338

# On-site Prothrombin Time, Activated Partial Thromboplastin Time, and Platelet Count

## A Comparison between Whole Blood and Laboratory Assays with Coagulation Factor Analysis in Patients Presenting for Cardiac Surgery

G. J. Despotis, M.D.,* S. A. Santoro, M.D., Ph.D.,† E. Spitznagel, Ph.D.,‡ K. M. Kater, M.S.N.,§
P. Barnes,‖ J. L. Cox, M.D.,# D. G. Lappas, M.D.**

*Background:* Although available hemostasis assays from institutional laboratories permit an analytical approach to diagnosis and treatment of coagulation disorders following cardiopulmonary bypass, their clinical utility has been limited by delays in obtaining results. The development of instrumentation for on-site testing allows rapid return of results. This study was designed to compare whole blood (WB) results obtained from on-site coagulation assays with values provided by our institutional laboratory (LAB).

*Methods:* After Institutional Human Studies Committee approval, 362 patients presenting for cardiac surgery requiring cardiopulmonary bypass were enrolled in this study. Prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count (PLT) assays were performed in both WB and LAB systems. PT, aPTT, and PLT measurements were compared between WB and LAB assays using blood specimens obtained from at least two time points for each patient. Normal range values for both PT and aPTT methods were determined by using measurements from a normal reference population. Coagulation factor levels were measured in a sub-set of patients to characterize the response of PT and aPTT assays to individual and multiple factor levels. To employ Bayes' theorem and calculate predictive indexes (*e.g.*, sensitivity, specificity), the disease or factor deficiency was determined using factor levels. Predictive indexes were used to evaluate the ability of PT and aPTT assays to identify factor deficiency.

*Results:* PLT counts were similar between systems. Linear regression and bias analysis demonstrated similar results for WB and LAB PT and discordant results for aPTT measurements. Both PT assays had a similar normal range, whereas a wider distribution of results was evident for the WB aPTT normal range. Although statistically greater slopes for factor:aPTT regressions were observed for the WB system, WB aPTT correlated better with factor V and with factor V, VIII, and XII levels (multivariate linear regression). Diagnostic performance for factor levels less than 0.3 and 0.4 U/ml was similar for both WB and laboratory PT and aPTT assays. WB and LAB PT and aPTT assays performed similarly in detecting factor deficiency in the period after cardiopulmonary bypass.

*Conclusions:* WB PT and PLT values correlate well with those obtained from the LAB. The discrepancy between measurement systems in aPTT values is probably a reflection of both different normal ranges and responsiveness to factor deficiency. These WB assays provide coagulation results that can accurately identify patients with quantitative deficiencies in platelets and coagulation factors. (Key words: Coagulation: activated partial thromboplastin time; platelet count; prothrombin time. Monitoring: coagulation. Surgery: cardiac.)

* Assistant Professor of Anesthesiology.

† Professor of Pathology and Medicine.

‡ Professor of Mathematics.

§ Cardiovascular Nurse Specialist.

‖ Assistant Director of Laboratories, Barnes Hospital, St. Louis, Missouri.

# Professor of Surgery; Chief of Cardiothoracic Surgery.

** Professor of Anesthesiology; Chief of Cardiothoracic Anesthesiology.

COAGULATION disorders following cardiopulmonary bypass (CPB) pose diagnostic and therapeutic challenges because of their multifactorial etiology and potentially life-threatening nature.[1–6] Use of a panel of rapidly performed screening tests such as the prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time, platelet count (PLT), and fibrinogen level has been recommended to delineate the etiology of intraoperative disorders of hemostasis.[7] Although laboratory coagulation assays facilitate ra-

tional diagnosis and treatment of coagulation disorders following CPB, delays in obtaining results limit their clinical use. The clinical utility of rapid determination of whole blood (WB) PT, aPTT, and PLT in the operating room has been evaluated in a randomized, prospective trial using a transfusion algorithm based on these on-site coagulation results.[8] This study demonstrated that use of on-site coagulation assays can reduce blood product administration, decrease operative time, and minimize mediastinal chest tube drainage. This study did not directly address the diagnostic performance of these WB coagulation assays or compare them to corresponding assays from our institutional laboratory.

As previously addressed, three questions commonly asked when evaluating the performance of a new assay include: Is there a difference between results from the new assay and a "gold standard"? If there is a difference, is this difference great enough to make one of the methods inaccurate? When the measurements from the new test are repeated, what is the precision of the new test?[9] This approach provides an appropriate comparison of PLT measurements between a laboratory "gold standard" and an on-site measurement obtained by nonlaboratory personnel. Comparison of aPTT assays between coagulation monitoring systems is complicated by the fact that several variables can influence aPTT values measured by two different laboratory systems.[10,11] Therefore, an aPTT standard does not exist because of the inconsistent sensitivity of available reagents to heparin or coagulation factor deficiency and because of the variability associated with different methods. Similarly, comparisons of PT assays are complicated by significant measurement variability secondary to the variation in performance between different thromboplastin reagents.[12] Moreover, in patients with reductions of multiple factors, significant variability (30–35%) unrelated to underlying clotting factor levels can occur in PT results.[13] Comparison of PT and aPTT (PT:aPTT) assays between methods, therefore, should not be limited to the absolute difference of measurements between assay systems with standard statistical analysis. These analyses should be replaced with statistical methods that assess the correlation of measurements from each method with coagulation factor levels. In addition, statistical methods that evaluate diagnostic accuracy or a test's ability to predict factor deficiency should be employed.

The present study compares results obtained from on-site WB assays with those obtained from corresponding assays performed in our institutional laboratory. The performance of PT and aPTT assays from both systems is evaluated with factor level analysis.

## Methods and Materials

Patients in this study were drawn from a series of 362 consecutive adult patients undergoing cardiac surgery requiring CPB at the authors' institution after approval by the Institutional Human Studies Committee. All patients were anesthetized with an opioid-based technique, and the anesthetic was supplemented with inhalational anesthetic agents, muscle relaxants, and benzodiazepines. CPB was accomplished with a Biomedicus centripetal pump and a Cobe membrane oxygenator. Our perfusion staff routinely primed the CPB system with 2 l of Plasmalyte solution, 50 mEq sodium bicarbonate, 25 g Mannitol, and 5,000 U of porcine heparin. During cardioplegia, 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 anticoagulation for CPB was assessed by means of the activated clotting time (ACT), and further doses of heparin were administered as needed to maintain an ACT of >480 s. After rewarming the patient to 37° C, extracorporeal circulation was discontinued and heparin was neutralized with protamine (0.8 mg of protamine per milligram of total heparin administered before and during CPB).

Times for collecting blood specimens for hematologic assays were as follows: period 1 (pre-CPB), before systemic anticoagulation with heparin for CPB; period 2 (post-CPB), after the neutralization of heparin with protamine; and period 3 (pre-ICU), at the termination of the operation. Aliquots from the same blood specimen obtained *via* radial or femoral intraarterial catheters after removal of six deadspace volumes were used for hemostasis analysis by both laboratory and on-site laboratory systems.

On-site hematologic assays included WB PT, aPTT (WB aPTT), PLT, and ACT. On-site PLTs (T540 PLT) were determined electronically by the Coulter T540 hemocytometer (Hialeah, FL). WB PT and aPTT were determined by a battery-powered portable instrument (Biotrack 512, Ciba Corning, Medfield, MA) that uses disposable plastic reagent cartridges as described by Lucas *et al.*[14] After cartridge prewarming (to 37° C), a drop (minimum of 25 μl) of nonanticoagulated WB was applied to the cartridge. The specimen was drawn

by capillary action into the reagent chamber where the reagent was rehydrated with either thromboplastin (PT) or a chemical activator and soybean phosphatide (aPTT). The cessation of blood flow when the blood sample coagulates is sensed by a laser photometer. The elapsed time to coagulation is converted mathematically to a plasma equivalent PT or aPTT. WB ACT also was determined intraoperatively with a Hemochron instrument (International Technidyne, Edison, NJ). On-site WB PT, aPTT, and PLT results were obtained within 1 to 2 min and were assayed in duplicate.

