Original Article

Correlation of ACT as Measured with Three Commercially Available Devices with Circulating Heparin Level during Cardiac Surgery

Scott D. Niles, BA, Robin G. Sutton, MS, CCP, James Ploessl, CCP, Beverly Pennell, MS

Perfusion Technology Program, University of Iowa Hospitals and Clinics, Iowa City, Iowa

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ABSTRACT

Automated activated clotting time (ACT) is utilized as the primary means of assessing anticoagulation status for cardiopulmonary bypass (CPB) procedures. Influences on the clotting cascade during CPB such as hypothermia, hemodilution, and platelet dysfunction are known to affect ACT.

The recently introduced Thrombolytic Assessment System (TAS) has been reported to be less sensitive to changes in hemodilution and hypothermia during CPB than more conventional ACT devices. This study evaluated the ability of TAS, and two other commercially available automated ACT systems, the HemoTec and Hemochron, to correlate with circulating heparin levels. Reference standards for circulating heparin were determined by inactivation of factor Xa assay.

Nineteen patients undergoing moderate hypothermic CPB served as subjects for this investigation. Blood samples were obtained for study at four time periods: 1) baseline (control), 2) post heparin administration (300-400 U/kg) prior to CPB, 3) during CPB, and 4) post protamine. Study results demonstrated a high correlation between the HemoTec and Hemochron ($r = 0.99$), increased heparin dose response on CPB compared to pre-CPB activity ($p < 0.05$), and a significant ($p<0.05$) negative correlation between devices and patient hematocrit during CPB. Additionally, device correlation with anti-Xa assay during collection periods 2 and 3 showed negative correlations in each of the three devices evaluated.

We conclude that all automated devices tested demonstrated an inability to predict circulating heparin at levels necessary for CPB, and that these discrepancies become magnified during CPB procedures.

Address correspondence to:
Scott D. Niles, B.A.
Perfusion Technology Program
200 Hawkins Drive
Iowa City, Iowa 52242

INTRODUCTION

Since the late 1970's automated activated clotting time (ACT) has been utilized as the primary means of assessment of anticoagulation status for cardiopulmonary bypass (CPB) procedures. ACT use in the determination of anticoagulation effects after heparin administration has been widely documented (1-5); however, the ability of ACT to predict circulating heparin levels has been challenged (1-4). The level of heparin present within samples, as determined by ACT clot formation, demonstrates a linear correlation in individuals provided that variations in temperature, hematocrit, platelet count, patient medications, and high heparin concentrations are avoided (4-8). For this reason, correlation of ACT and heparin concentrations cannot be extrapolated among populations (2,3). Since ACT is a functional measure of the intrinsic clotting cascade, it may be influenced by factors other than heparin during CPB (4-8). Among the factors altering ACT times during CPB are hypothermia, hemodilution, and platelet dysfunction (2,4-8).

An alternative automated ACT system has recently become available for determination of systemic heparinization. Using Heparin Management Testing (HMT) with the Thrombolytic Assessment System (TAS)[a] a citrated whole blood sample may be analyzed for heparin concentrations from 1.0 to 10 units (U)/ml. The manufacturer's reported benefits of this device suggest that is not affected by hemodilution levels up to fourfold, and that hypothermic samples to two degrees Celsius do not affect device linearity. Additionally, preliminary data provided by the manufacturer details improved TAS correlation with heparin concentration than ACT during CPB.

The purpose of this study was to assess the efficacy of three commercially available devices to predict the degree of systemic heparinization during CPB by measuring ACT. Devices 1 and 2 both utilize kaolin based cartridges, and were chosen to measure ACT, while TAS was chosen to measure HMT clotting time. Reference heparin level testing will be accomplished utilizing a heparin specific anti-Xa assay.

MATERIALS AND METHODS

Nineteen patients undergoing primary cardiopulmonary bypass procedures were randomly chosen for participation in this study. Subjects with known blood dyscrasia were excluded from participation in the study. Patient demographic data (mean ± standard error of the mean) including age (59.6 yrs. ± 4.0), mean body surface area (BSA)($1.91 m^2 \pm 0.07$), procedure, and preoperative medications were documented prior to investigation. Bypass time (124.0 minutes ± 8.1), and aortic cross clamp time (75.11 minutes ± 6.7) were also recorded for each case.

