

# Correlation of perioperative platelet function and coagulation tests with bleeding after cardiopulmonary bypass surgery

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The authors evaluated the correlation of post-cardiopulmonary bypass surgery bleeding, measured as 24-hour chest tube output/kilogram body weight, with platelet function tests using glass bead adhesion and Thrombelastograph Platelet Mapping (Haemoscope Corporation, Niles, Ill); coagulation tests; patient characteristics; surgery parameters; and visual assessment of surgical field bleeding before closure as not bleeding (code 1), oozing (code 2), and excessive bleeding (code 3). All platelet function and coagulation tests indicated significant dysfunction 15 minutes after protamine neutralization of heparin. With the exception of glass bead adherence, these assays indicated poor recovery of function 1 hour postoperatively. By multiple regression, the most significant predictors of postoperative bleeding were a low body mass index (BMI) ( $P < 0.0001$ ), lowest core body temperature ( $P = 0.0006$ ), and cross clamp time ( $P < 0.0001$ ). Low core temperature was significantly ( $P < 0.0001$ ) correlated with cross clamp time, which the authors believe is the most likely cause of coagulation and platelet dysfunction. None of the platelet function tests significantly correlated with bleeding. Looking at the highest quartile of chest tube output patients ( $n = 19$ ) versus the upper and lower 50th percentile of coagulation and platelet function, bleeding could be explained for 11 patients by BMI plus surgery parameters along with coagulation and/or platelet dysfunction. In three cases without negative surgery parameters, coagulation dysfunction was observed. The remaining five cases did not give a clear indication of which parameters were primarily responsible for the bleeding. (J Lab Clin Med 2006; 147:197-204)

**Abbreviations:** ACT = activated clotting time; ADP = adenosine diphosphate; ANOVA = analysis of variance; BMI = body mass index; INR = international normalized ratio; MA = maximum amplitude; MAKH = TEG MA with kaolin and heparinase; NSAID = nonsteroidal anti-inflammatory drug; PT = prothrombin time; PTT = partial thromboplastin time

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Platelet dysfunction and coagulation changes after bypass surgery and their association with microvascular bleeding have been well documented.<sup>1,2</sup> There have been attempts to correlate the degree of platelet dysfunction as measured by various point of care tests with the occurrence of postoperative bleeding.<sup>3-5</sup> A recent study suggested that postoperative bleeding correlates with platelet dysfunction as measured by glass bead adherence after cases with prolonged coagulation times have been excluded.<sup>6</sup> The utility of various coagulation tests to identify the cause of postoperative bleeding has also been examined.<sup>7,8</sup> The purpose of this study was to evaluate platelet mapping with the Thrombelastograph (Haemoscope Corporation, Niles, Ill) and glass bead adherence as methods of monitoring platelet dysfunction postoperatively and to determine whether these tests correlated with postoperative bleeding in cases not explained by prolonged coagulation times.

## METHODS

The institutional review board of the University of Tennessee Medical Center in Knoxville approved this research protocol as complying with the declaration of Helsinki. A total of 75 patients undergoing elective cardiopulmonary bypass (CPB) and giving informed consent were enrolled over a 1-year period. The authors excluded patients who were on prophylactic heparin, antiplatelet drugs, or had a history of clotting/bleeding. Patients are routinely instructed to discontinue antiplatelet drugs such as clopidogrel and NSAID for at least 10 days before surgery and are put back on antiplatelet therapy no sooner than 24 hours postoperatively. The average age of this patient population was 66 years, ranging from 40 to 83 years and included 25 women. The mean BMI was 30.9, ranging from 20.5 to 46.3 kg/m<sup>2</sup>. There were 50 bypasses, including 1 redo, 6 valve replacements, and 19 patients having multiple procedures. The mean cross-clamp time was 71 minutes, ranging from 17 to 198 minutes. Average extracorporeal circulation time was 119 minutes, ranging from 52 to 271 minutes. Core body temperatures were taken from the bladder and averaged 32.2°C ranging from 27 to 35.4°C. End temperatures averaged 36°C ranging from 33.9 to 37.9°C. At the end of the surgery, before closing, an evaluation of the surgical field was made by both surgeon and anesthesiologist. Bleeding was assessed by agreement between the observers as not bleeding (coded 1), oozing (coded 2), and excessive bleeding (coded 3). Postoperative bleeding was additionally assessed by measuring 24-hour chest tube output milliliter per kilogram body weight.

