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Evaluation of a New Point-of-care Celite-activated Clotting Time Analyzer in Different Clinical Settings

The i-STAT Celite-activated Clotting Time Test

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Background: **Activated clotting time (ACT) is used to monitor heparin therapy during cardiopulmonary bypass, interventional cardiology, and hemodialysis. Traditionally, ACT is performed by use of the Hemochron system. Recently, a new device, the i-STAT system, has been introduced to measure ACT. The aim of this study was to correlate the performances of these two systems and to compare ACT values with heparin levels.**

Methods: **One hundred sixty-five samples from 29 patients undergoing cardiopulmonary bypass or hemodialysis were assayed in duplicate with two Hemochron and two i-STAT devices. Heparin levels were determined by anti–factor Xa assay.**

Results: **The Hemochron ACT ranged from 88 to 1,028 s, and the i-STAT ACT ranged from 80 to 786 s. Heparin plasma levels ranged from 0.01 to 10.8 U/mL. Bland–Altman analysis showed a mean difference between the two methods of 24 ± 101 s. Strong relationships between anti–factor Xa activity and Hemochron ACTs ($r^2 = 0.69$, $P < 0.001$) and i-STAT ACTs ($r^2 = 0.79$, $P < 0.001$) were observed. During cardiac surgery, significant correlations were found: Hemochron, $r^2 = 0.61$, $P < 0.001$ and i-STAT, $r^2 = 0.74$, $P < 0.001$. During hemodialysis, relationships between anti–factor Xa activity and ACTs were found: Hemochron, $r^2 = 0.62$, $P < 0.001$ and i-STAT, $r^2 = 0.55$, $P < 0.001$.**

Conclusions: **During cardiopulmonary bypass procedure and hemodialysis, i-STAT provides measurements of clotting time quite similar to Hemochron ACT, which were significantly correlated with heparin levels.**

IN different clinical settings, such as cardiopulmonary bypass (CPB), interventional cardiology procedures, and hemodialysis, the need exists for adequate anticoagulation and its rapid assessment to prevent thrombosis of circuits used during extracorporeal circulation (ECC). The current practice is to rapidly monitor the degree of heparin-induced anticoagulation and its reversal by means of activated clotting time (ACT), which is performed with automated bedside devices.[1]

The ACT, described by Hattersley[2] in 1966, measures the time required by whole-blood samples to clot after contact activation. Because this test reflects the activity of heparin administered during any cardiovascular procedure, it has a widespread clinical use for CPB, interventional cardiology procedures, and hemodialysis. The old automated system traditionally used to perform ACT, derived from the technique originally described, is Hemochron 401 (ITC, International Technidyne Corp., Edison, NJ),[3] which registers ACT in seconds by a mechanical device using celite, a diatomaceous earth, as activator. However, this technique has considerable drawbacks, such as a lack of sensitivity and poor reproducibility, and many investigations have reported significant disparities between heparin doses and measurable heparin effects.[4,5]

In an attempt to improve the monitoring of heparin therapy, new technologies have been introduced. Recently, a new instrument for celite-ACT measurement has become available: the i-STAT device (Abbott Laboratories, Abbott Park, IL).[6,7] It measures an ACT on the basis of the conversion of a thrombin substrate (other than fibrinogen), and an electrochemical sensor is used to indicate this conversion.

The purpose of this study was twofold: (1) to determine whether there is a relationship between i-STAT celite-ACT and Hemochron ACT, and (2) to compare the correlations between plasma levels of heparin measured by anti–factor Xa (anti-Xa) activity and i-STAT celite-ACTs and Hemochron ACTs. The study was performed on patients undergoing cardiac surgery with ECC and on patients undergoing hemodialysis.

