J CARDIOVASC SURG 2003;44:205-8

Tranexamic acid reduces bleeding after off-pump coronary artery bypass grafting

M. JARES, T. VANEK, Z. STRAKA, P. BRUCEK

Department of Cardiac Surgery
3rd Medical School of Charles University
Kralovske Vinohrady University Hospital
Prague, Czech Republic

Aim. **To assess the ability of tranexamic acid, compared with an untreated control group, to decrease bleeding and transfusion requirements in patients undergoing coronary artery bypass grafting on the beating heart.**

Methods. **Forty-nine randomly selected patients were enrolled to elective coronary artery bypass grafting without the use of cardiopulmonary bypass. Of these, 23 received tranexamic acid (bolus of 1 g before surgical incision, followed by infusion 200 mg/hour during surgery) and 26 patients were enrolled into a control group. Preoperative hematological variables, postoperative blood loss at 4 and 24 hours, transfusion requirements of packed red blood cells,and postoperative thrombotic events such as a myocardial infarction, stroke and pulmonary embolism were recorded.**

Results. **The two groups were similar in terms of patients' characteristics. Postoperative bleeding was significantly lower in the tranexamic acid group compared with the control group (median [25th-75th percentiles]): 115 [92-148] *vs* 230 [170-260] mL at 4 hours, p<0.001; 420 [330-523] *vs* 550 [500-650] mL at 24 hours, p<0.01). Transfusion requirements were lower in the tranexamic acid group compared with the control group (RBC 9% *vs* 28%), but the difference was not statistically significant. Treatment with tranexamic acid was not associated with a higher incidence of myocardial ischemia or other thrombotic events.**

Conclusion. **Tranexamic acid reduces postoperative blood loss after coronary artery bypass grafting on the beating heart. Evaluation of transfusion requirements warrants further study.**

KEY WORDS: Coronary artery bypass - Postoperative complications - Tranexamic acid - Hemorrage.

Tranexamic acid as a synthetic antifibrinolytic drug has been shown to reduce postoperative bleeding in patients after cardiac surgery with the use of cardiopulmonary bypass (CPB).[1-7] There are also data showing efficiency of tranexamic acid in patients receiving aspirin before coronary artery bypass operations.[8,9] However, there is only one study evaluating the effect of antifibrinolytic agent use during off-pump coronary surgery on postoperative blood loss and transfusion requirements.[10] The aim of our prospective randomized study was to evaluate the efficacy of tranexamic acid in decreasing bleeding and transfusion requirements in patients undergoing coronary artery bypass grafting on the beating heart.

Materials and methods

Patient population

From January 1 through June 30, 2001, we conducted an unblinded prospective study in 49 patients undergoing elective coronary artery bypass grafting without CPB, who had given their informed consent. Exclusion criteria included impaired renal function (S-Cr >150 mmol/L), hematological diseases, preoperative anemia (Hb <11 g/dL, Htc <32) and conversion to CPB. All of the patients were medicated by aspirin before operation, with withdrawal 5 days before surgery in elective cases. Treatment with preoperative heparin infusion was not a contraindication to inclusion into the study.

Address reprint requests to: M. Jares, Kralovske Vinohrady University Hospital, Srobarova 50, 100 34 Praha 10, Czech Republic.
E-mail: martin.jares@gmx.net

TABLE I.—*Basic characteristics of the tranexamic acid and control groups of patients.*

Parameters	Tranexamic acid group (n=22)	Control group (n=25)
Number	22	25
Gender (% of males)	68.2	80
Weight (kg)	74.5±16.8	77.4±13.2
Distal grafts (no.)	1.9±0.8	1.9±0.6

Plus-minus values are mean ± standard deviation. No variable differs significantly between the groups. Two-sample "t"-test or χ^2 test was used for comparison between the groups as appropriate.

TABLE II.—*Preoperative treatment with aspirin or heparin and hematological variables.*

Parameters	Tranexamic acid group (no. 22)	Control group (no. 25)	p
Aspirin <5 days (no./%)	11/50.0	11/44.0	NS
Preoperative heparin (no./%)	5/22.7	7/28.0	NS
Hemoglobin (g/dL)	14.4±1.3	14.2±1.5	NS
Hematocrit (%)	42.9±4.0	42.2±4.2	NS
Platelet count (x10^3/mm^3)	231 (193-272)	223 (173-247)	NS
Pt (s)	1.0 (0.9-1.0)	1.0 (1.0-1.0)	NS
aPTT (s)	32.0 (28.5-36.9)	35.0 (33.0-39.5)	NS
Fibrinogen (g/L)	3.4 (3.2-4.1)	3.8 (3.6-4.5)	NS

Plus-minus values are mean ± standard deviation. Non-normally distributed data are indicated as median and (in brackets) 25th and 75th percentiles. Two-sample "t"-test, χ^2 test or Wilcoxon's rank sum test was used for comparison between the groups as appropriate. No variable differs significantly between the groups. Pt: prothrombin time; aPTT: activated partial thromboplastin time.

Intraoperative management

Twenty-three patients were randomized to receive tranexamic acid (Exacyl Sanofi Winthrop Industrie, Ambares, France) 1 g, 10 min before surgical incision followed by continuous infusion at a rate of 200 mg/hour until the end of the procedure. Twenty-six patients were randomized to a control group not given any antifibrinolytic agents.

Anesthetic management

The standard technique of balanced anesthesia with sufentanil, midazolam, vecuronium and isoflurane was used routinely. Heparin (100 IU/kg) was administered to obtain activated clotting time (Hemochron, International Technidyne Corp., Edison, N.J., USA) greater than 250 s before the start of the 1st anastomosis. After the end of the revascularization the effect of heparin was neutralized by protamine with 1:1 ratio.

Surgical technique

All patients were operated through a median sternotomy. The left internal thoracic artery was harvested routinely. Mechanical stabilization was used to perform peripheral anastomosis using an Access Ultima System mechanical stabilizer (Cardio Thoracic Systems, Cupertino, USA). In some cases, an intraluminal Flo Coil Shunt (Cardio Thoracic Systems, Cupertino, USA) was employed.

Postoperative period

Criteria for transfusion of packed red blood cells were as follows: hematocrit value less than 25% and hemoglobin value less than 8 g/dL associated with signs of hypovolemia.

Measurement

Blood loss from the mediastinal chest tubes was recorded at 4 and 24 hours from the time the patient had arrived at the ICU. Transfusion requirements of packed red blood cells were documented throughout the postoperative period. Preoperative hematological variables and preoperative treatment with aspirin or heparin were recorded.

Statistical analysis

Values are given as mean±standard deviation or as median and 25th to 75th percentiles as appropriate. To test the normality of distribution of the continuous variables, tests based on skewness were performed. Comparison between the two groups was made using Wilcoxon"s rank sum test, the two-sample "t"-test or the χ^2 test as appropriate. A p value lower than 0.05 was regarded as statistically significant. Data were analyzed using Matlab5 5.3 software (MathWorks, Massachusetts, USA).

Results

Of the 49 patients selected for the study, 2 patients (one each in the tranexamic acid and control groups) were excluded due to conversion to CPB. A total of 47 patients completed the study and were evaluated by statistical analyses. Analysis of these patients revealed no significant differences between the two groups with respect to weight, number of anastomoses and preoperative hematological variables (Tables I, II).

There was no in-hospital death. Two patients (one

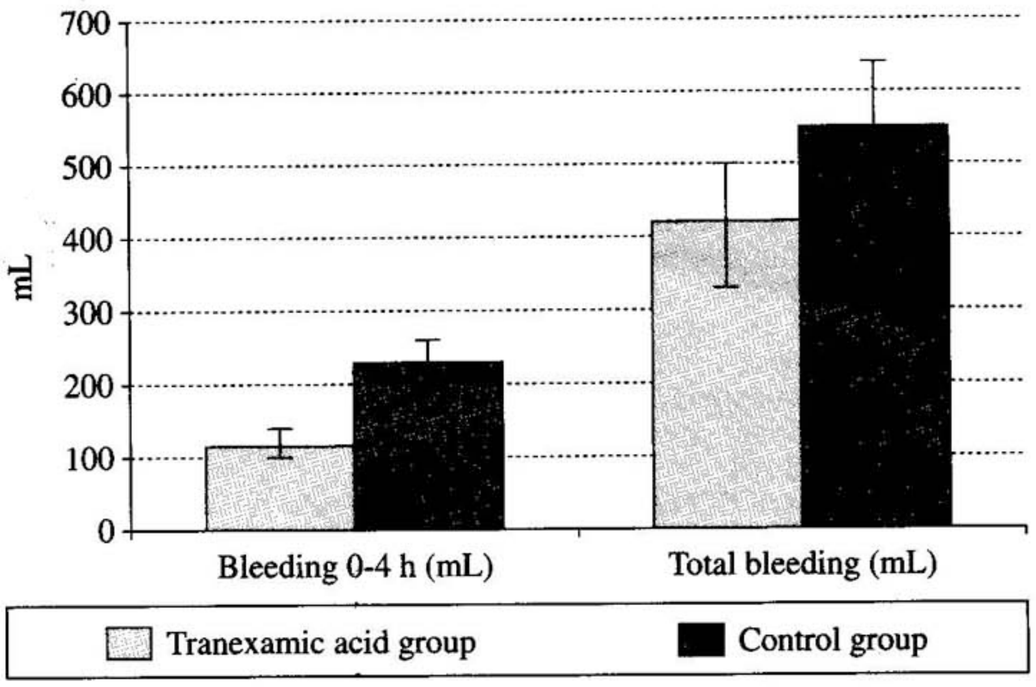


Fig. 1.—Postoperative bleeding. Data are reported as median. Error bars indicate the 95% confidence interval of median. Wilcoxon's rank sum test was used for comparison between the groups: Bleeding 0-4 h, $p<0.001$; total bleeding, $p<0.01$.

each in the tranexamic acid and control groups) had postoperative myocardial infarction. No patient developed postoperative stroke or pulmonary embolism. One patient (control group) required reoperation for early postoperative bleeding.

Four- and 24-hour chest tube blood loss was significantly lower in the tranexamic acid group compared with the control group (Figure 1). There was no statistically significant difference between the two groups with respect to total allogenic blood transfusion (Table III).

TABLE III.—*Transfusion requirements and reoperation for bleeding.*

Parameters	Tranexamic acid group No. (%)	Control group No. (%)	p
Patients transfused with PRBC	2 (9.1)	7 (28.0)	NS
Reoperation for bleeding	0	1 (4.0)	NS

Values are expressed as number and percentage. χ^2 test was used for comparison between the groups. PRBC = packed red blood cell.

Discussion

In our study we have shown that tranexamic acid is effective in reducing postoperative bleeding after off-pump coronary artery bypass grafting. There is a potential risk of an increased thrombotic tendency during treatment with fibrinolysis inhibitors, and there have been sporadic case reports of coronary graft occlusion in patients receiving tranexamic acid during cardiac surgery with CPB,[11] but these observations have not been supported by results of controlled clinical studies.[12-14] Mariani *et al.* evaluated coagulation systems during off-pump procedures and they evidenced procoagulant activity, which is not mediated by platelet-related factors and found activation of fibrinolysis after this type of operations.[15] In our study we observed 2 postoperative myocardial infarctions (one in each group). We have not noticed any cerebrovacular event or pulmonary embolism. So, in the population of our patients we did not observe a tendency to clinical evident thrombotic events in the tranexamic acid group. This observation is in accordance with the recently published study by Casati *et al.*[10] Anyway, a larger number of patients is required to better assess the incidence of these possible complications.

Tranexamic acid is a synthetic antifibrinolytic drug used routinely in cardiac surgery with the use of CPB. Tranexamic acid exerts its antifibrinolytic effect by blocking lysine binding sites on plasminogen molecules thereby inhibiting the interaction of plasminogen and the heavy chain of plasmin with lysine residues on the surface of fibrin. An increase in fibrinolytic activity during off-pump operations is supposedly due to increased release of tissue plasminogen activator from the vascular endothelium, which starts during skin incision and continues throughout sternotomy and surgical tissue manipulation.[12]

To the best of our knowledge, this is currently a second study investigating the effects of tranexamic acid in patients undergoing coronary artery bypass grafting without CPB use. Although beating-heart coronary surgery has been shown to be associated with a significant reduction in postoperative bleeding and transfusion requirements, about 20-25% of these patients still require red blood cell transfusion, with the associated risk of transfusion-related complications.[16] We found lower transfusion requirements in the tranexamic acid group compared with the control group without statistical significance, but it was probably due to the small number of patients.

Conclusions

Our study demonstrates that tranexamic acid is clinically effective and safe in reducing postoperative

bleeding after off-pump coronary artery bypass grafting, but we observed no significant difference in the need for allogenic transfusion. However, evaluation of transfusion requirements warrants further study in a larger group of patients.

References

1. Wong BI, McLean RF, Fremes SE, Deemar KA, Harrington EM, Christakis GT *et al.* Aprotinin and tranexamic acid for high transfusion risk cardiac surgery. Ann Thorac Surg 2000;69:808-16.
2. Levi M, Cromheecke ME, de Jonge E, Prins MH, de Mol BJ, Briet E *et al.* Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. Lancet 1999;354:1940-7.
3. Casati V, Guzzon D, Oppizzi M, Bellotti F, Franco A, Gerli C *et al.* Tranexamic acid compared with high-dose aprotinin in primary elective heart operations: effects on perioperative bleeding and allogenic transfusions. J Thorac Cardiovasc Surg 2000;120: 520-7
4. Casati V, Guzzon D, Oppizzi M, Cossolini M, Torri G, Calori G *et al.* Hemostatic effects of aprotinin, tranexamic acid and epsilon-aminocaproic acid in primary cardiac surgery. Ann Thorac Surg 1999;68:2252-6.
5. Coffey A, Pittmam J, Halbrook H, Fehrenbacher J, Beckman D, Hormuth D. The use of tranexamic acid to reduce postoperative bleeding following cardiac surgery: a double-blind randomized trial. Am Surg 1995;61:566-8.
6. Laupacis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. The International Study of Perioperative Transfusion (ISPOT) Investigators. Anesth Analg 1997;85: 1258-67.
7. Barrons RW, Jahr JS. A review of post-cardiopulmonary bypass bleeding, aminocaproic acid, tranexamic acid, and aprotinin. Am J Ther 1996;3:821-38.
8. Bernet F, Carrel T, Marbet G, Skarvan K, Stulz P. Reduction of blood loss and transfusion requirements after coronary artery bypass grafting: similar efficacy of tranexamic acid and aprotinin in aspirin-treated patients. J Card Surg 1999;14:92-7.
9. Landymore RW, Murphy JT, Lummis H, Carter C. The use of low-dose aprotinin, epsilon-aminocaproic acid or tranexamic acid for prevention of mediastinal bleeding in patients receiving aspirin before coronary artery bypass operations. Eur J Cardiothorac Surg 1997;11:798-800.
10. Casati V, Gerli C, Franco A, Torri G, D'Angelo A, Bennusi S *et al.* Tranexamic acid in off-pump coronary surgery: a preliminary, randomized, double-blind, placebo-controlled study. Ann Thorac Surg 2001;72:470-5.
11. Robblee JA. Graft occlusion following administration of tranexamic acid. Anesth Analg 1995;80 Suppl:SCA141.
12. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs 1999;57:1005-32.
13. Ruel MA, Wang F, Bourke ME, Dupuis JY, Robblee JA, Keon WJ *et al.* Is tranexamic acid safe in patients undergoing coronary endarterectomy? Ann Thorac Surg 2001;71:1508-11.
14. Horrow JC, Van Riper DF, Strong MD, Brodsky I, Parmet JL. Hemostatic effect of tranexamic acid and desmopressin during cardiac surgery. Circulation 1991;84:2063-70.
15. Mariani MA, Gu YJ, Boonstra PW, Grandjean JG, van Oeveren W, Ebels T. Procoagulant activity after off-pump coronary operation: is the current anticoagulation adequate? Ann Thorac Surg 1999;67:1370-5.
16. Nader D, Khadra Z, Reich T, Bacon R, Salerno A, Panos L. Blood product use in cardiac revascularization: comparison of on- and off-pump techniques. Ann Thorac Surg 1999;68:1640-3.

EUROPEAN JOURNAL OF
CARDIO-THORACIC
SURGERY

Fibrinolytic inhibitors in off-pump coronary surgery: a prospective, randomized, double-blind TAP study (tranexamic acid, aprotinin, placebo)

Tomas Vanek, Martin Jares, Richard Fajt, Zbynek Straka, Karel Jirasek, Miroslav Kolesar, Petr Brucek and Marek Maly

Eur J Cardiothorac Surg 2005;28:563-568
DOI: 10.1016/j.ejcts.2005.06.027

ELSEVIER

European Journal of Cardio-thoracic Surgery 28 (2005) 563–568

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

Fibrinolytic inhibitors in off-pump coronary surgery: a prospective, randomized, double-blind TAP study (tranexamic acid, aprotinin, placebo)

Tomas Vanek[a,*], Martin Jares[a], Richard Fajt[a], Zbynek Straka[a], Karel Jirasek[a], Miroslav Kolesar[a], Petr Brucek[a], Marek Maly[b]

[a]*Department of Cardiac Surgery, 3rd Medical School of Charles University Prague, Kralovske Vinohrady University Hospital, Srobarova 50, CZ-100 34 Prague 10, Czech Republic*

[b]*Department of Biostatistics and Informatics, National Institute of Public Health, Prague, Czech Republic*

Received 9 May 2005; received in revised form 11 June 2005; accepted 28 June 2005; Available online 25 August 2005

Abstract

Objective: To evaluate and compare hemostatic effects of tranexamic acid vs. aprotinin vs. placebo in off-pump coronary artery bypass (OPCAB) surgery and, in addition, to assess the safety of fibrinolytic inhibitors therapies. **Methods**: In a prospective, randomized, double-blind study finally 91 patients undergoing OPCAB were investigated (group A, $n=32$, tranexamic acid 1 g before skin incision and continuously 200 mg/h; group B, $n=29$, aprotinin 1,000,000 IU before skin incision and 250,000 IU/h; group C, $n=30$, placebo). **Results**: Highly significant inter-group differences were found in cumulative blood loss within 4 h (geometric means [95% confidence intervals]—group A: 89.3 [72.7, 109.8] mL, group B: 72.3 [49.2, 106.3] mL and group C: 192.3 [151.8, 243.5] mL) ($P<0.001$), within 8 h (group A: 152.1 [120.7, 191.6] mL, group B: 130.3 [88.1, 192.8] mL and group C: 283.8 [226.0, 356.3] mL) ($P=0.001$), and within 24 h postoperatively (group A: 410.3 [337.6, 498.6] mL, group B: 345.8 [256.0, 398.2] mL and group C: 619.8 [524.3, 732.8] mL) ($P<0.001$). At all time points, placebo group C was significantly distinct from the groups treated with fibrinolytic inhibitors (groups A and B). However, no differences between groups A and B were found. Both mean hemoglobin and hematocrit values 24 h postoperatively were different between the groups ($P=0.018$ and $P=0.077$, respectively), acheiving the lowest value in group C. Number of re-transfuzed patients was highest in group C, but without statistical significance (either packed red blood cells, $P=0.119$ or fresh-frozen plasma, $P=0.118$). We observed one postoperative myocardial infarction in aprotinin treated group B and one temporary postoperative myocardial ischemia in placebo group C, no cerebrovascular or pulmonary embolism was noticed. Treated groups A and B did not demonstrate postoperative increase in mean levels of myocardial enzymes, compared with group C. Significantly higher mean values of D-dimer were found in group C 24 h postoperatively ($P<0.001$). **Conclusions**: Both tranexamic acid and aprotinin seem to be similarly effective in the reduction of postoperative blood loss in OPCAB. Tranexamic acid appears to be cost-effective and safe alternative to aprotinin.

Keywords: Tranexamic acid; Aprotinin; Off-pump coronary artery bypass; Hemostasis

1. Introduction

The favourable effect of fibrinolytic inhibitors (aprotinin, tranexamic acid, aminocaproic acid) on the decrease in perioperative bleeding in on-pump coronary surgery has been confirmed in a large number of controlled trials [1–4]. In many centers these pharmacological strategies are used on a routine basis [5,6]. However, only few studies have been concerned with the use of antifibrinolytic drugs in off-pump coronary artery bypass (OPCAB) surgery [7–10], although perioperative hemorrhagic complications and the consequent need for allogenic transfusions are still one of the major problems in this type of surgery [11–13].

The aim of this prospective, randomized, double-blind, placebo-controlled study was to evaluate and compare hemostatic effects of tranexamic acid and aprotinin in OPCAB surgery. In addition, the risk of perioperative myocardial ischemia was assessed.

2. Material and methods

After obtaining the Medical Faculty Ethics Committe approval (EK/243/2003, October 1, 2003) and the informed consent from all participants, from October 15, 2003 to July 31, 2004, 100 patients scheduled for OPCAB were enrolled in the study. The criteria for non-enrollment to the study were as follows: previous cardiac surgery, myocardial infarction <7 days prior to surgery, history of hematological or liver disordes, renal insufficiency (serum creatinine >150 μmol/L) and preoperative anemia (hemoglobin <11 g/L, hematocrit <32). Preoperative treatment

* Corresponding author. Tel.: +420 267 163 422; fax: +420 267 163 260.
E-mail address: vanek@fnkv.cz (T. Vanek).

1010-7940/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejcts.2005.06.027

with antiaggregative/anticoagulant drugs (aspirin withdrawal <5 days before surgery, low-molecular heparin withdrawal <24 h before surgery, continuous heparin infusion) was not a contraindication to the inclusion into the study, but the number of medicated patients was carefully monitored. Nobody from the study subjects was preoperatively under the influence of potent antiplatelet agents, such as ADP inhibitors and GP IIb/IIIa antagonists.

According to our predetermined exclusion criteria nine enrollees were withdrawn from the study: six of them for a conversion on cardiopulmonary bypass in the course of surgery (presence of small intramuscular arteries and heavy calcification, hemodynamic instability), three of them for the need of postoperative re-exploration for hemorrage with the finding of an evident surgical source of bleeding (once the perforation of venous bypass by the edge of chest tube, twice bleeding from the branch of internal thoracic artery, which was used as a conduit). Finally, 91 patients were assessed in the study.

2.1. Pharmacological protocol

After the enrollment into the study, the patients were randomized by an independent pharmacologist of the study into three groups (A–C), the envelope method with random numbers was used. The independent pharmacologist prepared coded infusions with the study drug/placebo and was not directly involved in the clinical treatment of randomized patients. Both the operation theater staff and that of the intensive care unit were blinded regarding the study drug. The patients from group A ($n=32$) were given tranexamic acid (Exacyl, Sanofi Winthrop, France) 1 g before skin incision and a continuous infusion of 200 mg/h during the whole surgical procedure. The patients from group B ($n=29$) were given aprotinin (Gordox, Gedeon Richter, Hungary) 1 million IU before skin incision and onward 250,000 IU/h. The patients from group C ($n=30$) were infused normal saline as a placebo. The basic characteristics of the patient groups are shown in Table 1.

2.2. Anaesthesiological and surgical protocols

Remifentanil-based ultra-fast-track anaesthesia (with the application of propofol, midazolam, atracurium and inhaled isoflurane) was performed in all patients. This type of general anaesthesia, without the use of an epidural catheter, is a standard method for OPCAB surgery in our center [14–16].

During the procedure and postoperatively the patients were administered crystalloid solutions and 5% albumin solution if necessary, synthetic colloidal solutions were strictly not used. A red blood cell transfusion was administered when hemoglobin decreased to less than 8.5 g/dL and/or hematocrit less than 26. A transfusion of fresh frozen plasma was instituted (to correct a suspected deficiency of coagulation factors) when chest drain bleeding increased to >150 mL/h or to >100 mL/h for two consecutive hours.

The patients were operated on from full midline sternotomy, the left internal mammary artery was harvested in all cases with possible harvest of other grafts (great saphenous vein and /or radial artery). The verticalization of the beating heart was achieved using an Axius Xpose Device (Guidant, Cupertino, CA) while an Ultima Vacuum Assist (Guidant, Cupertino, CA) was used for the stabilization of the anastomosis site. The initial dose of intravenous heparin 100 IU/kg was administered after harvesting the left internal mammary artery with target activated clotting time (ACT)—Celite-activated system—(Hemochron 401, International Technidyne Corporation, Edison, NJ) over 250 s. On the completion of anastomoses, heparinization was partially reversed with half-dose of protamine chloride, regardless of ACT value.

A surgical postoperative re-exploration was based on our standard criterion: chest drainage 300 mL/h for two consecutive hours, or 200 mL/h for 3 h, or signs of cardiac tamponade verified by echocardiography.

