

Expanding Perfusion Services Through Mobile Point-of-Care Coagulation Monitoring

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Abstract: Current trends in cardiac surgery have challenged perfusionists to seek diversification of services. Point-of-care coagulation (POCC) monitoring represents a desirable area of perfusion service expansion. The purpose of the study was to create a series of hemostatic conditions to assess the functionality of

blood) were created. Five POCC devices were used to evaluate activated clotting time, thrombin time, fibrinogen, platelet function, prothrombin time, activated partial thromboplastin time and thromboelastograph. Results are reported as percentage change from control for each test (abstract table).

Summary of results for induced coagulopathies.

Device	Hypofibrinogenemia	Thrombocytopenia	Platelet Dysfunction	Hyperfibrinolysis
TEG index	-146% $p < .05$	-84% $p < .05$	-415% $p < .05$	-90% $p < .05$
ACT	23% $p < .05$	4% $p = \text{NS}$	89% $p < .05$	27% $p < .05$
Thrombin time	16% $p = \text{NS}$	-4% $p = \text{NS}$	19% $p = \text{NS}$	20% $p = \text{NS}$
Fibrinogen	-47% $p < .05$	-19% $p < .05$	12% $p = \text{NS}$	5% $p = \text{NS}$
Platelet function	No result	-43% $p < \text{NS}$	No result	-19% $p = \text{NS}$

POCC monitors to identify specific coagulopathies with identifiable profiles for algorithm development. Fresh (<4 h) bovine blood, anticoagulated with anticoagulant citrate dextrose, was adjusted to a hematocrit of $30.0 \pm 2.0\%$. Hypofibrinogenemia (≤ 90 mg/dL), thrombocytopenia ($\leq 70,000/\text{mm}^3$), platelet dysfunction (850 $\mu\text{g}/\text{mL}$ of nitroglycerin/mL of blood) and hyperfibrinolysis (0.40 units of urokinase/mL of

Each test performed showed specificity and sensitivity for certain coagulopathies, however variability amongst monitors was encountered. In conclusion, the development of a mobile cart incorporating POCC monitors with knowledge of specific coagulopathic conditions may expand perfusion service. **Keywords:** point of care, coagulation monitoring, algorithm. *JECT. 2002; 34:190-196*

Beating heart coronary revascularization (OPCAB) is fast becoming a popular alternative to the traditional revascularization utilizing cardiopulmonary bypass (CPB). Numerous studies have suggested potential benefits for OPCAB versus conventional CPB (1, 2) and as this practice continues, the technical aspects will only be refined

(3). These trends may place perfusionists at certain institutions in a precarious situation, creating the possibility for expansion of services beyond the operating suite. Point-of-care coagulation (POCC) monitoring is an expandable area as coagulopathies were credited in a recent survey with 44% of serious injuries and 33% of mortalities in cardiac surgery (4).

Despotis (5) demonstrated that prompt availability of coagulation results from an on-site laboratory system resulted in a reduction in blood product use and decreased operative times in the cardiac surgical patient. Considering that patients undergoing cardiac surgery represent

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nearly 10% of the estimated 3.2 million annual recipients of red blood cell transfusions (6), the benefits of prompt diagnosis and the resultant decrease in blood usage with POCC devices extends to the patient and provider. Other potential areas targeted for POCC include emergency rooms, cardiac catheterization laboratory, and general treatment areas (7) as well as emergent CPR and organ procurement (8). The fast turnaround time available with POCC would have made an earlier therapeutic decision possible in 19% of emergency room cases according to one study (8).

The purpose of this study was to generate commonly encountered hemostatic abnormalities to assess the functionality of POCC monitors to identify specific coagulopathies. A diagnostic algorithm was then created to enhance the speed and accuracy of the diagnosis allowing for prompt initiation of treatment.

MATERIALS AND METHODS

Experiment

With the written consent and assistance from slaughterhouse management, fresh bovine blood (<4 h) was collected in a reservoir and anticoagulated with a 10:1 ratio of anticoagulant citrate dextrose (ACD). The collected blood was used to create the following coagulopathies: hyperfibrinolysis, hypofibrinogenemia, platelet dysfunction, and thrombocytopenia (9). The hematocrit for each condition was adjusted to $30.0 \pm 2.0\%$, and the total protein was measured for each coagulopathy. Platelet counts and fibrinogen levels were performed for each created abnormality by the hospital central laboratory.

