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Comparison of activated clotting times measured using the Hemochron Jr. Signature and Medtronic ACT Plus during cardiopulmonary bypass with acute normovolemic haemodilution

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Abstract

Objective: This study compared the activated clotting time (ACT) measured using the Hemochron Jr. Signature (HACT) with the ACT measured using the Medtronic ACT Plus (MACT) during cardiopulmonary bypass (CPB) with acute normovolemic haemodilution (ANH) in patients undergoing cardiac surgery.

Methods: The ACT was checked at baseline with both devices after inducing anaesthesia, and 400 to 800 mL of whole blood was withdrawn to induce moderate ANH. Before initiating CPB, a 300-IU/kg bolus dose of heparin was administered to maintain the HACT at >400 s; protamine was later given to reverse the anticoagulation. The ACT was checked using both devices at baseline, during heparinisation, and after protamine administration.

Results: In total, 106 pairs of samples from 29 patients were analysed. The ACT showed a good correlation between the two devices ($r = 0.956$). However, Bland–Altman analysis showed that the MACT was higher, particularly at baseline and during heparinisation. Multiple regression analysis showed that the blood glucose concentration significantly influenced the differences between the two ACT devices.

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Conclusions: The HACT was lower than the MACT during CPB with ANH in patients undergoing cardiac surgery. Clinicians should be cautious when using each ACT device within generally accepted reference ACT values.

Keywords
Activated clotting time, cardiopulmonary bypass, haemodilution, kaolin, heparin, cardiac surgery

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Introduction

Anticoagulation with heparin is used routinely during cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation, haemofiltration, and cardiac catheterisation.[1] The activated clotting time (ACT) is defined as the duration of time until clot formation initiated by activators of the intrinsic pathway (celite, kaolin, or glass particles)[2] and is used to monitor anticoagulation during many procedures using heparin.[3]

The Hemochron Jr. Signature (Accriva Diagnostics, San Diego, CA, USA) uses silica, kaolin, and phospholipid as activators.[4] The Hemochron Jr. Signature automatically mixes a blood sample with the kaolin activator while the sample is moved back and forth. A series of light-emitting diode optical detectors assesses the velocity of this movement. When the blood clots, the velocity of the blood sample within the test channel is impeded, reducing its rate of flow. The Hemochron Jr. Signature measures the elapsed time between the start of the test and clot formation, and the ACT is automatically converted to a reference celite-based ACT value.[5] The Medtronic ACT Plus (Medtronic, Minneapolis, MN, USA) uses a cartridge with a liquid buffer containing a kaolin activator.[6] It detects fibrin formation by measuring the rate of fall of the plunger-flag mechanism in each cartridge channel. The plunger assembly falls rapidly through an unclotted sample until fibrin is formed and detected by a photo-optical system.

ACT measurement is a device-specific point-of-care test, even if the same activator is used.[2] Other factors that affect the reliability and sensitivity of ACT results are hypothermia, haemodilution, and medications such as warfarin, glycoprotein IIb/IIIa inhibitors, and aprotinin.[7] Therefore, the present study was performed to compare the ACT measured using the Hemochron Jr. Signature (HACT) and the ACT measured using the Medtronic ACT Plus (MACT) during CPB performed with acute normovolemic haemodilution (ANH) in patients undergoing cardiac surgery.

Methods

Patients

This study was approved by the Institutional Review Board of Hallym University Sacred Heart Hospital. All patients provided written informed consent that a single investigator would perform and record the ACT using two devices. The study was registered at clinicaltrials.gov (NCT02484157). Patients scheduled for open heart surgery using CPB were randomly enrolled in this study from December 2012 to December 2013. Patients with a known history of hereditary or acquired coagulation disorders (e.g., haemophilia, von Willebrand disease, disseminated intravascular coagulation syndrome, liver disease, remaining anticoagulant effect, etc.), abnormal preoperative coagulation tests (prothrombin time of >18s,

international normalised ratio of >1.5, or activated partial thromboplastin time of >50 s), platelet count of <100 G/L, or preoperative haemoglobin (Hb) level of <11g/dL were excluded from the study.