The standard laboratory assays included the one-stage PT, a modification of the method initially described by Quick *et al.,*[15] performed on citrate anticoagulated plasma using a rabbit brain thromboplastin (Ortho Diagnostics, Raritan, NJ) and a Coagulab 40A analyzer (Ortho Diagnostics); and the aPTT, a modification of the method initially described by Proctor and Rapaport,[16] also performed on citrate anticoagulated plasma using the Coagulab 40A analyzer and Thrombosil reagent (Ortho Diagnostics). Thrombin times with protamine correction were determined by a modification of the method as described by Jim.[17] Fibrinogen levels were determined by the method of Clauss.[18] Fibrin split product levels were measured with Dade reagent using the latex method as described by Allington.[19] Bleeding times were performed with the Simplate technique as described by Babson and Babson.[20] PLTs were performed electronically with the Coulter S + 4, an automated Coulter hemocytometer.

After laboratory processing, a plasma aliquot of each blood specimen collected from two periods (pre-CPB and post-CPB) was labeled, frozen, and stored for potential factor analysis. Levels for factors V, VII, VIII, IX, X, and XII were determined on a subset of patients (n = 73) from both pre-CPB and post-CPB intervals; one-stage factor assays were done by the method of Quick[15] for the PT-based assays and by the method of Langdell *et al.*[21] for the aPTT-based assays. Patient selection for factor analysis was based on the distribution of patients (%) within three laboratory aPTT categories. 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. The aPTT categories included: category 1, aPTT < 1.5 × C

‡‡ British Standards Institution: Precision of Test Methods I: Guide for the Determination and Reproducibility for a Standard Test Method. British Standards 5497, Part 1. London, British Standards Institute, 1979.

(mean result derived from a normal reference population); category 2, 1.5 × C < aPTT < 1.8 × C; and category 3, 1.8 × C < aPTT.

All test results were recorded, and PT:aPTT values obtained from WB and LAB assays were expressed as the mean of duplicate measurements. Blood specimens were obtained in the pre-CPB interval from a normal population of patients who were not receiving preoperative heparin or warfarin. WB and laboratory PT: aPTT measurements from this normal reference population of patients were used to determine normal range values (n = 189). The normal range was defined as the mean or control (C) value ± 2 SD obtained from a normal reference population.

Ordinary (nonweighted) least squares linear regression was used to estimate a linear relationship between measurements obtained from the PT, aPTT, and PLT assays for the two methods ($P < 0.05$ considered statistically significant). Bias analysis was used to test agreement between values obtained from each method for the PT, aPTT, and PLT assays.[22] Between-machine repeatability of the WB PT and aPTT assays was assessed by calculating the coefficient of repeatability (defined as twice the standard deviation of the difference between replications of a measurement)‡‡ using two separate Biotrack machines.

WB and LAB methods were compared by analyzing the response of PT and aPTT assays to individual coagulation factor levels with univariate linear regression. These relationships were illustrated with logarithmically transformed variables on log-log plots to generate a better linear fit, as previously described.[23] Coagulation factors that demonstrated a significant association with both PT and aPTT assays with univariate analysis were subjected to stepwise multivariate linear regression analysis using a backward elimination procedure. At each stage of the elimination procedure, the coagulation factor with the largest current $P$ value was eliminated until all remaining factors were or became statistically significant ($P < 0.05$). This resulted in three significant factors for each assay: factors V, VII, and X for the PT assay and factors V, VIII, and XII for the aPTT assay. Additional comparisons between methods were made by analyzing the response of PT and aPTT assays to each set of the three remaining factors with multivariate linear regression. These comparisons were illustrated graphically with logarithmically transformed variables on log-log plots for each assay, PT and aPTT. The bootstrap method was used to test for equality of slopes for each regression.[24]
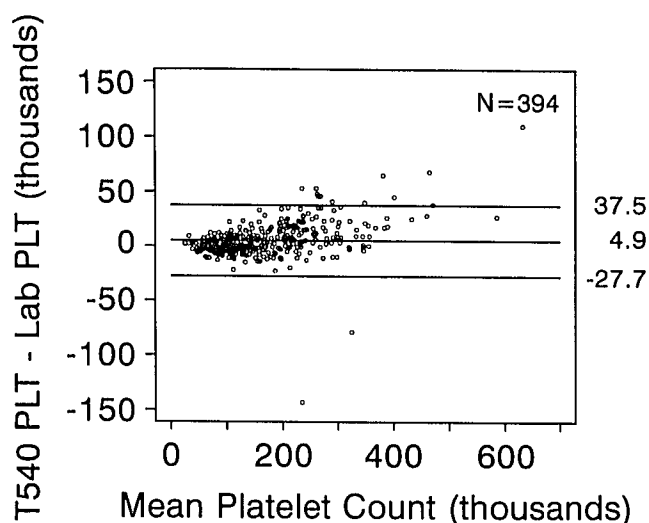
Fig. 1. Bias analysis of laboratory (LAB PLT) *versus* Coulter T540 (T540 PLT) platelet count measurements (in thousands). The difference between T540 PLT and LAB PLT measurements is plotted on the y axis, and the average of these two PLT measurements is plotted on the x axis. The mean differences ±2 SD are recorded on along the right axis and represented by the horizontal lines in the graph. N = number of measurements used in the analysis.

Bayes' theorem has been used in previous reports to evaluate the diagnostic performance of assay systems.[25] Using this statistical method to evaluate diagnostic accuracy of an assay requires the definition of two fundamental variables: (1) a disease state and (2) an abnormal test result. In the analysis of our data, the disease state was coagulation factor deficiency and this state was defined at three separate factor levels (set-points): detection of at least one coagulation factor less than 0.20, 0.30, or 0.40 U/ml. Positive test results were defined using two criteria: (1) PT or aPTT measurements were positive when equal to or greater than the upper limit of the normal range (mean + 2 SD) derived from a normal reference population, as previously described;[26] and (2) PT or aPTT measurements were positive when equal to or greater than a defined control value (*e.g.*, 1.5 C, 1.8 C). For each factor deficiency state (set-point) and positive test result, Bayes' theorem was used to calculate predictive indexes. Sensitivity is defined as the percentage of patients with a factor deficiency who have a positive test result. The specificity is defined as the percentage of patients without a factor deficiency who have a negative test result. Positive predictive value is defined as the percentage of patients with a positive test result who have a factor deficiency.

Negative predictive value is defined as the percentage of patients with a negative test result who do not have a factor deficiency. Accuracy was defined as the proportion of correctly predicted cases, positive or negative.

To compare the diagnostic performance of PT and aPTT assays between systems, predictive indexes (*e.g.*, sensitivity, specificity) were calculated using pre- and post-CPB data. Commonly defined positive PT and aPTT test results (PT or aPTT result at or above the upper limit of the normal range) along with two representative reagent sensitivities (0.3 and 0.4 U/ml factor level set-points) were used in this analysis. In a separate analysis using post-CPB results, predictive indexes were calculated over a series of control values (PT or aPTT result ≥1.5 C, 1.8 C, and so on) to enable clinicians to evaluate the predictive value (positive and/or negative) of a particular result in this critical period. Accordingly, predictive indexes were generated over various control values at the 0.20 and 0.30 U/ml factor level set-points because it has been suggested that these levels of factor V and X are required for normal hemostasis.[27]

## Results

### Linear Relationship and Bias Analysis of PT, aPTT, and PLT Measurements between Methods

**Platelet Count Measurements.** Linear regression revealed a good relationship between the PLT obtained from the on-site laboratory (T540) to that obtained from the institutional laboratory (T540 = 1.07LAB − 5.73, $r^2$ = 0.98). Figure 1 depicts the bias analysis that demonstrated a mean difference of +4,900 with ± 2 SD limits of −27,700 to +37,500. A value less than 150,000 is considered to be an abnormal result in our institutional laboratory. When the range of PLT measurements is divided into those equal to or less than 150,000 and those greater than 150,000, the mean difference with ± 2 SD limits is much smaller for the group less than 150,000 (+580: −12,900 to 14,100) than for the group greater than 150,000 (+10,340: −34,000 to 55,700).