Baseline: Nontreated whole blood samples were collected, and all tests were performed to create a control for all assays.

Hyperfibrinolysis: A hyperfibrinolytic state was created by adding 0.40 units of urokinase (Sigma Chemical Co., St. Louis, MO) to 1 mL of blood. The state was determined by performing a thromboelastograph (TEG) (Haemoscope Corp., Skokie, IL) with acceptance of lysis at 30 minutes of >50%.

Platelet: Platelet dysfunction was created by adding 850 μL of nitroglycerin (50 mg/mL) to 1 mL of whole blood (10) and was defined as a reduction in the MA by 50% from the normal baseline values. Thrombocytopenia was created via centrifugation, removing platelet-rich plasma. A platelet count was performed to ensure a platelet level below $70,000/\text{mm}^3$ was achieved.

Hypofibrinogenemia: Blood samples were centrifuged at 5,600 rpm, and a known quantity of plasma was replaced with an equal amount of normal saline. A platelet count was performed to ensure a state of thrombocytopenia was not induced ($150,000/\mu\text{L}$). A fibrinogen level of <90 mg/dL was created.

Point-of-Care Monitoring Devices and Assays

Hepcon Hemostasis Management System (HMS) and ACT II (Medtronic USA, Inc. Parker, CO): A plunger assembly system within the test cartridge is the principal mechanism for this device. This assembly is lifted and dropped through the reagent and sample mixture by a lifting mechanism in the HMS actuator. As the clot forms, fibrin forms around the daisy located on the bottom of the plunger. Photocells within the instrument detect this change in rate and signify the end point of the test. The hemoSTATUS[®]2 platelet function test (PFT) was performed with the HMS instrument. Each assay contains four channels with equal amounts of heparinase, sufficient to reverse up to 6 units of heparin, and argatroban, a thrombin inhibitor that maintains the sensitivity of platelet function. Platelet function is assessed with a different concentration of platelet-activating factor in each test cartridge. Kaolin activated, low-range activated clotting time (LR-ACT) was performed on the ACT II.

Response (International Technidyne Corp., Edison, NJ): This device contains two test wells into which coagulation test tubes can be inserted. These test tubes contain reagents for a particular test and a magnet, which are rotated at a constant speed within the well. When a fibrin clot begins to form, the magnet in the test tube is displaced. As the two magnetic sensors located in the test wells detect a specific displacement of the magnet, the coagulation time in seconds is displayed.

Assays performed on the response included celite-activated ACT, fibrinogen, thrombin time (TT), heparin neutralized thrombin time (HNNT), activated partial thromboplastin time (aPTT), and prothrombin time (PT). The fibrinogen utilizes thrombin as the reagent and is not affected by low levels of heparin or fibrin degradation products. The formation of a clot results in a clotting time, which is applied to a standard fibrinogen curve to determine the fibrinogen level in mg/dL. TT and HNNT both contain human thrombin, and the HNNT contains protamine sulfate. These tests are useful in quantifying circulating fibrinogen, detecting the presence of heparin, diagnosing intravascular coagulation, and assessing thrombolytic therapy. APTT utilizes kaolin as well as a platelet factor 3 substitute to monitor the intrinsic and common pathways. PT utilizes a thromboplastin reagent to assess the extrinsic and common pathways and is widely used to monitor oral anticoagulant therapy.

Jr. Signature (International Technidyne Corp., Edison, NJ): This instrument detects the end point of clot formation through optical monitoring. The device measures 15 μL of blood and automatically moves it into the test channel of the cuvette. The sample and reagent mixture moves back and forth within the test channel to detect clot formation. Clot formation impedes the movement of blood

flow, and this change in speed is measured. End point of clot formation is achieved when the movement falls below a predetermined rate. Assays performed on this instrument included the previously described aPTT, PT, and LR-ACT

Thromboelastograph®: Parameters of the TEG are as follows.

