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Plasma activity of individual coagulation factors, hemodilution and blood loss after cardiac surgery: A prospective observational study

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ABSTRACT

Background: Hemodilution and consumption of coagulation factors during cardiopulmonary bypass has been suggested to contribute to bleeding complications after cardiac surgery. The aim was to describe the activity of individual coagulation factors after CABG in relation to hemodilution and postoperative bleeding.
Materials and Methods: Plasma concentrations of fibrinogen and plasma activity of FII, FV, FVII, FVIII, FIX, FX, FXI and FXIII adjusted for hemodilution were analysed in 57 CABG patients before, and 2 h and 24 h after surgery. Postoperative bleeding was registered and correlations to coagulation factor activity were calculated.
Results: Adjusted plasma concentration of fibrinogen (-14 ± 6%), and plasma activity of FII (-9 ± 6%), FV (-13 ± 8%), FX (-13 ± 7%) and FXIII (-9 ± 14%) were reduced two hours after surgery compared to baseline (all $p<0.001$). FVII (+3 ± 12%, $p=0.34$) and FXI (+1 ± 19%, $p=0.50$) were unchanged, while FVIII (+23 ± 44%, $p=0.006$) and FIX (+23 ± 17%, $p<0.001$) increased. Twenty-four hours after surgery fibrinogen (+45 ± 27%), FVIII (+93 ± 66%) and FIX (+33 ± 26%) were all increased (all $p<0.001$), while FVII (-37 ± 14%, $p<0.001$), FXI (-4 ± 18%, $p=0.02$) and FXIII (-6 ± 15%, $p=0.004$) were decreased.
Median postoperative blood loss was 380 ml/12 h. There were significant inverse correlations between postoperative blood loss and fibrinogen concentration 2 h after surgery ($r=-0.33$, $p=0.019$) and between postoperative blood loss and pre- and postoperative FXIII activity ($r=-0.34$, $p=0.009$ and $r=-0.41$, $p=0.003$, respectively), but not between blood loss and any of the other factors.
Conclusions: There is a marked dissociation in plasma activity of individual coagulation factors after CABG. Plasma concentration of fibrinogen and factor XIII activity correlates inversely to postoperative blood loss after CABG.

Introduction

Significant bleeding after cardiac surgery may be caused by both impaired hemostasis and surgical factors [1]. Impaired hemostasis may occur due to enhanced fibrinolysis, platelet dysfunction or loss, and/or coagulopathy secondary to the exposure of blood to artificial surfaces, hemodilution and the surgical trauma [2–4].

Consumption of coagulation factors during cardiopulmonary bypass has been suggested to contribute to coagulopathy after cardiac surgery [2,3]. It is, however, not evident whether the activity of all coagulation factors responds similarly to cardiopulmonary bypass and surgical trauma. Furthermore, more refined methods to treat coagulopathies, including plasma-derived and recombinant coagulation factors, have in recent years become available. Increased knowledge about how individual coagulation factor activity varies after surgery may improve treatment. The first aim of the present study was to describe the activity of individual coagulation factors after cardiac surgery with cardiopulmonary bypass in relation to the inevitable hemodilution during and after the operation.

Our group and others have reported that the preoperative and postoperative plasma concentration of fibrinogen is associated with postoperative bleeding volume after cardiac surgery [5,6]. The results indicate that plasma concentration of fibrinogen is a limiting factor for postoperative hemostasis, and that preoperative fibrinogen concentration may be used as a biomarker to identify groups of patients with increased bleeding risk. The second aim was to investigate whether

Abbreviations: ACT, Activated clotting time; BMI, Body mass index; CABG, Coronary artery bypass grafting; CPB, Cardiopulmonary bypass; ECAT, External quality Control of diagnostic Assays and Tests.

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activity of any other plasma coagulation factor correlates to bleeding volume after cardiac surgery.

Material and Methods

Patients

Initially 59 consecutive patients, (mean age 65 ± 7 years, 77% males) undergoing first time elective CABG with cardiopulmonary bypass (CPB) at Sahlgrenska University Hospital, were enrolled in a prospective descriptive non-interventional study. Predefined exclusion criteria were acute CABG and known bleeding disorder. Two patients were excluded from analysis: one due to change of surgical approach (off-pump instead of on-pump CABG), and one because of on-going medication with clopidogrel at the time of surgery, not noticed at inclusion. Thus, 57 patients were finally included in the study. All patients gave informed written consent before inclusion. The protocol was approved by the local Research Ethics Committee. Patient characteristics are given in Table 1.

Clinical management

Anesthesia in all patients was induced with 200-300 μg of fentanyl and 3-5 mg/kg of thiopentone, followed by 0.1 mg/kg pancuronium and maintained with sevoflurane. During CPB, anesthesia was maintained with propofol. The patients received heparin (350 units/kg bodyweight) in order to maintain an activated clotting time (ACT) of more than 480 seconds. After CPB, the heparin was reversed by the administration of protamine sulphate (1 mg protamine/100 units of heparin) to an ACT of less than 130 s.

