Factor XII Deficiency and Cardiopulmonary Bypass: Use of a Novel Modification of the Activated Clotting Time to Monitor Anticoagulation

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FACTOR XII is a component of the contact activation complex that contributes to initiation of the intrinsic pathway of coagulation. Although Factor XII deficiency is relatively common in the general population (2.3%),¹ and is more prevalent in patients with coronary artery disease,² severe Factor XII deficiency is rare. Despite a markedly prolonged activated partial thromboplastin time (aPTT) in the presence of severe Factor XII deficiency, these patients do not experience an increased risk of bleeding. Monitoring a heparin effect during cardiac surgery in patients with severe Factor XII deficiency is problematic because the usual in vitro tests of the intrinsic coagulation pathway (e.g., activated clotting time [ACT], aPTT) require Factor XII to accurately reflect in vivo anticoagulation. There are no published methods that allow appropriate monitoring of heparin therapy in Factor XII deficient patients without additional risks. We present a modification of the ACT test that compensates for the absence of Factor XII to provide an accurate measure of heparin effect.

Case Report

A 74-yr-old man with mitral regurgitation due to chronic rheumatic heart disease was scheduled to undergo elective mitral valve replace-
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Fig. 1. The effect of increasing concentrations of FFP on the measurement of the modified ACT.

ment. Coexisting diseases included chronic renal insufficiency and hypothyroidism. Relevant preoperative laboratory studies included (normal values shown in parentheses): Factor XII level < 1.3% (42–161%); aPTT > 150 s (27–38 s); PT, 12.4 s; international normalized ratio (INR) 1.1 (0.75–1.50); platelet count, 291,000/µl; hematocrit, 35%; serum creatinine, 2.8 mg/dl; Factor VIII level, 136% (54–195%); Factor IX level, 127% (59–191%); and Factor XI level, 119% (62–169%).

The Modified ACT Test Technique

The evening before surgery, whole blood samples were obtained for coagulation testing. We empirically determined that 0.1 ml (0.465 mg/kg) of 10% calcium gluconate (American Reagents Laboratories, Inc., Shirley, NJ) was required to neutralize calcium chelators in a 2-ml sample containing 1 ml of blood and 1 ml of donor fresh frozen plasma (FFP; data not shown). A titration curve measuring the ACT with varying ratios of patient blood mixed with FFP was then performed (fig. 1) to identify assay conditions that would provide sufficient Factor XII activity from donor FFP to a achieve “normal” baseline ACT. As shown in figure 1, 0.1 ml CaCl₂ and 10% FFP, both added directly to the whole blood (per 2 ml aliquot), were required to normalize the ACT. We then chose to use 25% FFP in our assay because this ratio was on the linear portion of the modified ACT titration curve. In multiple experiments, 1.5 ml of Factor XII deficient patient blood with 0.5 ml FFP and 0.1 ml CaCl₂ consistently normalized the prolonged ACT from >500 s to <140 s (fig. 1). Modified ACT test assay conditions were then tested to confirm a normal dose-response curve (fig. 2) to various concentrations of heparin (Elkins-Sinn, Cherry Hill, NJ). The ACT was measured with a Hemochron Whole Blood Coagulation System (Technidyne Corporation, Edison, NJ).