1. Reaction Time (R): The latency period from the time the TEG analyzer begins until initial fibrin formation, which correlates with the whole blood clotting time. R time is defined when the amplitude reaches 2 mm in the TEG tracing.
2. Clot Growth Kinetics (K Time and Alpha Angle): The period from a defined R time until a fixed level of clot firmness, represented by an amplitude of 20 mm, which describes the polymerization of the structural elements involved in clotting.
3. Maximum Amplitude (MA): A measurement of the developed clot's maximum strength of stiffness, which represents the ability to form hemostasis. The amplitude (A) is the width of the tracing at any point and is equal to the MA at the highest point.
4. Lysis at 30 and 60 minutes: These parameters measure the percentage of lysis at 30 and 60 minutes after the MA is reached. It is used to identify fibrinolytic states.
5. TEG Index: The TEG index describes the patient's overall coagulation status. It is a mathematical formula derived from other TEG parameters.

Sample Procedure

All assays were performed in quadruplicate after the creation of each coagulopathy, with randomization of each assay. The blood samples were recalcified with 0.2M CaCl₂ before performing the individual assays as specified in the instructions for use. Control TEG assays were performed on the blood to ensure the stability of the collected blood over time.

Statistical Analysis

Data were collected and entered onto a spreadsheet for analysis and were reported as mean \pm standard deviation of the mean or percentage change from control. Differences between control and treatment groups were analyzed with one-way analysis of variance (ANOVA) with a

commercially available statistics program (SuperANOVA, Abacus Concepts, Berkeley, CA). Significant differences ($p < .05$) were further evaluated with a post hoc test (Fisher's least significant different).

RESULTS

There was no significant difference in hematocrit between the control and the created coagulopathies. Total protein was significantly different between the control and hypofibrinogenemia (6.10 ± 0.0 vs. 1.2 ± 0.0 , respectively, $p < .05$). There were no other significant differences between control and experimental when comparing total protein. Time control TEG produced no significant change for the duration of the experiment.

Table 1 shows TEG parameters and p -values for each of the coagulopathies. The greatest change in the TEG index was with platelet dysfunction, while thrombocytopenia produced the smallest reduction in TEG index. Hyperfibrinolysis was the only condition that caused fibrinolytic activity as indicated by a percentage lysis of 100%. Results of the ACT tests are shown in Figure 1. The three instruments utilized to perform ACT measurements trended similarly. The greatest percentage change was with platelet dysfunction, while the smallest change was, again, in the fibrinolytic coagulopathy. The Signature Jr. did not produce results for platelet dysfunction and hypofibrinogenemia.

Figure 2 demonstrates a significant decrease in fibrinogen levels resulted for both hypofibrinogenemia and thrombocytopenia. With removal of platelets in the latter of the two, the fibrinogen level dropped from 200 mg/dL to 180 mg/dL from control to treatment. This corresponds to the percentage change in fibrinogen for thrombocytopenia. No significant change in fibrinogen levels for platelet dysfunction and hyperfibrinolysis occurred. The PFT (Figure 3) produced no significant results for any of the created hemostatic abnormalities. Platelet function decreased for both thrombocytopenia and hyperfibrinolysis, and no both platelet dysfunction and hypofibrinogenemia had no result. The Signature Jr. produced no value in any created condition for PT, as shown in Figure 4. The Response produced a significant increase for both thrombocytopenia and hypofibrinogenemia.

Table 1. Thromboelastograph data.

Emostatic Abnormality	Teg Index		R		K		MA		% Lysis	
	% Change	p -Value	% Change	p -Value	% Change	p -Value	% Change	p -Value	% Change	p -Value
Plt dysf	-415 \pm 38	0.0001	219 \pm 148	0.0001	658 \pm 68	0.0001	-61 \pm 2	0.0001	0.0000	NS
Hypofib	-145 \pm 40	0.0001	37 \pm 32	0.0170	104 \pm 30	0.0019	-30 \pm 2	0.0012	0.0000	NS
Tcytopenia	-84 \pm 8	0.0043	18 \pm 10	NS	83 \pm 17	0.0097	-21 \pm 2	0.0155	0.0000	NS
Fbrnlytic	-90 \pm 8	0.0043	10 \pm 10	NS	0 \pm 0	NS	-51 \pm 0	0.0001	100 \pm 0	0.0001

Key: Plt dysf = Platelet dysfunction; Hypofib = Hypofibrinogenemia; Tcytopenia = Thrombocytopenia; Fbrnlytic = Hyperfibrinolysis.