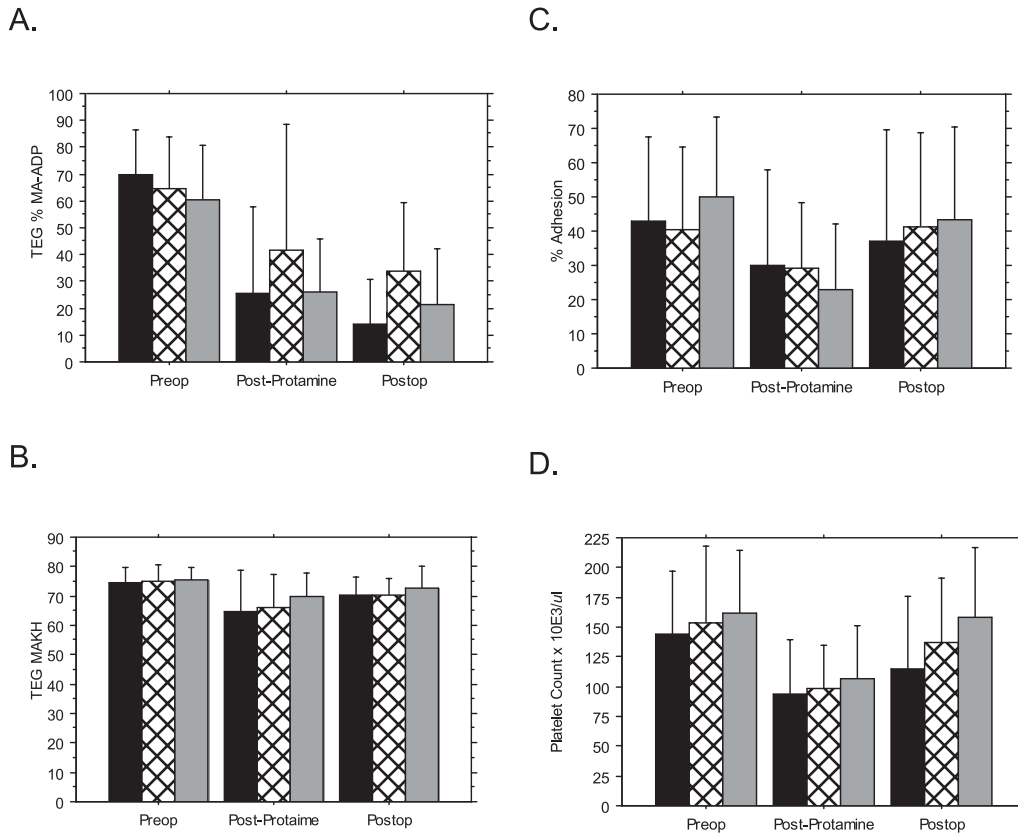
No modifications to our clinical anesthesia care were made for this study. Anesthesia was induced with etomidate, midazolam, fentanyl, and vecuronium and maintained by intravenous narcotics, volatile agent, and vecuronium. Blood samples were taken from the arterial line in the operating room before heparin administration, 15 minutes after heparin reversal with protamine and 1 hour post-operation. At each blood draw, 10 mL of blood and intravenous fluid were drawn and

discarded. Using a new syringe, 30 mL of blood was drawn into heparin anticoagulated tubes (Becton Dickinson Vacutainer Systems, Franklin Lakes, NJ, 14.7 units heparin/milliliter final concentration). Initial heparin dosing (300 units/kg) followed a standard procedure, guided by the Hepcon HMS (Medtronic Inc., Minneapolis, Minn), with a kaolin ACT target of >450 seconds for the heparin dose response cartridge. Heparin maintenance was guided by six channel heparin-protamine-titration cartridges. Normothermic to mildly hypothermic CPB (bladder temperatures averaged 32.2 ± 2.8°C, standard deviation) was carried out with non-heparin-coated systems. Aprotinin is routinely used in CPB procedures at this institution. The pump primed with 200 mL of aprotinin (10,000 kiu/mL). Each patient was initially given a bolus of 100-mL aprotinin, and infusion was continued at the rate of 50 mL/h during CPB. Additional heparin was administered to maintain the hepcon HMS kaolin ACT greater than 450 seconds. Vasoactive and inotropic drugs were administered as necessary during the procedures. Protamine reversal at the end of bypass was monitored by Hepcon HMS protamine titration cartridges.