2.3. Laboratory analyses

Blood samples for evaluation of hematological parameters (hemoglobin, hematocrit, platelet count, prothrombin time,

Table 1
Basic demographic, preoperative hematological, and intraoperative characteristics

		Group A ($n=32$) tranexamic acid	Group B ($n=29$) aprotinin	Group C ($n=30$) placebo	P-value
Age (years)	Arithm.	68.4 (64.6,72.2)	67.3 (64.2,70.4)	68.9 (65.8,72.0)	0.783
Gender (male/female) (no. of pts, percentage)		16 (50.0%)/16	20 (69.0%)/9	22 (73.3%)/8	0.144
Weight (kg)	Arithm.	80.4 (74.9,86.0)	80.9 (77.1,84.7)	82.6 (77.7,87.5)	0.794
Additive EuroSCORE	Arithm.	4.28 (3.16,5.40)	3.66 (2.76,4.55)	3.73 (2.85,4.62)	0.599
Logistic EuroSCORE	Geom.	3.33 (2.40,4.63)	2.77 (2.04,3.75)	2.59 (1.97,3.40)	0.458
Hematocrit	Geom.	42.00 (40.87,43.15)	43.24 (41.66,44.87)	42.79 (41.43, 44.20)	0.413
Hemoglobin (g/dL)	Geom.	14.24 (13.81,14.68)	14.81 (14.21,15.43)	14.58 (14.11,15.08)	0.261
Platelet count (10^9/L)	Geom.	238.8 (218.5,260.9)	224.1 (200.8,250.1)	230.9 (208.3,256.0)	0.656
Fibrinogen (g/L)	Geom.	3.975 (3.667,4.308)	3.938 (3.608,4.299)	4.309 (3.853,4.819)	0.323
aPTT (sec.)	Geom.	36.39 (30.81,42.98)	36.36 (33.11,39.94)	35.90 (33.89,38.02)	0.983
INR	Geom.	1.030 (1.007,1.054)	1.045 (1.019,1.071)	1.053 (1.029,1.077)	0.408
Preoperative aspirin (no. of pts, percentage)	Yes/no	13 (40.6%)/19	11 (37.9%)/18	10 (33.3%)/20	0.836
Preoperative LMWH (no. of pts, percentage)	Yes/no	2 (6.3%)/30	4 (13.8%)/25	7 (23.3%)/23	0.157
Preoperative UFH (no. of pts, percentage)	Yes/no	12 (37.5%)/20	11 (37.9%)/18	16 (53.3%)/14	0.367
Operating time (min)	Geom.	141.7 (129.8,154.7)	139.6 (127.5,152.8)	152.1 (137.7,168.1)	0.370
Number of grafts	Arithm.	1.88 (1.59,2.16)	1.76 (1.50,2.02)	1.87 (1.61,2.12)	0.789

Data are presented as arithmetic means (arithm.) or geometric means (geom.) and 95% confidence intervals, unless otherwise specified (LMWH, low molecular weight heparin; UFH, unfractioned heparin).

activated partial thromboplastin time, and fibrinogen) were taken and processed by a routine way. Myocardial enzymes were assessed before the operation, and 8 and 24 h postoperatively. Creatine phosphokinase (CK) and isoenzyme MB (CK-MB) levels were determined by a dry chemistry method with the Vitros 950 analyzer (Ortho-Clinical Diagnostic and Johnson & Johnson, Raritan, NJ). Troponin I levels were analyzed by a chemiluminiscence method with Immulite Turbo analyzer (DPC, Los Angeles, CA), using specific antibodies Turbo Troponin I (DPC, Los Angeles, CA). D-dimer levels were assessed by a micro-latex imunoassay procedure for a quantitative measurement of D-dimer on the Stago Compact analyzer (Diagnostica Stago, Parsippany, NJ) using Liatest Stachrom D-D antibodies (Diagnostica Stago, Parsippany, NJ).

2.4. Statistical analysis

Statistical analysis was done by statistical software Stata, release 7.0 (Stata Corporation, College Station, TX) and SPSS, version 12.0.1 (SPSS, Inc., Chicago, IL). The location of the continuous variables was characterized by arithmetic or geometric means (for normally or log-normally distributed data, respectively) and their variability was shown by 95% confidence intervals. Categorical data were described using absolute and relative frequencies (expressed as percentages).

The statistical evaluation was based on various models of the analysis of variance. If a statistically significant result was obtained, Sidak's and Dunnett's post hoc tests were used to locate the differences between the groups. For categorical data, χ^2 test and Fisher's exact test were applied. The comparison of postoperative blood loss between the groups was adjusted with respect to the preoperative treatment with antiaggregative/anticoagulant drugs. Troponin I values were analyzed using a specific form of the analysis of variance suitable for left censored data. All statistical tests were evaluated at significance level of 0.05.

3. Results

From 100 patients enrolled to the study, one patient (with emergent re-exploration for massive bleeding with the peroperative findig of perforation of venous bypass) died on postoperative day 10 from multiorgan failure and sepsis. Except for three patients, who underwent a postoperative surgical revision with the finding of an apparent surgical source of bleeding, no other patient required re-exploration in the ensuing course. Altogether nine enrollees (six patients converted to on-pump surgery+3 patients with surgical cause of hemorrhage) were withdrawn from the study, so the following data concern 91 assessed patients. Median intensive care unit length of stay was similar for all regimens ($P=0.691$): 23 (min—max 6–84) h (group A), 22 (15–72) h (group B) and 24 (3.5–69) h (group C), respectively. The median length of in-department stay was 6 days for all groups (group A: min—max 3–11, group B: 3–10, group C: 3–41). Two patients with the longest hospitalization (12 and 41 days) originated from group C, but the in-patient difference between groups was not significant ($P=0.824$). In group A, the tranexamic acid total cost was estimated at EUR 2.0 per patient, vs. the aprotinin total cost in group B estimated at EUR 82.5 per patient, on average, calculated from the Czech Republic market prices.

Groups A–C showed comparable demographic, preoperative hematological and basic intraoperative characteristics, with the exception of male/female ratio. In group A, an equal numbers of male and female patients were enrolled, in contrast to groups B and C with the majority of male study subjects. However, this inequality did not reach a statistical significance ($P=0.144$).

The number of patients under the influence of aspirine was almost the same in all groups ($P=0.836$). However, a slightly (but non-significantly) higher percentage of patients in group C had a low-molecular heparin withdrawal <24 h before surgery ($P=0.157$) and a preoperative continuous unfractioned heparin infusion ($P=0.367$), in comparison with groups A and B. Neverthless, additional covariates were entered into the statistical model to control a potential confounding effect of antiaggregative/anticoagulant drugs on the inter-group comparison of postoperative bleedning.

3.1. Intraoperative and postoperative blood loss

No statistically significant differences were found between the groups in the intraoperative blood loss (geometric means [95% confidence intervals]—group A: 267.2 [215.8, 330.8] mL, group B: 241.9 [198.4, 294.8] mL and group C: 319.3 [256.0, 398.2] mL) ($P=0.134$).

Blood loss during the first 4 h postoperatively shows highly significant differences between the groups (Fig. 1) (geometric means [95% confidence intervals]—group A: 89.3 [72.7, 109.8] mL, group B: 72.3 [49.2, 106.3] mL and group C: 192.3 [151.8, 243.5] mL) ($P<0.001$). Significant inter-group differences were also found in a cumulative blood loss within the first 8 h (group A: 152.1 [120.7, 191.6] mL, group B: 130.3 [88.1, 192.8] mL and group C: 283.8 [226.0, 356.3] mL) ($P=0.001$) and within the first 24 h postoperatively (group A: 410.3 [337.6, 498.6] mL, group B: 345.8 [256.0, 398.2] mL and group C: 619.8 [524.3, 732.8] mL) ($P<0.001$), respectively. There were no differences between the treated groups A and B at any time, but placebo group C marks off both

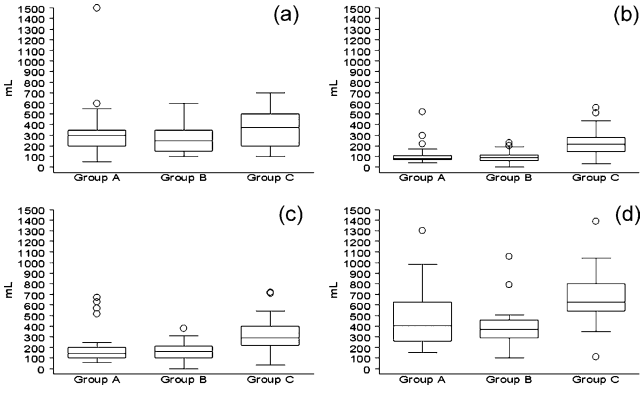


Fig. 1. Intraoperative (a) and postoperative cumulative blood loss in 4 h (b), 8 h (c) and 24 h (d). Inter-group differences (a, NS; b, $P<0.001$; c, $P=0.001$; d, $P<0.001$).

Table 2
Hematological parameters 24 h postoperatively and the number of re-transfused patients

		Group A ($n=32$) tranexamic acid	Group B ($n=29$) aprotinin	Group C ($n=30$) placebo	P-value
Hematocrit	Geom.	33.12 (31.47,34.85)	35.00 (33.34,36.73)	32.00 (29.94,34.21)	0.077
Hemoglobin (g/dL)	Geom.	11.17 (10.56,11.82)	11.85 (11.30,12.42)	10.70 (10.24,11.18)	0.018
Platelet count (10^9/L)	Geom.	199.2 (177.9,223.0)	190.0 (169.3,213.3)	184.8 (163.1,209.5)	0.645
Fibrinogen (g/L)	Geom.	4.430 (4.102,4.784)	4.724 (4.424,5.044)	4.593 (4.208,5.013)	0.489
aPTT (sec.)	Geom.	35.61 (32.73,38.75)	34.36 (32.49,36.35)	37.60 (34.43,41.06)	0.266
INR	Geom.	1.278 (1.229,1.329)	1.270 (1.228,1.314)	1.314 (1.261,1.369)	0.412
PRBC received (no. of pts, percentage)	Yes/no	3 (9.4%)/29	1 (3.4%)/28	6 (20.0%)/24	0.119
FFP received (no. of pts, percentage)	Yes/no	2 (6.3%)/30	0 (0.0%)/29	4 (13.3%)/26	0.118

Data are presented as geometric means (geom.) and 95% confidence intervals, except for the number of re-transfused patients (PRBC, packed red blood cells; FFP, resh-frozen plasma).

groups A and B. The power of ANOVA test was higher than 0.95 at all postoperative time points.

3.2. Hematological parameters and transfusion requirements

Hematological parameters 24 h postoperatively are presented in Table 2. Both mean hematocrit and hemoglobin values are the lowest in placebo group C and the highest in aprotinin group B. Based on the analysis of variance, means in groups A–C were statistically different as a whole for hemoglobin ($P=0.018$). For hematocrit, borderline differences were found ($P=0.077$). A subsequent pairwise comparison revealed significant differences between groups B and C in both parameters. Groups A and B, as well as C and A were statistically indistinguishable. Inter-group differences in other hematological parameters (platelet counts, fibrinogen levels, aPTT and INR) were statistically non-significant.

There were no intraoperative transfusion requirements. The percentage of patients receiving allogenic blood products in the postoperative period (either packed red blood cells or fresh-frozen plasma) was not significantly different between the groups ($P=0.119$ and $P=0.118$, respectively). In both cases, the total number of re-transfused patients was the highest in placebo group C.

3.3. Postoperative myocardial ischemia, myocardial enzymes, and levels of D-dimer

Electrocardiographical signs of myocardial ischemia in the very early postoperative period was detected in two patients (patient J.Z. from aprotinin group B and patient M.K. from placebo group C). Patient J.Z. underwent a single coronary artery bypass grafting (a free graft of left internal thoracic artery was used as a conduit to the circumference of extremely sclerotic left anterior descending coronary artery). Patient M.K. underwent double bypass technically without any complications. In both hemodynamic stable patients, urgent echocardiographical examinations showed no new myocardial wall motion hypokinesis and the situation was solved in a conservative manner by coronary dilatating therapy. In both cases, after a few hours of treatment the electrocardiographical signs of myocardial ischemia disappeared and the ensuing course of the patients was without complications, although patient J.Z. showed postoperative peak troponin I value 27.8 μg/L. No signs of low cardiac

Table 3
Time course of myocardial enzymes and D-dimer levels

		Group A ($n=32$) tranexamic acid	Group B ($n=29$) aprotinin	Group C ($n=30$) placebo	P-value
CK μkat/L					
Preoperatively	Geom.	0.94 (0.77,1.16)	1.07 (0.83,1.38)	1.17 (0.93,1.48)	0.394
At 8 h	Geom.	5.62 (4.73,6.68)	5.57 (4.48,6.92)	5.30 (4.46,6.30)	0.888
At 24 h	Geom.	10.77 (8.67,13.37)	10.93 (8.89,13.44)	9.85 (7.58,12.80)	0.779
CK-MB μkat/L					
Preoperatively	Geom.	0.114 (0.083,0.157)	0.121 (0.090,0.162)	0.106 (0.077,0.147)	0.838
At 8 h	Geom.	0.051 (0.033,0.079)	0.053 (0.033,0.084)	0.052 (0.032,0.084)	0.996
At 24 h	Geom.	0.254 (0.183,0.354)	0.256 (0.167,0.393)	0.245 (0.165,0.365)	0.985
CK-MB/CK					
Preoperatively	Geom.	0.121 (0.093,0.157)	0.113 (0.082,0.156)	0.091 (0.063,0.130)	0.375
At 8 h	Geom.	0.009 (0.006,0.013)	0.009 (0.006,0.014)	0.010 (0.007,0.015)	0.966
At 24 h	Geom.	0.024 (0.019,0.030)	0.023 (0.017,0.032)	0.025 (0.019,0.032)	0.937
Troponin I μg/L					
Preoperatively	Geom.	0.240 (0.128,0.450)	0.166 (0.071,0.388)	0.159 (0.068,0.388)	0.391
At 8 h	Geom.	0.841 (0.513,1.376)	0.380 (0.214,0.674)	1.084 (0.671,1.753)	0.015
At 24 h	Geom.	0.631 (0.344,1.155)	0.604 (0.321,1.138)	0.961 (0.535,1.726)	0.490
D-dimers ng/mL					
Preoperatively	Geom.	387.5 (263.7,469.4)	283.1 (193.5,414.3)	473.8 (332.8,674.7)	0.147
At 24 h	Geom.	627.8 (494.2,797.5)	871.8 (690.8,1100.3)	1537.4 (1106.6,2136.0)	<0.001

Data are presented as geometric means (geom.) and 95% confidence intervals (CK, creatin phosphokinase; CK-MB, isoenzyme MB; CK-MB/CK, ratio [relative index] of CK-MB/CK).

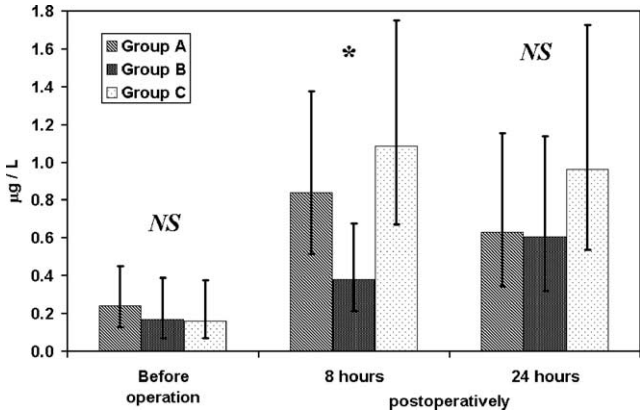


Fig. 2. Time course of troponin I levels. Data are presented as geometric means, error bars indicate 95% confidence intervals. Significant inter-group differences at 8 h postoperatively were found (*$P=0.015$).

output syndrome were observed in the postoperative period of all the assesed patients, and so no Swan-Ganz catheter utilization was required.

The time course of creatine phosphokinase (CK) levels, isoenzyme MB (CK-MB) levels and the ratio (relative index) of CK-MB/CK are shown in Table 3. No statistically significant inter-group differences were found at any time (before the operation, 8 h, and 24 h postoperatively). Fig. 2 presents the development of troponin I levels. Troponin I levels differed between the three groups 8 h postoperatively ($P=0.015$). The geometric mean of troponin I level was the highest in placebo group C; post hoc tests showed first of all a statistically significant difference between groups B and C ($P<0.001$), and then a less noticeable difference between groups A and B ($P=0.047$).

Table 3 also demonstrates the time course of D-dimer levels (preoperatively, at 24 h postoperatively). The preoperative mean levels of D-dimer were comparable in all the study groups ($P=0.147$). The increase in D-dimer levels 24 h postoperatively was the highest and statistically significant in placebo group C compared with those of the other groups ($P<0.001$), which were statistically indistinguishable.

4. Discussion

Drugs that preserve hemostasis through plasmin inhibition include synthetic lysine analogues, such as tranexamic acid and the most potent, naturally occuring antifibrinolytic agent aprotinin, which is called 'a broad-spectrum antifibrionolysin' due to its antiinflammatory and endothelial modulating properties.The efficacy of these pharmacological strategies on the decrease in the frequency of surgical reexploration and the need of allogenic blood transfusion in on-pump cardiac surgery has been proved many times; according to meta-analysis of Levi et al. treatment with aprotinin in this type of surgery decreased mortality almost 2-folds [17]. Only a limited number of studies have been concerned with the use of antifibrinolytics in OPCAB surgery, and have demonstrated its effectiveness, although the surgical aggression in OPCAB may be as important as (or even more important than) the use of cardiopulmonary bypass in terms of coagulation–fibrinolytic pathway activation [18]. An increase in fibrinolytic activity in OPCAB is supposedly due to the release of a tissue plasminogen activator, which starts during the skin incision and sternotomy and continues through the surgical tissue manipulation. To the best of our knowledge, this is currently the first prospective, randomized, double-blind study comparing tranexamic acid vs. aprotinin vs. placebo in OPCAB surgery. In our study we have proved that both tranexamic acid and aprotinin are likewise effective in reducing postoperative bleeding in OPCAB patients in comparison with placebo. This finding is in agreement with separate considerations for tranexamic acid [7,9,10] and aprotinin [8] in OPCAB surgery, as well. Our data does not show a significant difference in blood loss between tranexamic acid group A and aprotinin group B. According to published data in on-pump coronary surgery, blood loss at 24 h in the tranexamic acid treated patients was altogether higher in comparison with the aprotinin treated patients ($P=0.03$), but with the similar perioperative transfusion requirements [19]. In our study we have demonstrated that the mean values of hemoglobin at 24 h postoperatively were significantly lowest in placebo group C and that the borderline differences have been found in mean hematocrit values. We have not found any statistically significant differences in transfusion requirements (percentage of patients who received packed red blood cells or fresh-frozen plasma), but the total number of re-transfused patients was the highest in placebo group C. The lack of statistical significance is probably due to the small number of re-transfused patients on the whole.

The question of safety associated with the use of antifibrinolytic drugs has been discussed in on-pump cardiac surgery, as well [17,20]. There is a theoretical risk of an increased thrombotic tendency during the treatment with fibrinolytic inhibitors, and several earlier sporadic reports on coronary graft occlusion in patiens receiving these therapies have been published [21,22]. These observations have not been supported by any results of large clinical studies [17,23,24]. In our study we observed only one postoperative myocardial infarction in aprotinin treated group B and one temporary postoperative myocardial ischemia in placebo group C, and no cerebrovascular or pulmonary embolism was noticed. There were no inter-group differences in the mean levels of myocardial enzymes observed, with the exception of the highest troponin I level 8 h postoperatively in placebo group C. Our experience thus indicates that the use of fibrinolytic inhibitors seems to be safe in OPCAB surgery, as well, but a larger number of safety trials is required for a better assessment of possible thrombotic complications [25].

Looking into the coagulation–fibrinolytic pathway activation, we found significantly higher mean values of D-dimer in placebo group C at 24 h postoperatively, compared with groups A and B, treated with antifibrinolytic drugs. The post OPCAB finding of elevated values of D-dimer and the inhibition of D-dimer levels by fibrinolitic inhibitors is in agreement with Casati et al. [7] and Englberger et al. [8].

Based on the results of our prospective, randomized, double-blind TAP study we conclude that both tranexamic acid and aprotinin significantly reduce the postoperative blood loss in OPCAB patients, and the efficacy of tranexamic

acid and aprotinin, respectively, seems to be quite similar. We did not observe any statistically significant difference in the need for allogenic transfusion, although the total number of re-transfused patients was the highest in placebo group. Tranexamic acid appears to be a potent, cost-effective and safe alternative to aprotinin in OPCAB surgery.

Acknowledgements

Financial support by the Cardiovascular research project of the Charles University Prague, Czech Republic, no. MSM0021620817.

References

[1] Barrons RW, Jahr JS. A review of post-cardiopulmonary bypass bleeding, aminocaproic acid, tranexamic acid, and aprotinin. Am J Ther 1996;3:821–38.
[2] Laupacis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using peri-operative blood transfusion as the outcome. The international study of perioperative transfusion (ISPOT) investigators. Anaesth Analg 1997;85:1258–67.
[3] Wong BI, McLean RF, Fremes SE, Deemar KA, Harrington EM, Christakis GT, Goldman BS. Aprotinin and tranexamic acid for high transfusion risk cardiac surgery. Ann Thorac Surg 2000;69:808–16.
[4] Andreasen JJ, Nielsen C. Prophylactic tranexamic acid in elective, primary coronary bypass surgery using cardiopulmonary bypass. Eur J Cardiothorac Surg 2004;26:311–7.
[5] Levy JH. Pharmacologic preservation of the hemostatic system during cardiac surgery. Ann Thorac Surg 2001;72:S1814–S20.
[6] Despotis GJ, Avidan MS, Hogue Jr CW. Mechanisms and attenuation of hemostatic activation during extracorporeal circulation. Ann Thorac Surg 2001;72:S1824–S31.
[7] Casati V, Gerly Ch, Franco A, Torri G, D'Angelo A, Benussi S, Alfieri O. Tranexamic acid in off-pump coronary surgery: a preliminary, randomized, double-blind, placebo-controlled study. Ann Thorac Surg 2001;72:470–5.
[8] Englberger L, Markart P, Eckstein FS, Immer FF, Berdat PA, Carrel TP. Aprotinin reduces blood loss in off-pump coronary artery bypass (OPCAB) surgery. Eur J Cardiothorac Surg 2002;22:545–51.
[9] Jares M, Vanek T, Straka Z, Brucek P. Tranexamic acid reduces bleeding after off-pump coronary artery bypass grafting. J Cardiovasc Surg (Torino) 2003;44:205–8.
[10] Casati V, Della Valle P, Benussi S, Franco A, Gerli C, Baili P, Alfieri O, D'Angelo A. Effects of tranexamic acid in postoperative bleeding and related hematological variables in coronary surgery: comparison between on-pump and off-pump techniques. J Thorac Cardiovasc Surg 2004;128:83–91.
[11] Nader ND, Zhadra WZ, Reich NT, Bacon DR, Salerno TA, Panos AL. Blood product use in cardiac revascularization: comparison of on- and off-pump techniques. Ann Thorac Surg 1999;68:1640–3.
[12] Straka Z, Widimsky P, Jirasek K, Stros P, Votava J, Vanek T, Brucek P, Kolesar M, Spacek R. Off-pump versus on-pump coronary surgery: final results from a prospective randomized study PRAGUE-4. Ann Thorac Surg 2004;77:789–93.
[13] Frankel TL, Stamou SC, Lowery RC, Kapetanakis EI, Hill PC, Haile E, Corso PJ. Risk factors for hemorrhage-related reexploration and blood transfusion after conventional versus coronary revascularization without cardiopulmonary bypass. Eur J Cardiothorac Surg 2005;27:494–500.
[14] Vanek T, Brucek P, Straka Z. Fast track as a routine for open-heart surgery. Eur J Cardiothorac Surg 2001;21:369.
[15] Straka Z, Brucek P, Vanek T, Votava J, Widimsky P. Routine immediate extubation for off-pump coronary artery bypass grafting without thoracic epidural analgesia. Ann Thorac Surg 2002;74:1544–7.
[16] Brucek PJ, Straka Z, Vanek T, Jares M. Less invasive cardiac anesthesia: an ultra-fast-track procedure avoiding thoracic epidural analgesia. Heart Surg Forum 2003;6:E107–E10.
[17] Levi M, Cromheecke ME, de Jonge E, Prins MH, de Mol BJM, Briët E, Büller HR. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. Lancet 1999;354:1940–7.
[18] Biglioli P, Cannata A, Alamanni F, Naliato M, Porqueddu M, Zanobini M, Tremoli E, Parolari A. Biological effects of off-pump vs. on-pump coronary artery surgery: focus on inflammation, hemostasis and oxidative stress. Eur J Cardiothorac Surg 2003;24:260–9.
[19] Hekmat K, Zimmermann T, Kampe S, Kasper SM, Weber HJ, Geissler HJ, Mehlhorn U. Impact of tranexamic acid vs. aprotinin on blood loss and transfusion requirements after cardiopulmonary bypass: a prospective, randomised, double-blind trial. Curr Med Res Opin 2004;20:121–6.
[20] Smith PK, Muhlbaier LH. Aprotinin: safe and effective only with the full-dose regimen. Ann Thorac Surg 1996;62:1575–7.
[21] Cosgrove DM, Heric B, Lytle BW, Taylor PC, Novoa R, Golding LAR, Stewart RW, McCarthy PM, Loop FD. Aprotinin therapy for reoperative myocardial revascularization—a placebo-controlled study. Ann Thorac Surg 1992;54:1031–8.
[22] Lemmer JH, Dilling EW, Morton JR, Rich JB, Robicsek F, Bricker DL, Hantler CB, Copeland 3rd JG, Ochsner JL, Daily PO, Whitten CW, Noon GP, Maddi R. Aprotinin for primary coronary artery bypass grafting: a multicenter trial of three dose regimens. Ann Thorac Surg 1996;62:1659–67.
[23] Alderman EL, Levy JH, Rich JB, Nili M, Vidne B, Schaff H, Uretzky G, Pettersson G, Thiis JJ, Hantler CB, Chaitman B, Nadel A. Analyses of coronary graft patency after aprotinin use: results from the international multicenter aprotinin graft patency experience (IMAGE) trial. J Thorac Cardiovasc Surg 1998;116:716–30.
[24] Levy JH. Efficacy and safety of aprotinin in cardiac surgery. Orthopedics 2004;27:S659–S62.
[25] Mariani M, Gu Y, Boonstra P, Grandjean JG, van Oeveren W, Ebels T. Procoagulant activity after off-pump coronary operation: is the current anticoagulation adequate? Ann Thorac Surg 1999;67:1370–5.

