J Anesth (2007) 21:297–303
DOI 10.1007/s00540-007-0506-1

Journal of Anesthesia

Original articles

Heparin anticoagulation in patients undergoing off-pump and on-pump coronary bypass surgery

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Abstract
Purpose. The authors analyzed the coagulation data of patients who underwent on-pump coronary artery bypass graft (CABG) or off-pump coronary artery bypass surgery (OPCAB) in a randomized prospective trial.
Methods. CABG and OPCAB patients received heparin anticoagulation at 400 U·kg^{-1}, and 180 U·kg^{-1} plus 3000 U every 30 min, respectively. In addition, OPCAB patients received a rectal aspirin, 650 mg, during the procedure. Perioperative coagulation test results (platelet count, fibrinogen, prothrombin time, partial thromboplastin time [PTT], activated clotting time [ACT], and thromboelastography [TEG; Haemoscope] were collected from CABG (n = 99) and OPCAB (n = 98) patients. Residual heparin activity after protamine was measured, using an anti-activated factor X (Xa) assay, in 10 patients from each group.
Results. Our study showed that the current anticoagulation regimen in the OPCAB patients achieved a peak ACT of 445 ± 73 s, and it preserved platelet counts and fibrinogen levels. A residual heparin effect was detected, with residual anti-Xa heparin activity of 0.2 U·ml^{-1} up to 2 h after surgery in the OPCAB group. Despite the residual anticoagulation, the OPCAB group had a similar TEG index of native blood, postoperative chest tube drainage, and non-erythrocyte transfusion rate as compared with the CABG group.
Conclusion. We have shown that the heparin anticoagulation regimen in OPCAB patients does not lead to an immediate hypercoagulable state. Total doses of heparin and protamine were lower in the OPCAB group compared with the CABG group, and there was a residual heparin effect on TEG and PTT in the early postoperative period in the OPCAB group.

Key words Off-pump coronary bypass surgery · Heparin · Aspirin · Coagulation

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Received: October 2, 2006 / Accepted: January 19, 2007

Introduction

A growing number of patients are undergoing coronary artery surgery without cardiopulmonary bypass (CPB) [1–3]. Conventional on-pump coronary surgery coronary artery bypass graft [CABG] routinely utilizes anticoagulation with high-dose heparin (≥300 U·kg^{-1}), whereas the heparin protocol in off-pump coronary bypass (OPCAB) varies among surgeons. Current literature on the subject has reported heparin doses ranging from 80 U·kg^{-1} to 350 U·kg^{-1}, with target activated clotting times (ACTs) from 250 s to more than 400 s [4–11]. The evidence for supporting either low or high heparin dosing is limited, and short-term outcome studies of OPCAB have been conducted using various heparin regimens [10,11]. A recently completed follow-up study of the randomized prospective trial of OPCAB or conventional on-pump CABG surgery indicated graft patency and thromboembolic complication rates were comparable in the two groups for a short term (30 days) and for 1 year [12]. The safety of our current anticoagulation using heparin, 180 U·kg^{-1} plus 3000 U every 30 min with intraoperative aspirin, 650 mg, in OPCAB patients is thus supported by clinical outcome data. Because there is a paucity of literature on coagulation management in patients undergoing OPCAB or CABG in a controlled randomized setting, detailed description and analysis of coagulation status from our recent OPCAB trial would be useful for practicing physicians who manage anticoagulation during coronary bypass surgery [3,12].

Methods

The protocol was approved by the institutional review board, and patients gave written consent to the study. Detailed information on the patients who were enrolled in the SMART study (Surgical Management of Arterial

Revascularization Therapies) has been described previously [3]. Briefly, 200 patients were randomized to OPCAB or conventional on-pump CABG. Patients with chronic renal insufficiency (creatinine > 2.5 mg·dl^{-1}) were not excluded, and the main exclusion criteria for the study were cardiogenic shock or preoperative use of intraaortic balloon counterpulsation. In all patients, anesthesia was induced with thiopental, fentanyl, and pancuronium, and maintained with isoflurane and fentanyl supplementation. Cardiopulmonary bypass (CPB) was performed according to the routine protocol, with a roller pump, non-heparin coated circuit, and moderate hypothermia (32°C–34°C) in the on-pump CABG group. The CPB priming solution included heparin 10 000 U, crystalloid 1000–1400 ml, hetastarch 500 ml, and mannitol 37.5 g.