Platelet function assays were started within 30 minutes of drawing the blood. Patients were assayed preoperatively, 15 minutes after protamine reversal, and 1 hour post-operation. Platelet Mapping was done with the Thrombelastograph, with 2-μM ADP as the platelet activator. The assay was performed with 350-μL heparinized whole blood clotted with a 10-μL mixture of reptilase-factor XIIIa plus 10-μL ADP stock solution, provided by the manufacturer. The MA was determined from the TEG trace. These assays were done with and without 5-μg/mL d-phenylalanine-proline-arginine-chloromethylketone (PPACK) to determine whether the MA0 (the MA obtained without platelet activator) was stable (with PPACK < 10-mm difference from the standard MA0). This occurred in 7 out of the 75 preoperative samples, none of the post-protamine samples, and 1 sample postoperative (not observed in the preoperative sample of the same patient). In addition, an MAKH was obtained to give the maximal response with thrombin generation in the presence of kaolin and heparinase. The percent MA response to ADP (TEG %MA-ADP) was determined by the following formula:

$$\%MA-ADP = \frac{([MA-ADP - MA0] / [MAKH - MA0]) * 100\%}{}$$

Platelet adhesion on glass beads was assayed essentially as described,<sup>6</sup> except 8-mL samples were run through the column within 30 minutes instead of 1 minute. This blood was additionally anticoagulated with 5-μg/mL PPACK to preclude thrombin generation and platelet activation during this delay. Comparison studies with normal donor blood showed no significant effect of this delay compared with immediately assayed samples. Blood was placed in a 20-mL syringe and flowed by a Harvard infusion pump set at 6.75 mL/minute through a 12-cm × 6.4-mm internal diameter tygon tubing column clamped to the syringe and containing 4-g glass beads (150–212 μm, acid washed, Sigma-Aldrich, St. Louis, Miss) retained by 105-μm polypropylene mesh clamped to the distal end. The percent platelet adherence was calculated by dividing the average platelet counts of the first 4 × 1-mL



**Fig 1.** Perioperative changes between excessive bleeders (solid black bars), oozing (hatched bars), and not bleeding (gray bars) in (A) TEG %MA-ADP, (B) TEG MAKH, (C) glass bead % platelet adhesion, and (D) platelet count. Errors bars indicate standard deviations.

aliquots collected after flow through the glass bead column by the pre-column platelet count and then multiplying by 100%. Platelet counts were determined on a PlateletWorks instrument (Helena Labs, Beaumont, Tex).