**PT Measurements.** A good relationship between WB PT values (WB measurements that are converted mathematically to plasma equivalent values) and the LAB PT is demonstrated with linear regression (WB = 1.07LAB − 1.30, $r^2$ = 0.86). Figure 2 characterizes the bias analysis that demonstrated a mean difference of −0.1 s with 2 SD limits of −3.5 to +3.3 s.
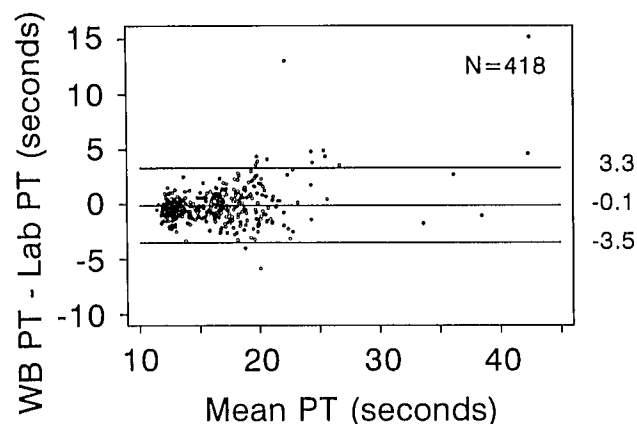
Fig. 2. Bias analysis of prothrombin time (PT) measurements (in s) of laboratory (LAB PT) *versus* whole blood (WB PT). WB PT measurements are converted mathematically to plasma equivalent values derived from the Biotrack 512. The difference between WB PT and LAB PT measurements is plotted on the y axis, and the average of these two PT measurements is plotted on the x axis. The mean differences ±2 SD are recorded on along the right axis and represented by the horizontal lines in the graph. N = number of measurements used in the analysis.

**aPTT Measurements.** In contrast, linear regression reveals a variable relationship between WB aPTT values (WB measurements that are converted mathematically to plasma equivalent values) to LAB aPTT measurements (WB = 0.85LAB + 16.45, $r^2$ = 0.63). This variability in aPTT values obtained from both methods also is demonstrated with bias analysis, which reveals a mean difference of +10 s with 2 SD limits of −18.8 to +38.8 s (fig. 3).

*Between-machine Reproducibility for WB PT and aPTT.* Between-machine reproducibility of the WB PT assay was assessed with bias analysis with results from two Biotrack machines (A:B). Bias analysis revealed a mean PT measurement difference of +0.1 s (2 SD −1.3 to +1.6 s; range −3.9 s to +2.6 s) between machines. Similarly, between-machine reproducibility of the WB aPTT assay was assessed with bias analysis. Bias analysis revealed a mean aPTT measurement difference of +0.5 s (2 SD −2.5 to +3.4 s; range −6.2 to +8.1 s) with results from two machines. Both WB assays perform well in repeatability as assessed by the coefficient of repeatability (twice the standard deviation of the difference between replications of a measurement) for each assay (PT: 1.44 s;aPTT:2.94 s).**

*Normal Range for PT and aPTT Measurements.* Normal range values, defined as the range of measurements (mean ± 2 SD) obtained from a normal reference population were determined for both PT and aPTT assays from both systems. The mean (WB 12.8 s, LAB 13 s) and normal range (WB 11–14.7 s, LAB 11.4–14.6 s) values for the PT assay are similar between methods. Although the mean aPTT values for a normal population are comparable between methods (WB 32 s, LAB 29 s), WB aPTT values have a wider distribution than those from the laboratory, as indicated by a wider normal range (WB 19–45 s, LAB 23–36 s).

*Response of PT:aPTT to Factor Levels.* Factors V and X had the most significant impact on both the PT and aPTT assays as assessed by univariate regression. The relationship of both assays to factor X and factor V had a similar fit with both PT methods, as illustrated by the $r^2$ values in figure 4. Both WB and laboratory PT methods responded similarly to factor X and factor V levels as assessed by the comparison of slopes between regressions (factor V regression slopes −0.30 *vs.* −0.29, respectively, *P* = 0.177; factor X slopes −0.39 *vs.* −0.37, respectively, *P* = 0.083). In contrast, the regression lines in figure 5 illustrate a different response to factor V and factor X between aPTT methods. The slopes for both factor V and X regressions *versus* aPTT result (fig. 5) were different between WB and laboratory
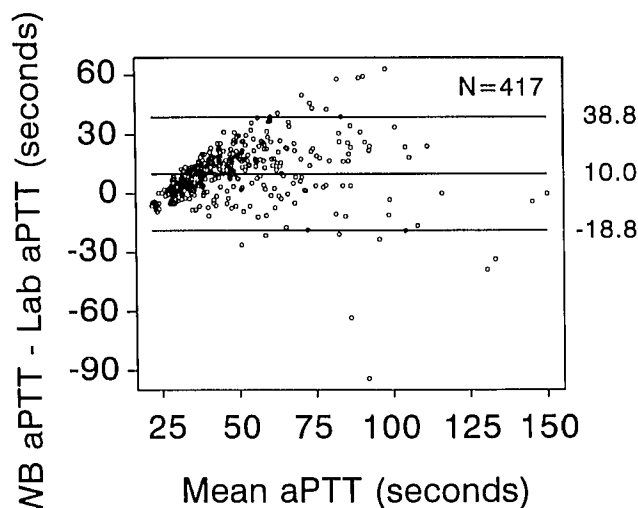


Fig. 3. Bias analysis of activated partial thromboplastin time (aPTT) measurements (in s) of laboratory (LAB aPTT) *versus* whole blood (WB aPTT). WB aPTT measurements are converted mathematically to plasma equivalent values derived from the Biotrack 512. The difference between WB aPTT and LAB aPTT measurements is plotted on the y axis, and the average of these two aPTT measurements is plotted on the x axis. The mean differences ±2 SD are recorded on along the right axis and represented by the horizontal lines in the graph. N = number of measurements used in the analysis.
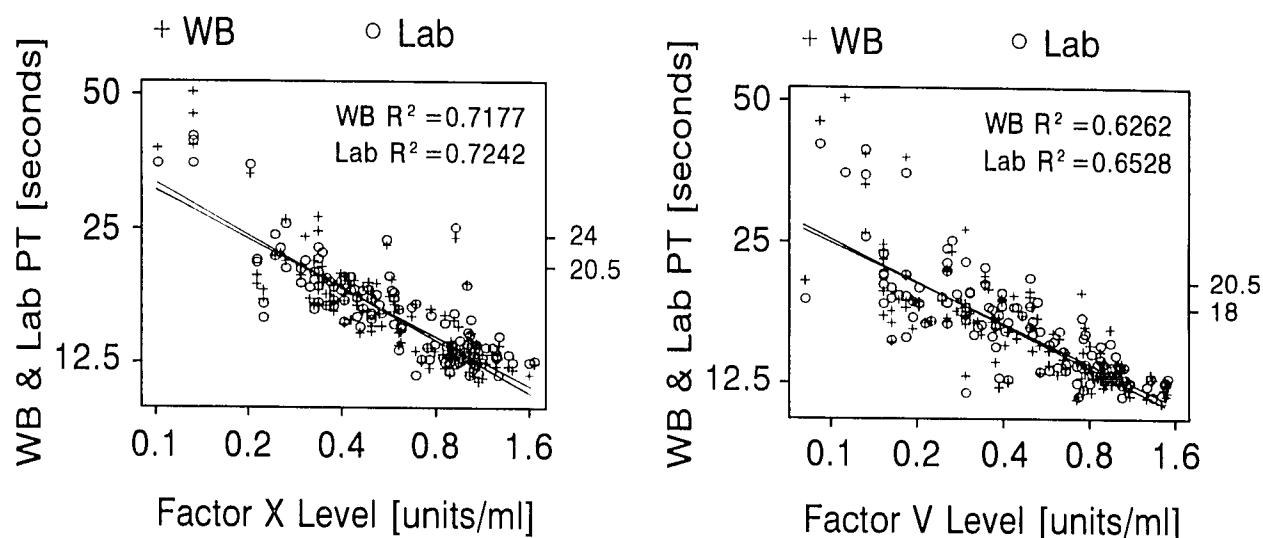
343

