Antiphospholipid syndrome in cardiac surgery—an underestimated coagulation disorder?*

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Received 6 October 2004; received in revised form 2 December 2004; accepted 29 December 2004; Available online 24 February 2005

Abstract

Objective: Antiphospholipid syndrome (APS) is a rare coagulation disorder associated with recurrent arterial and venous thrombotic events. We analysed our experience with five APS patients who underwent cardiac surgery. In three of them the diagnosis of APS had been established before surgery, two patients were diagnosed after surgery.

Methods: From March 1999 to March 2004 five patients with APS underwent cardiac surgery using cardiopulmonary bypass (CPB). We retrospectively reviewed their clinical data, operative and postoperative courses, and the long-term results.

Results: Procedures performed were heart and lung transplantation (patient 1), endoventriculoplasty and CABG (patient 2), biventricular resection of endoventricular fibrosis and thrombus (patient 3), mitral valve repair repair and coronary artery bypass grafting (CABG, patient 4), and mitral valve replacement with closure of a patent foramen ovale (patient 5). There were three perioperative deaths (patients 1, 2 and 3), two of three patients in whom the diagnosis was known before surgery, survived (patients 4 and 5). In these patients, only half the dose of protamin (patient 4) and no protamin at all (patient 5) was applied to reduce the probability of postoperative thromboembolic complications. At 1 year follow up, only patient 4 had survived, patient 5 had died of the complications of intestinal thromboembolism.

Conclusions: Patients with APS undergoing cardiac surgery belong to a high risk subgroup. Thus, though rare, APS can be a critical issue in cardiac surgery. Some of the cardiac patients with unexplained perioperative thromboembolic complications, such as graft occlusion, may turn out to have an undiagnosed APS.

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Keywords: Antiphospholipid syndrome; Coagulation disorder

1. Introduction

The antiphospholipid syndrome is defined clinically by recurrent arterial and venous thrombotic events as well as recurrent pregnancy loss and serologically by unequivocal positive testing for antiphospholipid antibodies (i.e. lupus anticoagulant and/or moderate to high titers of anticardiolipin antibodies). Originally described and most often found in patients with systemic lupus erythematoses (SLE), it has later been recognised, that also patients without signs of an underlying autoimmune disease may harbour antiphospholipid antibodies (aPL) and suffer from thromboembolic events, leading to the (more academic) distinction between primary and secondary APS [1].

Among young, apparently healthy control subjects, aPL are found with a prevalence of 1-5%, in SLE patients in up to 30% [2,3]. Many patients with infectious conditions (classically in syphilis) have laboratory evidence of aPL without clinical symptoms. Therefore, identification of patients with aPL who are at an increased risk of thromboembolic events is a critical issue. Important risk factors seem to be a past history of recurrent thrombosis, the presence of lupus anticoagulant and/or high levels of IgG anticardiolipin antibodies accompanied by antibodies against j2-glycoprotein-1 [4]. Venous thrombosis, especially deep venous thrombosis of the legs, is the most common manifestation, occurring in 29-55% of patients during an average follow-up of less than 6 years [4]. Arterial thromboses are less frequent with the brain being the most common site and strokes and transient ischemic attacks accounting for almost 50 percent of arterial manifestations [4]. Valvular heart disease (Libman-Sachs-Endocarditis) with a predilection for mitral valvular dysfunction is another clinical feature of APS [5]. Only few case reports have been published about APS in...
cardiac surgery [6-8]. Very recently, 10 cases of valve replacement, operated in a 13 year interval, were published, reporting a considerably increased mortality and morbidity in these patients [9].

In the present study, we report on four patients with primary and one patient with secondary APS. In two of the patients, APS was diagnosed post mortem, after ‘catastrophic’ thromboembolic events had occurred, raising the suspicion of a systemic coagulation disorder.

2. Material and methods

2.1. Patients

Of 5706 patients who underwent cardiac surgery using CPB at our institution from March 1999 to March 2004, five patients were diagnosed to have antiphospholipid syndrome (APS). All of these five patients fulfilled the classification criteria for definite APS [10]. Four of them were female, one was male. At the time of surgery, mean age was 55 years with a range from 28 to 78 years. The preoperative condition of the patients is shown in Table 1. In the two patients in whom APS was not known before surgery, the postoperative diagnosis was possible because serum samples of all patients undergoing surgery are preserved until 6 months after surgery. All five patients had antiphospholipid syndrome, three of them had been admitted with the established diagnosis of APS, in two of them the diagnosis was made postoperatively. As the clinical manifestation of APS, patient 3, besides the existence of left and right ventricular thromus, had a history of ischemic stroke. Patient 4 had consecutive unexplained complications of pregnancy and patient 5 had suffered from recurrent peripheral thromboembolism and from pulmonary embolism, the latter treated with streptokinase rescue therapy.