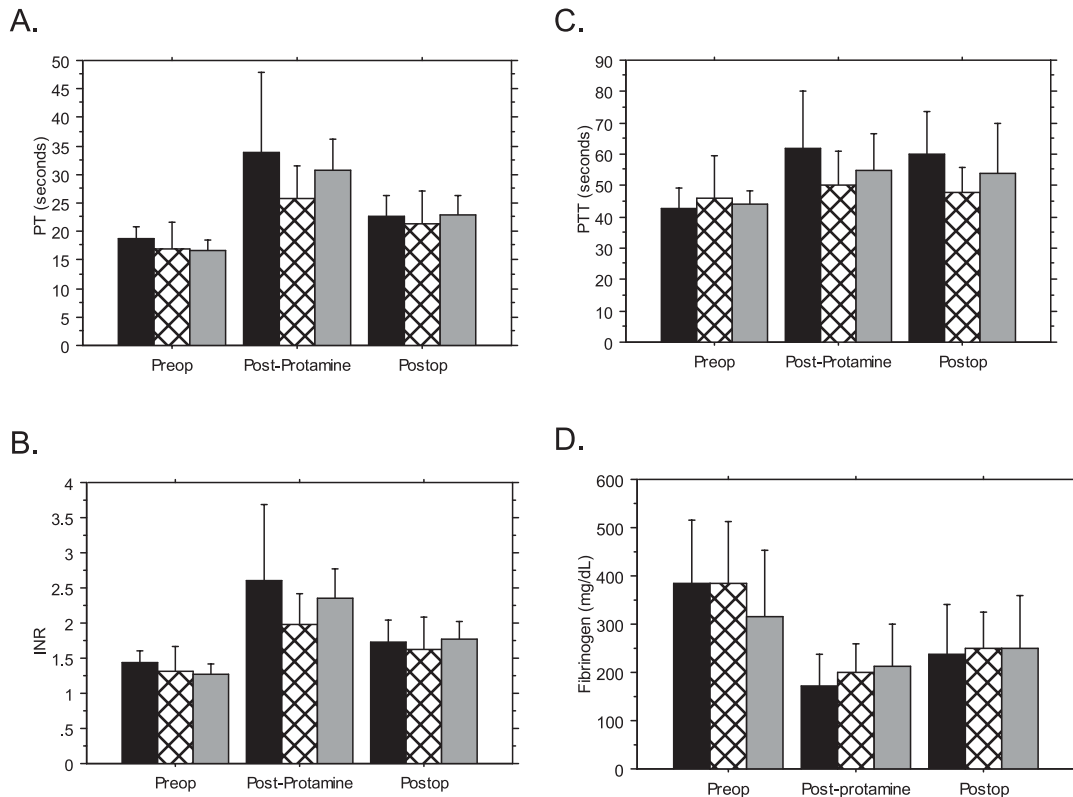
Coagulation tests were the PT with a calculated INR and PTT performed on the Hemochron Jr. Signature (International Technidyne, Edison, NJ). The patients received standard care using the Hepcon device without any impact from results of the other assays. Plasma was prepared from the PPACK and heparinized blood by centrifugation twice for 15 minutes at  $1000 \times g$ , and samples were immediately frozen at  $-70^{\circ}\text{C}$  until assayed. Fibrinogen levels were determined with a radial immunodiffusion kit (The Binding Site Ltd, Birmingham, UK). D-dimer levels were determined with a semiquantitative BioPool latex agglutination test (Trinity Biotech Plc, Wicklow, Ireland). Results were coded for statistical comparison with  $<250 \mu\text{g/mL}$  (code 1),  $250\text{--}500 \mu\text{g/mL}$  (code 2),  $500\text{--}1000 \mu\text{g/mL}$  (code 3),  $1000\text{--}2000 \mu\text{g/mL}$  (code 4), and  $>2000 \mu\text{g/mL}$  (code 5).

Statistical analysis was done using Statview software. Two-way repeated measures ANOVA was used to test for platelet and coagulation assay differences among the three visually assessed bleeding categories and three sampling times. Nonparametric chi-square testing was done for categorical data and Spearman rank testing for correlation of

coded visual bleeding to chest tube drainage/kilogram. Sequential multiple regression analysis was used to determine which patient characteristics and assay parameters were related to chest tube drainage.

## RESULTS

TEG %MA-ADP (Fig 1, A) or MAKH (Fig 1, B) showed a significant loss of platelet function at the post-protamine time point (repeated-measures ANOVA,  $P < 0.0001$ ). The TEG MAKH did not completely recover by 1 hour post-operation, and the TEG %MA-ADP response continued to decline compared with the post-protamine sample ( $P = 0.046$ ). A similar significant ( $P < 0.0001$ ) loss of platelet adhesion was observed post-protamine (Fig 1, C), but there was significant (compared with post-protamine,  $P < 0.0001$ ) recovery of this parameter by 1 hour post-operation with no significant difference from the preoperative adhesion. There were no significant differences ( $P > 0.14$ ) on any of these platelet function tests 1 hour post-operation among the three visual assessments of bleeding. Platelet counts per microliter were also evaluated as shown in Fig 1, D. There were significant drops from preoperative platelet counts both post-protamine ( $P$



**Fig 2.** Perioperative changes between excessive bleeders (solid black bars), oozing (hatched bars), and not bleeding (gray bars) in (A) PT, (B) INR, (C) PTT, and (D) fibrinogen levels. Error bars indicate standard deviations.