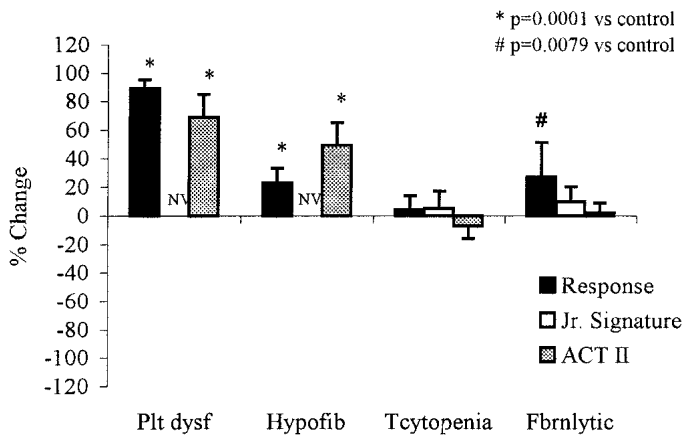


Figure 1. Activated clotting time. Plt dysf = Platelet dysfunction; Hypofib = Hypofibrinogenemia; Tcytopenia = Thrombocytopenia; Fbrnlytic = Hyperfibrinolysis; NV = No value.

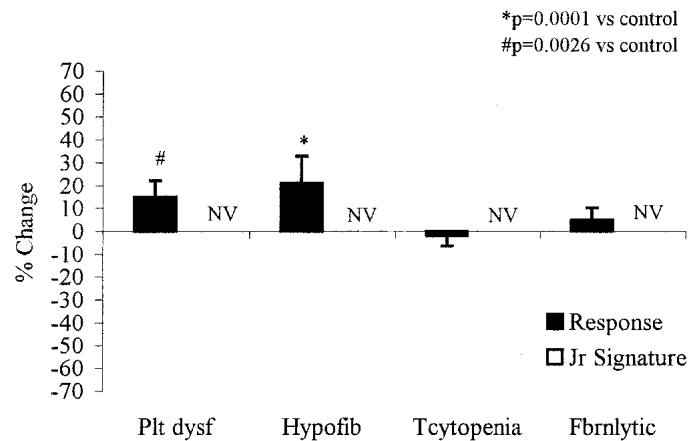


Figure 4. Prothrombin time. Plt dysf = Platelet dysfunction; Hypofib = Hypofibrinogenemia; Tcytopenia = Thrombocytopenia; Fbrnlytic = Hyperfibrinolysis; NV = No value.

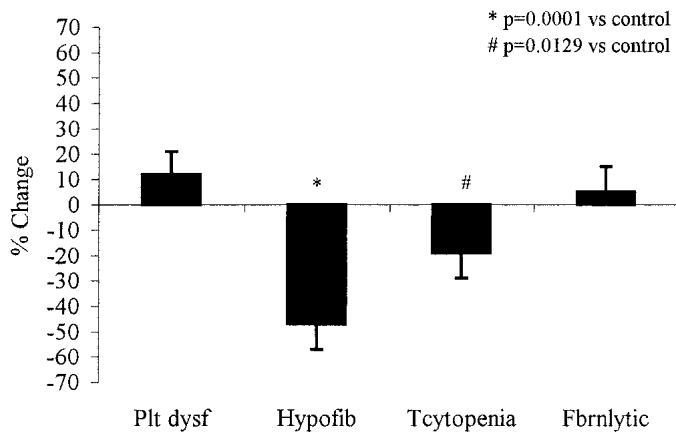


Figure 2. Fibrinogen. Plt dysf = Platelet dysfunction; Hypofib = Hypofibrinogenemia; Tcytopenia = Thrombocytopenia; Fbrnlytic = Hyperfibrinolysis.

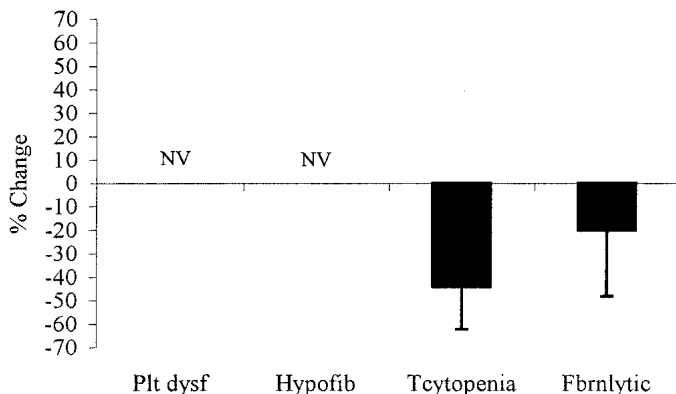


Figure 3. Platelet function test. Plt dysf = Platelet dysfunction; Hypofib = Hypofibrinogenemia; Tcytopenia = Thrombocytopenia; Fbrnlytic = Hyperfibrinolysis; NV = No value.

