Case Report

An Unanticipated Prolonged Baseline ACT During Cardiac Surgery Due to Factor XII Deficiency

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ABSTRACT

Factor XII (FXII) deficiency is a congenital disorder inherited as an autosomal recessive condition. In his heterozygous form, it is relatively common in the general population. However, a total absence of FXII as seen in homozygous patients, is rare, with an incidence of approximately 1/1,000,000 individuals. Surprisingly, FXII deficiency is rather associated with thromboembolic complications. Patients do not experience a higher risk of surgical bleeding despite a markedly prolonged activated partial thromboplastin time. Given its low incidence in the general population, the finding of an unknown FXII deficiency is rare during cardiac surgery. This unique case describes a patient with an unanticipated prolonged baseline activated clotting time (ACT) during cardiac surgery in which his bleeding history and rotational thromboelastometry tracings lead us to the diagnosis of a FXII deficiency. The finding of a hypocoagulable INTEM tracing and a concurrent normal EXTEM tracing in a sample of a patient with prolonged ACT and adverse anamnestic bleeding history should prompt clinicians to consider a FXII deficiency. It may help clinicians in further perioperative management where there is not enough time to wait for the results of individual coagulation factor testing.

Keywords: ACT, cardiopulmonary bypass, factor XII deficiency, ROTEM

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INTRODUCTION

Factor XII (FXII) deficiency is a congenital disorder inherited as an autosomal recessive condition. In his heterozygous form (25--50% of normal FXII plasma levels), it is relatively common in the general population (2.3%).[1] However, a total absence of FXII as seen in homozygous patients, is rare, with an incidence of approximately 1/1,000,000 individuals.[2] Surprisingly, FXII deficiency is rather associated with thromboembolic complications. Patients do not experience a higher risk of surgical bleeding despite a markedly prolonged activated partial thromboplastin time (aPTT).[3,4] Indeed, preoperative bleeding history and clinical examination will not suggest the presence of a bleeding disorder. Consequently, the condition can only be revealed preoperatively if routine coagulation screening is undertaken. Because FXII is required for the standard *in vitro* tests of the intrinsic coagulation [e.g., activated clotting time (ACT), aPTT], the monitoring of the heparin effect during cardiopulmonary bypass (CPB) is problematic. Since the principles for the management during CPB are based on a limited number of case reports, an individualized strategy to monitor the heparin effect during CPB requires special attention.

Herein, we report the case of a patient with a homozygous FXII deficiency that highlights the limitations of the

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available coagulation monitoring strategies in these patients and the discussion for the need for routine preoperative coagulation screening in cardiac surgery. In this particular setting, rotational thromboelastometry (ROTEM) showed to be useful in the rapid perioperative differentiation of this specific coagulation factor deficiency.

CASE REPORT

A 67-year-old male with significant two-vessel coronary disease (left anterior descending and obtuse marginal coronary artery) and severe aortic stenosis (peak gradient 100 mmHg, mean gradient 63 mmHg, AVA 0.7 cm^2) presented for a coronary artery bypass graft (CABG) with an aortic valve replacement. Past medical history recorded fibromyalgia, migraine aura, and hip osteoarthritis. Preoperative medications included low dose acetylsalicylacid 80 mg and metoprolol 50 mg. During the preoperative screening, he did not report a positive personal or family history of bleeding and had undergone minor prior interventions without any notable bleeding complications. Standard preoperative testing for patients undergoing cardiac surgery at our institution revealed no abnormalities (hemoglobin 10 mmol/L, platelet count 164 × 10^9/L, normal kidney function, and electrolytes). After induction of general anesthesia and before unfractionated heparin administration, a baseline ACT (I-STAT alinity, Abbott, Princeton, NJ) was noted to be prolonged at 804 s (normal range 84--139 s). To exclude device malfunctioning, we performed a second test (814 s) with a different instrument of the same make. By the time the results were available, sternotomy was already undertaken. Whole blood ROTEM was performed, and a hematologist was consulted. In addition, we performed a standard coagulation screening which showed a severe prolonged aPTT (>150 s; normal range 23--32 s), normal fibrinogen (3.0; normal range 1.7--4.0 mg/dL) and a normal prothrombin time (PT) (11.4 s; normal range 9.9--12.4 s). Furthermore, ROTEM showed normal EXTEM and HEPTEM tracings, and an abnormal INTEM [Figure 1]. Given the available test results at that time, we presumed a FXII deficiency. Our consulting hematologist advised either to give three units of fresh frozen plasma to enable heparin effect monitoring by ACT or to abandon surgery.