Laboratory coagulation tests

Preoperative laboratory coagulation data (less than 24 h prior to surgery) were recorded, including hematocrit (%), platelet count (×10^3·µl^{-1}), fibrinogen level (mg·dl^{-1}), and international normalized ratio (INR) of prothrombin time. Intraoperatively, similar laboratory values were obtained within 2 h from the end of surgery. Thromboelastography (TEG; Haemoscope Niles, IL, USA; Fig. 1) was performed with a celite activator at baseline, and after protamine administration. Analyzed TEG variables were as follows: reaction time (onset of clotting; R, min), K time (time from onset to 20-mm amplitude; K, min), angle (rate of fibrin polymerization α°), maximum amplitude (peak clot strength; MA, mm), extent of fibrinolysis at 30 min after AM (LY30 %), and the TEG index. This index was calculated using the formula: index = –0.6516 × R – 0.3772 × K + 0.1224 × MA + 0.0759 × α – 7.7922. An index value over +3 was considered hypercoagulable, and less than –3 was considered hypercoagulable. Additionally, post-protamine TEG was also performed with heparinase (final concentration, 4 U·ml^{-1}) to evaluate the residual anticoagulant effects of heparin.

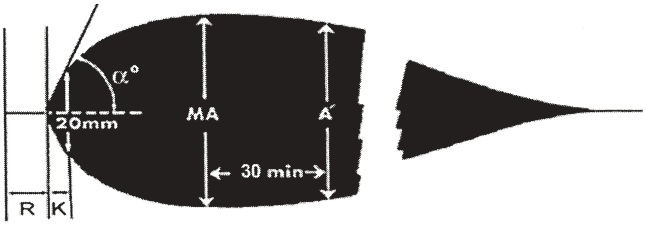

Fig. 1. Thromboelastography (TEG: Haemoscope). Analyzed TEG variables were: reaction time (*R*); angle (α); maximum amplitude (*MA*); and percent fibrinolysis at 30 min after MA, which was calculated as (MA-A′)/MA × 100 (%). The TEG index was computed according to the following formula: index = – 0.6516 × R – 0.3772 × K + 0.1224 × MA + 0.0759 × α – 7.7922 where *K* is the time from onset to ZO-mm amplitude. An index over +3 was considered hypercoagulable, and less than –3 was considered hypocoagulable

Heparin ant-activated factor X (Xa) activity was measured using a commercial chromogenic assay (Stachrom Heparin; Diagnostica Stago, Parsippany, NJ, USA). Briefly, plasma anti-Xa activity was measured by adding exogenous antithrombin, followed by a known excess amount of Xa to the plasma sample containing an undetermined amount of heparin. Heparin-antithrombin complexes are formed, and inactivate Xa to their limit; the residual Xa activity, measured chromogenically, is inversely proportional to the amount of heparin in the original plasma sample. This measurement was performed in ten subjects of each surgery group, at 15 min after protamine administration, and at 2 h after surgery to confirm the residual anticoagulant activity of heparin.

Coagulation management

All patients who were chronically treated with aspirin, 81 mg, received the dose until the day before surgery. For all patients randomized to OPCAB, a rectal aspirin, 650 mg, was administered upon arrival in the operating room. Anticoagulation for OPCAB was performed with an initial dose of heparin, 180 U·kg^{-1}, followed ay a 3000-U bolus every 30 min, to maintain the ACT at 350 s or more. ACT was measured with a celite activator (or kaolin for CABG patients receiving aprotinin) using a Hemochron 401 device (ITC, Edison, NJ, USA). After graft anastomoses were completed, protamine 50–75 mg was administered to return the ACT to 150 s. Additional protamine 25 mg was given if the ACT was 200 s or more. None of the OPCAB patients received antifibrinolytic therapy. In the CABG patients, anticoagulation was obtained with an initial dose of heparin, 400 U·kg^{-1}, to maintain an ACT over 400 s. The majority of CABG patients received prophylactic antifibrinolytic therapy with ε-aminocaproic acid (initial dose, 10 g followed with 1 g·h^{-1}), while three patients received aprotinin (total dose, 6 million KU). Heparin reversal was achieved with protamine 200–250 mg to achieve a normal ACT.

Postoperative mediastinal bleeding necessitating return to the operating room was defined as chest tube drainage of more than 1000 ml in 4 h despite hemostatic product transfusion.

