Cardiopulmonary Bypass in a Patient with Factor XII Deficiency

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Factor XII (F XII), or Hageman factor, is the first enzyme of the intrinsic loop of blood coagulation cascade. Despite marked laboratory abnormalities, congenital deficiency of F XII is not associated with abnormal bleeding diathesis. However, standard tests to monitor heparin activity intraoperatively depend on the activation of F XII. We describe a patient who required open heart surgery and in whom standard preoperative hemostatic evaluation and perioperative assessment of heparin activity could not be performed because of his congenital F XII deficiency.

CASE REPORT

A 56-yr-old man with a 6-yr history of stable angina increasing to the grade of New York Heart Association III or IV within the preceding 6 months was scheduled for coronary artery bypass grafting. His medications included metoprolol, nifedipine, and isosorbide dinitrate. Coronary arteriography showed triple-vessel disease and well-preserved left ventricular function (ejection fraction 70%). Chest x-ray showed bilateral diffuse infiltrates compatible with sarcoidosis, but this diagnosis had not been verified. Pulmonary function was normal. The patient reported no history of bleeding, but he had not undergone surgery before. The family history was noteworthy, in that a sister had been advised to request therapy with fresh frozen plasma before any surgical procedures.

Routine preoperative blood coagulation scan showed platelet count 221,000 platelets per ml, template bleeding time 5.5 min, prothrombin time 14 s, and activated partial thromboplastin time (APTT) Cephotest reagent, Nycomed, Oslo) > 240 s. Because of prolonged APTT a more thorough coagulation factor evaluation was performed and yielded the following additional results: factor V 195%, factor VII 115%, factor VIII:C 111%, von Willebrand factor antigen 124%, von Willebrand factor ristocetin cofactor 96%, factor IX 111%, factor X 107%, and F XII < 1%. A diagnosis of F XII deficiency was made, and according to the hematologist consultation, no substitution therapy was planned before the operation.

Anesthesia was induced with fentanyl 30 μg·kg⁻¹ and maintained with an infusion of 0.15 μg·kg⁻¹ thereafter. Pancuronium was used for muscle relaxation; anesthesia was supplemented with diazepam as an anesthetic adjuvant in divided doses (total dose up to 0.3 mg·kg⁻¹) and brief periods of enflurane. Cardiopulmonary bypass (CPB) was performed with a membrane oxygenator (Capiox®-E, Terumo). The circuit was primed with Ringer’s acetate, and the patient was cooled to 28° C. A three-vessel bypass was performed using two saphenous vein grafts and left internal mammary artery as conduits. Subsequent separation from CPB was uneventful, and no vasoactive medications were needed. A cell saver was used preoperatively, but no attempts to retransfuse shed mediastinal blood postoperatively were made.

A specimen of arterial blood obtained before anesthesia induction demonstrated a hemoglobin concentration of 15.6 g/100 ml and a hematocrit of 45%. Activated clotting time (ACT, Hemochron®) using standard saline tubes was 541 and 560 s, performed with two separate machines. Clotting time performed with the tube without an activator (Hemochron®) was 840 s. A thromboelastographic tracing (fig. 1) was grossly abnormal, with a reaction time of 96 min (95% confidence limits for normal values in coronary artery bypass graft patients at our institution = 6–11 min), an α-angle of 34° (95% confidence limits = 41–46°), and a maximum amplitude of 42 mm (95% confidence limits = 46–52 mm)—values indicative of hypocoagulability in vitro. Heparin (porcine mucosa heparin) was given in a dose of 300 U/kg.

Thereafter, and in the second sample, drawn during CPB, no clotting was detected in ACT tubes within a 30-min observation period. No additional heparin was given during the 82-min bypass time. After removal of the cannulas heparin was antagonized with 3 mg/kg of protamine sulfate. ACT after protamine was 386 s. Two hours after protamine ACT was 382 s, APTT was > 240 s, platelet count was 121 000 platelets per ml, and template bleeding time 8.5 min. In the thromboelastographic tracing, the R value, 24 min, was shorter after CPB. The tracing was otherwise nearly indistinguishable from the preoperative tracing (fig. 1). An assay for fibrin (and fibrinogen) degradation products was negative. Postoperative bleeding loss was 860 ml up to the first postoperative day, when the chest tubes were removed. Two units of packed red cells were used to increase the hematocrit to greater than 30% postoperatively.

The patient made an uneventful recovery and was discharged from the hospital on the eighth postoperative day.