Antifibrinolytika u kardiochirurgických operací bez mimotělního oběhu – analýza krevních ztrát, bezpečnosti a efektivity nákladů

Vaněk T.[1], Jareš M.[1], Fajt R.[1], Straka Z.[1], Malý M.[2]

[1]Kardiochirurgická klinika, Univerzita Karlova, 3. LF a FNKV, Praha
[2]Oddělení biostatistiky a informatiky, SZU, Praha

Souhrn

Cíl studie: Porovnat hemostatické účinky antifibrinolytik (tranexamové kyseliny, aprotininu) a placeba u revaskularizačních operací myokardu bez mimotělního oběhu a zhodnotit vliv této terapie na efektivitu nákladů.
Typ studie: Prospektivní, randomizovaná, dvojitě slepá studie.
Název a sídlo pracoviště: 3. LF UK a FNKV, Praha.
Materiál a metoda: Do studie bylo zařazeno 100 pacientů, hodnoceno bylo 91 nemocných (skupina A, n = 32, tranexamová kyselina 1 g do kožního řezu a dále kontinuálně 200 mg/h; skupina B, n = 29, aprotinin 1000 000 m. j. do kožního řezu a dále 250 000 m. j./h; skupina C, n = 30, placebo).
Výsledky: Vysoce signifikantní rozdíly mezi skupinami byly nalezeny v kumulativních krevních ztrátách za 4 h (geometrické průměry [95% intervaly spolehlivosti] – skupina A: 89,3 ml [72,7 ml; 109,8 ml], skupina B: 72,3 ml [49,2 ml; 106,3 ml] a skupina C: 192,3 ml [151,8 ml; 243,5 ml]) ($p < 0,001$), za 8 h (skupina A: 152,1 ml [120,7 ml; 191,6 ml], skupina B: 130,3 ml [88,1 ml; 192,8 ml] a skupina C: 283,8 ml [226,0 ml; 356,3 ml]) ($p = 0,001$), a během 24 h po operaci (skupina A: 410,3 ml [337,6 ml; 498,6 ml], skupina B: 345,8 ml [256,0 ml; 398,2 ml] a skupina C: 619,8 ml [524,3 ml; 732,8 ml]) ($p < 0,001$). Ve všech časech byla skupina C (s placebem) signifikantně odlišná od skupin léčených antifibrinolytiky (skupiny A a B), přičemž nebyly nalezeny zásadní rozdíly mezi skupinami A a B. V léčených skupinách nedošlo k elevaci průměrných hodnot kardiospecifických enzymů v porovnání se skupinou C. Nezjistili jsme statisticky významnou odlišnost mezi skupinami v počtu pacientů, kterým byl během prvních 24 hodin po operaci podán krevní derivát (resuspendované erytrocyty, $p = 0,119$, nebo plazma z plné krve, $p = 0,118$), avšak počet nemocných retransfundovaných resuspendovanými erytrocyty během celé hospitalizace byl statisticky významně vyšší ve skupině C v porovnání se skupinou B ($p = 0,002$). Efektivita průměrných nákladů na antifibrinolytikum a transfuzní přípravky se jeví jako nejpříznivější ve skupině pacientů, kterým byla podávána tranexamová kyselina.
Závěr: Tranexamová kyselina a aprotinin se zdají být podobně účinné v redukci krevních ztrát u kardiochirurgických operací bez mimotělního oběhu. Tranexamová kyselina se jeví jako cenově výhodnější a bezpečná alternativa k aprotininu.
Klíčová slova: tranexamová kyselina – aprotinin – kardiochirurgické operace – aortokoronární rekonstrukce bez mimotělního oběhu

Abstract

Antifibrinolytic agents in off-pump cardiac surgery: analysis of blood loss, safety and cost-effectiveness

Objective: To compare the haemostatic effects of fibrinolytic inhibitors (tranexamic acid, aprotinin) vs. placebo in off-pump coronary artery bypass surgery and to evaluate the impact of this therapy on cost-effectiveness.
Design: Prospective, randomized, double-blind study.
Setting: University Teaching Hospital, Prague, Czech Republic.
Material and Method: 100 patients were enrolled in the study and 91 of them were assessed (group A, n = 32, tranexamic acid 1 g before skin incision followed by continuous infusion at 200 mg/h; group B, n = 29, aprotinin 1,000,000 IU before skin incision and 250,000 IU/h afterwards; group C, n = 30, placebo).
Results: Highly significant inter-group differences were found in the cumulative blood loss within 4 h (geometric means [95% confidence intervals] – group A: 89.3 [72.7, 109.8] mL, group B: 72.3 [49.2, 106.3] mL and group C: 192.3 [151.8, 243.5] mL) ($P < 0.001$), within 8 h (group A: 152.1 [120.7, 191.6] mL, group B: 130.3 [88.1, 192.8] mL and group C: 283.8 [226.0, 356.3] mL) ($P = 0.001$), and within 24 h postoperatively (group A: 410.3 [337.6, 498.6] mL, group B: 345.8 [256.0, 398.2] mL and group C: 619.8 [524.3, 732.8] mL) ($P < 0.001$). At all time points, group C (placebo) was significantly distinct from the groups treated with fibrinolytic inhibitors (groups A, B). However, no essential differences between groups A and B were found. Treated groups did not demonstrate postoperative increase in mean levels of myocardial enzymes compared with group C. No statistically significant inter-group difference was found in the number of re-transfused patients (either packed red blood cells, $P = 0.119$, or fresh-frozen plasma, $P = 0.118$) during the first 24 h postoperatively, but the number of re-transfused patients during the hospital stay was statistically significantly higher in group C compared with group B ($P = 0.002$). Cost effectiveness of

the antifibrinolytic agent and blood product treatment seems to be on average the most favourable in the tranexamic acid group.
Conclusion: Both tranexamic acid and aprotinin seem to be similarly effective in the reduction of postoperative blood loss in off-pump cardiac surgery. Tranexamic acid appears to be a cost-effective and safe alternative to aprotinin.
Key words: tranexamic acid – aprotinin – cardiac surgical procedures – off-pump coronary artery bypass

Anest. intenziv. Med., 2006, 17, č. 1, s. 6–13.

Úvod

Problematika zvýšeného perioperačního krvácení v kardiochirurgii je stále v centru pozornosti anesteziologů a chirurgů na celém světě. Některé literární prameny uvádějí, že incidence excesivního krvácení po operacích srdce dosahuje až 11 %, podle jiných zdrojů má 5–7 % pacientů pooperační krevní ztráty větší než 2 l během prvních 24 hodin po výkonu [1, 2].

Jedním z mechanismů, které se na zvýšeném perioperačním krvácení podílejí (při nepřítomnosti chirurgického zdroje), je nepochybně zvýšená fibrinolýza. Teoreticky dochází k aktivaci fibrinolýzy během klasické kardiochirurgické operace s použitím mimotělního oběhu (MO) ve dvou momentech: za prvé od počátku operace dochází k uvolnění tkáňového aktivátoru plazminogenu (kožní řez, sternotomie, chirurgické manipulace s nitrohrudními tkáněmi), za druhé během MO, kdy je běžně do náplně přístroje pro mimotělní oběh navracena krev z operačního pole, která obsahuje velké množství cytokinů, tkáňového faktoru a tkáňového aktivátoru plazminogenu [3]. Aktivace fibrinolýzy nevede pouze ke zvýšenému perioperačnímu krvácení, ale může mít i další negativní dopady na pacienta: Cvachovec et. al. v retrospektivní studii zahrnující 142 dospělých kardiochirurgických nemocných nalezli u pacientů s hyperfibrinolýzou zvýšenou mortalitu a potřebu vyšší vazopresorické a objemově-koloidní podpory [4].

Příznivý účinek peroperačně podaných antifibrinolitik (aprotinin, analoga lysinu – tranexamová kyselina, ε-aminokapronová kyselina) na krvácení u kardiochirurgických výkonů s použitím MO byl opakovaně prověřen. Levi et. al. v metaanalýze, která zahrnovala 72 randomizovaných a klinicky relevantních studií (8 409 pacientů) prokázali, že léčba aprotininem a analogy lysinu signifikantně snížila frekvenci pooperačních chirurgických revizí pro krvácení a počet krevních transfuzí a v případě podání aprotininu došlo dokonce k signifikantnímu snížení perioperační mortality [5]. Bezpečnost této terapie (ve smyslu potenciálního nebezpečí uzávěru vytvořených bypassů) byla ověřena mezinárodní multicentrickou studií IMAGE, která hodnotila pooperační katetrizační výsledky u 860 nemocných z 13 kardiocenter [6].

Počet prací, které se zabývají podáním jednotlivých antifibrinolytik u kardiochirurgických operací bez použití MO, tzv. operace na „bijícím srdci" – Off-Pump Coronary Artery Bypass (OPCAB), je ve světovém písemnictví dosud omezený [7, 8, 9, 10]. Samotné chirurgické trauma a agrese přitom mohou být u tohoto typu výkonů stejně důležité jako užití MO ve smyslu aktivace koagulační a fibrinolytické kaskády.

Cílem výzkumu bylo porovnat perioperační krevní ztráty u pacientů, kteří podstoupili revaskularizační operaci myokardu bez MO a bylo jim peroperačně podáváno antifibrinolytikum/placebo. Bezpečnost antifibrinolytické terapie byla ověřována klinicky, monitorováním EKG a především sledováním vývoje hladin myokardiálních enzymů v pooperačním období. Sekundárním cílem výzkumu bylo posouzení nákladů na antifibrinolytika a krevní deriváty.

Soubor pacientů a metoda

V době od 15. října 2003 do 31. července 2004 proběhla na Kardiochirurgické klinice 3. LF UK a FNKV v Praze prospektivní, randomizovaná, dvojitě slepá studie TAP (tranexamová kyselina vs aprotinin vs placebo). Tato studie byla povolena Etickou komisí FNKV (EK/243/2003). Do studie bylo po získání informovaného souhlasu zařazeno 100 nemocných. Kritéria pro nezařazení byla následující: předchozí kardiochirurgická operace, akutní infarkt myokardu < 7 dnů před operací, anamnéza hematologického nebo hepatálního onemocnění, renální insuficience (kreatinin v séru > 150 μmol/l) a předoperační anémie (hemoglobin < 11 g/dl, hematokrit < 32%). Předoperační medikace antiagregancii nebo antikoagulancii (acetylsalicylová kyselina < 5 dnů před operací, nízkomolekulární heparin < 24 hodin před výkonem, kontinuální přívod nefrakcionovaného heparinu) nebyla vylučovacím kritériem, ale počet takto předoperačně léčených pacientů byl sledován. Nikdo z pacientů nebyl pod vlivem potentní protidestičkové léčby (inhibitory ADP, antagonisty receptorů GP IIb/IIIa).

Po zařazení do studie byli nemocní rozděleni nezávislým farmakologem studie do 3 skupin (A, B, C), randomizace byla prováděna obálkovou metodou. Ani personál operačních sálů, ani lékaři a sestry pooperačního oddělení nebyli informováni o typu podaného antifibrinolytika či o aplikaci placeba. Farmakolog studie připravil před operací infuzní láhve a injekční perfuzorové stříkačky s příslušným antifibrinolytikem podle randomizace, nebo s placebem. Pacientům ze skupiny A byla podána tranexamová kyselina (Exacyl, Sanofi Winthrop, Francie) 1 g do kožního řezu a dále kontinuálně v dávce 200 mg/hod.

Nemocným ze skupiny B byl aplikován aprotinin (Gordox, Gedeon Richter, Maďarsko) 1 000 000 m. j. do kožního řezu a dále kontinuálně 250 000 m. j./hod. Pacientům ze skupiny C byl podáván stejným způsobem fyziologický roztok jako placebo.

Kritéria pro převod transfuzních přípravků během operace a v době do 24 hodin po operaci jsme stanovili následujícím způsobem: podání resuspendovaných erytrocytů při poklesu hemoglobinu < 8,5 g/dl a/nebo hematokritu < 26, podání plazmy z plné krve ke korekci předpokládaného deficitu koagulačních faktorů při krvácení > 150 ml/h nebo > 100 ml/h po dvě následující hodiny za sebou. Pacientům byly podávány infuze krystaloidů a 5% albuminu podle potřeby; syntetické koloidní objemové náhrady nebyly používány. Po uplynutí 24 hodin od operace byly transfuzní přípravky aplikovány podle klinického stavu na základě rozhodnutí ošetřujícího lékaře.

Aktivovaný čas srážení (Activated Clotting Time – ACT) byl stanovován přímo na operačním sále před operací a na konci operace přístrojem Hemochron 401 (ITC, USA).

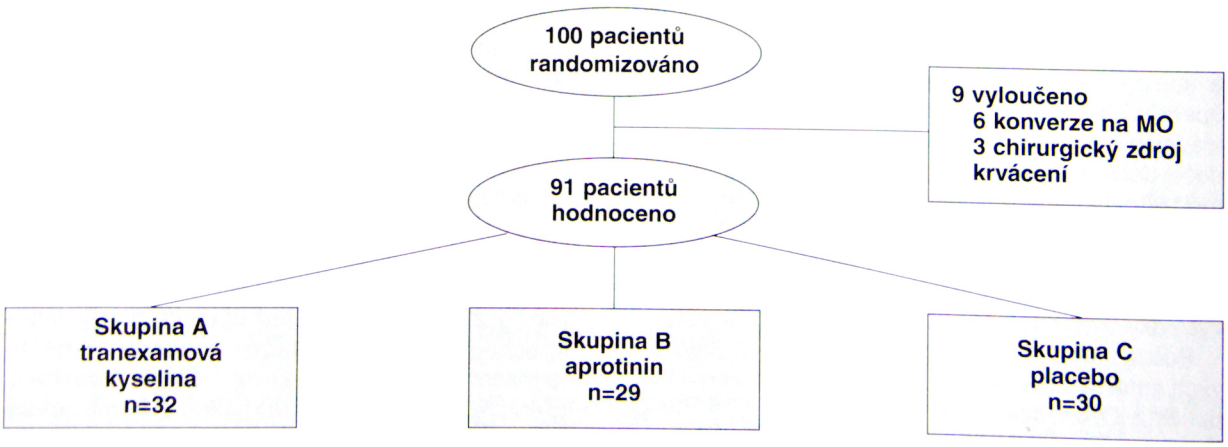
Krevní vzorky pro vyšetření kardiospecifických enzymů (kreatinkináza – CK, MB frakce kreatinkinázy – CK-MB, troponin I) byly nabírány před operací, 8 hod. a 24 hod. po operaci. U části nemocných byla též stanovována kreatinkináza MB mass – CK-MB mass. Hladiny D-dimerů byly zjišťovány předoperačně a 24 hodin po operaci.

Nemocní byli operováni v celkové ultra-fast-track anestezii za použití remifentanilu, midazolamu, atrakuria a inhalačně podávaného izofluranu. Tento typ anestezie, bez zavedení hrudního epidurálního katétru, je na našem pracovišti standardem pro kardiochirurgické operace bez MO [11]. Operačním přístupem byla ve všech případech klasická podélná sternotomie s odběrem levostranné vnitřní prsní tepny (*a. thoracica int. l. sin.*), vertikalizace bijícího srdce byla uskutečněna pomocí Axius Xpose Device (Guidant, USA) a stabilizace místa anastomózy bylo dosaženo pomocí Ultima Vacuum Assist (Guidant, USA). Úvodní dávka heparinu 100 m. j./kg byla po našití anastomóz částečně neutralizována poloviční dávkou protaminchloridu, bez ohledu na dosaženou hodnotu aktivovaného času srážení.

Statistická analýza byla prováděna softwarem Stata verze 7.0 (Stata Corporation, USA) a SPSS verze 12.0.1 (SPSS, USA). Střední hodnoty jsou uváděny jako aritmetické, respektive geometrické průměry (pro data s normálním, respektive logaritmicko-normálním rozložením) a jejich variabilita je vyjádřena 95% intervalem spolehlivosti. Statistické hodnocení bylo založeno na různých modelech analýzy rozptylu a pokud byl nalezen statisticky signifikantní rozdíl, byly pro zjištění, které skupiny se od sebe významně liší, použity Šidákovy a Dunnettovy postupy mnohonásobného porovnávání. Kategorická data uspořádaná v kontingenčních tabulkách byla hodnocena χ^2 testem dobré shody a Fisherovým faktoriálovým testem. Statistické porovnání pooperačních krevních ztrát mezi jednotlivými skupinami bylo adjustováno vzhledem k předoperační medikaci antiagregancii nebo antikoagulancii (do výpočtu pomocí analýzy rozptylu bylo zahrnuto dichotomické rozlišení mezi pacienty s medikací a bez ní, v důsledku čehož byly s ohledem na typ medikace korigovány p-hodnoty pro porovnání krevních ztrát). Všechny statistické testy byly prováděny na 5% hladině významnosti.

Výsledky

Na základě předem daných kritérií bylo ze 100 pacientů zařazených do studie vyloučeno 9 nemocných: 6 z nich bylo vyřazeno pro peroperační konverzi na MO (z důvodů intramuskulárního průběhu věnčitých tepen či hemodynamické nestability), 3 byli vyřazeni pro pooperační chirurgickou revizi pro krevní ztráty s jasným nálezem chirurgického zdroje krvácení (ve dvou případech krvácení z odstupu levostranné vnitřní prsní tepny, v jednom případě perforace žilního bypassu okrajem hrudního drénu). Ve studii tedy bylo nakonec hodnoceno zbývajících 91 nemocných (obr. 1). Základní charakteristiku souboru podává tabulka 1. Mediány doby pobytu na jednotce



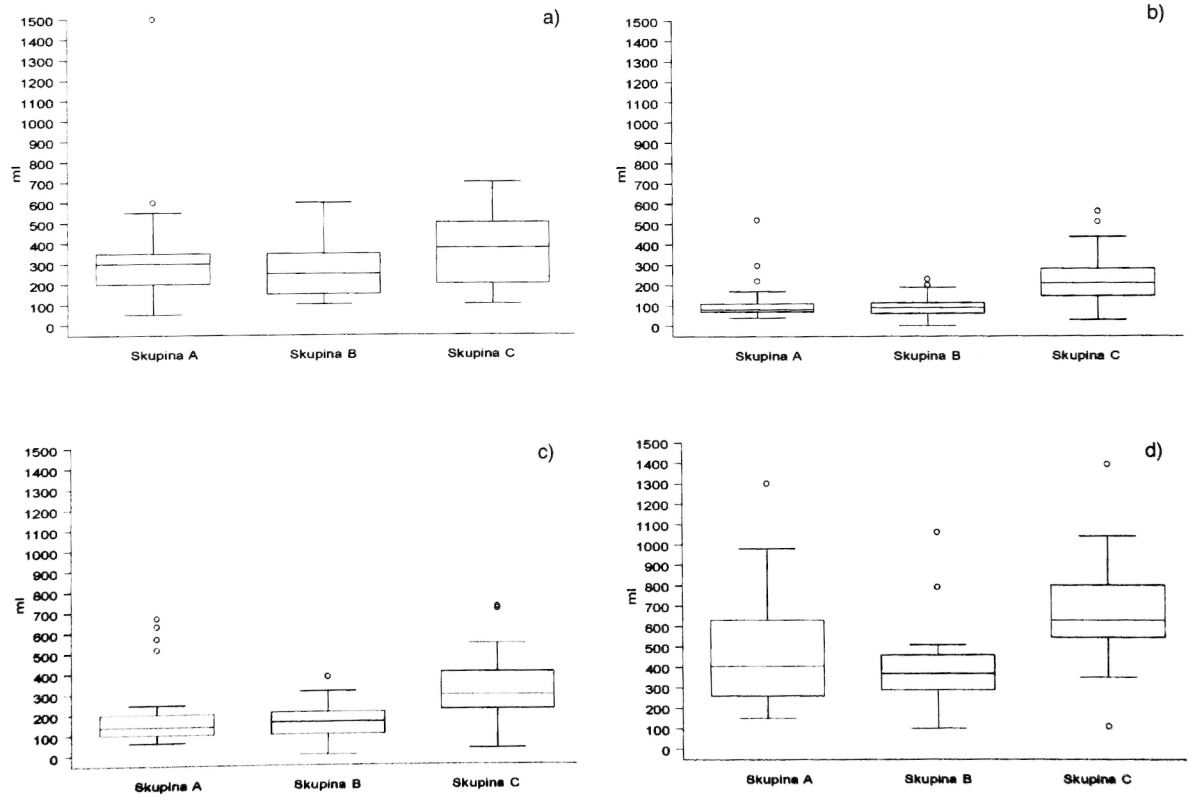
Obr. 1. Postupový diagram pacientů ve studii

Tabulka 1. Základní demografické údaje, předoperační hodnoty hematologických parametrů a hlavní peroperační údaje

		Skupina A	Skupina B	Skupina C	Hodnota *P*
Věk (roky)	aritm.	68,4 (64,6; 72,2)	67,3 (64,2; 70,4)	68,9 (65,8; 72,0)	0,783
Pohlaví	M/Ž	16 (50,0 %)/16	20 (69,0 %)/9	22 (73,3 %)/8	0,144
Hmotnost (kg)	aritm.	80,4 (74,9; 86,0)	80,9 (77,1; 84,7)	82,6 (77,7; 87,5)	0,794
Aditivní EuroSCORE	aritm.	4,28 (3,16; 5,40)	3,66 (2,76; 4,55)	3,73 (2,85; 4,62)	0,599
Hematokrit (%)	geom.	42,00 (40,87; 43,15)	43,24 (41,66; 44,87)	42,79 (41,43; 44,20)	0,413
Hemoglobin (g/dl)	geom.	14,24 (13,81; 14,67)	14,81 (14,21; 15,43)	14,58 (14,11; 15,08)	0,261
Trombocyty (10^9/l)	geom.	238,8 (218,5; 260,9)	224,1 (200,8; 250,1)	230,9 (208,3; 256,0)	0,656
Fibrinogen (g/l)	geom.	3,975 (3,667; 4,308)	3,938 (3,608; 4,299)	4,309 (3,853; 4,819)	0,323
aPTT (sec.)	geom.	36,39 (30,81; 42,98)	36,36 (33,11; 39,94)	35,90 (33,89; 38,02)	0,983
INR	geom.	1,030 (1,007; 1,054)	1,045 (1,019; 1,071)	1,053 (1,029; 1,077)	0,408
Acetylsalicylová kyselina (před operací)	ano/ne	13 (40,6 %)/19	11 (37,9 %)/18	10 (33,3 %)/20	0,836
LMWH před operací	ano/ne	2 (6,3 %)/30	4 (13, 8%)/25	7 (23,3 %)/23	0,157
UFH před operací	ano/ne	12 (37,5 %)/20	11 (37,9 %)/18	16 (53,3 %)/14	0,367
ACT před operací (sec.)	geom.	156,7 (146,3; 167,8)	156,2 (142,2; 171,5)	170,7 (155,0; 188,1)	0,295
ACT po operaci (sec.)	geom.	151,2 (143,4; 159,4)	166,3 (151,4; 182,7)	167,2 (150,5; 185,6)	0,173
Čas operace (min.)	geom.	141,7 (129,8; 154,7)	139,6 (127,5; 152,8)	152,1 (137,7; 168,1)	0,370
Počet bypassů	aritm.	1,88 (1.59; 2,16)	1,76 (1,50; 2,02)	1,87 (1,61; 2,12)	0,789

Data jsou uváděna jako aritmetické (aritm.) či geometrické (geom.) průměry a 95% intervaly spolehlivosti nebo počet pacientů (relativní četnost).
Vysvětlivky: LMWH – nízkomolekulární heparin; UFH – nefrakcionovaný heparin; ACT – aktivovaný čas srážení.

intenzivní péče byly podobné ve všech skupinách (p = 0,691): 23 hod. (min.-max. 6–84 hod.) ve skupině A, 22 hod. (15–72 hod.) ve skupině B a 24 hod. (3,5–69 hod.) ve skupině C. Stejně tak mediány celkové doby hospitalizace byly 6 dnů pro všechny skupiny a rozdíly v době celkové hospitalizace mezi skupinami nebyly významné (p = 0,824).



Obr. 2. Peroperační (a) a pooperační kumulativní krevní ztráty za 4 hod. (b), 8 hod. (c) a 24 hod. (d)
Rozdíly mezi skupinami: (a) NS, (b), p < 0,001; (c) p = 0,001, (d) p < 0,001.

Peroperační a pooperační krevní ztráty, intraoperační aktivované časy srážení

Rozdíly v peroperačních krevních ztrátách mezi skupinami nebyly statisticky významné (geometrické průměry [95% intervaly spolehlivosti] – skupina A: 267,2 ml [215,8 ml; 330,8 ml], skupina B: 241,9 ml [198,4 ml; 294,8 ml] a skupina C: 319,3 ml [256,0 ml; 398,2 ml] (p = 0,134), i když nejvyšší průměrné ztráty byly zaznamenány ve skupině C (obr. 2).

Nebyl zjištěn statisticky významný rozdíl v hodnotách aktivovaného času srážení mezi skupinami před operací (p = 0,295) a na konci operace (p = 0,173), i když v tomto odběrovém čase jsou průměrné hodnoty ACT poněkud kratší ve skupině A oproti skupinám B a C a skupina C vykazuje větší variabilitu hodnot (viz tab. 1).

Pooperační krevní ztráty během prvních 4 hodin byly mezi skupinami vysoce signifikantně odlišné (geometrické průměry [95% intervaly spolehlivosti] – skupina A: 89,3 ml [72,7 ml; 109,8 ml], skupina B: 72,3 ml [49,2 ml; 106,3 ml] a skupina C: 192,3 ml [151,8 ml; 243,5 ml] (p < 0,001). Značně signifikantní rozdíly mezi skupinami byly též nalezeny v kumulativních krevních ztrátách za 8 hodin (skupina A: 152,1 ml [120,7 ml; 191,6 ml], skupina B: 130,3 ml [88,1 ml; 192,8 ml] a skupina C: 283,8 ml [226,0 ml; 356,3 ml] (p = 0,001) a za 24 hodin po operaci (skupina A: 410,3 ml [337,6 ml; 498,6 ml], skupina B: 345,8 ml [256,0 ml; 398,2 ml] a skupina C: 619,8 ml [524,3 ml; 732,8 ml] (p < 0,001). V žádném čase nebyla shledána odlišnost mezi skupinami A a B, avšak ve všech sledovaných časech byla skupina C rozdílná od skupin A a B. Síla statistického testu byla vyšší než 0,95 ve všech sledovaných pooperačních časech.