Statistical analysis

Categorical data were compared between groups using the Wilcoxon rank sum test. Continuous data were analyzed using Student's *t*-test or two-way analysis of vari-

ance. A P value less than 0.05 was considered significant. Discrete data are presented in percentages; continuous data are presented as means ± SD.

Results

Laboratory coagulation tests

The percentage of patients who were taking oral aspirin preoperatively was similar in the two groups (54% vs 58% for OPCAB and CABG). Preoperative platelet count was comparable: 234 ± 72 vs 231 ± 63 ($\times 10^3 \cdot \mu l^{-1}$) for OPCAB and CABG, respectively. The preoperative fibrinogen level was significantly higher in the OPCAB group (489 ± 138 vs 431 ± 128 $mg \cdot dl^{-1}$; $P < 0.01$). Postoperatively, the platelet count was higher in the OPCAB group compared to the CABG group; 198 ± 63 vs 137 ± 42 ($\times 10^3 \cdot \mu l^{-1}$; $P < 0.01$). The percentage of patients who had a platelet count less than $100 \times 10^3 \cdot \mu l^{-1}$ was less in the OPCAB group (4 of 98; 4.1%) than in the CABG group (22 of 99; 22.2%). Postoperatively, the fibrinogen level remained significantly higher in the OPCAB group (416 ± 87 vs 332 ± 109 $mg \cdot dl^{-1}$; $P < 0.01$). There was no difference between the percentages of patients who had a fibrinogen level less than 150 $mg \cdot dl^{-1}$ (1 of 98 and 2 of 99 for OPCAB and CABG).

Preoperative INR and partial thromboplastin time (PTT) were comparable between the OPCAB and CABG groups (INR, 1.01 ± 0.08 vs 1.05 ± 0.28; $P = 0.63$; PTT, 41.2 ± 22.6 vs 51.5 ± 36.7 s; $P = 0.079$). Postoperatively, INR was lower in the OPCAB group (1.23 ± 0.18 vs 1.35 ± 0.19; $P < 0.02$), and PTT was higher in the OPCAB group (44.0 ± 19.3 vs 36.9 ± 9.65; $P < 0.01$). The mean values of pre- and postoperative TEG variables are presented in Table 1. Preoperative variables were comparable, except for MA, which was significantly larger in OPCAB patients ($P < 0.05$). This difference was most likely due to higher fibrinogen levels in OPCAB patients, because TEG MA reflects the interaction of fibrin and activated platelets, and there was no difference in baseline platelet counts. Based on the preoperative TEG index, 62.8% of OPCAB and 60.0% of CABG patients were considered hypercoagulable (index > 3) preoperatively (no significant difference), and the percentages of patients considered hypocoagulable (index < –3) were also not different (1.2% for both groups). In the CABG group, the postoperative angle and MA values were significantly smaller and K time was longer than the preoperative values ($P < 0.01$ for all variables), and the postoperative native TEG index indicated that fewer patients were considered hypercoagulable in the CABG group than in the OPCAB group (10.8% vs 35.1%; $P < 0.01$). The percentages of patients considered hypocoagulable (index < –3 using native TEG) were not significantly different for the CABG and OPCAB groups (8.4% vs 10.6%, respectively).

Table 1. Thromboelastography (TEG; Haemoscope) variables

	Preoperative	Postoperative	
	Native	Native	Heparinase
CABG			
R (min)	5.7 ± 6.3	6.8 ± 4.2	6.0 ± 4.7
K (min)	1.9 ± 1.1	3.2 ± 1.9	3.0 ± 2.0
Angle (°)	72.4 ± 6.2	63.7 ± 8.4	64.0 ± 11
MA (mm)	66.8 ± 8.1	55.9 ± 8.0	56.6 ± 9.6
LY30 (%)	3.1 ± 3.7	2.3 ± 5.1	1.7 ± 2.9
Index	2.6 ± 4.1	0.3 ± 2.6	0.6 ± 2.9
OPCAB			
R (min)	5.2 ± 3.2	8.6 ± 9.5	5.3 ± 3.6
K (min)	2.0 ± 1.5	3.0 ± 5.9	2.0 ± 1.3
Angle (°)	72.3 ± 6.2	68.3 ± 14*	72.0 ± 6.6*
MA (mm)	69.3 ± 5.7*	64.0 ± 11*	65.6 ± 9.4*
LY30 (%)	3.3 ± 5.8	2.3 ± 3.8	2.5 ± 4.4
Index	3.4 ± 1.7	0.3 ± 8.8	3.0 ± 1.8*