A follow-up inquiry was performed after 12 months in both patients surviving surgery.

2.2. Anesthesia and surgery

Anesthesia was induced with intravenous sufentanil (1 μg/kg), etomidate (50 μg/kg), and pancuronium (100 μg/kg). After endotracheal intubation, patients were mechanically ventilated with an end-expiratory pressure of 5 cmH2O. Inspired oxygen fraction was 0.5 and endtidal carbon-dioxide tension at 30–35 mmHg. Anesthesia was maintained with isoflurane (0.6-1.0%), discontinuously given sufentanil (0.3-0.5 μg/kg), and pancuronium (30 μg/kg). Lungs were mechanically ventilated with a tidal volume of 8 mL/kg with respiratory rate adjusted to obtain an end-expiratory carbon dioxide tension of 35-40 mmHg. A PaO2 of at least 200 mmHg was the target during bypass.

Half the dose of aprotinin (Trasylol®, Bayer, Leverkusen, Germany) defined by the Hammersmith protocol (reduced dose of 3 million KIU) was applied to every patient. All five patients were operated using cardiopulmonary bypass (CPB). After systemic heparinisation the target ACT was 400 s 5000 IU heparin (Ratiopharm, Ulm, Germany) and 2 million KIU aprotinin were added to the prime. Conventional CPB
roller pumps (Stöckert, Munich, Germany) and a disposable membrane oxygenator (Jostra, Hirrlingen, Germany) were used following priming with 1600 mL (1030 mL of lactated Ringer’s solution, 445 mL Hydroxy-Ethyl-Starch, 10%, 90 mL Mannitol and 35 mL Sodium Bicarbonate). During bypass, a positive end expiratory pressure of 5 cmH₂O was applied using an oxygen flow of 200 mL/min without phasic ventilation. With a systemic flow of 2.4 L/min/m² mean arterial pressure was adjusted to 60 mmHg by repetitive intravenous neosynephrine injections, if required. The patients were cooled (32 °C) and 1500 mL of cold Bretschneider cardioplegic solution (Custodiol K, Kohler Chemie, Alsbach-Hähnlein, Germany) were infused into the aortic root after cross clamping (except in the patient receiving a heart/lung transplant). The lowest hematocrit accepted was 18%, with packed red cells transfused, if necessary. After termination of bypass, blood remaining in the CPB circuit was retransfused.

2.3. Measurements

Cardiolipin antibody levels were determined in four different laboratories, each having its own reference level. This was due to the fact that in three of five patients the laboratory diagnosis of APS had already been established elsewhere. For better comparison, all individual cardiolipin antibody levels are given with their respective reference level. The determination of the intraoperative activated clotting time (ACT) was performed using a Hemochron 400 instrument (International Technidyne Corp, Edison NJ, USA). Before application of aprotinin, celite ACT was determined, after application of aprotinin, kaolin ACT was determined. For pressure measurements, a pulmonary artery catheter (7.5 F, Baxter, Irvine, CA, USA) was inserted via the right internal jugular vein through an introducer sheath (8.5 F, Arrow, Reading, MA, USA), in addition to a central venous catheter, and two large-bore peripheral intravenous catheters. Cardiac output (CO) was measured in triplicate by the thermodilution technique using 10 mL bolus of cold normal saline. Heart rate (ECG) and mean pressures in radial artery, superior caval vein, pulmonary artery, and in the pulmonary capillary wedge position were measured by electromanometry relative to barometric pressure and referenced to the mid-axillary line. Cardiac index (CI) and systemic vasular resistance index were calculated using standard formulae.

