

# Platelet Hyperreactivity in Response to On- and Off-pump Coronary Artery Bypass Grafting

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**Abstract:** Hypercoagulability has been reported after off-pump coronary artery bypass grafting (OPCAB) compared with patients undergoing standard coronary artery bypass grafting (CABG) with cardiopulmonary bypass. The aim of this study was to evaluate the changes in platelet reactivity in response to cardiac surgery, both OPCAB and CABG. Platelet reactivity was monitored pre- and postoperatively (days 1 and 4) in elective OPCAB ( $n = 29$ ) and CABG ( $n = 24$ ) patients using the maximal amplitude (MA) parameter obtained with thrombelastography. Platelet reactivity was also examined at 1 month in 30 of the 53 patients. Twenty-three percent of the patients (12/53) had a preoperative MA value above normal reference value (MA > 69 mm). By postoperative day 4, 88% of the patients presented with an MA > 69 mm, and significant increases in MA were shown in

both groups ( $p < .0001$ ). Of the 30 patients examined at 1 month after surgery, 75% of the patients with high preoperative MA (6/8) remained at this level. In contrast, only 4.5% of patients with normal preoperative MA (1/22) presented with high MA at day 30. MA has previously been shown to correlate with the incidence of thrombotic and ischemic complications and this study identified 23% of patients needing coronary bypass surgery to be at high risk for recurrent ischemic events at 1 month after surgery, based on the MA. These results suggest that a more aggressive antithrombotic treatment might be warranted for patients undergoing coronary artery bypass grafting, both OPCAB and CABG, presenting with a high MA pre- and post-surgery. **Keywords:** off-pump, on-pump, platelets, thrombelastography, hypercoagulability. *JECT. 2009;41:15–19*

No uniform guidelines exist for the postoperative prevention of thrombotic complications after coronary artery bypass (CAB) surgery (1). Although the results from several studies have been inconclusive, there is a concern regarding an increased frequency in the development of graft failure caused by thrombotic events in off-pump CAB grafting surgery (OPCAB) procedures compared with conventional CAB grafting surgery (CABG) (2–4).

The term “hypercoagulable state” or “preserved hemostasis” in response to OPCAB surgery has received considerable attention recently because several studies have reported a tendency toward an increase in graft failure attributed to thrombotic complications (5–8). As a result, additional

antithrombotic prophylaxis has been instituted in most Nordic cardiac centers when performing OPCAB surgery, whereas CABG patients are treated with aspirin alone (1).

Most of the studies reporting on the hemostatic response after OPCAB surgery have focused on the first 24 hours postoperatively (5–8). The aim of this study was to investigate hemostatic alterations in terms of clot strength, mainly representing platelet reactivity, as evaluated by thrombelastography maximal amplitude (TEG-MA) during the first 4 postoperative days after CABG/OPCAB surgery to study whether the previously reported changes persist after the first postoperative day. Furthermore, the aim was to evaluate whether OPCAB patients have higher TEG-MA compared with CABG patients.

## MATERIALS AND METHODS

Fifty-three consecutive patients scheduled for elective CAB grafting were enrolled in the study. All patients signed

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an informed consent before participation, and the study was approved by the local Ethics Committee (December 9, 2005) and in accordance with the Helsinki 2 Declaration. Patients were excluded for the following reasons: myocardial infarction (MI) within the last 10 days before surgery, previous cardiac surgery, severe pulmonary disorders, renal or liver dysfunctions, or preoperative anticoagulation therapy. Twenty-nine patients undergoing OPCAB surgery and 24 patients undergoing CABG surgery using cardiopulmonary bypass were included. The surgeon solely decided whether a patient was operated on or off pump. None of the patients received aspirin or clopidogrel within 7 days before surgery, whereas postoperatively all patients received life-long treatment with aspirin (150 mg/day) from the first day after surgery. In addition, OPCAB patients received Klexane, a low-molecular-weight heparin (LMWH; 4000 IU/day) for the first 4 days postoperatively.

### Blood Sampling

Blood samples were obtained from indwelling catheters when possible or through direct venipuncture. The blood was collected into Vacutainer tubes containing 1/10 volume of sodium citrate 3.2% (BD Biosciences, Plymouth, UK). Blood was collected before surgery (preoperatively) and at postoperative days 1 and 4 (POD1 and POD4, respectively). Additionally, blood was collected at 1 month after surgery from 30 of the 53 patients. Because of logistic reasons, not all patients revisited after 1 month.

