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Title: Antithrombin activity and outcomes in patients undergoing cardiac surgery with cardiopulmonary bypass

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Running head: AT activity and heparin efficacy in CPB

ABSTRACT

Background: We recently reported prospective results from a cohort of patients scheduled for elective cardiac surgery with cardiopulmonary bypass (CPB) in which most baseline clinical parameters of patients and surgery outcomes failed to demonstrate relationships with post-CPB antithrombin (AT) activity. *Objective and Methods*: In this extension study, a larger sample size (250 patients) was analyzed following general linear models. Patients' sociodemographic and pre-CPB clinical data as well as pre/post-CPB AT activity and outcomes were collected. *Results*: There was a significant decrease of post-CPB AT activity (95.6±13.7% to 64.6±12.1%; p<0.001). Univariate and multivariate analyses revealed that a decrease of ~1% post-CPB AT activity may be expected per 3 years increase in patient's age. Univariate analysis showed that post-CBP AT activity was inversely related to the need for transfusions, acute renal failure and occurrence of any complication (re-intervention, low cardiac output, arrhythmia, lung dysfunction, stroke, acute renal failure, mesenteric ischemia and re-hospitalization; P<0.05). Multivariate analysis adjusted for age and pre-CPB AT did not show statistical significance. Odds ratio (OR) <1 was observed in most outcomes (0.8 in average), which suggested a reduction of the probability for an increase of 10% in post-CBP AT. *Conclusions*: Our results confirm the role of low post-surgery AT activity influencing outcomes in patients undergoing CPB.

Keywords: Antithrombin; cardiopulmonary bypass; extracorporeal circulation

INTRODUCTION

Cardiac surgery with cardiopulmonary bypass (CPB) poses a threat to the delicate balance between procoagulant and anticoagulant proteins due to the high amounts of thrombin produced by the contact of blood with the artificial surfaces of the bypass circuit [1]. Antithrombin (AT), the strongest endogenous anticoagulant [2], has been reported to decrease its activity by 40-60% during and after CPB in comparison to baseline values. This is mainly due to consumption and reduced hepatic synthesis [3], which has been correlated with worse postoperative outcomes [4].

In an attempt to describe the profile of a Spanish population, we prospectively studied 149 patients scheduled for elective cardiac surgery with CPB to elucidate possible relationships between AT activity and a subject's clinical profile or surgery characteristics [5]. In that study we found that 29.5% patients required an additional dose of heparin during CPB to achieve activated clotting time (ACT) target. Mean pre-CPB AT was 96.5±13.9%, undergoing a significant decrease during CPB (59.7%) and upon leaving the operating room (65.6%). Most baseline clinical parameters of patients and outcomes of surgery failed to present relationships with AT activity values before, during and after CPB. However, a small but significant inverse correlation was observed between AT at the end of CPB and the patient's age, as well as between baseline pre-CPB AT and total heparin administered. These results partially corresponded with previous reports [6,7], which led to the conclusion that patient's age could be a moderate indicator of decreasing AT activity and that low pre-CPB AT activity could be a predictive sign of reduced anticoagulant efficacy of heparin during CPB. However, the possibility that a larger sample size could reveal other associations encouraged us to continue recruiting patients, to confirm the extent of relationships between AT activity and outcomes in patients undergoing CPB.

PATIENTS AND METHODS

Study characteristics

In order to find out determinant factors of post-CBP AT activity as well as the association of post-CBP AT activity with outcomes, we conducted an extension of a previous study [5] statistically focused in general linear models. The study was set up in accordance with the Declaration of Helsinki, the Good Clinical Practice and the local ethics committee from the La Ribera University Hospital. Written informed consent was obtained from all patients. As in the former report [5], patients under 18 years of age scheduled for elective CPB were excluded, as well as repair of congenital disease, off-pump or any emergency cardiac surgery, and pre-CPB use of intra-aortic balloon pump. For each patient, sociodemographic pre-CPB variables, baseline clinical parameters, anticoagulant and antiplatelet therapy, Euroscore risk estimate, data of surgery, AT activity and laboratory values, and outcomes at discharge were collected.

