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Point-of-Care Measurement of Kaolin Activated Clotting Time during Cardiopulmonary Bypass: A Single Sample Comparison between ACT Plus and i-STAT

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Abstract: Heparin anticoagulation monitoring by point-of-care activated clotting time (ACT) is essential for cardiopulmonary bypass (CPB) initiation, maintenance, and anticoagulant reversal. Concerns exist regarding the comparability of kaolin activated ACT devices. The current study, therefore, evaluated the agreement of ACT assays using parallel measurements performed on two commonly used devices. Measurements were conducted in a split-sample fashion on both the ACT Plus (Medtronic, Minneapolis, MN) and i-STAT (Abbott Point of Care, Princeton, NJ) analyzers. Blood samples from 100 adult patients undergoing elective cardiac surgery with CPB were assayed at specified time points: before heparinization, following systemic heparinization, after CPB initiation, every 30 minutes during CPB, and following protamine administration. A cutoff value of 400 seconds (s) was used as part of the local protocol. Measurements were compared using *t* tests or Wilcoxon signed-rank tests, linear regression, and Bland–Altman analyses. Parallel ACT measurements demonstrated a good linear correlation ($r = .831$, $p < .001$). The overall median difference between both measurements was significantly different from zero, amounting to 87 (14–189) ($p < .001$), with limits of agreement of −124 and 333s. The i-STAT-derived ACT values were systematically lower than the ACT Plus values, which was more pronounced during CPB. Fourteen patients received additional heparin during CPB at a median ACT Plus value of 414s, with a concomitant median i-STAT value of 316s. Assuming 308s as the theoretical i-STAT cutoff value based on the linear regression equation and an ACT Plus threshold of 400s, 29 patients would have received additional heparin. Based on these results, kaolin point-of-care ACT devices cannot be used interchangeably. Device-specific predefined target values are warranted to avert heparin overdosing during CPB. **Keywords:** cardiopulmonary bypass, activated clotting time, threshold value. *J Extra Corpor Technol. 2021;53:57–61*

Systemic anticoagulation is a prerequisite for safe cardiopulmonary bypass (CPB) during cardiac surgery. Intermittent and reliable measurements of the patient's current coagulation status are crucial while initiating, maintaining, and terminating bypass, as well as reversal of anticoagulation. Several Food and Drug Administration (FDA)-approved devices are available for monitoring the activated clotting time (ACT) during surgery, including the ACT Plus (Medtronic, Minneapolis, MN), i-STAT Alinity analyzer (Abbott Point of Care, Princeton, NJ), and Hemochron Signature Elite and Hemochron Jr (Instrumentation laboratory, Bedford, MA). Concerns exist regading the comparability of kaolin activated ACT devices, with merely few studies published focusing on threshold values and their use across devices. Several studies compared one of the Hemochron devices and i-STAT, and showed significant discrepancies between derived measurement values (1–3), indicating that devices cannot be used interchangeably. Recommendation followed to validate devices against each other before transitioning from one to another in clinical

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practice (1). On the contrary, another study compared the ACT Plus and i-STAT and reported a high level of agreement between the two devices, and concluded that they can be used interchangeably without adjusting the threshold for administrating additional heparin (4). Despite several studies assessing differences between devices, interpretation of its consequences for clinical use remains challenging. Besides differences in measurement principles, devices may differ in available options with regard to sample pre-warming and cartridges with varying coagulation activators, which also may affect measurement values.

The current study aimed to evaluate the agreement of ACT assays using parallel measurements performed on the Medtronic HemoTec ACT Plus ("ACT Plus") and i-STAT Alinity ("i-STAT"), and, additionally, to define a device-specific cutoff value for the i-STAT Alinity analyzer based on current clinical practice using the ACT Plus.