< 0.0001) and 1 hour post-operation ( $P = 0.006$ ). Again there were no significant differences ( $P > 0.14$ ) among the visual assessment groups.

PT (Fig 2, A), INR (Fig 2, B), and PTT (Fig 2, C) coagulation parameters were also evaluated by repeated-measures ANOVA. PT and INR post-protamine and postoperatively were significantly higher than preoperatively ( $P < 0.0001$ ), and both were significantly higher for excessive bleeders compared with the not bleeding groups ( $P < 0.02$ ) but not between oozing and not bleeding groups (both  $P = 0.1$ ). PTT was significantly ( $P = 0.019$ ) longer for excessive bleeders compared with not bleeding, but there was no significant difference between oozing and the other groups ( $P > 0.2$ ). There was significantly ( $P < 0.0001$ ) longer PTT both post-protamine and postoperatively relative to preoperatively. Fibrinogen levels were also evaluated perioperatively (Fig 2, D). Fibrinogen was lower both post-protamine and postoperatively, but there was no significant differences among groups ( $P > 0.4$ ). Coded D-dimer levels, evaluated by Spearman rank correlation, showed no significant relationship ( $P = 0.4$ ) with the coding for visual bleeding. By repeated-

measures ANOVA, there were no significant changes in D-dimer levels comparing preoperative with post-protamine and 1-hour postoperative samples.

The authors then evaluated by multiple regression analysis (Table I) the relationship between the postoperative observations and patient characteristics with chest tube drainage milliliter/kilogram ( $r^2 = 0.519$ ,  $P < 0.0001$ ). This analysis was done after removing a significant outlier in the postoperative PT data. This PT was 53.6 seconds compared with a mean of  $21.6 \pm 4.6$  seconds standard deviation. The next highest time was 29.9 seconds, and it was determined that this one point had a large effect on the regression analysis in favor of the PT significance. After removing the nonsignificant variables, chest tube drainage was significantly ( $r^2 = 0.416$ ,  $P < 0.0001$ ) predicted by BMI (coefficient  $-0.120$ ,  $P < 0.0001$ ), cross-clamp time (coefficient  $0.036$ ,  $P < 0.0001$ ), and lowest core body temperature (coefficient  $0.341$ ,  $P = 0.0006$ ). Lowest core body temperature was significantly correlated with the cross-clamp time by simple regression analysis ( $r^2 = 0.575$ , coefficient  $-0.052$ ,  $P < 0.0001$ ) but not with BMI ( $r^2 = 0.018$ , coefficient  $= 0.089$ ,  $P = 0.131$ ), although

**Table I.** Multiple regression correlation of postoperative platelet function and coagulation assays with chest tube drainage

Parameter	Slope Coefficient	Multiple Regression (P Value)
TEG %MA-ADP	0.031	0.070
TEG MAKH	0.007	0.810
Adhesion	0.007	0.379
Platelet count	-0.001	0.898
PT	0.374	0.251
INR	-3.524	0.384
PTT	0.010	0.668
Fibrinogen	-0.007	0.037
D-Dimer code	-0.032	0.878
Visual code	0.928	0.018
Total pump time	-0.008	0.542
Cross-clamp time	0.044	0.011
Lowest core body c° temperature	0.510	0.0003
End core body c° temperature	-0.442	0.111
Age	-0.024	0.389
BMI	-0.090	0.006

the slope was in the expected direction of higher core temperature with greater BMI.

Ereth et al<sup>6</sup> suggested that the relationship between platelet adhesion and chest tube drainage depends on PT. To test this observation, the authors divided the patients into upper and lower 50th percentiles based on platelet function tests to see whether it would alter the correlation of chest tube drainage with PT. Table III gives the quartile ranges for the patient characteristics, surgical parameters, and assay values. Division of either adhesion (Fig 3, A and B) or TEG %MA-ADP (Fig 3, C and D) into upper or lower 50th percentiles did not appreciably alter the correlation of PT (again with the outlier point removed) with chest tube drainage. Similar results were obtained comparing upper and lower 50th percentiles for TEG MAKH.

