Kaolin-Based Activated Coagulation Time Measured by Sonoclot in Patients Undergoing Cardiopulmonary Bypass

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Objectives: **In vivo data for the kaolin-based ACT test from the Sonoclot Analyzer (SkACT, Sienco Inc, Arvada, CO) are lacking. The aim of this study was to compare SkACT with an established kaolin-based ACT from Hemochron (HkACT) and anti-Xa activity in patients undergoing cardiopulmonary bypass (CPB).**

Design: **Prospective observational study.**

Setting: **Community hospital.**

Participants: **Fifty patients scheduled for elective cardiac surgery.**

Interventions: **Blood samples were taken before CPB at baseline (T0) and after heparinization (T1 and T2), on CPB after administration of aprotinin (5, 15, 30, 60 minutes; T3-T6), and at the end after protamine infusion (T7).**

Measurements and Main Results: **A total of 375 blood samples were analyzed. ACT measurements were comparable for SkACT and HkACT at each measurement time point. Overall bias ± standard deviation between SkACT and HkACT was −19 ± 75 seconds (−2.4% ± 11.7%). Mean bias between SkACT and HkACT at each time point ranged from −35 to 3 seconds (−4.5% to 2.6%) and showed no statistical significance over time. Heparin sensitivity of SkACT and HkACT, defined as $(ACT_{Tx}\text{-}ACT_{T0})/(\text{anti-}Xa_{Tx}\text{-anti-}Xa_{T0})$, significantly increased for measurements during CPB ($p < 0.001$) but without significant difference between the 2 methods. Test variability was comparable for both ACT measurement techniques. Overall test variability was 7.5% ± 7.4% for SkACT and 7.8% ± 11% for HkACT.**

Conclusions: **Accuracy and performance of SkACT and HkACT were comparable for heparin monitoring in patients undergoing CPB for elective cardiac surgery. However, both tests were affected significantly after initiating CPB and aprotinin infusion.**

KEY WORDS: activated coagulation time, kaolin, anticoagulation, heparin, blood coagulation, Sonoclot analysis, cardiopulmonary bypass

ADEQUATE ANTICOAGULATION is mandatory to prevent overt thrombosis of the extracorporeal circuit and to minimize cardiopulmonary bypass (CPB)-related activation of the hemostatic and inflammatory systems. Activated coagulation time (ACT) is used to monitor heparin anticoagulation during CPB. Whole blood is added to test tubes containing celite, kaolin, glass, or a combination of activators, and the time is measured until the blood begins to coagulate. Different coagulation activators have different characteristics and interactions, and even the same coagulation activator manufactured by varying companies responds differently under similar conditions.[1]

Kaolin-based ACT measurement is a clinical standard for heparin management alone and combined with aprotinin during cardiopulmonary bypass (CPB). The Hemochron system (Hemochron 801; International Technidyne Corp, Edison, NJ) with its kaolin-based ACT test (HkACT) is widely used and accepted in cardiac surgery, and its accuracy and performance have been shown in a variety of studies.[2-4] However, no clinical study is available evaluating the kaolin-based ACT test from the Sonoclot Analyzer (SkACT, Sonoclot Coagulation & Platelet Function Analyzer; Sienco Inc, Arvada, CO) despite the fact that this test has been commercially available for several years.

The SkACT test has been previously tested in vitro in the presence of clinically relevant concentrations of heparin, hemodilution, and aprotinin; the accuracy and performance of SkACT were comparable to HkACT.[5] The aim of the present study was to evaluate in vivo the SkACT test from the Sonoclot Analyzer in patients undergoing CPB in the presence of heparin and aprotinin and to compare SkACT with the established kaolin-based ACT from Hemochron (HkACT), as well as with plasma levels of heparin measured by anti-factor Xa activity (anti-Xa).

METHODS

With local ethics committee approval and written informed consent, patients >18 years of age scheduled for elective cardiac surgery with CPB were enrolled. Patients scheduled for repair of congenital heart defects and patients with hereditary or acquired coagulation disorders (pretreatment with anticoagulants or antiplatelet drugs) were excluded.