Materials and Methods

Patients and General Procedure

A total of 330 duplicate i-STAT and Hemochron ACT measurements was obtained simultaneously from 165 samples. There were 130 samples from 20 patients (8 women and 12 men; mean age, 68 ± 5 yr) affected by stable angina pectoris with one-, two-, or three-vessel disease who underwent CPB for elective coronary artery bypass graft surgery without concomitant valve replacement. Antianginal therapy was continued until the morn-

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Table 1. Demographic and Preoperative Clinical Data of Coronary Artery Bypass Surgery Patients

Age, yr	68 ± 5
Sex, M/F	12/8
Stable angina pectoris	20
Previous acute myocardial infarction	18
Diabetes mellitus	12
Hypertension	18
Hypercholesterolemia (>200 mg/dl)	15
Smoking/nonsmoking	16/4
Medications used	
Nitrates	19
β-Blockers	7
Calcium channel blockers	11
Heparin	4
Aspirin	18
Diuretics	5
Angiographic findings	
One vessel with stenosis >75%	1
Two vessels with stenosis >75%	5
Three vessels with stenosis >75%	14

Values are numbers of patients.

ing of surgery and included β-blockers, calcium channel blockers, nitrates, and aspirin. Table 1 shows the demographic and preoperative clinical characteristics of these patients. Thirty-five samples were from nine uremic patients who underwent hemodialysis (five women and four men; mean age, 58 ± 10 yr). All patients gave informed consent according to the protocol of the human ethics committee of Azienda Ospedaliera Careggi. The investigation was approved by the Department of Area Critica Medico-Chirurgica of the University of Florence and by the Azienda Ospedaliera Careggi. The study was conducted according to the principles of the Declaration of Helsinki.

For cardiac surgery procedures, all patients were premedicated 1 h before surgery with morphine (0.1 mg/kg), scopolamine (0.2 to 0.4 mg), and diazepam (0.1 to 0.2 mg/kg). Anesthesia was induced with fentanyl (10 to 25 μg/kg) and pancuronium bromide (0.1 mg/kg) and maintained with supplements of the same drugs and low concentrations of isoflurane (0.6 to 1.0%). Full anticoagulation was achieved with 300–400 U/kg of porcine sodium heparin (Vister, Parke-Davis, Linate, Italy). All patients received an additional 5,000 U of heparin in CPB primer. Heparin reversal with protamine was obtained by use of a heparin dose–response curve. In no patient was aprotinin or other antifibrinolytic drugs administered. All CPB procedures were performed under conditions of moderate hypothermia (29 to 32°C). Blood samples and ACT measurements were taken during the procedures to achieve effective anticoagulation (1) at baseline, before the administration of heparin; (2) 5 min after heparin bolus and before CPB; (3) during the ECC period (at least three times, every 20 to 30 min); and (4) 5 min after the protamine infusion. All the samples were obtained from an arterial sheath. Five milliliters (0.5 ml of flush solution and 4.5 ml of arterial blood) was discarded before the drawing of samples for coagulation testing. Five milliliters of fresh whole blood was used to measure the celite-ACT by the two coagulation monitors, and 4.5 ml of blood was collected in 5-ml Vacutainer tubes (Becton Dickinson, Meylan Cedex, France) containing 0.5 ml of sodium citrate (0.129 M) to measure anti-Xa activity. Hematocrit and body temperature were monitored at the same time points.

The uremic patients had hemodialysis scheduled three times a week using a cellulose membrane dialyzer, and each session lasted between 2 and 4 h. They had been undergoing dialysis for a mean period of 3.4 ± 3.4 yr. Causes of end-stage renal disease were glomerulonephritis (n = 7) and interstitial nephritis (n = 2). During the initial training sessions of hemodialysis, a fixed hourly dose of heparin infusion (1,000 to 2,500 U/h) was assigned to each patient. Blood samples to determine ACT were performed every hour and at the end of hemodialysis. The procedure for sampling was identical to that performed during CPB.