The sample size was determined from a previous study that obtained a correlation coefficient of 0.526 between Hemochron Jr. and HemoTec (Medtronic) ACT measurements,[4] with a 30% dropout rate ($\alpha = 0.05$, power = 0.8).

Procedures and statistical analyses

After successful induction of anaesthesia, the ACT was checked at baseline with both devices. Next, 400 to 800 mL of whole blood was withdrawn from the patient via a central line to induce moderate ANH to a target Hb level of 9 g/dL, and an equal volume of 6% hydroxyethyl starch was administered simultaneously. All patients were given a bolus dose of heparin (300 IU/kg) before initiating CPB to maintain the HACT at >400 s; they were later given protamine to reverse the anticoagulation. The HACT and MACT were checked at baseline, during heparinisation, and after protamine administration. If the HACT did not reach 400 s after the initial bolus dose of heparin, patients were given an additional dose of heparin (100–150 UI/kg). The target HACT after heparin neutralisation was <150 s. Arterial blood gas analysis and measurement of Hb, haematocrit, electrolytes (sodium, potassium, and calcium), and glucose were also performed during the procedures.

The agreement between the HACT and MACT values was tested using linear regression and Pearson correlation coefficients. Bland–Altman analysis was used to assess bias. The limits of agreement between the two devices were calculated from the mean difference ± 1.96 standard deviation. Multiple regression analysis was used to identify possible factors associated with the ACT differences between the two devices. A p-value of <0.05 was considered statistically significant. The statistical analysis was performed using IBM SPSS Statistics for Windows' version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Thirty patients were enrolled in this study, and 106 pairs of ACT and arterial blood gas samples from 29 patients were analysed (Table 1). One patient who had an initial Hb level of <11 g/dL after induction of anaesthesia was excluded from the study.

The ACT values measured with the two devices showed a good correlation ($r = 0.956$, $p = 0.0001$) (Figure 1). Bland–Altman analysis showed that the mean bias between the HACT and MACT was 19.50s (limit of agreement, −81.03 to 120.03s) (Figure 2); the MACT was higher than the HACT. The ACT at baseline showed no significant correlation, and the difference between the HACT and MACT was not associated with the preoperative coagulation test results. However, there was a good correlation between the two devices after heparin injection ($r = 0.772$, $p = 0.0001$) (Figure 3(a)), with a mean bias of 34.43 s (limit of agreement, −143.53 to 212.39 s) (Figure 4(a)).

Table 1. Patients' characteristics

Variables	
Number of patients	29
Age (years)	66.5 ± 11.0
Height (cm)	162.3 ± 10.3
Weight (kg)	64.7 ± 12.7
Anaesthesia time (min)	466.6 ± 100.9
Operation time (min)	387.9 ± 99.7
CPB time (min)	133.9 ± 73.8
Pre-ANH Hb (g/dL)	12.6 ± 1.4
Post-ANH Hb (g/dL)	9.4 ± 0.7

Values are given as mean ± standard deviation.
CPB, cardiopulmonary bypass; ANH, acute normovolemic haemodilution; Hb, haemoglobin

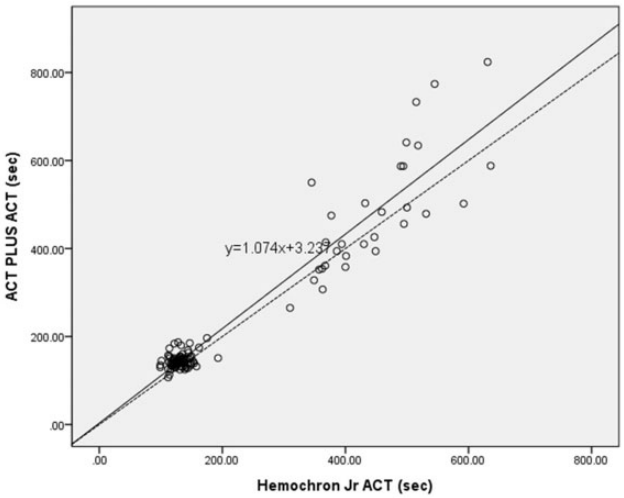

Figure 1. Linear regression analysis of activated clotting times measured with the Hemochron Jr. and Medtronic ACT Plus during cardiac surgeries with cardiopulmonary bypass and acute normovolemic haemodilution ($n = 106$, $r = 0.956$, $p = 0.0001$). ACT, activated clotting time; SD, standard deviation.