DISCUSSION

F XII is a single-chain glycoprotein with a molecular weight of approximately 80,000 D. Deficiency of F XII is a rare congenital disorder first identified by Ratnoff and Colopy; subsequently, the requirement of two abnormal alleles for the complete deficiency of this factor has been documented. F XII undergoes autocatalytic activation upon contact with artificial surfaces like glass and particularly silicates like celite and kaolin. The physiologic activator has been postulated to be subendothelial basement membrane. The intrinsic coagulation pathway is initiated when the activated serine protease (F XIIa) acts on its substrate factor XI. Factor XIIa also is involved
are compatible with impaired contact activation and mal-function of the intrinsic coagulation pathway. Of course, these tests have no value in monitoring heparin in patients with F XII deficiency. It is surprising that, in the only earlier report of cardiac surgery in a patient with F XII deficiency, ACT was used to assess adequacy of heparinization and its reversal, although the authors do not document any actual ACT values.\textsuperscript{11}

The test of the extrinsic system, prothrombin time, and the final common pathway, thrombin time, are prolonged over their measurement range with the high doses of heparin needed for anticoagulation. If there is doubt about unneutralized heparin after protamine in patients with F XII deficiency, thrombin time measurement is the best way to detect residual heparin, as it is in patients with a normal coagulation cascade. Heparin concentration can be detected indirectly using protamine titration \textit{in vitro}. The clinically available devices (Hepcon A-10\textsuperscript{10} and HMS\textsuperscript{8}, Hemotec, Inc.) use exogenous thromboplastin to accelerate the coagulation process. This approach relies only on the extrinsic and common pathways, and will work normally in F XII-deficient patients. Heparin concentration monitoring should be helpful in these patients in order to ascertain stable heparin concentrations and completeness of reversal of heparin by protamine. Unfortunately, this methodology was unavailable to us at the time we took care of this patient.

The optimal heparin dose for CPB in the patients with F XII deficiency is not known. The capacity of heparin to inhibit kallikrein and factor X\textsubscript{IIIa} is limited.\textsuperscript{12} Since these steps are not operational in a F XII-deficient patient, there might be fewer activated clotting factors consuming heparin cofactors like antithrombin III. A heparin-sparing effect by this mechanism has been recently proposed after pharmacologic kallikrein inhibition by aprotinin.\textsuperscript{15} The inhibition of early steps of the intrinsic coagulation cascade, however, do not allow for reduced heparin requirements in clinical practice, because the compensatory capacity of the alternate pathways is unpredictable.

Patients with a congenital F XII deficiency usually are identified by routine preoperative blood coagulation screening. An isolated markedly prolonged aPTT with a negative bleeding history strongly suggests an F XII defect. The equally rare deficiencies of the two other contact activation factors, high-molecular-weight kininogen and prekallikrein, can be responsible for a similar clinical presentation. An acquired circulating anticoagulant must be excluded and the diagnosis confirmed with a specific assay using F XII-deficient plasma. The kindred should be screened with aPTT to identify the homozygotes. Heterozygotes show abnormal F XII values, but these do not always affect the routine coagulation tests. No substitution therapy is needed for these patients even in cardiac sur-

\begin{figure}[h]
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\caption{Thromboelastographic tracings before (pre-CPB) and after (post-CPB) cardiopulmonary bypass. Arrows indicate the reaction time of the sample blood from our patient ($R$) with factor XII deficiency and the mean reaction time in our laboratory ($R_n$).
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\end{figure}
gery, with inevitable further compromise to the coagulation system, as shown by the uneventful course of our patient. If perioperative bleeding occurs in these patients during their cardiac surgery, its cause and therapeutic approach should be no different from those of patients with normal secondary hemostasis.

Surface activation of F XII is an essential requirement for many in vitro assays used for coagulation monitoring in cardiac surgical patients. Such tests are unable to assess clinical hemostasis and heparin activity in F XII-deficient patients, because in vivo alternate modes of activation can compensate for the defect. In the absence of a clinically feasible method to assess surgical anticoagulation rapidly in these patients, heparin must be given according to weight-based protocols, and a normal dose-response relationship must be assumed. Measuring heparin concentrations during and after CPB could assist in the maintenance of anticoagulation and its reversal in the F XII-deficient patient.

REFERENCES

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Epidural Opioid Analgesia Does Not Obscure Diagnosis of Compartment Syndrome Resulting from Prolonged Lithotomy Position

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Extensive genitourinary or gynecologic surgery often requires prolonged anesthesia and the lithotomy position. Many anesthesiologists prefer to conduct these cases under combined epidural and general anesthesia and then to use epidural analgesia for postoperative pain. A rare complication of prolonged lithotomy position under general anesthesia is lower-extremity compartment syndrome.1 It has been suggested that postoperative epidural analgesia may obscure symptoms of compartment syndrome and delay diagnosis and treatment.2 We report two cases of patients who underwent prolonged genitourinary surgery while in the lithotomy position under combined general and epidural anesthesia. Postoperatively, while receiving intermittent epidural morphine, both patients developed readily diagnosed unilateral compartment syndrome requiring fasciotomies.

CASE REPORTS
Case 1. A 52-yr-old, 85-kg woman, ASA physical status 2, with carcinoma of the bladder underwent a radical cystectomy with urinary

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Key words: Analgesia: epidural; postoperative; opioid. Complications: compartment syndrome. Position: lithotomy.