Standardized institutional protocols were used for anesthesia, heparin anticoagulation, CPB, protamine reversal, and transfusion therapy. Anesthesia was induced and maintained with propofol and fentanyl, and neuromuscular blockade was achieved by pancuronium bromide. Lactated Ringer's solution (Laboratory Dr. Bichsel AG, Switzerland) and 6% hydroxyethyl starch solution (HES 130/0.4, Voluven; Fresenius Kabi, Bad Homburg, Germany) were given for fluid replacement. Anticoagulation for CPB was attained with intravenous porcine heparin (Liquemin; Roche Pharma, Basel, Switzerland), 300 U/kg. Heparin management was guided by HkACT, and HkACT >480 seconds was accepted as adequate anticoagulation for CPB. CPB was performed with a membrane oxygenator (Quadrox HMO1010; Maquet Cardiopulmonary AG, Hirlingen, Germany) under moderate hypothermia (28°-32°C) at flows between 2.2 and 2.4 L/min/m^2. Ten thousand units of heparin and 2 million kallikrein-inhibiting units (KIU) of aprotinin

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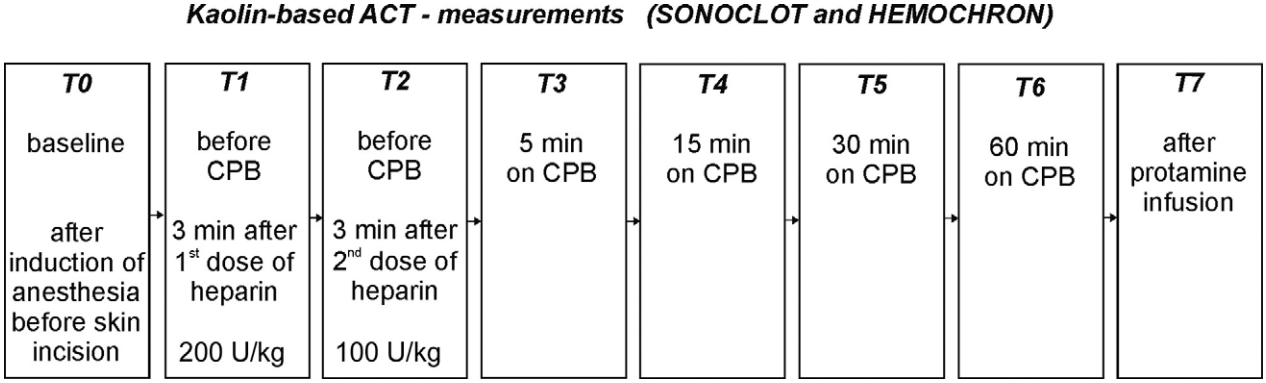

Fig 1. Study overview. At each time point, kaolin-based ACT was immediately measured with Sonoclot (SkACT) and Hemochron (HkACT), both in duplicate. Furthermore, citrated blood samples were taken for later analysis of anti-Xa and antithrombin III activity. A total of 50 patients were included.

(Trasylol; Bayer Pharmaceuticals Corp, Leverkusen, Germany) were added to the standard priming volume (1,800 mL) of the CPB circuit. Maintaining HkACT >480 seconds, additional heparin in 5,000 U increments were administered during CPB, if necessary. Anticoagulation was reversed after rewarming and separation from CPB with protamine up to a maximum dose of 1 mg/100 U of the total heparin dose administered.

Blood was withdrawn from an unheparinized radial arterial catheter after removing 5 dead-space volumes of blood at each measurement time point (Fig 1). ACT was measured by using the SkACT and the HkACT. ACTs were measured in duplicate in both devices. For SkACT measurements, 360 μL of whole blood was filled into the cuvette, mixed, and analyzed. Immediately thereafter, 2 mL of the same blood sample was filled into a HkACT cuvette, mixed, and analyzed. The performance of each machine was verified with recommended quality-control tests according to the manufacturers. Results were recorded as the mean of duplicate measurements for both devices. All measurements were performed by the same investigator to avoid interobserver variability.

