

Disseminated intravascular and intracardiac thrombosis after cardiopulmonary bypass

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Abstract

Massive intracardiac and intravascular thrombosis is a rare complication following cardiopulmonary bypass (CPB). Most of the cases of the disseminated thrombosis have been reported in patients undergoing complex cardiac surgeries and those receiving antifibrinolytic agents during CPB. We report the occurrence of disseminated intravascular and intracardiac thrombosis after CPB in a patient undergoing mitral valve replacement in which no antifibrinolytic agent was used. The possible pathophysiology and management of the patient is discussed.

Key words: Cardiopulmonary bypass, intracardiac, intravascular, protamine, thrombosis, thrombosis

Introduction

Massive intravascular and intracardiac thrombosis after separation from cardiopulmonary bypass (CPB) is a very rare, but dreaded complication.^[1] Preexisting thromboembolic diseases or acquired coagulation disorders (related to antifibrinolytic therapy) have been associated with this unusual life-threatening complication.^[2-5]

We report the occurrence of severe acute massive intracardiac and intravascular thrombosis during the immediate post-CPB period in a patient who underwent emergency mitral valve replacement (MVR).

Case Report

A 35-year-old male presented for emergency MVR for severe mitral stenosis with atrial fibrillation (AF) and acute

heart failure. He was receiving erythromycin, digoxin, furosemide, spironolactone, and warfarin therapy. Preoperative transthoracic echocardiography (TTE) showed severely calcific and stenosed MV with an area of 0.9 cm² in two-dimensional echocardiography and 0.6 cm² using pressure half time, and the peak and mean pressure gradients of 11 and 7 mmHg, respectively. Associated findings included mild mitral regurgitation, presence of left atrial (LA) spontaneous echo contrast, right ventricular systolic pressure of 30 mmHg + right atrial pressure, and an ejection fraction of 60% with no regional wall motion abnormality at rest. The LA diameter was 5.9 cm and the aortic diameter was 3.2 cm. Preoperative laboratory investigations were within normal limits, except elevated serum glutamic-pyruvic transaminase (152 U/L) levels. Preoperative international normalized ratio was 1.5. There was no preexisting history suggestive of deep vein thrombosis and drug allergy. Family history was insignificant for stroke, deep vein thrombosis or pulmonary embolism.

The preoperative evaluation revealed a cachectic appearance (weight - 48 kg, height - 170 cm), irregular pulse with heart rate 102 beats/min, blood pressure (BP) 96/60 mmHg, raised jugular venous pressure, bilateral crepitations in both the lung fields, muffled S1 and a mid-diastolic murmur (grade III/IV) at the cardiac apex area. Warfarin therapy was discontinued. In the operating room standard monitoring was applied, 0.9% saline infusion started and right radial artery cannulation performed. The patient was preoxygenated in semirecumbent position and furosemide 20 mg was administered IV. Arterial blood gas (ABG) analysis revealed metabolic acidosis with a pH of 7.22 and HCO₃ of 16 mmol/l, Na 117 mmol/l, PO₂

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298 mmHg and PCO₂ 40 mmHg. Sodium bicarbonate 50 mEq was administered IV. General anesthesia was induced with fentanyl 500 µg and thiopentone 50 mg, and rocuronium 60 mg was administered to facilitate tracheal intubation with a cuffed orotracheal tube of size 9. Soon after induction, BP decreased to 60/40 mmHg and adrenaline infusion was started, which was titrated up to 0.13 µg/kg/min to maintain systolic BP of 90 mmHg. Right internal jugular vein cannulation revealed a central venous pressure (CVP) of 18 mmHg. Adrenaline infusion was then administered through the central line. Intraoperative transesophageal echocardiography (TEE) confirmed the preoperative TTE findings of a severely thickened and calcified MV with a valve area of 0.6 cm² and the presence of spontaneous echo contrast in LA [Figure 1].

Standard CPB techniques with crystalloid prime and mild hypothermia (32°C) were used. Heparin was used as an anticoagulant in the dose of 300 IU/kg and half the initial dose was repeated at hourly intervals with a target activated clotting time (ACT) of >450 s. A large thrombus was found on opening the LA and was evacuated. The patient underwent MVR with a 33 mm prosthetic valve (Medtronic ATS Medical, Inc., Minneapolis, USA). The heart was de-aired, and the aortic cross clamp was released (clamp time 56 min). Valve prosthesis function was found to be normal on TEE and no apparent thrombus was observed in any heart chamber [Figure 2]. Two units packed cell volume (PCV) were administered through the CPB pump. The patient was separated from CPB after a bypass time of 90 min on inotropic support with epinephrine 0.1 µg/kg/min, dopamine 5 µg/kg/min and nitroglycerin 1 µg/kg/min with BP 85/45 mmHg and CVP 7 cm H₂O.

