

# Anticoagulation Management in a Patient with an Acquired Antithrombin III Deficiency

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**ABSTRACT:** We report a case of heparin resistance and its management during cardiopulmonary bypass (CPB). A 63-year-old, 96 Kg female with a posterior myocardial infarction (MI) with previous deep venous thrombosis was treated with intravenous (IV) heparin infusion for 7 days before myocardial revascularization surgery. The patient required 1200 IU/Kg of beef lung heparin to extend the activated clotting time (ACT) in order to initiate CPB. A total of 1562 IU/Kg of heparin was administered throughout the procedure. This acquired heparin resistance was attributed to an antithrombin (AT III) deficiency, and was treated with fresh frozen plasma (FFP) to restore ad-

equate anticoagulation. The patient's heparinized ACTs ranged between 368 seconds and 387 seconds before FFP administration as opposed to 626 seconds to 1329 seconds after treatment with FFP and additional heparin once on CBP. The patient experienced an uneventful postoperative course. Future treatment with AT III concentrate rather than FFP may reduce heparin requirements that will, in turn, reduce protamine reversal dose, postoperative bleeding attributable to heparin rebound, and its associated complications. **Keywords:** heparin resistance, cardiopulmonary bypass, antithrombin III deficiency. *JECT 2001;33:245–248*

Antithrombin III (AT III) is a serine protease inhibitor *in vivo*, which inhibits thrombin (1), thereby inhibiting the conversion of fibrinogen to fibrin. In the presence of sodium heparin, the interaction between AT III and thrombin is accelerated 10,000-fold, accounting for heparin's anticoagulant effects (2). Sodium heparin is used preoperatively in the management of patients with unstable angina as well as in the treatment of deep venous thrombosis. Patients on heparin therapy can develop a heparin-induced decrease in the circulating levels of AT III, presenting a significant challenge to anticoagulant management during cardiopulmonary bypass (CPB). This mechanism of a heparin-induced decrease in the circulating AT III level is of an acquired nature. Congenital AT III deficiency, an autosomal dominant trait, occurs in less than 0.05 % of the population. In both acquired and congenital forms, functioning AT III levels in the plasma are reduced to 30–60% of normal (3).

Heparin resistance is defined as the failure of 500 IU per kilogram body weight of heparin to prolong the activated clotting time (ACT) to  $\geq 480$  seconds (4). There are numerous factors that can contribute to the clinical observation of heparin resistance as noted in Table 1 (5–8). Sab-

bagh et al. describes FFP administration as a treatment for heparin resistance during CPB (9). We report a case of acquired AT III deficiency based on clinically evident heparin resistance, and its treatment during CPB.

## CASE REPORT

A 63-year-old, 96Kg female with a recent posterior MI was scheduled for coronary artery bypass surgery. Her past history included hypertension, obesity, tobacco abuse, and recurrent venous thrombosis, which was previously treated with heparin therapy. Cardiac catheterization revealed left main coronary artery stenosis (80%), severe triple vessel disease, and chronic atrial fibrillation. Her estimated ejection fraction was 50% with mild mitral valve regurgitation. The patient was placed on IV heparin infusion for a total of 7 days preoperatively. On the morning of surgery the prothrombin time (PT) was 12.5 seconds (control 12.5 seconds), the aPTT was 80 seconds (control 24 seconds), fibrinogen was 934 mg/dL (control 200–400 mg/dL), the platelet count was 268,000 per mm<sup>3</sup>. This extended fibrinogen along with the aPTT and previous thrombotic tendencies were suspect of a hypercoagulable state (10). The patient underwent uneventful general anesthesia.

The baseline celite ACT was 158 seconds. The ACTs were measured using a Hemochron 01 ACT device (International Technodyne, Edison, NJ.) that requires 2 mL of whole blood placed in a prewarmed glass tube that

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**Table 1.** Situations causing increased heparin resistance (5–8).