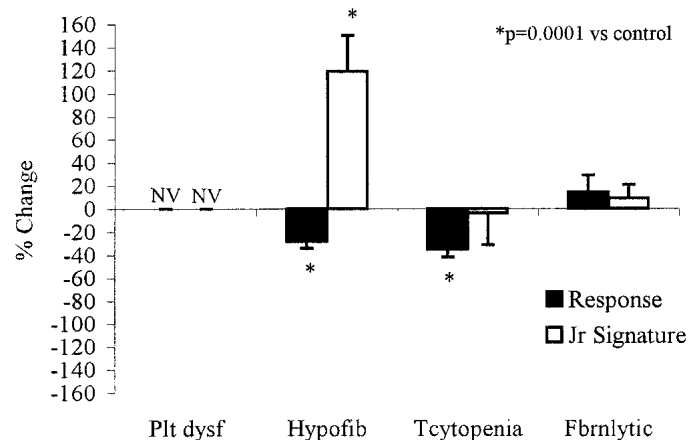


Figure 5. Activated partial thromboplastin time. Plt dysf = Platelet dysfunction; Hypofib = Hypofibrinogenemia; Tcytopenia = Thrombocytopenia; Fbrnlytic = Hyperfibrinolysis; NV = no value.

Figure 5 represents aPTT. The Response showed a significant decrease for both hypofibrinogenemia and thrombocytopenia, while the Jr. Signature had a significant increase for hypofibrinogenemia. The two instruments produced no value for platelet dysfunction. TT and HNTT, demonstrated by Fig. 6, trended the same for hypofibrinogenemia, thrombocytopenia, and hyperfibrinolysis; whereas, platelet dysfunction had contradicting results. The only significant change was a HNTT increase for hypofibrinogenemia. Figure 7 is the cumulation of all results into a diagnostic algorithm leading to each of the four created coagulopathies

DISCUSSION

Coagulation disorders in the cardiac surgical patient may include one or more of the following: qualitative (11) or quantitative platelet abnormalities (12), depletion of coagulation factors (13, 14), and less commonly primary

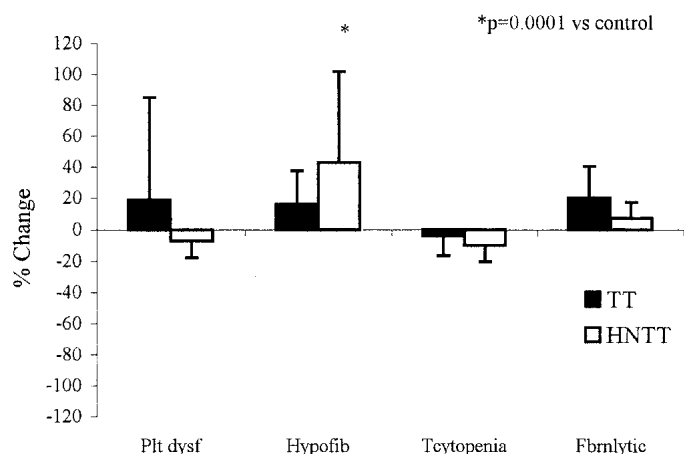


Figure 6. Thrombin time and heparin neutralized thrombin time. Plt dysf = Platelet dysfunction; Hypofib = Hypofibrinogenemia; Tcytopenia = Thrombocytopenia; Fbrnlytic = Hyperfibrinolysis.

fibrinolysis (15). Although advancements in both pharmacological and mechanical technology have improved the therapeutic options offered to these patients (16), each of these abnormalities requires separate treatment. They are, however, often treated with a shotgun effect of blood products. Perhaps the greatest benefit in the utilization of POCC devices is the reduction in time to generate results when compared to the central laboratory of the hospital (17). The utilization of a series of POCC assays and a diagnostic algorithm, such as that created in this experiment, allows for rapid assessment of the abnormality followed by specific treatment. Therapies may then be dictated by treatment algorithms, which have been shown to result in fewer hemostatic blood transfusions in patients clinically diagnosed with nonsurgical microvascular bleed-

ing after cardiac surgery (5, 18). Algorithm therapies based on TEG have been proposed to guide transfusion therapy for patients who have excessive bleeding post CPB (19).