3. Results

Three perioperative deaths occurred. Patient 1 died 10 h after surgery on ICU in myocardial failure. During surgery, the extracorporeal circuit clotted leading to microembolisation in the patient’s periphery and the whole bypass circuit had to be replaced. After surgery, CPB could only be terminated using intra aortic balloon pumping (IABP), with high dose adrenaline (1.5 μg/kg/min) and an excessive noradrenaline dose (8.3 μg/kg/min) because of peripheral vasoplegia. Patient 2 died after 15 h on ICU in therapy refractory myocardial failure. After an initial uneventful operative course, 3 h after arrival on ICU, the dosage of adrenaline had to be increased significantly (1.5 μg/kg/min) to maintain a mean systolic blood pressure of 50 mmHg. An IABP was installed and an emergency coronary angiography showed that three of four distal anastomoses were occluded. Rescue stenting and dilatation were performed but the patient died in myocardial failure. At autopsy, thrombotic graft occlusion was found. Patient 3 was the first patient with known APS. She was extremely compromised before the operation and surgery was looked upon as a last chance maneuver. With improving left and right ventricular function (as controlled by transesophageal echocardiography), the postoperative dosage of catecholamines could be reduced. The patient was free from catecholamines on the fifth postoperative day and an IABP, placed intraoperatively, could be removed. The patient was on plasmapheresis because of the known APS. However, 6 days after surgery, she suffered from recurrent arterial thromboembolic events in both the upper and lower extremities. Meanwhile, floating structures on the aortic valve, presumably thrombotic, could be detected in transesophageal echocardiography and hemodynamic instability recurred. The patient died 10 days after surgery from left and right myocardial failure.

Two patients had an uneventful postoperative recovery. In both patients, a modified protamin strategy was applied. Patient 4 received half the dose of protamin to intraoperatively reverse heparin, patient 5 received no protamine at all.

Further intraoperative patient data are shown in Table 2. Additional protamin was given in patient 1, because more than twice the usual dose of heparin had been applied after thrombotic occlusion of the extracorporeal circuit. In all patients, anticoagulant treatment with low dose heparin was started within 2 h after arrival on ICU. In addition, patients 2 and 5 received 500 mg intravenous acetylsalicylic acid within 4 h after arrival on ICU, which is part of our standard regimen in CABG patients. Postoperative data are given in Table 3. Blood loss was increased in patient 5 who did not receive any protamin to reverse intraoperative heparin.

At 1 year follow-up, only patient 4 was alive and well. Patient 5 had died of the complications of intestinal thromboembolism 8 months after cardiac surgery.

4. Comment

Any experienced cardiac surgeon has encountered cases with sudden thrombotic occlusion of coronary bypass grafts either on the operating table or in the early postoperative period, despite a normalized coagulatory state and the conviction that surgery was technically adequate. In many cases, the routine intraoperative application of Doppler transit time determination of bypass graft flow, gives the surgeon some additional certainty concerning graft function.

Aprotinin has been suspected to be a causative agent for such events but has never been identified in clinical observational studies to cause overcoagulation, thus leaving other possibilities such as kinking of bypass grafts by displacement of emphysematous lungs. However, systemic coagulation disorders could also be an explanation for
a sudden thrombotic event, which prompted us to scrutinize cases of unexplained bypass occlusion for additional coagulation disorders incorporating tests for APS.

The cardiac surgical experience with APS patients relies on case reports describing one or two patients. A very recent publication described an increased morbidity and mortality in a group of 10 patients with APS undergoing valve replacement [9]. In all 10 patients, the diagnosis of APS had already been established at the time of surgery.

In the present study we report on our experience with five patients with antiphospholipid syndrome undergoing cardiac surgery. In two patients the diagnosis of APS was established after surgery and post mortem after the occurrence of ‘catastrophic’ thromboembolic events. Indeed, this is the first study to report the experience with cardiac surgical patients in whom the diagnosis of APS had not been known before surgery. In the other three APS patients reported here, the diagnosis had already been known on admission. Two of the latter had an uneventful perioperative course, one died after multiple thromboembolic events 10 days after surgery.