Pooperační ischémie myokardu, vývoj hladin kardiospecifických enzymů a D-dimerů

Elektrokardiografické známky ischémie myokardu (elevace úseků S-T) v časném pooperačním období se objevily u dvou pacientů (nemocný č. 64 ze skupiny B a nemocný č. 94 ze skupiny C). Pacientovi č. 64 byl našit jednonásobný bypass do distálního povodí extrémně sklerotického *r. interventricularis anterior*, štěp *a. thoracica interna l. sin.* musel být z důvodu nedostatečné délky použit jako free-graft. Pacient č. 94 podstoupil revaskularizaci myokardu 2násobným aortokoronárním bypassem, technicky byla operace bez jakýchkoliv komplikací. U obou hemodynamicky stabilních pacientů bylo provedeno urgentní echokardiografické vyšetření, které neprokázalo novou poruchu kinetiky myokardu a další postup byl v obou případech konzervativní (koronarodilatační terapie). Po několika hodinách léčby elektrokardiografické známky ischémie myokardu v obou případech ustoupily a další klinický průběh nemocných byl již bez komplikací.

Na základě vývoje kardiospecifických enzymů (hodnoty maxima: CK-MB 2,02 μkat/l, CK-MB mass 136,0 μg/l, troponin I 27,8 μg/l) hodnotíme myokardiální ischémii u pacienta č. 64 jako perioperační infarkt myokardu, který byl pravděpodobně způsoben vlastním kardiochirurgickým výkonem při hraničně revaskularizovatelném nálezu na věnčitých tepnách. Maximální hodnoty kardiospecifických enzymů u pacienta č. 94 byly mnohem nižší (CK-MB 0,59 μkat/l, CK-MB mass 15,5 μg/l, troponin I 2,4 μg/l) a událost u tohoto nemocného tedy posuzujeme jako přechodnou myokardiální ischémii.

Tabulka 2 ukazuje vývoj kardiospecifických enzymů u pacientů ve skupinách A, B, C (před operací, v čase 8 hod. a 24 hod. po operaci). V časovém vývo-

Tabulka 2. Časový vývoj kardiospecifických enzymů a hladin D-dimerů

		Skupina A	Skupina B	Skupina C	Hodnota *P*
CK (μkat/l)					
Před operací	geom.	0,94 (0,77; 1,16)	1,07 (0,83; 1,38)	1,17 (0,93; 1,48)	0,394
8 hod. po operaci	geom.	5,62 (4,73; 6,68)	5,57 (4,48; 6,92)	5,30 (4,46; 6,30)	0,888
24 hod. po operaci	geom.	10,77 (8,67; 13,37)	10,93 (8,89; 13,44)	9,85 (7,58; 12,80)	0,779
CK-MB (μkat/l)					
Před operací	geom.	0,114 (0,083; 0,157)	0,121 (0,090; 0,162)	0,106 (0,077; 0,147)	0,838
8 hod. po operaci	geom.	0,051 (0,033; 0,079)	0,053 (0,033; 0,084)	0,052 (0,032; 0,084)	0,996
24 hod. po operaci	geom.	0,254 (0,183; 0,354)	0,256 (0,167; 0,393)	0,245 (0,165; 0,365)	0,985
CK-MB/CK					
Před operací	geom.	0,121 (0,093; 0,157)	0,113 (0,082; 0,156)	0,091 (0,063; 0,130)	0,375
8 hod. po operaci	geom.	0,009 (0,006; 0,013)	0,009 (0,006; 0,014)	0,010 (0,007; 0,015)	0,966
24 hod. po operaci	geom.	0,024 (0,019; 0,030)	0,023 (0,017; 0,032)	0,025 (0,019; 0,032)	0,937
Troponin I (μkat/l)					
Před operací	geom.	0,240 (0,128; 0,450)	0,166 (0,071; 0,388)	0,159 (0,068; 0,388)	0,391
8 hod. po operaci	geom.	0,841 (0,513; 1,376)	0,380 (0,214; 0,674)	1,084 (0,671; 1,753)	0,015
24 hod. po operaci	geom.	0,631 (0,344; 1,155)	0,604 (0,321; 1,138)	0,961 (0,535; 1,726)	0,490
D-dimery (ng/ml)					
Před operací	geom.	387,5 (263,7; 469,4)	283,1 (193,5; 414,3)	473,8 (332,8; 674,7)	0,147
24 hod. po operaci	geom.	627,8 (494,2; 797,5)	871,8 (690,8; 1100,3)	1537,4 (1106,6; 2136,0)	<0,001

Data jsou uváděna jako geometrické (geom.) průměry a 95% intervaly spolehlivosti.

Vysvětlivky: CK – kreatinkináza; CK-MB – MB frakce kreatinkinázy; CK-MB / CK – podíl CK-MB na celkové aktivitě CK.

Tabulka 3. Hematologické parametry 24 hodin po operaci, počet retransfundovaných pacientů za prvních 24 hodin a za celkovou dobu hospitalizace

		Skupina A	Skupina B	Skupina C	Hodnota *P*
Hematokrit	geom.	33,12 (31,47; 34,85)	35,00 (33,34; 36,73)	32,00 (29,94; 34,21)	0,077
Hemoglobin (g/dl)	geom.	11,17 (10,56; 11,82)	11,85 (11,30; 12,42)	10,70 (10,24; 11,18)	0,018
Trombocyty (10^9/l)	geom.	199,2 (177,9; 223,0)	190.0 (169,3; 213,3)	184,8 (163,1; 209,5)	0,645
Fibrinogen (g/l)	geom.	4,430 (4,102; 4,784)	4,724 (4,424; 5,044)	4,593 (4,208; 5,013)	0,489
aPTT (sec.)	geom.	35,61 (32,73; 38,75)	34,36 (32,49; 36,35)	37,60 (34,43; 41,06)	0,266
INR	geom.	1,278 (1,229; 1,329)	1,270 (1,228; 1,314)	1,314 (1,261; 1,369)	0,412
EBR za 24 hod.	ano/ne	3 (9,4 %)/29	1 (3,4 %)/28	6 (20,0 %)/24	0,119
P za 24 hod.	ano/ne	2 (6,3 %)/30	0 (0,0 %)/29	4 (13,3 %)/26	0,118
EBR celkem	ano/ne	10 (31,3 %)/22	3 (10,3 %)/26	14 (46,7 %)/16	0,009
P celkem	ano/ne	4 (12,5%)/28	2 (6,9%)/27	4 (13,3%)/26	0,691

Data jsou uváděna jako geometrické (geom.) průměry a 95% intervaly spolehlivosti, anebo počet pacientů (relativní četnost).
Vysvětlivky: EBR – resuspendované erytrocyty; P – plasma z plné krve

ji CK a CK-MB nebyly shledány žádné statisticky významné rozdíly mezi skupinami. Hladiny troponinu I byly odlišné mezi skupinami 8 hodin po operaci (p = 0,015), a ani 24 hodin po operaci nebyl rozdíl prokázán (p = 0,490), avšak v obou těchto časech byly geometrické průměry hladin troponinu I evidentně nejvyšší ve skupině C (placebo).

Tabulka 2 též obsahuje časový vývoj D-dimerů (před operací, 24 hodin po operaci). Předoperační hladiny D-dimerů byly srovnatelné ve všech skupinách (p = 0,147). Vzestup průměrných hodnot D-dimerů po operaci byl nejvyšší a statisticky významný ve skupině C (p < 0,001), zatímco rozdíl mezi skupinami A a B byl po operaci statisticky nerozlišitelný.

Pooperační výsledky hematologických vyšetření a převody transfuzních přípravků

Výsledky hematologických vyšetření 24 hodin po operaci ukazuje tabulka 3. Průměrná hodnota hemoglobinu byla mezi skupinami signifikantně odlišná (p = 0,018), zatímco odlišnosti v průměrné hodnotě hematokritu byly na hranici statistické významnosti (p = 0,077). Rozdíly mezi skupinami v ostatních hematologických parametrech byly statisticky neprokazatelné.

Žádnému z pacientů nemusel být převeden během operace krevní derivát (resuspendované erytrocyty, plasma z plné krve). Relativní četnost pacientů, kteří byli retransfundováni v prvních 24 hodinách po operaci, nebyla mezi skupinami A, B, C statisticky odlišná (p = 0,119 pro resuspendované erytrocyty, p = 0,118 pro plasmu z plné krve), ačkoliv pro oba krevní deriváty platí, že absolutní počet retransfundovaných pacientů byl nejvyšší ve skupině C (placebo).

Procentuální zastoupení pacientů, kterým byly podány resuspendované erytrocyty během celkové doby hospitalizace, bylo signifikantně odlišné mezi skupinami (p = 0,009). Statisticky významně vyšší bylo ve skupině C (placebo) v porovnání se skupinou B (aprotinin) (p = 0,002). V případě skupiny A (tranexamová kyselina) se nepodařilo prokázat statisticky významnou odlišnost ve srovnání se skupinou C (p = 0,213). Počty pacientů, kterým byla podána plasma, se nelišily v žádné z porovnávaných skupin (p = 0,691).

Náklady na transfuzní přípravky a antifibrinolytika

Signifikantně nižší počet pacientů ve skupině B, kteří byli retransfundováni resuspendovanými erytrocyty během celkové doby hospitalizace v porovnání se skupinou C, se promítl i do signifikantně nižších nákladů na resuspendované erytrocyty (p = 0,018) (tab. 4). Analogicky, statisticky nevýznamná odlišnost v počtu pacientů ze skupin A a C, kterým byly podány erytrocyty během hospitalizace, koresponduje s nevýznamnou odlišností v cenách erytrocytů (p = 0,200). Pro průměrné náklady v případě plasmy nebyla prokázána statisticky významná odlišnost mezi jednotlivými skupinami (A, B, C) (p = 0,413, skupina C vs skupina B, respektive p = 0,922, skupina C vs skupina A), i když průměrné náklady ve skupině C byly více než dvojnásobné oproti skupině A i B. Průměrná cena podaných antifibrinolytik byla 48 Kč (tranexamová kyselina) ve skupině A a 2 720 Kč (aprotinin) ve skupině B.

Tabulka 4. Průměrné ceny krevních derivátů podaných pacientům ve studii za celou dobu hospitalizace

	Resuspendované erytrocyty	Plasma z plné krve	Celkem
Skupina A	1154	208	1362
Skupina B	364	172	536
Skupina C	2051	443	2494

Ceny jsou uvedeny v Kč.

Diskuse

Základní výstupy z uváděné studie TAP již byly uveřejněny [12]; cílem tohoto sdělení je podat rovněž poněkud detailnější analýzu efektivity nákladů na jednotlivá antifibrinolytika, respektive podané krevní deriváty.

Práce, která by srovnávala vliv tranexamové kyseliny a aprotininu na redukci krevních ztrát u kardiochirurgických operací bez MO, dosud ve světovém písemnictví chyběla. V naší studii prokazujeme, že ve srovnání s placebem jsou jak tranexamová kyselina, tak aprotinin stejně účinné ve snižování pooperačního

krvácení. Tento závěr je ve shodě s oddělenými pozorováními pro tranexamovou kyselinu [7, 9, 10] a aprotinin [8] u výkonů bez MO. Podle recentních údajů pro kardiochirurgické operace s použitím MO jsou krevní ztráty u pacientů léčených tranexamovou kyselinou o něco vyšší v porovnání s nemocnými léčenými aprotininem (p = 0,030), avšak s podobnými nároky na podání krevních derivátů [13].

Zdá se, že terapie antifibrinolytiky je bezpečná (z pohledu tendence k trombogenicitě a potenciálnímu nebezpečí uzávěru vytvořených bypassů) i u kardiochirurgických operací bez užití MO. V naší studii jsme zaznamenali 1 perioperační infarkt myokardu ve skupině B léčené aprotininem a 1 přechodnou ischémii myokardu ve skupině C s placebem. V klinickém průběhu nemocných jsme nezaznamenali žádnou embolizační příhodu (cerebrovaskulární, ani pulmonální). Ve skupinách pacientů léčených antifibrinolytikem nedošlo pooperačně k elevaci kardiospecifických enzymů, oproti skupině s placebem.

V naší studii jsme pozorovali, že 24 hodin po operaci byly průměrné hodnoty hemoglobinu signifikantně nižší ve skupině C (placebo) a že rozdíly v průměrech hematokritů mezi skupinami byly na hranici statistické významnosti. Nezjistili jsme statisticky signifikantní odlišnost v použití krevních derivátů během prvních 24 hodin po operaci (kdy byla kritéria pro podání těchto transfuzních přípravků pevně stanovena), i když celkový podíl nemocných, kteří dostali v této době krevní derivát, byl nejvyšší ve skupině C. Počet pacientů, kterým byly převedeny erytrocyty během celkové doby hospitalizace, byl statisticky významně vyšší ve skupině C (placebo) v porovnání se skupinou B (aprotinin), což se promítlo i do významně vyšších nákladů na tento krevní derivát ve skupině C. Sečteme-li průměrnou cenu aplikovaných antifibrinolytik a podaných krevních přípravků (jak resuspendovaných erytrocytů, tak plasmy z plné krve), dojdeme k průměrným celkovým nákladům 1410 Kč ve skupině A, 3256 Kč ve skupině B a 2494 Kč ve skupině C. Efektivita nákladů na antifibrinolytika a krevní deriváty se tedy ukazuje být v cenách existujících t. č. v České republice nejpříznivější pro tranexamovou kyselinu. Je však pravděpodobné, že v odlišném systému zdravotnictví s jinou strukturou cen a nákladů (zvláště na transfuzní přípravky) by tato cost-effectiveness analýza vyšla výhodněji pro antifibrinolytickou léčbu aprotininem [14, 15]. Důkladnější statistické šetření nákladů nebylo možné provést z důvodu nedostatečného vzorku dat (malý celkový počet retransfundovaných nemocných i celkový počet podaných krevních derivátů).

V prospektivní, randomizované, dvojitě slepé studii TAP jsme prokázali stejnou účinnost tranexamové kyseliny a aprotininu na redukci krevních ztrát u kardiochirurgických operací bez extrakorporální cirkulace. V léčených skupinách nedošlo k elevaci kardiospecifických enzymů v porovnání se skupinou placeba. Nezjistili jsme statisticky významnou odlišnost mezi skupinami v počtu pacientů, kterým byl během prvních 24 hodin po operaci podán krevní derivát, avšak počet nemocných retransfundovaných resuspendovanými erytrocyty během celé hospitalizace byl statisticky významně vyšší ve skupině placeba, v porovnání se skupinou léčenou aprotininem. Efektivita nákladů na antifibrinolytikum a transfuzní přípravky se jeví jako nejpříznivější ve skupině pacientů, kterým byla podávána tranexamová kyselina.

Literatura

1. **Nuttall, G. A., Oliver, W. C., Santrach, P. J. et. al.** Efficiacy of a simple intraoperative transfusion algorithm for non-erythrocyte component utilization after cardiopulmonary bypass. *Anaesthesiology*, 2001, 94, p. 773–781.
2. **Despotis, G. J., Filos, K. S., Zoys, T. N., Hogue, C. W., Jr., Spitznagel, E., Lappas, D. G.** Factors associated with excessive postoperative blood loss and hemostatic transfusion requirements: a multivariete analysis in cardiac surgical patients. *Anesth. Analg.*, 1996, 82, p. 13–21.
3. **Biglioli, P., Cannata, A., Alamanni, F. et. al.** Biological effects of off-pump vs. on-pump coronary artery surgery: focus on inflammation, hemostasis and oxidative stress. *Eur. J. Cardio-thoracic Surg.*, 2003, 24, p. 260–269.
4. **Cvachovec, K., Horáček, M., Vislocký, I.** A retrospective survey of fibrinolysis as an indicator of poor outcome after cardiopulmonary bypass and a possible early sign of systemic inflammation syndrome. *Eur. J. Anaesthesiol.*, 2000, 17, p. 173–176.
5. **Levi, M., Cromheecke, M. E., de Jonge, E. et. al.** Pharmacological strategies to decrease blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet*, 1999, 354, p. 1940–1947.
6. **Alderman, E. L., Levy, J. H., Rich, J. B. et. al.** Analyses of coronary graft patency after aprotinin use: results from the international multicenter aprotinin graft patency experience (IMAGE) trial. *J. Thorac. Cardiovasc. Surg.*, 1998, 116, p. 716–730.
7. **Casati, V., Gerly, Ch., Franco, A. et. al.** Tranexamic acid in off-pump coronary surgery: a preliminary, randomized, double-blind, placebo-controlled study. *Ann. Thorac. Surg.*, 2001, 72, p. 470–475.
8. **Englberger, L., Markart, P., Eckstein, F. S., Immer, F. F., Berdat, P. A., Carrel, T. P.** Aprotinin reduces blood loss in off-pump coronary artery bypass (OPCAB) surgery. *Eur. J. Cardio-thorac. Surg.*, 2002, 22, p. 545–551.
9. **Jareš, M., Vaněk, T., Straka, Z., Brůček, P.** Tranexamic acid reduces bleeding after off-pump coronary artery bypass grafting. *J. Cardiovasc. Surg. (Torino)*, 2003, 44, p. 205–208.
10. **Casati, V., Della Valle, P., Benussi, S. et. al.** Effects of tranexamic acid in postoperative bleeding and related hematological variables in coronary surgery: a comparison between on-pump and off-pump techniques. *J. Thorac. Cardiovasc. Surg.*, 2004, 128, p. 83–91.
11. **Vaněk, T., Brůček, P., Straka, Z.** Fast track as a routine for open-heart surgery. *Eur. J. Cardio-thorac. Surg.*, 2001, 21, p. 369–370.
12. **Vaněk, T., Jareš, M., Fajt R. et. al.** Fibrinolytic inhibitors in off-pump coronary surgery: a prospective, randomized, double-blind TAP study (tranexamic acid, aprotinin, placebo). *Eur. J. Cardio-thorac. Surg.*, 2005, 28, p. 563–568.
13. **Hekmat, K., Zimmermann, T., Kampe, S. et. al.** Impact of tranexamic acid vs. aprotinin on blood loss and transfusion requirements after cardiopulmonary bypass: a prospective,

randomized, double-blind trial. *Curr. Med. Res. Opin.*, 2004, 20, p. 121–126.
14. **Green, J. A., Reynolds, P. S., Makhoul, K. et. al.** Potential financial savings of a "bloodless" cardiac surgery initiative. *Anesth. Analg.*, 2003, 96, Abstracts SCA 17.
15. **Robinson, D., Bliss, E.** A model of direct and indirect effects of aprotinin administration on the overall costs of coronary revascularization surgery in a university teaching hospital cardiothoracic unit. *Clin. Ther.*, 2002, 24, p. 1677–1689.

Podpořeno Kardiovaskulárním výzkumným záměrem Univerzity Karlovy v Praze č. MSM0021620817.

Došlo 26. 9. 2005.
Přijato 25. 11. 2005.

Adresa pro korespondenci:
Doc. MUDr. Tomáš Vaněk, CSc.
Holandská 11, 101 00 Praha 10
e-mail: vanek@fnkv.cz

Aprotinin Reduces Troponin I Levels in OPCABG

Tomas Vanek, Martin Jares, Zbynek Straka and MSM0021620817 Study Group

Ann Thorac Surg 2006;82:1950-1951
DOI: 10.1016/j.athoracsur.2006.03.110

Simplified Risk Stratification System for Open Heart Surgery

To the Editor:

We refer to the commentary by Edwards on the article by Berman and colleagues [1].

Our original scoring system had two goals: (1) to compare results of one institution with another to correct for case mix severity, and (2) to predict the chance of death in any individual. Then the late 1980s operative mortality rates for routine open heart surgery were high, but today rarely exceed 1%. Competition for area-wide recognition has abated, and the need for fairly precise risk stratification has decreased.

Doctor Edwards was critical of our simplified method because handheld personal digital assistants (PDAs) can be used more easily than paper and pencil. When we conceived this method, PDAs were not ubiquitous, but now that would be our approach.

Even simpler, just the number of risk factors in the individual patient correlated well with the outcome (unpublished data—see Fig 1). These data were derived from 16,246 coronary bypass procedures in New Jersey in 1996–1997 versus the same patient cohort with risk-adjusted rates as calculated by the New Jersey Department of Health and Senior Services (dark bars) used at that time.

We agree with the authors that the simplicity of our method has much to offer, because it requires so little data entry, especially when it is used for bedside use. It is comforting to find that others agree.

Victor Parsonnet, MD

Division of Surgical Research
Newark Beth Israel Medical Center
201 Lyons Ave
Newark, NJ 07112
e-mail: vpacel@earthlink.net

Reference

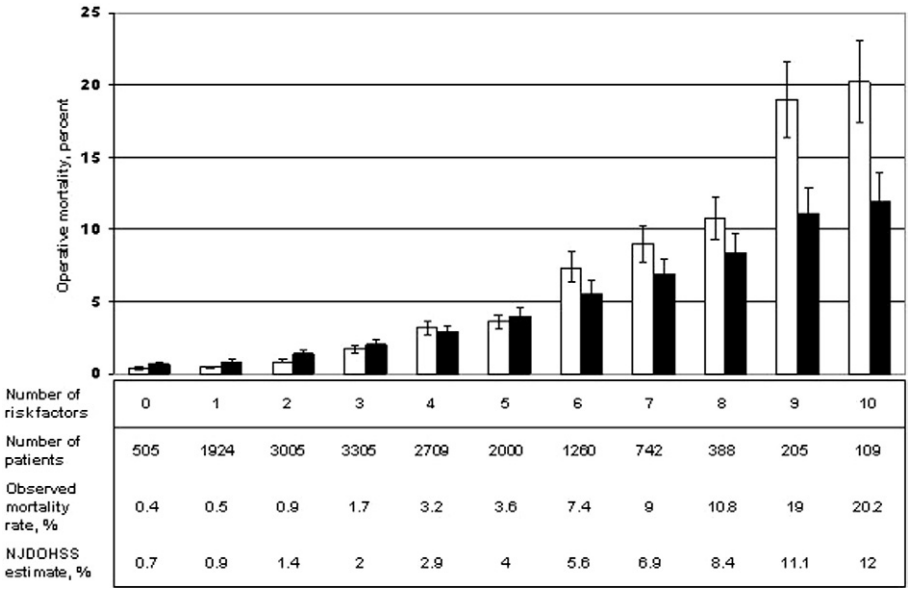
1. Berman M, Stamler A, Sahar G, et al. Validation of the 2000 Bernstein–Parsonnet score versus the EuroSCORE as a prognostic tool in cardiac surgery. Ann Thorac Surg 2006;81:537–41.

Aprotinin Reduces Troponin I Levels in OPCABG

To the Editor:

We congratulate Poston and colleagues [1] on their interesting article dispelling a little of the concerns or fears of an increase in graft failure in off-pump coronary artery bypass grafting (OPCABG) when aprotinin is used to reduce blood loss. Last year we published the results of a prospective, randomized, double-blind study comparing hemostatic effects of tranexamic acid versus aprotinin versus placebo in OPCABG [2]. In addition, and for safety evaluation reasons, the time course of myocardial enzymes in the very early postoperative period was assessed. We found no statistically significant intergroup differences at any time (preoperatively, 8 hours, and 24 hours postoperatively) within the time course of creatine phosphokinase (CK) levels, isoenzyme MB (CK-MB) levels and the relative index of CK-MB and CK, but troponin I levels differed between our study groups 8 hours postoperatively ($p = 0.015$) (Table 1).

Post hoc tests showed above all the most significant difference between the aprotinin treated group and the placebo group ($p < 0.001$) due to the lowest mean values of troponin I in the aprotinin group. Twenty-four hours postoperatively the mean levels of troponin I remained lowest in the aprotinin treated group and highest in the placebo group, but these differences were already without statistical significance. We assume that our findings concerning the time course of troponin I levels support the conclusions of Poston and colleagues [1] that aprotinin shows not only hemostatic, but also antithrombotic (and prob-



Number of riskfactors	0	1	2	3	4	5	6	7	8	9	10
Number of patients	505	1924	3005	3305	2709	2000	1260	742	388	205	109
Observed mortality rate, %	0.4	0.5	0.9	1.7	3.2	3.6	7.4	9	10.8	19	20.2
NJDOHSS estimate, %	0.7	0.9	1.4	2	2.9	4	5.6	6.9	8.4	11.1	12

Fig 1. Observed mortality rates (clear bars) for 16,246 isolated aortocoronary-bypass procedures performed during 1996 and 1997 at 13 New Jersey hospitals, with 95% binomial confidence limits superimposed. Included for comparison are risk-adjusted mortality-rate estimates (dark bars) for the same procedures as calculated from a 9-factor logistic-regression model published by the New Jersey Department of Health and Senior Services (NJDOHSS).

0003-4975/06/$32.00

Table 1. Time Course of Troponin I Levels (μg/L) in Off-Pump Coronary Artery Bypass Grafting[a]

	Tranexamic Acid Treated Group (n = 32)	Aprotinin Treated Group (n = 29)	Placebo Treated Group (n = 30)	*p* Value
Before operation	0.240 (0.128,0.450)	0.166 (0.071,0.388)	0.159 (0.068,0.388)	0.391
8 Hours postoperatively	0.841 (0.513,1.376)	0.380 (0.214,0.674)	1.084 (0.671,1.753)	0.015
24 Hours postoperatively	0.631 (0.344,1.155)	0.604 (0.321,1.138)	0.961 (0.535,1.726)	0.490

[a] Data are presented as geometrical means and 95% confidence intervals.

ably vein graft endothelium preservation) mechanism during OPCABG.

Tomas Vanek, MD, PhD
Martin Jares, MD
Zbynek Straka, MD, PhD
on behalf of the MSM0021620817 Study Group

Department of Cardiac Surgery
3rd Medical School of Charles University
Srobarova 50
100 34 Prague 10, Czech Republic
e-mail: vanek@fnkv.cz

References

1. Poston RS, White Ch, Gu J, et al. Aprotinin shows both hemostatic and antithrombotic effects during off-pump coronary artery bypass grafting. Ann Thorac Surg 2006;81:104–11.
2. Vanek T, Jares M, Fajt R, et al. Fibrinolytic inhibitors in off-pump coronary surgery: a prospective, randomized, double-blind TAP study (tranexamic acid, aprotinin, placebo). Eur J Cardio-thorac Surg 2005;28:563–8.