1. Infective endocarditis
2. Intraaortic balloon counterpulsation
3. Oral contraceptives
4. Shock
5. Low grade intravascular coagulation
6. Previous heparin therapy
7. Previous streptokinase
8. Presence of a clot within the circulation
9. Congenital antithrombin III deficiency
10. Pregnancy
11. Neonatal respiratory distress syndrome
12. Increased platelet levels
13. Increased factor VIII levels
14. Secondary decrease in AT III levels
15. Continual clotting and utilization of heparin

contains diatomaceous earth and a magnet activator. When this magnet is displaced by clot formation, the test time ends (11). One limitation of this instrument is the nonlinear relationship of heparin concentration to ACT values over 600 seconds (12).

A heparin loading dose of 400 IU/Kg (institutional policy) with an additional 12,000 IU for an anticipated hypercoagulable state was administered intravenously at 7:52 AM (timetable). At 8:00 AM, the ACT was 368 seconds, at which time an additional bolus of 30,000 IU of heparin was given, and two units of FFP were ordered, once the ACT was not responsive to the additional heparin bolus. Approximately 6 minutes later another ACT revealed a value of 387 seconds, still below an acceptable minimum of 480 seconds. The diagnosis of heparin resistance due to AT III deficiency was suspected based on the patient's preoperative heparin therapy, as well as her history of clinical thrombotic tendencies. Another 30,000 IU bolus of heparin was given at 8:16 AM. These additional doses were empirically given in attempt to extend the ACT. At 8:28 AM, the ACT was 404 seconds after approximately 1200 IU/Kg (110,000 IU of heparin). Thirty minutes from the initial postheparin ACT at 8:00 AM, 20 minutes for the FFP to thaw and additional time to administer more heparin, it was elected to initiate bypass while administering the FFP along with additional heparin (20,000 IU).

At 8:30 AM bypass was initiated with one unit of FFP given by the anesthesiologist and the other units administered directly in the bypass circuit, while two more units of FFP were ordered. The patient was immediately cooled to 29°C to aid in the extension of the ACT by mild hypothermia and hemodilution. The ACT obtained 3 minutes later was 626 seconds, and the procedure commenced. The second ACT on bypass, taken at 8:40 AM, was 470 seconds. Two more units of FFP and 20,000 IU of additional heparin were then given. The ACT peaked during the bypass run at 1329 seconds at 9:17 AM. At 9:32 AM, the ACT dropped once again to 647 seconds requiring a fifth unit of FFP and 10,000 IU of heparin to be given. The ACT was maintained between 739 seconds and 647 seconds for the remainder of the bypass procedure. The CABG × 4 was performed without incident, and the patient was weaned off CPB without difficulty at 10:16 AM. The patient's urine output on CPB was 360 cc, 3.87 cc/Kg/hr. Heparin was reversed with a total of 2950 mg of protamine using a 1:1.5 reversal rate with additional subsequent protamine requested by the surgeon. The postprotamine ACT was 222 seconds. The ACT fell to within normal limits, 132 seconds, 4 hours postoperatively with minimal chest tube drainage or visual bleeding. The patient's postoperative course was uneventful, and she was discharged from the hospital 6 days later.

**DISCUSSION**

Systemic anticoagulation is a prerequisite for the institution of CPB and is achieved by the administration of fixed doses of heparin based on patients' body weight or surface area. Hill et al. (13) described the ACT as a means of determining heparin and protamine doses during CPB. Although the ACT may not reflect the circulating heparin level, as evidenced in this case, it is the most commonly used test to monitor heparin's effect on coagulation (14,15). Bull et al. (16) empirically arrived at an ACT level of 480 seconds as the safe minimum level of anticoagulation during CPB.