MATERIALS AND METHODS

Before initiation of CPB, all patients received 300 IU/kg bodyweight heparin (porcine origin, Leo Pharmaceutical Products BV, Weesp, the Netherlands). In case of an insufficient ACT following heparinization (i.e., <400s), 10,000 IU heparin were administered as an extra dose, irrespective of the patients' body weight. In case of an insufficient ACT during CPB, an additional 5,000 IU of heparin were administered. Measurements were conducted in a split-sample fashion on both the ACT Plus and i-STAT kaolin analyzers. Blood samples from 100 consecutive adult patients undergoing elective cardiac surgery with CPB were assayed at specified time points: before heparinization, i.e., baseline; following systemic heparinization; after CPB initiation; every 30 minutes during CPB; and following protamine administration. Patients with any known coagulopathy were excluded from the study. The current local protocol consists of an ACT cutoff value of 400s as measured by the ACT Plus to administer an additional dose of heparin (5,000 IU bolus). According to the instructions for use, all sample tubes were pre-warmed and i-STAT was set to pre-warm mode. The derived i-STAT values did not affect the heparin dosing decision, since the clinical perfusionist acted solely on the ACT Plus measurement values.

This study was approved by the Institutional Review Board (METC 2020-1328), whom confirmed that Law for Medical Research Involving Human Subjects Act (WMO) does not apply; hence, informed consent was waived.

Statistical analysis

Numerical variables are expressed as mean ± SD or median (interquartile range), depending on data distribution. Differences between ACT Plus and i-STAT values were assessed using either the paired samples *t* test or the Wilcoxon signed-rank test, as well as the one-sample *t* test or one sample Wilcoxon signed-rank test, depending on data distribution. Similarly, either the Pearson's r or Spearman's rho was used for initial assessment of the association between ACT Plus and i-STAT measurement values. In case of a moderate to strong correlation between the two measurements as revealed by the correlation coefficient, linear regression analysis was performed to compute the regression equation as well as R^2.

A Bland–Altman plot was created to graphically illustrate the bias and calculate the limits of agreement.

A two-sided alpha <.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 26.0 (IBM Corp, New York, NY).

RESULTS

A total of 100 adult patients with a median age of 66 (58–72) years underwent elective cardiac surgery with CPB. The proportion of female patients was 22%, and the most commonly performed procedure (59%) in this cohort was isolated coronary artery bypass grafting as shown in Table 1. No thromboembolic complications occurred in the perioperative period.

The number of available ACT samples is depicted in Table 2. Because of varying CPB times across cases, analyses of samples derived during CPB were performed focusing on the first four samples derived during CPB, if available (up to 90 minutes CPB time). The i-STAT–derived ACTs were systematically lower than the ACT Plus values, which were more pronounced during CPB (Figure 1). Following initiation of bypass, ACT values from both devices decreased over time (Figure 1). This is illustrated by the fact that in both devices, the median difference between the first (CPB 1) and fourth CPB measurement (CPB 4) was significantly different from zero ($p < .001$ for both).

The median ACT values (Table 2) showed to differ significantly between devices at each time point ($p < .001$)

Table 1. Patient demographics.

Total, n = 100	
Female gender (n)	22
Age (y)	66 (58–72)
Normothermic CPB (n)	68
CPB time (min)	88 (62–149)
Type of surgery (n) CABG	59
Valve	22
Aortic	8
CABG + valve	8
CABG + Bentall	1
Other	2

CABG, coronary artery bypass grafting.

Table 2. Median ACT values measured by the ACT Plus and i-STAT.

	N	ACT Plus (s)	i-STAT (s)	*p*-Value
Baseline	97	137 (129–144)	126 (120–137)	<.001
Heparinization	94	482 (433–583)	472 (428–567)	.392
CPB 1	100	628 (543–720)	439 (375–522)	<.001
CPB 2	99	570 (495–668)	373 (328–422)	<.001
CPB 3	92	536 (457–605)	351 (324–401)	<.001
CPB 4	51	507 (452–560)	346 (318–390)	<.001
Protamine	99	146 (138–159)	126 (120–131)	<.001

ACT, activated clotting time; CPB 1, after initiation of bypass; CPB 2, 30 minutes on CPB; CPB 3, 60 minutes on CPB; CPB 4, 90 minutes on CPB. Total number of split-sample measurements: 708.

except for following heparinization ($p = .392$). Although the difference in ACT at baseline showed to be statistically significant ($p < .001$), the difference is probably not of clinical relevance (9s). In addition, the overall median values of the ACT Plus and i-STAT showed to amount to 478 (155–593) and 351 (137–434), respectively ($p < .001$). During CPB, the overall median ACT values were 560 (486–659)s and 379 (329–439)s, respectively ($p < .001$). During cardiac surgery with CPB, a threshold of 400s is currently used at our institution. Collecting all ACT Plus measurements with values situated around this threshold resulted in 16 measurements with values ranging between 390 and 410s. Whereas the ACT Plus showed a median ACT of 399 (395–406)s, the parallel i-STAT values showed a much larger variation with a median of 379 (304–433)s (Table 3).

