

Case Reports

Use of Aprotinin During Cardiopulmonary Bypass in a Patient with Protein C Deficiency

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Abstract: This case study reviews cardiopulmonary bypass (CPB) management in a Protein C deficient patient undergoing reoperation for an atrioventricular (AV) valve replacement with the use of aprotinin. Protein C inhibits factors Va and VIIIa in the coagulation cascade and inactivates tissue plasminogen activator inhibitor, thus maintaining hemostasis. Protein C deficiency can cause hypercoagulability and may result in thrombotic episodes, especially in areas of low blood flow or during activation of the coagulation cascade. A 17-year-old male presented with a functional single ventricle and AV valve regurgitation. The patient had a history of three previous AV valve replacements. Protein C deficiency was first diagnosed after thrombosis of the first valve prosthesis. Other case studies in protein C deficient patients suggested the use of fresh frozen plasma (FFP) before bypass to restore protein C levels, ATIII replacement before heparin administration, and avoidance of aprotinin because of its known competitive inhibition of activated protein C. Two units of FFP were given by anesthesia before the adminis-

tration of aprotinin, and two units of FFP were added to the pump prime. The full Hammersmith loading dose of aprotinin was administered just before initiation of CPB. The same dose of aprotinin was added to the pump prime just before initiation of CPB. Additional heparin (100 U/kg) was administered every hour during bypass. Activated clotting time tests (ACTs) were performed every 15 min, and thromboelastographs (TEGs) were performed every hour. The patient recovered from surgery without major complications, and there were no perioperative thrombotic events. The patient was discharged on day 41 and is doing well. Postoperative atrial arrhythmias were a contributing factor to his delayed discharge. The use of aprotinin in a protein C deficient patient undergoing open-heart surgery may be safe if protein C levels are restored before administration of aprotinin, and anticoagulation is carefully monitored. **Keywords:** protein C, protein C deficiency, aprotinin, trasyolol, cardiopulmonary bypass. *JECT. 2003;35:39–43*

Protein C is a naturally occurring anticoagulant in the blood. Protein C is a vitamin K- dependent plasma protein that is synthesized in the liver and circulates in the plasma at a concentration of 3–5 mg/L. The presence of protein C helps to maintain hemostasis by inhibiting thrombotic episodes. Protein C becomes activated on the endothelial cell surface by the thrombin–thrombomodulin complex. Activated protein C then binds with protein S. This complex inhibits factors Va and VIIIa in the coagulation cascade. In addition, the activated protein–C–protein S complex is

responsible for the neutralization of tissue plasminogen activator (t-PA) inhibitor (Figures 1,2). Normal levels of protein C are 70–150% activity. Clinical signs of deficiency occur when levels fall below 55% activity.

A deficiency of protein C can cause hypercoagulability and may cause episodes of venous thrombosis (1). High-risk procedures, such as open-heart surgery, may increase the risk of hypercoagulability in patients with protein C deficiency.

Protein C deficiency can be either acquired or inherited. Acquired protein C deficiency can result from factors that decrease their production, such as liver disease, vitamin K deficiency, warfarin therapy, chemotherapy, disseminated intravascular coagulation (DIC), or Factor V Leiden (a mutation of protein C) (2). Inherited protein C deficiency is a rare autosomal dominant genetic disorder affecting

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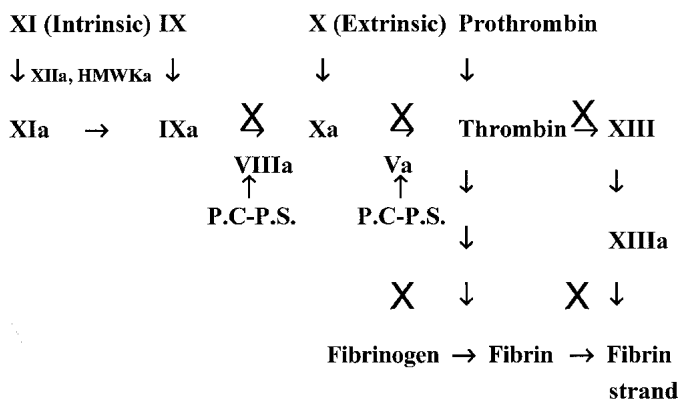


Figure 1. Effect of PC–PS complex on the coagulation cascade.

approximately 0.2% of the general population. There are two types of protein C deficiency. Type I is a quantitative deficiency, resulting in low levels of protein C that function normally. Type II is a qualitative deficiency, where the patient has normal levels of protein C, but the protein C molecule is defective and, therefore, unable to interact with other molecules in the coagulation cascade. Patients that are homozygous for protein C deficiency often present at birth with severe venous thrombosis causing clots throughout much of the body, often resulting in death. This condition is known as *neonatal purpura fulminans* (3). These patients often have protein C levels in the range of <1% activity (4). Heterozygous patients often have protein C levels below 55% activity. Heterozygous patients are often asymptomatic and require additional risk factors to provoke thrombosis.

