

The Role of Antithrombin III in Heparin Resistance

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Abstract

Resistance to the anticoagulation action of sodium heparin during cardiopulmonary bypass is a serious concern and a poorly understood phenomenon. In the majority of cases, the desired prolongation of the activated clotting time (ACT) is achieved by administration of additional heparin. A patient's previous exposure to heparin has been suggested as the cause of this clinical dilemma. The administration of fresh frozen plasma to patients who demonstrated a heparin resistance have been shown to produce a normalization of their heparin/ACT dose response curve and a decrease in total heparin requirements during cardiopulmonary bypass. These results could be an indication of a deficiency of a component in patient's plasma.

This study was designed to compare antithrombin III (AT III) in two patient populations. Group A consisted of 15 patients receiving intravenous heparin therapy prior to cardiopulmonary bypass for greater than 24 hours. Population B included 15 patients who had not been exposed to heparin therapy preoperatively. All patients were candidates for coronary artery bypass grafting. The quantitative assay utilized the Loyal Rocket Immunoelectrophoresis Technique and the qualitative assay was determined by the AT III Anti-10A Activity Assay.

Two sample t-test analyses of variance revealed no statistical significance ($p < 0.05$) between the two populations in either quantitative assay ($p = 0.054$) or the qualitative assay ($p = 0.06$). A comparison of the ration (qualitative/quantitative) showed a statistical difference ($p = 0.016$).

It can be suggested from these results that the resistance to heparin demonstrated in heparin therapy patients is the result of a combination of factors associated with AT III. Administration of heparin decreases the available AT III and decreases its function. The combination of these two factors contributes to this resistance phenomenon.

Introduction

The most common method of manipulating the human coagulation system during cardiopulmonary bypass is through the administration of heparin (1). Heparin, a naturally occurring mucopolysaccharide, combines with antithrombin III (AT III) and certain other coagulation proteases with varying degrees of acceleration (2). The distribution of heparin is limited to the

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plasma volume and it is eliminated via the reticuloendothelial system. The half-life of heparin is approximately 90 minutes. This half-life increases with an increase in plasma concentration; therefore, it can be considered a concentration-dependent drug (3).

The amount of heparin necessary to produce a prolongation of the activated clotting time varies from patient to patient. Heparin has been shown to be a dose-dependent drug (4). However, it is difficult to determine the exact level of patient reactivity prior to heparin administration.

AT III is an alpha two globin molecule found in the blood which slowly neutralizes thrombin in-situ (5). In the presence of heparin, this activity is increased by 1,000 (6). The response to this catalyst varies. Individuals receiving continuous IV heparin therapy prior to cardiac surgery have been shown to be less sensitive to this catalytic effect (7,8,9).

The administration of fresh frozen plasma to patients who demonstrate heparin resistance produces a normalization of their heparin/ACT dose response curve. A concomitant decrease in total heparin requirements during cardiopulmonary bypass is also seen (10). These results indicate a preexisting deficiency of one or more plasma-clotting factors.

The objective of the study was to quantify and characterize the AT III activity in two patient populations. The control group, Group I, received no preoperative intravenous (IV) heparin (Figure 1). The patients who received IV heparin preoperatively comprise (Group II (Figure 2)). All patients not meeting criteria were excluded from this study. The study was approved by the Office of the Joint Committee on Clinical Investigation from the School of Medicine.

FIGURE 1: Criteria for Control Group

No Preoperative IV Heparin	
BT	< 5 Minutes
pT	< 12 Seconds
pTT	< 40 Seconds
PLT	< 150,000 MM ³

FIGURE 2: Preoperative Heparin Group

PLT	> 150,000 MM ³
Heparin Therapy	> 12 Hours

Materials and Methods

A 5 cc blood sample was obtained from an in-dwelling radial artery catheter prior to the administration of heparin required for extracorporeal circulation. Each sample was placed in a glass test tube containing sodium citrate and placed in an ice bath until analysis was performed. All assays were completed within 12 hours of the sample. The quantitative assay utilized the Loyal Rocket Immunoelectrophoresis Technique and the qualitative assay used the AT III Anti-10A Activity Assay. The two sample t-test analysis of variance was used to determine statistical significance.

Results

The quantitative assay revealed a decreased level of AT III in patients receiving heparin therapy prior to cardiac surgery relative to patients who had not received preoperative IV heparin therapy ($p=.06$). Patients in the IV heparin therapy group received IV heparin an average of 72 hours prior to surgery.

The qualitative assay revealed a decrease in AT III activity in the heparin therapy population ($p=.54$). There was a statistical significance between the two groups when combining the level and activity of AT III. The activity to quantity ratio was statistically significant ($p<.05$). The preoperative IV heparin group demonstrated both a reduction in level and function of AT III when compared to the non-heparin group.

Discussion

Heparin acts as a catalyst for the AT III reaction. To initiate this reaction, a binding of the heparin molecule to the AT III molecule must occur. Recent studies have revealed that AT III has more than one binding site for heparin (11). The primary site has a high affinity for heparin. Once this site is bound, a conformational change occurs with the AT III molecule exposing additional sites of action. These secondary sites have a lower affinity for heparin (12). Patients who receive IV heparin therapy prior to cardiac surgery may have the AT III/heparin primary sites unavailable, allowing only secondary sites to be available to the heparin administered prior to cardiopulmonary bypass. Therefore, a resistance to the administered heparin is observed. The results of this study support the fact that patients who are on IV heparin therapy have a lower number of AT III and of the present AT III, a lower function. Both changes contribute to heparin resistance.

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Questions and Answers

Jeff Riley, Charleston, SC

Q. Your optimized hemofiltration is pretty aggressive. Did you measure any differences in plasma free hemoglobin between optimizing?

A. We didn't but transmembrane pressures are always in the range of 500 ml of mercury. We didn't see any difference.

Paul Wagner, Stockton, CA

Q. Do you know when you gave your blood cardioplegia did you have to, as I understand it, stop the hemofiltration?

A. After giving the blood cardioplegia we stopped hemofiltration, yes.

Q. Did you analyze the filtrate for potassium concentrations?

A. No

Q. Did you see any difference?

A. No we didn't, but it should be the same thing as in the blood.

Q. Did you see any difference in the quality of myocardial arrest as far as potassium?

A. No, certainly not.