Massive Intravascular Thrombosis and Thromboembolism after Cardiopulmonary Bypass
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Citation

Abstract
This report describes two patients who underwent cardiac surgery utilizing cardiopulmonary bypass (CPB). Both patients were fully heparinized during the bypass period; however, both of them developed massive intravascular thrombosis and thromboembolism after initiation of heparin reversal with protamine. The surgeries were prolonged extensive procedures but and heparinization was carefully monitored throughout. The potential etiologies of this devastating, and very rare occurrence are explored.
A less severe similar complication has been reported on one occasion previously from this institution. It is of interest that both patients described in these reports received prophylactic antifibrinolytic therapy, as did the patient in the previous earlier case report. The safety of administrating prophylactic antifibrinolytic therapy given routinely to patients undergoing on-pump cardiac surgery is examined.

ATTRIBUTE WORK TO
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CASE REPORTS
CASE 1
A 50-yr-old 43 kg woman, noted as cyanotic at birth, was diagnosed with congenital heart disease at age 6 months. A cardiac catheterization performed at age 4 years was interpreted as showing a Fallot tetralogy. She underwent a left thoracotomy for a planned Blalock-Taussig shunt. However, a transposition of great vessels was noted and the procedure was aborted. A repeat cardiac catheterization revealed a univentricular heart with a hyperplastic right ventricle, left transposition, ventricular septal defect and an atrial septal defect, resulting in a double inlet left ventricle. This condition was felt to be inoperable. A catheterization performed 20 years later confirmed the Eisenmenger Syndrome diagnosis.

At age 40 years, she became disabled because of increasing shortness of breath. A re-evaluation was performed, and pulmonary hypertension was noted. The pulmonary artery pressure was 112/40 mmHg with a pulmonary vascular resistance of 1200 dyne·sec·cm⁻⁵ and a right atrial pressure of 7 mmHg. Cardiac output measured 3.6 L/min with a cardiac index of 2.5 L/min/m². Systemic pressure was 108/65 mmHg; oxygen saturation was 68%. She was prescribed oxygen therapy. Two years before admission, the patient was noted to have developed atrial fibrillation and administered warfarin. An echocardiogram confirmed a univentricular heart with a double-inlet left ventricle, levo-transposition and hyperplastic right ventricle.

The patient was considered for combined heart and lung transplant and admitted for the procedure at age 50 years. On admission, she was taking digoxin 0.25 mg, aspirin 81 mg, fluoxetine 20 mg, and levothyroxine 0.25 mg daily, enalapril 10 mg bid, and warfarin 2.5 mg on alternate days. Notable laboratory values were a hematocrit of 58%, a prothrombin time of 21 seconds (INR 2.1) and a platelet count of 205,000/mm³. The warfarin was discontinued 3 days before the surgery.

At surgery, a left brachial artery catheter was inserted, and a right internal jugular vein pulmonary artery catheter was placed so the tip was in the superior vena cava and could be advanced into position after the new graft implantation.
Anesthesia was induced with midazolam, fentanyl and vecuronium, and the trachea intubated. A full-dose Hammersmith regimen of aprotinin (2 x 10^6 KIU loading dose, 2 x 10^6 KIU into the CPB circuit and 5 x 10^5 KIU/h infusion during the procedure) was administered after a test dose. A transesophageal echocardiograph (TEE) probe was carefully inserted; cardiac function was continuously monitored.

A bilateral trans-sternal anterior thoracotomy was performed; both sides of the chest were entered through the fourth intercostal space. The initial activated clotting time (ACT) using a kaolin tube was 165 seconds. After the administration of porcine heparin (400 U/kg), the ACT was recorded as > 1000 seconds. Hydrocortisone 1 gm was given intravenously before bypass. The aorta, superior and inferior vena cavae were cannulated, CPB instigated and the patient cooled to 28°C. Additional heparin was administered to maintain an ACT of > 1000 seconds, measured every 30 minutes throughout bypass. The heart and lungs were excised and the donor heart and lungs placed in the mediastinum. After all anastomoses were completed, reperfusion occurred, and the heart was de-aired under TEE surveillance. Four units of banked red cells were added to the pump to maintain a hematocrit in the range of 24% to 35%. On bypass platelet counts ranged from 65,000/mm³ to 83,000/mm³.