ACT Measurements

The two systems use different techniques to determine ACT. The Hemochron machine uses a magnet inside glass specimen tubes containing celite. After blood is placed in the tubes, the tubes are rotated inside the instrument. As the blood clots, it displaces the magnet, thus activating a proximity switch. The clotting time is the time the clot takes to displace the magnet a given distance.[3]

The i-STAT analyzer system consists of a microprocessor-based analyzer that can use specific cartridges containing celite (celite-ACT test).[8,9] The principles of the i-STAT celite-ACT test are similar to those of Hemochron ACT, because celite is used as activator. However, the endpoint of this method is indicated by the conversion of a thrombin substrate (inside the cartridge) other than fibrinogen. The substrate used in the electrogenic assay (*H*-D-phenylalanyl-pipecolyl-arginine-*p*-amino-*p*-methoxydiphenylamine, which has the structure phenylalanine-pipecolic acid-arginine═NH-C_6H_4-NH-C_6H_4-OCH_3) has an amide linkage that mimics the thrombin-cleaved amide linkage in fibrinogen. Thrombin cleaves the amide bond at the carboxy-terminus of the arginine residue (denoted by the double bond symbol). This reaction produces an electroactive compound (NH^+-C_6H_4-NH-C_6H_4-OCH_3) that is detected amperometrically, and the time of detection is measured in seconds.

For the Hemochron ACT, 2 ml of fresh whole blood was dispensed into each of two celite-activated tubes, and the start button of the device was immediately depressed. Each tube was agitated 10 times by inversion (for approximately 10 s) and placed at 37°C in the incubation well of the Hemochron ACT analyzers.

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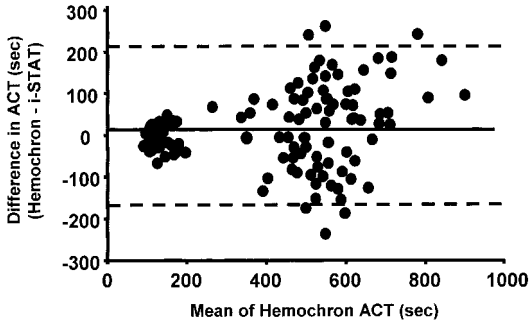

Fig. 1. Bias-plot of Hemochron ACT and i-STAT ACT analytic precision with 95% of limits of agreement (*broken lines*): difference between Hemochron ACT and i-STAT ACT measurements against Hemochron data.

For the i-STAT celite-ACT, a drop of fresh whole blood was put into each well of two i-STAT celite-ACT cartridges already inserted in the analyzers.

Determination of Heparin Plasma Levels

Anti-Xa activity was assessed in citrated plasma collected and separated within 30 min by centrifugation at 2,500 × *g* for 20 min at 4°C and stored at −70°C. Heparin concentrations were determined by assessing the level of inhibition of the hydrolysis of a chromogenic substrate (by the factor Xa) in the presence of heparin–antithrombin complexes (Berichrom® Heparin, Dade Behring, Marburg, Germany).[10]

The bedside coagulation tests and the measurements of plasma heparin were performed by two of the authors (R.P. and B.B.).

Statistical Analysis

All results are reported as mean and SD. The Hemochron ACT and i-STAT ACT values were compared by the Bland–Altman bias analysis.[11,12] For paired comparisons, Student *t* test was used. Chi-square analysis was used to compare the ACT measurements of the two systems by dividing values into those above and those below prefixed targets. Pearson's correlation was used to assess the relationship between both Hemochron ACT and i-STAT ACT and heparin levels. A value of $P \leq 0.05$ was considered statistically significant.

Results

The measurements of Hemochron ACT ranged from 88 to 1,028 s, and those of the i-STAT ACT ranged from 80 to 786 s. The results of chromogenic anti-Xa activity ranged from 0.01 to 10.80 U/mL. The Bland–Altman analysis was performed by plotting the difference between ACT measurements obtained with the two methods *versus* the Hemochron data (considered the reference method). This analysis showed a mean difference of 21.51 ± 92.04 s between the two systems, with a relationship between the differences of the two measurements and Hemochron values of 0.36. The difference between the two systems increased for ACT values greater than 400 s (fig. 1). The 81 ACT values obtained during hemodialysis and during cardiac surgery (at baseline and after protamine) in the presence of low or no heparin levels did not differ significantly between the two methods. The 84 ACT values obtained in cardiac surgery patients after heparin administration and during CPB were significantly higher when measured with the Hemochron system than with the i-STAT machine (table 2). Using the usual therapeutic target of 480 s for ACT measurements, differences were found between the two systems (table 3). Sixty-eight ACT values (81%) were classified as therapeutic by the Hemochron system, whereas this was the case for only 56 (67%) by the i-STAT instrument. There were 19 ACT values (23%) in which the Hemochron ACT was therapeutic and the i-STAT ACT was subtherapeutic, whereas 7 measurements (8%) were subtherapeutic for Hemochron ACT and therapeutic for i-STAT ACT (table 3). In an attempt to improve the concordance between the two systems, we assessed the performance of lower ACT therapeutic targets for the i-STAT device. The best concordance was obtained with a value of 400 s. There were 66 ACT values (78%) classified as therapeutic (n = 60) or subtherapeutic (n = 6) for both the Hemochron and i-STAT devices. Moreover, there were 9 ACT values (11%) in which the Hemochron ACT was therapeutic and the i-STAT ACT was subtherapeutic, and 9 measurements (11%) were subtherapeutic for the Hemochron ACT and therapeutic for the i-STAT ACT (table 4).