Assessing the relationship of the two measurements by correlation analysis revealed a Spearman's rho of .831 ($p < .001$) with concomitant R^2 of .69. A scatterplot revealed a data point cloud with a visually detectable positive correlation (Figure 2). The derived linear regression line revealed the following equation: i-STAT = 44.19 + .66 × ACT Plus. Applying the currently used ACT Plus threshold value of 400s revealed the following theoretical concomitant i-STAT threshold value: i-STAT = 44.19 + .66 × 400 = 308s. Since ACT values show negligible differences in pre- and post-bypass measurement in both devices, another regression line was yielded to predict the concomitant i-STAT value specifically during systemic anticoagulation: i-STAT = 117 + .54 × ACT. Applying the currently used ACT Plus threshold value of 400s revealed the following theoretical concomitant i-STAT threshold value for application during systemic heparinization: i-STAT = 117 + .54 × 400 = 333s. Assessing the different samples through time shows clustering of ACT Plus and i-STAT values at baseline and following protamine administration, while following systemic anticoagulation (after heparinization and during CPB), ACT Plus and i-STAT values are translated into a more diffuse cloud of data points (Figure 3).

Table 3. ACT Plus measurements around its currently used threshold values with parallel i-STAT measurement values.

	ACT Plus Values ±400s (n = 16)	Corresponding i-STAT Values (s), n = 16
Median	399	379
Interquartile range	395–406	304–433
Minimum ACT value	391	251
Maximum ACT value	407	654

Figure 4 shows the overall difference between the ACT Plus and i-STAT, plotted against the mean of the two measurements. Although the Bland–Altman plot traditionally requires normal distribution of differences, the plot is used solely for the purpose of graphical representation of agreement between the two devices (5). Besides the condensed cloud of data points representing ACT values at baseline and protamine administration, the measurements show little agreement, as shown by the diffuse cloud of data points situated around the red line, depicting the mean difference (105s).

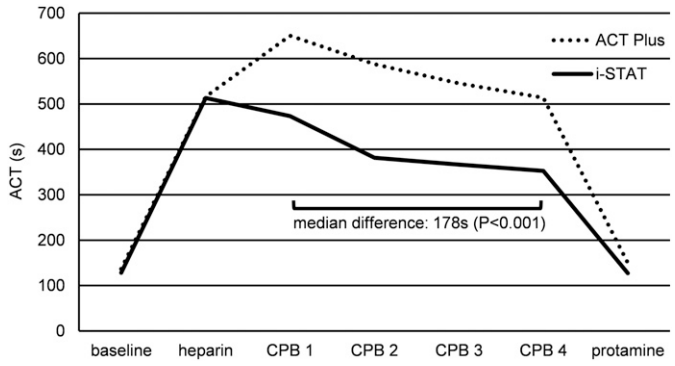

Figure 1. Median ACT values before CPB, during CPB, and following cessation of CPB. Between CPB initiation and 90 minutes on bypass, the median difference between the ACT Plus and i-STAT is 178s, which is significantly different from zero ($p < .001$). ACT, activated clotting time; CPB 1, after initiation of bypass; CPB 2, 30 minutes on CPB; CPB 3, 60 minutes on CPB; CPB 4, 90 minutes on CPB.

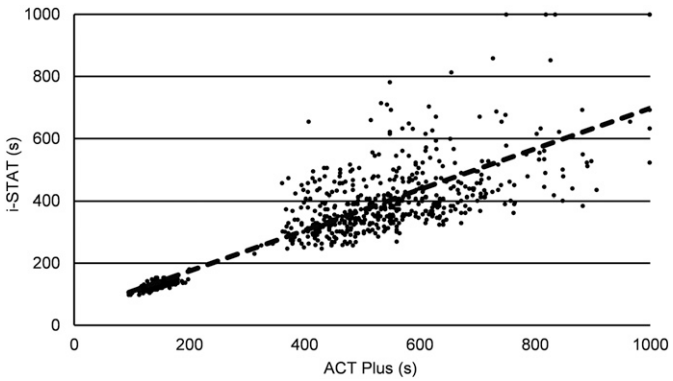

Figure 2. Scatterplot of retrieved ACT values for i-STAT and ACT Plus.