Intraoperative Course

After sternotomy, the patient was given a bolus dose of heparin (500 uspu/kg). Additionally, γ-aminobutyric acid was administered intravenously as a 10-g bolus followed by an infusion (1 g/h) for 5 h. Duplicate samples of blood were withdrawn at intervals before and after heparin administration, and a modified ACT test was performed as previously described. To minimize variability, the same donor FFP and ACT machine were used for preoperative and intraoperative coagulation assays. After heparin administration, the modified ACT results were markedly prolonged (550–750 s) from baseline values (168 s), and cardiopulmonary bypass (CPB) was instituted. The modified ACT value began to decrease with rewarming (559 s). An additional heparin dose (100 uspu/kg) was administered, resulting in an increase in the modified ACT (695 s). Aortic cross-clamp and CPB times were 91 and 108 min, respectively. Protamine, 3.65 mg/kg, was administered after separation from CPB returning the modified ACT to baseline values (129 s). During the operative course, the patient received 1 unit of packed erythrocytes for anemia, but no other blood products were required. Laboratory analysis at ICU admission demonstrated the following: aPTT > 150 s, PT, 16.2 s, INR, 1.7; fibrinogen, 107 mg/dl; D-dimer < 0.25 µg/ml; platelet count, 240,000/µl; hematocrit, 31%; ionized calcium, 1.10 mm; unfractionated porcine heparin level, 0.17 uspu/ml (<0.1 uspu/ml). A repeat assay in 6 h yielded an unfractionated porcine heparin level of <0.1 uspu/ml.

Discussion

We present a method to determine a patient-specific, appropriately modified ACT test in patients with Factor XII deficiency. Previous reports describe three methods for managing anticoagulation in the patient with Factor XII deficiency. One approach involves empiric dosing of heparin for CPB without monitoring anticoagulation. A second technique involves managing anticoagulation for CPB in Factor XII-deficient patients by obtaining an unmodified baseline ACT (prolonged) and subsequently confirming a heparin effect by monitoring prolongation of the ACT. Because results of the ACT

Fig. 2. Modified ACT in a Factor XII-deficient patient, demonstrating a linear relationship between heparin levels in the normal therapeutic range and test results. Note also that the baseline (no heparin) ACT value is within normal limits.
are abnormal before heparin therapy, interpretation of the ACT after heparin administration would be speculative at best. The third strategy has been to increase patient Factor XII levels with FFP transfusion preoperatively. Although this method facilitates testing by allowing standard ACT monitoring of heparin therapy, the patient is exposed to an unnecessary FFP transfusion with the attendant risks and expense. The modified ACT described in this report provides an alternative method of correcting the ACT to reflect heparin effect without exposing the patient to the risks of transfusion-associated complications.

Although other monitors of anticoagulation may be used to treat a patient with severe Factor XII deficiency for cardiac surgery, they also have limitations, and no reports attest to their efficacy. The high dose thrombin time (International Technidyne) assesses heparin anticoagulation through the common pathway and therefore does not require the presence of Factor XII. However, it has rarely been used for cardiac surgery. The ACT remains the most widely used method for monitoring anticoagulation during cardiac surgery, and the presented modification of the assay provides an effective means for monitoring the patient with severe Factor XII deficiency.

There are some limitations associated with this technique. It involves in vitro replacement of Factor XII activity in the patient’s blood with exogenous Factor XII from donor FFP. Factor XII deficiency of donor FFP would be unexpected; nonetheless, a normal baseline modified ACT should be obtained before heparin administration. In addition, differences between donor and patient plasma proteins may affect validity of the modified ACT. Antithrombin III (AT III) is required for a heparin effect, and a disparity between donor and patient AT III levels might cause modified ACT results to misrepresent the in vivo heparin effect. In the presence of patient AT III deficiency, the modified ACT may underestimate the anticoagulant effect. To safeguard against the possibility of AT III deficiency, we increased the heparin dose used for CPB. Dilution of the patient blood sample and heparin level by donor FFP in the modified ACT should also reduce the likelihood of overestimating the heparin effect. Further, during CPB, the ACT correlates poorly with AT III and heparin levels. Interpatient variables, such as the extent of plasma protein binding by heparin, and the concentration of calcium required to activate clotting mandate that the modified ACT be validated in each patient before, rather than during, cardiac surgery. In the case presented, a single unit of FFP was refrigerated at the time of preoperative testing and subsequently used for the intraoperative testing.

We believe the modified ACT will prove useful for monitoring heparin effect in Factor XII-deficient patients not only during cardiac surgery, but also during interventional cardiac procedures and dialysis. Further, this methodology should also be effective in deficiencies of high molecular weight kinogen and prekallikrein, additional components of the contact activation complex.

References