Considering all determinations, significant correlations were observed between anti-Xa activity and ACT

Table 2. Mean ACT Measured during Hemodialysis (Low Concentrations of Heparin Infusion) and Cardiac Surgery (Baseline and after Protamine Infusion) and during Cardiac Surgery (after Heparin and during Cardiopulmonary Bypass)

		ACT		
Measurements	n	Hemochron	i-STAT	*P**
Hemodialysis and cardiac surgery (baseline and after protamine)	81	129.8 ± 21.0	130.6 ± 32.2	NS
Cardiac surgery (after heparin and during CPB)	84	580.9 ± 141.4	538.1 ± 146.0	<0.01

* *t* test for paired samples was used to compare ACT values obtained with the two methods. ACT = activated clotting time; CPB = cardiopulmonary bypass.

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Table 3. Application of a 480-s Target Time to 84 Paired Hemochron and i-STAT ACT Determinations Obtained after Heparin Bolus and during Cardiopulmonary Bypass

	Hemochron ACT ≥480 s	Hemochron ACT <480 s
i-STAT ACT ≥480 s	49 (58%)	7 (8%)
i-STAT ACT <480 s	19 (23%)	9 (11%)

$P < 0.05$ by chi-square analysis. Values indicate number of measurements. ACT = activated clotting time.

performed with both the Hemochron (n = 165; $y = 146.09 + 51.36x$, $r^2 = 0.69$, $P < 0.001$) and the i-STAT (n = 165; $y = 129.64 + 49.48x$, $r^2 = 0.79$, $P < 0.001$). Correlations were significant also when considering only those samples taken during cardiac surgery (n = 130; Hemochron: $y = 169.56 + 48.59x$, $r^2 = 0.61$, $P < 0.001$; and i-STAT: $y = 125.17 + 49.99x$, $r^2 = 0.74$, $P < 0.001$) or samples taken during hemodialysis (n = 35; Hemochron: $y = 96.06 + 102.81x$, $r^2 = 0.62$, $P < 0.001$; and i-STAT: $y = 111.34 + 125.58x$, $r^2 = 0.55$, $P < 0.001$).

For the CPB group, a specific analysis of data obtained after heparin bolus (but before CPB) and during CPB was also performed. As a whole, ACT values obtained by the two devices showed only weak correlations with anti-Xa activity results (Hemochron ACT [1] after heparin bolus and before CPB: $y = 288.94 + 26.24x$, $r^2 = 0.21$, n = 20, $P < 0.05$; [2] during CPB: $y = 324.19 + 29.99x$, $r^2 = 0.002$, n = 60, P = NS, fig. 2, *A* and *B*; i-STAT ACT: [1] after heparin bolus and before CPB: $y = 189.56 + 36.52x$, $r^2 = 0.21$, n = 20, $P < 0.05$; [2] during CPB: $y = 324.19 + 29.99x$, $r^2 = 0.01$, n = 60, $P = 0.001$, fig 2, *C* and *D*).