The benefits of utilizing TEG coagulation testing have been well reported. TEG has been shown to be a sensitive and specific coagulation test for abnormal hemorrhage, capable of discerning a surgical bleed with greater than 90% confidence (20). Transfusion therapy based on TEG results has resulted in decreased administration of blood products during liver transplantation (21) and cardiac surgery patients as well as a decrease in mediastinal re-exploration (22).

By definition of TEG parameters, this instrument most clearly demonstrated hyperfibrinolysis, as the only coagulopathy to indicate lysis. Isolated thrombocytopenia or platelet dysfunction should result in a small MA and normal R, K, and alpha angle. Decreased platelet function in bovine blood produced the greatest change in the TEG profile with significant changes for each parameter except the percentage lysis. A decreased platelet count had no effect on the R time, but the K and MA both decreased. These parameters are interrelated because of the interaction between fibrinogen and platelets, which together form the fibrin-platelet bonding to produce the final clot.

The ACT is currently the gold standard for monitoring anticoagulation status during CPB, but has a limited role in determining microvascular bleeding following CPB (23). The ACT has been reported to be both nonspecific and insensitive to various coagulation abnormalities (24). Among the three instruments used to measure ACT, thrombocytosis consistently produced the largest percentage change in ACT values, while thrombocytopenia had no significant effect on ACT values. Hypofibrinogenemia consistently produced a significant increase on ACT times, indicating that, although perhaps nonspecific, ACT values were not insensitive to coagulation abnormalities.

A fibrinogen level is routinely requested after cardiac surgery cases to assess the clotting ability of the patient. A deficiency often results in the administration of fresh frozen plasma or cryoprecipitate. A significant decrease in fibrinogen was noted in both the hypofibrinogenemia and thrombocytopenia groups, whereas, the other conditions produced no significant change. The decrease in the low fibrinogen condition is expected. The decrease in fibrinogen in the thrombocytopenic condition can, in part, be explained by the creation of the condition.

Transient platelet dysfunction post CPB is a common hemostasis defect in the early postoperative period following CPB (25). The PFT has been shown to be potentially useful in the identification of patients at risk for excessive blood loss and who could benefit from administration of DDAVP or platelet transfusion (26). If the only defect is a low platelet count, the platelet function does not change

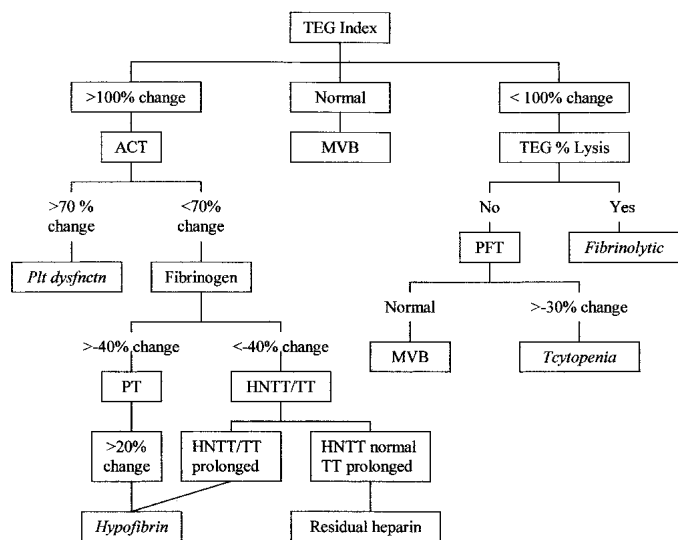


Figure 7. Diagnostic algorithm. Plt dysf = Platelet dysfunction; Hypofib = Hypofibrinogenemia; Tcytopenia = Thrombocytopenia; Fbrnlytic = Hyperfibrinolysis; MVB = Microvascular bleeding.

until the count drops below 20,000–30,000/mm³ (27), well below the platelet count in the created thrombocytopenia (66,000/mm³). As a result, no significant change in platelet function was noted; however, the instrument did produce a –43% change in platelet function showing sensitivity to a decreased platelet count.