A joint decision was reached to proceed with an off-pump CABG (OPCAB) LIMA-LAD and to perform a percutaneous coronary intervention (PCI) of the stenotic circumflex artery in combination with a transaortic valve replacement (TAVR) at a second stage. The OPCAB procedure was performed uneventfully. At the intensive care unit (ICU), results of specific coagulation factor testing became available and confirmed our suspicion of severe FXII deficiency (FVIII 133%; normal range 50--200%, FIX 88%; normal range 60--140%, FXI 51%; normal range 60--140%, FXII <6%; normal range 60--140%).

The postoperative course was further complicated by acute cholangitis that warranted an endoscopic retrograde cholangiopancreatography (ERCP). The TAVR procedure was successfully performed 6 weeks later without procedure related complications.

DISCUSSION

Factor XII, or Hageman factor, is a single chain glycoprotein present in plasma as the zymogen of serine protease factor XIIa. It is a coagulation protein that performs a primary role in the initiation of the intrinsic coagulation cascade and fibrin formation.[3,5]

A deficiency of FXII mimics a bleeding disorder, although it does not result in clinical bleeding tendency.[3,4] Adequate anticoagulation before the establishment of CPB is monitored by the ACT. The ACT in healthy blood is 130 ± 22 s and is prolonged after heparinization. An ACT >400 s implies a sufficient heparin effect for CPB. The ACT relies on the presence of factor XII for activation. A deficiency of this factor makes the test unreliable.[4,6-13]

Multiple strategies are proposed for the monitoring of anticoagulation during CPB in patients with FXII deficiency. These include empiric dosing of heparin for CPB without monitoring,[4] confirming a heparin effect by subsequently monitoring a prolongation of the baseline (prolonged) ACT,[6,14] increasing endogenous FXII levels by transfusion of donor fresh frozen plasma preoperatively,[12,13] using a modified ACT technique with the *in vitro* replacement of FXII in patient's blood sample with donor plasma,[10] and the monitoring of the heparin effect by an anti-Xa assay.[15] All of the above-mentioned strategies have their limitations and lack reproducibility.

Clearly, preoperative diagnosis and implementation of an alternative strategy for coagulation monitoring during cardiopulmonary bypass in case of a FXII deficiency are key in managing these patients. We presented a rare example of a patient with an unknown FXII deficiency diagnosed intraoperatively during cardiac surgery, which directly impacted the further treatment of the patient's condition. Therefore, it reintroduces the discussion for routine preoperative coagulation screening in all patients undergoing cardiac surgery. Since it is no longer a standard practice to perform coagulation screening in