When rewarming was completed, the patient was transitioned off CPB without difficulty receiving low-dose inotropic support with dobutamine 5 µg/kg/min-1. Hemodynamics were excellent with systemic blood pressure of 100/60 mmHg, pulmonary artery pressure of 25/12 mmHg, cardiac output of 5.6 L/min, cardiac index of 4.1 L/min/m² and mixed venous oxygen saturation of 75%. After 30 min of hemodynamic stability, heparin reversal began with protamine. Approximately half way through protamine infusion, a large embolus was noted to pass rapidly through the right ventricle into the pulmonary artery. A sudden increase in pulmonary artery pressure, right ventricular failure and profound systemic hypotension occurred. The inferior vena caval cannula was still in place. The patient was reheparinized, but initial attempts to return to bypass were unsuccessful because of poor venous return through the inferior caval cannula, which was previously satisfactory. The superior vena caval cannula was, therefore, reinserted and directed inferiorly toward the right atrium, which permitted satisfactory CPB. The inferior cannula was removed, and a long thrombus was extracted from the cannula and the right heart.

After arresting the heart for one hour, bypass weaning was attempted unsuccessfully because of the recurrence of right heart failure and pulmonary hypertension. A right-ventricular assist device was placed without difficulty, and flow rates of > 4 L/min (index of 2.7 l/min/m²) were achieved. The patient could then be extracted from CPB but with significant inotropic support.

Following 30 min of hemodynamic stability, heparin reversal began with protamine. After approximately half the protamine dose administration, the patient became acutely hypotensive. Heparinization was reinstituted, anticipating return to CPB. However, this was impossible because both venous canulas and the complete right ventricular assist device contained blood clot. The heart arrested and would not resuscitate.

**CASE 2**

A 56-yr-old 39 kg woman developed rheumatic heart disease as a child and underwent a mitral valve commissurotomy at age 30 years. She developed chronic atrial fibrillation and sustained a cerebral embolism resulting in a left hemiparesis. She eventually developed severe restenosis of her mitral valve, aortic valvular stenosis and tricuspid valve regurgitation. She was admitted for mitral and aortic valve replacements and possible tricuspid valve repair.

On admission, she was taking daily warfarin 1 mg, levothyroxine 0.05 mg, digoxin 0.0625 mg and metaprolol 25 mg. Notable laboratory values were prothrombin time 15.5 seconds (INR 1.5), hematocrit 31.3% and serum creatinine of 1.8 mg/dL.

At surgery, radial artery and pulmonary artery catheters were placed. Induction was with etomidate, fentanyl, midazolam and rocuronium and maintained with the inhalation of air, oxygen, isoflurane and supplemental fentanyl. A half-dose Hammersmith aprotinin regimen (1 x 10^6 KIU loading dose, 1 x 10^6 KIU into the CPB circuit prime and 2.5 x 10^5 KIU infusion during the procedure) was administered after a test dose. Cardiac function was monitored continually by TEE.

The heart was approached via a median sternotomy incision. Initial ACT (kaolin) was 159 seconds. Porcine heparin 400 IU/kg was administered, and the repeat ACT was >1000 seconds. Hydrocortisone 100 mg was administered.
intravenously just before initiating bypass. After initiation of CPB the patient was cooled to 25°C. A large clot was found and removed from the left atrium and atrial appendage. The mitral and aortic valves were replaced; the heart de-aired and reper fused. Heparinization was maintained throughout the 3 h 23 min CPB to maintain an ACT of > 1000 seconds. The hematocrit, measured approximately every 15 min, ranged from 14% to 27%.

Five units of packed red cells were added to the venous reservoir of the CPB circuit. The platelet counts ranged from 41,000/mm³ to 58,000/mm³ during the bypass.