* $P < 0.05$ versus CABG group in each category
Values are means ± SD

Heparinase modification minimally changed parameters. In the OPCAB group, the postoperative reaction time of heparinase-TEG was significantly shorter than that of native TEG ($P < 0.05$). Other parameters, K, angle, and MA, did not significantly change from preoperative values. Using heparinase-modified TEG, postoperative K, angle, MA, and index values were significantly better preserved in the OPCAB than in the CABG group ($P < 0.01$). Without heparinase, there was a trend of a longer reaction time in the OPCAB than in the CABG group ($P = 0.059$). Clinical fibrinolysis was not observed on TEG, and the lysis variable (LY30) values were comparable between the two groups.

In the CABG group ($n = 85$), we analyzed the relationship of changes in platelet count, fibrinogen, and TEG variables, because there were significant decreases in these variables after CPB. The overall changes in platelet count and fibrinogen were weakly correlated with the change in the angle of TEG ($r^2 = 0.16$; $P < 0.001$). The change in platelet count and fibrinogen did not show a statistically significant correlation with the change in the MA of TEG ($r^2 = 0.03$; $P = 0.25$).

The residual heparin activity, measured by anti-Xa activity, in the OPCAB group was 0.32 ± 0.02 $U \cdot ml^{-1}$, and 0.21 ± 0.03 $U \cdot m^{-1}$, respectively, after protamine administration and 2 h after surgery. These levels were significantly higher than the anti-Xa levels observed in the CABG group, i.e., 0.058 ± 0.01 $U \cdot m^{-1}$, and 0.043 ± 0.01 $U \cdot m^{-1}$. ($P < 0.05$ vs. OPCAB at the respective time points).

Coagulation management

Total heparin and protamine doses were lower in the OPCAB group (Table 2; $P < 0.01$). The heparin/protamine ratio (total heparin units $\times 100^{-1}$/total mg of protamine) in the OPCAB group was approximately twice that in the CABG group. The highest ACT values were significantly higher in the CABG group ($P < 0.01$), but post-protamine ACT values were comparable between the two groups. The plasma half-life of heparin may be affected by body temperature, and it was notable that the lowest core temperature in the OPCAB group was higher than that in the CABG group (35.8 ± 0.45°C vs 34.2 ± 1.09°C; $P < 0.05$).

Total intraoperative cell saver units that were infused in patients were comparable (644 ± 370 vs 805 ± 433 ml for OPCAB and CABG). The median amount of chest tube drainage (CTD) was comparable between the two groups (Table 3). The mean units of non-erythrocyte transfusions were comparable, although there was a trend of more platelet transfusion in the CABG group (Table 3).

Bleeding complications in the OPCAB and CABG groups during the 30-day postoperative period were comparable; bleeding reexploration occurred in 1 of 98 vs 2 of 99, and gastrointestinal bleed occurred in 3 of 98 vs 2 of 99 for the OPCAB and CABG groups, respectively.

Table 2. Summary of anticoagulation

	CABG	OPCAB
Heparin	38364 ± 8505	25399 ± 7355*
Protamine	234 ± 39	83 ± 27*
H/P ratio	1.7 ± 0.5	3.2 ± 0.9*
Base ACT	143 ± 31	138 ± 21
High ACT	754 ± 200	445 ± 73*
Post ACT	129 ± 11	131 ± 12

* $P < 0.001$ versus GABG group
Values are means ± SD
Heparin, total dose (units); protamine, total dose (mg); H/P ratio, (total heparin dose $\times 10^{-2}$)/(total protamine dose); ACT, activated clotting time at baseline (base), peak (high) and post-protamine (post)

Table 3. Summary of non-erythrocyte transfusions and CTD

	CABG	OPCAB
PLT	0.08 ± 0.34	0.01 ± 0.1
Cryo	0.04 ± 0.2	0.01 ± 0.1
FFP	0.05 ± 0.2	0.02 ± 0.1
CTD 4 h	205 (170, 350)	225 (181, 352)
CTD 8 h	350 (250, 510)	395 (296, 525)
CTD 12 h	445 (350, 680)	495 (396, 680)

Data are shown as means ± SD for blood products, or medians (25%, 75%) for cumulative chest tube drainage (CTD; ml) for 4, 8, and 12 h
No statistically significant difference was found between the CABG and OPCAB groups
PLT, platelet concentrate (units); Cryo, cryoprecipitate (units); FFP, fresh frozen plasma (units)

Discussion

Our study showed that the current anticoagulation regimen in the OPCAB patients achieved a peak ACT of 445 ± 73 s, and it preserved platelet counts and fibrinogen levels. A residual heparin effect was detected with prolonged TEG reaction time and PTT during the early postoperative period in the OPCAB group. Despite the residual anticoagulation, the OPCAB group had a similar TEG index of native blood, postoperative CTD, and non-erythrocyte transfusion rate as compared with the CABG (on-pump) group.

