

Fletcher Factor Deficiency in Cardiac Anesthesia A Case Report

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Abstract

INTRODUCTION

Fletcher-factor deficiency (Fletcher-trait) was first described by Hathaway et al. in 1965¹. The asymptomatic clotting defect is characterized by a prolonged partial thromboplastin time APTT, normal prothrombin time PT and bleeding time. In 1973 and 1974 other authors identified Fletcher-factor as plasma prekallikrein_{2,3}. The coagulation disorder is considered as very rare and as clinically non-significant⁴. We describe for the first time the management of anticoagulation in a patient with Fletcher-factor deficiency undergoing cardiopulmonary bypass for coronary artery bypass graft surgery.

CASE REPORT

A 64-year-old white woman was admitted to the hospital with severe retrosternal pain with radiation to the neck and left shoulder. In her medical history she was known to have hypertension and coronary artery disease with myocardial infarction. In addition, the patient had a history of peptic ulcer disease, GI bleeding, transient ischemic attack and mild stroke in the past. The cardiac enzymes did not show evidence of acute myocardial infarction. The patient was diagnosed with severe coronary artery disease, hypertension, progressive angina pectoris and abdominal aortic aneurysm. Left heart catheterization showed a 70 -80% stenosis of the mid-portion of the left anterior descending (LAD), a 70% stenosis of the obtuse marginal (OM) and a 80% stenosis of the proximal circumflex coronary artery (RCX). Ejection fraction (EF) measured by cardiac echocardiography was 35 - 40%. There was a global left-ventricular hypokinesis. The patient was scheduled for coronary artery bypass graft surgery.

During the preanesthetic evaluation she disclosed that she had a Fletcher-factor deficiency. Prothrombin time (PT =

11.3 sec.) and partial thromboplastin time (APTT = 27 sec.) were normal. She denied having a clinically significant bleeding disorder. It was decided that heparinization for cardiopulmonary bypass should be monitored with the protamine-titration-test (Hepcon HMS, Medtronic, Hemotec Inc) rather than be guided by the routinely used activated clotting time (ACT). We did not know what impact the Fletcher-factor deficiency may have on ACT's, therefore we preferred direct heparin measurements.

After induction of anesthesia a blood sample was taken for baseline heparin level and ACT. The celite-based ACT (Hemochron 801, International Technidyne Corporation, Edison, NJ) showed a baseline ACT of 320 sec., the Hepcon-test a baseline heparin level of 0 mg/kg and the kaolin-based ACT a baseline ACT of 449 sec. Subsequently the patient was heparinized with 240 mg (4 mg/kg) porcine heparin prior to connection to the cardiopulmonary bypass. Thereafter a heparin level of 3 mg/kg, a celite-based ACT of 648 sec. and a kaolin-based ACT of >1000 sec. were measured. Another 50 mg heparin were added to the cardiopulmonary bypass machine (CPB). The surgeon found on exposure an ascending aortic aneurysm which ruptured slightly during administration of the cardioplegic solution after aortic cross-clamping. He decided to replace the proximal portion of the ascending aorta. 30 minutes later we obtained a heparin level of 3 mg/kg and a kaolin-based ACT of >1000 sec. Celite-based ACT was not measured at this time. Additional 50 mg heparin were added to the CPB. After the next 30 minutes the heparin level was 2.5 mg/kg, the celite ACT 528 sec. and the kaolin ACT >1000 sec. Additional 50 mg heparin were added to the CPB. After another 25 minutes the heparin level was 2.5 mg/kg and the kaolin ACT >1000 sec. Celite-based ACT was not measured at this time. During the surgery 3 vessel coronary artery bypass graft and ascending aorta repair was performed. The

patient was then separated from the CPB. Heparin reversal was accomplished with 240 mg of protamine. The patient received a transfusion of 3 singles units of fresh frozen plasma FFP and 10 units of platelets. 5 minutes after completion of the protamine infusion a heparin level of 0 mg/kg was obtained. The celite ACT was 138 sec. and the kaolin ACT 150 sec.

Figure 1

Table 1: Monitoring of anticoagulation during cardiopulmonary bypass

Time	Baseline	3 min after administration of 240mg Heparin	30 min after initial dose heparin (another 50 mg heparin added)
ACT Celite	320 sec.	648	not measured
ACT Kaolin	449 sec.	> 1000 sec.	> 1000 sec.
Heparin-level	0 mg/kg	3 mg/kg	3 mg/kg

Time	60 min after initial dose heparin (another 50 mg heparin added)	85 min after initial dose heparin (another 50 mg heparin added)	120 min after initial dose heparin (5 min after administration of 240 mg protamine and 2 U FFP)
ACT Celite	528 sec.	not measured	138 sec.
ACT Kaolin	> 1000 sec.	> 1000 sec.	150 sec.
Heparin-level	2.5 mg/kg	2.5 mg/kg	0 mg/kg

The patient received a total transfusion of 8 cellsaver units, 10 packed red cells, 3 single units FFP and 10 single units of platelets. The coagulation profile showed a prothrombin time of 15.2 sec., a partial thromboplastin time of 39 sec., fibrinogen of 130 mg/dl, platelets of 98 K/UL, a hemoglobin of 11.9 g/dl and a hematocrit of 33.9 %. The patient was transferred to the ICU without complications.