The 19 patients (14 men) in the upper 75th quartile of 24-hour chest tube output (>5.49 mL/kg) were examined for which of these coagulation and platelet function variables might explain their bleeding (Table II). Visual assessment included six with excessive bleeding, five with oozing, and eight not excessively bleeding at time of closure. Ten of these patients (53%) were subsequently given transfusions compared with 52% in the lowest quartile of chest tube drainage and 58% overall. Overall, 15 patients had BMI in the lower 50th percentile. One patient had re-exploration surgery with a bleeding site on a graft that was repaired. This was the only case of re-exploration surgery within the study group. This patient also had a consensus of negative surgery characteristics, coagulation, and platelet dysfunction. Looking at the overall consensus of patient

characteristics, it seems that five cases of bleeding were not explained by surgical parameters or any of the measured coagulation or platelet function parameters. In four cases, unfavorable surgical parameters and both coagulation and platelet dysfunction in terms of 50th percentile rank were observed. Five cases indicated predominantly coagulation dysfunction, whereas only two cases indicated predominantly platelet dysfunction. The remaining five cases did not give a clear indication of which parameters were primarily responsible for the bleeding.

## DISCUSSION

The platelet function postoperative tests did not have an overall predictive value for chest tube output. In the multiple regression analysis, the coagulation parameter most predictive of postoperative bleeding was postoperative fibrinogen level, in agreement with a previous report.<sup>9</sup> As has been observed,<sup>10</sup> the most significant predictors in this study for excessive postoperative bleeding were low BMI, longer cross-clamp times, lowest core body temperature and visual assessment. As suggested in the results, longer cross-clamp times and lower core temperatures are related. Although there is also a weak relationship between low core temperatures and low BMI, the strong relationship ( $P < 0.0001$ ) between a low BMI and excessive bleeding remains unexplained. The predominant cause of coagulation and platelet dysfunction would most likely be cross-clamp times due to increased mechanical stress and foreign surface exposure.

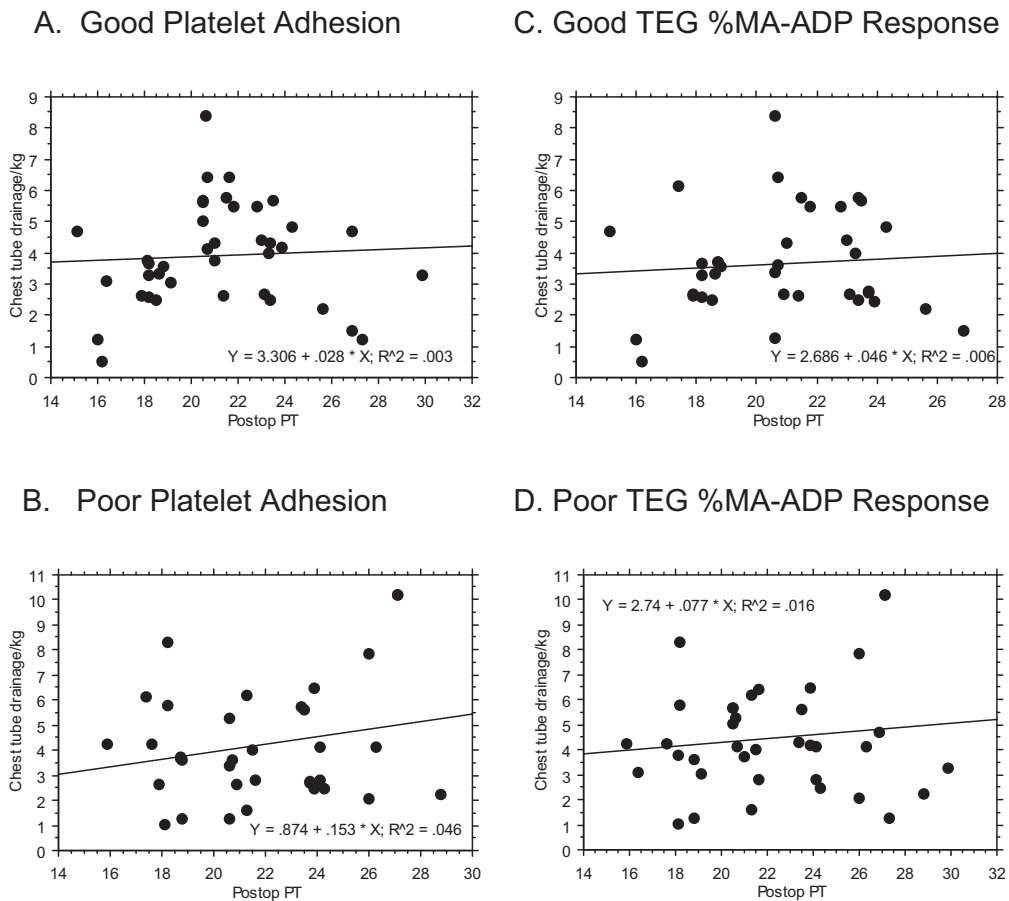
The suggestion that bleeding not explained by coagulation dysfunction might be explained by platelet dysfunction seems reasonable.<sup>6</sup> However, these data using either the glass bead adhesion or TEG %MA-ADP and TEG MAKH tests did not bear this out, perhaps because the adhesion test was run at 1 hour instead of 2 hours postoperatively. However, these data are similar to Ereth et al<sup>6</sup> in terms of the percent preoperative adhesion and rapid postoperative recovery of adhesion function. In addition, there may have been a beneficial effect of aprotinin on this parameter,<sup>11</sup> potentially limiting applying these findings to groups that do not routinely administer this agent intraoperatively.