The anticoagulation regimen in OPCAB varies among surgeons, and among institutions, and it is not known if a low-dose heparin regimen, similar to that used in percutaneous coronary intervention, can be applied to OPCAB surgery. Mariani et al. [7] expressed a concern about OPCAB anticoagulation with heparin at 100 U·kg^{-1} to maintain ACT less than 300 s, because they found increased prothrombin fragment 1.2 (activation marker of prothrombin) and fibrin degradation product levels, and decreased factor VII levels at 24 h after surgery. This finding was further corroborated by Cartier and Robitaille [4], who reported a 1% incidence of deep venous thrombotic complication in a retrospective review of 500 OPCAB patients who received heparin at 100 U·kg^{-1}, with ACT maintained over 300 s. In our study, approximately 60% of patients in both the OPCAB and CABG groups were considered hypercoagulable preoperatively, based on a high TEG index. Hypercoagulable OPCAB patients may develop subclinical coagulation activation under low-intensity heparin anticoagulation (80–100 U·kg^{-1}), which is a well-known phenomenon during coronary interventions. Increased incidences of intravascular thromboses after coronary interventions have been found in patients who had an ACT less than 300 s after heparin, at 100 U·kg^{-1}. Improved clinical outcomes have been shown with the addition of antiplatelet agents to heparin anticoagulation during coronary interventions, and several studies have shown decreases in prothrombin activation and thrombin generation, with increased ACTs, in patients receiving abciximab or tirofiban [13–16].

Maintaining high levels of anticoagulation with heparin titration or supplemental antithrombin has been shown to reduce the activation of coagulation [17,18]. Current literature suggests that the main activator of thrombin during cardiac surgery is the tissue factor that is released from injured tissue, and it is most prevalent in the pericardial cavity. [19–22]. The importance of

tissue injury was also indicated by increases of complement (C3a) in OPCAB patients who received median sternotomy with heparin at 100 U·kg^{-1} [5]. Similar amounts of erythrocyte concentrate in both groups were salvaged in our study, and blood many have been exposed to pericardial tissue factor, contributing to the activation of coagulation, although it had been washed and transfused through a leukocyte reduction filter.

Another distinct difference between OPCAB and CABG patients is the core-body temperature maintained during surgery. Intraoperatively, every effort was made to maintain normothermia in our OPCAB patients (lowest temperature, 35.8°C ± 0.45°C). The elimination half-life of heparin is intimately influenced by the heparin dose and body temperature. When 100, 200, or 400 U of intravenous heparin is administered at 37°C, the approximate half-life is 60, 90, and 150 min, respectively [23], and decreases in the body temperature prolong the elimination half-life [24]. It is possible that faster thrombin generation and heparin turnover occur in OPCAB patients, necerssitating higher heparin dosing to maintain effective heparin concentratins. In the present study, in the OPCAB group, a lower amount of protamine than that in the CABG group was required to achieve a comparable ACT, which suggests faster heparin turnover. The lack of difference in ACT an values does not necessarily exclude residual heparin, because the ACT is designed to monitor high levels of heparin by using a high level (4%) of celite as an activator (1% celite is used in TEG). In fact, the significant change in TEG variables with heparinase in our OPCAB group suggests residual heparin. The higher postoperative PTT in the OPCAB group also underlies partial heparin reversal. A low level of heparin does not generally affect the INR, which was significantly lower in the OPCAB group, and most likely reflected a better-preserved physiological coagulation system in the OPCAB group.