Reply

To the Editor:

As suggested by Vanek and colleagues [1], a growing body of evidence supports the safety of aprotinin use during OPCAB. Their own report [2], published while our off-pump coronary artery bypass (OPCAB) trial in *The Annals of Thoracic Surgery* was in press [3], highlights two points that are becoming increasingly clear about aprotinin. First, aprotinin provides a hemostatic benefit that exceeds the lysine analogues, likely due to the ability to preserve platelet function in addition to blocking fibrinolysis. Second, aprotinin does not create a hypercoagulable tendency. The clinical safety of aprotinin use during high risk groups such as OPCAB, vascular [4], and orthopedic surgery [5], and its ability to modulate the thrombin receptor, protease-activated receptor-1 (PAR-1) [6], provide strong evidence to the contrary. In fact, it is these patients who are at greatest risk for perioperative hypercoagulability and the propensity to generate thrombin in which the impact of PAR-1 inhibition by aprotinin may be most relevant.

Table 1. Transcardiac (Coronary Sinus-Aorta) Release of Inflammatory Markers in Off-Pump Coronary Artery Bypass

	Aprotinin Group (n = 6)	Placebo Group (n = 7)	*p* Value
Myoglobin (ug/g protein)	3.78	34.3	0.110
sICAM (ng/g protein)	0.33	3.08	0.149
sVCAM (ng/g protein)	0.10	1.29	0.028
IL-6 (ng/g protein)	2.58	8.23	0.116
IL-8 (ng/g protein)	2.63	7.05	0.368
TNFα (ng/g protein)	8.76	14.7	0.558

IL = interleukin; sICAM = soluble intercellular adhesion molecule; sVCAM = soluble vascular cell adhesion molecule; TNF = tumor necrosis factor.

In their letter, Vanek and colleagues [1] raise the intriguing notion that a significant reduction in troponin I release after aprotinin use in both of our trials may represent a clinical antithrombic effect during OPCAB. Randomized trials done in on-pump coronary artery bypass grafting patients have shown no difference in troponin I or other myocardial injury markers after aprotinin administration [7]. During cold, cardioplegic arrest, troponin I release is confounded by variations in the quality of myocardial preservation and does not solely reflect intracoronary thrombosis. On the other hand, brief, regional warm ischemia incurred during OPCAB activates inflammatory and thrombotic pathways that have been shown to be influenced by aprotinin in several animal models [8–10]. We recently reanalyzed the subset of our cohort that had coronary sinus samples obtained to define the impact of aprotinin on these pathways by comparing the difference in the transcardiac release (ie, coronary sinus—aortic levels) of markers of cardiac inflammation and injury. In addition to a significant reduction in the gradient of the thrombin formation marker F1.2 (already reported), the aprotinin group showed trends toward a reduction in the release of a number of these markers immediately after OPCAB (see Table 1). These data suggest the mechanism for the reduction in troponin I in both of our OPCAB studies may be related to the ability of aprotinin to help protect the myocardium against brief warm ischemia. This benefit may prove valuable in the growing population of OPCAB referrals with limited myocardial reserve.

Robert Poston, MD
Ozeki Toshinaga, PhD

Division of Cardiac Surgery
University of Maryland School of Medicine
N4W94 22 S. Greene St
Baltimore, MD 21201
e-mail: rposton@smail.umaryland.edu

References

1. Vanek T, Jares M, Straka Z, on behalf of the MSM0021620817 Study Group. Aprotinin reduces troponin I levels in OPCABG (letter). Ann Thorac Surg 2006;82:1950–1.
2. Vanek T, Jares M, Fajt R, et al. Fibrinolytic inhibitors in off-pump coronary surgery: a prospective, randomized, dou-

Aprotinin Reduces Troponin I Levels in OPCABG

Tomas Vanek, Martin Jares, Zbynek Straka and MSM0021620817 Study Group

Ann Thorac Surg 2006;82:1950-1951
DOI: 10.1016/j.athoracsur.2006.03.110

Off-Pump Versus On-Pump Coronary Artery Surgery

Identification of Fibrinolysis Using Rotation Thromboelastography; A Preliminary, Prospective, Randomized Study

Martin JARES,[1] MD, Tomas VANEK,[1] MD, Frantisek BEDNAR,[1] MD, Marek MALY,[2] MSc, Jana SNIRCOVA,[1] MD, *and* Zbynek STRAKA,[1] MD

SUMMARY

The aim of this preliminary, prospective, randomized study was to compare rotation thromboelastography (roTEG) results and D-dimer levels in off-pump versus on-pump coronary surgery in order to identify the activation of fibrinolysis.

Twenty patients scheduled for coronary bypass grafting were assessed (off-pump group A, $n = 10$; on-pump group B, $n = 10$). Blood samples for roTEG examination were taken preoperatively (t_0), 15 minutes after sternotomy (t_1), on the completion of peripheral bypass anastomoses (t_2), and at the end of procedures (t_3). The time points for D-dimer levels analyses were before operation, at the end of procedures, and 24 hours later.

A certain degree of roTEG signs of fibrinolysis was noticed at time t_2 in both groups and in group B these marks were quite widely, but not significantly expressed (P for intergroup differences for Lysis on Set Time at 60 and 150 minutes were $P = 0.190$ and $P = 0.122$, respectively), borderline differences were found for Maximum Clot Firmness ($P = 0.082$) with a lower mean value for group B (arithmetic means [95% confidence intervals] - 57.7 [54.2; 61.2] mm). Completely expressed roTEG signs of hyperfibrinolysis were observed in 2 patients from group B. In group B also the highest geometric means of D-dimers (1326.0 [943.5; 1863.6] ng mL^{-1}) and thus a dramatic intergroup difference ($P < 0.001$) were observed at the end of surgery; 24 hours later the significantly elevated D-dimer levels in both groups (A: 1070.0 [723.5; 1582.6] versus B: 1093.3 [732.0; 1632.9] ng mL^{-1}) were equalized ($P = 0.932$).

Our roTEG results display a slightly greater, but fairly subtle activation of fibrinolysis during the course of cardiopulmonary bypass, compared to off-pump cardiac surgery.
(Int Heart J 2007; 48: 57-67)

Key words: Cardiopulmonary bypass, Hemostasis, Beating heart surgery, D-dimers, Cardiac surgical procedures

THE issue of massive bleeding following heart surgery, and subsequent need for

From the [1] Department of Cardiac Surgery, Third Faculty of Medicine, Charles University in Prague, Kralovske Vinohrady University Hospital, [2] Department of Biostatistics and Informatics, National Institute of Public Health, Prague, Czech Republic.

Address for correspondence: Martin Jares, MD, Department of Cardiac Surgery, Third Faculty of Medicine, Charles University in Prague, FNKV, Srobarova 50, 100 34, Prague 10, Czech Republic.

Received for publication October 2, 2006.

Revised and accepted December 11, 2006.

allogenic blood transfusion, is a permanent focus of cardiac surgeons worldwide. The favourable effect of different fibrinolytic inhibitors (aprotinin, and lysine analogues, such as tranexamic acid) on the decrease in perioperative bleeding in cardiac surgery with the use of cardiopulmonary bypass (on-pump cardiac surgery) was confirmed in a large number of controlled trials, and has been included in relevant meta-analyses.[1,2] However, only a limited number of studies have been concerned with the use of antifibrinolytic drugs in cardiac surgery without the use of extracorporeal circulation (off-pump cardiac surgery), and have demonstrated its effectivenes, as well.[3-7] The safety question of fibrinolytic inhibitors in coronary surgery is permanently under discussion and has been accelerated by 2 recently published important observational studies.[8,9]

Information concerning the activation of the coagulation-fibrinolytic pathway during off-pump and on-pump cardiac surgery procedures is still limited. To the best of our knowledge, only one recent nonrandomized study[10] and one prospective, randomized[11] study have investigated coagulation and fibrinolysis variables in off-pump versus on-pump up to 24 hours after cardiac surgery. Cardiac surgery involving cardiopulmonary bypass leads to fulminant activation of the hemostatic-inflammatory system.[12] Theoretically, there are 2 time points with increased fibrinolytic activity during this type of surgery: firstly, the release of tissue plasminogen activator, which starts during the skin incision and sternotomy, and secondly, the time period of cardiopulmonary bypass with suctions from the surgical field (shed blood from the pericardium containing a great amount of cytokines, tissue factor and tissue plasminogen activator). The surgical trauma/aggression itself may be as important as, or even more important than, the use of cardiopulmonary bypass in terms of coagulation-fibrinolytic pathway activation.[13]

Thromboelastography is a measuring method based on the continuous registration of blood clot firmness during the entire coagulation process. Thus, the beginning of clot formation, clot formation kinetics, and maximum clot firmness are assesed as well as its stability or lysis.

The aim of this prospective, randomized study was to identify fibrinolysis using rotation thromboelastography (roTEG) in off-pump versus on-pump coronary surgery patients. In addition, D-dimer levels between the study groups were compared.

METHODS

After obtaining approval from the Medical Faculty Ethics Committe and informed consent from all the participants, 20 patients scheduled for coronary artery bypass grafting from January 3, 2005 to February 15, 2005 were enrolled

Table I. Basic Demographic, Preoperative Hematological, and Intraoperative Characteristics

		Off-pump group A	On-pump group B	*P*
Age (years)	Arithm.	65.5 (58.7; 72.3)	62.6 (56.4; 68.8)	0.486
Gender (male/female)		6 (60%) / 4	8 (80%) / 2	0.314
Weight (kg)	Arithm.	78.7 (73.2; 84.1)	86.9 (77.5; 96.2)	0.108
Additive EuroSCORE	Arithm.	4.40 (2.67; 6.13)	3.90 (1.95; 5.88)	0.672
Logistic EuroSCORE	Geom.	3.39 (1.98; 5.80)	2.92 (1.52; 5.61)	0.694
Hematocrit	Geom.	44.86 (41.68; 48.28)	44.93 (42.00; 48.07)	0.971
Hemoglobin (g dL^{-1})	Geom.	15.21 (14.11; 16.41)	15.25 (13.99; 16.62)	0.964
Platelet count (10^9 L^{-1})	Geom.	225.4 (190.7; 266.4)	259.5 (226.4; 297.3)	0.158
Fibrinogen (g L^{-1})	Geom.	4.29 (3.79; 4.86)	3.85 (3.60; 4.10)	0.098
aPTT (sec)	Geom.	40.21 (30.82; 52.46)	34.95 (32.49; 37.60)	0.276
INR	Geom.	1.044 (0.981; 1.112)	1.051 (0.992; 1.113)	0.873
Operating time (min)	Geom.	149.9 (131.9; 170.3)	176.1 (163.0; 190.2)	0.028
Number of grafts	Arithm.	2.00 (1.66; 2.34)	2.60 (2.23; 2.97)	0.014
CPB duration (min)	Geom.	-	47.8 (40.3; 56.7)	-
AC duration (min)	Geom.	-	26.8 (22.5; 32.1)	-

Data are presented as arithmetic means (arithm.) or geometric means (geom.) and 95% confidence intervals, unless otherwise specified. CPB indicates cardiopulmonary bypass; and AC, aortic clamp; aPTT, activated partial thromboplastin time; and INR, international normalized ratio of prothrombin time.

in the study. The consecutive patients were randomized to off-pump or on-pump surgery using the envelope method with random numbers (groups A, B; 10 patients in each group). The basic characteristics of the patient groups and surgical procedures are shown in Table I. The criteria for nonenrollment in the study were as follows: previous cardiac surgery, myocardial infarction < 7 days prior to the surgery, history of haematological or liver disorders, renal insufficiency (serum creatinine > 150 μmol L^{-1}) and preoperative anaemia (hemoglobin < 11 g dL^{-1}, hematocrit < 32). None of the study subjects were under the influence of antiaggregative/anticoagulant drugs (aspirin withdrawal < 5 days before surgery, low-molecular heparin withdrawal < 24 hours before surgery, a continuous unfractioned heparin infusion, or medication with potent antiplatelet agents, such as ADP inhibitors and GPIIb/IIIa antagonists). No fibrinolytic inhibitors were used in the perioperative period in any of the patients evaluated.

Remifentanil based ultra-fast-track anesthesia (with the application of propofol, midazolam, atracurium, and inhaled isofluran) was performed in all cases. This type of general anaesthesia, without the use of an epidural catheter, is a standard method for coronary artery surgery in our department.[14] Surgical access was through a full midline sternotomy in all cases. In off-pump procedures, heparin was given at a dose of 100 IU kg^{-1} and verticalization of the beating heart was achieved using an Axius Xpose Device, while the Ultima Vacuum Assist

(Guidant, Cupertino, CA) was used for the stabilization of the anastomosis site. Upon completion of the anastomoses, heparinization was partially reversed with a half-dose of protamine chloride. In on-pump surgery, normothermic perfusion was used with the same type of noncoated capillary oxygenator (D 703 Compact-flo, Dideco, Mirandola, Italy) with crystalloid priming of 750 mL. Heparin was administered at a dose of 300 IU kg^{-1} to achieve an activated clotting time > 480 seconds. Upon completion of all anastomoses, a full dose of protamine chloride was used to reverse the effects of heparin.

The blood for roTEG examination was sampled from the arterial line into tubes containing sodium citrate (Greiner Bio-One, Kremsmuenster, Austria) and processed immediately after sampling using a ROTEG® Whole Blood Haemostasis System, model 05 (Pentapharm, Munich, Germany) with heparinase HEPTEG (Nobis, Endingen, Germany) for heparin removal and EXTEG (Nobis, Endingen, Germany) including thromboplastin for the extrinsic pathway activation. The sampling time points were as follows: preoperatively (t_0), 15 minutes after sternotomy (t_1), on the completion of peripheral bypass anastomoses (t_2), and at the end of the procedure (t_3). Blood samples for the preoperative evaluation of haematological parameters (haemoglobin, haematocrit, platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen) were taken and processed in a routine way. Blood samples for D-dimer examination were obtained before the operation, at the end of surgery, and 24 hours later. D-dimer levels were assessed by a micro-latex imunoassay procedure for a quantitative measurement of D-dimer on the Stago Compact analyser using Liatest Stachrom D-D antibodies (Diagnostica Stago, Parsippany, NJ, USA).

Figure 1 describes the basic measured parameters assessed by rotation thromboelastography: Clotting Time (CT) [sec]: time from the start of the measurement until the start of a clot formation; Clot Formation Time (CFT) [sec]: time from the beginning of the clot formation until an amplitude of 20 mm is achieved; and Maximum Clot Firmness (MCF) [mm] marking clot stability/strength; Alpha-angle [°] and Lysis on Set Time (LOT) [%] in 30 minutes, 60 minutes, and 150 minutes, respectively.

Statistical analysis was performed using SPSS statistical software, version 12.0.1 (SPSS Inc., Chicago, IL). Values are presented as arithmetic or geometric means (for normally or log-normally distributed data, respectively) and their variability was characterized by 95% confidence intervals. For statistical testing, the data were log-transformed when appropriate. The comparison between the 2 groups was made using a 2-sample *t*-test, and within-group comparisons of different time points were based on a paired *t*-test. In both tests, Bonferroni-type correction for multiple comparisons was applied. A more complex evaluation was performed using a multivariate repeated-measures analysis of variance.

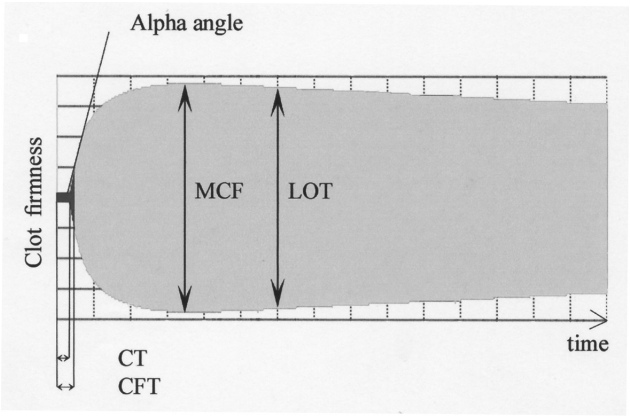


Figure 1. Basic rotation thromboelastographic (roTEG) parameters.

Spearman's rank correlation coefficient was used to measure the association between D-dimers and LOT. All statistical tests were evaluated at a significance level of 0.05.

RESULTS

Both the off-pump and on-pump group showed comparable demographic, preoperative haematological, and basic intraoperative characteristics, with the exception of the mean operating time and the number of created peripheral anastomoses, respectively (Table I). The duration of the on-pump surgery was significantly longer ($P = 0.028$) and the number of grafts was significantly higher ($P = 0.014$) in contrast to the off-pump surgery. This finding is not surprising and exceptional given our experience with off-pump versus on-pump cardiac surgery.[15)]

Table II presents a comparison of the parameters assesed by thromboelastography in monitored time points for off-pump (group A) and on-pump (group B) surgery, respectively. At sampling times t_0 (preoperatively), t_1 (15 minutes after sternotomy) and t_3 (the end of the procedure) no statistically significant intergroup differences were observed. At time t_2 (completion of peripheral anastomoses), borderline differences were found for MCF ($P = 0.082$) with a lower mean value for on-pump group B compared to off-pump group A. For LOT at 60 and 150 minutes, respectively, significantly different intergroup differences were not proven ($P = 0.190$ and $P = 0.122$, respectively), but in on-pump group B more pronounced lysis (in terms of means) was observed. It is worth mentioning that

Table II. Comparison of Thromboelastographic Parameters at Monitored Time Points

Time point / Parameter		Off-pump group A	On-pump group B	*P*
Preoperatively (t_0)				
CT [sec]	geom.	65.5 (52.4; 81.8)	76.0 (61.9; 93.4)	0.279
CFT [sec]	geom.	69.9 (54.6; 89.4)	67.8 (55.6; 82.6)	0.830
MCF [mm]	arithm.	65.7 (60.4; 71.0)	66.3 (63.8; 68.8)	0.820
Alpha-angle [°]	arithm.	75.7 (71.8; 79.6)	75.9 (73.5; 78.3)	0.964
LOT (30 min.) [%]	arithm.	98.0 (98.0; 98.0)	97.8 (97.3; 98.3)	0.343
LOT (60 min.) [%]	arithm.	94.3 (92.6; 96.0)	93.9 (91.9; 95.9)	0.732
LOT (150 min.) [%]	arithm.	85.7 (82.8; 88.5)	85.3 (82.8; 87.9)	0.848
15 mins after sternotomy (t_1)				
CT [sec]	geom.	82.6 (62.3; 109.6)	71.6 (57.8; 88.8)	0.376
CFT [sec]	geom.	72.3 (59.3; 88.1)	67.5 (56.8; 80.3)	0.567
MCF [mm]	arithm.	66.9 (64.6; 69.2)	65.2 (61.5; 68.9)	0.392
Alpha-angle [°]	arithm.	75.0 (72.3; 77.7)	76.4 (73.7; 79.1)	0.420
LOT (30 min.) [%]	arithm.	97.8 (97.3; 98.3)	97.4 (96.0; 98.8)	0.540
LOT (60 min.) [%]	arithm.	94.0 (91.6; 96.4)	93.9 (91.2; 96.7)	1.000
LOT (150 min.) [%]	arithm.	85.9 (82.7; 89.1)	86.4 (82.7; 90.1)	0.815
Completion of anastomoses (t_2)				
CT [sec]†	geom.	129.3** (86.1; 194.2)	145.8* (95.9; 221.6)	0.647
CFT [sec]†	geom.	114.1^{NS} (65.8; 190.2)	110.6** (91.3; 134.1)	0.901
MCF [mm]†	arithm.	62.5^{NS} (57.8; 67.2)	57.7*** (54.2; 61.2)	0.082
Alpha-angle [°]†	arithm.	65.8^{NS} (54.6; 77.0)	68.2** (63.9; 72.4)	0.833
LOT (30 min.) [%]†	arithm.	98.0^{NS} (98.0; 98.0)	97.2^{NS} (95.4; 99.0)	0.343
LOT (60 min.) [%]†	arithm.	96.3^{NS} (95.3; 97.3)	79.6^{NS} (53.0; 106.2)	0.190
LOT (150 min.) [%]†	arithm.	88.0^{NS} (86.3; 89.7)	68.2^{NS} (42.0; 94.4)	0.122
End of procedure (t_3)				
CT [sec]	geom.	89.3 (65.6; 121.6)	84.0 (67.4; 104.8)	0.720
CFT [sec]	geom.	83.2 (72.8; 95.1)	80.9 (69.4; 94.4)	0.760
MCF [mm]	arithm.	65.4 (62.4; 68.4)	63.9 (60.5; 67.3)	0.465
Alpha-angle [°]	arithm.	73.2 (71.2; 75.2)	73.9 (71.5; 76.3)	0.604
LOT (30 min.) [%]	arithm.	98.0 (98.0; 98.0)	98.0 (98.0; 98.0)	1.000
LOT (60 min.) [%]	arithm.	94.4 (92.5; 96.3)	95.6 (94.6; 96.6)	0.221
LOT (150 min.) [%]	arithm.	85.8 (83.3; 88.4)	85.8 (80.3; 91.2)	0.993

Data are presented as arithmetic means (arithm.) or geometric means (geom.) and 95% confidence intervals. CT indicates clotting time; CFT, clot formation time; MCF, maximum clot firmness; and LOT, lysis on set time.

† At time t_2, statistical significance of paired comparisons between the times t_2 and t_0 is indicated in both groups as follows: nonsignificant (NS), significant at $P \leq 0.05$ (*), significant at $P \leq 0.01$ (**), and significant at $P \leq 0.001$ (***).

this was primarily caused by 2 patients (numbers B1 and B10) with extreme fibrinolysis (LOT at 60 minutes, 0% resp. 19%; LOT at 150 minutes, 0% resp. 0%) (Figure 2). At 150 minutes this finding was supported by another 2 patients (B4 and B9) with LOT values of 74% and 73% respectively. These values were distinct from those of the remaining study subjects from on-pump group B,

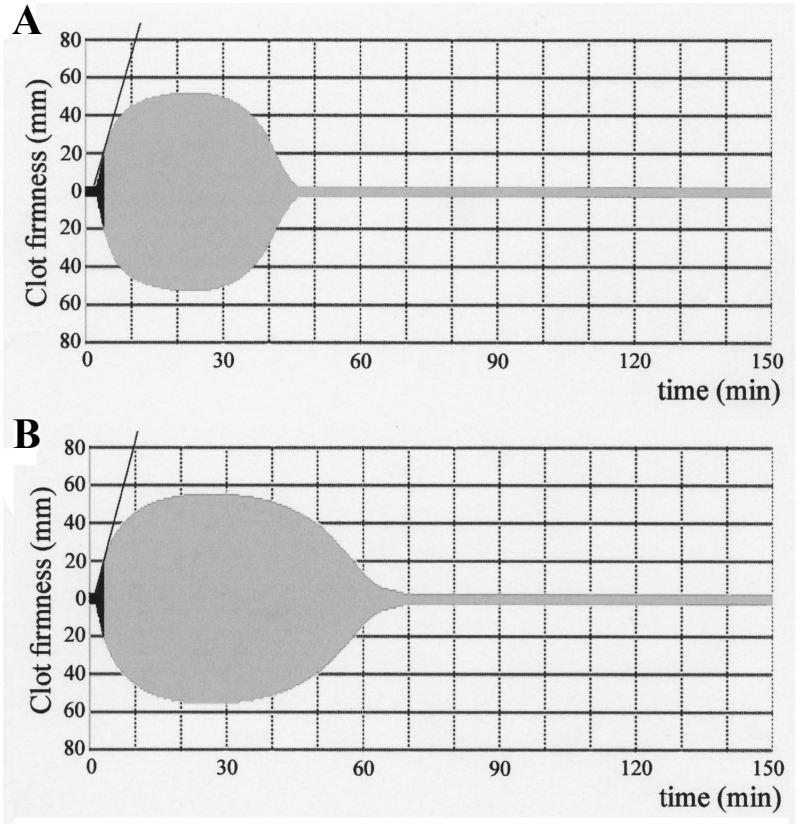


Figure 2. Rotation thromboelastographic (roTEG) traces in 2 patients with hyperfibrinolysis (on-pump group B). Patient B1 (**A**): CT 135 sec, CFT 95 sec, alpha angle 71° , MCF 55 mm, LOT at 30 min 90%, at 60 min 0%, and at 150 min 0%. Patient B10 (**B**): CT 78 sec, CFT 115 sec, alpha angle 68° , MCF 54 mm, LOT at 30 min 98%, at 60 min 19%, and at 150 min 0%.

whose mean value of LOT at 150 minutes (89.1%) was very close to the mean value in off-pump group A (88.0%). Looking at the time course of the other thromboelastographic parameters, CT, CFT, MCF and Alpha-angle show at time t_2 significant differences in comparison with the other time points in both groups. When comparing t_2 to preoperative t_0, a statistically significant prolongation of CT and nonsignificant prolongation of CFT were observed in off-pump group A ($P = 0.002$, $P = 0.122$, respectively). In on-pump group B, a statistically significant prolongation of both CT and CFT was noticed ($P = 0.036$ and $P = 0.006$, respectively), as well. For roTEG parameters MCF and Alpha-angle, apparent decreases in the mean values were found in on-pump group B at time t_2. When comparing t_2 to t_0, statistically significant differences were seen in both parameters in on-pump group B ($P = 0.001$ and $P = 0.008$, respectively), while nonsig-

Table III. Time Course of D-Dimer Levels (ng mL^{-1})

Time point		Off-pump group A	On-pump group B	*P*
Preoperatively	geom.	244.2 (183.3; 325.4)	294.8 (184.2; 471.9)	0.451
End of the procedure	geom.	297.0 (189.6; 465.1)	1326.0 (943.5; 1863.6)	< 0.001
Postoperative day 1	geom.	1070.0 (723.5; 1582.6)	1093.3 (732.0; 1632.9)	0.932

Data are presented as geometric means (geom.) and 95% confidence intervals.

nificant differences were observed in off-pump group A ($P = 0.221$ and $P = 0.132$, respectively).

Using the complex model of multivariate analysis of variance with repeated measurements (for all assessed roTEG parameters at all times), the distinctiveness of time t_2 from the other times was confirmed ($P < 0.001$). Moreover, some evidence of divergence in time trend between groups was observed ($P = 0.089$). No age or gender differences were detected ($P = 0.573$ and $P = 0.261$, respectively).