CPB procedures

Details of anesthesia and CPB equipment and technique were carried out as described previously [5]. Briefly, after anesthesia (etomidate, remifentanil and midazolam plus cisatricurium) CPB was established through a standard median sternotomy, aortic root cannulation, and single or bi-caval atrial cannulation for venous return. The circuit priming volume before beginning CPB was 600 ml. Antegrade/retrograde intermittent cold blood cardioplegia (4:1) was used. The pump flow was set at 2.4-2.6 ml/m^2 and the target mean arterial pressure at 65-70 mm Hg. Body temperature during CPB was maintained between 32º-37ºC. All patients received tranexamic acid intraoperatively

(15-30 mg/kg bw intravenously before the induction of anesthesia, 1 mg/kg bw/min during CPB, and finally, 15-30 mg/kg bw after the protamine dose).

The ACT was determined immediately after the induction of anesthesia (3 minutes after the loading heparin dose (300 IU/kg b/w), 5 minutes after the initiation of CPB, and subsequently every 15 min). An ACT of 460 s or greater was considered satisfactory. A specific perioperative transfusion algorithm was applied to maintain hematocrit above 25%, according to the clinical condition, hemodynamic status, need for inotropic support, and age of the patient [5]. After the operation, all patients were released to the intensive care unit (ICU). The clinical course of patients and post surgery complications were followed until discharge.

Sampling and data collection

Blood samples were collected and immediately centrifuged to obtain the plasma fraction to be frozen for analysis (serum creatinine, hematocrit, minimum protrombin time [PT] and AT activity levels (pre- and post-CPB) [5]. With regard to CPB operation, the type of surgery and duration of CBP were collected. Outcomes considered for analysis were: need for transfusion, re-intervention and cause (due to bleeding, infection or other), low cardiac output syndrome, perioperative acute myocardial infarction (AMI), arrhythmia, lung dysfunction, stroke, mesenteric ischemia, acute renal impairment, re-hospitalization, mortality after day 28, length of stay in ICU (days) and length of hospitalization (days).

Statistical Analysis

Values are expressed as percentage (%), mean ± standard deviation (SD), median ± interquartile range (IQR) or odds ratio (OR) ± 95% confidence interval (CI) as appropriate. The difference in AT activity from pre- to post-CPB was analyzed by a paired Student's t-test. The association between pre- or operative data and post-CBP AT was assessed by univariate analysis (Wilcoxon, Kruskal-Wallis or Spearman correlation tests as appropriate) and multivariate analysis (general linear models). This included as covariates those variables that appeared in the univariate analysis at the 5% significance level. The association of post-CPB AT to outcome variables was investigated by univariate analysis (univariate logistic regression or Spearman correlation as appropriate) and multivariate analysis (logistic regression or general linear models) including pre-operative and operative variables that were significantly associated with post-CPB AT in the previous multivariate analysis. A value of $P \leq 0.05$ was considered statistically significant.

RESULTS

Patient and CPB profiles

We collected data from 250 patients, of which 165 (66%) were male. Mean age was 67±11.6 years with average body mass index (BMI) of 29.1±4.5. Pre-CPB analytics showed mean serum creatinine: 1.2±1.0 mg/dL, hematocrit: 37.1±4.8%, prothrombin time (PT): 13.6±0.9 s, and median Euroscore: 5.4±4.9. Most surgeries were coronary revascularization (46.8%), valve replacement (34.4%) or both combined (14.4%). Median CPB duration was 75.5±35.0 min. Outcome variables are shown in Table 1. Median lengths of ICU and hospital stay were 3±3 days and 8±7 days, respectively. There was a significant decrease in AT activity from pre-CPB to post-CPB (from 95.6±13.7% down to 64.6±12.1%, $t=36.6$; $df=249$; $p<0.001$), which represented a drop of 31% (95% CI: 29%-33%) in AT activity levels.

Determinants of post-CPB AT activity

Univariate analysis detected three pre-CPB factors associated with post-CPB AT activity: age (r=-0.33; p<0.001), Euroscore (r=-0.19; p<0.05) and pre-CPB AT activity (r=0.47; p<0.001). In the multivariate analysis, both age and pre-CPB AT activity remained significantly associated to AT activity post-CPB (r=-0.31 and r=0.38; p<0.001). As illustrated in the regression plane in Figure 1, highest post-CPB AT activity was favored by young age in combination with high pre-CPB AT activity (e.g., around 95% post-CPB AT may be expected in a 30 years old patient with 140% pre-CPB AT, whereas at the opposite edge, one would expect post-CPB AT activity of around 40% in a 90 years old patient with 50% pre-CPB AT activity.