Devices utilized in this study design were the HemoTec[b], Hemochron[c], and the Thrombolytic Assessment System[a]. Confirmation of device integrity was verified by device specific quality control testing before performance evaluation. Blood specimens were obtained for determination of ACT, HMT, and Anti Xa during four discrete time periods: 1. Patient baseline, 2. Pre-CPB (post heparin administration 300-350 U/kg), 3. During CPB, and 4. Post protamine administration. High thrombin times (HiTT) were evaluated at: 1. Baseline, and 2. Pre-CPB (post heparin administration). Baseline specimens were drawn prior to surgical incision. All tests were run immediately, with the exception of the Anti-Xa assay, where samples were placed in 0.2 ml of 0.105 molar buffered citrate and placed on ice. Heparin Anti-Xa assays were then processed by the medical pathology laboratory and frozen (minus 70°Celsius) for later batch processing. Heparin Anti-Xa assays were analyzed using a technique described by Teien (9).

An adult cardiopulmonary bypass circuit was constructed for each patient utilizing a roller pump, hollow fiber membrane oxygenator, closed venous reservoir, and polyvinyl chloride tubing. A loading dose of 300-400 U/kg of bovine lung heparin[d] was given. Initiation of bypass was delayed until confirmation of an ACT greater than 480 seconds as measured by the HemoTec. Cardiac indexes during CPB ranged from 1.8 to 2.4 $L/min/m^2$. Moderate hypothermia (mean nasopharyngeal temperature 29.1°C, mean rectal temperature 29.2°C) was employed universally during CPB. The priming solution for CPB consisted of 1800 ml Plasmalyte-A[e], 25 g mannitol, 50 g albumin, 22 mEq sodium bicarbonate, and 10,000 U sodium heparin[d]. Additional heparin was administered during CPB as necessary to maintain ACT values greater than 480 seconds as determined by the Hemotec. Reversal of heparin was effected with the utilization of protamine sulfate[d](3-5 mg/kg) upon completion of the operative procedure. Statistical interpretation and summary of data including Students' t-test, regression, and correlation analysis were accomplished utilizing BMDP[f], and spreadsheet[g] statistical software. Significance was determined to exist for $p < 0.05$.

RESULTS

Experimental results of ACT and HMT testing, and their correlation with actual heparin concentration (anti-Xa), are summarized in Table 1. Device output was not statistically different ($p<0.05$) between the HemoTec and Hemochron, but was statistically different between each of these and the TAS. A high device correlation was also established between mean HemoTec and Hemochron ACT values ($r = 0.99$). The pre-CPB dose response to heparin (seconds/unit/ml) increased sig-

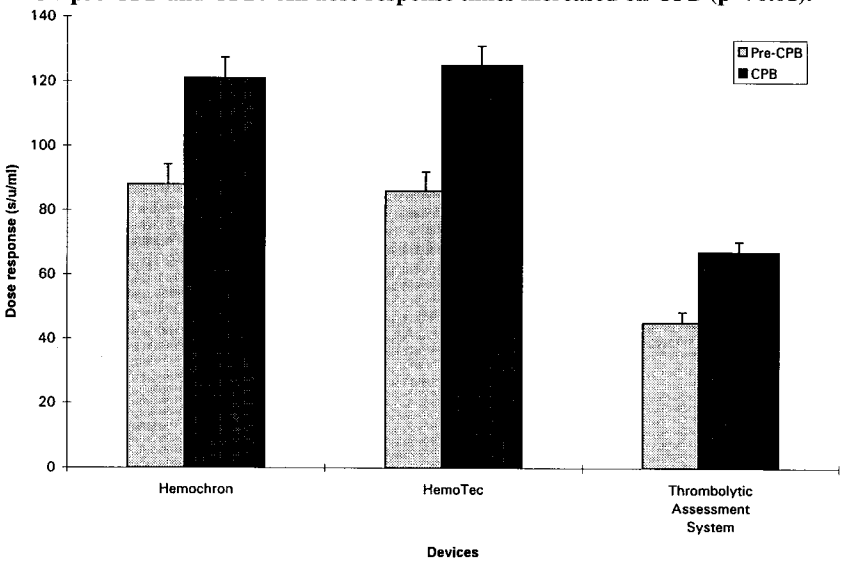
a Thrombolytic Assessment System, Cardiovascular Diagnostics, Inc., Raleigh, NC 27604
b Model 400-01, Medtronic HemoTec, Inc., Englewood, CO 80112
c Model 8000, International Technidyne Corp., Edison, NJ 08820
d Elkins-Sinn, Inc., Cherry Hill, NJ 08003
e Baxter Healthcare Corp., Deerfield, IL 60015
f BMPD Statistical Software, Inc., Los Angeles, CA 90025
g Microsoft Excel, Microsoft Corporation, Redmond, WA 98052

