Prospective evaluation and clinical utility of on-site monitoring of coagulation in patients undergoing cardiac operation

Although laboratory coagulation tests permit a rational approach to both diagnosis and management of coagulation disorders after cardiopulmonary bypass, their clinical utility is limited by delays in obtaining results. This study was designed to evaluate prospectively the impact of on-site coagulation testing on blood product use, operative time, and intraoperative management of microvascular bleeding. Patients who underwent cardiac procedures involving cardiopulmonary bypass and subsequently developed microvascular bleeding were randomly assigned to receive either standard therapy ($n = 36$) or therapy defined by a treatment algorithm based on results from an on-site coagulation monitoring laboratory ($n = 30$). No differences were found between treatment groups in hematologic assay data, operative procedures, or duration of cardiopulmonary bypass. Patients treated in accordance with on-site laboratory results (algorithm therapy) received significantly less intraoperative fresh frozen plasma (0.4 ± 1.1 U versus 2.4 ± 2.8 U; $p = 0.0006$) during the treatment interval, had shorter operative times, and had less mediastinal chest tube drainage during the initial perioperative interval (158 ± 169 ml versus 326 ± 258 ml; $p = 0.003$) than did patients in the standard therapy group. Patients who underwent algorithm therapy also received fewer platelet (1.6 ± 5.9 versus 6.4 ± 8.2 U; $p = 0.02$) and red blood cell (1.9 ± 1.7 U versus 4.1 ± 4.1 U; $p = 0.01$) transfusions after the operation. Nine of 36 (25 %) standard group patients received initial therapy which differed from that which would have been guided by the on-site algorithm protocol. Our findings indicate that rapid and accurate coagulation test results can guide specific therapy and optimize treatment of microvascular bleeding in patients who undergo cardiac operations. (*J THORAC CARDIOVASC SURG* 1994;107:271-9)

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Prophylactic administration of platelets¹ and fresh frozen plasma² has been shown to be unwarranted during cardiac surgical procedures. A recent study indicated that transfusion rates for red cells, platelets, and fresh frozen

plasma varied significantly from institution to institution.³ Transfusion practices for hemostatic blood products are complicated by the multifactorial nature of coagulation disorders (microvascular bleeding) after cardiopulmonary bypass (CPB).⁴⁻¹⁵ Because of the frequent absence of available laboratory data, standard treatment of microvascular bleeding after CPB is often nonspecific (e.g., additional protamine, fresh frozen plasma, and platelet concentrates).¹⁶ In addition, hemostatic blood products are frequently administered on a prophylactic basis in an attempt to distinguish microvascular bleeding from surgical bleeding.^{17, 18} Neither approach constitutes an optimal strategy for patient treatment.

Laboratory coagulation tests can provide a rational basis for diagnosis and therapy.¹⁹ A panel of rapidly performed screening tests for factors such as prothrombin time (PT), activated partial thromboplastin time (aPTT),

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thrombin time, platelet count, and fibrinogen level may be useful in the differential diagnosis of intraoperative disorders of hemostasis.²⁰ The clinical utility of laboratory tests is often limited by long turnaround, and waiting for laboratory coagulation results can potentially prolong operative time and increase blood loss. Accordingly, an on-site coagulation laboratory may help physicians establish more appropriate management of microvascular bleeding according to abnormalities in the coagulation system and facilitate a change in transfusion behavior. This prospective study was designed to compare standard empiric therapy for microvascular bleeding with treatment administered according to a transfusion algorithm that is dependent on coagulation results from an on-site laboratory system.

Patients and methods

Patient population. Adult patients undergoing cardiac operations requiring CPB were eligible to participate in this study. Informed consent was obtained under the approval of the Institutional Human Studies Committee. All patients were anesthetized with an opioid-based technique supplemented with inhalational anesthetic agents, muscle relaxants, and benzodiazepines. CPB was accomplished with a Bio-Medicus centrifugal pump (Medtronic Bio-Medicus, Eden Prairie, Minn.) and a Cobe membrane oxygenator (Cobe Laboratories, Inc., Lakewood, Colo.). The CPB system was routinely primed with 2 L of Plasma-Lyte solution, 50 mEq of sodium bicarbonate, 25 gm of mannitol, and 5000 U of porcine heparin. During the administration of cardioplegic solution, systemic hypothermia was maintained at 28° C. Systemic anticoagulation for CPB was accomplished with porcine heparin at an initial dose of 250 U/kg body weight. Adequate heparinization for CPB was assessed with the activated clotting time (ACT); further doses of heparin were administered as needed to maintain an ACT of greater than 480 seconds. After rewarming to 37° C, extracorporeal circulation was discontinued, heparin was neutralized with protamine (0.8 mg per milligram of heparin), and patients were observed for evidence of microvascular bleeding.