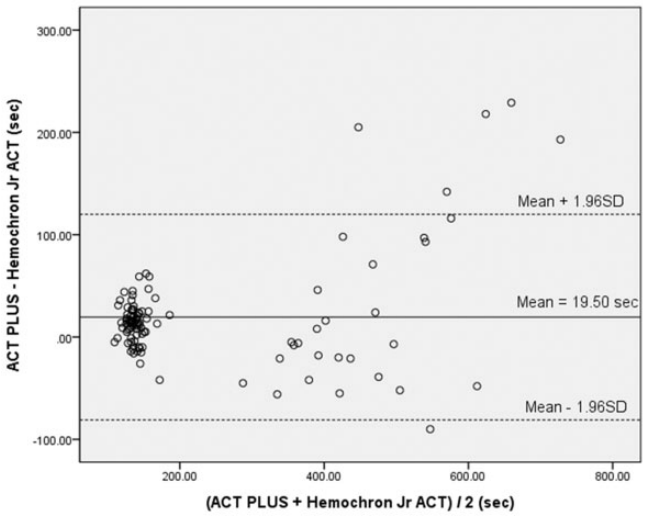

Figure 2. Bland–Altman analysis of activated clotting times measured with the Medtronic ACT Plus and Hemochron Jr. ($n = 106$). ACT, activated clotting time; SD, standard deviation.

After protamine administration, the HACT and MACT showed a significant correlation ($r = 0.32$, $p = 0.034$) (Figure 3(b)) with a mean bias of 10.26 s (limit of agreement, −27.58 to 48.11 s) (Figure 4(b)).

Among the ACT values of <400 s following heparin injection (10 samples), seven patients had both an HACT and MACT of <400 s, one patient had an HACT of <400 s and an MACT of >400

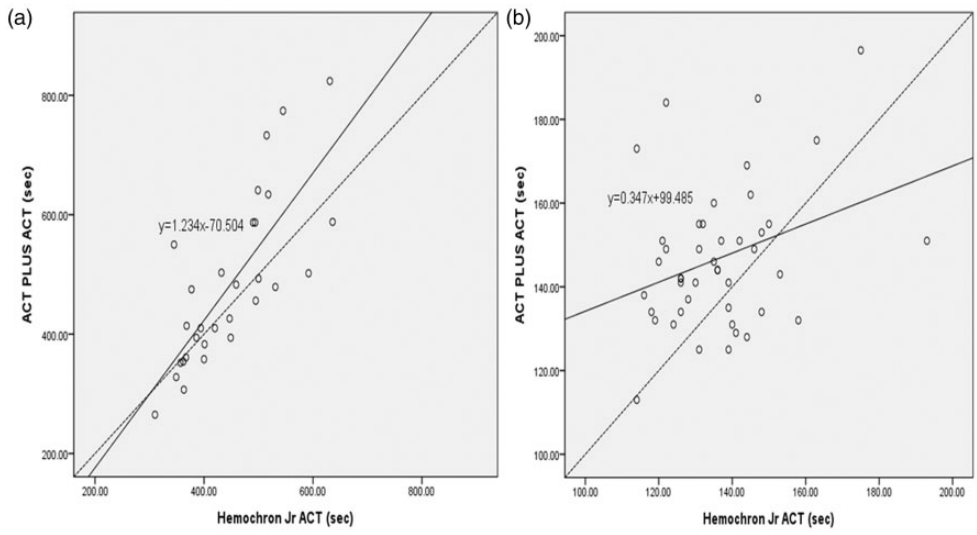

Figure 3. Linear regression analysis of activated clotting times measured with the Hemochron Jr. and Medtronic ACT Plus during cardiac surgeries with cardiopulmonary bypass and acute normovolemic haemodilution. (a) During heparinisation ($n = 30$, $r = 0.772$, $p = 0.0001$). (b) After protamine administration ($n = 44$, $r = 0.32$, $p = 0.034$). ACT, activated clotting time.