In the time course of D-dimers (Table III), a significant increase in D-dimer levels in both groups was found ($P < 0.001$). In on-pump group B the highest mean value of D-dimer was already reached at the end of surgery, while in off-pump group A the maximum values were observed only on postoperative day 1. As a consequence of this fact, a dramatic intergroup difference ($P < 0.001$) was found at the end of the procedure.

Spearman's correlation coefficient between D-dimer levels at the end of surgery and LOT (t_3) at 60 and 150 minutes was -0.047 and -0.086, respectively, in group A, and -0.123 and -0.323, respectively, in group B. All correlations were low and insignificant.

DISCUSSION

Our roTEG data indicate that a certain degree of fibrinolysis developed both in off-pump group A and in on-pump group B at time t_2 (on the completion of peripheral bypass anastomoses) and that fibrinolysis at this time point was quite widely expressed in group B. Theoretically, in both types of cardiac surgery the fibrinolytic activity is initiated with the release of a tissue plasminogen activator, which starts during the skin incision and sternotomy and continues through the surgical tissue manipulation. In operations using cardiopulmonary bypass, additional massive activation of coagulation by the contact of blood with foreign, negatively charged, nonendothelial surfaces is described with presumable consequent activation of the fibrinolytic system.[16] A very important mechanism acti-

vating the coagulation-fibrinolytic system seems to be retransfusion of pericardial blood collected intraoperatively to the extracorporeal circuit, as this shed blood contains a great amount of tissue factor and tissue plasminogen activator.[17] For this reason, a strategy based on the use of biocompatible surfaces with low thrombogenicity (eg. heparin-, polymethoxyacrylate-, phosphorylcholin-coated materials) and the use of closed extracorporeal circuits with the separation of suctions from the surgical field is currently recommended.[18-21]

At time point t_2 quite completely expressed thromboelastographic signs of hyperfibrinolysis were observed in 2 patients (20%) (B1 and B10) from the on-pump group and partial signs of increased fibrinolysis were noticed at 150 minutes of roTEG analyses in 2 other patients (B4, B9) originating from the same group. The preoperative characteristics and intraoperative course of these 4 male individuals were similar to the other patients in group B. The times of cardiopulmonary bypass for these patients were 55, 37, 31, and 57 minutes, respectively, while the range of times of the other patients in group B was 41-67 minutes. In contrast to the results of another thromboelastographic study that reported poor clinical outcome in fibrinolytic patients (eg. more colloid and vasopressor support, increased mortality),[22] no complications in the postoperative period (including bleeding tendency) of our probands with fibrinolysis were noticed. However, the frequency of detected hyperfibrinolysis in that retrospective on-pump study (14%) was quite similar to our results (20%).

In theory some roTEG parameters should be modified by a substantial hemodilution during extracorporeal circulation, in comparison to the off-pump group. In our practice with low pump prime the hemodilution was just moderate, which can be supported with the evidence of hematological parameters during cardiopulmonary bypass (medians [25^{th}-75^{th} percentiles]): hemoglobin 11.9 [10.5-12.1] g dL^{-1}, and hematocrit 36.5 [32.5-37.3], respectively.

The observation of significantly increased D-dimer levels in on-pump group B at the end of surgery and the equalization of elevated D-dimer levels between the on-pump and off-pump groups 24 hours after the surgery is in agreement with the findings of others.[10,11] The question of a possibly delayed increase in coagulant and fibrinolytic activity in off-pump surgery arises and slightly controversial clinical conclusions[23-25] should warrant further studies.

Thromboelastography provides a complete graphical representation of blood coagulation and eventual subsequent lysis of the clot in almost real time. Our 2 patients with an extreme degree of on-pump fibrinolysis showed a spontaneous tendency in the normalization of roTEG analysis at the end of procedures and did not display increased bleeding postoperatively, and thus no antifibrinolytic treatment was used. However, we assume that this point-of-care test is an excellent clinical tool for instant therapeutical decisions in situations of aug-

mented bleeding. Presently, we do not have enough data in available literature comparing roTEG signs of fibrinolysis with relevant plasma markers (fibrin degradation products, D-dimer) to determine which test is superior, but thromboelastography seems to be a fast and reliable method for the immediate evaluation of hyperfibrinolysis during cardiac surgery.[26)]

Although in many cardiac surgery centers pharmacological strategies based on fibrinolytic inhibitors are used on a routine basis, and their clinical effectiveness has been clearly validated,[27,28)] we unexpectedly did not find evident and explicit roTEG signs of hyperfibrinolysis in the majority of patients investigated. Our preliminary roTEG results display a slightly greater activation of fibrinolysis in on-pump coronary surgery during the course of cardiopulmonary bypass, but the off-pump versus on-pump differences are fairly subtle and imply a need for subsequent randomized trials with considerably larger numbers of patients allowing to justify the results by power analysis. It is necessary to clarify existing limitations of available literature evidence of fibrinolytic activity comparing off-pump versus on-pump cardiac operations.

ACKNOWLEDGEMENTS

Financial support for this study was received from the Cardiovascular Research Project of Charles University in Prague, Czech Republic, no. MSM0021620817.

REFERENCES

1. Levi M, Cromheecke ME, de Jonge E, *et al*. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. Lancet 1999; 354: 1940-7.
2. Sedrakyan A, Treasure T, Elefteriades JA. Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. J Thorac Cardiovasc Surg 2004; 128: 442-8. (Review)
3. Casati V, Della Valle P, Benussi S, *et al*. Effects of tranexamic acid on postoperative bleeding and related hematochemical variables in coronary surgery: Comparison between on-pump and off-pump techniques. J Thorac Cardiovasc Surg 2004; 128: 83-91.
4. Casati V, Gerli C, Franco A, *et al*. Tranexamic acid in off-pump coronary surgery: a preliminary, randomized, double-blind, placebo-controlled study. Ann Thorac Surg 2001; 72: 470-5.
5. Englberger L, Markart P, Eckstein FS, Immer FF, Berdat PA, Carrel TP. Aprotinin reduces blood loss in off-pump coronary artery bypass (OPCAB) surgery. Eur J Cardiothorac Surg 2002; 22: 545-51.
6. Jares M, Vanek T, Straka Z, Brucek P. Tranexamic acid reduces bleeding after off-pump coronary artery bypass grafting. J Cardiovasc Surg (Torino) 2003; 44: 205-8.
7. Vanek T, Jares M, Fajt R, *et al*. Fibrinolytic inhibitors in off-pump coronary surgery: a prospective, randomized, double-blind TAP study (tranexamic acid, aprotinin, placebo). Eur J Cardiothorac Surg 2005; 28: 563-8.
8. Karkouti K, Beattie WS, Dattilo KM, *et al*. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. Transfusion 2006; 46: 327-38.
9. Mangano DT, Tudor IC, Dietzel C. The risk associated with aprotinin in cardiac surgery. N Engl J Med 2006; 354: 353-65.

10. Casati V, Gerli C, Franco A, *et al*. Activation of coagulation and fibrinolysis during coronary surgery: on-pump versus off-pump techniques. Anesthesiology 2001; 95: 1103-9.
11. Vedin J, Antovic A, Ericsson A, Vaage J. Hemostasis in off-pump compared to on-pump coronary artery bypass grafting: a prospective, randomized study. Ann Thorac Surg 2005; 80: 586-93.
12. Koster A, Fischer T, Praus M, *et al*. Hemostatic activation and inflammatory response during cardiopulmonary bypass: impact of heparin management. Anesthesiology 2002; 97: 837-41.
13. Biglioli P, Cannata A, Alamanni F, *et al*. Biological effects of off-pump vs. on-pump coronary artery surgery: focus on inflammation, hemostasis and oxidative stress. Eur J Cardiothorac Surg 2003; 24: 260-9. (Review)
14. Brucek PJ, Straka Z, Vanek T, Jares M. Less invasive cardiac anesthesia: an ultra-fast-track procedure avoiding thoracic epidural analgesia. Heart Surg Forum 2003; 6: E107-10.
15. Straka Z, Widimsky P, Jirasek K, *et al*. Off-pump versus on-pump coronary surgery: final results from a prospective randomized study PRAGUE-4. Ann Thorac Surg 2004; 77: 789-93.
16. Mannucci L, Gerometta PS, Mussoni L, *et al*. One month follow-up of haemostatic variables in patients undergoing aortocoronary bypass surgery. Effect of aprotinin. Thromb Haemost 1995; 73: 356-61.
17. Chung JH, Gikakis N, Rao AK, Drake TA, Colman RW, Edmunds LH Jr. Pericardial blood activates the extrinsic coagulation pathway during clinical cardiopulmonary bypass. Circulation 1996; 93: 2014-8.
18. Hazama S, Eishi K, Yamachika S, *et al*. Inflammatory response after coronary revascularization: off-pump versus on-pump (heparin-coated circuits and poly2methoxyethylacrylate-coated circuits). Ann Thorac Cardiovasc Surg 2004; 10: 90-6.
19. Lindholm L, Westerberg M, Bengtsson A, Ekroth R, Jensen E, Jeppsson A. A closed perfusion system with heparin coating and centrifugal pump improves cardiopulmonary bypass biocompatibility in elderly patients. Ann Thorac Surg 2004; 78: 2131-8; discussion 2138.
20. Ranucci M, Isgro G, Soro G, Canziani A, Menicanti L, Frigiola A. Reduced systemic heparin dose with phosphorylcholine coated closed circuit in coronary operations. Int J Artif Organs 2004; 27: 311-9.
21. Zimmermann AK, Aebert H, Reiz A, *et al*. Hemocompatibility of PMEA coated oxygenators used for extracorporeal circulation procedures. Asaio J 2004; 50: 193-9.
22. Cvachovec K, Horacek M, Vislocky I. A retrospective survey of fibrinolysis as an indicator of poor outcome after cardiopulmonary bypass and a possible early sign of systemic inflammation syndrome. Eur J Anaesthesiol 2000; 17: 173-6.
23. Englberger L, Immer FF, Eckstein FS, Berdat PA, Haeberli A, Carrel TP. Off-pump coronary artery bypass operation does not increase procoagulant and fibrinolytic activity: preliminary results. Ann Thorac Surg 2004; 77: 1560-6.
24. Mariani MA, Gu YJ, Boonstra PW, Grandjean JG, van Oeveren W, Ebels T. Procoagulant activity after off-pump coronary operation: is the current anticoagulation adequate? Ann Thorac Surg 1999; 67: 1370-5.
25. Quigley RL, Fried DW, Pym J, Highbloom RY. Off-pump coronary artery bypass surgery may produce a hypercoagulable patient. Heart Surg Forum 2003; 6: 94-8.
26. Whitten CW, Greilich PE. Thromboelastography: past, present, and future. Anesthesiology 2000; 92: 1223-5. (Review)
27. Andreasen JJ, Nielsen C. Prophylactic tranexamic acid in elective, primary coronary artery bypass surgery using cardiopulmonary bypass. Eur J Cardiothorac Surg 2004; 26: 311-7.
28. Diprose P, Herbertson MJ, O'Shaughnessy D, Deakin CD, Gill RS. Reducing allogeneic transfusion in cardiac surgery: a randomized double-blind placebo-controlled trial of antifibrinolytic therapies used in addition to intra-operative cell salvage. Br J Anaesth 2005; 94: 271-8.

Interactive CardioVascular and Thoracic Surgery

Fibrinolysis in coronary artery surgery: detection by thromboelastography

Tomas Vanek, Martin Jares, Jana Snircova and Marek Maly

Interact CardioVasc Thorac Surg 2007;6:700-704; originally published online Aug 20, 2007;
DOI: 10.1510/icvts.2007.161463

doi:10.1510/icvts.2007.161463

INTERACTIVE CARDIOVASCULAR AND THORACIC SURGERY

Interactive CardioVascular and Thoracic Surgery 6 (2007) 700–704

www.icvts.org

Work in progress report - Coronary

Fibrinolysis in coronary artery surgery: detection by thromboelastography☆

Tomas Vanek[a,*], Martin Jares[a], Jana Snircova[a], Marek Maly[b]

[a]*Department of Cardiac Surgery, 3rd Faculty of Medicine, Charles University Prague and University Hospital Kralovske Vinohrady, Czech Republic*
[b]*Department of Biostatistics and Informatics, National Institute of Public Health, Prague, Czech Republic*

Received 13 June 2007; received in revised form 30 July 2007; accepted 2 August 2007

Abstract

Sixty-five patients scheduled for coronary surgery were randomized into three groups: A – conventional coronary artery bypass grafting, B – off-pump surgery, C – coronary artery bypass grafting with modified, rheoparin coated cardiopulmonary bypass with the avoidance of re-infusion of cardiotomy blood into the circuit. On the completion of peripheral bypass anastomoses, highly significant inter-group differences were found in the thromboelastographic parameter lysis of set time at 60 min of assessment ($P=0.003$) and at 150 min of assessment ($P<0.001$), the mean values of these parameters were significantly lower in group A as compared with both groups B and C, which were statistically indistinguishable. Lysis on set time on the completion of peripheral bypass anastomoses <50% was detected in 12 patients (52.2%) originating from group A. At the other sampling times (preoperatively, 15 min after sternotomy, at the end of the procedures, and 24 h later) thromboelastographic parameters were similar in all groups. In group A no significant correlations between lysis on set time, postoperative blood loss and D-dimer levels were found. Based on our results, thromboelastographic signs of fibrinolysis were clearly detectable during cardiopulmonary bypass in group A, but not at any time in groups B and C.

Keywords: Coronary artery surgery; Beating heart surgery; Cardiopulmonary bypass; Hemostasis; Thromboelastography; D-dimer

1. Introduction

Although in many centers pharmacological strategies based on fibrinolytic inhibitors are used on a routine basis, detailed knowledge of fibrinolysis during cardiac surgery is still limited. The aim of this prospective, randomized study was to search for fibrinolysis by the method of rotation thromboelastography/thromboelastometry (ROTEM) in different settings of coronary artery surgery.

Thromboelastography is a measuring method, based on the continuous registration of blood clot firmness during the entire coagulation process. Thus, the beginning of clot formation, clot formation kinetics and the maximum clot firmness are assessed as well as its stability or lysis [1]. The most important parameter for detection of fibrinolysis in ROTEM analysis is lysis on set time (LOT), which describes the reduction of clot firmness during measurement (Fig. 1).

2. Material and methods

With the Medical Faculty Ethics Committee approval, and after obtaining the informed consent from all participants, 65 patients with ischemic heart disease scheduled for coronary surgery were enrolled in the study. The criteria for non-enrollment to the study were as follows: emergency procedures, previous cardiac surgery, concomitant surgery (valvular or aortic), myocardial infarction <7 days prior to surgery, history of hematological or liver disorders, renal insufficiency (serum creatinine >150 μmol/l), and preoperative anemia (hemoglobin <11 g/l, hematocrit <32). A strict contraindication to the inclusion in the study was preoperative treatment with antiaggregative or anticoagulant drugs. No fibrinolytic inhibitors were used in the perioperative period in any of the evaluated patients.

After the enrollment into the study, the patients were randomized into three groups: A (conventional CABG), B (OPCAB surgery), and C (CABG with modified cardiopulmonary bypass), the envelope method with random numbers was used. The feasibility of randomization for on-pump or off-pump coronary surgery in our center was proven by previous experiences [2, 3].

2.1. Surgical and cardiopulmonary bypass techniques

2.1.1. Group A – conventional CABG

Cardiopulmonary bypass in a standard setting was established by ascending aortic cannulation and two-stage venous cannulation of the right atrium, non-coated extracorporeal circuit (Dideco D 903 Avant, Mirandola, Italy) with crystalloid pump prime 750 ml was used. Heparin was

☆ Financial support by the Cardiovascular research project of the Charles University Prague, Czech Republic, no. MSM0021620817.

*Corresponding author. Department of Cardiac Surgery, FNKV, Srobarova 50, 100 34 Prague 10, Czech Republic. Tel.: +420 267 163 422; fax: +420 267 163 260.

E-mail address: vanek@fnkv.cz (T. Vanek).

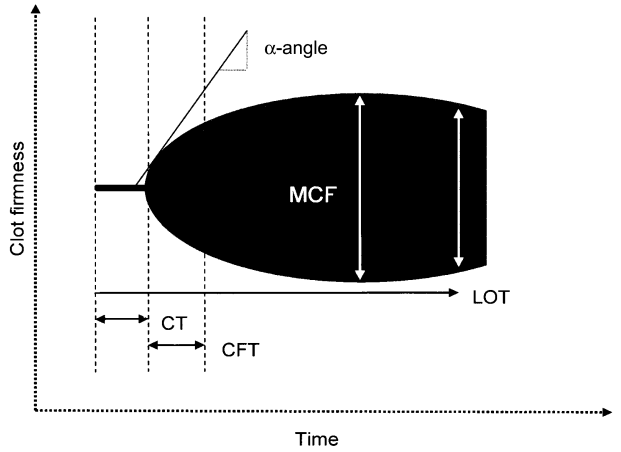


Fig. 1. Parameters of ROTEM analysis (scheme). [α-angle – the angle between the center line and a tangent to the curve through the 2 mm amplitude point (°); CFT = clot formation time – time from the onset of clot formation until an amplitude of 20 mm is reached (s); CT = clotting time – time from the start of measurement until the start of clot formation (s); LOT = lysis on set time (% of MCF); MCF = maximum clot firmness (mm)].

given at an initial dose of 300 IU/kg to achieve an activated clotting time (ACT) >480 s. Normothermic perfusion (2.5 l/m², roller pump) with antegrade intermittent warm blood cardioplegia and re-infusion of cardiotomy suction blood were used. On the completion of all anastomoses, full-dose protamin chloride was given to reverse the effect of heparin.

2.1.2. Group B – OPCAB surgery

The patients were operated on from full midline sternotomy. The verticalization of the beating heart was achieved using an Axius Xpose Device while the Acrobat SUV Vacuum Stabilizer, and Axius Blower/Mister (Guidant, Santa Clara, CA) were used for the stabilization and visualization of the anastomosis site. No cell-saver device was used and no blood was returned to the patients. The dose of heparin, 100 IU/kg, was used with target ACT over 250 s. On the completion of anastomoses, heparinization was partially reversed with a half-dose of protamin, regardless of ACT value.

2.1.3. Group C – modified cardiopulmonary bypass

A rheoparin coated cardiopulmonary bypass system (oxygenator Medos Hilite 7000, Stolberg, Germany + hardshell venous reservoir, tubing, cannules) was utilized. The blood suctioned from the pericardium was collected in a separate reservoir and was not returned routinely into the extracorporeal circulation. Heparin, perfusion, and cardioplegia managements were the same as described in group A.

2.2. Transfusion policy

During the procedures the patients were administered crystalloid solutions and 5% albumin solution, if necessary, synthetic colloidal solutions and fresh frozen plasma were not used. Determined borderlines for administration of red blood cell transfusion (or reinfusion of collected autologous blood in group C) were hemoglobin decrease to <8.5 g/dl and/or hematocrit <26. The same threshold for allogenic blood transfusion was used 24 h postoperatively.

2.3. ROTEM and laboratory analyses

The blood for ROTEM examination was sampled from the arterial line into tubes containing sodium citrate (Greiner Bio-One, Kremsmuenster, Austria) and processed immediately after sampling by ROTEG® Whole Blood Haemostasis System, model 05 (Pentapharm, Munich, Germany) using heparinase HEPTEG for heparin removal and EXTEG (Nobis, Endingen, Germany) including thromboplastin for the extrinsic pathway activation. The sampling time points were as follows: preoperatively (t_1), 15 min after sternotomy (t_2), on the completion of peripheral bypass anastomoses (t_3), at the end of the procedures (t_4), and 24 h after the end of surgery (t_5). Blood samples for D-dimer examination were taken before the operation, at the end of surgery, and 24 h later.

2.4. Statistical analysis

Statistical analysis was performed by statistical software Stata, release nine (Stata Corp LP, College Station, TX). All statistical tests were evaluated at a significance level of 0.05.

3. Results

For all three study groups no significant differences in the basic demographic data and preoperative hematological variables were found.

Only one patient originally randomized to group B was intraoperatively (but before initiating of revascularization) converted to group A. The reason for this was the presence of small intramuscular coronary arteries. One patient from group C was re-infused by collected shed blood (900 ml) during cardiopulmonary bypass, the data of this patient were withdrawn from the study. Four patients (1 originating from group A, 1 from group B, 2 from group C, respectively) underwent re-exploration postoperatively with the finding of an evident surgical source of bleeding, and so their following postoperative data were not included in the study, either.

The differences between groups in the mean number of grafts [arithmetic means and 95% confidence intervals – group A: 2.43 (2.12; 2.75), group B: 2.09 (1.73; 2.45), group C: 2.63 (2.34; 2.92)] were close to the significance level ($P = 0.059$) due to the lower number of grafts per patient in group B. The mean intraoperative blood loss was slightly higher in group C [geometric means and 95% confidence intervals – group A: 326.0 (269.1; 394.9) ml, group B: 346.2 (258.6; 463.6) ml, group C: 441.9 (354.3; 551.1) ml, $P = 0.066$]. In this group the volume of blood collected in the separate reservoir – median 150 ml, min–max 100–650 ml – was included in the evaluated blood loss. The hemodilution during extracorporeal circulation in on-pump groups was just moderate [medians (25–75th percentiles) – group A: hemoglobin 11.6 (10.3; 12.0) g dl^{-1}, hematocrit 35.6 (31.0; 36.9), group C: hemoglobin 10.5 (10.0; 12.0) g dl^{-1}, hematocrit 32.1 (30.9; 36.9)]. Neither cardiopulmo-

nary bypass nor aortic clamp durations showed any differences between groups A and C.

The highest mean postoperative blood loss (in 24 h) was observed in group C, while the lowest mean blood loss was detected in group B [group A: 686.7 (570.8; 826.1) ml, group B: 555.3 (441.3; 698.9) ml, group C: 775.6 (645.1; 932.3) ml, $P=0.157$].

Only one patient in each group was re-transfused by packed red cells intraoperatively. The number of patients re-transfused postoperatively with packed red cells was 9 (40.9%), 5 (23.8%) and 9 (52.9%) in groups A, B and C, respectively. The differences in proportions are not significant ($P=0.176$), although transfusion requirements were lower in group B as compared to the other two groups.

3.1. ROTEM analyses, association with blood loss and D-dimer levels

Comparison of LOT in monitored time points is given in Table 1. While parameters were similar in groups A, B and C in sampling times t_1, t_2, t_4 and t_5, in sampling time t_3 (on the completion of peripheral bypass anastomoses) highly significant inter-group differences were found in LOT (60 min) ($P=0.003$) and in LOT (150 min) ($P<0.001$). The mean values of these parameters were significantly lower in group A as compared with both of the other groups B and C, which were statistically indistinguishable – LOT (60 min) ($P=0.968$), LOT (150 min) ($P=0.979$). Parameter LOT (150 min) <50% of maximum clot firmness was detected in 12 individual patients (52.2%) originating from the group A. The time course of LOT (150 min) over the sampling times is shown in Fig. 2; group A differs significantly from the other two groups ($P<0.001$).

In group A, the association between LOT (150 min) in sampling time t_3 and postoperative blood loss was tested.

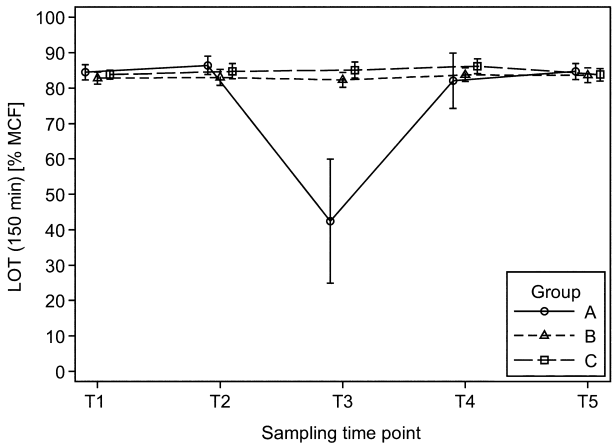


Fig. 2. Time course of LOT (150 min) over the sampling times. Group A differs significantly from the groups B and C ($P<0.001$).

Spearman correlation coefficient was 0.39 ($P=0.075$) in this case. In patients with apparent ROTEM signs of hyperfibrinolysis (LOT equal to 0) a wide range of bleeding occurred (min–max 440–1310 ml).

The time course of D-dimer levels is presented in Fig. 3. A significant increase in D-dimer levels in all groups was found. In group A the highest mean value of D-dimer was already reached at the end of surgery, while in groups B and C the maximum values were observed as late as on postoperative day one. As a consequence of this fact, a dramatic inter-group difference ($P<0.001$) was found at the end of procedures; the mean value of D-dimer in group A was distinct from groups B and C ($P=0.001$, $P<0.001$, respectively), while the difference between groups B and C was not significant ($P=0.231$).