Table 1: Device results (mean ± standard error of the mean) and correlation with Anti-Xa. CPB = Cardiopulmonary bypass. Conc. = Concentration. * = p < 0.01 ** = Not significant

Device/Test	Baseline	Data Sampling Period Pre-CPB	CPB	Post Protamine	Anti-Xa Correlation all collection periods	Anti-Xa Correlation collection periods 2 and 3
HemoTec ACT (sec)	139.2 ± 6.28	550.9 ± 15.2	586.8 ± 4.52	117.9 ± 3.75	r = 0.83*	r = -0.21**
Hemochron ACT (sec)	146.8 ± 7.29	564.3 ± 12.2	583.0 ± 5.05	130.0 ± 5.88	r = 0.84*	r = -0.12**
TAS ACT (sec)	181.7 ± 7.53	405.9 ± 10.8	435.6 ± 7.68	182.6 ± 7.97	r = 0.78*	r = -0.09**
Heparin conc. (U) (Anti-Xa assay)	0.14 ± 0.03	5.16 ± 0.28	4.14 ± 0.20	0.03 ± 0.01		

nificantly after CPB initiation, among all devices, and is illustrated graphically in Figure 1. CPB patient hematocrit (%) was found to be negatively correlated with device output in the HemoTec (r = -0.46), Hemochron (r = - 0.46), and TAS (r = - 0.37). Device correlations with anti-Xa assay during collection periods 2 and 3 showed negative correlations in each of the three devices evaluated [HemoTec (r = -0.21), Hemochron (r = - 0.12), and TAS (r = -0.09)].

Figure 1: Differences between pre-CPB and CPB mean ACT heparin dose response. CPB = Cardiopulmonary bypass. Bars show mean dose response ± standard error of the mean ACT pre-CPB and CPB. All dose response times increased on CPB (p < 0.01).



DISCUSSION

The usefulness of ACT in determining the degree of anticoagulation in individuals undergoing CPB has been well documented (1-5). Although criteria for assessing adequacy of heparinization utilizing ACT is often debated, many authors report clinically satisfactory heparinization with ACT values greater than 400 seconds (1,3). The ability of ACT to predict circulating heparin levels, however, has been challenged extensively (1-8). Disparity among individual response to heparin has been attributed to a variety of factors. Platelet dysfunction, circulating anti-thrombin III levels, and medications are often cited as sources of this discrepancy (4-8,10). Additionally, the effect of CPB has been implicated as contributing to ACT nonlinearity (2-8,10). The results of this study confirm these findings. While overall device correlation with heparin anti-Xa inactivation (sampling periods 1, 4) ranged from r = 0.84 to r = 0.78, correlation with high heparin concentration periods (sampling periods 2,3) were found to be negative in all devices tested (Table 1). The dose response activity of heparin from pre-CPB to CPB increased significantly in all devices tested (p < 0.01)(Figure 1) suggesting that initiation of CPB alone may account for observed differences. Further support of this observation is detailed by our findings of a negative correlation in each device with patient hematocrit during CPB. In other words, decreasing hematocrit during CPB increased the response time of each device.