Fig. 4. Factor V and factor X levels (normal range 0.5–1.5 U/ml) *versus* laboratory (LAB) and whole blood (WB) prothrombin time (PT). WB PT measurements are converted mathematically to plasma equivalent values derived from the Biotrack 512. $r^2$ = % variance explained. Numbers along the right axis of the factor X graph represent LAB and WB PT values at 0.2 (24 s) and 0.3 U/ml (20.5 s). Numbers along the right axis of the factor V graph represent LAB and WB aPTT values at 0.2 (20.5 s) and 0.3 U/ml (18 s). Linear regression slopes and correlations ($r^2$) of PT to factors V and X were statistically the same ($P > 0.05$) between WB and LAB assays.
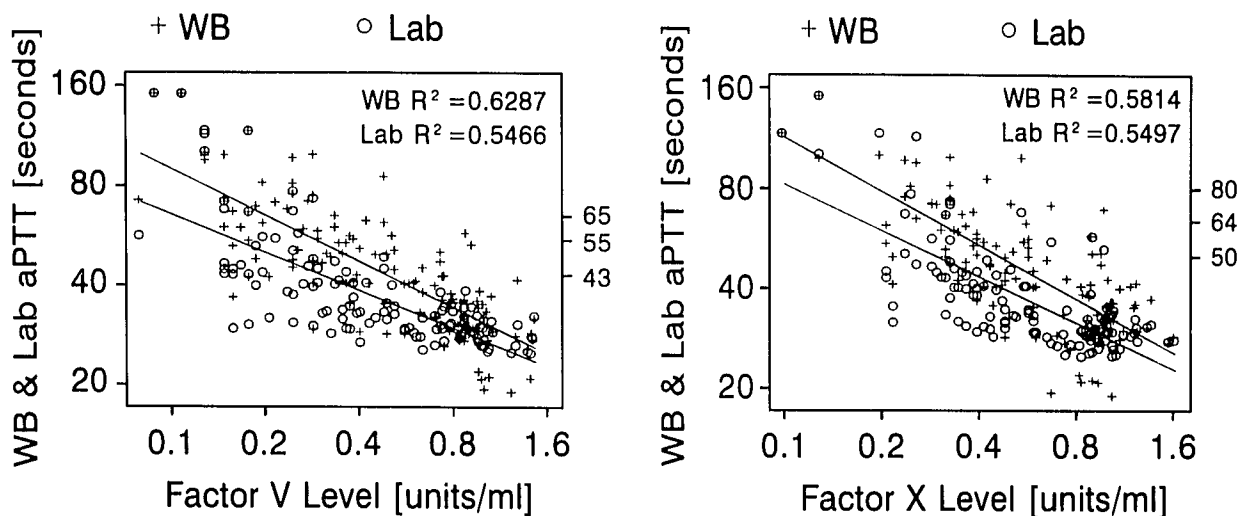


Fig. 5. Factor V and factor X levels (normal range 0.5–1.5 U/ml) *versus* laboratory (LAB) and whole blood (WB) activate partial thromboplastin time (aPTT). WB aPTT measurements are converted mathematically to plasma equivalent values derived from the Biotrack 512. $r^2$ = % variance explained. Numbers along the right axis of the factor V graph represent LAB values at 0.2 (55) and 0.3 (43) U/ml; numbers along the right axis of the factor V graph represent WB values at 0.2 (65) and 0.3 (55) U/ml. Numbers along the right axis of the factor X graph represent LAB aPTT values at 0.2 (64) and 0.3 (50) U/ml; numbers along the right axis of the factor X graph represent WB values at 0.2 (80) and 0.3 (64) U/ml. An increased sensitivity of WB aPTT (top line) to both factor V ($P = 0.003$) and factor X ($P = 0.03$) is illustrated by greater linear regression slopes when compared to LAB aPTT (bottom line). When compared to LAB aPTT, WB aPTT correlated better with factor V, as indicated by a greater $r^2$ value ($P = 0.01$); both aPTT assays correlated similarly to factor X.

methods (factor V slopes −0.46 *vs.* −0.38, respectively, $P = 0.003$; factor X slopes −0.54 *vs.* −0.46, respectively, $P = 0.034$). Linear regression analysis involving single coagulation factors (fig. 5) revealed that WB aPTT correlates better to factor V than does LAB aPTT, as illustrated by a statistically greater $r^2$ value ($P = 0.01$). Both aPTT assays had a similar correlation to factor X levels.

A multivariate linear regression model was used to determine the impact of variable levels of multiple coagulation factors on PT and aPTT assays. Factors V, VII, and X correlated with results from both PT assays (WB $r = 0.9$; LAB $r = 0.9$), whereas factors V, VIII, and XII correlated with results from both aPTT assays (WB 0.88; LAB 0.82). Three factor composite values were derived from the multivariate regression between PT and aPTT assays and respective coagulation factors (PT factors V, VII, X; aPTT factors V, VIII, XII). These composite factor values (x) were used to generate graphs to compare the PT and aPTT response between methods (fig. 6). The superimposed regression lines in the PT graph illustrate the similarity in response to factors V, VII, and X depletion between methods (WB PT = −0.47x + 4.78, LAB PT = −0.44x + 4.67). In contrast, the

regression lines in the aPTT graph illustrate the difference in aPTT response to reductions in factors V, VII, and XII between methods (WB aPTT = −0.68x + 6.60, LAB aPTT = −0.57x + 5.94). This disparity is statistically significant, as confirmed by a greater WB aPTT response to factors V, VIII, and XII (WB −0.68, LAB −0.57, $P = 0.004$). When compared to LAB aPTT, WB aPTT correlates better to factors V, VIII, and XII, as illustrated by statistically greater $r^2$ values in figure 6 ($P = 0.002$).

*Diagnostic Performance of PT:aPTT Assays to Factor Deficiency.* To assess diagnostic performance, predictive indexes (*e.g.*, sensitivity, specificity) for the PT and aPTT assays were determined using two criteria for factor deficiency (factor level set-points): (1) at least one coagulation factor less than 0.30 U/ml, and (2) one coagulation factor less than 0.40 U/ml. Table 1 summarizes the predictive indexes for positive PT and aPTT results for each method at each factor level set-point (n = 126). Inspection of table 1 verifies that the highest levels of accuracy (asterisks) are at the same factor level set-point for both PT assays. Table 1 also confirms that the WB aPTT assay predicts factor deficiency in a similar fashion.
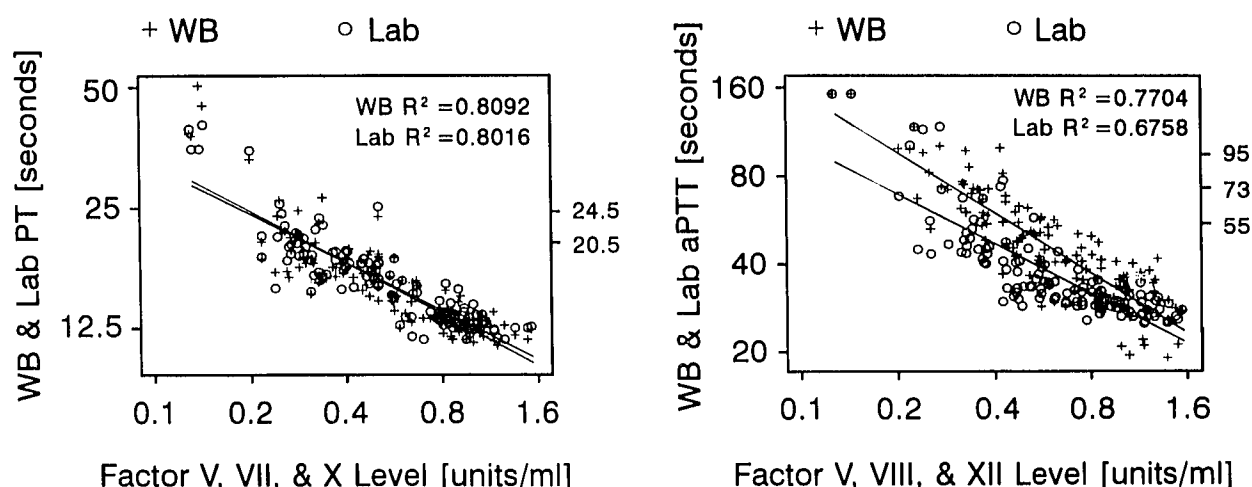


Fig. 6. Factors V, VII, and X *versus* laboratory (LAB) and whole blood (WB) prothrombin time (PT); factors V, VII, and XII *versus* LAB and WB activated partial thromboplastin time (aPTT). The relationship of WB and LAB PT to factors V, VII, and X is illustrated in the graph to the left. The relationship of WB and LAB aPTT to factors V, VIII, and XII is illustrated in the graph to the right. These factor composites were generated from the factors that were significant ($P < 0.05$) with multivariate linear regression (see text). WB PT and aPTT measurements are converted mathematically to plasma equivalent values derived from the Biotrack 512. $r^2$ = % variance explained. Numbers along the right axis in the PT graph represent LAB and WB PT values at 0.2 (24.5 s) and 0.3 (20.5 s) U/ml. Numbers along the right axis in the aPTT graph represent LAB aPTT values at 0.2 (73 s) and 0.3 (55 s) U/ml *versus* WB aPTT values at 0.2 (95 s) and 0.3 (73 s) U/ml. An increased sensitivity of WB aPTT (top line) to factors V, VIII, and XII is illustrated by a greater linear regression slope ($P = 0.001$) when compared to LAB aPTT (bottom line). When compared to LAB aPTT, WB aPTT correlated better with factors V, VIII, and XII, as indicated by a greater $r^2$ value ($P = 0.002$). In contrast, both PT assays correlated similarly to factors V, VII, and X.