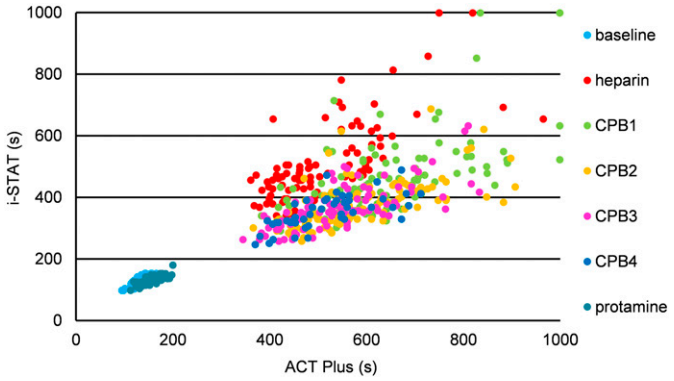

Figure 3. Scatterplot of retrieved ACT values for i-STAT and ACT Plus with color-coded sample points.

For adequate interpretation of the current clinical situation in which the current data were collected, the rate of bleeding complications in the early postoperative period amounted to approximately 5.5% of patients undergoing cardiac surgery with CPB in the past 5 years. Due to the retrospective nature of the consulted date, it was not possible to discriminate by cause of bleeding, i.e., surgical bleeding or other causes. In addition, no perioperative thromboembolic complications have occurred in the past 5 years.

DISCUSSION

Theoretically, the best way to assess (new) measurement devices would be to include a gold standard, which unfortunately does not exist in case of ACT assessment. Therefore, the next best thing would be to compare several devices and objectify the differences between devices through parallel measurements. The current study compared ACT values derived from ACT Plus and i-STAT by conducting split-sample measurements in 100 adult patients undergoing cardiac surgery with CPB. Samples were drawn at several distinctive time points before, during, and following cessation of bypass. Before systematic heparinization and following protamine administration, ACT Plus and i-STAT showed similar values. During systematic heparinization, i-STAT consistently showed significantly lower ACT values than ACT Plus (median of 178s during bypass). In addition to this consistent offset, a relatively large variation in i-STAT values was observed, which is illustrated by the large SD and range based on 16 samples (Table 3), as well as the diffuse cloud of data points as shown in Figures 2–4.

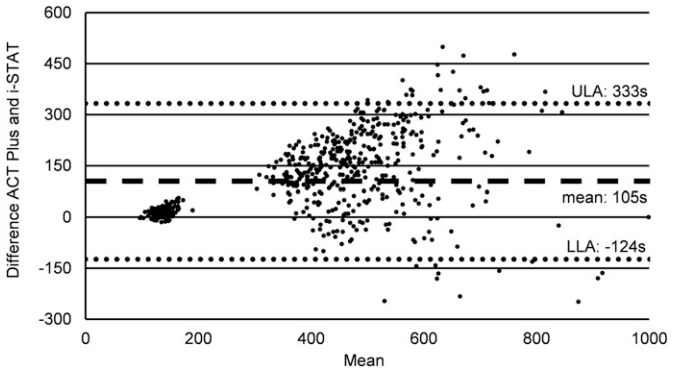

Figure 4. The Bland–Altman plot. Mean difference of 105s (dashed line), with the upper (ULA) and lower (LLA) limits of agreement of −124 to 333s (dotted lines). The median overall difference is 87 (14–189)s.

The thought experiment showed a large variation in numbers of patients who would theoretically receive additional heparin in several i-STAT threshold values. Adapting one of the proposed i-STAT ACT threshold values would result in a two- to six-fold increase in the number of patients receiving additional heparin. The dose of heparin, also in case of larger quantities administrated than necessary, should be remitted by an equal dose of protamine at cessation of bypass, limiting the risk of bleeding complications postoperatively. However, it remains evident that administration of larger quantities of heparin than necessary to safely execute CPB is undesirable. In the current clinical setting, no thromboembolic complications or potentially related problems occurred, suggesting that the current regime of heparin dosing and monitoring systemic anticoagulation status is safe and no patients were obviously under heparinized.