Aprotinin is routinely used at this institution, although at a half dose that inhibits fibrinolysis but not the kallikrein inflammatory pathway.<sup>12,13</sup> TEG-%MA-ADP and TEG-MAKH measures of function were still depressed at 1 hour. This may reflect a lack of a protective effect of half-dose aprotinin.<sup>11,13,14</sup> However, aprotinin has been shown to reduce blood loss at both low and regular doses with no significant differences in preserving postoperative platelet function.<sup>14</sup> A recent study has found a significant correlation of low

**Table II.** Quartile ranges for patients' postoperative coagulation and platelet function assays as well as chest tube drainage

Quartile	1st	2nd	3rd	4th	Preoperative (Mean ± SD)
BMI	< 27.5	27.5–29.6	29.7–34.0	> 34.0	NA
CCT (min)	< 39	39–59	60–92	> 92	NA
LBT (°C)	< 28.5	28.5–33.6	33.7–34.0	> 34.0	NA
PT (s.)	< 18.7	18.7–21.3	21.4–23.9	> 23.9	16.8 ± 2.1
INR	< 1.4	1.4–1.6	1.7–1.8	> 1.8	1.3 ± 0.2
PTT (s.)	< 43.2	43.2–47.0	47.1–55.0	> 55.0	44.2 ± 9.1
Fibrinogen (mg/dL)	< 177	177–238.8	238.9–290.9	> 290.9	359.6 ± 128.7
Adhesion	< 17.9	17.9–34.9	35.0–59.5	> 59.5	43 ± 25
TEG MAADP	< 3.7	3.7–21.0	21.1–50.7	> 50.7	65.3 ± 18.2
TEG MAKH	< 66.2	66.2–71.1	71.2–74.9	> 74.9	75.1 ± 5.3
Platelet count × 10 <sup>3</sup> /μL	< 100	100–129	130–176	> 176	153 ± 59
Chest tube drainage mL/kg	< 2.66	2.66–3.74	3.75–5.49	> 5.49	NA

Abbreviations: CCT, cross clamp time; LBT, lowest core body temperature; NA, not applicable; SD, standard deviation.



**Fig 3.** Correlations of chest tube drainage milliliter/kilogram with postoperative PT after dividing patients' data into (A) good and (B) poor glass bead platelet adhesion or into (C) good and (D) poor TEG %MA-ADP.

