Journal of Cardiothoracic and Vascular Anesthesia 36 (2022) 2031–2034

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Case Report

The Standard Point-of-Care Hemochron Jr. ACT+ Test in Monitoring Heparin Administration for Cardiopulmonary Bypass in Severe Factor XII Deficiency

Tiina Erkinaro, MD, PhD*,[1], Janne Moilanen, MD*, Jarmo Lahtinen, MD, PhD*, Martti Mosorin, MD*, Eeva-Riitta Savolainen, MD, PhD†

*Research Group of Surgery, Anesthesiology and Intensive Care Medicine, Medical Research Center Oulu, Oulu University Hospital, University of Oulu, Finland

†Nordlab Oulu Hematology Laboratory, Medical Research Center Oulu, Oulu University Hospital, University of Oulu, Finland

Coagulation factor XII (FXII) is a plasma serine protease that belongs to the contact activation complex responsible for initiating the intrinsic coagulation pathway. FXII deficiency is a rare congenital disorder that is not associated with an increased tendency for bleeding. However, as contact activation is impaired in FXII deficiency, both the celite- and kaolin-initiated activated clotting time (ACT) measurements are prolonged markedly, which poses a challenge for anticoagulation monitoring in patients undergoing cardiac surgery. The authors successfully have used the standard Hemochron Jr. ACT+ test, which is activated by silica and phospholipid in addition to kaolin, to monitor anticoagulation for cardiopulmonary bypass in two patients with severe FXII deficiency. The ACT+ test showed low baseline values, increased adequately in response to heparin, and decreased to baseline after protamine. Importantly, there was no abnormal intra- or postoperative bleeding nor any thrombotic complications. Furthermore, in vitro dose-response ACT+ testing of FXII-deficient blood with increasing heparin concentrations supports the use of ACT+ in FXII deficiency.

Key Words: FXII deficiency; cardiopulmonary bypass; heparin; contact activation; activated clotting time

COAGULATION FACTOR XII (FXII) is a plasma serine protease that belongs to the contact activation complex responsible for initiating the intrinsic coagulation pathway in vitro. FXII deficiency is a rare congenital disorder with autosomal recessive inheritance. In heterozygous individuals, FXII activity is usually between 25% and 50%, while homozygotes have a severe deficiency with undetectable FXII levels.[1] FXII deficiency is not associated with an increased tendency for bleeding, even in severe cases undergoing cardiac surgery.[2-8] Although graft thrombosis following coronary artery bypass graft surgery in FXII deficiency has been described,[3] it remains unclear whether the risk of thromboembolism generally is elevated. As most patients remain asymptomatic, the exact prevalence of severe FXII deficiency is unknown. When 300 Austrian blood donors were screened for FXII activity, one severe deficiency was detected, suggesting a maximal prevalence of 0.3% in the normal European population.[1] However, an incidence of one in one million individuals has been estimated.[8]

Both the activated partial thromboplastin time (aPTT) and the activated clotting time (ACT) are screening tools for the

[1]*Address correspondence to* Tiina Erkinaro, MD, PhD, Oulu University Hospital, Department of Anesthesiology, PL 21, 90029 OYS, Finland.

E-mail address: tiina.erkinaro@oulu.fi (T. Erkinaro).

https://doi.org/10.1053/j.jvca.2021.05.021

intrinsic coagulation pathway and are prolonged markedly when contact activation is impaired. In severe FXII deficiency, aPTT values of more than 120 seconds are common[1-5] while ACT values frequently exceed 500 seconds.[2,5,6] As the point-of-care ACT measurements remain the cornerstone in monitoring the adequacy of intraoperative heparin administration, FXII deficiency poses a real challenge in patients undergoing cardiac surgery. Surrogate monitoring strategies have been described in various case reports,[2-7] but these often are time-consuming and not readily available. Undoubtedly, there still is a need for a simple bedside test in patients with contact factor deficiencies.