Table 1
Comparison of lysis on set time at monitored time points

Time point	Group A ($n=23$)[a]	Group B ($n=22$)[a]	Group C ($n=19$)[a]	P-value
t_1				
LOT (30 min)	97.9 (97.6; 98.1)	98.0 (98.0; 98.0)	97.9 (97.8; 98.1)	0.542
LOT (60 min)	93.7 (92.5; 94.8)	92.9 (92.0; 93.7)	93.9 (92.8; 95.0)	0.305
LOT (150 min)	84.5 (82.3; 86.6)	82.8 (81.1; 84.5)	83.8 (82.5; 85.1)	0.401
t_2				
LOT (30 min)	97.6 (97.0; 98.1)	97.8 (97.6; 98.0)	97.9 (97.7; 98.0)	0.387
LOT (60 min)	94.3 (93.2; 95.4)	93.3 (92.1; 94.4)	94.1 (92.6; 95.5)	0.431
LOT (150 min)	86.4 (83.8; 89.0)	83.0 (80.7; 85.3)	84.7 (82.6; 86.9)	0.113
t_3				
LOT (30 min)	96.9 (95.1; 98.7)	97.8 (97.4; 98.2)	98.0 (98.0; 98.0)	0.340
LOT (60 min)	76.3 (62.0; 90.6)	93.6 (92.4; 94.9)	96.3 (95.2; 97.3)	0.003
LOT (150 min)	42.4 (24.9; 59.9)	82.3 (80.2; 84.4)	85.1 (82.8; 87.4)	<0.001
t_4				
LOT (30 min)	98.0 (97.9; 98.0)	97.9 (97.8; 98.0)	97.9 (97.8; 98.1)	0.796
LOT (60 min)	95.6 (94.6; 96.6)	93.5 (92.1; 94.9)	95.1 (93.8; 96.4)	0.038
LOT (150 min)	82.1 (74.3; 89.9)	83.7 (81.8; 85.7)	86.2 (84.1; 88.2)	0.519
t_5				
LOT (30 min)	97.9 (97.7; 98.1)	98.0 (98.0; 98.0)	97.9 (97.8; 98.1)	0.569
LOT (60 min)	93.8 (92.5; 95.0)	93.0 (91.8; 94.1)	93.4 (92.4; 94.3)	0.571
LOT (150 min)	84.7 (82.4; 86.9)	83.6 (81.5; 85.7)	83.8 (82.0; 85.5)	0.714

Data are presented as arithmetic means and 95% confidence intervals. Sampling time points: t_1 = preoperatively; t_2 = fifteen minutes after sternotomy; t_3 = on the completion of peripheral bypass anastomoses; t_4 = at the end of the procedures; t_5 = 24 h after the end of surgery. [a]At the sampling time t_5 four patients with postoperative re-exploration were excluded (1 originating from group A, 1 from group B, 2 from group C, respectively). LOT = lysis on set time (at 30, 60, and 150 min of assessment).

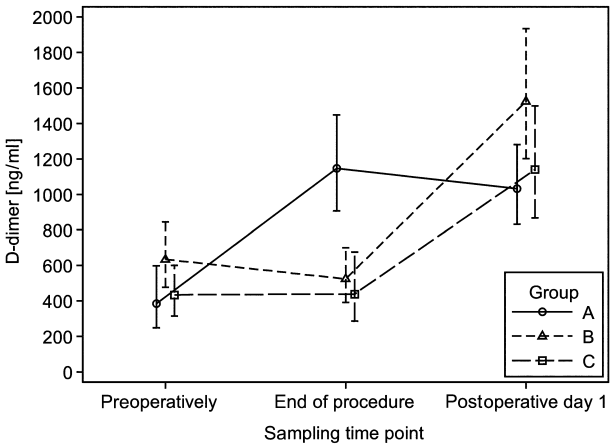


Fig. 3. Time course of D-dimer levels over the sampling times. Significant inter-group difference was found at the end of procedures ($P<0.001$).

In group A, the relationship between LOT (150 min) in sampling time t_3 and D-dimer levels at the end of procedures was examined. The association between the variables was insignificantly negative with Spearman correlation coefficient equal to 0.16 ($P=0.463$). In patients with apparent ROTEM signs of hyper-fibrinolysis (LOT equal to 0) there was a wide range of D-dimer levels (min–max 520–2210 ng/ml).

4. Discussion

The main finding of this randomized trial is apparent thromboelastographic detection of fibrinolysis/hyper-fibrinolysis in conventional CABG (group A) at the time of extracorporeal circulation. In theory, fibrinolytic activity during cardiac surgery is initiated by the release of tissue plasminogen activator; this starts with the skin incision and sternotomy and continues throughout the surgical tissue manipulation. In operations where cardiopulmonary bypass is used, additional massive activation of coagulation occurs related to the contact of blood with foreign, negatively charged non-endothelial surfaces and consequent activation of the fibrinolytic system is described. Re-infusion of the suctioned fluids from the surgical field (shed blood from the pericardium contains large amounts of cytokines, tissue factors and tissue plasminogen activator) thereafter enhances these pathological processes [4–6].

No ROTEM signs of fibrinolysis were detected in OPCAB group B, and in modified cardiopulmonary bypass group C at the critical sampling time of the completion of peripheral bypass anastomoses. No ROTEM signs of fibrinolytic activity were found in all the evaluated groups at the other sampling times. In agreement with available literature we, therefore, consider that the main important triggers of fibrinolytic pathways are the usage of non-coated, less-biocompatible cardiopulmonary bypass and, principally, direct re-infusion of suctioned fluids exposed to pericardial and mediastinal surfaces into the extracorporeal circuit [7]. The actual impact of either biocompatible coating or avoidance of re-infusion of shed blood on ROTEM results should be verified by further investigation with a different study design (modified cardiopulmonary bypass group split into two separate sub-groups). Even though there is growing literary evidence that fibrinolytic inhibitors reduce postoperative blood loss in OPCAB [8–11], based on our results, the impact of sternotomy/surgical tissue manipulations does not seem to be as important as the practice of cardiopulmonary bypass.

The consequences of this study are supported by the results of our prospective, randomized pilot study, which had been realized previously with different patients [12].

Although in the present study approximately half of the patients (52.2%) in the conventional CABG group A expressed thromboelastographic signs of fibrinolysis during the period of cardiopulmonary bypass, these signs of fibrinolysis resolved spontaneously and were not detectable at the end of procedures and 24 h later, and thus no anti-fibrinolytic treatment was used. Surprisingly, in group A we did not find any association between ROTEM signs of fibrinolysis and postoperative blood loss. This finding is in contrast to results of another thromboelastographic retrospective survey with a poor clinical outcome in cardiac surgery patients with detected fibrinolysis [13]. A limitation of our study was the fact that in group C only modified, but not really condensed (miniaturized) closed 'minimally invasive' cardiopulmonary bypass was used, thus our expectations of decreased postoperative blood loss and the subsequent reduction of allogenic blood transfusion were not fulfilled [14].

The observation of significantly increased D-dimer levels in conventional CABG group A at the end of surgery and the equalization of elevated D-dimer levels between the on-pump group A and OPCAB group B 24 h after the surgery is in agreement with the findings of others [15]. According to our observations, the time course of D-dimer levels in modified CABG (group C) is similar to that in OPCAB surgery. In group A, a low and insignificant negative correlation between LOT (150 min) at sampling time t_3 and D-dimer levels at the end of surgery seems to be difficult to explain. Presently, we have not enough data in available literature comparing thromboelastographic signs of fibrinolysis with relevant plasma markers.

In conclusion, our prospective, randomized study demonstrated that thromboelastographic signs of fibrinolysis are clearly detectable in the important part of coronary surgery patients operated on with the use of conventional cardiopulmonary bypass, but not in off-pump patients and those operated on with the biocompatible surface-modified circuit without re-infusion of cardiotomy suction blood.

Acknowledgments

We are grateful to chief perfusionist BA Stepanka Suchoparova for her helpful contribution to this study.

References

[1] Spalding GJ, Hartrumpf M, Sierig T, Oesberg N, Kirsche CG, Albes JM. Cost reduction of perioperative coagulation management in cardiac surgery: value of 'bedside' thromboelastography (ROTEM). Eur J Cardiothorac Surg 2007;31:1052–1057.

[2] Straka Z, Widimsky P, Jirasek K, Stros P, Votava J, Vanek T, Brucek P, Kolesar M, Spacek R. Off-pump versus on-pump coronary surgery: final

results from a prospective randomized study PRAGUE-4. Ann Thorac Surg 2004;77:789–793.

[3] Widimsky P, Straka Z, Stros P, Jirasek K, Dvorak J, Votava J, Lisa L, Budesinsky T, Kolesar M, Vanek T, Brucek P. One-year coronary bypass graft patency: a randomized comparation between off-pump and on-pump surgery angiographic results of the PRAGUE-4 trial. Circulation 2004;110:3418–3423.

[4] Vedin J, Antovic A, Ericsson A, Vaage J. Hemostasis in off-pump compared to on-pump coronary artery bypass grafting: a prospective, randomized study. Ann Thorac Surg 2005;80:586–593.

[5] Biglioli P, Cannata A, Alamanni F, Naliato M, Porqueddu M, Zanobini M, Tremoli E, Parolari A. Biological effects of off-pump vs. on-pump coronary artery surgery: focus on inflammation, hemostasis and oxidative stress. Eur J Cardiothorac Surg 2003;24:260–269.

[6] Cannata A, Biglioli P, Tremoli E, Parolari A. Biological effects of coronary surgery: role of surgical trauma and CPB. Eur J Cardiothorac Surg 2004;26:664; author reply 664–665.

[7] Shann KG, Likosky DS, Murkin JM, Baker RA, Baribeau YR, DeFoe GR, Dickinson TA, Gardner TJ, Grocott HP, O'Connor GT, Rosinski DJ, Sellke FW, Willcox TW. An evidence-based review of the practice of cardiopulmonary bypass in adults: a focus on neurologic injury, glycemic control, hemodilution, and the inflammatory response. J Thorac Cardiovasc Surg 2006;132:283–290.

[8] Casati V, Della Valle P, Benussi S, Franco A, Gerli C, Baili P, Alfieri O, D'Angelo A. Effects of tranexamic acid on postoperative bleeding and related hematochemical variables in coronary surgery: comparison between on-pump and off-pump techniques. J Thorac Cardiovasc Surg 2004;128:83–91.

[9] Jares M, Vanek T, Straka Z, Brucek P. Tranexamic acid reduces bleeding after off-pump coronary artery bypass grafting. J Cardiovasc Surg (Torino) 2003;44:205–208.

[10] Vanek T, Jares M, Fajt R, Straka Z, Jirasek K, Kolesar M, Brucek P, Maly M. Fibrinolytic inhibitors in off-pump coronary surgery: a prospective, randomized, double-blind TAP study (tranexamic acid, aprotinin, placebo). Eur J Cardiothorac Surg 2005;28:563–568.

[11] Murphy GJ, Mango E, Lucchetti V, Battaglia F, Catapano D, Rogers CA, Angelini GD. A randomized trial of tranexamic acid in combination with cell salvage plus a meta-analysis of randomized trials evaluating tranexamic acid in off-pump coronary artery bypass grafting. J Thorac Cardiovasc Surg 2006;132:475–480, 480 e471–478.

[12] Jares M, Vanek T, Bednar F, Maly M, Snircova J, Straka Z. Off-pump versus on-pump coronary artery surgery – Identification of fibrinolysis using rotation thromboelastography; a preliminary, prospective, randomized study. Int Heart J 2007;48:57–67.

[13] Cvachovec K, Horacek M, Vislocky I. A retrospective survey of fibrinolysis as an indicator of poor outcome after cardiopulmonary bypass and a possible early sign of systemic inflammation syndrome. Eur J Anaesthesiol 2000;17:173–176.

[14] Remadi JP, Rakotoarivelo Z, Marticho P, Benamar A. Prospective randomized study comparing coronary artery bypass grafting with the new mini-extracorporeal circulation Jostra System or with a standard cardiopulmonary bypass. Am Heart J 2006;151:198.

[15] Paparella D, Galeone A, Venneri MT, Coviello M, Scrascia G, Marraudino N, Quaranta M, de Luca Tupputi Schinosa L, Brister SJ. Activation of the coagulation system during coronary artery bypass grafting: comparison between on-pump and off-pump techniques. J Thorac Cardiovasc Surg 2006;131:290–297.

Postoperative Blood Loss in Coronary Surgery

No Real Impact of Fibrinolysis Detected by Thromboelastography and D-Dimers. A Prospective, Randomized Study

Jana SNIRCOVA,[1] MD, Martin JARES,[1] MD, Marek MALY,[2] MSc, Zbynek STRAKA,[1] MD, Jan SPEGAR,[1] MD, *and* Tomas VANEK,[1] MD

SUMMARY

Although in many cardiac surgery centers pharmacological strategies based on fibrinolytic inhibitors are used on a routine basis, detailed knowledge of fibrinolysis during various settings of coronary surgery is still limited.

Sixty-five patients scheduled for coronary surgery were randomized into 3 groups: group A - conventional coronary artery bypass grafting, group B - off-pump surgery, and group C - coronary artery bypass grafting with modified, rheoparin coated cardiopulmonary bypass with the avoidance of reinfusion of cardiotomy blood into the circuit. The sampling time points for rotation thromboelastographic evaluations were as follows: preoperatively, 15 minutes after sternotomy, on the completion of peripheral bypass anastomoses, at the end of the procedures, and 24 hours after the end of surgery. D-dimer levels were evaluated before surgery, at the end of procedures, and 24 hours after surgery.

Thromboelastographic signs of fibrinolysis (evaluated by Lysis Onset Time-intergroup differences at 60 and 150 minutes of assessment: $P = 0.003$ and $P < 0.001$, respectively) were clearly detectable during cardiopulmonary bypass in group A, but not at any time in groups B and C. At the other sampling times all thromboelastographic parameters were similar in all groups. In group A, no exceptional bleeding tendency (during 24 hours), as compared to groups B and C (geometric means and 95% confidence intervals: group A: 686.7 [570.8; 826.1] mL, group B: 555.3 [441.3; 698.9] mL, group C: 775.6 [645.1; 932.3] mL, $P = 0.157$), and no significant correlations between Lysis Onset Time, postoperative blood loss, and D-dimer levels were found. No significant differences in postoperative blood loss related to cardiac surgeons and assistant surgeons were detected.

Thromboelastographic signs of increased fibrinolysis were detectable in the important proportion of coronary surgery patients operated on with the use of conventional cardiopulmonary bypass, but not in off-pump patients and those operated on with the biocompatible surface-modified circuit without reinfusion of cardiotomy suction blood. These signs resolved spontaneously at the end of surgery and were not associated with increased postoperative bleeding. No significant correlation with D-dimer levels was found. (Int

From the [1] Department of Cardiac Surgery, Third Faculty of Medicine, Charles University in Prague, Kralovske Vinohrady University Hospital, and [2] Department of Biostatistics and Informatics, National Institute of Public Health, Prague, Czech Republic.

Address for correspondence: Jana Snircova, MD, Department of Cardiac Surgery, Third Faculty of Medicine, Charles University in Prague, FNKV, Srobarova 50, 100 34 Prague 10, Czech Republic.

Received for publication October 15, 2007.

Revised and accepted January 17, 2008.

Heart J 2008; 49: 25-38)

Key words: Coronary artery surgery, Beating heart surgery, Cardiopulmonary bypass, Hemostasis, Thromboelastography, D-dimer

THE beneficial effect of different fibrinolytic inhibitors on the reduction of postoperative bleeding in cardiac surgery has been proven in large meta-analyses of randomized trials.[1,2] Only a limited number of studies have been concerned with the use of antifibrinolytic agents in off-pump coronary artery bypass (OPCAB) surgery, and these demonstrated its effectiveness as well.[3-8] The safety question of fibrinolytic inhibitors in coronary surgery is permanently under discussion. Two up-to-date published and widely discussed observational studies reported an increase in renal dysfunction plus ischemic events in aprotinin treated on-pump coronary artery bypass grafting (CABG).[9,10] Although in many centers pharmacological strategies based on fibrinolytic inhibitors are used on a routine basis, detailed knowledge of fibrinolysis during cardiac surgery and its real clinical impact is still limited.

The aim of this prospective, randomized study was to search for fibrinolysis (by the method of rotation thromboelastography, and by the examination of D-dimer levels), and to evaluate blood loss plus transfusion requirements in 3 different settings of coronary artery surgery.

METHODS

Sixty-five patients with ischemic heart disease scheduled for isolated coronary surgery from December 2005 to November 2006 were enrolled in the study. The study was approved by the Medical Faculty Ethics Committee (EK/48/2005, September 21, 2005) and informed consent was obtained from all participants. The criteria for nonenrollment were as follows: emergency procedures, redo surgery, recent myocardial infarction, history of hematological or liver disorders, renal insufficiency (serum creatinine higher than 150 μmol/L), and preoperative anemia (hemoglobin less than 11 g/L, hematocrit less than 32). A strict contraindication to inclusion in the study was preoperative treatment with antiaggregative or anticoagulant drugs (aspirin withdrawal within less than 5 days, and clopidogrel withdrawal within less than 14 days before surgery, low-molecular heparin withdrawal within less than 24 hours before surgery). No fibrinolytic inhibitors were used in the perioperative period in any of the evaluated patients.

After enrollment into the study, the patients were randomized into 3 groups; A (conventional CABG), B (OPCAB surgery), and C (CABG with modified car-

diopulmonary bypass), by the envelope method with random numbers. The patients were randomized to the surgical and cardiopulmonary bypass techniques, but not to the operating surgical teams. The setting of procedures was as follows:
Group A - conventional CABG. Cardiopulmonary bypass with a noncoated extracorporeal circuit (Dideco D 903 Avant, Mirandola, Italy) - crystalloid pump prime 750 mL-was used. Heparin was given at an initial dose of 300 IU/kg to achieve an activated clotting time (ACT) over 480 seconds. Normothermic perfusion (2.5 L/m^2) with antegrade intermittent warm blood cardioplegia and reinfusion of cardiotomy suction blood were used. On the completion of all anastomoses, full-dose protamine chloride was given to reverse the effect of heparin;
Group B - OPCAB surgery. The patients underwent a full midline sternotomy. The verticalization of the beating heart was achieved using an Axius Xpose Device (Guidant, Santa Clara, CA) while an Acrobat SUV Vacuum Stabilizer and an Axius Blower/Mister (Guidant, Santa Clara, CA) were used for the stabilization and visualization of the anastomosis site, respectively. The dose of heparin was 100 IU/kg with a target ACT over 250 seconds. Upon completion of the anastomoses, heparinization was partially reversed with a half-dose of protamine, regardless of the ACT value;
Group C - modified cardiopulmonary bypass. A rheoparin coated cardiopulmonary bypass system (oxygenator Medos Hilite 7000, Stolberg, Germany + hard-shell venous reservoir, tubing, cannules) was utilized. The blood suctioned from the pericardium was collected in the separate reservoir (Dideco D 742 D.A.C., Mirandola, Italy) and was not returned routinely into the extracorporeal circulation. Heparin, perfusion, and cardioplegia managements were the same as described in group A.

Intraoperative borderlines for administration of red blood cell transfusion (or reinfusion of collected autologous blood in group C) were a hemoglobin decrease to less than 8.5 g/dL and/or a hematocrit less than 26. The same threshold for allogenic blood transfusion was used 24 hours postoperatively; a transfusion of fresh frozen plasma was instituted (to correct a suspected deficiency of coagulation factors) when chest drain bleeding exceeded 150 mL/h, or 100 mL/h for two consecutive hours. No cell-saver device was used during the perioperative period in any group.

The blood for thromboelastography was processed immediately after sampling by a ROTEG® Whole Blood Haemostasis System, model 05 (Pentapharm, Munich, Germany) using heparinase HEPTEG (Nobis, Endingen, Germany) for heparin removal and EXTEG (Nobis, Endingen, Germany) including thromboplastin for the extrinsic pathway activation. Blood was aspirated from an arterial catheter after the withdrawal of 3 dead-space volumes to prevent massive contamination by heparin flush. The sampling time points were as follows: preoper-

atively (t_1), 15 minutes after sternotomy (t_2), on the completion of peripheral bypass anastomoses (t_3), at the end of the procedures (t_4), and 24 hours after the end of surgery (t_5). Blood samples for the evaluation of haematological parameters (haemoglobin, haematocrit, platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen) were taken and processed in a routine way. Blood samples for D-dimer examination were taken before the operation, at the end of surgery, and 24 hours later. D-dimer levels were assessed by a microlatex immunoassay procedure for a quantitative measurement of D-dimer on the Stago Compact analyser using Liatest Stachrom D-D antibodies (Diagnostica Stago, Parsippany, NJ).

Statistical analysis was performed using statistical software (Stata, release 9, Stata Corp LP, College Station, TX). The values of continuous variables were given as arithmetic or geometric means (for normally or log-normally distributed data, respectively) and their variability was characterized by 95% confidence intervals. For the statistical testing, the data were log-transformed when appropriate. The comparison between groups was made using various models of analysis of variance followed by Sidak's test for multiple comparisons and (in case of two groups) using a two-sample *t*-test. Within-group comparisons of different time points were based on a repeated-measures analysis of variance. The degree of relationship between two continuous variables was quantified by Spearman's rank correlation coefficient. For categorical data, the differences in proportions between groups were analyzed using the generalized Fisher's exact test and Pearson's χ^2 test in a contingency table. All statistical tests were evaluated at a significance level of 0.05.

RESULTS

The basic demographic study data for all 3 study groups are presented in Table I. No significant differences among the groups were found. There was no in-department death; the median in-department length of stay was 6 days (min-

Table I. Basic Demographic Characteristics

		Group A (n = 23)	Group B (n = 22)	Group C (n = 20)	P
Age (years)	Arithm.	66.7 (62.5;70.8)	66.1 (61.9;70.3)	65.2 (61.5;68.8)	0.860
Gender (male/female) (no. of pts, percentage)		18 (78%) / 5	17 (77%) / 5	12 (60%) / 8	0.334
Weight (kg)	Arithm.	85.2 (79.1;91.3)	83.5 (77.3;89.7)	80.8 (73.6;88.0)	0.610
Additive EuroSCORE	Arithm.	3.17 (1.97;4.38)	3.82 (2.81;4.83)	3.55 (2.47;4.63)	0.683
Logistic EuroSCORE	Geom.	2.21 (1.52;3.20)	2.76 (2.02;3.78)	2.51 (1.78;3.54)	0.624

Data are presented as arithmetic means (arithm.) or geometric means (geom.) and 95% confidence intervals, unless otherwise specified.

max 4-13) and all patients were discharged home or to other health care facilities for the completion of postoperative rehabilitation. One patient originally randomized to group B was intraoperatively (but before initiating revascularization) converted to group A due to the presence of small intramuscular coronary arteries. One patient from group C was reinfused by collected shed blood (900 mL) during cardiopulmonary bypass; the data for this 63-year-old lady (Additive EuroSCORE 2, Logistic EuroSCORE 1.59, number of bypasses,4) were entered into the demographic description, but her ensuing results were withdrawn from the study. Four patients (1 originating from group A, 1 from group B, and 2 from group C) underwent re-exploration postoperatively with the finding of an evident surgical source of bleeding, and so their following postoperative data were also

Table II. Basic Haematological Characteristics

		Group A (n = 23)[a]	Group B (n = 22) [a]	Group C (n = 19) [a]	P
Preoperative					
Haematocrit	Geom.	42.37 (40.57;44.26)	42.73 (40.54;45.04)	40.52 (34.00;48.29)	0.741
Haemoglobin (g dL^{-1})	Geom.	14.25 (13.61;14.91)	14.70 (14.11;15.32)	14.85 (14.34;15.38)	0.311
Platelet count (10^9 L^{-1})	Geom.	230.7 (209.2;254.4)	235.9 (217.6;255.6)	260.0 (233.4;289.7)	0.169
INR	Geom.	1.05 (1.03;1.07)	1.05 (1.03;1.08)	1.03 (1.00;1.05)	0.162
aPTT (sec.)	Geom.	35.36 (33.20;37.65)	33.67 (32.01;35.42)	35.07 (32.70;37.62)	0.446
Fibrinogen (g L^{-1})	Geom.	4.25 (3.85;4.68)	4.47 (4.07;4.92)	4.51 (4.06;5.02)	0.615
AT III (%)	Arithm.	97.2 (91.7;102.7)	101.3 (95.2;107.4)	95.5 (90.0;101.1)	0.335
Postoperative (at the end of procedures)					
Haematocrit	Geom.	36.85 (34.61;39.24)	37.48 (35.63;39.44)	37.04 (34.85;39.38)	0.905
Haemoglobin (g dL^{-1})	Geom.	12.11 (11.37;12.90)	12.49 (11.93;13.08)	12.13 (11.41;12.88)	0.659
Platelet count (10^9 L^{-1})	Geom.	160.0 (141.0;181.4)	175.8 (159.3;194.0)	165.1 (144.3;189.0)	0.488
INR	Geom.	1.35 (1.31;1.39)	1.28 (1.23;1.33)	1.40 (1.36;1.45)	0.001
aPTT (sec.)	Geom.	33.81 (32.25;35.44)	41.37 (35.11;48.76)	42.08 (33.68;52.58)	0.066
Fibrinogen (g L^{-1})	Geom.	3.26 (2.87;3.70)	3.33 (3.00;3.69)	3.25 (2.88;3.66)	0.947
AT III (%)	Arithm.	77.3 (73.5;81.1)	74.0 (68.5;79.6)	69.7 (65.0;74.5)	0.076
ACT	Geom.	130.0 (124.4;136.0)	140.8 (131.8;150.5)	133.0 (126.5;139.8)	0.085
Postoperative (24 hours after the end of surgery)					
Haematocrit	Geom.	30.33 (28.90;31.84)	31.94 (30.21;33.76)	29.37 (28.06;30.74)	0.063
Haemoglobin (g dL^{-1})	Geom.	10.24 (9.73;10.77)	10.96 (10.35;11.61)	9.91 (9.51;10.33)	0.020
Platelet count (10^9 L^{-1})	Geom.	169.4 (154.0;186.5)	186.1 (168.8;205.2)	160.0 (121.5;210.6)	0.378
INR	Geom.	1.24 (1.20;1.27)	1.26 (1.21;1.32)	1.26 (1.20;1.32)	0.715
aPTT (sec.)	Geom.	36.61 (34.87;38.44)	41.77 (36.26;48.13)	41.97 (33.87;52.01)	0.242
Fibrinogen (g L^{-1})	Geom.	4.70 (4.26;5.18)	4.40 (4.07;4.75)	4.26 (3.89;4.66)	0.257
AT III (%)	Arithm.	78.3 (74.3;82.4)	73.6 (68.8;78.4)	71.2 (65.9;76.5)	0.076

Data are presented as arithmetic means (arithm.) or geometric means (geom.) and 95% confidence intervals. aPTT indicates activated partial thromboplastin time; AT III, antithrombin; and INR, international normalized ratio of prothrombin time.

[a] At sampling time 24 hours after the end of surgery 4 patients with postoperative re-exploration were excluded (1 originating from group A, 1 from group B, 2 from group C).