Discussion

The ACT, initially described as a manual technique by Hattersley[2] and introduced into cardiac surgery by Bull *et al.*,[13,14] is the most frequently used method to assess the degree of anticoagulation induced by heparin during different clinical procedures such as CPB, interventional cardiology procedures,[15] and hemodialysis.[16] The concept of a target ACT after heparin administration that indicates an adequate anticoagulation is associated with the prevention of thrombus formation and was considered early[13,14] during ECC in cardiac surgery. A high variability was demonstrated in the ACT response after a fixed dose of heparin, which advocated the routine use of ACT measurements to guide heparin dosing during surgery.[14,15] New reports exist that again document disparities among heparin dose, heparin effect, and heparin blood concentration.[4,5,17,18]

Table 4. Application of a 480-s Target Time to Hemochron ACT Values and a 400-s Target Time to i-STAT ACT Determinations Obtained from the 84 Paired Samples after Heparin Bolus and during Cardiopulmonary Bypass

	Hemochron ACT ≥480 s	Hemochron ACT <480 s
i-STAT ACT ≥400 s	60 (71%)	9 (11%)
i-STAT ACT <400 s	9 (11%)	6 (7%)

$P < 0.05$ by chi-square analysis. Values indicate number of measurements. ACT = activated clotting time.

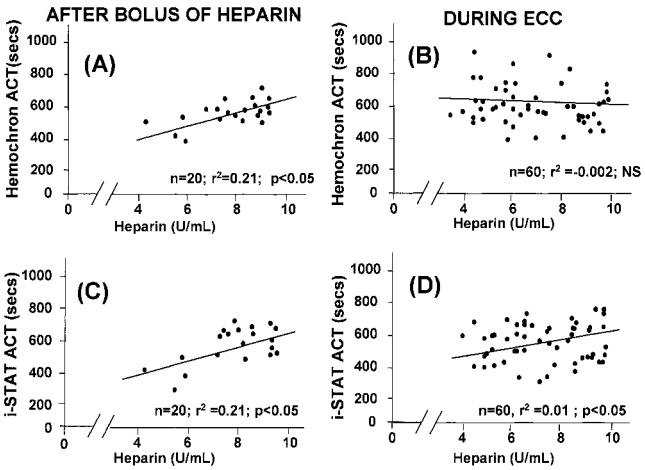

Fig. 2. CPB group specific relationships between the different ACT measurements and anti-Xa activity. Correlations after bolus of heparin: Hemochron ACT (*A*) and i-STAT ACT (*C*). Correlations during ECC: Hemochron ACT (*B*) and i-STAT ACT (*D*).

Although widely used, the ACT is subject to bias from various interventions that are typical during cardiac surgery, particularly hemodilution and hypothermia.[4,19,20] Depending on the activator used (celite or kaolin), ACT values may also be falsely elevated in the presence of certain current drug therapies, such as aprotinin administration.[21,22] Factors known to shorten the ACT include surgical incision[23] and the decrease in antithrombin often observed during CPB.[24,25]

The i-STAT ACT has been introduced as an alternative method for measuring heparin effect. In an attempt to compare the performance of Hemochron ACT and i-STAT ACT to provide a measure of heparin effect, bias analysis between these two tests was performed. These measurements of heparin effect were also compared with heparin concentration assessed by plasma anti-Xa activity.

To compare the performance of the two instruments, we used Bland–Altman bias analysis,[11,12] which assesses the level of agreement between two methods of clinical measurement. This analysis uses graphical plots of the difference between values measured by different techniques *versus* a reference method. Because the Hemochron instrument is our common and institutional method, in this study it was considered the reference system, and the mean of the duplicate Hemochron ACT measurements was used as the abscissa of the Bland–Altman graph. The mean difference between the two methods is the bias, and the mean difference ± 2 SD is the limit of agreement. In other words, calculation of the mean difference of the values derived from two methods