In the authors' hospital, point-of-care ACT measurements are performed using Hemochron Signature Elite analyzers (Instrumentation Laboratory, Bedford, MA). Two types of test cuvettes are available: the ACT-LR test calibrated for baseline and postprotamine ACT measurements, and the ACT+ test calibrated to be used during full heparinization for cardiopulmonary bypass (CPB). Herein the authors describe two cases of CPB with severe FXII deficiency in which the standard ACT+ test was used to monitor both heparin and protamine administration. The authors also present the in vitro dose-response curve of ACT+ testing of FXII-deficient blood with increasing heparin concentrations. Written informed consent for this publication was obtained from each patient.

Case Reports

Patient 1

A 72-year-old man with a history of coronary artery disease and diabetes was scheduled for elective bioprosthetic aortic valve replacement due to severe aortic stenosis with a mean pressure gradient of 63 mmHg. Previously, he had undergone percutaneous coronary intervention of the left anterior descending and circumflex coronary arteries, and a recent coronary angiography revealed no in-stent or other significant stenoses. His regular medication included aspirin, but he was not taking any other antithrombotic or anticoagulant agents. His renal function was normal. Routine coagulation tests showed a normal platelet count and prothrombin time (international normalized ratio, INR), while preoperative aPTT was 89 seconds, which was not noted.

After the induction of anesthesia, an infusion of 2.5 g of tranexamic acid was initiated. Baseline ACT-LR measurements were repeatedly out of range (>400 celite-based seconds, S). Thromboelastography (TEG) (Haemonetics Corporation, Niles, IL) was performed and both the kaolin test and the heparinase test showed reaction times (R) of 45-48 minutes (normal range, 4-8 minutes). Based on prolonged ACT and aPTT and normal INR values, as well as the lack of evidence of accidental heparin effect in TEG, a suspicion of a contact phase coagulation disorder was raised, and various monitoring options were considered. However, an ACT+ test also was performed incidentally and surprisingly gave a normal result of 123 S. After full heparinization of 30,000 IU, ACT+ increased to 707 S. It was decided to guide heparin administration using ACT+, but to maintain a higher-than-normal ACT. Accordingly, over the course of 114 minutes of CPB, ACT+ ranged between 621 and 707 S while the patient received three extra boluses of heparin 5,000 IU each, plus 7,500 IU in the CPB prime. After weaning from CPB, the patient received an infusion of 300 mg of protamine. Simultaneously, four units of solvent/detergent plasma were administered to enable the measurement of ACT also with the ACT-LR test.[6] Thereafter, ACT+ was at the preoperative level while ACT-LR was 208 S. In addition, the TEG R value was within the normal range (<eight minutes) and did not differ between the kaolin and heparinase tests. Total intraoperative blood loss was 700 mL. In the intensive care unit, chest tube drainage was 520 mL, and no further protamine dosing was required. The patient made an uneventful recovery and was discharged from the hospital on the sixth postoperative day.

A full coagulation factor analysis was performed before discharge on the fifth postoperative day while the patient was receiving warfarin and enoxaparin in addition to aspirin and revealed a FXII activity of 3.7% (normal range, 52-142%). In addition, lupus anticoagulant was positive. A severe FXII deficiency (<2%) was verified in another test after the three-month postoperative warfarin treatment period was accomplished. Antiphospholipid antibodies were not discovered in this latter analysis.

Patient 2

A 69-year-old woman was scheduled for elective surgery for severe aortic stenosis with a mean pressure gradient of 65 mmHg. She had no significant comorbidities, and her renal function was normal. Just before the surgery she had been diagnosed with paroxysmal atrial fibrillation. However, she was not on anticoagulants, because a coagulation factor analysis had been performed based on family history and suspected bleeding diathesis in 2004, suggesting type 1 von Willebrand disease. Preoperatively, however, von Willebrand factor activity was within the normal range. Instead, aPTT was >180 seconds and FXII activity was <2%, confirming severe FXII deficiency. Based on the experience with the previous patient, the authors decided to monitor anticoagulation using ACT+.