**Table 1. Diagnostic Performance of Activated Partial Thromboblastin Time (aPTT) and Prothrombin Time (PT) to Factor Deficiency**

|  | Assay | Method | Sensitivity | Specificity | Predictive Value (+) | Predictive Value (−) | Accuracy |
|---|---|---|---|---|---|---|---|
| 1 factor <0.3 U/ml | PT | WB | 98 | 74 | 68 | 98 | 83 |
|  |  | Lab | 98 | 68 | 64 | 98 | 79 |
| 1 factor <0.4 U/ml | PT | WB* | 93 | 85 | 85 | 93 | 89 |
|  |  | Lab* | 95 | 79 | 80 | 95 | 87 |
| 1 factor <0.3 U/ml | aPTT | WB | 85 | 78 | 68 | 90 | 80 |
|  |  | Lab* | 83 | 89 | 81 | 90 | 87 |
| 1 factor <0.4 U/ml | aPTT | WB* | 81 | 89 | 88 | 83 | 85 |
|  |  | Lab | 73 | 97 | 96 | 79 | 85 |

Method refers to either whole blood (WB: Biotrack 512) or laboratory (Lab) assays. Specimens from both pre- and post-CPB intervals were used to evaluate depletion of coagulation factors that affect the aPTT assay (V, VIII, IX, X) and the PT assay (V, VII, X). Factor depletion was defined at two factor level setpoints: detection of at least one coagulation factor <0.3 and <0.4 U/ml. Predictive indices (e.g., sensitivity, specificity) were calculated using Bayes' theorem at each factor level setpoint when a result was considered positive (see text). PT or aPTT results are considered positive when results are equal or greater than the upper limit (mean + 2 SD) of the normal range (from a normal reference population): WB PT ≥15 s, Lab PT ≥16 s, WB aPTT ≥45 s, Lab ≥35 s.

* Optimal diagnostic performance as determined by the greatest accuracy value for each respective assay.

But unlike the PT assay, the highest level of accuracy for the WB aPTT is at a higher coagulation factor level set-point (0.4 U/ml).

*Diagnostic Performance of PT:aPTT Assays to Factor Deficiency in the Post-CPB Interval.* Using post-CPB results, predictive indexes (e.g., sensitivity, specificity) were calculated over a series of control values (PT or aPTT >1.5 C, 1.8 C, and so on). As previously addressed, control values are defined as the mean value from a normal reference population. Table 2 lists the predictive

indexes for both WB and LAB methods when the diagnostic criterion is set at one coagulation factor less than 0.30 U/ml (n = 71). Table 3 lists the predictive indexes for both methods when the diagnostic criteria is set at one coagulation factor less than 0.20 U/ml (n = 71). Within these tables, the asterisk identifies the ratio value at which the positive predictive value approximates 90%. Predictive indexes for the PT assay are similar at the same control value for both WB and LAB methods. Similar predictive indexes for the aPTT assay are

**Table 2. Predictive Indices for a Coagulation Factor Level <0.3 U/ml (Normal Range 0.5–1.5 U/ml) in the Post-Cardiopulmonary Bypass Interval over a Series of Control Values (e.g., 1.5C, 1.8C)**

|  | Method | Result (s) | Sensitivity | Specificity | Predictive Value (+) | Predictive Value (−) |
|---|---|---|---|---|---|---|
| PT >1.3C | WB | 16.6 | 89 | 64 | 66 | 85 |
|  | Lab | 16.9 | 85 | 60 | 65 | 82 |
| PT >1.5C | WB* | 19.2 | 46 | 96 | 91 | 67 |
|  | Lab* | 19.5 | 48 | 100 | 100 | 69 |
| PT >1.8C | WB | 23 | 22 | 100 | 100 | 60 |
|  | Lab | 23.4 | 20 | 100 | 100 | 59 |
| aPTT >1.3C | WB | 41.6 | 93 | 33 | 54 | 82 |
|  | Lab | 38 | 80 | 78 | 75 | 82 |
| aPTT >1.5C | WB | 48 | 80 | 50 | 57 | 75 |
|  | Lab* | 43.5 | 60 | 97 | 93 | 73 |
| aPTT >1.8C | WB* | 57.6 | 69 | 93 | 89 | 78 |
|  | Lab | 52 | 38 | 100 | 100 | 66 |
| aPTT >2.1C | WB | 67.2 | 47 | 96 | 91 | 68 |
|  | Lab | 60.9 | 27 | 100 | 100 | 62 |

Control values (C) are defined as the mean result from a normal reference population for each respective assay. Prothrombin Time (PT) and Activated Partial Thromboblastin Time (aPTT) values for each control value were determined by multiplying the control value by corresponding numeric values (WB PT: 1.5C = 1.5 × 12.8 s = 19.2 s) for both WB and laboratory assays. Method refers to either whole blood (WB: Biotrack 512) or laboratory (Lab) assays. Bayes' Theorem was used to calculate predictive indices for the PT assay using factors V, VII, and X or the aPTT assay using factors V, VIII, IX, and X (see text).

* Control values and predictive indices when positive predictive value approximates 90%.

Table 3. Predictive Indices for a Coagulation Factor Level <0.2 U/ml (Normal Range 0.5-1.5 U/ml) in the Post-Cardiopulmonary Bypass Interval Over a Series of Control Values (*e.g.,* 1.5C, 1.8C)

|  | Method | Result (s) | Sensitivity | Specificity | Predictive Value (+) | Predictive Value (−) |
|---|---|---|---|---|---|---|
| PT >1.3C | WB | 16.6 | 88 | 49 | 34 | 93 |
|  | Lab | 16.9 | 88 | 49 | 36 | 92 |
| PT >1.5C | WB | 19.2 | 50 | 84 | 48 | 84 |
|  | Lab | 19.5 | 54 | 87 | 57 | 86 |
| PT >1.8C | WB* | 23 | 33 | 97 | 80 | 82 |
|  | Lab* | 23.4 | 25 | 97 | 75 | 80 |
| PT >2.1C | WB | 26.9 | 21 | 100 | 100 | 80 |
|  | Lab | 27.3 | 21 | 100 | 100 | 80 |
| aPTT >1.3C | WB | 41.6 | 96 | 26 | 28 | 91 |
|  | Lab | 38 | 91 | 65 | 44 | 96 |
| aPTT >1.5C | WB | 48 | 87 | 43 | 31 | 92 |
|  | Lab | 43.5 | 70 | 83 | 55 | 89 |
| aPTT >1.8C | WB | 57.6 | 78 | 78 | 51 | 92 |
|  | Lab | 52.2 | 48 | 93 | 69 | 86 |
| aPTT >2.5C | WB | 80 | 35 | 93 | 62 | 83 |
|  | Lab* | 72.5 | 26 | 97 | 75 | 81 |
| aPTT >3.0C | WB* | 96 | 26 | 97 | 75 | 81 |
|  | Lab | 87 | 26 | 100 | 100 | 82 |

Control values (C) are defined as the mean result from a normal reference population for each respective assay. PT and aPTT values for each control value were determined by multiplying the control value by corresponding numeric values (WB PT: 1.5C = 1.5 × 12.8 s = 19.2 s) for both WB and laboratory assays. Method refers to either whole blood (WB: Biotrack 512) or laboratory (Lab) assays. Bayes' theorem was used to calculate predictive indices for the PT assay using factors V, VII, and X or the aPTT assay using factors V, VIII, IX, and X (see text).
* Control values and predictive indices when positive predictive value approximates 90%.

achieved for each method, but because of the scale differences of the two measurement systems, comparable predictive indexes are achieved at different control values. If diagnostic performance is defined as comparable predictive indexes, then the WB aPTT assay predicts factor deficiency similarly but at a different control value.