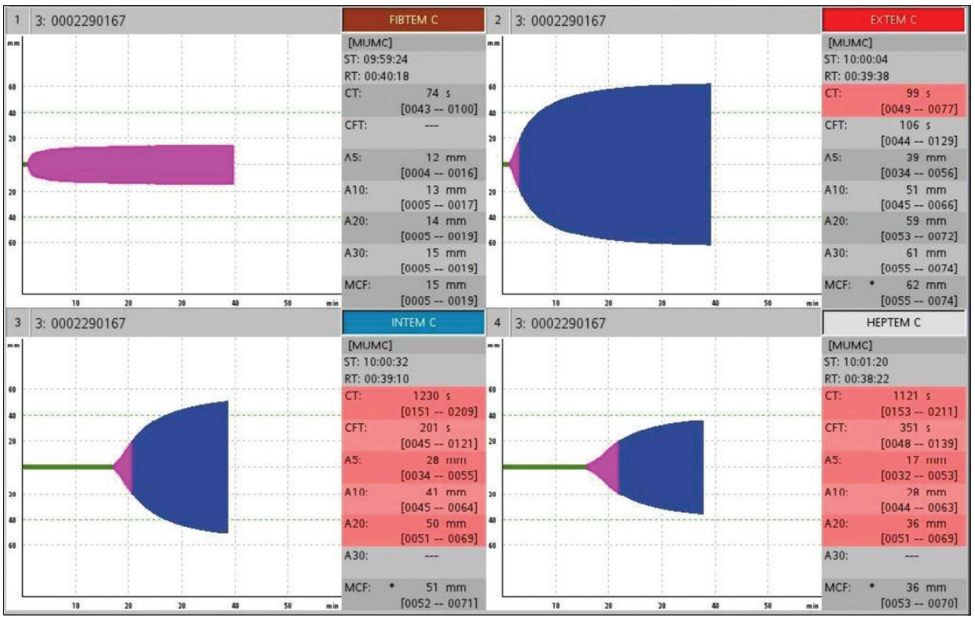

Figure 1: Rotational thromboelastogram (ROTEM) obtained after induction of anesthesia

our institution, we could not detect an FXII deficiency preoperatively. As recommended by the European Society of Anesthesiology guidelines, our preoperative hemostatic assessment consists of a standardized questionnaire on bleeding and drug history and a physical examination.[16] Only in selected cases, we perform further laboratory testing. Routine unselected testing is no longer supported by current evidence. It has a limited impact on the perioperative outcome, may unnecessarily postpone required surgery, and patients may be subjected to unwarranted tests.[17]

Given that the patient described here had a negative bleeding history as obtained by a standardized patient questionnaire, a negative clinical examination and had no history of postinterventional bleeding, laboratory coagulation screening was not performed. However, the National Institute for Health and Care Excellence (NICE) recommends hemostasis tests in all patients who are ASA physical status 3 or 4 and before intermediate or major surgery.[18] Preoperative coagulation screening would presumably cause a considerable difference in the further perioperative course since it would enable us to design a strategy preoperatively for the monitoring of heparin effect during CPB so that the planned surgery could be performed.

ROTEM has extensively been used to assess the cause of coagulopathy during cardiac surgery. In the presented case, the ROTEM study helped us during the surgery to diagnose a FXII deficiency. To our knowledge, this is the first case report that reports the diagnosis of a FXII deficiency with the help of a ROTEM study during cardiac surgery. This patient had a normal EXTEM and FIBTEM tracing [Figure 1]. However, the INTEM and HEPTEM tracing showed a markedly delayed clotting time (CT), as well as a decreased clot strength. The role of FXII in clot initiation is still not fully understood. Activation of FXII occurs initially via the intrinsic pathway. Clot consolidation and clot strength, as assessed by CFT and MCF parameters of ROTEM, were typical in the EXTEM tracing. Given that the patient bleeding history was unremarkable, in combination with a prolonged ACT and an abnormal INTEM and HEPTEM tracing, the diagnosis of a FXII deficiency was made intraoperatively. After multidisciplinary consultation with the responsible surgeon, anesthetist, hematologist, and perfusionist, we decided to refrain from performing on-pump surgery and choose a hybrid procedure consisting of an off-pump CABG with a PCI and TAVR a later stage.

CONCLUSION

This unique case describes a patient with an unanticipated prolonged baseline ACT during cardiac surgery. His negative anamnestic bleeding history, negative clinical examination, and abnormal ROTEM tracings intraoperatively, with a hypocoagulable INTEM tracing and a concurrent normal EXTEM tracing, lead us to the diagnosis of a FXII deficiency.

Declaration of patient consent

Written informed consent for this publication was obtained from the patient.

Abbreviations: ACT, Activated clotting time; ROTEM, Rotational thromboelastometry; CABG, Coronary artery bypass graft; aPTT, activated partial thromboplastin time; PT, prothrombin time; LAD, Left anterior descending; LIMA, Left internal mammary artery, PCI, percutaneous coronary intervention; TAVR, Transcatheter aortic valve replacement; OPCAB, off-pump coronary artery bypass; ICU, intensive care unit; CPB, cardiopulmonary bypass; NICE, National Institute for Health and Care Excellence.

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Conflicts of interest
There are no conflicts of interest.

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