The patient underwent bioprosthetic aortic valve replacement and closure of the left atrial appendage, and a small atrial septal defect was closed. After the induction of anesthesia, an infusion of 2.5 g of tranexamic acid was started. Baseline ACT was screened, with ACT-LR expectedly out of range while ACT+ remained at 109 S. In addition, thromboelastometry (RoTEM, Instrumentation Laboratory) was performed, with a normal coagulation time (CT) (63 seconds) in the ExTEM test but markedly prolonged CT in both the InTEM (1355 seconds) and the HepTEM (1234 seconds) tests. Following the initial dose of 28,000 IU of heparin, ACT+ was elevated to 567 S. During the 178-minute CPB, the patient received three additional boluses of heparin, totaling 12,500 IU, plus 7,500 in the CPB prime, and ACT+ ranged between 517 and >999 S. Because of heparinization, RoTEM CT was prolonged to 135 seconds in the ExTEM test and over the measurement range in

InTEM and HepTEM tests. After weaning from CPB and administration of 200 mg of protamine, ACT+ decreased to 109 S. In addition, RoTEM CT returned to its preoperative level in all three tests. Based on the history of previously suspected von Willebrand disease, 24 μg of desmopressin was infused. The total intraoperative blood loss was 550 mL, and one unit of packed red blood cells was transfused, while no other blood products were needed. In the intensive care unit, chest tube drainage was 430 mL, and no extra protamine was given. After an uneventful recovery, the patient was discharged home on the sixth postoperative day.

In Vitro Dose-Response ACT+ Testing

After obtaining informed consent, the authors collected blood from patient one on an annual control visit into six Vacutainer tubes containing 3.2% citrate. The authors added increasing amounts of heparin in all but one tube, resulting in heparin concentrations of 0, 1, 2, 4, 6, and 8 IU/mL. From each tube, 340 μl of blood was pipetted into a cuvette, where citrate was neutralized by carefully mixing the sample with 20 μl of 0.2 M calcium chloride. Thereafter, ACT+ measurements were performed according to routine practice. For quality assurance, three samples were prepared from each tube, and these were analyzed with three separate Hemochron Signature Elite devices. From the tube containing no heparin, the authors also performed three ACT-LR tests, all of which were out of range. All tests were performed by the first two authors (T.E. and J.M.) experienced in manual pipetting. The dose-response relationship of ACT+ tests to increasing heparin concentrations appeared to be linear (Fig 1). Importantly, baseline ACT+ values were low while at heparin concentration of 4 IU/mL, which is considered relevant for CPB, they ranged from 458 to 520 S.

Discussion

To the authors' knowledge, this is the first report on the use of the standard Hemochron Jr. ACT+ test to monitor heparin and protamine administration in patients with severe FXII deficiency undergoing cardiac surgery. In the authors' patients, the ACT+ test performed convincingly. It showed low baseline values, increased adequately in response to heparin, and decreased to baseline after protamine. Importantly, there was no abnormal intra- or postoperative bleeding nor any thrombotic complications. Since severe FXII deficiency is a rare condition,[1] these findings cannot be confirmed in future clinical trials. However, the dose-response curve presented in Figure 1 supports the idea that the ACT+ test can safely be used for anticoagulation monitoring in FXII deficiency.

Until now, it has been thought that standard ACT tests have little value in FXII deficiency.[2] In various case reports, at least five surrogate options to monitor anticoagulation in FXII-deficient patients undergoing CPB have been described. One is to use empirical, weight-based dosage of heparin, assuming a normal dose-response relationship.[2,3] In case of heparin resistance, however, this strategy bears a potential risk of inadequate anticoagulation. Another approach is the administration of fresh frozen plasma to increase FXII levels in vivo, after which routine ACT monitoring is feasible.[6] Although the authors partly used this strategy while treating patient 1, they acknowledge that the patient was exposed to the well-known risks of allogeneic transfusion for monitoring purposes only. It is also possible to add a predetermined amount of donor plasma into the patient's blood sample in vitro,[4] but this modified ACT technique requires that a patient-specific plasma titration curve is created in advance before heparinization. An alternative strategy is to monitor anti-Xa levels,[5] yet the long turnaround times of this laboratory-based assay limit its usability in cardiac surgery. Bedside assessment of heparin concentrations also has been used successfully in FXII deficiency.[7] Unfortunately, this method is not widely available.