## Discussion

The etiology of coagulation disorders after CPB may include one or more of the following: (1) qualitative[3,4] or quantitative platelet abnormalities,[1,2] (2) isolated or combined coagulation factor depletion,[4-6] and less commonly, (3) excess heparin, (4) disseminated intravascular coagulation (DIC),[28-30] or (5) isolated primary fibrinolysis.[31-33] The ACT, which remains the accepted standard for the determination of adequate anticoagulation during CPB, has a limited role in determining the etiology of microvascular bleeding following CPB. Unfortunately, the ACT is both nonspecific[34-38] and insensitive to various coagulation abnormalities[39,40] including an effect due to circulating heparin.[41] Other tests of coagulation include the Sonoclot and the thromboelastogram (TEG). TEG has been

shown to identify a subset of patients with qualitative platelet abnormalities that respond to desmopressin treatment.[42] In one report, thromboelastography has been shown to predict the risk of postoperative bleeding,[43] whereas other reports have failed to confirm its diagnostic ability to predict either intraoperative[44] or postoperative bleeding.[45] The clinical use of TEG and Sonoclot is limited by the following: Correlation of TEG and Sonoclot viscoelastic measurements to quantitative abnormalities in both PLT and factor levels have not been adequately defined, and a prolonged measurement response time is associated with this instrument.[46] In addition, a prospective, randomized trial to assess the efficacy of hemostatic blood product administration as directed by the either the TEG or Sonoclot is not currently found in the literature. A complete coagulation profile including PT, aPTT, PLT, fibrinogen level, fibrin split product level, and bleeding time can facilitate acquisition of the correct etiology of microvascular bleeding. Unfortunately, results of these coagulation tests often come too slowly, which limits their diagnostic utility. Rapid determination of the etiology of post-CPB microvascular bleeding, therefore, can be difficult to ascertain.

Use of WB PT, aPTT, and PLT in the operating room has been shown to reduce blood product use, operative time, and mediastinal chest tube drainage.[8] This previous study did not directly address the diagnostic performance of these WB coagulation assays or compare them to corresponding assays from our institutional laboratory. In the present study, we compared measurements obtained from these on-site coagulation assays to corresponding assays from our institutional laboratory. In addition, we assessed the correlation and diagnostic performance of PT and aPTT assays from both systems to factor levels. As a first step in the transfusion algorithm, PLT measurements played a fundamental role in the previously addressed efficacy of on-site coagulation monitoring.[8] In this previous trial, quantitative platelet assessment was performed with an established method of assessing PLTs *via* the Coulter T540 hemocytometer (T540). In our current analysis, linear regression and bias analysis data demonstrate that T540 hemocytometer performed similarly to the automated unit from our laboratory. The mean difference is much less in the less-than-150,000 range (+580) than in greater-than-150,000 range (+10,340). The T540 hemocytometer assesses quantitative platelet disorders similarly to the laboratory assay in the critical range at which physicians would make decisions to transfuse platelet concentrates.

It has been recommended that PT and aPTT assays be used to evaluate the need for transfusion of fresh frozen plasma.[7,47,48] This approach has been limited by delays in obtaining PT and aPTT results from institutional laboratories.[8] A new technology can now provide WB PT and aPTT results in a timely fashion at the bedside. In a previous trial, results from the WB PT component of this on-site system have been shown to be useful when assessed in reference to patient self-management of oral anticoagulation.[49] The PT evaluates the extrinsic and common pathways of the coagulation system; significant prolongation occurs when there is a deficiency of factors VII, V, X, prothrombin, or fibrinogen or when there is a circulating inhibitor. Data analysis with both linear regression (r = 0.93) and bias analysis (mean difference −0.1 s) revealed a good correlation for the WB PT with our laboratory method. Analysis of between-machine reproducibility demonstrated that the WB PT assay performed well, as indicated by a low coefficient of repeatability (1.44 s). This is consistent with results obtained from a five-center study that revealed a good correlation between the WB PT and laboratory reference methods (r = 0.96); within-day pre-

cision analysis revealed a good coefficient of variation (4.9%) for the WB PT.[14] Although, the WB PT measurements were comparable with results from our laboratory, it is known that significant measurement variability can occur as a result of the variation in performance between different thromboplastin reagents.[12]

The aPTT evaluates the intrinsic and common pathways; inhibitors that affect function or deficiency of factors XII, XI, IX, VIII, X, V, prothrombin, and fibrinogen prolong the aPTT. Data analysis revealed a disparity in measurements obtained from the WB assay as compared with those obtained from the laboratory aPTT. This is not unexpected given the nonstandardized nature of the aPTT assay. Several variables can influence aPTT measured by two different systems: the nature and concentration of both the activator and phospholipid in the reagent, the buffering of the reagent, ionic strength and concentration of the calcium chloride, *p*H and temperature of the system, the type of instrument, and the variable sensitivity of different commercially available aPTT reagents.[10,11] The bias analysis in figure 3 illustrates the variability in aPTT results obtained between both systems. Bias analysis characterizes this variability as a mean difference of +10 s, indicating that the WB assay returns a consistently greater aPTT value than the aPTT from our laboratory. A similar mean difference (+7 s) was reported in another recent bias analysis.[50] In addition, an extensive comparison of aPTT measurements between the WB assay and standard reference methods was performed in a recent four-center investigation.[51] This study revealed that the correlation coefficients (r) for the WB aPTT and the standard laboratory aPTT ranged from 0.79 to 0.83, depending on the reference reagent and instrumentation used. These correlation coefficients were similar to those obtained for standard LAB aPTTs using different reagents (0.79). While assessed in only two Biotrack instruments, between-machine repeatability of the WB aPTT assay was validated in the present study by a low coefficient of repeatability (2.94 s) obtained from simultaneous measurements of WB aPTT from two separate machines. A high degree of precision was demonstrated in the multicenter trial for the WB aPTT assay.[51] This precision was reflected in low between-day (5.2–8.1%) and within-day (4.9–7.1%) coefficients of variation.

The discrepancy in aPTT measurements between assays can be explained by examining two important characteristics of these systems: normal range and assay response to factor levels. Although mean aPTT values between systems approximate each other in our normal

reference population, the range (±2 SD) of aPTT values is much wider with the WB system. Because of this wider normal range, one might expect abnormal WB aPTT values to be correspondingly farther from the mean result. The PT assays, in contrast, have similar normal distribution curves. The relationship of each aPTT assay to factor reductions with univariate/multivariate regression analyses and predictive performance as assessed with Bayes' theorem uncovers the reason for a variation in aPTT measurements. In contrast, these statistical methods reveal that the PT assays respond in a similar fashion to reductions in factor levels.

Figures 4, 5, and 6 illustrate the incomplete relationship of PT and aPTT measurements to factor levels. In reference to the aPTT assay, this relationship, in part, may be due to our incomplete analysis, which did not include all of the coagulation factors that might affect this assay. In addition, this variability may be a function of the impact of moderate reductions of multiple factors on these assays. Within-method variability of PT and aPTT measurements that is unrelated to factor levels has been described.[13] PT response to reductions of single and multiple factors is similar between systems (figs. 4 and 6). As assessed by regression slopes, WB aPTT response to both isolated (fig. 5) and multiple factors (fig. 6) is statistically greater than LAB aPTT. Although WB aPTT is more sensitive to factor depletion, it correlates better with factor V (fig. 5) and factors V, VIII, and XII (fig. 6).