DISCUSSION

Plasma kallikrein (Fletcher factor) is a hepatic serine proteinase present in normal plasma. It is of importance in the early phase of blood coagulation. Fletcher factor deficiency (Fletcher trait = FT) is caused by a genetic disorder, first described in 1965 in Kentucky ¹. Gene structure and chromosomal localization of rat plasma kallikrein was reported by Beaubien et al. in 1991 ⁵. Heterogeneity of FT has been shown by Saito et al. ⁶ and is has been postulated that this coagulation abnormality may be caused by deficiency of normal prekallikrein or by presence of nonfunctional prekallikrein. The T-globulin prekallikrein as well as the structurally and functionally related proteins kininogen and Hageman factor (factor XII) is involved in the early contact phase of the intrinsic coagulation cascade ^{7,8}. It is also involved in activation of the fibrinolytic, kinin, and

complement system ⁹.

Patients with FT do not have a clinically significant bleeding disorder ^{1,2}. Some authors suggest even a increased risk for thromboembolic diseases in patients with Fletcher factor deficiency due to defective fibrinolysis ^{9,10,11,12}. Diagnostic is performed by obtaining a prolonged activated partial thromboplastin time APTT in presence of a normal prothrombin time PT and bleeding time. Relative sensitivity of various APTT reagents in prekallikrein deficient plasma was determined at different incubation times by Abildgaard et al. ¹³. Reagents containing celite or kaolin were sensitive to FT, whereas reagents with ellagic acid did not detect the abnormality. Prolongation of incubation times in celite or kaolin containing reagents resulted in normal APTT's in patients with FT, but did not correct abnormal clotting times in deficiencies of factors VIII, IX, XI or XII. The routinely preoperatively performed coagulation screening test in our patient (celite reagent with incubation of 10 minutes) resulted in normal values for APTT and PT. FT was discovered by obtaining the medical history and asking questions about any possible bleeding disorders in the family.

Heparinization of patients undergoing surgery with cardiopulmonary bypass is mandatory in order to avoid blood clotting in the CPB machine. The management of anticoagulation during CPB is routinely performed with guidance of the activated clotting time ACT. ACT's can easily be obtained at the bedside in the operating room. The impact of Fletcher factor deficient plasma on celite or kaolin based ACT's has not been described previously. The high baseline values caused by the absence of prekallikrein could indicate a coagulation problem or overestimation of anticoagulation and consequent underdosage of heparin leading to possible lethal blood clotting during CPB. Anticipating possible problems with ACT measurements we decided to use a heparin-assay by protamine titration (HPT) for maintaining adequate heparin levels during CPB. However, one has to be aware about the limitations of the HPT. Monitoring of the heparin concentration does not reflect heparin response and may therefore not detect cases of heparin resistance. The heparin level in the HPT reflects total circulating heparin instead of functional heparin (heparin bound to antithrombin III).

Measurement of the high-dose thrombin time (HiTT), a test not available at our institution, may be the best alternative to monitor anticoagulation with heparin in patients with FT.

Instead of measuring the intrinsic coagulation pathway the HiTT measures the final step in the coagulation cascade, independent of contact activation of factor XII. HiTT provides information about functional circulating heparin and heparin response in a single test. It should not be affected by prekallikrein deficient plasma. The impact of Fletcher-factor deficiency on thrombelastography is not known. Unfortunately, at occurrence of the case, this test was not yet available at our institution. To learn more about thrombelastography click [here](#).

Despite a normal APTT, the baseline celite ACT and kaolin ACT were 320 respectively 449 seconds (normal 80-150 sec.). False high ACT values may lead to overestimation of heparinization and therefore result in the possible lethal blood clotting during CPB. This complication is feared in cases using aprotinin in combination with celite ACT instead of kaolin ACT during CPB^{14 15}. In our case, the kaolin based ACT's were significantly higher than the celite based ACT's. This phenomenon might be caused by higher absorption of deficient prekallikrein or other factors of the early phase of activation of the intrinsic coagulation cascade by kaolin. Normal ACT's (celite ACT 138 sec. and kaolin ACT 150 sec.) after reversal of heparin with protamine and transfusion of FFP suggest that prekallikrein levels in 1 to 2 single units of FFP are sufficient to correct the abnormality in patients with FT.

In the meantime, two more cases occurred at our institution. Both patients were treated with 2 units FFP. ACT levels were corrected to normal values prior heparinization. Both cases were detected because of high baseline ACT's combined with normal preoperative PT's and APTT's.

CONCLUSION

In summary, we conclude:

- Baseline measurements of ACT's in cardiac anesthesia are important
- ACT's are not reliable in patients with Fletcher-factor deficiency
- The impact of Fletcher-factor deficiency on the kaolin ACT was greater than on the celite ACT
- Management of anticoagulation during cardiopulmonary bypass in patients with Fletcher-factor deficiency should be guided by methods not

sensitive to Fletcher trait such as HPT or HiTT. According to our data, routinely used ACT measurements are not the appropriate monitoring technique of heparinization in such cases.

- If HPT or HiTT are not available, one should consider a preoperative transfusion of 1-2 units fresh frozen plasma to correct the abnormality

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