Table III. Basic Intraoperative Characteristics

		Group A (n = 23)	Group B (n = 22)	Group C (n = 19)	P
Operating time (min.)	Geom.	166.1 (151.5;182.1)	153.3 (137.9;170.3)	166.2 (146.8;188.2)	0.433
Number of grafts	Arithm.	2.43 (2.12;2.75)	2.09 (1.73;2.45)	2.63 (2.34;2.92)	0.059
Blood loss (mL)	Geom.	326.0 (269.1;394.9)	346.2 (258.6;463.6)	441.9 (354.3;551.1)	0.066
CPB duration (min.)	Geom.	41.86 (37.40;46.84)	-	42.22 (37.58;47.42)	0.943
AC duration (min.)		24.10 (21.66;26.80)	-	24.54 (21.40;28.15)	0.728

Data are presented as arithmetic means (arithm.) or geometric means (geom.) and 95% confidence intervals. AC indicates aortic clamp; aPTT, activated partial thromboplastin time; AT III, antithrombin; CPB, cardiopulmonary bypass; and INR, international normalized ratio of prothrombin time.

not included in the study.

The means and corresponding 95% confidence intervals of the basic preoperative haematological variables can be found in Table II. The 3 groups showed comparable characteristics. The differences between groups in the mean number of grafts (Table III) were close to the significance level (P = 0.059) due to the lower number of grafts per patient in group B. The mean intraoperative blood loss was slightly higher in group C (in this group the volume of blood collected in the separate reservoir - median 150 mL, min-max 100-650 mL - was included in the evaluated blood loss). Neither cardiopulmonary bypass nor aortic clamp durations showed any differences between groups A and C.

The basic postoperative haematological characteristics are also presented in Table II. A statistically significant intergroup difference was detected in the international normalized ratio of prothrombin time (INR). Patients in group B showed slightly lower mean INR values compared to the other two groups. The maximum individual INR value did not exceed 1.58 in any group. Apparent but still nonsignificant differences between groups were observed in activated partial thromboplastin time (aPTT); the increase in geometric means in groups B and C was caused by several patients with remarkably high values.

Postoperative blood loss (in 24 hours) was as follows (geometric means and 95% confidence intervals): 686.7 (570.8; 826.1) mL, 555.3 (441.3; 698.9) mL, and 775.6 (645.1; 932.3) mL in groups A, B, and C, respectively. The highest mean postoperative blood loss was observed in group C, while the lowest mean blood loss was detected in group B. The difference between groups did not reach statistical significance (P = 0.157). At 24 hours after the end of surgery for both haematocrit and haemoglobin parameters the lowest mean values were seen in group C and the highest mean values in group B (Table II). Only one patient in each group was retransfused by packed red cells intraoperatively. The number of patients retransfused postoperatively with packed red cells was 9 (40.9%), 5

Table IV. Comparison of Thromboelastographic Parameters at Monitored Time Points

Time point		Group A (n = 23)[a]	Group B (n = 22)[a]	Group C (n = 19)[a]	P
t_1					
CT [sec]	Geom.	59.5 (54.6;64.8)	52.0 (43.4;62.3)	62.6 (58.3;67.2)	0.094
CFT [sec]	Geom.	66.4 (60.2;73.2)	73.6 (63.0;85.9)	71.8 (61.4;83.9)	0.498
MCF [mm]	Arithm.	69.7 (65.5;73.8)	70.4 (64.6;76.2)	68.5 (62.7;74.2)	0.867
Alpha-angle [°]	Arithm.	77.1 (75.9;78.3)	75.4 (73.7;77.1)	75.2 (73.1;77.2)	0.155
LOT (30 min.)	Arithm.	97.9 (97.6;98.1)	98.0 (98.0;98.0)	97.9 (97.8;98.1)	0.542
LOT (60 min.)	Arithm.	93.7 (92.5;94.8)	92.9 (92.0;93.7)	93.9 (92.8;95.0)	0.305
LOT (150 min.)	Arithm.	84.5 (82.3;86.6)	82.8 (81.1;84.5)	83.8 (82.5;85.1)	0.401
t_2					
CT [sec]	Geom.	87.2 (64.1;118.7)	76.2 (59.6;97.4)	80.9 (64.5;101.5)	0.746
CFT [sec]	Geom.	78.8 (64.1;97.0)	71.9 (63.0;82.1)	73.6 (65.0;83.3)	0.684
MCF [mm]	Arithm.	63.9 (61.0;66.7)	64.5 (61.9;67.0)	65.3 (63.2;67.3)	0.730
Alpha-angle [°]	Arithm.	73.5 (69.9;77.1)	75.1 (73.3;76.9)	74.8 (73.0;76.6)	0.609
LOT (30 min.)	Arithm.	97.6 (97.0;98.1)	97.8 (97.6;98.0)	97.9 (97.7;98.0)	0.387
LOT (60 min.)	Arithm.	94.3 (93.2;95.4)	93.3 (92.1;94.4)	94.1 (92.6;95.5)	0.431
LOT (150 min.)	Arithm.	86.4 (83.8;89.0)	83.0 (80.7;85.3)	84.7 (82.6;86.9)	0.113
t_3					
CT [sec]	Geom.	110.5 (90.4;135.1)	127.7 (100.7;161.9)	136.7 (103.7;180.1)	0.404
CFT [sec]	Geom.	90.0 (80.4;100.8)	82.8 (72.1;95.0)	104.2 (85.5;127.0)	0.087
MCF [mm]	Arithm.	58.6 (56.1;61.0)	62.8 (59.1;66.6)	60.3 (55.3;65.2)	0.225
Alpha-angle [°]	Arithm.	72.1 (70.1;74.1)	72.8 (70.5;75.1)	68.6 (64.3;72.9)	0.088
LOT (30 min.)	Arithm.	96.9 (95.1;98.7)	97.8 (97.4;98.2)	98.0 (98.0;98.0)	0.340
LOT (60 min.)	Arithm.	76.3 (62.0;90.6)	93.6 (92.4;94.9)	96.3 (95.2;97.3)	0.003
LOT (150 min.)	Arithm.	42.4 (24.9;59.9)	82.3 (80.2;84.4)	85.1 (82.8;87.4)	< 0.001
t_4					
CT [sec]	Geom.	68.7 (54.1;87.1)	73.9 (64.2;85.2)	72.3 (56.9;91.8)	0.861
CFT [sec]	Geom.	78.1 (70.1;86.9)	67.3 (59.9;75.7)	76.7 (68.0;86.5)	0.118
MCF [mm]	Arithm.	64.7 (62.4;66.9)	65.5 (63.4;67.6)	65.9 (63.7;68.1)	0.695
Alpha-angle [°]	Arithm.	74.7 (73.2;76.1)	76.5 (75.0;77.9)	74.6 (72.6;76.6)	0.162
LOT (30 min.)	Arithm.	98.0 (97.9;98.0)	97.9 (97.8;98.0)	97.9 (97.8;98.1)	0.796
LOT (60 min.)	Arithm.	95.6 (94.6;96.6)	93.5 (92.1;94.9)	95.1 (93.8;96.4)	0.038
LOT (150 min.)	Arithm.	82.1 (74.3;89.9)	83.7 (81.8;85.7)	86.2 (84.1;88.2)	0.519
t_5					
CT [sec]	Geom.	62.5 (48.8;79.9)	64.3 (54.4;75.9)	58.2 (50.3;67.3)	0.759
CFT [sec]	Geom.	66.8 (59.2;75.4)	69.9 (63.1;77.3)	70.3 (59.3;83.3)	0.815
MCF [mm]	Arithm.	70.9 (66.6;75.1)	73.6 (69.1;78.1)	66.9 (63.7;70.2)	0.078
Alpha-angle [°]	Arithm.	76.7 (75.2;78.3)	76.3 (75.1;77.5)	76.2 (74.4;78.1)	0.876
LOT (30 min.)	Arithm.	97.9 (97.7;98.1)	98.0 (98.0;98.0)	97.9 (97.8;98.1)	0.569
LOT (60 min.)	Arithm.	93.8 (92.5;95.0)	93.0 (91.8;94.1)	93.4 (92.4;94.3)	0.571
LOT (150 min.)	Arithm.	84.7 (82.4;86.9)	83.6 (81.5;85.7)	83.8 (82.0;85.5)	0.714

Data are presented as arithmetic means (arithm.) or geometric means (geom.) and 95% confidence intervals. Sampling time points: t_1 = pre-operatively; t_2 = 15 minutes after sternotomy; t_3 = on the completion of peripheral bypass anastomoses; t_4 = at the end of the procedures; t_5 = 24 hours after the end of surgery. [a] At sampling time t_5, 4 patients with postoperative re-exploration were excluded (1 originating from group A, 1 from group B, 2 from group C).

CFT indicates clot formation time (time from the initiation of clotting to the detection of a clot firmness 20 mm); CT, clotting time (time from the start of measurement to the initiation of clotting); LOT, lysis onset time (at 30, 60, and 150 minutes of assessment); and MCF, maximum clot firmness (maximum stabilization of the clot).

(23.8%), and 9 (52.9%) in groups A, B, and C, respectively. The differences in proportions are not significant (P = 0.176), although transfusion requirements were lower in group B as compared to the other two groups. The number of patients retransfused postoperatively with fresh frozen plasma was 14 (63.6%), 9 (42.9%), and 9 (52.9%) in groups A, B, and C, respectively. None of the patients received fresh frozen plasma intraoperatively.

Comparison of thromboelastographic variables at the monitored time points is given in Table IV. While all examined parameters were similar in groups A, B and C for sampling times t_1, t_2, t_4 and t_5, at sampling time t_3 (on the completion of peripheral bypass anastomoses) highly significant intergroup differences were found in the most important parameter for detection of fibrinolysis - lysis onset time (LOT) - LOT (60 min.) (P = 0.003) and in LOT (150 min.) ($P <$ 0.001). The mean values of these parameters were significantly lower in group A as compared

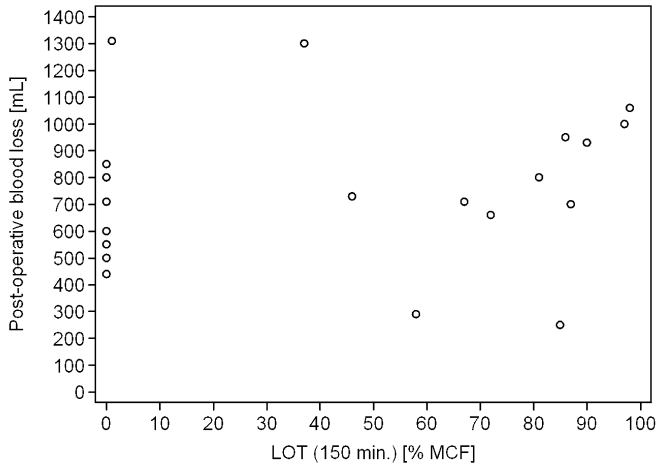


Figure 1. Association between LOT (150 min.) in sampling time t_3 and postoperative blood loss (24 hrs), group A.

Table V. Time Course of D-dimer Levels (ng mL^{-1})

Time point		Group A (n = 22)	Group B (n = 21)	Group C (n = 17)	P
Preoperatively	Geom.	384.7 (247.4;598.3)	634.2 (476.3;844.6)	434.4 (314.4;600.3)	0.107
End of procedures	Geom.	1146.7 (907.5;1449.0)	523.7 (392.1;699.5)	438.8 (285.1;675.3)	< 0.001
24 hrs after surgery	Geom.	1032.5 (832.3;1281.0)	1524.1 (1201.1;1933.9)	1139.1 (866.2;1498.1)	0.046

Data are presented as geometric means (geom.) and 95% confidence intervals.

with both groups B and C, which were statistically indistinguishable; LOT (60 min.) ($P = 0.968$), LOT (150 min.) ($P = 0.979$). Parameter LOT (150 min.) lower than 50% of maximum clot firmness was detected in 12 (52.2%) individual patients originating from group A.

In group A, the association between LOT (150 min.) at sampling time t_3 and postoperative blood loss is shown in Figure 1. The Spearman correlation coefficient was 0.39 ($P = 0.075$) in this case. In patients with apparent ROTEM signs of hyper-fibrinolysis (LOT equal to 0), a wide range of bleeding occurred (min-max 440-1310 mL).

The time course of D-dimer levels is presented in Table V. A significant increase in D-dimer levels was found in all groups. In group A the highest mean value of D-dimer was already reached at the end of surgery, while in groups B and C the maximum values were observed as late as on postoperative day 1. As a consequence of this fact, a dramatic intergroup difference ($P < 0.001$) was found at the end of procedures; the mean value of D-dimer in group A was distinct from groups B and C ($P = 0.001$, $P < 0.001$, respectively), while the difference between groups B and C was not significant ($P = 0.231$).

According to the mechanism of fibrinolysis expected at time t_3, there was a time delay of increased D-dimer levels expected at the end of procedures. In group A, the relationship between LOT (150 min.) in sampling time t_3 and D-dimer levels at the end of procedures is given in Figure 2. The association between the variables is insignificantly negative with a correlation coefficient

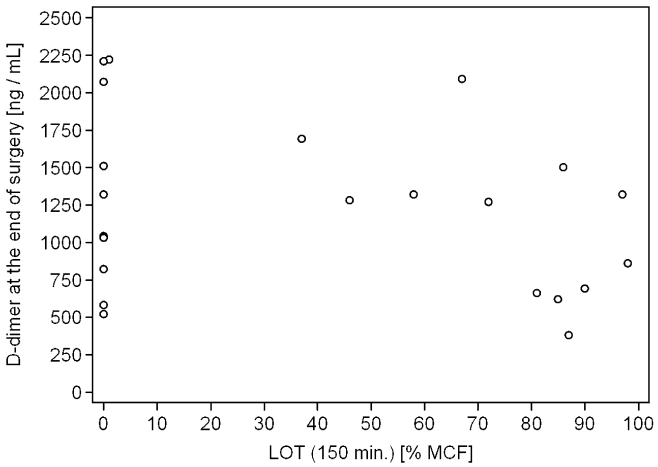


Figure. 2. Relationship between LOT (150 min.) in sampling time t_3 and D-dimer levels (at the end of surgery), group A.

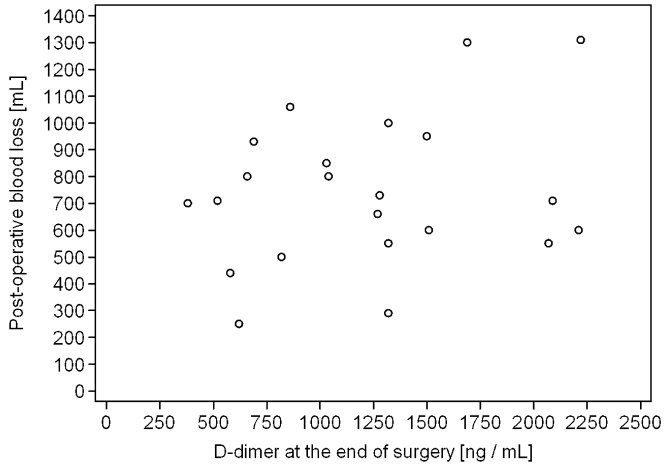


Figure 3. Association between D-dimer levels (at the end of surgery) and postoperative blood loss (24 hrs), group A.

Table VI. Spearman Correlation Coefficients Between Selected Variables for Groups A, B, and C

	Group A	Group B	Group C
LOT (150 min.) at t_3 versus blood loss	0.39 (P = 0.075)	-0.48 (P =0.027)	0.21 (P = 0.433)
LOT (150 min.) at t_3 versus D-dimer	-0.16 (P = 0.463)	0.57 (P = 0.006)	-0.23 (P = 0.350)
LOT (150 min.) at t_4 versus blood loss	-0.10 (P = 0.652)	-0.23 (P = 0.325)	0.16 (P = 0.547)
LOT (150 min.) at t_4 versus D-dimer	0.02 (P = 0.933)	0.45 (P = 0.037)	0.17 (P = 0.482)
D-dimer versus blood loss	0.21 (P = 0.354)	-0.29 (P = 0.21)	0.14 (P = 0.580)

Data are presented as Spearman correlation coefficients and P-value for test of the hypothesis that correlation equals zero. Sampling time points: t_3 = on the completion of peripheral bypass anastomoses; t_4 = at the end of the procedures; D-dimer - D-dimer levels at the end of surgery; blood loss - postoperative blood loss in 24 hours.
LOT indicates lysis onset time (at 150 minutes of assessment).

equal to -0.16 (P = 0.463). In patients with apparent ROTEM signs of hyperfibrinolysis (LOT equal to 0) there was a wide range of D-dimer levels (min-max 520-2210 ng/mL). Similarly at sampling time t_4, the correlation between LOT (150 min.) and D-dimer levels was low (0.02) and insignificant (P = 0.933). The association between D-dimer levels at the end of procedures and postoperative blood loss in group A is presented in Figure 3. Even though an upward trend indicating a positive association is slightly noticeable on the scatterplot, the Spearman correlation coefficient is as low as 0.21 (P = 0.354).

The above-mentioned correlations for group A (with evident thromboelastographic signs of fibrinolysis) supplemented with the results for groups B and C

are summarized in Table VI.

In this trial all surgeries were performed by 5 cardiac surgeons (providing myocardial revascularization) and 5 assistant surgeons (opening the chest, harvesting left internal thoracic artery, and closing the sternotomy). No significant differences in postoperative blood loss related to the cardiac surgeons ($P = 0.849$) or assistant surgeons ($P = 0.276$) were found, although some distinctions between assistant surgeons can be seen.

DISCUSSION

Our trial discovered moderately lower mean INR values in off-pump group B compared to the other two on-pump groups, and 24 hours later the differences between groups were statistically almost indistinguishable. This finding may be explained by better preservation of the haemostatic system in off-pump surgery;[11] however, we consider these differences in INR fairly subtle.

The apparent thromboelastographic detection of fibrinolysis/hyperfibrinolysis in conventional CABG (group A), but not in OPCAB (group B) and modified cardiopulmonary bypass (group C) has already been published.[12] This finding is supported by the results of our prospective, randomized pilot study, which had been realized previously with different patients.[13] In that preliminary study we had compared results in 20 patients scheduled for coronary surgery (10 patients OPCAB, 10 patients conventional CABG). Completely expressed thromboelastographic signs of hyperfibrinolysis had been detected in 2 on-pump patients and partial signs of increased fibrinolytic activity had been noticed in another 2 patients originating from the same group, unlike the OPCAB group, in which no signs of fibrinolysis had been observed. However, differences between the evaluated groups in that trial had not reached statistical significance due to a small number of study subjects.

Although in the present study about a half of the patients (52.2%) in group A expressed thromboelastographic signs of fibrinolysis/hyperfibrinolysis during the period of extracorporeal circulation, no exceptional bleeding tendency in this group, as compared to groups B and C, and no correlation between these signs of fibrinolytic activity and postoperative blood loss were found. The thromboelastographic signs of fibrinolysis resolved spontaneously and were not detectable at the end of procedures and 24 hours later. Based on these observations we consider the clear thromboelastographic finding of fibrinolysis/hyperfibrinolysis in conventional CABG to be most likely without a real clinical impact. While the use of thromboelastography has been investigated in various methods of general surgery and orthopaedics, evaluation in a broad range of patients is clearly needed before its recommendation for routine use in cardiac surgery.[14,15]

In agreement with our results, OPCAB surgery has been shown to reduce postoperative blood loss and the need for allogenic blood products, compared to conventional CABG.[16] Surprisingly, our expectations of decreased postoperative blood loss and the subsequent reduction of allogenic blood transfusion were not fulfilled in modified cardiopulmonary bypass group C with the use of biocompatible coating and avoidance of reinfusion of suctioned fluids exposed to pericardial and mediastinal surfaces (containing large amounts of cytokines, tissue factor and tissue plasminogen activator) into the circuit.[17] The possible explanation is the fact that in group C only modified, but not really condensed (miniaturized) closed "minimally invasive" cardiopulmonary bypass was used.[18,19] The influence of surgical team set-up in our trial on higher bleeding in group C seems to be inconsequential.

The observation of significantly increased D-dimer levels in conventional CABG group A at the end of surgery and the equalization of elevated D-dimer levels between the on-pump group A and OPCAB group B 24 hours after the surgery is in agreement with the findings of others.[11,20,21] According to our observations, the time course of D-dimer levels in modified CABG (group C) is similar to that in OPCAB surgery. In group A, a low and insignificant correlation between LOT (150 min.) at sampling time t_3 and D-dimer levels at the end of surgery seems to be difficult to explain. To the best of our knowledge, this finding is supported only by one formerly published communication.[22] Presently, there is not enough recent data in the available literature comparing thromboelastographic signs of fibrinolysis with relevant plasma markers.

In on-pump groups A and C no significant associations between LOT (150 min.), D-dimer levels, and postoperative blood loss were found. In off-pump group B a negative correlation between LOT (150 min.) and postoperative blood loss was observed, being significant at sampling time t_3 and nonsignificant at t_4. Contrary to our expectations, a positive correlation between D-dimer levels at the end of procedures and LOT (150 min.) was discovered in this group.

In conclusion, the present prospective, randomized study demonstrated that thromboelastographic signs of fibrinolysis are clearly detectable in the important proportion of coronary surgery patients operated on using conventional cardiopulmonary bypass, but not in off-pump patients and those operated on using the biocompatible surface-modified circuit without reinfusion of cardiotomy suction blood. The signs of fibrinolysis resolved spontaneously at the end of surgery and were not associated with increased postoperative bleeding. No significant correlation with D-dimer levels was found.

ACKNOWLEDGEMENTS

Financial support was provided by the Cardiovascular Research Project of the Charles University in Prague, Czech Republic, no. MSM0021620817.

REFERENCES

1. Levi M, Cromheecke ME, de Jonge E, *et al*. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. Lancet 1999; 354: 1940-7.
2. Sedrakyan A, Treasure T, Elefteriades JA. Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. J Thorac Cardiovasc Surg 2004; 128: 442-8. (Review)
3. Casati V, Della Valle P, Benussi S, *et al*. Effects of tranexamic acid on postoperative bleeding and related hematochemical variables in coronary surgery: Comparison between on-pump and off-pump techniques. J Thorac Cardiovasc Surg 2004; 128: 83-91.
4. Casati V, Gerli C, Franco A, *et al*. Tranexamic acid in off-pump coronary surgery: a preliminary, randomized, double-blind, placebo-controlled study. Ann Thorac Surg 2001; 72: 470-5.
5. Jares M, Vanek T, Straka Z, Brucek P. Tranexamic acid reduces bleeding after off-pump coronary artery bypass grafting. J Cardiovasc Surg (Torino) 2003; 44: 205-8.
6. Vanek T, Jares M, Fajt R, *et al*. Fibrinolytic inhibitors in off-pump coronary surgery: a prospective, randomized, double-blind TAP study (tranexamic acid, aprotinin, placebo). Eur J Cardiothorac Surg 2005; 28: 563-8.
7. Wei M, Jian K, Guo Z, *et al*. Effects of half-dose aprotinin in off-pump coronary artery bypass grafting. World J Surg 2006; 30: 1108-14.
8. Murphy GJ, Mango E, Lucchetti V, *et al*. A randomized trial of tranexamic acid in combination with cell salvage plus a meta-analysis of randomized trials evaluating tranexamic acid in off-pump coronary artery bypass grafting. J Thorac Cardiovasc Surg 2006; 132: 475-80.
9. Karkouti K, Beattie WS, Dattilo KM, *et al*. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. Transfusion 2006; 46: 327-38.
10. Mangano DT, Tudor IC, Dietzel C; Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation. The risk associated with aprotinin in cardiac surgery. N Engl J Med 2006; 354: 353-65.
11. Vedin J, Antovic A, Ericsson A, Vaage J. Hemostasis in off-pump compared to on-pump coronary artery bypass grafting: a prospective, randomized study. Ann Thorac Surg 2005; 2: 586-93.
12. Vanek T, Jares M, Snircova J, Maly M. Fibrinolysis in coronary artery surgery: detection by thromboelastography. Interact Cardiovasc Thorac Surg 2007; 6: 700-4.
13. Jares M, Vanek T, Bednar F, Maly M, Snircova J, Straka Z. Off-pump versus on-pump coronary artery surgery. Int Heart J 2007; 48: 57-67.
14. Ronald A, Dunning J. Can the use of thromboelastography predict and decrease bleeding and blood and blood product requirements in adult patients undergoing cardiac surgery? Interact Cardiovasc Thorac Surg 2005; 4: 456-63.
15. Spalding GJ, Hartrumf M, Sierig T, Oesberg N, Kirsche CG, Albes JM. Cost reduction of perioperative coagulation management in cardiac surgery: value of 'bedside' thromboelastography (ROTEM). Eur J Cardiothorac Surg 2007; 31: 1052-7.
16. Cheng DC, Bainbridge D, Martin JE, Novick RJ; Evidence-Based Perioperative Clinical Outcomes Research Group. Does off-pump coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials. Anesthesiology 2005; 102: 188-203.
17. Shann KG, Likosky DS, Murkin JM, *et al*. An evidence-based review of the practice of cardiopulmonary bypass in adults: a focus on neurologic injury, glycemic control, hemodilution, and the inflammatory response. J Thorac Cardiovasc Surg 2006; 2: 283-90. (Review)

18. Castiglioni A, Verzini A, Pappalardo F, *et al*. Minimally invasive closed circuit versus standard extracorporeal circulation for aortic valve replacement. Ann Thorac Surg 2007; 2: 586-91.
19. Remadi JP, Rakotoarivelo Z, Marticho P, Benamar A. Prospective randomized study comparing coronary artery bypass grafting with the new mini-extracorporeal circulation Jostra System or with a standard cardiopulmonary bypass. Am Heart J 2006; 1: 198.
20. Casati V, Gerli C, Franco A, *et al*. Activation of coagulation and fibrinolysis during coronary surgery: on-pump versus off-pump techniques. Anesthesiology 2001; 95: 1103-9.
21. Paparella D, Galeone A, Venneri MT, *et al*. Activation of the coagulation system during coronary artery bypass grafting: comparison between on-pump and off-pump techniques. J Thorac Cardiovasc Surg 2006; 131: 290-7.
22. Whitten CW, Allison PM, Latson TW, *et al*. Thromboelastographic fibrinolysis does not correlate with levels of D-dimers after cardiopulmonary bypass. Anesthesiology 1991; 75: A432.