The diagnosis of microvascular bleeding, made by our surgical staff, was defined as diffuse bleeding without an identifiable surgically correctable source after heparin neutralization. Of 362 consecutive patients undergoing cardiac procedures, 83 patients had evidence of microvascular bleeding and were categorized as bleeding patients; the 279 patients without evidence of microvascular bleeding were categorized as nonbleeding patients. Seventeen bleeding patients were excluded on the basis of the following criteria: (1) preoperative fibrinolytic therapy with tissue plasminogen activator or urokinase or streptokinase; (2) intraoperative antifibrinolytic therapy (aprotinin, aminocaproic acid); or (3) treatment when personnel were unavailable for coagulation analysis. The remaining 66 patients with microvascular bleeding were incorporated in the study to compare treatment protocols.

These 66 patients were randomly assigned to either a standard therapy group ($n = 30$) or to an algorithm therapy group ($n = 36$). Therapy options for microvascular bleeding after CPB included additional protamine, thawed fresh frozen

plasma, platelet concentrates, cryoprecipitate, and 1-deamino-8-D-arginine vasopressin (DDAVP). Hemostatic therapy for standard group patients was guided by hematologic assays obtained from the hospital laboratory, subjective assessment of bleeding according to routine practices, or both. When the patient was assigned to the standard therapy group, physicians and operating room personnel were unaware of parallel data obtained by the on-site laboratory. Hemostatic therapy for patients in the algorithm therapy group was based on an on-site protocol with the use of a transfusion algorithm (Fig. 1) and results from the on-site laboratory. When the patient was assigned to the algorithm therapy group, physicians and operating room personnel were unaware of parallel hematologic data from the institutional laboratory.

Hematologic assays. Blood specimens were collected for hematologic assays at three times: before systemic anticoagulation with heparin for CPB, after the neutralization of heparin with protamine (after CPB), and after the administration of hemostatic therapy and the termination of microvascular bleeding. The same blood specimen used for hemostasis analysis by both laboratory and on-site laboratory systems was obtained via radial or femoral intraarterial catheters after removal of six dead-space volumes.

On-site hematologic assays included whole blood PT and aPTT measured with the Biotrack 512 coagulation monitor (Ciba Corning Diagnostics Corp., Medfield, Mass.), and the platelet count by the Coulter T540 hemocytometer (Coulter Electronics, Hialeah, Fla.). Whole blood PT and aPTT were determined by a battery-powered portable unit that uses disposable plastic reagent cartridges as described by Lucas and associates.²¹ After an initial warming period to 37° C, a drop (minimum of 25 μ l) of nonanticoagulated whole blood was applied to the cartridge. The blood is drawn by capillary action into the reagent chamber, which results in rehydration of the reagent, either with thromboplastin (PT) or with a chemical activator and soybean phosphatide (aPTT). After the blood sample coagulates, cessation of blood flow is sensed by a laser photometer and the elapsed time is converted mathematically to a plasma equivalent PT or aPTT. Whole blood platelet counts were determined electronically by the Coulter T540 hemocytometer (Coulter). On-site laboratory results were obtained within 3 to 6 minutes and were assayed in duplicate.

The standard laboratory assays included the one-stage PT, a modification of the method initially described by Quick, Stanley-Brown, and Bancroft,²² and the aPTT, a modification of the method initially described by Proctor and Rapaport.²³ PT and aPTT ratio values for both the on-site laboratory and the standard hospital laboratory were determined by dividing the PT or aPTT result by the mean value obtained from a normal reference population. Thrombin times with protamine correction were determined by a modification of the JIM method.^{24, 25} Fibrinogen levels were determined by the method of Klaus.²⁶ Fibrin split-product levels were measured with Dade reagent by means of the latex method as described by Allington.²⁷ Bleeding times were measured with the Simplate technique (Organon Teknica Corp., Durham, N.C.) as described by Babson and Babson.²⁸ Platelet counts were performed electronically with an automated Coulter S+4 hemocytometer (Coulter).

After laboratory processing, a plasma aliquot of each blood specimen collected from two time periods (before and after CPB) was labeled, frozen, and stored for potential coagulation factor analysis. Levels for factors V, VII, VIII, IX, X, and XII

Fig. 1. The three arms of the transfusion algorithm are based on the initial platelet count. An initial platelet count of less than 50,000 (*left arm*: severe platelet deficiency) warrants platelet transfusion. If the initial platelet count was greater than 50,000 (*middle and right arms*), the PT:aPTT ratio values would delineate whether platelet therapy versus thawed plasma were administered. PT:aPTT ratio values were determined by dividing the whole blood PT and aPTT measurements by the mean value derived from a normal reference population of patients for each respective assay. Whole blood PT and aPTT were measured with the Biotrack 512 coagulation monitor. Platelet count (*PLT Count*), expressed in thousands, was measured with a Coulter T540 hemocytometer. *Platelets*, Platelet transfusion (6 random donor units); *PLT RX*, platelet therapy (6 random donor units or 0.3 mg/kg DDAVP at physician's discretion); *FFP*, 2 units of thawed plasma; *[+]* *MVB*, persistent microvascular bleeding.

were determined on subsets of patients from both bleeding ($n = 42$) and nonbleeding ($n = 31$) patient populations. One-stage factor assays were done with the Quick²² method for the PT-based assays and by the Langdell²⁹ method for the aPTT-based assays. Patient selection for factor analysis was based on the distribution of patients within three laboratory aPTT categories. The categories included the following: category 1: $\text{aPTT} < 1.5 \times \text{control}$; category 2: $1.5 \times \text{control} < \text{aPTT} < 1.8 \times \text{control}$; and category 3: $1.8 \times \text{control} < \text{aPTT}$. The percentage of patients in each of the aPTT subsets was used to determine how many randomly designated patients were assayed within each aPTT subset. Whole blood ACT was also determined with a Hemochron instrument (International Technology Corp., Edison, N.J.) during the operation.

