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Perioperative management of cardiac surgery patients with factor XII deficiency — two cases report

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Abstract

This paper presents two patients with factor XII deficiency, a rare coagulation disorder, who successfully underwent surgery with cardiopulmonary bypass (CPB) in Cardiac Surgery Clinic of the 4th Military Clinical Hospital in Wroclaw. Diagnosis, intra- and postoperative course as well as proposed management strategy are described.

Key words: cardiopulmonary bypass (CPB), factor XII, coagulation system, fibrinolysis

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Factor XII, also called Hageman factor, is an enzyme initiating the coagulation cascade. The main laboratory abnormality, which characterises patients with factor XII deficiency, is an asymptomatic prolongation in activated partial thromboplastin time (APTT), whose incidence is relatively low (1/1,000,000 individuals). The qualification of patients for cardiac surgery with extracorporeal circulation presents potential problems due to difficulties in monitoring the anticoagulant effect of heparin and likely pro-thrombotic tendencies in the postoperative period associated with impaired fibrinolysis [1].

The previously used division of the coagulation process into the extrinsic and intrinsic pathway was markedly modified. The extrinsic, factor VII-dependent pathway was considered dominant for blood coagulation whereas the intrinsic, factor XII-dependent pathway was found to be of an auxiliary, modulating role. The current theory of blood coagulation divides the process into 3 phases: induction, enhancement and the effector one. During the induction phase, the tissue factor is exposed to blood and binds its cofactor-factor VIIa; this complex activates factor IX. During the enhancement phase, with positive feedbacks involved, factor IXa and its cofactors form the complex called tenase, which activates factor X; factor Xa with its cofactors, in turn, forms the prothrombinase complex, which proteolytically converts prothrombin into thrombin. During the effector phase, fibrin monomers are cleaved from fibrinogen mediated by thrombin and polymerise forming fibrin. Factor XII is activated once the complex of factor XII, XI, prekallikrein and multi-molecular kininogen contacts the negatively charged surface. Factor XIIa plays a double role in the cascade reactions of coagulation. It can activate factor XI, which subsequently activates factor IX (previous intrinsic pathway); however, this is its marginal function. The conversion of plasminogen into plasmin by active factor XII and initiation of fibrinolysis is of greater importance. In the human body, the processes of coagulation and fibrinolysis are constantly in a dynamic equilibrium; therefore, factor XII deficiency can potentially increase the risk of thrombosis [2].

The aim of the present report was to describe the management of patients diagnosed with factor XII deficiency, who underwent cardiac procedures with extracorporeal circulation.

CASE REPORTS

CASE 1

A 54-year-old male patient (body weight 78 kg, height 176 cm) with the history of three anterior and lateral myocardial infarctions (left ventricular ejection fraction 60%)

Table 1. Clotting parameters — case 1

Parameter (reference values)	Before surgery	After surgery
Factor XII (50–150%)	9	19
APTT (24–36 s)	45.7	38.9
PT (78–120%)	92	90
INR (0.8–1.2)	1.05	1.1
Fibrinogen (2–4 g L^{-1})	3.5	4.1
D-dimers (0–0.25 μg mL^{-1})	0.16	0.38

Table 2. Clotting parameters — case 2

Parameter (reference values)	Before surgery	After surgery
Factor XII (50–150%)	21	Not determined
APTT (24–36 s)	121.3	50.1
INR (0.8–1.2)	1.18	1.42
Fibrinogen (2–4 g L^{-1})	3.1	Not determined
D-dimers (0–0,25 μg mL^{-1})	0.12	Not determined

was scheduled for coronary artery bypass grafting (CABG) with extracorporeal circulation. According to the commonly used European system of cardiac operative risk evaluation (EuroSCORE) [3], the patient's score was 0 (low risk). Routine coagulation testing carried out three years earlier revealed prolonged APTT to 112 s with the other clotting parameters within reference values. The extended tests demonstrated the following values: factor XII — 1%, factor VIII — 111%, factor IX — 139%, and factor XI — 145%. On the day preceding surgery, the clotting system was re-tested and factor XII was determined (Table 1). Since we had no experience with such a disorder, perioperative management was based on the method described by Wallock and colleagues in 1995 [4]. The method involves the administration of fresh frozen plasma (FFP) before extracorporeal circulation to interpret the intraoperative values of activated clotting time (ACT).

Activated clotting time measured before the induction of anaesthesia was 207 s whereas after the induction — 216 s. After transfusion of 1 unit of FFP (220 mL), ACT was 185 s. Once 250 mg of heparin was administered, ACT increased to 691 s. After another unit of FFP (220 mL), ACT measured 5 minutes after its administration was 509 s. On initiation of extracorporeal circulation, ACT was 641 s; during the procedure, due to the additional dose of heparin 50 mg, ACT was 630 s. The next measurement of ACT performed during surgery showed the value > 1000 s. Once the surgery and extracorporeal circulation were completed and 250 mg of protamine sulphate administered, ACT was found to be 175 s.

The time of extracorporeal circulation was 84 min and of aorta clamping — 50 min. Postoperative drainage recorded on the surgery day did not exceed 1250 mL. On postoperative day 1, clotting parameters were normalised (Table 1). No postoperative thrombotic complications developed and the patient in good condition was transferred to the Department of Cardiology on postoperative day 2.

