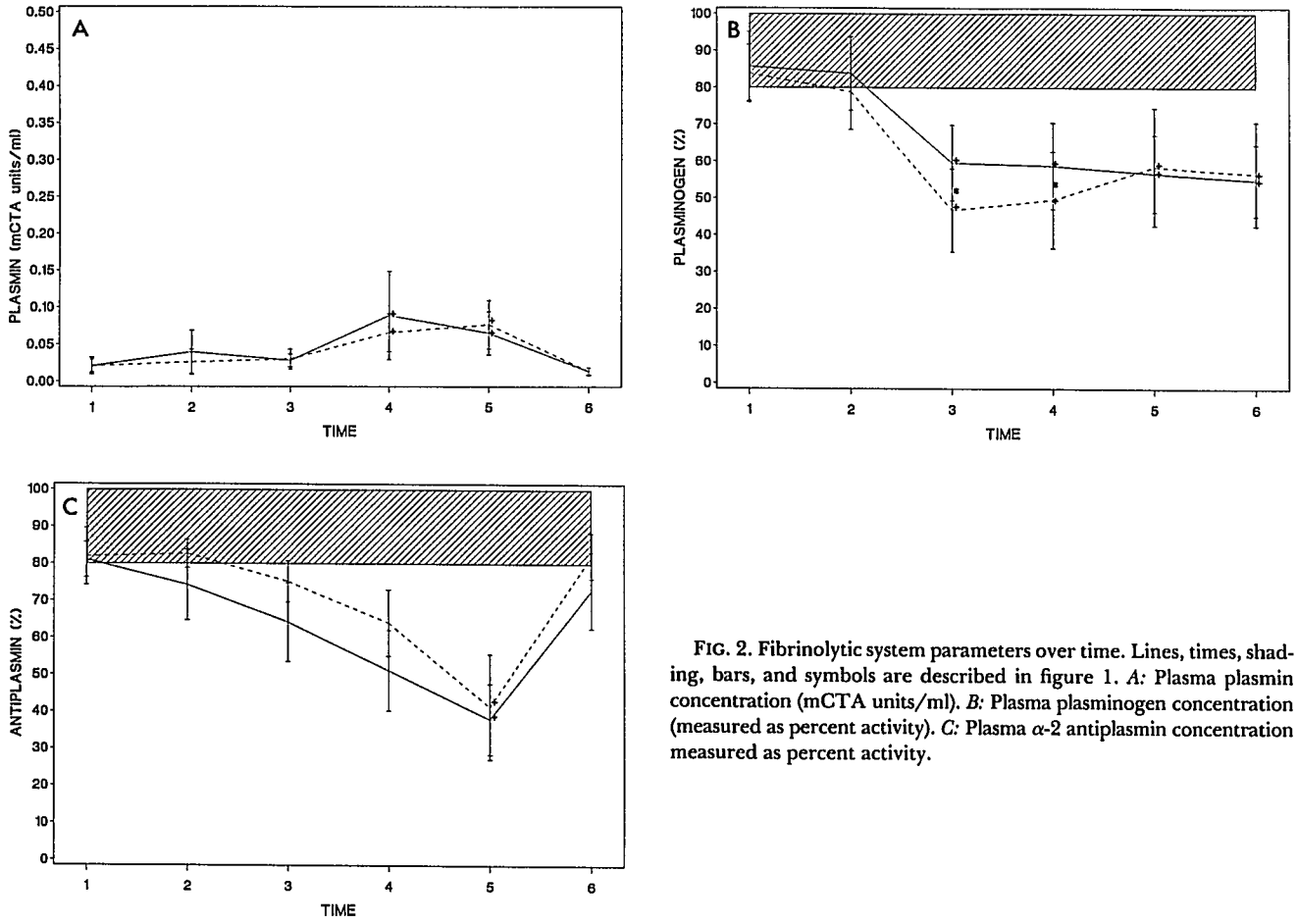

FIG. 2. Fibrinolytic system parameters over time. Lines, times, shading, bars, and symbols are described in figure 1. *A:* Plasma plasmin concentration (mCTA units/ml). *B:* Plasma plasminogen concentration (measured as percent activity). *C:* Plasma α-2 antiplasmin concentration measured as percent activity.

age. Total protamine dose in the operating room did not correlate with 8- or 24-h mediastinal drainage.

