J Extra Corpor Technol. 2018;50:38–43
The Journal of ExtraCorporeal Technology

Clinical Evaluation of Measuring the ACT during Elective Cardiac Surgery with Two Different Devices

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Presented in part at the 7th Networking World Anesthesia Convention, New York, April 20–23, 2016.

Abstract: Unfractionated heparin is the mainstay of anticoagulation during cardiac surgery on cardiopulmonary bypass (CPB) due to its low cost, quick onset, and ease of reversal. Since over 30 years, the activated clotting time (ACT) has been used to assess the level of heparin activity both before and after CPB. We compared two different methods of measuring the ACT: i-STAT, which uses amperometric detection of thrombin cleavage, and Hemochron Jr, which is based on detecting viscoelastic changes in blood. We included 402 patients from three institutions (Papworth Hospital, Cambridge, UK; Groote Schuur, Cape Town, South Africa; University Hospital Basel, Basel, Switzerland) undergoing elective cardiac surgery on CPB in our study. We analyzed duplicate samples on both devices at all standard measuring points during the procedure. The correlation coefficient between two Hemochron and two i-STAT devices was .9165 and .9857, respectively. The within-subject coefficient of variation (WSCV) ranged from 8.2 to 13.6% for the Hemochron and from 4.1 to 9.1% for the i-STAT. We found that the number of occasions where one of the duplicate readings was >1,000 seconds while the other was below or close to the clinically significant threshold of 400 seconds were higher for the Hemochron. We found the i-STAT to systematically return higher measurements. We conclude that the i-STAT provides a more reliable test for heparin activity and assesses safe anticoagulation during cardiac surgery on pump. The fact the that the i-STAT reads higher than the Hemochron leads to the recommendation to validate the methods against each other before changing devices. **Keywords:** activated clotting time (ACT), method comparison, anticoagulation, cardiopulmonary bypass. *J Extra Corpor Technol. 2018;50:38–43*

The Activated Clotting Time (ACT) is used to monitor coagulation. It measures the time in seconds taken for a blood sample to clot after it has been exposed to a catalyst activating the intrinsic pathway (1). It is the standard method to assess the adequacy of heparin therapy and anticoagulation during extracorporeal circulation, be this extracorporeal life support and cardiopulmonary bypass (CPB), or during interventional procedures in the catheter laboratory. The test is commonly performed at the point of care, i.e., at the patient's bedside or in the operating room (OR). A recent survey showed that most tests are done either in the OR during cardiac surgery (32.4%) or during cardiac catheterization (32.3%), the remaining third distributed over vascular procedures (10.1%), Intensive Care Units (13.8%), and others (11.3%) (2).

Adequate anticoagulation is essential for the safe conduct of CPB, as normally liquid blood clots when it comes in contact with foreign surfaces, damaged blood vessels, or is subjected to stasis. All these conditions are met in the course of a cardiac operation using CPB. Inadequate anticoagulation can lead to serious untoward events with often-fatal consequences, including oxygenator blockage causing cessation of extracorporeal support and multiorgan failure due to microemboli.

Microemboli also have the potential to trigger disseminated intravascular coagulation in already activated blood during CPB, rapidly consuming clotting factors and resulting in severe postoperative bleeding (3).

Although the ACT test has existed for 50 years (4) and has been used in the context of cardiac surgery since the 1970s (5–7), there are result discrepancies between various measuring devices. The reasons for these

Received for publication April 3, 2017; accepted October 23, 2017.
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discrepancies are poorly understood. Most devices rely on the detection of clot formation with the help of mechanical methods, such as using a mechanical plunger, displacement of a magnet, or blood flow through a narrowed tube. By contrast, the i-STAT assay (Abbott POC, Princeton, NJ) uses the amperometric detection of an electrochemical product resulting from thrombin cleavage.

We report the intra- and interdevice comparison of ACT values measured by i-STAT and by Hemochron Jr. (Accriva Diagnostics, San Diego, CA) during cardiac surgery at standard measuring points during cardiac surgery on CPB at three institutions.