After separation from CPB, the patient was bleeding from suture lines and there was generalized ooze. It was decided

to administer test dose of 20 mg protamine. Heparin reversal was commenced at a BP of 96/52 mmHg and a CVP of 7 mmHg. Soon after administration (1 min), the BP fell to 60/38 mmHg while the CVP was 6 cm H₂O. Protamine administration was stopped immediately. The surgeons were having difficulty in maintaining hemostasis, and there was continuous oozing on closure of LA and the aortic cannulation site. The heart was now visibly empty and fresh ABG revealed a hematocrit of 15%. Two units PCV were transfused. Still it was difficult to achieve hemostasis and BP decreased to 40/20 mmHg and could not be increased despite increasing inotropic support. Suspecting hemodilution and resultant deficiencies to be the cause of continuous oozing from the surgical field and hypotension; fresh frozen plasma (FFP), platelet concentrate, and PCV transfusion was considered. Protamine was re-started in consultation with the surgeon in slow, small aliquots of 10 mg to control microvascular bleeding. Administration of three aliquots of 10 mg protamine over next 10 min did not improve hemostasis, and further protamine administration was restricted in the absence of any positive effects.

Within 2-3 min of the last dose of protamine (40-45 min from its first dose), ST segment elevation was observed on electrocardiography and pulmonary artery could be felt tense. Milrinone infusion was started and the patient was transfused with two more units of fresh PCV and FFP. In view of failure to achieve an increase in BP and persistence of ST segment elevation, a decision was taken to insert an intra-aortic balloon pump and perform the TEE. TEE revealed thrombi in all the chambers of the heart and aortic root [Figure 3]. The surgeon could not palpate the femoral pulses bilaterally. Surgical exploration of the femoral arteries on both sides revealed thrombus. Visual monitoring of the CPB circuitry did not reveal any evidence of thrombosis or red blood cells agglutination at any time. The patient was immediately put on CPB after full heparinization. ACT at this time was >999 s and the opening of LA and right atrium revealed adherent fresh thrombi. The thrombi were extracted. Thrombus in coronaries could also be observed. Despite thrombi removal and high inotropic support, the ST segment elevation persisted, and the mean arterial pressure

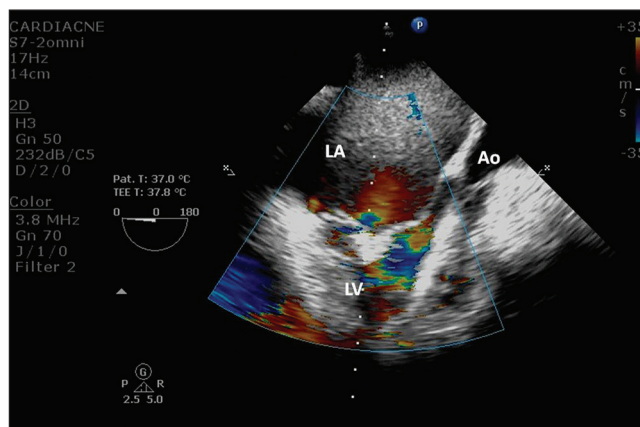


Figure 1: Midesophageal long-axis view showing thickened and calcified mitral valve with smoke in left atrium and turbulent flow across the valve (LA: Left atrium, LV: Left ventricle, Ao: Aorta)

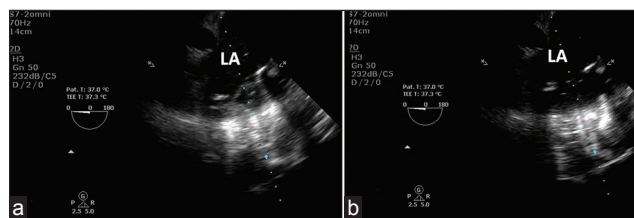


Figure 2: Modified midesophageal four-chamber view showing normal functioning bileaflet prosthetic valve *in situ* in closed (a) and open (b) position. Note the absence of thrombus in left atrium

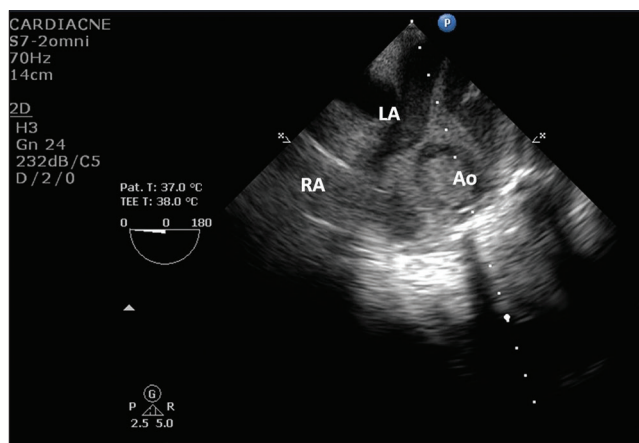


Figure 3: Modified aortic valve short-axis view showing thrombus in left atrium, aorta and right atrium

could not be achieved above 30-40 mmHg. The patient could not be revived and died after a futile attempt of prolonged resuscitation due to low cardiac output syndrome.

