

**Original Article**

***The Use of Human Antithrombin III Concentrate for Treatment of Heparin Resistance During Cardiopulmonary Bypass***

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**ABSTRACT**

We report the administration of biologic antithrombin III (AT III) concentrate for the treatment of heparin resistance in 44 patients undergoing cardiopulmonary bypass (CPB). During CPB, the amount of heparin required to maintain an activated clotting time greater than 480 sec was significantly reduced following the administration of AT III concentrate ( $p = .000$ ). The average increase in the ACT was 176 sec following the administration of AT III concentrate ( $p = .000$ ). Thirteen of 44 patients did not require any additional heparin for the duration of CPB after AT III therapy. AT III concentrate seemed to be efficacious in the treatment of heparin resistance attributable to presumed AT III deficiency. Moreover, the reduction in heparin requirements following administration of AT III concentrate may reduce postoperative bleeding associated with heparin rebound, protamine requirements, and its associated complications and threat of intravascular coagulation during CPB.

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## INTRODUCTION

Sodium heparin, a potent anticoagulant in the presence of endogenous antithrombin III (AT III), is routinely used preoperatively to treat patients with unstable angina/severe coronary artery disease. Although the dosage and duration of heparin therapy varies considerably, the depletion of the cofactor AT III during heparin therapy can present significant problems with respect to management of anticoagulation with heparin during cardiopulmonary bypass (CPB). AT III is a serine protease inhibitor, synthesized in the liver, whose major function is to bind thrombin at its active site, thereby inhibiting the conversion of fibrinogen to fibrin. The effects of heparin on AT III are twofold: heparin reduces serum concentration and half-life of AT III in blood (1). Other factors contribute to heparin resistance during CPB, including congenital and acquired AT III deficiencies. Although the incidence of congenital AT III deficiency is less than 0.05%, there is a noted increased incidence of deficiency in patients with liver dysfunction, gastrointestinal disease, estrogen and nitroglycerin therapy, major surgery, and disseminated intravascular coagulation (DIC).

Heparin resistance during CPB presents as an activated clotting time (ACT) less than the recommended standard (>480 sec), which is refractory to additional heparin therapy. Although a number of factors may contribute to an elevated ACT, reduced AT III level is the primary cause of a suboptimal ACT. Subclinical coagulation has been detected in patients with untreated heparin resistance, as defined by significantly reduced AT III levels in the presence of increased fibrinopeptide A (FPA) levels (2). The detection of FPA is indicative of thrombin-mediated conversion of fibrinogen into fibrin and intravascular coagulation (2). Activation of thrombin alone has been shown to convert plasminogen to plasmin, thereby initiating the hyperfibrinolytic pathway. Whether these findings manifest themselves clinically in the peri and postoperative recovery phase remains to be determined.

Historically, the widely accepted treatment of heparin resistance has been limited to the administration of AT III-enriched fresh frozen plasma (FFP) or large amounts of additional heparin (3). Unfortunately, the time involved for preparation of FFP in the blood bank may exceed 45 min. Moreover, the risks associated with transfusing homologous blood products remain. Administration of additional heparin without addressing the AT III levels can lead to subclinical coagulation. Dietrich described the use of an AT III concentrate for use during CPB as early as 1984 (4). We report the use of biologic AT III<sup>a</sup> to treat 44 patients with clinically evident heparin resistance.

## MATERIALS AND METHODS

We report a retrospective review of 44 patients who were

treated with AT III concentrate for heparin resistance during CPB. The patient population consisted of 31 males and 13 females with a mean age of 61 years of age (range 40–77). In the study group, all patients underwent coronary artery revascularization (one patient had concomitant mitral valve repair). Patients who received aprotinin during CPB were eliminated from the study group because of the unrelated prolongation of the celite and kaolin ACT. It should be noted that AT III concentrate is currently only approved for use in congenital AT III deficiency by the Food and Drug Administration.