MATERIALS AND METHODS

With appropriate Human Research Ethics Committee and Institutional Review Board approval at all three sites, we collected ACT data from 402 patients. The contributing hospitals and the number of patients were

- Papworth Hospital in Cambridge, UK, 234 patients
- Groote Schuur Hospital in Cape Town, South Africa, 103 patients
- University Hospital Basel, Switzerland, 65 patients.

Adult patients scheduled for routine cardiac surgery on CPB, but without deep hypothermic circulatory arrest, were included in this evaluation. It is common practice in all three institutions for elective patients to continue on aspirin until the day of surgery and to stop IIb/IIIa platelet antagonists 5 days earlier. Patients who omitted to stop IIb/IIIa platelet antagonists in time were excluded. Further exclusion criteria were solid organ transplantation, emergency cardiac or aortic surgery, and unwillingness or inability to give written informed consent. 1-mL blood samples for ACT testing were taken as given below at the normal, routine time points in accordance with the standard of care during the procedure and included into the dataset:

- Baseline—after establishment of intra-arterial access before the administration of heparin
- Heparin—after heparin administration (300 U/kg), but before commencing CPB
- CPB 1–4—during CPB at 20–30 minutes intervals
- After separation from CPB and reversal of heparin.

Samples were immediately processed in the OR by anesthesia staff or by perfusionists. All tests were done in accordance with manufacturers' guidelines and were dispensed into two i-STAT Celite ACT cartridges and two ACT+ cartridges. Once inserted, the devices perform the tests automatically.

All four ACT readings at each time point were included. Data were recorded in an anonymized manner.

Operator error was minimized by following the manufacturers' recommendations for each ACT test performed and by limiting the number of staff involved. Full training was provided to all personnel handling both devices using the manufacturers published recommendations for use.

A quality test control was carried out each night on the Hemochron devices using the Electronic system verification cartridges at high level (500 seconds) and low level (300 seconds) and the temperature verification cartridge. This is carried out to ensure correct instrument operation at the two levels and that the heating element of the device is heating up and maintaining the temperature of the test chamber for the correct duration. In addition, a liquid quality control was carried out once a week using the Level 1 (Normal) and Level 2 (Abnormal) assayed lyophilized whole blood preparations, ensuring all cartridge lot numbers ever in circulation were checked for quality. The liquid controls were refrigerated and kept within the limits of 2°C–8°C. Whereas the test cartridges were brought to room temperature before use and never exceeded 37°C. Before each test can be carried out, the device itself performs a self-check which checks the function of the light emitting diode detectors, ensures the cuvette temperature reaches 37 (±1°C), the sample size is sufficient, and the timer of the device is functioning properly. It is only after this self-test that an ACT measurement can be given. This rules out possible differences in measuring time and temperature.

i-STAT cartridges were delivered in a refrigerated box with temperature strips inside. Each shipment was checked to ensure that the temperature of cartridges was always within limits throughout transit. They were kept refrigerated

Table 1. Mean ACT reading at each measuring point per device.

	Reading			
	1		2	
Time	n	Mean (SD)	n	Mean (SD)
Hemochron				
Baseline	399	122.9 (21.1)	395	122.3 (20.5)
Heparin	369	571.9 (155.5)	359	566.7 (149.2)
CPB1	362	586.6 (165.6)	358	587.9 (159.8)
CPB2	366	549.4 (131.1)	368	546.6 (138.5)
CPB3	283	499.0 (107.1)	281	498.9 (97.2)
CPB4	153	490.1 (120.4)	154	490.4 (118.1)
Protamine	390	123.8 (17.4)	384	123.4 (19.4)
i-Stat				
Baseline	394	133.9 (19.8)	396	131.9 (17.9)
Heparin	329	614.3 (149.8)	334	612.8 (158.4)
CPB1	311	633.7 (148.3)	305	632.6 (150.8)
CPB2	346	589.1 (146.3)	347	587.8 (153.6)
CPB3	270	540.1 (139.0)	272	533.2 (137.9)
CPB4	157	538.1 (136.4)	154	530.4 (135.3)
Protamine	389	130.9 (20.0)	388	129.0 (19.4)

n = number of included patients.

Table 2. Intradevice difference at measuring points in %.