Medical clinicians, seeking to better qualify relationships between circulating heparin levels and their clinically appropriate measurement, have devised new strategies to address adequacy of heparinization. We investigated four such methods designed to assess circulating heparin levels. The HemoTec ACT uses a mechanical plunger that is dipped in and out of kaolin-activated blood samples in cartridges. The machine optically senses the time that it takes the plunger to move through the blood specimen; clotting time is defined as the time at which a certain "drop-time" threshold for the plunger is reached (11,12). The Hemochron device measures ACT by using a magnet inside prewarmed glass specimen tubes that may hold a number of different activators. After blood is placed in the tubes, the tubes are rotated inside the machine. As the blood clots, it displaces the magnet, thereby activating a proximity switch. The clotting time is the time it takes to displace the magnet a given distance (11,12). For the purpose of this study we chose the kaolin based activator substance for the Hemochron device for comparison with the HemoTec device. A relatively new device has recently become available to measure ACT. The TAS system

employs a dry reagent technology based on infrared sensing of the motion of paramagnetic iron oxide particles (PIOP) contained in the reagent in response to an oscillating magnetic field (12). Utilizing citrated blood in vitro thrombus formation is detected when PIOP entrapment during fibrin polymerization is sensed by infrared light (12).

Our study results did not demonstrate an increased ability of the TAS device to predict circulating heparin levels. Correlation with anti-Xa assay yielded an overall $r = 0.78$, which was the lowest correlation among devices tested. Correlation with anti-Xa assay at high heparin levels (sampling periods 2 and 3) resulted in negative correlation analysis similar to the HemoTec and Hemochron devices. Claims by the manufacturer that the TAS device is not influenced by hemodilution and hypothermia were not shown in this study. Heparin dose response increased during CPB with this device to the same extent as the HemoTec and Hemochron. Since the HemoTec, Hemochron, and TAS systems are all designed to evaluate an intact intrinsic clotting cascade, it is not suprising that they all exhibited similar dilutional and hypothermic responses.

The following conclusions can be drawn from this study: 1) That ACT, as measured by the TAS, HemoTec, and Hemochron, does not accurately predict blood heparin levels. 2) That these ACTs are influenced by CPB with hemodilution and hypothermia. 3) That the TAS system is affected by these factors to the same degree as more conventional ACT testing devices.

REFERENCES

1. Bull BS, Huse WM, Brauer FS, et al. Heparin therapy during extracorporeal circulation. J Thorac Cardiovasc Surg. 1975;69: 685-89.
2. Stead SW. Comparison of two methods for heparin monitoring: a semi-automated heparin monitoring device and activated clotting time during extracorporeal circulation. Int J Clin Monitoring Comput. 1989;6: 247-54.
3. Esposito RA, Culliford AT, Colvin SB, et al. The role of the activated clotting time in heparin administration and neutralization for cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1983;85: 174-85.
4. Baugh RF, Deemar KA, Zimmermann JJ, et al. Heparinase in the activated clotting time assay: monitoring heparin-independent alterations in coagulation function. Anesth Analg. 1992;74: 201-5.
5. Hattersley PG. Activated coagulation time of whole blood. JAMA. 1966;196: 436-40
6. Bode AP, Lust RM. Masking of heparin activity in the activated coagulation time (ACT) by platelet procoagulant activity. Thromb Res. 1994;73: 285-300.
7. Wang JS, Lin CU, Hung WT, et al. In vitro effects of aprotinin on activated clotting time measured with different activators. J Thorac Cardiovasc Surg. 1992;104: 1135-40.
8. Guffin AV, Dunbar RW, Kaplan JA, et al. Successful use of a reduced dose protamine after cardiopulmonary bypass. Anesth Analg. 1976;55: 110-113.
9. Teien AN, Lie M, Abildgaard U. Assay of heparin in plasma using a chromogenic substrate for activated factor X. Thromb Res. 1976;8: 413-416.
10. Tabuchi N, Njo TL, Tigchelaar I, et al. Monitoring of anticoagulation in aprotinin-treated patients during heart operation. Ann Thorac Surg. 1994;58: 774-7.
11. Ferguson JJ. All act's are not created equal. Tx Heart Ins. J. 1992;19:1-3.
12. Avendano A, Ferguson JJ. Comparison of Hemochron and HemoTec activated coagulation time target values during percutaneous transluminal coronary angioplasty. J Am College Cardiol. 1994;23: 907-10.
13. Oberhardt BJ. Advancing blood coagulation testing to the point of care in response to molecular biology - driven development of pharmaceuticals. Clin Chem. 1993;39: 1982-1984.