Complete antithrombin replacement for anticoagulation for cardiopulmonary bypass to repair severe infective mitral valve endocarditis

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We present a case of a 26-year-old patient with severe infective endocarditis complicated with cerebral septic emboli that required essentially complete replacement of his circulating antithrombin activity to achieve an activated coagulation time near 480 s. The need for this degree of antithrombin administration may have been secondary to ongoing systemic inflammation and consequent thrombin generation despite blood culture results demonstrating no bacteremia. In sum, ongoing loss of endogenous antithrombin activity secondary to inflammation and the need for more than 80% normal activity to conduct safe cardiopulmonary bypass may require extraordinary administration of exogenous antithrombin in similar settings. *Blood Coagul Fibrinolysis* 29:123–125

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Introduction

Heparin-mediated activation of antithrombin is the basis of safe extracorporeal circulation, with activated clotting time (ACT) values near 480 s accepted clinically as indicative of an acceptable degree of anticoagulation for cardiopulmonary bypass (CPB) [1,2]. The contribution of acquired antithrombin deficiency in cardiac surgical patients and its effective treatment with exogenous antithrombin to achieve safe heparin-mediated anticoagulation have long been established [1,2]. Patient blood concentrations less than 80% of normal have been associated with difficulty in obtaining effective heparin-mediated anticoagulation, often requiring antithrombin administration [3,4]. Although a variety of disease entities and surgical settings are known to inflict antithrombin deficiency, infection and sepsis are well known risk factors via production of endogenous thrombin with consequent binding to antithrombin forming thrombin–antithrombin complexes [5,6]. Thus, in the particularly precarious clinical situation of infective endocarditis with septic emboli to the brain and other organs, high-risk cardiac surgery may need to be performed [7] with even greater risk of acquired antithrombin deficiency than uncomplicated mitral valve surgery [5].

In this case report, we present a patient with infectious endocarditis and cerebral septic emboli that required essentially complete replacement of his antithrombin concentrations to be able to establish safe anticoagulation for CPB for mitral valve replacement.

Case report

Our patient was a 26-year-old, 81.6 kg, male with a history of intravenous drug abuse and recent bacterial meningitis who was admitted to our facility for worsening cough, shortness of breath, and palpitations. At presentation, the patient had decreased oxygen saturation and a computed tomographic study of his chest was obtained that was negative for pulmonary embolism but suggestive of possible pneumonia. He was also found to have a severe systolic murmur, with transthoracic echocardiogram performed that demonstrated acute infective endocarditis with involvement of the mitral valve leaflets, a 2.0-cm mobile mass with possible anterior leaflet perforation, flail chordae tendineae, and severe regurgitation. His left ventricular ejection fraction was 55%, the right ventricle size was mildly increased, moderate tricuspid regurgitation was present, and the left atrium was severely dilated. Blood cultures grew *Enterococcus faecalis*, resulting in ceftriaxone and ampicillin being administered. Lastly, septic emboli to his brain and liver were noted in additional studies with computed tomography. In sum, the patient was viewed as at great risk for ongoing embolic events, heart failure, and death despite medical therapy.

Once two sets of blood cultures returned with no growth, the decision was made to replace the patient's mitral valve. In the days prior to surgery, he was administered subcutaneous unfractionated heparin for deep venous thrombosis prophylaxis. On the day of surgery, his initial platelet count was 361 000/μl, and fibrinogen concentration was

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Table 1 Laboratory data

		Results with each intervention				
Parameters/treatments	Baseline	1	2	3	4	5
Activated clotting time (s)	140	365	365	387	439	476 (on CPB)
Heparin bolus (IU)	–	30 000	10 000	–	–	10 000 (CPB prime)
Antithrombin bolus (IU)	–	–	1145	2298	1713	571
Cumulative antithrombin (IU)	–	–	1145	3443	5156	5727
Antithrombin (IU/kg)	–	–	14	42.2	63.2	70.2
% Replaced antithrombin[a]	–	–	20%	60.3%	90.2%	100%

CPB, cardiopulmonary bypass. [a]Assuming 70 ml/kg estimated blood volume.