	Baseline	Heparin	CPB1	CPB2	CPB3	CPB4	Protamine
Hemochron	8.36	10.24	11.12	10.70	10.06	11.79	7.75
i-STAT	4.73	6.28	5.63	6.45	6.83	5.03	4.3

between 2°C and 8°C for storage and were brought to room temperature just before use and never exceeded 37°C. Clew updates were performed twice a year, this updates standardization values, and an external electronic simulator was used afterward. This verifies analyzer performance and thermal probes. The i-STAT has its own internal electronic simulator which verifies its own performance every 8 hours also. ACT testing was conducted in a random manner where sometimes samples were added to the Hemochron Jr. first and sometimes into the i-STAT first.

Statistics

The mean, SD, and within-subject coefficient of variation (WSCV) were chosen as methods to summarise reliability. Intra- and interdevice agreements were assessed using the Bland–Altman limits of agreement method.

RESULTS

Table 1 summarizes the measurements obtained at each measuring point. There was a good agreement between both device types. However, it was noted that the i-STAT tended to read slightly higher than the Hemochron Jr.

Table 2 shows the average percentage difference between the two measurements on each of the two devices at each time point.

Figures 1 and 2 show the relationship between all measurements for both devices. The correlation coefficients were .9165 for the Hemochron, and .9857 for the i-STAT ($p < .0001$).

Figures 1 and 2 illustrate the intradevice correlation (and thereby reliability) of the two devices. At values close to physiological ACT, reliability is maintained. However, as

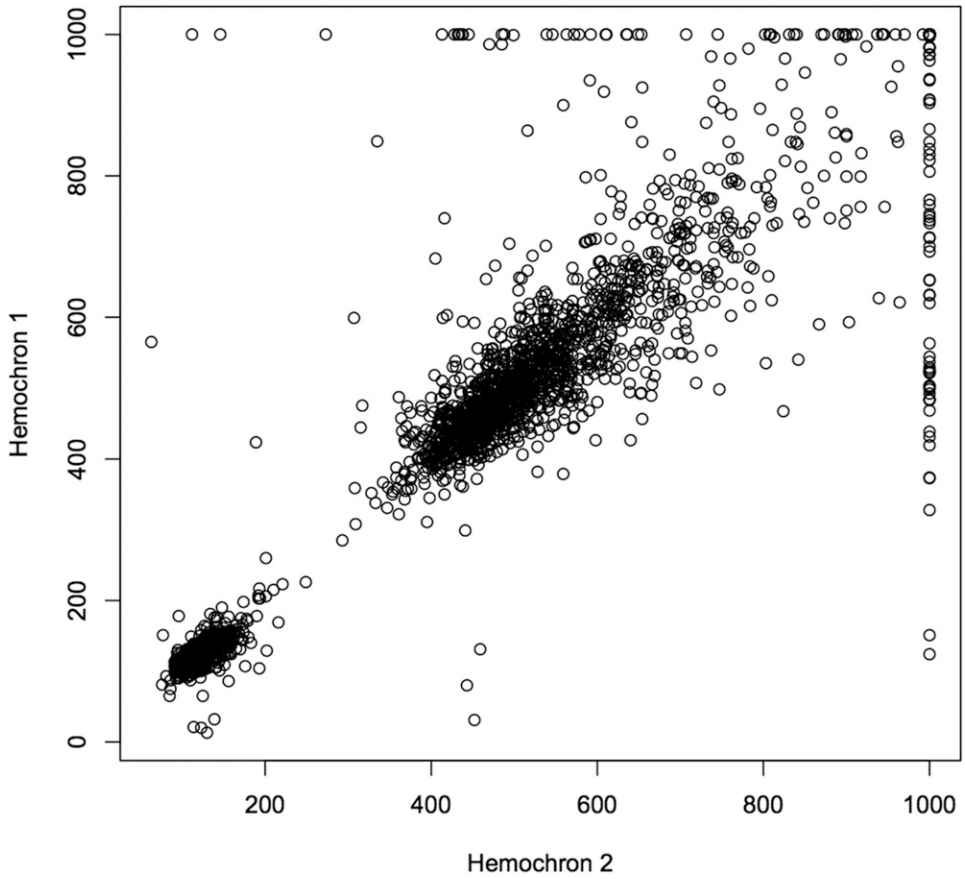

Figure 1. Scatter diagram of all paired Hemochron measurements.

