Predictors of Heparin Resistance Before Cardiovascular Operations in Adults

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Background. **Heparin resistance (HR) is often encountered during cardiovascular operations that require cardiopulmonary bypass. Clinical risk factors and the mechanism underlying heparin resistance are yet to be determined. The aim of this study was to elucidate the clinically valid preoperative predictors related to HR.**

Methods. **The study evaluated 489 patients undergoing cardiovascular operations. Of these, 25 patients presented with HR and received antithrombin III for the initiation of cardiopulmonary bypass with an effective activated coagulation time. The remaining 464 patients, who did not receive antithrombin III, served as controls (NHR). Preoperative patient demographic and laboratory data were analyzed to identify risk factors for HR.**

Results. **The preoperative laboratory data showed platelet count, fibrinogen, D-dimer, creatinine, and C-reactive protein were significantly higher in the HR group than in the NHR group. As expected, the antithrombin III level was significantly lower overall in the HR group (86.0% vs 95.5%, $p = 0.009$); however, 80% of the patients in the HR group showed normal antithrombin III levels preoperatively. Multivariable logistic regression analysis identified chronic aortic dissection, chronic obstructive pulmonary disease, smoking, and elevated fibrinogen levels as independent predictors for HR.**

Conclusions. **HR was shown to be associated with preoperative high fibrinogen levels, a smoking habit, and a preoperative diagnosis of chronic, but not acute, aortic dissection, with chronic obstructive pulmonary disease as comorbidity. Administration of antithrombin III resolved HR in all of the affected patients, even when their preoperative antithrombin III level was within the normal limit.**

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Heparin resistance (HR) may be observed before cardiopulmonary bypass (CPB) for cardiovascular operations. The condition has been defined as the failure to achieve the desired activated clotting time (ACT) after a standard dose of heparin and reported in 4% to 22% of patients who underwent operations with CPB [1–3]. However, clinical indices for related risk factors and the mechanism underlying HR have not been fully determined.

Heparin alone has no direct anticoagulant effect, but it inhibits thrombin, factor Xa, and other coagulation factors by binding to antithrombin III (AT-III) [4]. Diminished antithrombin activity is considered to be a factor in HR. When HR occurs, the additional administration of heparin is usually insufficient; instead, its treatment necessitates fresh frozen plasma or the administration of human AT-III [5, 6]. These maneuvers and the assessment time necessary for their effectiveness by measuring ACT level multiple times are time consuming. Prolonged surgical time may not be beneficial for patients requiring surgical repair because of the potentially increased risk of infection. Identification of patients at risk for HR and prompt management with appropriate intervention may be useful in view of ideal control of anticoagulation status; furthermore, overdosing of heparin before AT-III administration can also be avoided.

Ranucci and colleagues [7] suggested that the risk factors for HR in patients undergoing coronary artery bypass grafting, in addition to a low antithrombin level, were older age (>65 years), preoperative heparin therapy, and a high platelet count (>300,000 cells/mm^3) [7]. With regard to the key component of AT-III, the recent AT-III level assay in laboratories has used a synthesized substrate without interaction with heparin [8]. There is therefore a concern that the results of AT-III assays may not correspond precisely with the real in vivo AT-III levels with coexisting heparin. Indeed, patients with a

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Abbreviations and Acronyms

ACT = activated clotting time
APTT = activated partial thromboplastin time
ATAD = acute thoracic aortic dissection
AT-III = antithrombin III
COPD = chronic obstructive pulmonary disease
CPB = cardiopulmonary bypass
CRP = C-reactive protein
CTAD = chronic thoracic aortic dissection
DIC = disseminated intravascular coagulation
HR = heparin resistance
NHR = no heparin resistance
PT% = prothrombin time percentage activity
PT-INR = prothrombin time international normalized ratio

low level of antithrombin measured in the laboratory do not always exhibit HR, and some patients show HR despite their antithrombin level being in the normal reference range according to laboratory testing.

We therefore hypothesized that other factors may be related to HR in cardiovascular operations. The aim of this study was to elucidate clinically valid preoperative predictors related to HR, which was achieved by a retrospective comparison of groups of patients with and without HR.

Patients and Methods

This was a single-center, retrospective, nonrandomized study conducted at Tohoku University Hospital, Japan. The Institutional Review Board reviewed and approved the study protocol. Considered for inclusion were all adult patients (aged >20 years) who underwent cardiovascular operations that required CPB between January 2010 and December 2012, including those receiving emergency operations and reoperations. Patients' baseline preoperative characteristics and laboratory data were obtained from their clinical records and the Japan Adult Cardiovascular Surgery Database [9]. These included the platelet count, prothrombin time (PT) percentage activity, PT international normalized ratio, activated partial thromboplastin time, and the levels of fibrinogen, D-dimer, AT-III, and C-reactive protein (CRP). Informed consent from the patients for data acquisition and subsequent analysis was obtained comprehensively at the time of their participation in Japan Adult Cardiovascular Surgery Database.

Anticoagulant Protocol

The anticoagulant protocol for CPB was as follows: After anesthesia was induced, blood samples were collected, and the baseline ACT was measured. The initial volume of heparin (300 U/kg) was administered. Blood samples were taken 2 minutes later, and the ACT was then measured using a Hemochron Response coagulation analyzer (Accriva Diagnostics, Inc, San Diego, CA). When the ACT exceeded 400 seconds, CPB was commenced. If the ACT remained below 400 seconds, an additional dose of heparin was administrated, calculated according to the change rate of ACTs between baseline and after heparin administration. The calculation formula of additional heparin dose was as follows: additional heparin dose (IU) = [(400 – ACTi) × initial heparin dose (IU)]/[(ACTi – ACTb)], where *ACTb* is baseline ACT and *ACTi* is ACT after initial heparin administration

If the ACT remained less than 400 seconds even after the additional heparin, 1,500 to 3,000 U of purified AT-III concentrate (Neuart; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan, now Japan Blood Products Organization, Tokyo, Japan) was administered.

The patients were classified into two groups. Those who achieved appropriate anticoagulation before CPB through just the heparin administration only were categorized to the no HR (NHR) group, and those who received AT-III administration to achieve sufficient anticoagulation were defined as having HR and categorized to the HR group.

Statistical Analysis

The continuous variables were all distributed nonnormally by the Kolmogorov-Smirnov test. The results for these variables are therefore expressed as medians with interquartile ranges and were compared by using the Mann-Whitney *U* test. Categoric variables are expressed as the number and percentage and were compared by using the χ^2 test. Logistic regression analysis was used to identify the independent predictors of HR. Predictors associated with a significant p value (<0.05) in the univariate analysis were entered into the multivariate analysis using the stepwise selection method. Results are expressed using odd ratios and 95% confidence intervals. A p value of less than 0.05 was considered statistically significant. Data analyses were performed with SPSS 24.0 software (IBM, Armonk, NY).

Results

The clinical record review identified 497 adult patients who underwent cardiovascular operations that required CPB during the study period, including emergency cases and reoperations. Of these, 464 patients achieved effective anticoagulation (ACT > 400 seconds) solely through heparin administration (without additional AT-III administration) and were classified as the NHR group. The study excluded 6 patients who were treated with AT-III product simultaneously with the initial dose of heparin at the surgeon's discretion because of concerns about a significantly low preoperative AT-III level. Also excluded were 2 patients who were given argatroban for intraoperative anticoagulation. The remaining 25 patients, who were administered AT-III after the second dose of heparin to achieve the desired ACT, were classified as the