Association of post-CBP AT activity to outcomes

Univariate analysis showed that post-CBP AT activity was inversely related to the need for transfusion, acute renal failure and the occurrence of any complication (see Table 1). Mortality at day 28 showed a close-to-significant association (P=0.051). OR point estimates were lower than 1 (0.8 in average) for all outcomes (except perioperative AMI) in the univariate analysis, which suggests a reduction in the odds of an outcome related to an increase of 10% in post-CPB AT activity. However, when age and pre-CPB AT activity were adjusted for the multivariate analysis, the statistical significance was lost, despite OR estimates being similar. These results are summarized in Table 1. Similar to what happened in the univariate analysis, OR point estimates were lower than 1 (0.8 in average) or very close to 1 in most outcomes.

DISCUSSION

The role of pre-CPB AT activity in patients undergoing cardiac surgery with CPB on postoperative outcomes is a subject of debate. In this report we aimed to shed some light on this subject. As could be somewhat expected, the profile of the patients included in this extension study was similar to that from the original report [5] and comparable to that of other studies [8,9]. In our study the mean pre-CPB AT activity level (around 95%) was within the normally accepted range of 80-120%, and predictably after CPB AT activity dropped down to around 65%. Apart from pre-CPB AT activity, our univariate analysis detected Euroscore to be associated with post-CPB AT activity, a relationship somewhat expected since Euroscore is a recognized method of calculating predicted operative mortality for these patients [10]. However, multivariate analysis only confirmed post-CPB AT activity association with regard to patient's age, which was in accordance with previous findings [8].

Unlike our previous report, in this extension study some outcomes such as transfusions and acute renal failure were associated with post-CPB AT levels. In contrast with the findings of others we did not detect association of major adverse cardiac events [7]. Interestingly, when outcomes were considered as a group (the so-called "any complication" variable), there was a significant inverse association with post-CPB AT levels. In multivariate analysis, the trend was similar to that observed in univariate analysis, although not reaching statistical significance.

To summarize, the results from this extension study allowed going a step further than those of the former report. It confirms a role of low AT activity influencing the incidence of outcomes in patients undergoing CPB, although its precise effects could not be clearly established. Inverse association of post-CPB AT activity with age would support AT preventive treatment in elderly patients, which constitute a high risk group.

DISCLOSURES

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Table 1: Incidence of post-surgery outcome variables and their association with antithrombin (AT) activity levels. (CPB: cardiopulmonary bypass; AMI: acute myocardial infarction; LR: logistic regression analysis; OR: odds-ratio; CI: confidence interval; * P<0.05)

Variable	**Patients n (%)**	**Association to post-CPB AT**	
		Univariate LR OR¶ (95% CI)	**Multivariate LR OR¶ (95% CI)**
Arrhythmia	86 (34.4)	0.88 (0.71-1.09)	1.02 (0.78-1.34)
Transfusions	80 (32.0)	0.77 (0.61-0.96)*	0.83 (0.62-1.09)
Low cardiac output	34 (13.6)	0.97 (0.72-1.31)	1.03 (0.71-1.50)
Lung dysfunction	30 (12.0)	0.87 (0.64-1.19)	1.02 (0.69-1.51)
Acute Renal Failure	18 (7.2)	0.67 (0.45-0.99)*	0.78 (0.48-1.25)
Mortality at day 28	15 (6.0)	0.66 (0.43-1.00)	0.64 (0.38-1.07)
Re-hospitalization	12 (4.8)	0.78 (0.49-1.24)	0.67 (0.39-1.14)
Re-intervention	11 (4.4)	0.95 (0.58-1.57)	0.88 (0.49-1.60)
Stroke	9 (3.6)	0.74 (0.43-1.26)	0.66 (0.35-1.24)
Perioperative AMI	8 (3.2)	1.23 (0.67-2.24)	1.20 (0.58-2.49)
Mesenteric ischemia	1 (0.4)	- -	- -
Any complication#	- -	0.76 (0.62-0.95)*	0.83 (0.64-1.07)
ICU stay >7 days	- -	0.84 (0.63-1.12)	0.92 (0.65-1.30)
Hospital stay >14 days	- -	0.87 (0.68-1.11)	0.96 (0.71-1.30)

¶ OR corresponding to an increase of 10% in post-CBP antithrombin activity.

Re-intervention, low cardiac output, arrhythmia, lung dysfunction, stroke, acute renal failure, mesenteric ischemia and re-hospitalization.

Figure 1. Regression plane of patient's age in combination with pre-operative AT activity (AT_pre), with respect to post-operative AT activity (AT_pos) ($r=-0.31$ and $r=0.38$, respectively; $p<0.001$) as obtained in the multivariate analysis. Age values are shown in years old and AT activity values represent percentage.