TEG-MA for native blood plus kaolin at 24 hours post-operation with chest tube drainage/kilogram.<sup>15</sup> Possibly, TEG assays at longer postoperative times between 1 and 24 hours might reveal more persistent

platelet dysfunction, and this will be the subject of future studies with this point of care test. Another factor in this study is the exclusion of patients on antiplatelet medications. The impact of NSAID on TEG-%MA-

**Table III.** Patient's surgery, coagulation, and platelet dysfunctional 50th percentiles association with the highest quartile of chest tube drainage (mL/kg)

Type	Surgery Parameters Quartile			Coagulation Quartile				Platelet Function Quartile				Cause of Bleeding (Y/N)		
	BMI	CCT	LBT	PTT	PT	INR	FIB	MAKH	ADP	ADH	PLT #	SURG	COAG	PLT
Multiple	2	4	1	4	4	4	1	1	1	2	1	YYYY	YYYY	YYYY
Multiple	2	4	1	4	4	4	1	1	1	2	1	YYYY	YYYY	YYYY
Multiple*	4	4	2	3	4	4	3	2	2	2	1	YNYN	YYYN	YYYY
Bypass	1	4	2	1	3	3	1	1	1	3	2	NYYY	NYYY	YNYN
Bypass	2	3	2	4	4	3	2	4	2	2	3	NYYY	YYYY	NYYN
Multiple	3	4	1	4	3	3	1	4	3	4	2	YNYN	YYYY	NNNY
Aneurysm	2	4	1	1	3	1	1	1	1	2	4	NYYY	NYNY	YYYN
Multiple	1	4	1	3	1	1	4	3	1	2	1	YYYY	YNNN	NYYY
Valve	2	3	1	4	2	2	2	2	1	3	4	NYYY	YNNY	YNNN
Bypass	2	3	2	1	1	1	3	3	1	2	3	NYYY	NNNN	NYYN
Valve	1	3	2	3	3	3	2	3	3	3	3	NYYY	YNYN	NNNN
Bypass	3	2	4	3	3	3	1	1	2	1	1	NNNN	YYYY	YYYY
Bypass	3	2	3	4	3	3	1	2	3	3	3	NNNN	YYYY	YNNN
Bypass	1	1	2	2	3	3	1	3	3	1	3	NYNY	NYYY	NNYN
Bypass	1	3	3	1	3	3	3	2	4	4	2	NYYN	NYYN	YNNY
Bypass	2	1	3	4	2	2	1	3	1	4	4	NYNN	YNNY	NYNN
Bypass	2	2	2	3	2	2	1	2	4	4	3	NYNY	YNNY	YNNN
Bypass	1	1	3	2	1	1	2	3	4	2	3	NYNN	NNNY	NNYN
Multiple	1	1	3	2	2	2	2	3	4	4	3	YYNN	NNNY	NNNN

Abbreviations: Surgery, multiple indicates more than one procedure (i.e., bypass and valve) with \* indicating a re-exploration. Y, parameter in dysfunctional 50th percentile; N, functional 50th percentile; Y and N correspond to the order of the assay columns; BMI, body mass index; CCT, cross-clamp time; LBT, lowest core body temperature; MAKH, TEG maximum amplitude with kaolin and heparinase; ADP, TEG %MA-ADP; ADH, adhesion; FIB, fibrinogen; SURG, Surgery; PLT, platelet; COAG, coagulation.

ADP, although significant by paired *t*-test, is not significant by unpaired *t*-test because it is small.<sup>16</sup> It is likely that antiplatelet therapies such as clopidogrel and NSAID would further depress platelet function in the postoperative period although this may be modified by aprotinin in the case of clopidogrel.<sup>17,18</sup>

The statistical power of these analyses is admittedly low with only 75 patients undergoing diverse cardiac surgeries in the absence of a strong correlation with postoperative bleeding. The hypothesis that bleeding not explained by coagulation dysfunction might be due to platelet dysfunction was not supported by this study. Again, in the absence of a strong trend, this study has a low power to rule out this hypothesis. Given the average *r*<sup>2</sup> value of 0.02 for these regressions, it would require a little over 1000 subjects to adequately test this hypothesis with a power of >0.8. The clinical impact on patient management for these tests with such weak trends that are revealed as statistically significant only after enrolling large numbers of subjects is doubtful.

For those cases without a clear consensus of coagulation or platelet dysfunction, perhaps re-exploration surgery would be indicated. It is worth noting that only one patient in this study had a re-exploration that did reveal a bleeding site. However, this patient also had a consensus of negative surgical parameters, coagulation, and platelet dysfunction. The surgeons were not guided

by the assay results in this study except for routine PTT, PT, and INR. In any event, for some patients with excessive bleeding, these tests may still guide in the proper course of therapy.

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