Discussion

Postoperative Bleeding

Predictors of excessive postoperative bleeding following cardiac surgery prove difficult to identify. Using standard coagulation tests as well as a Duke's (earlobe) bleeding time, Gravlee *et al.* were unable to identify either laboratory tests or patient parameters (age, sex, type of surgery, CPB duration, *etc.*) that predicted postoperative mediastinal drainage.[12] Harker *et al.*[13] found that markedly prolonged Ivy bleeding times correctly identified patients who bled excessively, and Spiess *et al.*[14] correlated thromboelastographic abnormalities with postoperative bleeding.

In a smaller study investigating subclinical plasma coagulation activity during CPB, Gravlee and colleagues found higher postoperative blood loss in patients whose anticoagulation was managed as in group H when compared to patients managed as in group A of the present study.[7] In the group comparable to group H, this occurred despite biochemical evidence of better suppression of plasma coagulation activity, as determined by measuring fibrinopeptide A levels. Enhanced suppression of subclinical coagulation was observed only during the hypother-

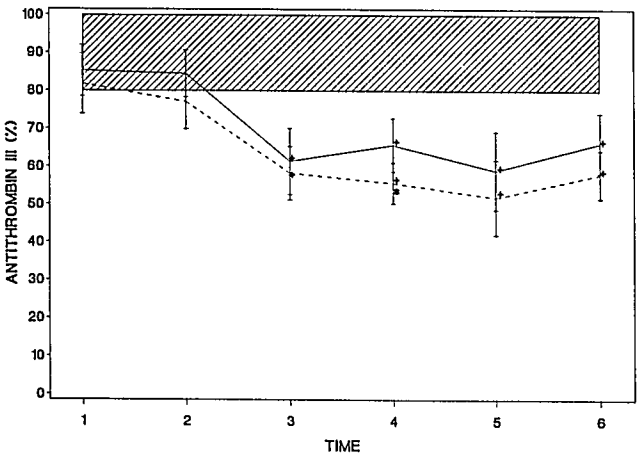

FIG. 3. Plasma antithrombin III concentration over time measured as percent activity. Lines, times, shading, bars, and symbols are described in figure 1.

TABLE 3. Postoperative Heparin Rebound Incidence, Treatment, and Blood Loss

	Group A (n = 30)	Group H (n = 31)	P
Heparin rebound*	16	26	0.005
24-h blood loss (ml)	791 ± 347	991 ± 489	0.17
Protamine treatment†	1	8	0.01
24-h blood loss (ml)	700	1529 ± 446	0.12

Mean ± SD where appropriate.

* Number of patients meeting laboratory criteria for heparin rebound (activated clotting time increase ≥ 10% from postprotamine value or activated partial thromboplastin time > 1.5 × control values).

† Number of patients meeting laboratory criteria for heparin rebound and demonstrating excessive mediastinal drainage.

mic phase of CPB and was significantly associated with the higher blood heparin concentrations present in that group. Based upon earlier work performed in primates by Young *et al.*, one might expect that higher fibrinopeptide A levels during CPB would reflect a greater propensity to consume coagulation factors and platelets and thus predispose to a coagulopathy after CPB.[15] The present study infers that this is not the case, and our previous study did not find an independent relationship between CPB fibrinopeptide A levels and postoperative blood loss.[7] The present findings strongly suggest that, when ACT values during CPB exceed 400 s, the amount of heparin administered and the extent of ACT prolongation do not influence postoperative bleeding when a consistent protamine neutralization technique is used. Previous findings to the contrary may have resulted from random variation or from less aggressive diagnosis and treatment of postoperative heparin rebound.[7] Metz and Keats recently used standardized heparin dosing and retrospectively examined ACT values that were taken blindly during CPB in 193 patients.[16] They did not identify a relationship between ACT and postoperative bleeding, which is consistent with the present findings.