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is equivalent to the accuracy of the new method considered, and the 95% CIs for the bias represent the precision of the new method. This type of analysis showed the variability of the measurements with the new method over the entire range of application and was useful to indicate whether this type of reading could be used interchangeably with the reference method. As depicted in figure 1, i-STAT ACT measurements tend to be shorter than Hemochron ACT values, and the degree of variability increases after administration of high levels of heparin. The magnitude of the differences between the two methods appears substantial and variable when the ACT is 480 s or more. When the achievement of the usual target of 480 s in cardiac surgery patients was considered an adequate anticoagulation, 81% of patients were found to have adequate anticoagulation with the Hemochron machine *versus* 67% patients with the i-STAT instrument. The ability to accurately detect therapeutic target times is important for the purpose of going onto bypass and/or adjusting heparin levels accordingly. In this study, the anesthetists took into account the Hemochron ACT measurements as the reference values to be considered. During cardiac surgery, when the i-STAT machine read more than the target time and the Hemochron did not (8%), the anesthetists gave more heparin to the patients. Conversely, no subsequent boluses of heparin were administered in those 19 patients (23%) who had Hemochron ACT values greater than the target time with the corresponding i-STAT ACT values below it. These differences between the two methods must be considered when attempting to establish a correct target ACT. We looked for a different therapeutic target ACT for i-STAT to improve concordance with the Hemochron. We found that for a target of 400 s, 82% of values were concordant for both systems. Further studies are needed to evaluate whether the i-STAT analyzer can be used safely to monitor heparin administration during cardiac surgery with different therapeutic target values from those validated for the Hemochron system.

Considering the heparin effect, statistically significant correlations ($P < 0.001$) were found between Hemochron ACT or i-STAT ACT values and heparin concentrations after both high-dose heparin administration (300 to 400 U/kg, during cardiac surgery) and moderate-dose heparin administration (*i.e.*, during hemodialysis). When these correlations were performed on separate settings (cardiac surgery or hemodialysis), similar statistically significant relationships were found. However, if we consider the correlations between both ACT results and heparin levels in samples obtained during CPB, only clinically meaningless results were obtained. Different methods are available to monitor heparin concentrations, but they have some limitations. Whole-blood heparin activity can be assessed at bedside with the automated heparin-protamine titration method,[1] but the use of standard algorithms to calculate blood volume that is variable is necessary. The anti-Xa chromogenic method, considered the usual system to determine plasma heparin levels and performed only in specialized laboratories, examines a substantially different endpoint, *i.e.*, heparin concentration, rather than heparin activity. Actually, this assay, performed on platelet-poor plasma, assesses heparin concentration,[4] but it does not reflect heparin antithrombotic properties, which can be influenced by different individual factors, such as antithrombin concentration.[25] This is highlighted by the weak and probably clinically nonuseful relationships between heparin levels and ACT readings derived from both devices obtained during ECC. Despite the high plasma levels of heparin found in patients, several mechanisms influence both the hemostatic process during CPB and the results of ACT. The Hemochron ACT has been reported to be affected not only by hypothermia and hemodilution[17,19,20] but also by a multitude of factors,[26] such as coagulation factor and antithrombin levels,[24–30] platelet count, and function.[31] The data produced in this study do not show that the i-STAT device has solved any of the important drawbacks of the Hemochron; therefore, further studies on the performances of this new device are needed. Such studies should also evaluate correlations of ACT with other heparin assays and markers of thrombin activity, such as thrombin–antithrombin complex, fibrin monomer, and fibrinopeptide A.

This first investigation on the i-STAT system has compared i-STAT ACT with Hemochron ACT and has evaluated the degree of response of the i-STAT ACT to heparin therapy. Our data indicate that Hemochron ACT and i-STAT ACT results were statistically different from each other after high levels of heparin were administered, when Hemochron ACT values were significantly longer.

In conclusion, in patients undergoing cardiac surgery or hemodialysis, the i-STAT and Hemochron instruments provide quite similar ACT values, but it is still difficult and too early to say whether they may be used interchangeably after heparin bolus administration. We believed in the importance of finding an appropriate therapeutic target for the i-STAT system when it is used to monitor anticoagulation treatment with high levels of heparin. Further studies should be performed to evaluate the effect of hemodilution *in vitro* and/or *ex vivo* on the i-STAT system using serial dilutions of whole-blood specimens. Moreover, more elaborate analyses should also be performed to compare this new system and the standard ACT results with markers of thrombin activity.

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