Several FDA-approved ACT assessment devices are available for monitoring the ACT during surgery. Devices may differ in the used measurement techniques, which could affect the absolute ACT measurement values. Few studies previously compared clinically available ACT devices. Similar to the current study, Lewandrowski et al. (4) compared the i-STAT and ACT Plus. This study also showed lower values measured by i-STAT, although nonsignificant. This difference can be explained by the fact that i-STAT quantifies thrombin formation occurring in an earlier phase in the anticoagulation cascade, unlike the ACT Plus which assesses physical clot formation. Moreover, in line with our current results, the authors show less agreement in ACT values > 450s. The authors concluded that the devices show a high correlation and that adaptation of threshold values was not necessary. This is contradictory to the current results, which showed a positive significant correlation, but large significant differences between absolute measurement values between devices. This might be explained by the fact that Lewandrowski et al. (4) used measurements derived from different subspecialties (cardiac surgery unit and the cardiac catheterization and electrophysiology laboratory), and only separated the electrophysiology ACT assays, whereas another separation was performed based on absolute ACT value (450s). In their article, the Bland–Altman plot

lacks information on the mean difference and limits of agreement, and together with the lack of reported SDs or any other measure of dispersion, interpretation of the actual differences between the two assays and dispersion of data points remains difficult.

Furthermore, the decrease in ACT through time that was shown in both devices (as depicted in Figure 1), could be partially due to metabolism of heparin (6). Another factor which might contribute to the decreasing ACT values, potentially in a different extent in i-STAT compared with ACT Plus, is the sensitivity of the assay to the effect of hemodilution. Because ACT depends on an intact intrinsic anticoagulation pathway, kaolin ACT assays have shown to be significantly affected by hemodilution (7,8).

Through this thought experiment, the authors aim to explicate the theoretical implications of several i-STAT threshold values in clinical use, based on current observations.

In the current study, 14 patients received additional heparin based on an ACT plus threshold of 400s, whereas purely based on the exact observed ACT measurement value, 12 patients would have received additional heparin. This small difference (n = 2) illustrates a slight difference between theory and practice in dosing heparin, which might occur in a situation where, e.g., the estimated remaining bypass time is considered too short to redose heparin. During CPB, the median ACT Plus value at which patients actually received additional heparin (n = 14) was 415s. In case of direct application of the same 400s threshold in i-STAT values, 86 individual patients show a measurement value below that threshold at least once, indicating that 86 patients theoretically would have received an additional dose of heparin. This is a little over a six-fold increase in patients who would have received additional heparin.

In patients who did actually receive additional heparin based on an ACT Plus threshold of 400s, the observed median parallel i-STAT value was 316s. Assuming 316s as a theoretical i-STAT cutoff value, 50 patients would have received additional heparin during bypass.

Based on the linear regression equation, the i-STAT value concomitant to the ACT Plus threshold of 400s should amount to 308s. Theoretically applying the i-STAT threshold of 308s, 29 patients would receive additional heparin, which is roughly double the current number of patients (n = 14). The linear regression line specifically calculated from values derived during systemic heparinization yielded an i-STAT threshold value of 333s. In this case, 52 patients would have received additional heparin.

In case the recommended threshold of 480s as described in the European 2019 guidelines on CPB in adult cardiac surgery would be applied (9), 47 patients would have received additional heparin based on the ACT Plus in contrast to 97 patients based on an ACT value measured by i-STAT.

Like in any other (observational) study, the presence of bias cannot be excluded. While performing the current study, ACT measurements using the ACT Plus were part of clinical practice, meaning that clinical decision-making was performed based on ACT Plus derived values. The i-STAT–derived values were not visible/available to the clinicians at the time of data collection, meaning that the risk of performance bias was limited. Because there were no predefined groups of patients and measurements were derived in parallel, the risk of measurement bias may be considered low.

The current results were obtained in the cardiac surgical setting. Application of ACT assays in other subspecialties, including cardiac catheterization or electrophysiology, yields different ACT values due to different anticoagulation strategies applied, with concomitantly different thresholds in use (4). Future studies should focus on the development of application and device-specific ACT threshold values to ensure safe and effective anticoagulation monitoring.

CONCLUSION

Based on these results, kaolin-activated point-of-care ACT devices cannot be used interchangeably. Device-specific predefined target values are warranted to avert overly dosing of heparin during CPB.

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