Bayes' theorem was used to derive the predictive indexes for the diagnosis of factor deficiency. These predictive indexes facilitated the assessment of diagnostic performance of both PT and aPTT assays between systems. Although predictive indexes were constructed using all factors that might affect the respective assays, they were predominately determined by factor V. Factors V and X constituted the factors most commonly reduced below 0.3 U/ml in patients with one factor less than 0.3 U/ml (FV 86%, FX 14%). Similarly, factor V was consistently the factor reduced below 0.2 U/ml in patients with one factor less than 0.2 U/ml (FV 100%). This is in agreement with previous investigations that have indicated that factor V is the most commonly reduced factor after CPB and also is reduced to the greatest degree.[5,52,53] Since our patient population is similar to others from a factor deficiency perspective, use of Bayesian analysis should be appropriate.

A positive PT or aPTT result is defined generally as a measurement that is greater than the normal range. As-

suming the absence of circulating inhibitors, this occurs when a factor is less than a certain level (PT factor II, V, VII, or X <0.3–0.4 U/ml; aPTT factor V, VIII, IX, X, XI, or XII <0.3–0.4 U/ml). Our data indicate that optimal diagnostic performance of the PT assay, as assessed by predictive indexes (*e.g.*, sensitivity, specificity), occurs at the 0.4 U/ml set-point for both methods (table 1). An increased sensitivity of the WB aPTT to reduced factor levels is confirmed by the optimal diagnostic performance of the WB aPTT at a different and higher factor level set-point (WB 0.4 U/ml; LAB 0.3 U/ml). Table 1 illustrates that PT and aPTT assays for both systems perform similarly in reference to diagnosis of factor deficiency states and that differences in aPTT measurements are probably a function of reagent-specific sensitivity. This variability in sensitivity to factor depletion is a well recognized function among numerous reagents. Factor levels required to prolong the aPTT vary from 25% to 40% of normal because of reagent-specific sensitivity.[10,11]

Predictive indexes (*e.g.*, sensitivity, specificity) were generated from results obtained in the period after CPB to assess the diagnostic performance of these assays to coagulation factor deficiency during the interval when treatment would be initiated. The diagnosis of a factor less than 0.2 and 0.3 U/ml was used as the basis for diagnostic performance because this level of either factor V or factor X is required for normal hemostasis.[27] Predictive indexes are tabulated over a series of PT: aPTT control values (*e.g.*, 1.5 C, 1.8 C) to evaluate the diagnostic performance of PT and aPTT assays to factor deficiency in the post-CPB setting (tables 2 and 3). Optimal positive predictive values are associated with lower sensitivities (tables 2 and 3). As previously mentioned, this partly is due to our study design, which involved incomplete but selective determination of factor levels. Predetermination of which coagulation factors were to be assayed was based on their potential importance with microvascular bleeding in this setting. Ultimately, these tables allow the clinician to determine the diagnostic accuracy of a particular result. Although sensitivity values are not optimal at greater control values, positive predictive values establish the probability of a factor deficiency state and, when not optimal, can help a clinician divert an unwarranted transfusion of plasma.

Deficiencies in the current on-site coagulation system include the inability to assess qualitative platelet disorders and excessive fibrinolysis and hypofibrinogenemia. In our cardiac surgical setting, primary fibrino-

lysis is an uncommon cause of microvascular bleeding after heparin neutralization.[8] Although qualitative assessment of circulating platelets would be beneficial, it can be assumed that every patient after CPB has a significant degree of qualitative dysfunction. Therefore, in patients with relatively normal PT:aPTT results, first-line therapy should be directed toward platelets because of the fundamental role qualitative and quantitative platelet dysfunction plays in hemostasis abnormalities in this setting.[48] Severe hypofibrinogenemia, although uncommon, can occur, and this coagulation abnormality can be assessed by prolongation of the PT measurement. In addition, the transfusion of plasma as a treatment of factor deficiency also would partially replenish circulating fibrinogen until a fibrinogen level is reported by the laboratory.

Current concerns regarding on-site patient testing include cost-containment and federal licensure under the recent Clinical Laboratory Improvement Amendments legislation. Our approach to the regulatory requirements consisted of early involvement and collaboration with laboratory personnel in both the establishment and maintenance (e.g., quality control, WB hemostasis patient records, billing) of these coagulation assays because of their "complex assay" designation within these regulations. Although nonquantifiable, on-site coagulation monitoring can reduce transfusion-related risk (e.g., human immunodeficiency virus, hepatitis) by reducing total donor exposures.[54] In addition, a financial analysis of on-site coagulation monitoring is warranted because of its importance as a current issue.

In our institution, the system would be used on 178 patients (annual incidence of microvascular bleeding of 23%). The annual maintenance cost for the on-site laboratory would be $9,250 (the cost of two WB PT: aPTT cartridges per patient, T540 reagents, and a hemacytometer with a maintenance agreement). Hospital revenues generated by patient charges for the tests would equal $11,730 (based on a Medicare/third-party insurance ratio of 60:40%). Therefore, the system would generate annual revenues that would support itself because net hospital revenues would equal $2,480 (test revenues − maintenance costs).

Use of these on-site assays has been shown to reduce operative time and blood product use.[8] Net savings to patients can be determined by subtracting the cost of the assays from monetary savings secondary to clinical benefits of on-site coagulation monitoring. Operative time charges can be computed by adding the following hourly charges: institutional operating room charges,

anesthesiology professional fees, and perfusion service fees. Accordingly, savings to patients based on a yearly institutional reduction in operative time can be calculated (39 min/patient × 178 patients × hourly charges). Revenues secondary to reduction in blood products can be calculated by adding patient charges for intraoperative plasma (178 patients × 2 U/patient × unit charge), postoperative erythrocyte (178 patients × 2.2 U/patient × unit charge), and postoperative platelet units (178 patients × 4.8 U/patient × unit charge). Therefore, yearly institutional net savings to patients can be derived by subtracting the charges related to assays from total charges secondary to reduced operative time and blood product use. This would be equivalent to $1,504 per patient or a yearly institutional savings to patients of $267,658.

In summary, this study illustrated that on-site PT and PLT measurements correlate well with those from our laboratory. A disparity between WB and laboratory aPTT measurements is probably a function of different normal distribution curves and an increased sensitivity of the WB assay to factor deficiency. Factor concentration-response of the PT to factor levels was similar between assays. Although the aPTT response to factor levels was significantly different between systems, predictive accuracy for factor reductions was similar for both PT and aPTT assays between systems. WB PT, aPTT, and PLT assays enable physicians to assess accurately the role quantitative platelet and factor deficiencies play as etiologies of microvascular bleeding. These on-site assays provide accurate coagulation results that can circumvent limitations of laboratory-based testing.

## References

1. Wolk LA, Wilson RF, Burdick M, Selik N, Brown J, Stearricco A, Mammen EF: Changes in antithrombin, antiplasmin, and plasminogen during and after cardiopulmonary bypass. Am Surg 51:309–313, 1985

2. Milam JD: Blood transfusion in heart surgery. Clin Lab Med 2: 65–85, 1982

3. Bick RL: Hemostasis defects associated with cardiac surgery, prosthetic devices and extracorporeal circuits. Semin Thromb Hemost 11:249–280, 1985

4. Holloway DS, Summaria L, Sanderesa J, Vagher JP, Alexander JC, Caprini JA: Decreased platelet number and function and increased fibrinolysis contribute to postoperative bleeding in cardiopulmonary bypass patients. Thromb Haemost 59:62–67, 1988

5. Mammen EF, Koets MH, Washington BC, Wolk LW, Brown JM, Burdick M, Selik NR, Wilson RF: Hemostasis changes during cardiopulmonary bypass surgery. Semin Thromb Hemost 11:281–292, 1985

6. Kalter RD, Cheri MS, Saul BS, Wetstein L, Soriano C, Reiss RF: Cardiopulmonary bypass: Associated hemostatic abnormalities. J Thorac Cardiovasc Surg 77:427–435, 1979

7. Counts RB: Transfusion Practice in Cardiac Surgery: Causes of Bleeding in Open-Heart Surgery. Arlington, American Association of Blood Banks, 1991, pp 1–10.