The CPB circuit included a membrane oxygenator and roller pumps. Standard non-pulsatile CPB technique with moderate hypothermia (bladder temperature 34-35 °C) and hemodilution was used. The CPB circuit was primed with 1400 ml of Ringer-Acetate (Fresenius Kabi AB, Uppsala, Sweden) and 200 ml of Mannitol (150 mg/ml) (Fresenius Kabi AB). Cardioprotection was achieved with antegrade cold blood cardioplegia. Weaning off CPB was performed after rewarming to a bladder temperature of 36 °C.

Aspirin was not discontinued before surgery. Clopidogrel was discontinued at least three days before surgery. All patients received 2 g tranexamic acid intravenously at anesthesia induction and at the end of surgery. Aprotinin was not used in any of the study patients.

Table 1
Patient characteristics. Mean and standard deviation or number (%).

Age (years)	65 ± 7
Male gender	44 (77%)
BMI (kg/m²)	27 ± 3.4
Euroscore	2.9 ± 3.1
CPB time (min)	72 ± 27 (40-187)
Aortic clamp time (min)	44 ± 17 (23-112)
Number of grafts	3.3 ± 0.9
Preop aspirin	57 (100%)
Preop clopidogrel	0*
Preop LMWH	0
Preop warfarin	0
Unstable angina	19 (33%)
Hemoglobin (g/L)	148 ± 14
Platelet count ($\times 10^9$/L)	279 ± 64
Serum-creatinine (μmol/L)	84 ± 24
Hematocrite	0.44 ± 0.04
ACT after protamine reversal (seconds)	122 ± 11
Blood group non 0	38 (67%)

Key: ACT = Activated clotting time, BMI = body mass index, CPB = cardiopulmonary bypass, L = litre, LMWH = low molecular weight heparin,*Clopidogrel was discontinued at least 3 days before surgery.

Study design and analyses

Plasma concentration of fibrinogen and plasma activity of coagulation factor II (FII), FV, FVII, FVIII, FIX, FX, FXI and FXIII were analyzed at three time points: the day before surgery and 2 and 24 hours after surgery. Hemoglobin concentration, hematocrit and platelet count were analyzed at the same three time points. Coagulation factor activity is reported both as absolute values and values adjusted for hemodilution according to the formula: Adjusted activity = absolute activity × (preoperative hematocrit / actual hematocrit) [7]. Correlation calculations between coagulation factor activity and postoperative bleeding were performed on absolute activity. The following pre- and perioperative patient variables were registered: age, gender, body mass index (BMI), Euroscore, type of angina, preoperative medication, number of grafts, CPB time and aortic clamp time. Postoperatively, the total amount of chest tube drainage was registered during the first 12 postoperative hours.

The preoperative blood samples were collected from an antecubital peripheral vein and the postoperative samples from a non-heparinized radial arterial line. During sampling, the first 10 ml of blood was discarded. Blood was collected in sodium citrate tubes (0.13 M, 9 parts blood, 1 part sodiumcitrate), and centrifuged at 2000 g for 20 minutes. The supernatant was filled in separate tubes and freezed in dry ice for further analysis.

All samples were analysed at the accredited coagulation laboratory at Sahlgrenska University Hospital. The laboratory participates in the ECAT foundation external quality assessment programme (www.ecat.nl). Fibrinogen (reference range 2.0-4.5 g/L) was measured by the modified method of Clauss. FII (reference range 70-130%), FV (reference range 60-140%), FVII (reference range 50-160%), FVIII (reference range 50-200%), FIX (reference range 45-190%), FX (reference range 70-130%) and FXI (reference range 60-140%) were determined using one stage clotting assay with specific factor deficient plasma samples. The thromboplastin used for analysis of FVIII, IX and XI was STA C.K. PREST® and for FII, V, VII and X - Neoplastine® CL plus (both STA® (Diagnostica Stago, Asnieres, France) and start of clot formation was detected by viscosity based chronometric measurement on instrument STA-R (Diagnostica Stago). Activity of FXIII (reference range 70-140%) was measured by photometric method (Berichrom FXIII/Dade Behring, Marburg, Germany) on the instrument Cobas Mira (Roche, Basel, Switzerland). Hemoglobin concentration, hematocrit and platelet count were analyzed with clinical standard methods.

Statistics

Results are expressed as mean and standard deviation (SD) or number and percent (%). Statistical significance was defined as a p-value <0.05. Since bleeding is not normally distributed, all statistical analyses involving bleeding were performed with non-parametric tests. Intergroup comparisons were performed with Mann-Whitney test, Kruskal–Wallis test or Chi-square-test, when appropriate. Correlation testing was performed with Pearson's test (normally distributed data) or Spearman rank sum test. Correlation between coagulation factor activity and postoperative bleeding volume was performed on absolute activities, without correction for hemodilution. Coagulation factor activity after surgery (normally distributed) was compared to baseline with paired T-test. The computer software used was SPSS 16.0 for Windows (SPSS Inc, Chicago Ill, USA).

Results

Clinical course

All patients could be discharged from hospital without serious complications.