The patient was transitioned from CPB with the assistance of an epinephrine infusion 0.1 μg/kg/min-1 and atrioventricular pacing. Good left ventricular function was noted and heparin reversal was commenced with protamine 1.3- mg/100 IU heparin. After one-quarter of the protamine dose had been administered, the blood pressure recording from the radial artery catheter was lost (later found to be clotted), despite what appeared to be good aortic blood pressure and heart action. Re-heparinization and return to CPB was attempted but prevented by the presence of large amounts of blood clot. The femoral artery was cannulated to obtain a blood pressure recording and found totally clotted, with the clot extending into the aorta. The patient also sustained a massive pulmonary embolus. Despite all efforts at declotting and thrombectomizing the blood vessels, the patient succumbed with biventricular failure.

**DISCUSSION**

Thrombosis, arterial or venous, is the most common cause of death in the United States, with about 2 million deaths per year attributable to such conditions as myocardial infarction, pulmonary embolism and cerebrovascular thrombosis. Hemostasis is the result of the fine balance between the enzyme-driven coagulation cascade and the opposing fibrinolytic system. Tilting that balance to profound coagulation is a concern when antifibrinolytic drugs are utilized, but the routine use of antifibrinolytic agents has not been shown to be associated with a procoagulant effect, has been demonstrated in patients undergoing liver transplantation.22

This report describes the development of severe hypercoagulation in two patients who received full- and half-dose aprotinin, respectively. The other common factors between the patients are that both received intraoperative corticosteroids possibly inhibiting fibrinolysis and both were taking warfarin and levothyroxine. Warfarin has been reported to deplete protein C levels, potentially causing a hypercoaguable state.23

The paucity of reports of thromboembolism associated with the use of antifibrinolytic agents raises the question of whether these patients had unique predisposing factors for developing or acquiring a hypercoaguable state. Rudolph Virchow identified over a century ago the three factors responsible for vascular thrombosis: vessel injury, alterations in blood flow and the coagulation state. These conditions exist after CPB but rarely lead to pathological thrombosis. The risks of thrombotic complications associated with vascular beds and polymorphism have been well described.24 These reports raise the question that the clinician should consider that individual patients may have an increased risk for developing a hypercoaguable state because of inherited or acquired defects that predisposes them to clot if coagulation is weighted in one direction by using antifibrinolitics.

Inherited hypercoaguability defects include activated protein C resistance (factor V Leiden), protein S deficiency, protein C deficiency, antithrombin 3 deficiency, hyperhomocysteinemia, prothrombin 20210A allele, dysplasminogenemia, increased plasminogen activator inhibitor, dysfibrinogenemia and elevated factor VII-25. Activated protein C resistance is the commonest defect found in patients having venous thromboembolism.26 The molecular basis for this resistance is a single-point mutation in the gene encoding for factor V. This mutation produces factor V Leiden, which is less effectively downgraded by activated protein C than normal factor V. However aprotinin has so far not been shown to be associated with a hypercoaguable state in patients with any of these defects.27,28 Platelets play a key role in the coagulation process; and genetic variations may occur, creating platelet receptor polymorphisms. Platelet glycoprotein 1b alpha is a
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major receptor for von Willebrand factor and thrombin, which initiates development of thrombus. Polymorphisms affecting the phenotype have been described.35,36

Acquired defects causing hypercoagulability include antiphospholipid syndrome, hyperhomocysteinemia, heparin-induced thrombocytopenia, thrombocytuthemia, dysproteinemia and estrogen ingestion. All of these described defects may increase the intravascular thrombosis risk.37,38,39

The patients in these two case reports had devastating outcomes that are extremely rare. However they raise a concern that individual variations occur in the hemostasis cascade, and that caution should be used in decisions to routinely administer antifibrinolytic agents during on-pump cardiac surgery. Screening tests for activated protein C resistance are now readily available and could be considered if there is any suspicion that a hypercoaguable state might exist. The routine use of the Thrombelastograph® (Haemoscope Corp., Skokie, IL.) as an adjunct to monitoring the integrity of the coagulation system during CPB may be another means of detecting rare abnormalities to the clotting mechanism.35,36

References

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