Risks increase if the production of protein C decreases. This can occur because of low levels of vitamin K, protein S, warfarin therapy, pregnancy, or hepatic or renal disease (1). In addition, chances of thrombosis increase in areas of stagnant blood, such as that seen in patients with valvular insufficiency.

Treatment of protein C deficiency is usually not advised until symptoms occur or when a protein C deficient patient undergoes a high-risk procedure. Symptomatic patients should be anticoagulated with heparin and then given long-term anticoagulation with a vitamin K antagonist, such as warfarin, to avoid further embolic events (1).

Clinicians must take special precautions when treating the protein C deficient patient perioperatively to avoid thrombosis. A case report by Ridley et al. showed massive

cerebral thrombosis following open-heart surgery in a patient with protein C deficiency (5). A case report by Lawson et al. during a repeat open-heart surgery case suggested administering fresh frozen plasma (FFP) just before going on cardiopulmonary bypass (CPB) to help normalize protein C levels. Protein C concentrate may also be administered where available. Their case report showed no evidence of coagulation problems during the patient’s admission. The authors also suggest the use of epsilon aminocaproic acid (Amicar) (American Regent Laboratories, Shirley, NY) instead of aprotinin (Trayslol) (Bayer, West Haven, CT) because of aprotinin’s competitive inhibition of activated protein C (6). Another case study by Grimmett et al. suggested the addition of FFP to the prime, AT-III replacement therapy, amicar, and hemoconcentration as a means to treat patients deficient in protein C, protein S, and AT-III while on CPB. AT-III replacement therapy was used before surgery and again just before cannulation to control the patient’s low AT-III levels. Hemoconcentration was used to control hemodilution and may have actually increased heparin concentrations attributable to the size of the heparin-AT-III complex. Grimmett, et al. efficiently maintained hemostasis throughout the surgery (7).

Antifibrinolytics are routinely used during open-heart surgery to help preserve clotting factors, adhesive glycoproteins, and platelets. Amicar is the most commonly used antifibrinolytic during routine heart surgery. This antifibrinolytic inhibits plasminogen activators to prevent conversion of plasminogen to plasmin. Similarly, aprotinin is used as an antifibrinolytic to decrease the turnover of coagulation factors. Aprotinin is a protease inhibitor, which inhibits plasmin, plasminogen, and kalikrein. This drug has also been found to preserve platelet activity while on CPB. The use of aprotinin has been discouraged in protein C deficient patients because of its known competitive inhibition of activated protein C (8,9). However, a study by Speekenbrink et al. indicates there is no significant difference in protein C levels with the use of aprotinin compared to absence of aprotinin during cardiac surgery (10). In addition, half-dose aprotinin, or a 10^6 KIU loading dose followed by a 2.5×10^5 KIU constant infusion, has successfully been administered to a protein S deficient patient undergoing CPB without evidence of thrombotic complications (11).

Based on these findings, an appropriate recommendation for hemostasis management in a patient with protein C deficiency undergoing CPB is to administer FFP or protein C concentrate before going on bypass to restore protein C levels, administer amicar as an antifibrinolytic, and heparin as an anticoagulant to keep activated clotting times (ACTs) above 400 seconds. This case report reviews CPB management in the protein C deficient patient with the use of aprotinin.

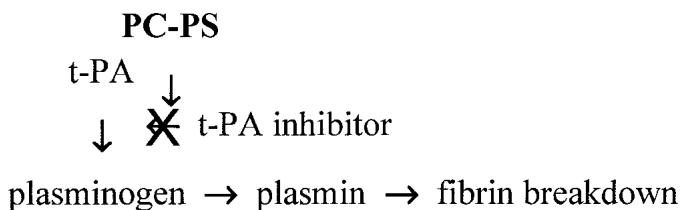


Figure 2. Effect of PC–PS complex on fibrinolysis.

CASE REPORT

Patient History

The patient, a 17-year-old black male with a history of congenital heart disease, born with double outlet right ventricle, mitral stenosis, hypoplasia of the left ventricle, a ventricular septal defect (VSD), valvular and subvalvular pulmonary stenosis, a bilateral superior vena cava (SVC), and interruption of the inferior vena cava (IVC) with azygous continuation to the left SVC. Past surgical history included atrial septectomy in 1987, modified Blalock-Taussig (B-T) shunt in 1989, and tricuspid valve replacements in 1987, 1988, and 1993. The patient's hospital course following his first valve replacement with a St. Jude prosthesis (St. Jude Biomedical, St. Paul, MN) was complicated by valve thrombosis, at which time he was diagnosed with Type I protein C deficiency. His subsequent two valve replacements were with pericardial bioprosthesis.