All test results, therapeutic interventions, duration of microvascular bleeding, time from heparin neutralization to arrival in the intensive care unit, and estimates of perioperative blood loss were recorded. Operative blood loss was assessed in two periods: blood loss before intervention was estimated by the measurement of Cell Saver red blood cell volume (volume of red blood cells processed via the Cell Saver and reinfused to patients), and blood loss after intervention was estimated by measuring the mediastinal chest tube drainage in the operative interval after CPB (chest tube insertion + first postoperative hour). Mediastinal chest tube drainage represented postoperative blood losses and was measured in the following postoperative intervals: hours 2 to 4, hours 5 to 8, hours 9 to 24.

Statistical analysis. Data were analyzed by correlation, t test for equal and unequal variances, one-way analysis of vari-

ance, analysis of covariance, two-sample Wilcoxon rank-sum, χ^2 analysis, Fisher's exact test, linear regression, and logistic regression, with $p < 0.05$ considered significant. When the assumption of homogeneity did not hold true, log transformations were used to equalize the variances and enable the use of analysis of covariance. When applicable, a score consisting of the count of multiple factors that may have an association with the risk of bleeding was constructed and used with analysis of variance.

Results

Characterization of microvascular bleeding. Demographic and operative variables that had a significant association with microvascular bleeding, as assessed by logistic regression ($p < 0.0001$, $\chi^2 = 37.96$), included age, history of a previous cardiac procedure (operative history), number of operative procedures, and duration of CPB. Patients with microvascular bleeding were significantly older (66 ± 12 versus 62 ± 14 years; $p = 0.03$) than those without evidence of microvascular bleeding. Fig. 2 illustrates the actual prevalence and lists the odds of microvascular bleeding developing in each of four categories on the basis of operative history and number of cardiac procedures. Both a history of a cardiac operation and more than one operative procedure independently

related to an increased prevalence of microvascular bleeding. The odds of microvascular bleeding developing in patients who had a previous cardiac procedure (reoperation) as compared with patients undergoing their first procedure (primary) was increased by a factor of 3 (95% confidence interval [CI] = 1.6 to 5.8). In contrast, the odds of microvascular bleeding developing in patients who required more than one procedure (combined) when compared with those that underwent a single procedure (single) was increased by a factor of 4.8 (95% CI = 2.71 to 8.5). In our patient population, the probability of microvascular bleeding tripled (0.25 to 0.75) as the duration of CPB increased from 2.5 to 4.5 hours.

Microvascular bleeding, a clinical diagnosis, was paralleled by quantifiable hematologic and chest tube drainage data. Significant differences were found in the prevalence of coagulation deficiencies after CPB between patients with and without microvascular bleeding (Table I). Factors V and X were the most commonly reduced factors below 30% activity (factor V 86%, factor X 14%) and below 20% activity (factor V 100%) in the patients with microvascular bleeding. In addition, operative blood losses were greater in patients with microvascular bleeding as indicated by the greater Cell Saver red blood cell volumes (1024 ± 1142 ml versus 672 ± 396 ml; $p = 0.009$) transfused and by the greater operative chest tube drainage (255 ± 239 versus 130 ± 104 ml; $p < 0.0001$) in these patients. Blood losses were also greater in patients with microvascular bleeding during the following postoperative intervals: hours 2 to 4 (424 ± 528 ml for patients with bleeding versus 199 ± 146 ml for those without; $p < 0.0001$), hours 5 to 8 (419 ± 545 ml for patients with bleeding versus 187 ± 147 ml for those without; $p < 0.0001$) hours 9 to 24 (908 ± 1480 ml for patients with bleeding versus 438 ± 260 ml for those without; $p < 0.0001$).