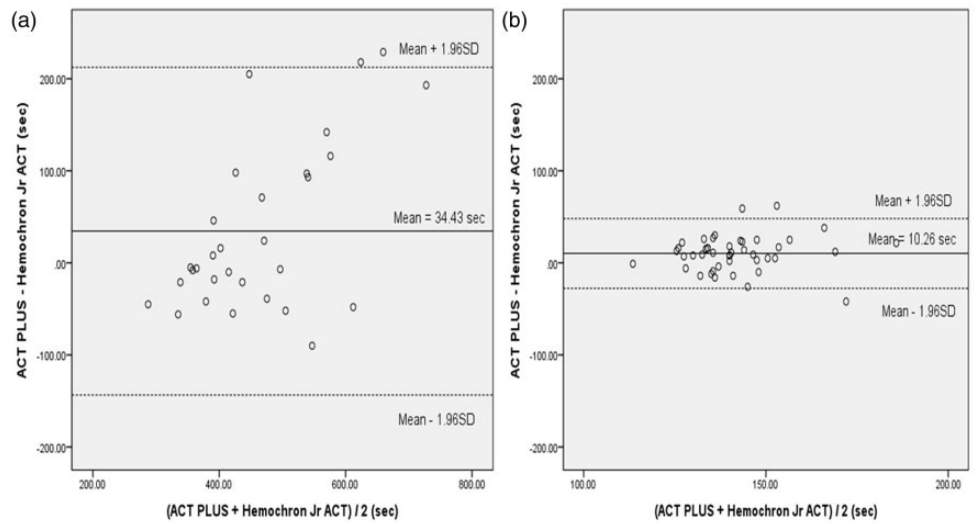

Figure 4. Bland–Altman analysis of activated clotting times measured using the Medtronic ACT Plus and Hemochron Jr. (a) During heparinisation ($n = 30$). (b) After protamine administration ($n = 44$). ACT, activated clotting time; SD, standard deviation.

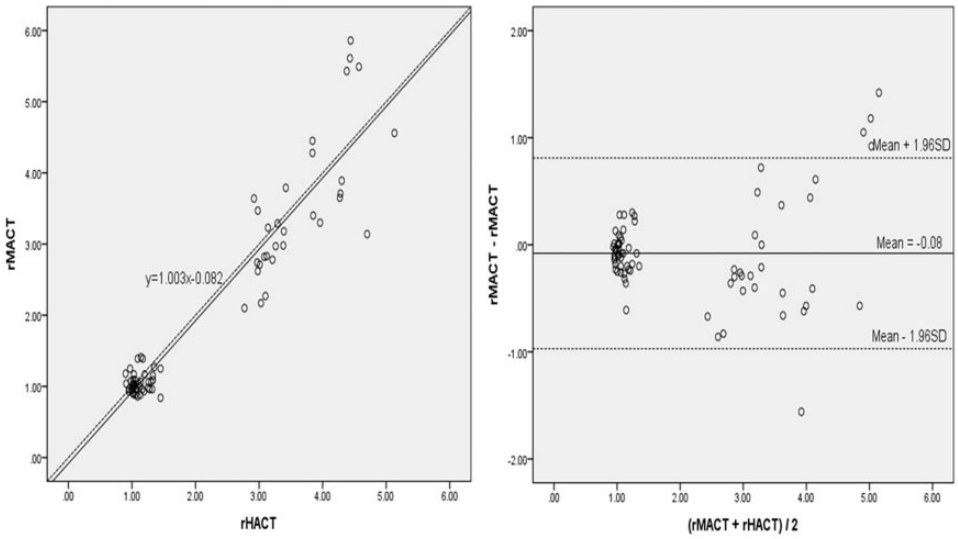

Figure 5. (a) Linear regression analysis of rHACT and rMACT ($n = 74$, $r = 0.945$, $p < 0.0001$) and (b) Bland–Altman analysis of rHACT and rMACT during cardiac surgeries with cardiopulmonary bypass and acute normovolemic haemodilution. rHACT = HACT after heparinisation or protamine injection/HACT at baseline; rMACT = MACT after heparinisation or protamine injection/MACT at baseline (where HACT is the ACT measured using the Hemochron Jr. Signature and MACT is the ACT measured using the Medtronic ACT Plus). ACT, activated clotting time; SD, standard deviation.

s, and two patients had an HACT of >400 s and MACT of <400 s. The bias between the two ACT devices was 14.3 s, suggesting that the HACT was higher than the MACT.