ACT measurement is a device- and activator-specific point-of-care test. The Hemochron Signature Elite analyzers use automatically aspirated blood microsamples in test cuvettes preprepared with activators. The elapsed time between test initiation and optically detected clot formation is converted to a celite-based ACT value. According to the package inserts, the

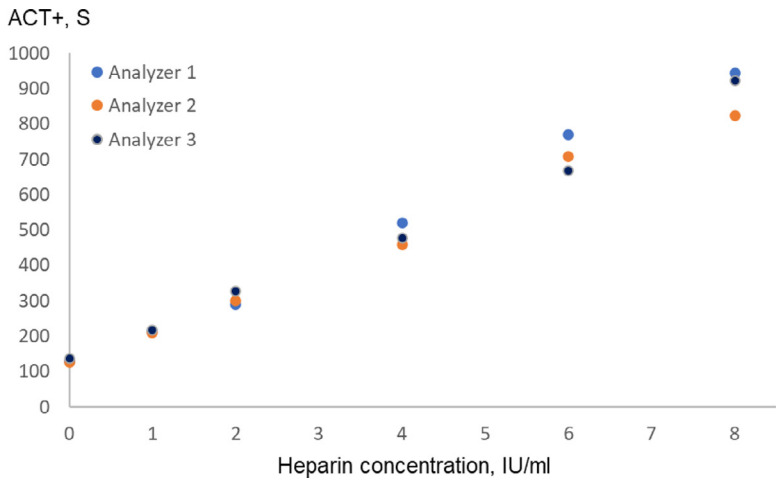

Fig 1. The dose-response relationship of ACT+ tests to increasing heparin concentrations (IU/mL) in severe FXII deficiency. Activated clotting time values are given in celite-based seconds (S).

celite-activated ACT-LR test is calibrated for blood heparin concentrations up to 2.5 IU/mL, whereas the ACT+ test, which is activated by a combination of kaolin, silica, and phospholipid, demonstrates linearity at heparin concentrations ranging from 1-6 IU/mL. It is a well-known fact that celite- and kaolin-based ACT measurements are not identical. Aprotinin is known to prolong celite ACT while kaolin ACT is not affected.[9] Without aprotinin, baseline celite measurements before heparinization tend to be 10% higher than those of kaolin tests, while kaolin ACT values generally exceed those of celite-based tests during CPB.[10] However, baseline ACT+ values are approximately 20% lower than those of standard celite ACT tests, and this difference seems to persist during full heparinization for cardiac surgery compared with both kaolin- and celite-activated tests.[11,12] This suggests that the combination of the three activators in the ACT+ test can initiate the intrinsic coagulation cascade more rapidly than celite or kaolin alone.

Although the authors can only speculate about the reasons why the ACT+ test seems to manage what other ACT tests have failed in patients with FXII deficiency, the most likely explanation is the presence of silica and phospholipids in addition to kaolin in the test cuvette. It has been demonstrated in rats that silica nanoparticles have direct interactions with FXII, leading to a prethrombotic state.[13] The authors therefore suggest that in the ACT+ test, the combination of kaolin and silica constitutes a trigger strong enough to initiate coagulation even if the FXII concentration in plasma is extremely low. Further in the cascade, the phospholipid component is likely to hasten markedly the coagulation process as phospholipids catalyze factor X activation.[14]

It has been shown previously that different aPTT reagents have distinct sensitivities to mild FXII deficiency.[15] Correspondingly, it might be expected that different ACT systems could have variable sensitivities to contact factor deficiencies. However, the authors are not aware of a single previous publication encouraging the use of any commercial ACT test to guide heparin anticoagulation in severe FXII deficiency. As for the ACT+ test, even the manufacturer's instructions do not mention such use. Consequently, the present report obviously adds to the existing knowledge. Although it is probable that the ACT+ test is functional also in other contact factor deficiencies, this remains to be demonstrated.