Twenty-one patients previously studied manifested smaller 24-h blood losses in the two groups analogous to group A (659 ± 270 ml and 738 ± 299 ml before *vs.* 901 ± 414 ml presently) than in the group analogous to group H (1104 ± 197 ml before *vs.* 1035 ± 501 ml presently).[7] The present study was therefore designed to detect a 1-SD difference with 90% confidence assuming that the SDs for 24-h blood loss within each group would approximate 250 ml. Because the actual SD for 24-h blood loss in the present study was almost twice that large, each group would have required 96 patients to detect a 200–250 ml (0.5 × SD) difference in 24-h blood loss with 90% power. The present study would detect a 0.5 × SD difference with approximately 50% power. No explanation arises for the increased variance in 24-h blood loss in the current study population, and we elected not to continue the study because it seemed unlikely that clinically significant differences in blood loss would develop with a larger population even if statistical significance were attained.

Heparin rebound was a common and usually clinically insignificant diagnosis, but table 3 indicates that the occurrence of clinically significant heparin rebound was more likely in group H. Higher CPB heparin doses are therefore more likely to produce clinically significant heparin rebound requiring supplemental protamine.

Other studies have related ACT-based heparin management to decreases in postoperative bleeding when compared to standardized heparin dosing protocols based on patient size and cumulative time on CPB.[17–19] This finding has not been universal, however.[20–24] Comparing an ACT-based protocol to a time-related heparin dosing protocol bears some similarity to the present comparison between group A and group H, because time-related heparin dosing schemes have most often resulted in higher total heparin doses, which also was the case in group H.[17–21,24,25] Previous studies comparing ACT-based management with time-related heparin dosing could have been biased by the simultaneous variation of the heparin and protamine dosing methods.[17–24] Guffin *et al.* showed that higher protamine doses caused greater postoperative blood loss when the heparin dosing method was constant.[26] In most studies comparing ACT-based to time-related heparin dosing, the protamine-to-heparin dose ratio was higher in the time-related heparin dosing group.[18,20–24] The present study isolated heparin dosing as the varied parameter while using the same method in both groups to determine protamine dose. The absence of a difference in postoperative blood loss suggests the need to confirm the findings of Guffin *et al.*[26] to determine if differences that other authors have found between ACT-based and time-related heparin dosing are more closely related to differences in protamine dosing than to differences in heparin dosing or monitoring.

COAGULATION TESTS

A previous study of 881 consecutive patients did not support any predictive value for traditional coagulation tests such as platelet count, PT, APTT, fibrinogen, and fibrin degradation products.[12] The present study, though much smaller, produced similar findings. The higher post-CPB APTT values in group H may reflect either less complete heparin neutralization or early heparin rebound (15–30 min after finding undetectable heparin concentrations in whole blood) in those patients, because the APTT is more sensitive to low blood concentrations of heparin than is the ACT.[27,28] However, neither the elevated APTT nor the occurrence of heparin rebound was associated with increased postoperative bleeding.

Except for ADP-induced aggregation, platelet aggregation diminished during and after CPB and increased toward preoperative values during the first postoperative

day. The subnormal ADP-induced platelet aggregation that was present before anesthetic induction possibly derives from effects of preoperative medications such as calcium blockers, nitrates, and β blockers.[29] Thrombin-induced platelet aggregation was normal except during systemic heparinization, which completely suppressed this response, as expected. The return to normal thrombin-induced platelet aggregation after protamine administration in both groups may contribute importantly to the absence of a bleeding difference between the two study groups, because thrombin is a potent physiologic stimulant of platelet aggregation that bypasses the arachidonic acid pathway initiated by ADP and epinephrine.[30] Thus, in the presence of an adequate thrombin response and an unrestricted physiologic supply of thrombin, platelet aggregation response to ADP, epinephrine, and collagen may have little clinical importance. Greater collagen-mediated platelet aggregation depression in group H during CPB suggests a dose–response relationship to heparin, which is consistent with the previous observation that heparin depresses collagen-mediated platelet activation.[31] The return toward normal of the platelet aggregation response to collagen after protamine administration is consistent with two previous reports.[13,31] The present perioperative study appears to show better preservation of platelet aggregation responses to ADP and collagen than those found by previous investigators, except for the collagen response in group H.[13,31] Some uncertainty remains because of incomplete data reporting[13] or different units of measurement.[31] The previous studies provide insufficient heparin dosing information to speculate whether differences in heparin management possibly affect platelet function tests. It is well accepted that both CPB and heparin impair platelet function,[13,32] and the present investigation enhances knowledge about heparin's role in post-CPB platelet dysfunction. Under the conditions observed, this role appears fairly minor.

