ELSEVIER

Atherosclerosis 186 (2006) 107–112

ATHEROSCLEROSIS

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Preoperative antithrombin III activity predicts outcome after surgical repair of acute type A aortic dissection

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Received 8 February 2005; received in revised form 20 June 2005; accepted 22 June 2005
Available online 25 July 2005

Abstract

Background: Acute Stanford type A aortic dissection is associated with substantial perioperative morbidity and mortality. A sepsis-like state may lead to antithrombin (AT) III consumption and deficiency. The impact of preoperative AT III activity on outcome in patients undergoing emergency surgery is yet unknown.
Methods: We measured preoperative AT III activity in 99 consecutive patients undergoing emergency aortic surgery for Stanford type A aortic dissection during a 4-year period in a retrospective study. Cardiovascular co-morbidities, risk factors and surgical data were recorded and patients were followed for 30-day mortality, and occurrence of multiple organ failure (MOF).
Results: During the first 30 days, 15 patients (15%) died, and 8 patients (8%) had MOF. Median AT III levels (IQR) in 30-day non-survivors versus survivors were 64% (52–72) versus 90% (75–97) ($p < 0.001$), and in patients with versus without MOF were 66% (52.3–77.3) versus 88% (72–96) ($p = 0.018$), respectively. Adjusted odds ratios for 30-day mortality and MOF for AT III activity (per % increments) were 0.92 ($p = 0.007$), and 0.96 ($p = 0.012$), respectively, indicating a significant inverse relationship between AT III activity and outcome.
Conclusion: There is a strong inverse association between preoperative AT III activity and adverse outcome in patients undergoing surgical repair of acute Stanford type A aortic dissection. Larger studies are necessary to determine a cut-off value for AT III and to assess whether patients with low AT III levels benefit targeted therapeutic interventions.

Keywords: Aorta; Aortic dissection; Coagulation; Prognosis; Outcome

1. Introduction

Surgery of patients with acute Stanford type A aortic dissection is associated with high morbidity and mortality rates [1–3]. Although substantial advances in surgical techniques like selective cerebral perfusion and deep hypothermic circulatory arrest helped to improve early and long-term outcome, in-hospital mortality rates remain excessively high [4–8].

Severe systemic inflammation and excessive vasodilation occur in up to one-third of patients after major cardio-thoracic surgery [9–11]. Subsequent inhibition of systemic fibrinolysis and enhanced thrombin generation seem to contribute to macrovascular thrombosis and thromboembolism, leading to single and multiple organ failure [1–11]. Postoperative multiple organ failure (MOF) is a major determinant for the occurrence of in-hospital death [1–8]. In this context, antithrombin III (AT III), which inhibits the coagulation cascade by blockage of factors IXa, Xa, XIa, XIIa, plasmin, kallikrein, trypsin and plasmin, has been identified as a powerful predictor of poor prognosis in non-surgical patients with sepsis,

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doi:10.1016/j.atherosclerosis.2005.06.031

disseminated intravascular coagulation and MOF [12–14]. It is yet unknown whether AT III activity has a prognostic value also in patients undergoing major cardio-thoracic surgery.

We hypothesized that preoperative AT III activity predicts outcome in patients undergoing emergency surgical repair of type A aortic dissection. Therefore, the aim of the study was to assess the association between preoperative AT III levels and 30-day mortality in these patients. Secondary objective was to assess the association between preoperative AT III levels and the occurrence of MOF during the hospital stay.

2. Methods

2.1. Study design

The study was designed as a retrospective cohort study including all consecutive patients who underwent immediate surgical repair of Stanford type A aortic dissections during a 52 months study period (from February 1999 to June 2003). Data were obtained from a prospective registry database from the Departments of Emergency Medicine and Cardiothoracic Surgery at our institution. Ethics approval by the local review board is not required at our institution for studies based on registry databases.

2.2. Patient data

Age, sex, total red cell count, platelet count, thrombin time, partial thromboplastin time, prothrombin time, antithrombin III levels and fibrinogen as established very early surrogate of inflammatory activity were recorded at the time of hospital admission. Cardiovascular risk factors and comorbidities were assessed on admission and by distinct review of medical charts. We documented the results of surgical and autopsy reports, as well as the use of deep hypothermic circulatory arrest and the time of extracorporal circulation.

2.3. Study endpoints

Primary endpoint was all-cause 30-day mortality. Secondary objective was the occurrence of MOF in the 30-day postoperative phase.

2.4. AT III measurements

AT III activity was measured at baseline immediately after admission to the Emergency Department in routine laboratory, fully certified by the International Organization of Standardization. For determination of AT III activity STA® Antithrombin III test (Roche Diagnostics Vienna, Austria) was used according to the manufacturer's recommendations [15]: The sample is incubated with a known excess of thrombin in the presence of heparin. The residual thrombin is quantitated by its amidolytic action on the synthetic chromogenic substrate CBS 61.50 (pNA release measured at 405 nm). Since the quantity of thrombin that is neutralized in the first reaction step is proportional to the AT III level present in the sample, it follows that the residual thrombin in the second reaction step (as measured by the pNA release) is inversely proportional to the AT III level of the sample.

2.5. Definitions

Acute aortic dissection was diagnosed and classified according to the guidelines published by the European Society of Cardiology [16].

Preoperative shock was defined as a permanent deterioration in systolic blood pressure below 90 mmHg at the Emergency Department and at the operating theatre and any need of preoperative advanced life support (ALS) measures including catecholamine support.

Postoperative MOF was defined according to criteria of the consensus of the critical care society [17]: Acute respiratory distress syndrome (ARDS), acute liver failure, acute heart failure, diffuse or focal neurologic ischemic damage, such as persistent paraparesis or paraplegia due to impairment of blood supply to the spinal cord or signs of central neurological damage following cerebral hypoperfusion, and septicemia. Acute renal failure (ARF) was defined as an increase in serum creatinine 44 mol/l (0.5 mg/dl) over the baseline-value (serum creatinine on admission) or the need for renal replacement therapy until day 30. Fulfilling at least two criteria of organ failure classified patients to suffer from postoperative multiple organ failure.

Severe bleeding was defined according to the guidelines of the Society of Thoracic Surgeons as the need of surgical reintervention for bleeding complications or as massive supplementation of red cell and platelet packs—based either on a decrease in hemoglobin by at least 2 mg/dl or by active bleeding of more than 200 ml/h in the drains.

2.6. Patients' risk factor assessment

Diabetes mellitus was defined as a serum HbA1c level greater than 6.0% on admission and/or patients on oral antidiabetic medication or insulin therapy. Hyperlipidemia was considered to be present in all patients receiving lipid lowering therapy or in patients with fasting total serum cholesterol greater than 200 mg/dl, LDL cholesterol greater than 130 mg/dl or serum triglycerides greater than 180 mg/dl. Arterial hypertension was assumed in patients with documented history of hypertension or that with chronic intake of antihypertensive drugs. History of typical symptoms or previous vascular intervention upon the arteries of lower extremities were considered as peripheral artery disease. Chronic renal insufficiency was defined as a stable elevation of creatinine greater than 2 mg/dl assessed prior to the current hospital admission. Cerebrovascular disease was defined as a history of ischemic cerebral events (e.g., transient ischemic attack (TIA), prolonged reversible neurologic deficiency (PRIND),