Comparison of standard therapy with algorithm therapy. Standard and algorithm therapy groups had similar demographic and hematologic profiles. Although the treatment groups differed in respect to male/female patient distribution and preoperative use of heparin (Table II), neither of these variables was associated with subsequent development of microvascular bleeding (logistic regression model). In addition, gender (women: 41% versus 32%) and preoperative use of heparin (heparin use: 52% versus 45%) were distributed equally between patients with and without microvascular bleeding, respectively. Heparin resistance was not evident in the standard therapy group because preoperative heparin use did not result in a statistically different mean ACT response between the algorithm and standard therapy groups (622 ± 175 seconds versus 595 ± 187 seconds,

respectively, $p = 0.56$); individual values were considered appropriate for CPB heparinization. Thus, the total heparin dose per kilogram of body weight was the same in the algorithm and standard therapy groups (431 ± 124 U/kg versus 443 ± 157 U/kg, respectively). Moreover, after initial heparinization of 66 study patients, the mean ACT result was also similar to the corresponding result from patients without bleeding (594 ± 169 seconds). No statistically or clinically significant differences in preoperative assay data were apparent between the two treatment groups when preoperative use of heparin was included as a covariate in analysis. Preoperative platelet function, as assessed by bleeding times in the algorithm and standard therapy groups (6.2 ± 2.8 minutes versus 6.9 ± 3.3 minutes, respectively; $p = 0.38$) was also similar. Hematologic data after CPB that included coagulation factor analysis revealed similar measurements between algorithm and standard therapy groups (Table III). Normothermia was achieved before discontinuation of CPB, and the first temperature recorded in the intensive care unit was the same between the algorithm and standard therapy groups ($35.8^\circ \pm 1.1^\circ$ C versus $35.5^\circ \pm 0.9^\circ$, respectively; $p = 0.22$). Similar Cell Saver red blood cell volumes between treatment groups indicate that both groups had comparable surgical blood loss before the intervention (Table II).

Patients treated with on-site laboratory results and the treatment algorithm received less fresh frozen plasma during the operation ($p = 0.0002$); patients who underwent standard therapy received six times more fresh frozen plasma during the operation (Table IV). Blood product use was also greater in the postoperative period in patients who underwent standard therapy. These patients required four times as many units of platelet concentrates ($p = 0.02$) and twice as many red cell units ($p = 0.01$). In addition, patients who underwent algorithm therapy had shorter operative intervals ($p = 0.0001$). This difference could be attributed to the duration of the microvascular bleeding interval (Table IV) that was twice as long in patients who underwent standard therapy as in those who underwent algorithm therapy ($p = 0.0001$). This prolonged operative interval was also significant after factoring in patients who received more than one round of blood products as a covariate in the statistical analysis. Patients who underwent algorithm therapy also had significantly lower operative chest tube drainage after the intervention (chest tube insertion + first postoperative hour [$p = 0.0002$]). Patients who underwent standard therapy had twice as much mediastinal blood loss during this interval. Bleeding rates (in milliliters per hour) were calculated to assess whether this difference in chest tube drainage was purely a function of longer operative time.

Fig. 2. Varying prevalence of microvascular bleeding (MVB) corresponding to number of procedures, operative history, or both. Actual incidence of microvascular bleeding is denoted by the fractions within the parentheses ( ), whereas fractions within the brackets [ ] represent the calculated probability from logistic regression (see text for details).

The rate of bleeding for patients who underwent standard therapy was nearly twice that of those who underwent algorithm therapy (114 ml/hr versus 69 ml/hr, respectively; $p = 0.01$). Although the difference in the reexploration rate among patients is not statistically significant ($p = 0.1$), four patients who underwent standard therapy and who required reexploration for persistent postoperative bleeding had a surgical source, compared with only one patient who underwent algorithm therapy. Actual initial therapy that was administered to the patients in the standard therapy group was compared with the therapy that would have been designated by the algorithm protocol. In nine of 36 patients treated with standard therapy (25%), initial therapy administered was different from that which would have been guided by the on-site algorithm protocol.

Discussion

During cardiac operations, coagulation disorders can develop with an increased prevalence in patients with preoperative hemostatic abnormalities³⁰ or with prolonged use of CPB.³¹ Our analysis revealed a significant association between the probability of microvascular bleeding and duration of CPB. Our prospective evaluation, which is in agreement with a previous retrospective analysis,³³ demonstrates that reoperation and more than one cardiac operative procedure are associated with an increased prevalence of microvascular bleeding requiring transfusion of hemostatic blood products. This increase

Table I. Moderate versus severe coagulation deficiencies after CPB

	Patients (%)	
	No microvascular bleeding (n = 115)	Microvascular bleeding (n = 66)
Thrombocytopenia		
Moderate: <100,000	39	77*
Severe: <50,000	2	23*
Factor deficiency†		
Moderate: 1 factor	41	79‡
<30% activity		
Severe: 1 factor	19	43§
<20% activity		
Hypofibrinogenemia		
Moderate: <100 mg/dl	3	15‡
Severe: <50 mg/dl	0	4

* $p < 0.001$.

†Refers to Factors V, VII, VIII, IX, X, and XII.

‡ $p < 0.01$.

§ $p < 0.05$.

was, at least in part, a result of the prolonged use of CPB with these procedures.