The prevalence of antiphospholipid antibodies in the normal population has been reported to be up to 2% in patients with a mean age of 39 years. In patients over 65 years of age, it has been reported to be as high as 12% [11]. For the definite diagnosis of an APS, however, clinical symptoms and laboratory features have to be present, as defined by a recent consensus statement [10]. Some patients have laboratory evidence of antiphospholipid antibodies without clinical consequences. For otherwise healthy control subjects, there are insufficient data to determine what percentage of those with antiphospholipid antibodies will eventually develop a thrombotic event or a complication of pregnancy consistent with the antiphospholipid syndrome [4]. In order to preoperatively identify patients with a yet undiagnosed APS, a history of unexplained thromboembolic events or complications during pregnancy is of great importance. Such patients may turn out to have an APS which seems to increase the perioperative risk dramatically as surgery itself together with withdrawal of anticoagulant therapy were reported to be precipitating factors for the occurrence of catastrophic events [4]. Catastrophic events in the context of APS are a well known, rare, but often fatal form of APS, leading to death in 50% of these cases [12]. We therefore changed our strategy to apply protamin to these patients in the last two of our APS patients with patient 4 receiving half the dose and patient 5 receiving no protamin at all to reverse intraoperative heparin. Patient 3, who had known APS, suffered from a catastrophic event 6 days after surgery inspite anticoagulant treatment plus corticosteroids and plasmapheresis, the combination of which has been reported to be successful in the treatment of the catastrophic APS [12].

### 4.1. Critical discussion of perioperative treatment

Patients 1 and 2 did not survive long enough to receive APS specific treatment. In the case of a catastrophic event, a combination of anticoagulants and steroids plus either plasmapheresis or intravenous immunoglobulin has been reported to lead to acceptable recovery [4]. Anticoagulants, steroids and plasmapheresis were applied to patient 3. Nevertheless, she developed more thrombo-embolic events.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Procedure</th>
<th>CPB time (min)</th>
<th>X-clamp time (min)</th>
<th>Reperfusion time (min)</th>
<th>ACT presurgery (s)</th>
<th>ACT max during CPB (s)</th>
<th>ACT min during CPB (s)</th>
<th>ACT postsurgery (s)</th>
<th>Protamin</th>
<th>Additional protamin</th>
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<tbody>
<tr>
<td>1</td>
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<td>135</td>
<td>49</td>
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<td>98</td>
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<td>550</td>
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<td>193</td>
<td>159</td>
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<td>129</td>
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<td>874</td>
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<td>None</td>
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<td>183</td>
<td>199</td>
<td>150</td>
<td>250</td>
<td>159</td>
<td>265</td>
<td>874</td>
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<tr>
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<td>107</td>
<td>16</td>
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<td>86</td>
<td>16</td>
<td>65</td>
<td>65</td>
<td>65</td>
<td>250</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Values in absolute numbers. HLTX, Heart and lung transplantation; CABG, coronary artery bypass graft; Dor, endoventriculoplasty; Thrombectomy, resection of fibrosis and biventricular thrombus; MVR, mitral valve replacement; PFO, occlusion of patent foramen oval; MVP, mitral valve plasty; CPB, cardiopulmonary bypass; X-clamp time, aortic cross clamp time; UI, international units; ACT, activated clotting time.
and did not survive. In the subsequent patient with known APS, only half the dose of protamin was given to intraoperatively reverse heparin (patient 4). Although postoperative ACT levels were increased, this regimen did not lead to increased postoperative blood loss. In the next patient, no protamin at all was given to reverse intraoperative heparin (patient 5). This patient had an increased postoperative blood loss, which had to be treated by transfusion of packed erythrocytes. If a bleeding tendency is not observed in the perioperative period of these patients with an increased risk of thromboembolism, a reduced protamin dose, early institution of antiplatelet therapy and anticoagulant treatment should thus be considered. The experience with inhibitors of fibrinolysis such as aprotinin in this setting is sparse. E-aminocapronic acid has been applied to patients with APS [8], but it may well be argued that any potentially procoagulant activity should be avoided in patients with APS.

In conclusion, when the diagnosis of APS is not known before surgery and a catastrophic perioperative event occurs, the chance for patient survival appears to be very low. However, even when the diagnosis is established, postoperative thromboembolic events can be devastating. A restrictive strategy of protamin application seems to be advisable in cases of known APS. An exchange of experience with sudden onset overcoagulatory disorders in cardiac surgery should be initiated under special consideration of a possibly underestimated APS.

Acknowledgements

The authors acknowledge the excellent laboratory work by Ms Kaiser and colleagues, as well as the dedicated work of the perfusionists Mr Schmidt, Mr Wiese, Mr von Manstein, Mr Deus, Mr Schön and Mr Graban.

References