Conclusions

The authors successfully have used the standard Hemochron Jr. ACT+ test to monitor anticoagulation for CPB in two patients with severe FXII deficiency. Furthermore, in vitro dose-response ACT+ testing of FXII-deficient blood with increasing heparin concentrations supports the use of ACT+ in FXII deficiency.

Acknowledgment

The authors wish to thank Michael Spalding, MD, PhD, for language revision. Riitta Lassila, MD, PhD, Tuukka Helin, MD, PhD, and Peter Raivio, MD, PhD, are acknowledged for valuable advice on in vitro ACT+ testing.

Conflict of Interest

None.

References

1 Halbmayer WM, Haushofer A, Schön R, et al. The prevalence of moderate and severe FXII (Hageman factor) deficiency among the normal population: Evaluation of the incidence of FXII deficiency among 300 healthy blood donors. Thromb Haemost 1994;71:68–72.
2 Salmenperä M, Rasi V, Mattila S. Cardiopulmonary bypass in a patient with factor XII deficiency. Anesthesiology 1991;75:539–41.
3 Moorman M, Reynolds D, Comunale ME. Management of cardiopulmonary bypass in a patient with congenital factor XII deficiency. J Cardiothorac Vasc Anesth 1993;7:452–4.
4 Gerhardt MA, Greenberg CS, Slaughter TF, et al. Factor XII deficiency and cardiopulmonary bypass: Use of a novel modification of the activated clotting time to monitor anticoagulation. Anesthesiology 1997;87:990–2.
5 Jair van Veen J, Laidlaw S, Swanevelder J, et al. Contact factor deficiencies and cardiopulmonary bypass surgery: Detection of the defect and monitoring of heparin. Eur J Haematol 2009;82:208–12.
6 Conaglen PJ, Akowuah E, Theodore S, et al. Implications for cardiac surgery in patients with factor XII deficiency. Ann Thorac Surg 2010;89:625–6.
7 Uppal V, Rosin M. Factor XII deficiency and cardiopulmonary bypass. J Extra Corpor Technol 2014;46:254–7.
8 Vuckovic J, Zdravkovic R, Stanic KB, et al. Incidental detection of factor XII deficiency following coronary artery bypass grafting. J Cardiothorac Vasc Anesth 2021;35:597–9.
9 Feindt P, Seyfert UT, Volkmer I, et al. Celite and kaolin produce differing activated clotting times during cardiopulmonary bypass under aprotinin therapy. Thorac Cardiovasc Surg 1994;42:218–21.
10 De Vries AJ, Lansink-Hartgring AO, Fernhout FJ, et al. The activated clotting time in cardiac surgery: Should celite or kaolin be used? Interact Cardiovasc Thorac Surg 2017;24:549–54.
11 Aylsworth CL, Stefan F, Woitas K, et al. New technology, old standards: Disparate activated clotting time measurements by the Hemochron Jr compared with the standard Hemochron. Ann Thorac Surg 2004;77:973–6.
12 Lee JM, Park EY, Kim KM, et al. Comparison of activated clotting times measured using the Hemochron Jr. Signature and Medtronic ACT Plus during cardiopulmonary bypass with acute normovolemic haemodilution. J Int Med Res 2018;46:873–82.
13 Jiang L, Li Y, Li Y, et al. Silica nanoparticles induced the pre-thrombotic state in rats via activation of coagulation factor XII and the JNK-NF-κB/AP-1 pathway. Toxicol Res 2015;4:1453–64.
14 Panteleev MA, Saenko EL, Ananyeva NM, et al. Kinetics of factor X activation by the membrane-bound complex of factor IXa and factor VIIIa. Biochem J 2004;381:779–94.
15 Toulon P, Eloit Y, Smahi M, et al. In vitro sensitivity of different activated partial thromboplastin time reagents to mild clotting factor deficiencies. Int J Lab Hematol 2016;38:389–96.