Considering the difference in the baseline ACT observed between the two devices, we also compared the following two ratios: HACT after heparinisation or protamine injection/HACT at baseline (rHACT) versus MACT after heparinisation or protamine injection/MACT at baseline (rMACT). The rHACT and rMACT were correlated ($r = 0.945$, $p < 0.0001$) (Figure 5 (a)) with a small bias of −0.08 (limit of agreement, −0.97 to 0.81) (Figure 5(b)).

Multiple regression analysis showed that the blood glucose concentration significantly influenced the differences between the two ACT devices. The difference in the ACT and glucose levels was significantly correlated ($r = 0.347$, $p = 0.0001$) (Figure 6), particularly at baseline ($r = 0.403$, $p = 0.022$) (Figure 7(a)) and during heparinisation ($r = 0.503$, $p = 0.005$) (Figure 7(b)). Although the total measured MACT was not correlated with the glucose level, the MACT showed a significant correlation between the ACT and glucose at baseline ($r = 0.471$, $p = 0.007$) (Figure 8(a)) and during heparinisation ($r = 0.410$, $p = 0.024$) (Figure 8(b)), while the HACT showed no correlation with the glucose level.

Discussion

ACT measurement is a simple way to monitor a patient's coagulation status during many procedures using heparin. Studies have compared the ACT among many devices, but no study has compared the ACT between the Hemochron Jr. and ACT Plus during CPB with ANH. In 1994, Avendaño and Ferguson[3] reported a significant correlation between the ACTs measured using

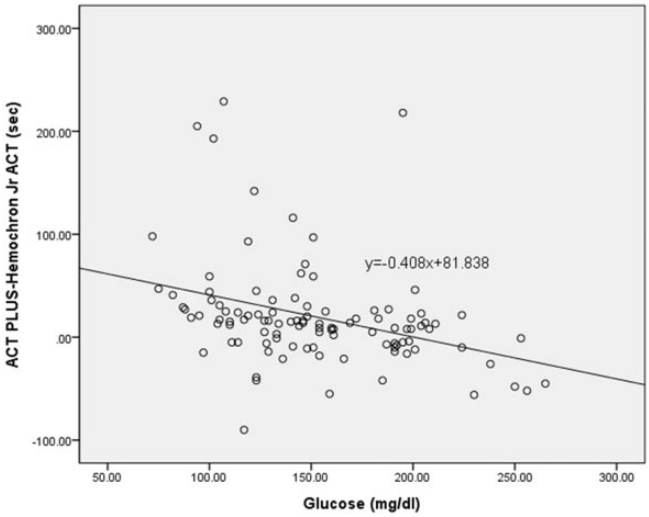

Figure 6. Linear regression analysis showing correlation between the glucose level and the difference in the activated clotting time measured using the Medtronic ACT Plus and Hemochron Jr. ($n = 104$, $r = 0.347$, $p = 0.0001$). ACT, activated clotting time.