Further blood samples were taken at each time point in citrated tubes (final concentration of sodium citrate 0.109 mol/L; Vacuette 9NC; Greiner Bio-One, Kremsmuenster, Austria) to measure the rate of factor Xa inhibition (anti-Xa) and the antithrombin III activity (AT). The samples were centrifuged (2,500 $\times$ g for 20 minutes at 4°C) and the supernatant (plasma) stored at −32°C for later measurements. Anti-Xa activity was determined by assessing the level of inhibition of the hydrolysis of a chromogenic substrate (by the factor Xa) in presence of heparin-antithrombin III complexes with the STA-Rotachrom-Heparin test (Diagnostica Stago, Asnière, France). This assay reflects a directly proportional relationship between the rate of factor Xa inhibition and the heparin concentration. Some of the samples had to be diluted with normal pooled plasma before the analysis in order to be on the linear part of the standard curve (0.10-0.70 U/mL). AT activity was determined with the use of the chromogenic STA-Antithrombin-III test. All coagulation tests and quality controls (on normal and abnormal levels) were performed according to the manufacturer's instructions.

To determine the number of patients in this study, a power analysis (power = 80%, α = 0.05) was conducted by using published and the authors' preliminary data on ACT measurements.[5-7] A sample size of >45 patients was calculated based on an expected difference between the 2 methods (SkACT and HkACT) of 10% after heparinization for ACT values >480 seconds and an expected standard deviation (SD) of 100 seconds.

StatView for Windows version 5.01 (SAS Institute Inc, Cary, NC) and SPSS for Windows Release 12.0.2 (SPSS Inc, Chicago, IL) were used to perform the statistical analyses. Bias (ie, mean of difference [SkACT − HkACT]) with limits of agreement (±2 SD) according to Bland and Altman was calculated to compare SkACT with HkACT.[8] Heparin sensitivity for SkACT and HkACT was assessed according to Culliford et al[9] and Leyvi et al.[10] The heparin sensitivity was defined as $(ACT_{Tx}\text{-}ACT_{T0})/(\text{anti-}Xa_{Tx}\text{-anti-}Xa_{T0})$. A Student t test was calculated to compare SkACT with HkACT and corrected for multiple measurements. A Hotelling's t-square test was used to assess changes of all parameters during the study period (SkACT, HkACT, anti-Xa, AT, hematocrit, body temperature, and heparin sensitivity). Test variability was calculated as the percent difference between duplicate measurements in relation to the mean of duplicate measurements. Data are reported as mean ± SD; p values <0.05 were considered statistically significant.

RESULTS

Fifty patients (American Society of Anesthesiologists III, female-to-male ratio = 22/28, age = 65.8 ± 12.8 years, body

Table 1. Sonoclot's and Hemochron's Kaolin-Based ACT Measurements

	T0	T1	T2	T3	T4	T5	T6	T7
SkACT (s)	120 ± 12	371 ± 48	497 ± 124	654 ± 162	685 ± 183	641 ± 171	605 ± 147	134 ± 16
HkACT (s)	124 ± 11	388 ± 67	524 ± 149	684 ± 181	704 ± 183	676 ± 183	627 ± 172	132 ± 13
Mean bias (s)	−4 ± 11	−18 ± 40	−27 ± 61	−30 ± 78	−19 ± 120	−35 ± 104	−22 ± 98	3 ± 15
(%)	−2.9 ± 8.4	−3.6 ± 9.0	−4.0 ± 9.5	−4.5 ± 9.6	−1.5 ± 15.4	−3.8 ± 14.1	−1.7 ± 13.2	2.6 ± 11.7

NOTE. Mean bias is defined as mean of difference between the 2 devices (SkACT − HkACT). Values are mean ± SD. Measurement time points: before CPB: baseline (T0); 3 minutes after the first (200 U/kg, T1) and 3 minutes after the second dose (100 U/kg, T2) of heparin; on CPB: 5, 15, 30, and 60 minutes (T3-6); and off CPB after protamine infusion (T7).