The patient presented to the Medical University of South Carolina on October 9, 2001 with severe prosthetic atrioventricular (AV) valvular insufficiency. His symptoms included shortness of breath at rest and fatigue. Important features of his physical exam included a systolic murmur, marked hepatomegaly and ascites, 2+ pitting edema, and clubbing of his digits. The patient weighed 35.6 kg, with a height of 150 cm (body surface area [BSA] 1.3 m²). Medications included coumadin, digoxin, lasix, and amiodarone.

A cardiac catheterization report confirmed the diagnosis of severe insufficiency of the prosthetic valve. Ventricular end diastolic pressure was elevated, and right ventricular function was also markedly depressed. The patient manifested pulmonary venous congestion, with a pulmonary venous saturation of 84–86% and an arterial saturation of 73%. The chest X-ray revealed severe cardiomegaly and pulmonary edema. Planned surgical intervention included replacement of the AV valve with a pericardial bioprosthesis.

Perfusion Management

Good communication between perfusion, anesthesia, and the surgeon was imperative to manage this patient adequately. After a thorough discussion and literature search, it was decided that aprotinin would be the best antifibrinolytic to use during surgery. A test dose was administered before surgery. Two units of FFP were administered following induction of anesthesia before the administration of aprotinin to help correct the patient's protein C deficit. It is important to note that the half-life of protein C is 6–8 h (1); therefore, FFP should be readministered if still on bypass 6 h after the initial dose. The full Hammersmith loading dose (2 × 106 KIU) of aprotinin was administered just before initiation of bypass.

Extracorporeal circuit components were based on Medical University of South Carolina's protocol for this

size patient. Circuit components consisted of a Capiiox SX-10 oxygenator and reservoir (Sarns-Terumo Corp., Ann Arbor, MI), Capiiox arterial blood filter (Sarns-Terumo Corp.), BCD Vanguard cardioplegia heat exchanger (Cobe Cardiovascular, Inc., Arvada, CO), and Minntech hemoconcentrator (Minntech Corp., Minneapolis, MN), with a Sarns 8000 roller pump filter (Sarns-Terumo Corp., Ann Arbor, MI). The total prime volume was 1300 mL, including 2 U of FFP (460 mL), 150 mL of 25% albumin, and 650 mL plasmalyte-A. Twenty mEq sodium bicarbonate and 1000 U of heparin were administered to the prime, based on surgeon's protocol. Two hundred mL (2 × 106 KIU) of aprotinin was added upon initiation of bypass.

Anticoagulation was carefully monitored throughout the surgery. ACTs were measured using a Haemochron 8000 (International Technidyne Corp., Edison, NJ). ACTs were repeated every 15 min and maintained for more than 480 sec. Heparinase thromboelastographs (TEGs) were performed every hour to evaluate coagulation status using a Haemoscope TEG machine (Haemoscope Corp., Skokie, IL). In addition, because no machine was available at this facility to measure the patient's actual heparin concentration, 100 U/kg of heparin were administered every hour while on bypass to maintain a heparin concentration greater than 3.5 U/kg (Figure 3).

Surgical Management

The patient was systemically anticoagulated using 400 µ/kg of heparin. The left femoral artery and vein were exposed, and an 8-mm Dacron graft was sewn to the left femoral artery and connected to the arterial line of the bypass circuit. The venous cannula was placed in the femoral vein. Repeat sternotomy was performed without incident, and most of the dissection was carried out before going on bypass. Once on bypass, the hepatic veins and

- Communication between perfusion, anesthesia, and surgeon
- Correction of PC deficiency prior to surgery
 - 2 units of FFP administered by anesthesia
 - 2 units of FFP in pump prime
- Aprotinin
 - Test dose
 - Hammersmith LD just prior to bypass
 - 200mL of Aprotinin was added to the prime at initiation of bypass
- Heparin
 - 400u/kg LD by anesthesia
 - 1000u in prime
 - 100u/kg administered every hour prophylactically
- ACTs
 - > 480s
 - Every 15 min
- TEGs
 - Hourly to evaluate coagulation status

Figure 3. MUSC recipe for managing a patient with protein C deficiency.

right SVC were cannulated. The left SVC was drained by femoral cannula. The patient was cooled to 28°C. The B-T shunt was clamped. The AV valve was replaced with 29-mm pericardial prosthesis. A permanent pacemaker was placed in the right atrium. The cross clamp was then removed, and the stenotic left pulmonary artery was patched with bovine pericardium. The patient was then rewarmed. The patient had low systemic pressures throughout his bypass run (29–63 mmHg mean arterial pressure) despite high perfusion flows and the use of neosynephrine and vasopressin. Initial attempts to wean from bypass were unsuccessful because of low blood pressure and high filling pressures. Inotropic support was increased, and the patient was successfully weaned from bypass on levophed and epinephrine drips. Total bypass time was 301 min. Aortic cross clamp time was 108 min.