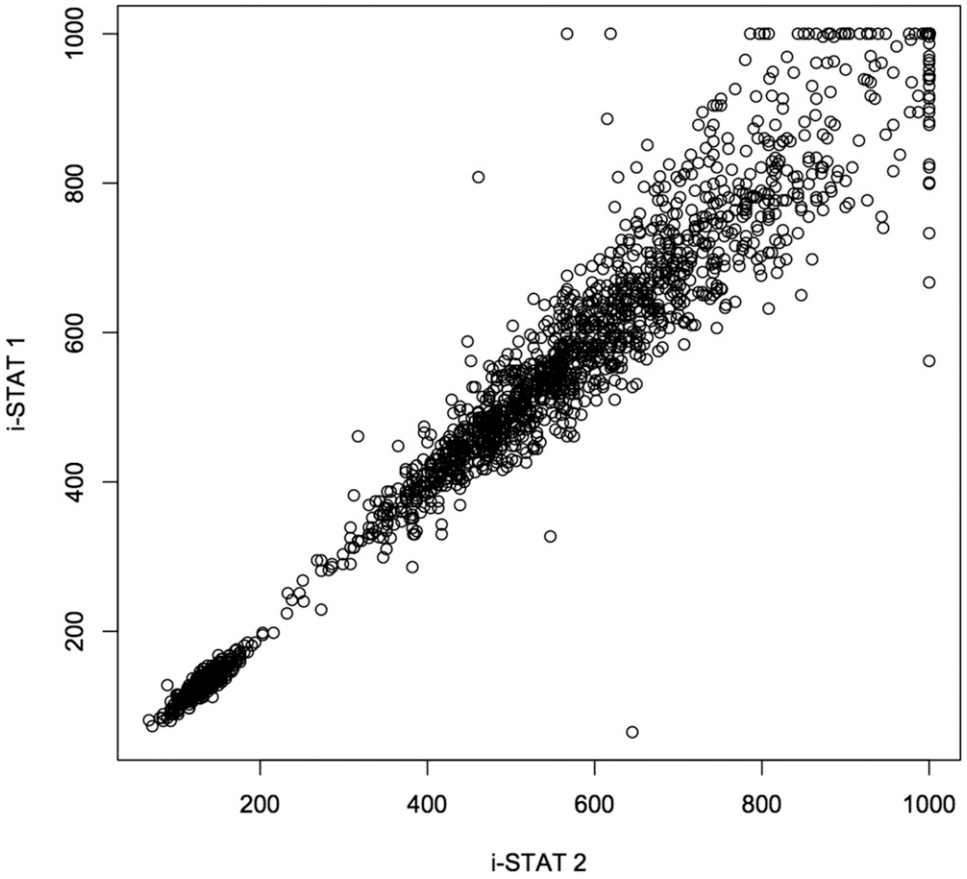

Figure 2. Scatter diagram of all paired i-STAT measurements.

ACT values increase to several times normal, correlation decreases and becomes very scattered at high values. This characteristic is more evident in the Hemochron Jr. measurements.

The WSCV was chosen as the method to summarize reliability. The WSCV was less at each time point for the i-STAT (Table 3).

Given the variability of WSCV, Table 4 shows the range 95% of ACT measurements will fall into if a patient's "true" ACT was 450 seconds at any of the given time points during cardiac surgery when heparinisation is required.

Agreement for values above and below the clinically meaningful threshold of 400 is generally excellent, although the i-STAT scores are higher in each instance (see Table 5).

Over all paired samples, the correlation coefficient between both devices was .73 [95% confidence interval {CI} .71–.74].

The Bland–Altman plot in Figure 3 shows a mean difference of 9.3% representing the systematic bias, meaning that across the totals of paired measurements the i-STAT reads, on average, 9.3% higher.