The percentage of patients who were at high risk (platelet count < $100 \times 10^3 \cdot \mu l^{-1}$) for platelet transfusion [25] was 4.1% in the OPCAB group and 22.2% in the CABG group, whereas the incidence of a low fibrinogen level (<150 mg·dl^{-1}) was similar in the two groups. This suggests that CPB induces more extensive changes in platelet counts than in fibrinogen levels, which was also reflected in the statistically significant correlation of changes in TEG angle and platelet count. The percentage of hypercoagulable OPCAB patients (native TEG index > 3) decreased from 62.8% to 35.1%, and overall coagulation was also maintained as indicated by the heparinase TEG index (Table 1). These data indicated that OPCAB patients have preserved coagulation function in the immediate postoperative period, without major procoagulant responses [9].

The rate of bleeding complications requiring re-exploration wass similar in the OPCAB and CABG groups. Nevertheless, OPCAB patients may present a hypercoagulable state because of the better-preserved coagulation factors, platelets, and fibrinogen [4,9]. In the present study, we observed residual anti-Xa heparin activity of 0.2 U·ml^{-1} up to 2 h after surgery in the OPCAB group. This level of anti-Xa activity is clinically achieved with anticoagulation with low-molecular-weight heparin for prophylaxis against deep venous thrombosis (DVT) [26]. We speculate that, in the current study, early postoperative thrombotic complications may have been prevented by residual heparin, in addition to intraoperative rectal aspirin. Maintaining this level of anticoagulation (1.5 times normal TEG R-times or PTT) beyond the early postoperative period may be necessary to prevent late DVTs in high-risk patients. Other risk factors for DVT, i.e., protein C resistance (Leiden V mutation), and antithrombin (AT) deficiency, were not investigated in our study.

In contrast to CABG patients who develop platelet dysfunction duing CPB, pharmacological palatelet inhibition with aspririn, 650 mg, was used routinely in our OPCAB group. This is a corollary to the management of percutaneous coronary interventions, in which antiplatelet drugs are routinely used to prevent acture thrombotic complications [16]. Our current results for coagulation and bleeding likely reflect the different degrees of platelet damage between CPB and aspirin-OPCAB protocols.

There are only few available pharmacokinetic data on the rectal administration of aspirin. Absorption o rectal aspirin was only 60% in a retention time of 4 to 5 h [27]. In neurosurgical patients, the bioavailability of rectal aspirin was 76% of oral administration, and the average peak salicylate level for the suppositories was approximately 50% of the level observed after oral administration [28]. Regardless of the formulations, platelet inhibition, using serum thromboxane B_2 level as a marker, occurs rather quickly after ingestion of aspirin, 325 mg. A 50% decrease in thromboxane B_2 level is achieved when plasma aspirin concentration is 1000 ng·ml^{-1} at approximately 5 min with chewables, and at 12 min with a tablet swallowed. In our study, aspirin, 650 mg, was given at the beginning of surgery. With a retention time of around 3.5 h (i.e., surgical duration), the bioavailability of aspirin should be comparable to that of an oral 325-mg dose, assuming 50% absorption. Platelet aggregation tests or bioassay of thromboxane B_2 were not performed, and therefore the degree of platelet inhibition by aspirin, and the incidence of "aspirin resistance" are not known in our patients. Nevertheless, the result of the present study proved the efficacy of the current antithrombotic regimen by showing a low incidence of arterial thromboembolic events

(i.e., stroke, 1 in 98; transient ischemic attack [TIA], 1 in 98; Q-Wave my ocardial infarction [MI], 1 in 98) in OPCAB patients within 30 days. Further, the 1-year follow-up of the study patients revealed that the graft patency and thrombotic complication rates were similar in the two groups [12], therefore, additional studies are necessary to establish the clinical definition and implications of "aspirin resistance" in patients with coronary bypass [29–31].

In conclusion, we have shown that a heparin anticoagulation regimen of $180\,U \cdot kg^{-1}$ plus 3000 U every 30 min, with intraoperative aspirin, 650 mg, in OPCAB patients does not lead to a hypercoagulable state. Total doses of heparin and protamine were smaller in the OPCAB group compared with the CABG group, and there was a residual heparin effect on TEG and PTT in the early postoperative period in the OPCAB group. A further study is required to evaluate the postoperative coagulation status in OPCAB patients, and the necessity for antithrombotic or anti-platelet therapy.

Acknowledgments. The authors thank Rebecca J. Petersen, R.N., Susan, A. McCall, R.N., and Fania Szlam, M.M.Sc., for their help in acquiring data and performing assays for the study. This work was supported in part by a grant from Medtronic Inc. (Minneapolis, MN, USA), and the Carlyle Fraser Heart Center Foundation (Atlanta, GA, USA).

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