The origins of coagulation disorders in the cardiac surgical setting may include one or more of the following: qualitative^{5,6} or quantitative platelet abnormalities^{7,8}; isolated or combined coagulation factor depletion^{6,9,10} and, less commonly, excess heparin; excess protamine; disseminated intravascular coagulation¹¹⁻¹³; and isolated primary fibrinolysis.¹⁴⁻¹⁶ Our data suggest that, in our patient population, the most common cause of microvascular bleeding was most likely a platelet disorder. This hypothesis is supported by the fact that, although mean factor levels for patients in the algorithm and standard therapy groups were similar, those in the algorithm therapy group required considerably less plasma transfusions and yet had less postoperative chest tube drainage. The second most common cause of microvascular bleeding in our patients was a factor deficiency (Table I). Although fibrinolysis may have contributed to a consumptive state, the prevalence of both moderate (<100 mg/dl) and severe (<50 mg/dl) reduction in fibrinogen was much lower than a factor V deficiency.

Rapid determination of the origin of microvascular bleeding after CPB can be difficult. Previously, the only rapid response monitor used to evaluate coagulation in the operating room was the ACT. The ACT, however, has a limited role in the evaluation of microvascular bleeding after CPB because it is insensitive³⁴⁻³⁶ to major defects in the coagulation system and nonspecific³⁷⁻⁴¹ when abnormal results are obtained. A complete coagulation profile

Table II. Demographic and operative data

	Algorithm therapy group (n = 30)	Standard therapy group (n = 36)
Age (yr)	69 ± 10	68 ± 10
Sex (% female)	23	50*
Weight (kg)	78 ± 14	74 ± 15
Operative procedures (%)		
Coronary artery bypass	60	39
EP mapping/ablation	7	6
Valve repair/replacement	3	3
Combined operations	30	52
VADS/circulatory arrest (%)	7	8
Reoperation (%)	17	25
Preoperative anticoagulation medications (%)		
Aspirin	53	56
Heparin	37	64*
Coumadin	13	8
CPB time (min)	187 ± 65	194 ± 74
XC time (min)	78 ± 39	86 ± 35
Cell Saver RBC volume (ml)	786 ± 521	858 ± 799

Values expressed as mean ± standard deviation or percentage. EP, Electrophysiologic; Combined operations, more than one operative procedure; VADS, ventricular assist devices; XC time, aortic crossclamp time; Cell Saver RBC volume, Cell Saver red blood cell volume administered to patient during intraoperative period.

* $p > 0.05$.

including PT, aPTT, platelet count, fibrinogen level, fibrin split-product level, and bleeding time can delineate the correct origin; however, results of these coagulation tests are difficult to obtain promptly. A 5-month audit at our institution revealed that mean turnaround was 44 minutes and 90th percentile turnaround was 77 minutes. A significant component of the turn-around time involves the time required for specimen delivery (mean = 11 minutes, 90% = 17 minutes). Therefore, a real-time assessment of the coagulation system with laboratory results is difficult to ascertain. In contrast, the on-site coagulation system used in this study provides coagulation results rapidly (mean = 4 minutes, 95% = 6 minutes).

Guidelines for transfusion of hemostatic blood products after CPB have recognized these limitations and recommend transfusion of 1 U of platelets per 10 kg body weight as initial treatment with laboratory testing before and after transfusion.⁴ This recommendation is probably based on the premise that quantitative or qualitative platelet defects represent the most important hemostatic derangement for microvascular bleeding in the period after CPB.⁴² Accordingly, the three arms of the transfusion algorithm used in the present study were based on the initial platelet count. Although the efficacy of DDAVP in minimizing postoperative blood loss after routine cardiac operations is controversial, DDAVP administration was included as a treatment option for qualitative platelet abnormality. This therapy may be efficacious in patients

Table III. Postcardiopulmonary hematologic data

	Algorithm therapy group (n = 30)	Standard therapy group (n = 36)
WB PT (sec)	19.7 ± 4.1	22.2 ± 7.9
Lab PT (sec)	19.6 ± 4.2	21.4 ± 5.9
WB aPTT (sec)	64.1 ± 15.6	73.2 ± 31.8
Lab aPTT (sec)	47.3 ± 15.7	61.2 ± 36.3
T540 PLT (thousands)	87 ± 36	74 ± 33
Fibrinogen level (mg/dl)	181 ± 81	162 ± 93
Fibrin split products (μg/ml)	13.3 ± 9.9	15.3 ± 17.2
Thrombin time (sec)	19.2 ± 3.6	19.6 ± 4.9
PC thrombin time (sec)	17.1 ± 1.5	17.0 ± 2.2
ACT (sec)	129 ± 17	130 ± 21
Factor V level (% activity)	27 ± 12	26 ± 12
Factor X level (% activity)	39 ± 18	33 ± 17
Hematocrit value (%)	24.1 ± 4.2	24.2 ± 3.7

Values expressed as mean ± standard deviation. WB PT, Biotrack 512 (Ciba/Corning Diagnostics) whole blood PT; LAB PT, laboratory PT; WBaPTT, Biotrack 512 coagulation monitor whole blood aPTT; LAB aPTT, Laboratory aPTT; T540 PLT, Coulter T540 hemocytometer PC; PC thrombin time, protamine-corrected thrombin time.