For the purpose of this analysis only the ACT readings up to 1,000 seconds were included. Table 6 shows the number of results at the time points where anticoagulation was necessary where one reading was >1,000 seconds and the other below 1,000 seconds. This is clinically significant as duplicate Hemochron Jr. measurements <1,000 seconds were generally lower and closer to or below the safe threshold of 400 seconds, whereas the lowest duplicate i-STAT measurements were always in the safe ACT range.

The Hemochron Jr. generated two duplicate readings where one was >1,000, whereas the second reading was close to baseline after Protamine had been given; there were no such events at baseline. There were no such discrepant readings for the i-STAT either at baseline or at Protamine.

DISCUSSION

Because of its short half-life and easy reversibility, unfractionated heparin is the anticoagulant of choice in most cardiac centers around the world. ACT values in the range of 400–550 seconds are generally accepted as safe, and testing is routinely performed at the point of care in the OR. The point of care testing provides rapid results which allow more timely interventions and also reduce the risk of sample mishandling or mislabelling (8). The sample

Table 3. Within-subject coefficient of variation (WSCV) at each measuring point.

Time	n	WSCV (%)	95% CI
Hemochron			
Baseline	393	9.3	6.6, 11.4
Heparin	350	13.6	7.8, 17.6
CPB1	341	11.3	7.1, 14.3
CPB2	349	8.6	7.0, 9.9
CPB3	272	8.8	5.5, 11.1
CPB4	147	8.2	4.4, 10.8
Protamine	381	12.0	6.6, 15.7
i-Stat			
Baseline	391	4.1	3.6, 4.5
Heparin	315	9.1	0.0, 12.9
CPB1	293	5.6	5.1, 6.0
CPB2	338	6.3	5.4, 7.1
CPB3	259	5.7	4.7, 6.6
CPB4	152	5.0	4.3, 5.6
Protamine	386	3.8	3.4, 4.2

CI, confidence interval.

volumes required are small and can be processed by nonlaboratory staff, which is also beneficial.

The safe ACT value that needs to be achieved before CPB can commence is largely determined by institutional preference and the device used (9). Despite cautions that values obtained by different methods should not be used interchangeably (10,11), other previously performed studies found excellent correlation comparing the Medtronic Plus (Medtronic, Minneapolis, MN) with the i-STAT ACT for the full range of values (70 to >999) (12), or the Hemochron to the i-STAT (13). Other studies have reported good correlations between ACT values measured with the i-STAT and Hemochron, albeit in the setting of the catheter laboratory or during haemodialysis, with ACT values approximately 250 seconds (13–15). Most of these studies are limited by the fact that they are single center investigations with limited sample sizes and do not focus exclusively on intraoperative testing during cardiac surgery, choosing rather to include patients undergoing different procedures. Our study only includes elective adult cardiac surgical patients from three centers in two continents, providing a homogeneous study population while not being constrained by a single operator practice. Nevertheless, previous findings are replicated in our study. We found an appropriate agreement between the two devices tested, although subject to the increasing variability

Table 4. ACT range for 95% of measurements if "true" ACT was 450 seconds.

		Heparin	CPB1	CPB2	CPB3	CPB4
Hemochron	Upper (seconds)	328	348	373	371	376
	Lower (seconds)	572	552	527	529	524
i-STAT	Upper (seconds)	368	400	393	399	405
	Lower (seconds)	532	500	507	501	495

Table 5. Percentage agreement for each device at each time-point.

	Hemochron		i-Stat	
Timing	n	% Agreement	n	% Agreement
Postheparin	350	94	316	97
CPB1	342	97	295	99
CPB2	349	95	338	97
CPB3	272	94	259	97
CPB4	147	92	153	95

Agreement determined by two results either both ≥400 or <400.

inherent in ACT values once they become several times normal. We did note that the i-STAT tends to return higher results than the Hemochron Jr. device. The clinical implications of this finding are unclear, but should lead to the recommendation to validate methods against each other before a change in clinical practice.