The base-clotting time of the PFT for both platelet dysfunction and hypofibrinogenemia exceeded 1,500 seconds, which, according to the instructions for use, does not provide enough data to calculate the platelet function. In the context of this study, platelet dysfunction was defined by the reduction of the MA by 50% through the addition of nitroglycerin. As previously described, the sensitivity of the platelet function test is maintained by extending the clotting times with a direct thrombin inhibitor, argatroban, thus isolating the platelets. Perhaps too much of the platelet function was eliminated by the nitroglycerin to reduce clot formation, producing the result of greater than 1,500 seconds. Hypofibrinogenemia had no manipulation to platelet function, and platelet number was within normal limits as well. Therefore, the resultant value is not easily explained other than perhaps sampling error.

The PT evaluates the extrinsic and common pathways of the coagulation system. Prolongation occurs when there is a deficiency of factors VII, V, X, prothrombin, or fibrinogen. Severe hypofibrinogenemia can be assessed by prolongation of the PT measurement (23). The results of this study significantly demonstrate this phenomena through a 21% change in PT. Platelet dysfunction also created a significant change in regard to the PT, although laboratory measurements showed normal level of fibrinogen in this group. The aPTT evaluates the intrinsic and common pathways of the coagulation system. Inhibitors that affect factors XII, XI, IX, VIII, X, V, prothrombin, and fibrinogen prolong the aPTT (23). Figure 5 shows the Signature Jr. produced results consistent with prolongation of the aPTT, while the Response had a decrease in aPTT.

The TT and HNTT assess the conversion of fibrinogen to fibrin. A prolonged TT and normal HNTT indicate the presence of residual heparin and necessitate additional protamine dosing in cardiac surgical patients (28). Prolongation of both TT and HNTT is indicative of abnormal fibrinogen function. Hypofibrinogenemia produced prolonged results for TT and a significant increase in HNTT. No other condition had a significant change.

Creating diagnostic and treatment algorithms for utilization with POCC monitoring is vital for success once a bedside mobile coagulation lab has been instituted. There are, however, many other issues associated with the use of portable POC testing and its implementation. Today, more than ever, economic factors are critical in the decision-making process. Performing POC analyses have vastly different allocation of costs. In a central laboratory,

fixed costs are higher, and the incremental costs of test performance, including labor and consumables, are lower. On the other hand, in POC testing, fixed costs are relatively low, and labor and consumables increase significantly with increased testing (29). Likewise, the cost of laboratory testing may be low when compared with the cost of the episode of care or the total lifetime medical costs to the patient. Therefore, the value of POC tests may be much greater than the cost of testing when considering such benefits as shortened episodes of care, lowered long-term follow-up costs, and improved long-term quality of life (29).

Another pertinent issue associated with the mobile laboratory is the allocation of responsibilities. A successful POC program requires the joint effort of both laboratory and clinical personnel, with each group providing primary control over its particular area of expertise. Laboratory responsibilities may include but are not limited to the initial evaluation of technology to assess accuracy and precision and coordination of correlation studies between new methodology and the laboratory standard (30). The laboratory may also be responsible for the procurement, storage, dissemination, maintenance, monitoring instruments, reagents as well appropriate documentation and obtaining the necessary licenses required by accreditation agencies (30). The responsibility of the individuals performing the POCC test may include, but are not limited to, the establishment of clinical need and determination of appropriate locations. Other duties include reporting results to the physician and patient charts, storage of limited supplies and equipment, and performance of tests and quality controls (31).

Limitations of this study include a lack of combination of coagulopathies. Combining these coagulopathies would have produced different results and possibly could have been incorporated into the diagnostic algorithm. The benefit of a platelet count in diagnosing hemostatic abnormalities is well known (23), and several POCC instruments are capable of performing this assay. This test was not incorporated into this study. Bovine blood was utilized rather than the gold standard human blood, making the application of these results to the human population not possible.

Mobile coagulation monitoring represents an opportunity center wherein perfusionists can expand their practice. Through the use of diagnostic and treatment algorithms, accurate and prompt diagnosis can be achieved, which could promote rapid intervention. There are many potential benefits to the hospital and patient with the implementation of this practice, including accurate assessment of the coagulopathic abnormality and decreased blood use. Such utilization of standard POCC monitors can promote expansion of perfusion service.

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