561 mg/dl. Given his clinical and laboratory evidence of a hypercoagulable state, the attending surgeon (Z.I.K.) and anesthesiologist (V.G.N.) made the decision to not administer antifibrinolytic therapy (e.g., aminocaproic acid) in the perioperative period for fear of systemic thromboembolism. Following induction and maintenance of general anesthesia and surgical dissection/preparation to commence CPB and repair the mitral valve, several assessments/interventions to establish safe anticoagulation were performed as outlined in Table 1. An ACT (performed with a Hemochron Signature Elite; International Technidyne Corporation, Edison, New Jersey, USA) assessment of arterial whole blood was performed shortly after induction of anesthesia, within the normal range of 80–160 s. However, administration of unfractionated heparin at the usual dosage of our protocol resulted in an inadequate increase in ACT values. It was suspected that the patient was afflicted with acquired antithrombin deficiency secondary to his endocarditis and consequent systemic inflammation, so antithrombin (Thrombate III; Grifols Therapeutics Inc., Research Triangle Park, North Carolina, USA) equivalent to a 20% replacement was administered with the assumption that he had less than 80% normal antithrombin activity. As can be seen in Table 1, repeated administrations of heparin and antithrombin were administered until an ACT value of 439 s were obtained after a 90% replacement of antithrombin had been administered. It was then felt safe to commence CPB, with additional antithrombin administered just prior to CPB with additional heparin in the pump prime as indicated in Table 1. During mitral valve placement and 171 min of CPB, ACT values varied between 478 and 565 s. After separation from CPB, the patient was administered 400 mg of protamine, with a resultant ACT value of 157 s. Aside from two units of packed red blood cells, no other transfusions of red cells, platelets, plasma, or cryoprecipitate were required to obtain hemostasis. The patient was hospitalized for 17 days and then discharged home.

Discussion

The fundamental finding of this case report was that this patient was not just antithrombin deficient, but also suffered systemic inflammation and ongoing thrombin generation as part of his thromboembolic endocarditis. The basis of this assertion is that typically a more than 80% circulating normal antithrombin activity is associated with an adequate anticoagulant response to heparin administration [3,4], and our patient required 100% replacement to achieve this goal (Table 1). Our patient clearly did not have a 0% circulating antithrombin activity as this is incompatible with life in mice [8], and activities of 50–60% are associated with spontaneous pulmonary embolism and death in humans [9]. Further, our patient's data demonstrated that the ACT value did increase with the first administration of heparin (Table 1), indicative of antithrombin presence. What we suspect occurred during this patient's care was that heparin administration activated endogenous and exogenously administered antithrombin, which was consumed rapidly by ongoing thrombin generation at the blood-vascular endothelial cell interface, a consequence of ongoing systemic inflammation secondary to infection despite blood cultures demonstrating no further bacterial presence. Once an equilibrium between the concentration of heparin-activated antithrombin activity and ongoing endogenous thrombin generation was achieved, then the additional exogenous antithrombin was available to enhance anticoagulation as assessed by ACT. The clinically rapid reversal of heparin-mediated anticoagulation with protamine, with surgical and medical hemostasis achieved without any further procoagulant administration, is also testament to the procoagulant state of this patient's blood composition and tissues. In sum, between endogenous antithrombin present and exogenous antithrombin administered, this patient required more than 100% normal activity to surmount his systemic thrombin generation secondary to ongoing inflammation and also be able to withstand the contact protein activation of coagulation associated with CPB.

Although we were successful with this particular case, one should not be cavalier when administering antithrombin to such patients. Although on one horn of the dilemma one may be forced to operate on such a patient to prevent ongoing embolization of vital organs, on the other horn is the possibility of conversion of ischemic stroke to hemorrhagic stroke and death during intense anticoagulation for CPB [7]. In sum, thoughtful patient selection, risk–benefit analysis, and detailed informed consent of the patient will be key in similar clinical situations.

In conclusion, this case demonstrates that essentially complete repletion of antithrombin levels may be needed to safely conduct CPB in patients with marked systemic inflammation secondary to acquired antithrombin deficiency caused by presumed ongoing thrombin generation. Individual risk–benefit analysis of similar patients must be conducted to optimize care and adequately inform the patient of potential outcomes.

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Conflicts of interest

There are no conflicts of interest.

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