Outcome

There were no perioperative thrombotic events. The patient's lowest ACT on pump was 439 sec, at which time a 3500 U bolus of heparin was administered (Figure 4). All other ACTs were in normal range (Figure 5). The TEG revealed increased clotting times (R-time) and time to reach clot strength (K-time) shortly after the onset of bypass, which persisted until the end of the case. The K-time ranged from 8–20 mm on bypass (normal values are 3–6mm). The patient's K-time ranged from 8–20mm while on bypass. Maximum amplitude, or clot strength, was also reduced. After surgery, a heparin drip was continued until postoperative day 10, when coumadin was started. Prothrombin time (PT) and partial thromboplastin time (PTT) values remained elevated, international normalized ratio (INR) was never less than 1.3. The patient was extubated on postoperative day 2. The patient was discharged to his home on post-operative day 41. Postoperative atrial arrhythmias and a decubitus ulcer were contributing factors to his delayed discharge. Discharge medications included vitamin C, multivitamin, digoxin, lasix, coumadin, mexiletine, prednisone, ranitidine, and bactroban ointment. Since his discharge, the patient has been seen in clinic and is doing well.

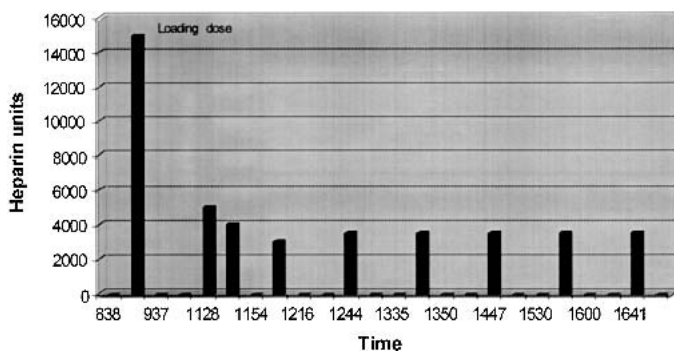


Figure 4. Heparin administration during surgery.

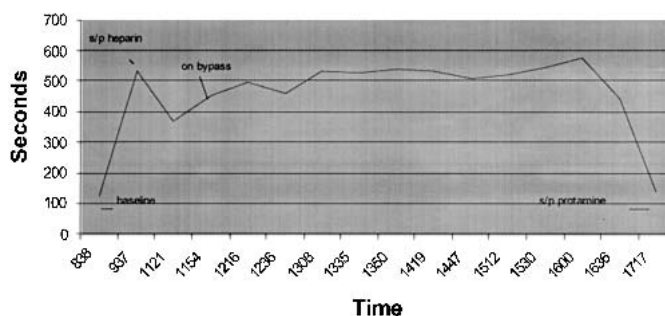


Figure 5. ACT levels during surgery.

DISCUSSION

Protein C is a necessary component in the maintenance of hemostasis. Protein C becomes activated by the thrombin–thrombomodulin complex, which inhibits factors Va and VIIIa, interrupting the coagulation cascade. In addition, activated protein C neutralizes plasminogen activator inhibitor, resulting in a profibrinolytic effect. Protein C deficiency is known to cause hypercoagulability, which may be problematic in patients undergoing high-risk procedures, such as CPB.

In this patient, the administration of FFP before surgery and careful anticoagulation monitoring helped to decrease the chance of thrombosis. Aprotinin was successfully used as an antifibrinolytic without apparent complications. We were unable to measure the effectiveness of our specific therapies because of the lack of information on pre-operative, peri-operative, and post-operative protein C levels. In future studies, measuring protein C levels throughout the patient's hospital stay would be advantageous.

Another consideration is the use of ultrafiltration during CPB. Due to high potassium levels during bypass, the patient was ultrafiltered perioperatively, using dilutional ultrafiltration (7800 mL total ultrafiltrate). The Minntech ultrafiltrator (Terumo Cardiovascular, Ann Arbor, MI) removes substances with a molecular weight up to 20,000 Daltons; however, the molecular weight of aprotinin is only 6512 Daltons; therefore, the use of ultrafiltration may have altered aprotinin levels on bypass. However, a recent study by Van Norman et al. has suggested that hemofiltration during bypass does not significantly alter serum aprotinin levels (12). It remains to be determined if the therapeutic level of aprotinin was maintained while on CPB.

This study suggests that the use of aprotinin in a protein C deficient patient undergoing open-heart surgery may be safe if protein C levels are restored before administration of aprotinin, and anticoagulation is carefully monitored throughout the case. In addition, we recommend that all facilities keep a protocol for dealing with the protein C deficient patient in their policies and procedures manuals.

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