**Table 2.** Anticoagulation and blood transfusion sequence

Time	Heparin Given IU	Total Heparin IU	Total Heparin IU/Kg	Other	ACT (s)
7:10 AM				preop PT = 12.5 s aPPT = 80 s	158
7:52 AM	40,000 IU	50,000 IU	400 IU/Kg	Fibrinogen = 934 mg/dL	368
8:00 AM	30,000 IU	80,000 IU	833 IU/Kg	Platelet count = 268,000/mm <sup>3</sup>	387
8:16 AM	30,000 IU	110,000 IU	1145 IU/Kg		404
8:30 AM	20,000 IU	130,000 IU	1354 IU/Kg	2 units FFP given/On CPB	626
8:40 AM					470
8:51 AM	10,000 IU	140,000 IU	1458 IU/Kg	1 unit FFP given	587
9:00 AM				1 unit FFP given	686
9:17 AM	10,000 IU	150,000 IU	1562 IU/Kg	1 unit FFP given Timetable (case)	1329

In the presence of heparin resistance, inadequate anticoagulation may occur, giving rise to complications ranging from subtle disturbances in the coagulation cascade that are not clinically significant, to severe coagulopathy. There are a number of causes of heparin resistance, all of which have an effect on serum AT III levels. Preoperative heparin therapy resulting in decreased circulating AT III levels was the most likely cause of heparin resistance in our patient. Patients who receive intravenous heparin therapy preoperatively show diminished anticoagulant response to heparin (17, 18). Staples et al. (19) recommend modifying standard heparin doses with close ACT monitoring in heparin resistant patients. Dietrich et al. (20) recommend a larger (500 IU/Kg) initial bolus of heparin be given before CPB in heparin-pretreated patients. Both modification of our existing protocol and a larger initial bolus of heparin were used in this particular case.

In retrospect, this case exemplifies a well-documented increasingly common problem. Not only is the treatment of acquired antithrombin III deficiency essential, but the realm of appropriate coagulation testing is also essential to enable the clinician to identify heparin resistance with possible associated deficiencies before CPB to manage these patients effectively. This case demonstrates what action is undesirable and is not having control over anticoagulation before CPB. Given the luxury that time affords, it would have been most desirable to wait for FFP and to confirm an extension of the ACT and then initiate CPB. The efficacy and availability of more definitive coagulation testing along with evolving protocols on how best to manage an AT III-deficient patient, needs exploration. The variables affecting ACTs [temperature, Antithrombin III, red cell vume, platelet count, patelet function, and a patient's own response to heparin, etc. (21)] are far too numerous for the current technology that exists with anticoagulation testing devices. Searles et al. compared existing coagulation monitors and their limitations, including automated monitors and variability in testing techniques (22).

The treatments available when a presumptive diagnosis of AT III deficiency is made include whole blood, fresh frozen plasma (FFP), or pooled AT III preparations. Transfusion of blood and blood products carry the risk of transmission of viral infections. Time is a factor when utilizing FFP while waiting for the product to thaw. Unfortunately, at the time of this case, AT III preparations were not available at our institution; therefore, FFP and additional heparin were the prescribed treatment. Treating patients with large amounts of heparin may lead to a phenomenon called "heparin rebound," whereby heparin is sequestered extravascularly and mobilizes to re-enter the systemic circulation postoperatively with possible anticoagulant effects. Gravlee et al. (23) demonstrated a correlation of large heparin requirements during CPB with an

increased incidence of postoperative bleeding and protamine requirements. Fortunately, neither excessive postoperative bleeding nor heparin rebound was seen in our patient as evidence of minimal chest tube drainage.

Perhaps the most appropriate treatment of heparin resistance because of an AT III deficiency is AT III concentrate. Although the risk of administering human blood components is still present with AT III concentrate, the process of preparation reduces the likelihood of contamination. AT III preparations are heat treated in a wet condition for 10 hours at 60°C, which reduces the infectious risk (24). AT III requires no additional administration time other than reconstitution, which is negligible, in comparison to thawing time for FFP. Brown et al. (25) describe a reduction in heparin requirements and a significant increase in ACT levels during CPB with the use of AT III concentrate.

In conclusion, we presented a patient with decreased heparin response because of a suspected acquired AT III deficiency following preoperative intravenous heparin therapy. Infusion of fresh frozen plasma with additional heparin, hemodilution, and hypothermia resulted in the extension of the ACT. Empirical formulas for heparin dosing may need to be altered and close scrutiny of ACT levels is essential for adequate anticoagulation during CPB. Administration of AT III concentrate may provide a safer and more effective method of treating this type of heparin resistant patient.

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