with uremia and von Willebrand's disease and in certain patient subsets. These subsets include patients requiring prolonged use of CPB,⁴³ patients receiving platelet-inhibiting drugs,⁴⁴ and a patient population defined by thromboelastography.⁴⁵ Therefore, if quantitative platelet adequacy is determined, platelet transfusion may be avoided in patients whose primary hemostatic derangement is either a qualitative platelet disorder or a depletion of coagulation factors. Because of the uncertainty of which degree of PT;aPTT abnormality correlates best with factor depletion,⁴⁶⁻⁴⁸ PT and aPTT ratio values were subdivided (PT;aPTT > 1.5 × control versus PT;aPTT > 1.8 × control). Accordingly, the administration of plasma was based on both the degree of PT;aPTT prolongation and magnitude of platelet reduction. Hence, a real-time PT;aPTT assessment would delineate the need for plasma administration and deter unwarranted transfusion.

The on-site system used in the comparison consisted of an established method of assessing platelet counts and a recently developed technology that can provide whole blood PT and aPTT results in a timely fashion. The whole blood PT has been evaluated previously and has been shown to correlate well (correlation coefficient = 0.96) with laboratory reference methods in a multicenter study.²¹ In addition, a recent publication has illustrated the usefulness of this new technology in patient self-management of oral anticoagulation.⁴⁹ The whole blood aPTT has been found to correlate well with the standard laboratory aPTT, with correlation coefficients ranging from 0.79 to 0.83, depending on the reference reagent and

instrumentation used. This correlation coefficient was in the same range as that obtained for standard laboratory aPTTs with the use of different reagents (0.79).⁵⁰ In this study, low coefficients of variation supported a high degree of precision for this technology.

Our data suggest that an on-site coagulation laboratory enables physicians to diagnose bleeding abnormalities and therefore administer specific hemostatic therapy promptly. In addition, rapid acquisition of coagulation data can allow physicians to differentiate between microvascular bleeding and surgical bleeding. In the present study, blood product use, operative times, and chest tube drainage were set as the clinical markers of treatment efficacy (Table IV). A definitive origin for microvascular bleeding that led to improved treatment was ascertained in patients who underwent algorithm therapy. In contrast, 25% of the patients in the standard therapy group were not treated with the same initial therapy as would have been guided by the algorithm protocol. Our data also indicate that operative times were reduced with prompt termination of microvascular bleeding by precise hemostatic therapy based on coagulation data and reduced hesitancy by surgical staff to proceed with closure because of an improved clinical condition, normal coagulation data, or both. A significant reduction in operative chest tube drainage in algorithm group patients provides quantifiable and objective support for the more effective management of excessive microvascular bleeding, a common intraoperative clinical problem. Mediastinal chest tube drainage was significantly less during the period after intervention (chest tube insertion + first postoperative hour) when patient treatment was guided in accordance with the algorithm protocol, and this was not due to increased operative times in standard therapy patients. After arrival at the intensive care unit, where similar therapy was initiated for both groups, chest tube drainage was similar between groups. In the postoperative period, patients who underwent algorithm therapy also required fewer red cell and platelet units. Although statistical significance was not attained, the discrepancy in the number of patients requiring exploration for postoperative bleeding between treatment groups may have been clinically significant. Four patients who underwent standard therapy had a defined surgical source on reexploration in contrast to one patient who underwent algorithm therapy. In patients with persistent bleeding as a result of a surgical source, the initial period after CPB may represent an opportune time for coagulation testing. In the setting of persistent bleeding and significant intravascular volume replacement, abnormal coagulation data may obscure the actual diagnosis.

Table IV. Blood product use, operative times, chest tube drainage, and exploration for postoperative bleeding

	Algorithm therapy group (n = 30)	Standard therapy group (n = 36)
Platelet concentrates		
Intraop (U)	3.9 ± 4.1	6.7 ± 6.0
Postop (U)	1.6 ± 5.9	6.4 ± 8.2*
Frozen plasma		
Intraop (U)	0.4 ± 1.1	2.4 ± 2.8†
Postop (U)	1.2 ± 1.9	2.7 ± 3.6
Cryoprecipitate		
Intraop (U)	0.0 ± 0.0	1.4 ± 4.4
Postop (U)	0.0 ± 0.0	1.5 ± 4.1
Red blood cells		
Intraop (U)	2.3 ± 1.5	3.6 ± 3.4
Postop (U)	1.9 ± 1.7	4.1 ± 4.1‡
DDAVP (%)	60%	44%
MVB time (min)	27 ± 16	66 ± 45†
Post-CPB time (min)	69 ± 24	108 ± 54†
Chest tube drainage (ml)		
Intraop + postop hour 1	158 ± 169	326 ± 258‡
Postop hours 2-4	299 ± 399	436 ± 444
Postop hours 5-8	258 ± 353	456 ± 431
Postop hours 9-24	501 ± 247	947 ± 1180
Exploration (%)	3%	14%

Values expressed as mean ± standard deviation or percentage. *Intraop*, During the intraoperative period; *Postop*, during the first postoperative 24 hours; *DDAVP*, percentage of patients receiving 1-deamino-8-D-arginine vasopressin; *MVB time*, time from start of microvascular bleeding (after heparin neutralization) to the termination of microvascular bleeding; *Post-CPB time*, time from start of microvascular bleeding (after heparin neutralization) to the end of the operation; *Exploration*, percentage of patients requiring exploration for postoperative bleeding.