CASE 2

A 73-year-old male patient (body weight 96 kg, height 164 cm) with the history of non-ST-elevation myocardial infarction (NSTEMI) three weeks earlier, arterial hypertension, paroxysmal atrial fibrillation, lower limb atherosclerosis, type 2 diabetes mellitus, and removal of clear cell carcinoma of the left kidney was scheduled for CABG. The ejection fraction was 55%. The patient's EuroScore was 7 (high risk) [3]. Routine coagulation testing carried out on the infarction day disclosed prolonged APTT to 61 s with the remaining clotting parameters within reference values. The patient did not receive anti-platelet drugs; enoxaparin was given at a dose of 80 mg once a day s.c. for 5 days.

During the day preceding surgery, the extended tests of the clotting system were performed (Table 2). Thromboelastography was additionally used to assess thrombus formation [5, 6]. The only abnormality found in both tests, EXTEM and INTEM, was the prolonged clotting time (Table 3), which could either suggest deficiency of clotting factors or presence of anticoagulants, which the patient did not receive.

Immediately before the induction of anaesthesia, ACT was measured — 193 s. Before the initiation of extracorporeal circulation, 2 units of FFP were administered (529 mL). ACT was determined 5 min later and was found to be 167 s. Subsequently, 300 mg of heparin was given, which prolonged ACT to 620 s. During the procedure, no further doses of heparin were added; yet due to low haematocrit, 1 unit of packed red blood cells was transfused. After the procedure of extracorporeal circulation was completed and heparin effects neutralised with protamine sulphate, ACT was 152 s. Repeated thromboelastography revealed the prolonged clotting time and increased thrombolysis, which might have evidenced that factor XII deficiency was well corrected by the supply of plasma. According to the INTEM test, the time of thrombus formation was also prolonged, which was likely to suggest dysfunction of platelets, fibrinogen deficiency or impaired polymerisation of fibrin (Table 3).

The time of extracorporeal circulation was 136 min and of aorta clamping 71 min. ACT determined after the procedure was 151 s, APTT — 50.1 s, INR — 1.42 (Table 2). Postoperative drainage during the surgery day was 1480 mL. On the same day, the patient received 4 units of packed red blood cells and 6 units of FFP. The postoperative period was uneventful and the patient in good condition was trans-

Table 3. Thromboelastographic results — case 2

Parameter (reference values)	Before extracorporeal circulation	After extracorporeal circulation
Clotting time		
EXTEM test (38–79 s)	120	108
INTEM test (100–240 s)	367	285
Time of thrombus formation		
EXTEM test (34–159 s)	57	113
INTEM test (30–110 s)	75	134
α angle		
EXTEM test (63–83)	78	71
INTEM test (70–83)	75	64
Maximum thrombus stability (50–72 mm)		
EXTEM test	68	55
INTEM test	61	50
Maximum thrombolysis (0–15%)		
EXTEM test	15	21
INTEM test	15	20

ferred to the Department of Cardiology on postoperative day 4. No thromboembolic complications were observed.

DISCUSSION

The management presented [4], which involved the transfusion of fresh frozen plasma to the patient with factor XII deficiency before the institution of extracorporeal circulation to interpret intraoperative ACT, was fully successful. The method prevented thrombotic complications in the postoperative period by affecting the fibrinolysis system, which is impaired in patients with factor XII deficiency. The supply of fresh frozen plasma corrects this disorder. Some other authors prefer to use heparin in the doses from 300 to 500 U kg^{-1} (comparable to those used in the present study) without referring to ACT measurements during extracorporeal circulation [1, 7].

Moreover, to provide safe and reliable control of blood coagulation during extracorporeal circulation, heparin levels are determined in blood and the thrombin time independent of clotting factors is measured after heparin administration, which is not prolonged in patients with factor XII deficiency [7]. According to some other authors, factor XII is not essential for coagulation but is relevant for fibrinolysis; hence, its deficiency impairs the production of plasmin from plasminogen, which can induce clotting of the implanted bypass grafts [8]. No such disturbances were observed in our patients.

The methods of management used in both cases were safe for the patients who were discharged after standard periods, did not require re-surgery and did not develop thrombotic complications manifested as perioperative infarctions or peripheral thrombosis in the early post-procedure period. In both patients, thoracic drainage on the surgery day was increased. The patient 2 required additional supply of packed red blood cells and plasma, which could have probably be avoided by using additional doses of protamine sulphate, tranexamic acid or even platelet preparations, which the results of thromboelastography performed after extracorporeal circulation suggested. However, this management was abandoned due to the risk of thrombophilia.

The difficulties in perioperative management of patients with factor XII deficiency scheduled for cardiac surgeries with extracorporeal circulation are associated with clotting monitoring as well as inapplicability of the patient's clinical state to the laboratory results. During the first stage before surgery, good blood clotting is accompanied by substantially prolonged APTT; after surgery, it is difficult to assess whether abnormal ACT or thromboelastography should be attributed to factor XII deficiency or real clotting disturbances. Another controversial issue is the mode of management when increased postoperative bleeding develops; should the clotting disturbances be intensively corrected or less aggressive measures taken, knowing that such patients are prone to thrombosis and accepting the excessive (above-standard) blood loss. Both options can be adopted; however, due to the irreversibility of thromboembolic complications (although most unlikely to develop), the majority of anaesthesiologists tend to choose the second method of management.

Based on our findings, it seems beneficial to control clotting parameters in patients with factor XII deficiency during the first 24–48 postoperative hours, particularly using thromboelastometry. Thanks to such an approach, optimal treatment can be instituted limiting the excessive coagulation. The supply of fresh frozen plasma is a safe and effective method of management in patients with factor XII deficiency enabling to perform surgery with extracorporeal circulation and routine ACT measurements.

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