All patients received 300 units bovine heparin/Kg bolus via the right atrial appendage before cannulation and initiation of CPB. In addition, 10,000 units of bovine heparin were added to the CPB prime. An ACT was performed after 3 min elapsed following the heparin bolus. Normothermic conditions were maintained throughout CPB. Single aortic occlusion with cold blood cardioplegia for distal and proximal anastomosis was employed. The CPB circuit consisted of 3/8 inch and 1/2 inch PVC tubing, hollow fiber membrane oxygenator, and 4:1 blood cardioplegia,<sup>b</sup> centrifugal pump,<sup>c</sup> venous reservoir bag, 40-micron arterial filter, and BCR 3500 cardiectomy reservoir.<sup>d</sup> The circuit was primed with 1.65 L Normosol R-pH 7.40, 25<sup>e</sup> mEq sodium bicarbonate, 12.5 g mannitol, 25 g albumin, and 10,000 units of bovine heparin. ACTs were performed at 20-min intervals or less using a Hemochron 8000.<sup>f</sup> Additional heparin administration was titrated in an attempt to maintain an ACT greater than 480 sec. Patients who exhibited an ACT <480 sec after additional heparin administration (600–800 units/Kg/min) were treated with AT III concentrate. Patients who exhibited nominal increases or in fact decreases in the ACT despite administration of large doses of heparin were treated immediately with AT III concentrate. Patients were administered a single vial of the AT III concentrate based on the manufacturer's recommendation that a single vial of AT III concentrate contains approximately the equivalent concentration of AT III in two units of fresh frozen plasma. The ACT was recorded before the administration of AT III and 10 min following the administration of AT III. Following the administration of AT III, no additional heparin was given before the subsequent ACT measurement. Thereafter, heparin was administered when necessary to maintain the ACT greater than 480 sec. Retrospectively, we calculated the heparin requirements (heparin given to maintain ACT >480 sec) during CPB based on units given/body weight/time, before and after the administration of AT III, as reported by Dietrich (4). We excluded the initial patient bolus and prime heparin from the calculation of pre-AT III concentrate heparin requirements. The data collected were subjected to a paired Student's *t*-test and are pre-

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sented as mean  $\pm$  the standard deviation of the mean. Statistical significance was accepted at the  $p < .05$  level.

## RESULTS

The patient characteristics are displayed in Table 1. The results of this study were subject to a paired Student's  $t$ -test and are listed in Table 2. There was a significant increase (average of 176 sec) in the ACT after the administration of AT III concentrate ( $p < .001$ ). In the absence of additional heparin, the administration of AT III concentrate resulted in higher ACT readings in 43/44 patients. In 44/44 patients, there was also a reduced heparin requirement to maintain an ACT of 480 sec ( $p < .001$ ) Following the administration of the heparin loading dose, additional heparin in the pump prime, and hemodilution, patients required an average of 7.14 units of heparin per kilogram per min of CPB. With the administration of ATIII, those same patients required only a mean of 1.79 units of heparin/kg/min ( $p < .001$ ).

## DISCUSSION

There are a number of causes of heparin resistance, all of which have in common a qualitative and quantitative effect on the serum levels of AT III. Congenital AT III deficiency has been reported as high as 0.05% in one study and is manifest most commonly as a reduction in AT III concentration or functional activity at the thrombin binding site (5). Studies have shown heparin infusions will reduce the AT III half-life (from 56.8 to 33.7 h) and serum concentrations (10–20%) in normal volunteers (6–8). The role of nitroglycerin-induced heparin resistance, although not fully understood, has been shown to reduce significantly the ability to anticoagulate patients in the treatment of critical coronary disease (9, 10). Table 3 illustrates the subgroups of patients on preoperative nitroglycerin, heparin, and aspirin. Ninety-five percent (42/44) of the patients were on heparin therapy before their surgery. There is much speculation as to the amount and duration of heparin therapy that results in measurable changes in serum AT III concentrations and subsequent heparin resistance. Congenital AT III deficiency is manifest by AT III levels that are 40–60% below normal values (11). The effects of CPB, including hemodilution and hypothermia, in conjunction with preoperative heparin and nitroglycerin therapy can result in an acquired AT III deficiency as well as a qualitative dysfunction of AT III.