*p < 0.05.

†*p* < 0.001.

‡*p* < 0.01.

In conclusion, microvascular bleeding after CPB during cardiac surgical procedures presents a unique and complex problem to physicians. Our data indicate that prompt availability of coagulation results from an on-site laboratory system and use of a transfusion algorithm resulted in a reduction in hemostatic blood product use and decreased operative time. Use of an on-site laboratory facilitated timely treatment of microvascular bleeding with specific hemostatic therapy. Consequently, prompt diagnosis of the origin of intraoperative bleeding resulted in improved patient treatment as indicated by reduced chest tube drainage.

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REFERENCES

1. Simon TL, Akl BF, Murphy W. Controlled trial of routine administration of platelet concentrates in cardiopulmonary bypass surgery. *Ann Thorac Surg* 1984;37:359-64.
2. Milam JD, Austin SF, Martin RF, et al. Alterations of coagulation and selected clinical chemistry parameters in patients undergoing open heart surgery without transfusions. *Am J Clin Pathol* 1981;76:155-62.
3. Goodnough LT, Johnston MFN, Toy PTYC, the Transfusion Medicine Academic Award Group. The variability of transfusion practice in coronary artery bypass surgery. *JAMA* 1991;265:86-90.
4. Bick RL. Hemostasis defects associated with cardiac surgery, prosthetic devices and extracorporeal circuits. *Semin Thromb Hemost* 1985;11:249-80.
5. Holloway DS, Summaria L, Sanderesa J, et al. Decreased platelet number and function and increased fibrinolysis contribute to postoperative bleeding in cardiopulmonary bypass patients. *Thromb Haemost* 1988;59:62-7.
6. Wolk LA, Wilson RF, Burdick M, et al. Changes in antithrombin, antiplasmin, and plasminogen during and after cardiopulmonary bypass. *Am Surg* 1985;51:309-13.
7. Milam JD. Blood transfusion in heart surgery. *Clin Lab Med* 1982;2:65-85.
8. Mammen EF, Koets MH, Washington BC, et al. Hemostasis changes during cardiopulmonary bypass surgery. *Semin Thromb Hemost* 1985;11:281-92.
9. Kalter RD, Cheri MS, Saul BS, Wetstein L, Soriano C, Reiss RF. Cardiopulmonary bypass: associated hemostatic abnormalities. *J THORAC CARDIOVASC SURG* 1979;77:427-35.
10. Bick RL. Alterations of hemostasis associated with cardiopulmonary bypass: pathophysiology, prevention, diagnosis, and management. *Semin Thromb Hemost* 1976;3:59-82.
11. Muller N, Popov-Cenic S, Buttner W, Kladetsky RG, Egli H. Studies of fibrinolytic and coagulation factors during open-heart surgery. II. Postoperative bleeding tendencies and changes in the coagulation system. *Thromb Res* 1975;7:589-98.
12. Gralnick HR, Fischer RD. The hemostatic response to open-heart operations. *J THORAC CARDIOVASC SURG* 1971;61:911-5.
13. Von Kaulla KN, Swan H. Clotting deviations in man during cardiac bypass: fibrinolysis and circulating anticoagulants. *J THORAC CARDIOVASC SURG* 1958;38:519-33.
14. Brooks DH, Bahson HT. An outbreak of hemorrhage following cardiopulmonary bypass. *J THORAC CARDIOVASC SURG* 1972;63:449-52.
15. O'Neill JA, Ende N, Collins IS, Collins HA. A quantitative determination of perfusion fibrinolysis. *Surgery* 1966;60:809-12.
16. Ellison N, Jobs DR. Effective hemostasis in cardiac surgery. Philadelphia: WB Saunders, 1988;195-202.
17. National Institutes of Health Consensus Conference. Platelet transfusion therapy. *JAMA* 1987;257:1777-80.
18. National Institutes of Health Consensus Conference. Fresh-frozen plasma. *JAMA* 1985;253:551-3.
19. Goodnough LT, Johnston MFM, Ramsey G, et al. Guidelines for transfusion support in patients undergoing coronary artery bypass grafting. *Ann Thorac Surg* 1990;50:675-83.
20. Counts RB. Transfusion practice in cardiac surgery: causes of bleeding in open-heart surgery. Arlington, Va.: American Association of Blood Banks, 1991;1-10.
21. Lucas FV, Duncan A, Jay R, et al. A novel whole blood capillary technic for measuring the prothrombin time. *Am J Clin Pathol* 1987;88:442-6.
22. Quick AJ, Stanley-Brown M, Bancroft FW. A study of the coagulation defect in hemophilia and jaundice. *Am J Med Sci* 1935;190:501-11.
23. Proctor RR, Rapaport SI. The partial thromboplastin time with kaolin. *Am J Clin Pathol* 1961;36:212-9.
24. Jim RTS. A study of the plasma thrombin time. *Lab Clin Med* 1957;50:45-60.
25. Harker LA. Hemostasis manual. 2nd ed. Philadelphia: F A Davis, 1974.
26. Klauss A. Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. *Acta Haematol* 1957;17:237-46.
27. Allington MJ. Detection of fibrinogen degradation products by a latex clumping method. *Scand J Haematol* 1971;13(suppl):115-9.
28. Babson SR, Babson AL. Development and evaluation of a disposable device for performing simultaneous duplicate bleeding time determination. *Am J Clin Pathol* 1978;70:406-8.
29. Langedell RD, Wagner RH, Brinkhous KM. Effect of antihemophilic factor on one-stage clotting test. A presumptive test for hemophilia and a simple one-stage antihemophilic factor assay procedure. *J Lab Clin Med* 1953;41:637-67.
30. Vander Woude JC, Milam JD, Walker WE, Houchin DP, Weiland AP, Cooley DA. Cardiovascular surgery in patients with congenital plasma coagulopathies. *Ann Thorac Surg* 1988;46:283-6.
31. Harker LA. Bleeding after cardiopulmonary bypass. *N Engl J Med* 1986;314:1446-8.
32. Hardy JF, Perrault J, Tremblay N, Robitaille D, Blain R, Carrier M. The stratification of cardiac surgical procedures according to use of blood products: a retrospective analysis of 1480 cases. *Can J Anaesth* 1991;38:511-7.
33. Weintrobe MW, Lee CR, et al., eds. Clinical hematology. 8th ed. Philadelphia: Lea and Febiger, 1981:1045-71.
34. Hattersley PG. Activated coagulation time of whole blood. *JAMA* 1966;196:436-40.
35. Gravlee G, Goldsmith J, Low J, Harrison G, Branch J. Heparin sensitivity comparison of the ACT, SCT, and APTT. *Anesthesiology* 1989;71:A4.
36. Hooper TL, Conroy J, McArdie B, et al. The use of the Hemochron in assessment of heparin reversal after cardiopulmonary bypass. *Perfusion* 1988;3:295-300.