The slightly elevated BTG levels that were present even before anesthetic induction possibly reflected systemic activation of platelets in patients with atherosclerotic or valvular heart disease.[33,34] Higher BTG levels in group H at the end of CPB suggest greater platelet activation from higher blood heparin concentrations, which is consistent with previous observations.[32] The striking elevation in BTG as CPB progresses probably indicates a cumulative response to sustained platelet activation, because the normal elimination half-life of BTG is approximately 100 min,[34] and it would be reasonable to speculate that hypothermic CPB prolongs the half-life. The moderately elevated BTG levels at 24 h after CPB suggest a continuing platelet activation response less intense than that observed during CPB. When compared to the previous study of Harker *et al.*,[13] the present study finds substantially lower BTG levels during CPB and after protamine in both groups. Harker *et al.*[13] reported mean BTG levels exceeding 700 ng/ml at periods comparable to times 4 and 5 in figure 1D.

AT III levels during CPB diminished beyond what would be expected from hemodilution alone. After rewarming during CPB, the AT III levels were significantly lower in group H than in group A. The continued depression of AT III into the postoperative period suggests the possibility of a clinically significant AT III deficiency following CPB, as chronic AT III levels similar to those observed in group H (40–60% activity) have been associated with an increased risk of intravascular thrombosis.[35] Judging from mediastinal blood loss figures, however, patients did not appear to experience a clinically significant hypercoagulable state on the first postoperative day.

Biochemical markers of fibrinolysis show activation of fibrinolytic pathways during and immediately following CPB. The nadir in α-2 antiplasmin levels after heparin neutralization is especially striking. Sustained plasmin-mediated fibrinolysis tends to deplete α-2 antiplasmin, which may explain these findings. Plasminogen levels differed from the α-2 antiplasmin pattern by tending to plateau at the reduced level attained early in the course of CPB. Our findings differ from those of Stibbe *et al.*, who suggested that enhanced fibrinolytic activity during CPB derives from extrinsic plasminogen activator.[36] The latter type of activation occurs at sites of fibrin deposition, tending not to elevate plasma plasmin activity or deplete α-2 antiplasmin. Our findings are more consistent with those of Harker *et al.*,[13] although the use of different markers of fibrinolysis complicates comparison.

Summary and Clinical Implications

The present investigation suggests that heparin dosing and the type of heparin monitoring for CPB have little effect on post-CPB bleeding and blood coagulation. Activation of platelets and the fibrinolytic pathway and some reduction in platelet function occur with two different CPB anticoagulation management protocols that result in markedly different heparin doses. Although the particular style of heparin management or monitoring did not appear to influence postoperative bleeding, this finding may have been influenced by aggressive treatment of heparin rebound when it was associated with excessive bleeding, which occurred more frequently in the group receiving higher CPB heparin doses. Some measurement of heparin effect (*e.g.*, ACT) is probably warranted to ensure that adequate heparin has been given and that the patient does not have clinically important resistance to heparin-induced anticoagulation. Beyond that, maintenance of a particular blood heparin concentration during CPB appears neither advantageous nor disadvantageous when compared to maintaining a particular ACT range. Defining the critical ACT or heparin level for safe conduct of CPB remains elusive,[7,16] because ethical considerations

preclude making this determination in humans. Further studies are needed to attempt to isolate the possible influence of protamine dosing on coagulation and bleeding following CPB.

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