Discussion

The present case showed fatal generalized intravascular and intracardiac thrombosis after CPB. CPB induces a systemic inflammatory response characterized by activation of the inflammatory, complement, coagulation and fibrinolytic pathways^[2,6] but it rarely leads to pathological thrombosis. The development of new thrombus during or following CPB may be a result of inherited or acquired coagulation defects, which increase the risk of developing a hypercoagulable state.^[2-8]

The reports of thrombosis and circulatory collapse associated with protamine reversal of heparin anticoagulation have been observed in patients undergoing complex cardiac surgeries for heart transplantation or mixed aortic and MV surgery and who had received aprotinin anticoagulation.^[5,7] The common features between the present case and these were the preoperative presence of congestive heart failure (CHF), AF, preoperative warfarin use, PCV transfusion before clot formation, formation of thrombi despite an on bypass ACT of >999 s on standard heparinization and high patient mortality. Thrombi formation in majority of these patients was observed after full dose administration of protamine, except two cases reported by Ramsey *et al.* where it was observed after quarter to half dose of protamine.^[7] Protamine administration was withheld initially in the present case considering a reaction, however, the persistent ooze and unstable hemodynamics despite transfusion led us to re-administer small aliquots of protamine in consultation with surgeon to control microvascular bleed. Also there was no evidence of decreased venous return or thrombosis in the circuit/peripheral catheters unlike previous reports,^[7] after

initial 20 mg of protamine. The aortic and radial pressures were also found to be similar when hypotension occurred.

In the present case, no antifibrinolytic medicines were administered and the patient had no known coagulation disorder. The patient was on warfarin therapy till the day of surgery. Warfarin has been reported to deplete protein C levels, potentially causing a hypercoagulable state.^[7] The postmortem evaluation for antithrombin deficiency, protein C and S deficiency, factor V Leiden, antiphospholipid and cardiolipin antibodies, heparin induced platelet activation assay could not be performed due to lack of testing facilities. The massive and diffuse thrombosis involving the systemic vessels, the cardiac chambers and coronaries along with circulatory collapse during administration of small doses of protamine in the absence of antifibrinolytic medication and elevated baseline ACT has not been documented before. Although highly probable, systemic organ involvement could not be ascertained as the relatives refused for postmortem.

In the present case, the pathophysiology of the hypercoagulable state is complex and probably multifactorial. The precipitating factors could be preoperative CHF,^[5] preoperative use of warfarin, perioperative hemodilution and antithrombin III consumption induced by CPB with the potential for acquired antithrombin deficiency,^[5] a postprotamine state with loss of heparin anticoagulant effect, perioperative blood product transfusion or any undiagnosed congenital defect. Undiagnosed platelet dysfunction, intraoperative heparin use, protein denaturation by CPB, inflammatory mediator release and hyperfibrinolysis during cardiac surgery has been attributed to intraoperative and postoperative bleeding during cardiac surgery.^[5] Although, cardiac surgery may be associated with an initial hypocoagulable state, hypercoagulability might be manifested later in the postoperative period.^[5] Delay in identification of initial thrombus formation leading to massive thrombosis is another possibility.

Patients with CHF require careful perioperative monitoring to identify any potential hazards. Despite adequate heparinization and more than desired kaolin ACT values, thrombosis has been observed.^[5] Such patients usually present in an emergency and the time for evaluation of antiphospholipid syndrome, factor V Leiden, protein C and S deficiency may not be there. Low cardiac output may cause acute renal and hepatic dysfunction though the preoperative laboratory values may be normal. This will impair endogenous anticoagulant synthesis on one hand from hepatic dysfunction and impair clearance of activated procoagulants on the other hand from renal dysfunction.^[5] Although, thromboelastography has been suggested to evaluate the coagulation states in such cases,^[7] its limited availability may be a hindering

factor. Moreover, hypocoagulable state has been observed on thromboelastography even in the event of new thrombus formation in LA.^[9] Facilities for antithrombin III levels if available may be helpful in these cases.^[5]

The authors believe that careful protamine administration guided by early intraoperative TEE and vigilance on the part of anesthetic and surgical team whenever there is an unexplained and persistent hemodynamic instability/excessive bleeding after weaning from CPB, even when preweaning TEE is absolutely normal, can prove to be beneficial in identifying unexpected thrombosis and prompt institution of therapeutic measures. The authors support the view of reporting such cases^[5] and formulation of an international registry^[10] to estimate the continuing incidence of this rare, but catastrophic complication. This would provide sufficient data to identify risk factors for such thrombosis so as to have a high degree of suspicion in at-risk patients and avoid any morbidity and mortality.

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