37. Ottesen S, Stormorken H, Hatteland K. The value of activated coagulation time in monitoring heparin therapy during extracorporeal circulation. *Scand J Thor Cardiovasc Surg* 1984;18:123-8.
38. Kase PB, Dearing JP. Factors affecting the activated clotting time. *J Extracorp Technol* 1985;17:27-30.
39. Moorehead MT, Westengard JC, Bull BS. Platelet involvement in the activated coagulation time of heparinized blood. *Anesth Analg* 1984;63:394-8.
40. Kesteven PJ, Pasaoglu I, Williams BT, Savidge GF. Significance of the whole blood activated clotting time in cardiopulmonary bypass. *J THORAC CARDIOVASC SURG* 1986;27:85-9.
41. Dutton DA, Hothersall AP, McLaren AD, Taylor KM, Turner MA. Protamine titration after cardiopulmonary bypass. *Anaesthesia* 1983;38:264-8.
42. Czer LSC. Mediastinal bleeding after cardiac surgery: etiologies, diagnostic considerations, and blood conservation methods. *J Cardiothorac Anesth* 1989;3:760-75.
43. Salzman EW, Weinstein MJ, Weintraub RM, et al. Treatment with desmopressin acetate to reduce blood loss after cardiac surgery. *N Engl J Med* 1986;314:1402-6.
44. Dilthey G, Dietrich W, Spannagl M, Richter JA. Influence of desmopressin acetate (DDAVP) on homologous blood requirement in cardiac surgical patients pretreated with platelet-inhibiting drugs. *J Cardiothorac Vasc Anesth* 1993;7:245-30.
45. Mongan PD, Husking MP. The role of desmopressin in patients undergoing coronary artery bypass surgery: a controlled clinical trial with thromboelastographic risk stratification. *Anesthesiology* 1992;77:38-46.
46. Counts RB, Haisch C, Simon TL, Maxwell NG, Heimbach DM, Carrico CJ. Hemostasis in massively transfused trauma patients. *Ann Surg* 1979;190:91-9.
47. Ellison N, Jobes DR. Effective hemostasis in cardiac surgery. Philadelphia: WB Saunders, 1988:75-6.
48. Ciavarella D, Reed RL, Counts RB, et al. Clotting factor levels and the risk of microvascular bleeding in the massively transfused patient. *Br J Haematol* 1987;67:365-8.
49. Ansell J, Holden A, Knapic N. Patient self-management of oral anticoagulation guided by capillary (fingerstick) whole blood prothrombin times. *Arch Intern Med* 1989;149:2509-11.
50. Ansell J, Tiarks C, Hirsh J, McGehee W, Adler D, Weibert R. Measurement of the activated partial thromboplastin time from a capillary (fingerstick) sample of whole blood. *Am J Clin Pathol* 1991;95:222-7.