We found the i-STAT ACT measurements to consistently have a lower WSCV, ranging from 3.8% to a maximum of 9.1% at the point of maximum heparin activity. This is in contrast to the Hemochron Jr., which has WSCV ranging from 8.2% to 13.6%. This is of clinical significance if the range within which 95% of all results will fall is taken into account. Table 4 gives these values for a presumed "true" ACT of 450 seconds. Based on the WSCV for each measuring point, the range for the Hemochron Jr. ACTs is demonstrably wider than that of the i-STAT, which makes the former less reliable for clinical decision-making at this level. This corroborates the findings of Ojito's study, comparing four different ACT methods in an in vitro setting (16).

This is further highlighted by the fact that the Hemochron Jr. devices produced more measurement pairs where one reading is >1,000 seconds and the other is dramatically less. Table 6 shows that in a number of cases, the duplicate reading below 1,000 seconds is below the threshold that

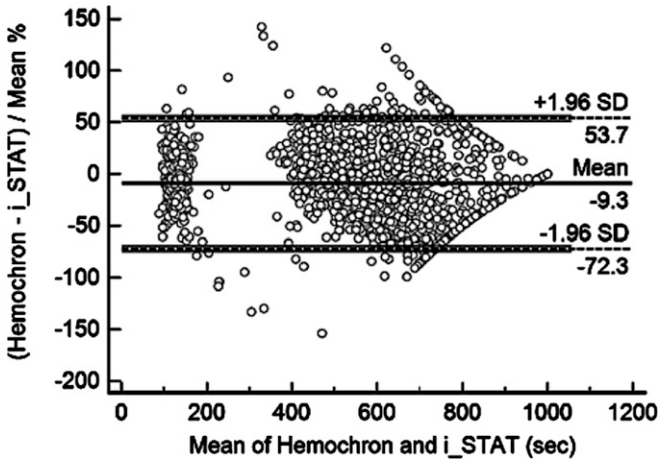

Figure 3. Bland Altman plot of all measurements obtained with both devices.

Table 6. Events with one reading >1,000 seconds and one <1,000 seconds.

	n	Range of Readings <1,000	Mean (SD) of Readings <1,000
Hemochron			
Postheparin	17	328–943	606 (183.6)
CPB1	25	431–997	605 (192.9)
CPB2	25	437–992	679 (195.3)
CPB3	10	374–653	568 (167.5)
CPB4	9	273–737	492 (138.7)
i-Stat			
Postheparin	12	667–998	930 (94.5)
CPB1	18	567–996	809 (115.4)
CPB2	9	562–996	888 (128.9)
CPB3	11	786–987	885 (57.5)
CPB4	3	882–983	938 (51.3)

most clinicians would view acceptable for CPB. These disparate measurements occurred at all centers and we, therefore, are confident that they are not the result of user error. In clinical practice, this will often result in additional heparin doses being given, with the potential for excessive haemmorhage and subsequent increased need for transfusion or adverse reactions after higher-than-necessary doses of protamine (17,18), increasing cost and patient risk.

A possible explanation for the better reliability of the i-STAT is the fact that its endpoint for measuring the ACT is the amperometric detection of an electroactive compound after the cleavage of thrombin. This method of detecting the beginning of clot formation may be inherently more sensitive than relying on the formation of fibrin strands that mechanical viscoelastic methods (such as used in the Hemochron Jr.) depend on. This difference in methods might also afford the i-STAT some mitigation against the numerous factors that influence the ACT during CPB. The majority of these, such as haemodilution, hypothermia, impaired platelet function, reduced fibrinogen level, reduced kidney function, or heparin resistance, are commonly seen in patients during cardiac surgery on bypass (19).

In summary, the comparison between two commercially available and widely used ACT devices, the Hemochron Jr. and the i-STAT Celite ACT, showed that there is good correlation between the devices and adequate agreement at close to physiological values. However, there is a difference in the precision. The Hemochron Jr. has a greater WSCV at all measuring points compared with the i-STAT. While the true implications of this are not clear, clinicians need to have a high index of suspicion during anticoagulation, particularly at the lower end of ACT values deemed clinically acceptable for the safe conduct of CPB. It is at these points where the reliable monitoring of the ACT is most essential to avoid the consequences of inadequate coagulation.

ACKNOWLEDGMENT

This study was supported by an unrestricted grant from Abbott Point of Care.

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