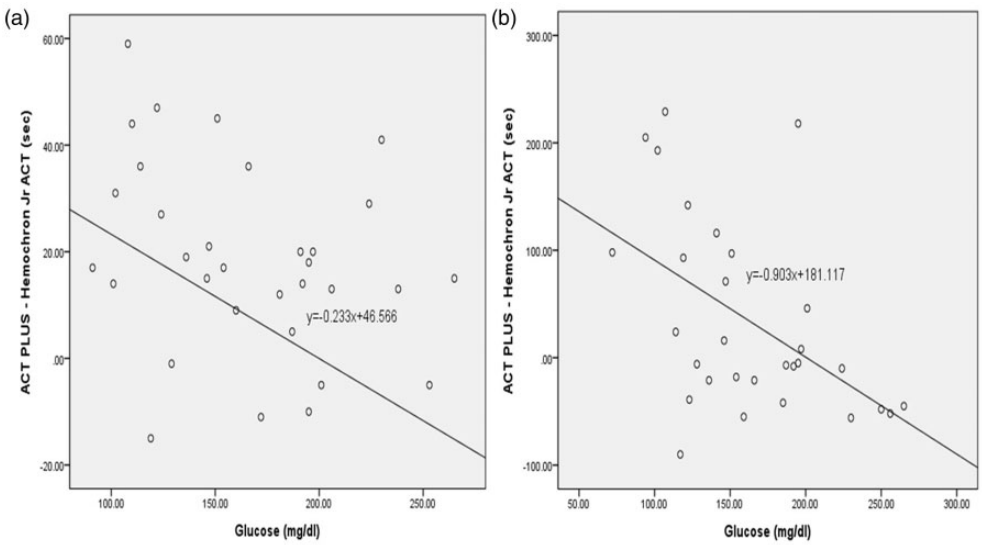

Figure 7. Linear regression analysis showing the correlation between the glucose level and difference in the activated clotting time measured using the Medtronic ACT Plus and Hemochron Jr. (a) at baseline ($n = 32$, $r = 0.403$, $p = 0.022$) and (b) during heparinisation ($n = 30$, $r = 0.503$, $p = 0.005$). ACT, activated clotting time.

the HemoTec and Hemochron during percutaneous transluminal coronary angiography, but the means differed notably after heparin administration. Another study recommended heparin administration during coronary angiography to maintain a HemoTec ACT of 250 to 300 s versus 300 to 350 s with the Hemochron,[8] after

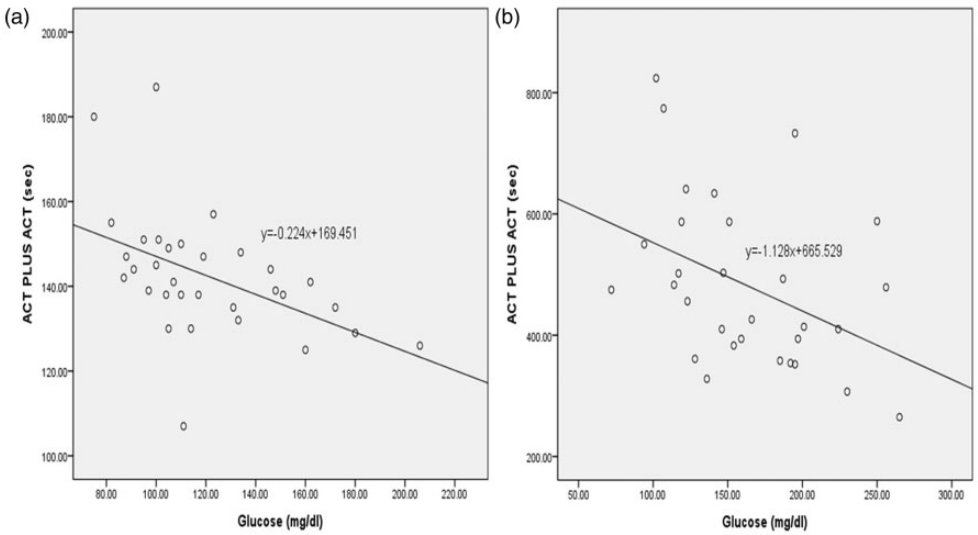

Figure 8. Linear regression analysis showing correlation between the glucose level and the activated clotting time measured using the Medtronic ACT Plus (a) at baseline ($n = 32$, $r = 0.471$, $p = 0.007$) and (b) during heparinisation ($n = 30$, $r = 0.410$, $p = 0.024$). ACT, activated clotting time.

demonstrating that the celite-based ACT was longer than the kaolin-based ACT during cardiac catheterisation.