**Table 1.**

Characteristics	Mean (SD)	Range
Body Surface Area (BSA) (M <sup>2</sup> )	2.00 $\pm$ 0.22	1.6–2.56
Body Weight (kg)	86.2 $\pm$ 16.45	59–136
CPB (min)	128.0 $\pm$ 38.27	78–219

**Table 2.**

Category	Before AT III*	Following AT III*	<i>p</i> Value
ACT Measurement	415.9 (43.43)	591.4 (159.6)	$p < .001$
Heparin Requirements	7.14 (3.9)	1.8 (1.9)	$p < .001$

ACT expressed in seconds, heparin requirements expressed in units of heparin per kilogram body weight per minute by bypass. \*Values expressed as: mean (standard deviation).

**Table 3.**

Preop Medications	Number of Patients
Intravenous Heparin	42/44 (95%)
Intravenous Hep/NTG	29/44 (66%)
Aspirin	42/44 (95%)

Kesteven and Pasaoglu reported a reduction in AT III levels of approximately 50% from hemodilution alone (12). Hashimoto et al. (2) demonstrated a correlation between low AT III levels and increased FPA. In their study of 21 patients, six patients who were pretreated with AT III before CPB demonstrated an increased response to heparin, with a significantly higher ACT, normal FPA levels, and AT III concentrations consistent with pre-CPB levels. Conversely, 15 patients who were not pretreated showed lower ACT, increased FPA levels, and AT III concentrations that were reduced 30% from pre-CPB values (1).

The treatment of patients with large amounts of heparin during CPB leads to significant morbidity and has been implicated in the post-CPB phenomena called heparin rebound. The correlation of large heparin requirements during CPB and the increased incidence of postoperative bleeding and protamine requirements was demonstrated by Gravlee et al (13). Kaul reported a study of 44 patients undergoing CPB who received either a fixed dose of heparin during CPB or additional heparin, based on heparin concentration (14). Results of his study showed that patients who received a fixed additional dose of heparin during CPB (1.5 mg/kg/h) had a significantly increased incidence of heparin rebound and postoperative bleeding. Heparin rebound can occur because of a number of factors: (1) incomplete protamine reversal in patients where large amounts of heparin have been administered; (2) extravascular sequestration of heparin with subsequent intravascular re-entry; and (3) postoperative binding of circulating heparin with AT III following post-CPB infusion of FFP (11).

Our results showed a significant reduction in heparin requirements during CPB following the administration of AT III associated with a mean rise in the ACT of 166 sec. In a prospective study, we intend to measure serum AT III, D-dimer, and FPA levels and confirm our hypothesis that the addition of AT III may avert conditions of inadequate anticoagulation.

Although the risk of administering a human blood component is evident, the process for preparation of AT III concentrate greatly reduces the threat of contaminated transmission. The purification process of AT III concentrate is such that the activity of the AT III is 95% pure with greater than 90% of the AT III found to be active with heparin under crossed immunoelectrophoresis (15). AT III concentrate is reported to be safer for human administration than normal serum albumin. The preparation of AT III concentrate requires only reconstitution and can be ready for administration in minutes, virtually eliminating the thawing time imposed with administration of FFP. AT III concentrate allows the clinician to treat the condition of heparin resistance specifically and greatly reduces the amount of volume transfused.

The ability of AT III concentrate to reduce heparin requirements significantly and improve the ACT during CPB was impressive. More detailed analysis of the clotting cascade and specific indicators of subclinical coagulation may provide greater insight as to the role of AT III concentrate in the treatment of heparin resistance and potential peri and postoperative clinical sequelae.

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