8. Despotis GJ, Santoro SA, Spitznagel E, Kater KM, Cox JL, Barnes P, Lappas DG: Prospective evaluation and clinical utility of on-site coagulation monitoring in cardiac surgical patients. J Thorac Cardiovasc Surg 107:271–279, 1994

9. Lamantia KR, O'Conner T, Barash PG: Comparing methods of measurement: Alternative approach. ANESTHESIOLOGY 72:781–783, 1990

10. Pederson P, Pincus MR, Rapiejko JA: Comparison of activated partial thromboplastin time reagents. Lab Med 19:421–424, 1988

11. Naghibi F, Yangsook H, Dodds WJ, Lawrence CE: Effects of reagent and instrument on prothrombin times, activated partial thromboplastin times and patient/control ratios. Thromb Haemost 59:455–463, 1988

12. Van den Besselaar AMHP, Evatt BL, Brogan DR, Triplett DA: Proficiency testing and standardization of prothrombin time: Effect of thromboplastin, instrumentation, and plasma. Am J Clin Pathol 82:688–699, 1984

13. Ciavarella D, Reed RL, Counts RB, Baron L, Pavlin E, Heimbach DM, Carrico CJ: Clotting factor levels and the risk of microvascular bleeding in the massively transfused patient. Br J Heamatol 67:365–368, 1987

14. Lucas FV, Duncan A, Jay R, Coleman R, Craft P, Chan B, Winfrey L, Mungall DR, Hirsh J: A novel whole blood capillary technic for measuring the prothrombin time. Am J Clin Pathol 88:442–446, 1987

15. Quick AJ, Stanley-Brown M, Bancroft FW: A study of the coagulation defect in hemophilia and jaundice. Am J Med Sci 190:501–511, 1935

16. Proctor RR, Rapaport SI: The partial thromboplastin time with kaolin. Am J Clin Pathol 36:212–219, 1961

17. Jim RTS: A study of the plasma thrombin time. Lab Clin Med 50:45, 1957

18. Clauss A: Gerinnungsphysiologische Schnellmethode sur Besttimmung des Fibrinogens. Acta Haematol 17:237–246, 1957

19. Allington MJ: Detection of fibrinogen degradation products by a latex clumping method. Scand J Haematol 13(suppl):115–119, 1971

20. Babson SR, Babson AL: Development and evaluation of a disposable device for performing simultaneous duplicate bleeding time determination. Am J Clin Pathol 70:406–408, 1978

21. Langedell RD, Wagner RH, Brinkhous KM: Effect of antihemophilic factor on one-stage clotting tests: A presumptive test for hemophilia and a simple one-stage anti-hemophilic factor assay procedure. J Lab Clin Med 41:637–647, 1953

22. Altman DG, Bland JM: Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1:307–310, 1986

23. Giddings JC: The investigation of hereditary coagulation disorders, Blood Coagulation and Haemostasis: A Practical Guide. Edited by Thompson JM. Edinburgh, Churchill Livingstone, 1980, pp 117–157

24. Efron B: The jackknife, the bootstrap and other resampling plans. Philadelphia, Society for Industrial and Applied Mathematics, 1982

25. Strike PW: Statistical Methods in Laboratory Medicine. Oxford, Butterworth-Heinemann, 1991

26. Tietz NW: Clinical Guide to Laboratory Tests. Philadelphia, WB Saunders, 1983, p 419

27. Jandl JH: Blood Textbook of Hematology. Boston, Little, Brown, 1987, pp 1122–1123

28. Bick RL: Alterations of hemostasis associated with cardiopulmonary bypass: Pathophysiology, prevention, diagnosis and management. Semin Thromb Hemost 3:59, 1976

29. 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 change in the coagulation system. Thromb Res 7:589, 1975

30. Gralnick HR, Fischer RD: The hemostatic response to open-heart operations. J Thorac Cardiovasc Surg 61:911–915, 1971

31. Von Kaulla KN, Swan H: Clotting deviations in man during cardiac bypass: Fibrinolysis and circulating anticoagulants. J Thorac Cardiovasc Surg 36:519, 1958

32. Brooks DH, Bahnson HT: An outbreak of hemorrhage following cardiopulmonary bypass. J Thorac Cardiovasc Surg 63:449, 1972

33. O'Neill JA, Ende N, Collins IS, Collins HA: A quantitative determination of perfusion fibrinolysis. Surgery 60:809, 1966

34. Ottesen S, Stormorken H, Hatteland K: The value of activated coagulation time in monitoring heparin therapy during extracorporeal circulation. Scand J Thorac Cardiovasc Surg 18:123–128, 1984

35. Kase PB, Dearing JP: Factors affecting the activated clotting time. J Extracorp Technol 17:27–30, 1985

36. Moorehead MT, Westengard JC, Bull BS: Platelet involvement in the activated coagulation time of heparinized blood. Anesth Analg 63:394–398, 1984

37. Kesteven PJ, Pasaoglu I, Williams BT, Savidge GF: Significance of the whole blood activated clotting time in cardiopulmonary bypass. J Thorac Cardiovasc Surg 27:85–89, 1986

38. Dutton DA, Hothersall AP, McLaren AD, Taylor KM, Turner MA: Protamine titration after cardiopulmonary bypass. Anaesthesia 38:264–268, 1983

39. Wintrobe MM, Lee GR, Boggs DR, Bithell TC, Foerster J, Athens JW, Lukens JN: Clinical Hematology. 8th edition. Philadelphia, Lea & Febiger, 1981, p 1057

40. Hattersley PG: Activated coagulation time of whole blood. JAMA 196:436–440, 1966

41. Hooper TL, Conroy J, McArdie B, Dell A, Watson B, Pearson DT, Kesteven PJ: The use of the Hemochron in assessment of heparin reversal after cardiopulmonary bypass. Perfusion 3:295–300, 1988

42. Mongan PD, Husking MP: The role of desmopressin in patients undergoing coronary artery bypass surgery: A controlled clinical trial with thromboelastographic risk stratification. ANESTHESIOLOGY 77:38–46, 1992

43. Tuman KJ, Spiess BD, MacCarthy RJ, Ivankovich AD: Comparison of viscoelastic measures of coagulation after cardiopulmonary bypass. Anesth Analg 69:69, 1989

44. Dorman HB, Spinale FG, Bailey MK, Kratz JM, Roy RC: Identification of patients at risk for excessive blood loss during coronary artery bypass surgery: Thromboelastograph versus coagulation screen. Anesth Analg 76:694–700, 1993

45. Wang JS, Lin CY, Hung WT, O'Connor MF, Thisted RA, Bryan KL, Karp RB, Yang MW: Thromboelastogram fails to predict post-

operative hemorrhage in cardiac patients. Ann Thorac Surg 53:435–439, 1992

46. Van Riper DF, Horrow JC, Osborne D: Is the thromboelastograph a clinically useful predictor of blood loss after bypass (abstract). ANESTHESIOLOGY 73:A1206, 1990

47. Ellison N, Jobes DR: Effective Hemostasis in Cardiac Surgery. Philadelphia, WB Saunders, 1988, pp 75–76

48. Goodnough LT, Johnston MFM, Ramsey G, Sayers MH, Eisenstadt RS, Anderson KC, Rutman RC, Silbersterin LE: Guidelines for transfusion support in patients undergoing coronary artery bypass grafting. Ann Thorac Surg 50:675–683, 1990

49. Ansell J, Holden A, Knapic N: Patient self-management of oral anticoagulation guided by capillary (fingerstick) whole blood prothrombin times. Arch Intern Med 149:2509–2511, 1989

50. Reich DL, Yananakis BA, Vela-Cantos FP, DePerio M, Jacobs E: Comparison of bedside coagulation monitoring tests with standard laboratory tests in patients after cardiopulmonary bypass. Anesth Analg 77:673–679, 1992

51. 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 95:222–227, 1991

52. Moriau M, Masure R, Hurlet A, Debeys C, Chalant C, Ponlot R, Jaumain P, Serzaye-Kestens W, Ravaux A, Louis A, Goenen M: Heart Surgery with extracorporeal circulation: Importance of the platelet function and the heparin neutralization. Vox Sang 32:41–51, 1977

53. Alter RD, Saul CM, Wetstein L, Soriano C, Feiss RF: Cardiopulmonary bypass: Associated hemostatic abnormalities. J Thorac Cardiovasc Surg 77:427–435, 1979

54. Despotis GJ, Grishaber JE, Goodnough LT: On-site coagulation monitoring in cardiac surgical patients: Evaluation of transfusion outcomes. Transfusion (in press)