In the current study, the HACT and MACT showed a good overall correlation ($r = 0.956$, $p = 0.0001$), especially during heparinisation ($r = 0.772$, $p = 0.0001$), with both values rising in tandem. However, this result does not mean that the two devices are interchangeable because bias existed during the procedures. The bias in the overall ACT values was about 19.50 s, with the MACT higher than the HACT, and the bias was pronounced during heparinisation (34.43 s; limit of agreement, −143.53 to 212.37 s) despite the fact that both devices are kaolin-based. Moreover, the decision to give additional heparin would have been different for two patients with an HACT of >400 s and MACT of <400 s.

Similarly, Svenmarker *et al.*[4] compared the ACT using the HemoTec and Hemochron Jr. during CPB. Both are kaolin-based devices. They found that the HemoTec and Hemochron Jr. measurements were correlated ($r = 0.526$) but that the Hemochron Jr. underestimated the ACT compared with the HemoTec, with a bias of 100 s. In patients undergoing cardiac catheterisation, Chia *et al.*[9] reported that the range of ACT values was 110 to 380 s and that the Hemochron values were higher than the Medtronic values. Although further studies are required because the number of ACT values of <400 s in this study was small ($n = 10$), it seems that Medtronic ACT values are higher than Hemochron values with results exceeding 400 s.

Various factors influence the ACT, including hypothermia, haemodilution, and the platelet count.[10] The haematocrit also influences ACT measurements among different devices; a significant association was reported between the erythrocyte volume fraction and ACT for the Hemochron Jr. but not for the HemoTec,[4] and the Medtronic ACT II was more susceptible to being influenced by the

intraoperative Hb level.[11] However, the ACT values in our patients who underwent ANH did not show a significant correlation with the haematocrit. Instead, the difference in the ACT was significantly correlated with the glucose level, particularly at baseline ($r = 0.403$, $p = 0.022$) and during heparinisation ($r = 0.503$, $p = 0.005$). While the HACT was not related to the glucose level, the MACT showed a significant correlation with the glucose level at baseline ($r = 0.471$, $p = 0.007$) and during heparinisation ($r = 0.410$, $p = 0.024$). Although no previous studies have examined the effects of glucose on the ACT, ingredients other than kaolin (such as liquid biological buffer, coagulants, or bacteriostatic agents) may also cause variation within samples during heparinisation, particularly with the Medtronic ACT Plus. Because the glucose level that minimised the difference between the MACT and HACT was about 200 mg/dL, the Medtronic ACT Plus may overestimate the heparin activity compared with the Hemochron Jr. Signature at glucose levels of <200 mg/dL, resulting in insufficient anticoagulation during CPB.

ANH decreases the antithrombin concentration, which affects the anticoagulation caused by heparin during CPB,[12–14] and haemodilution may theoretically increase the ACT.[10] One study revealed relative hypercoagulability as evidenced by thromboelastography after haemodilution by one unit (approximately 500 mL of the total blood volume) in healthy volunteers.[15] However, other studies showed that moderate ANH did not significantly reduce the antithrombin concentration[16] and did not cause significant changes in the ACT, activated partial thromboplastin time, D-dimer level, fibrinogen level, protein C and S levels, or platelet count during cardiac surgery.[17] Therefore, we postulated that the moderate ANH used during cardiac surgery would not significantly alter the coagulation system, including the ACT.

One limitation of this study is the lack of reference tests for systemic heparinisation, such as the anti-Xa level or heparin concentration. Such tests were not used because our hospital has no point-of-care monitoring system for measuring anti-Xa levels or heparin concentrations. Comparison of ACT devices and laboratory tests to measure anti-Xa for delayed analysis warrants further evaluation, although ACT measurement is the standard method for evaluating anticoagulation.[3]

In conclusion, the ACTs measured by the Hemochron Jr. Signature and Medtronic ACT Plus during cardiac surgery using CPB with ANH cannot be used interchangeably. ACT monitoring using the Medtronic device based on the Hemochron reference range may lead to insufficient anticoagulation. Further research is needed to determine the Medtronic device-specific ACT values with which to obtain adequate heparin levels during cardiac surgery. The differences between the two ACTs were dependent on the glucose level. The ACT depends on the device used; thus, caution is advised when using generally accepted reference ACT values to prevent over- or under-dosing of heparin.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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