### TEG Analysis

The blood was analyzed within 30–60 minutes from blood collection using the Thrombelastograph Hemostasis Analyzer system (Series 5000; Haemoscope Corp., Niles, IL) and reagents. Standard TEG analysis was performed by adding and gently mixing 1 mL citrated whole blood in a kaolin vial (Haemoscope Corp.). Within 30 seconds, 340  $\mu$ L of the kaolin-activated blood was transferred to a standard TEG cup preloaded with 20  $\mu$ L .2 mol/L  $\text{CaCl}_2$ . Data collection was started immediately using the TEG software version 4.2.3 (Haemoscope Corp.).

### Statistical Analyses

Data are presented as mean with SDs or mean with range as appropriate. The Wilcoxon rank-sum test was used to compare mean values between CABG and OPCAB patients. The Fisher exact test was used to compare categorical variables. Statistic significance was defined as  $p < .05$ .

## RESULTS

Preoperative patient characteristics were comparable in the two groups with respect to age, sex, ejection fraction (EF), and preoperative cardiac risk factors including hypertension, hypercholesterolemia, previous MI, previous transient ischemic attack (TIA), stroke, and EuroSCORE

(9). Compared with patients undergoing the OPCAB procedure, CABG patients had a higher body mass index (BMI; 26.9 vs. 29.8  $\text{kg/m}^2$ ,  $p = .018$ , OPCAB vs. CABG, respectively; Table 1), longer duration of surgery (139.1 vs. 173.8 minutes,  $p = .01$ ), more grafts (1.9 vs. 2.5,  $p = .02$ ), and a higher use of cycloaprone (tranexamic acid, an antifibrinolytic; 37.9% vs. 87.5%,  $p = .0003$ ; Table 2). None of the patients received aprotinin. There were no differences in perioperative bleeding, transfusion of blood products, intensive care unit (ICU) length of stay (LOS), or hospital LOS. One patient in each group needed re-exploration because of bleeding (Table 2).

The preoperative platelet reactivity, evaluated by the TEG-MA, was comparable between the two groups (Figure 1). At POD1, there was no significant change in TEG-MA from the preoperative value within both groups;

**Table 1.** Demographic data.

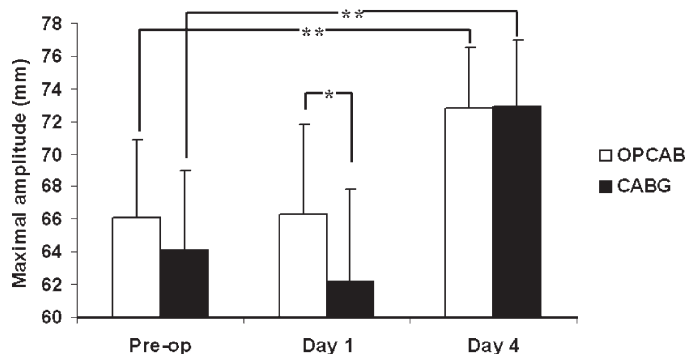
	OPCAB (n = 29)	CABG (n = 24)	p
Age (years)	65.4 (41–85)	65.0 (51–80)	NS
Male [n (%)]	19 (65.5)	19 (79.2)	NS
Weight (kg)	80.0 (55–128)	87.3 (70–122)	NS
BMI ( $\text{kg/m}^2$ )	26.9 (21.2–34.7)	29.8 (24.2–39.4)	.018
Hypertension [n (%)]	28 (96.6)	20 (83.3)	NS
Hypercholesterolemia [n (%)]	29 (100)	22 (91.7)	NS
Previous AMI [n (%)]	15 (51.7)	15 (62.5)	NS
Previous TIA/stroke [n (%)]	3 (10.3)	1 (4.2)	NS
Ejection fraction	52.4 (35–60)	48.3 (25–60)	NS
EuroSCORE	4.5 (0–9)	5.1 (1–10)	NS

Data are presented as mean (range) unless otherwise indicated. NS, not significant; BMI, body mass index; AMI, acute myocardial infarction; TIA, transient ischemic attack.

**Table 2.** Surgical and postoperative data.

	OPCAB (n = 29)	CABG (n = 24)	p
Number of grafts	1.9 (1–3)	2.5 (2, 3)	.02
CPB time (minutes)	—	70.8 (39–172)	—
Aortic cross clamping (minutes)	—	46.0 (24–133)	—
Priming volume (mL)	—	1725 (1500–2100)	—
Cycloaprone [n (%)]	11 (37.9)	21 (87.5)	.0003
Operation time (minutes)	139.1 (70–245)	173.8 (120–275)	.01
Perioperative bleeding (mL)	504.6 (50–1600)	475.0 (100–1000)	NS
Transfusions (number of transfused patients)			
Perioperative RBC	2	1	NS
Perioperative FFP	0	0	NS
Perioperative PC	0	0	NS
Postoperative RBC	8	8	NS
Postoperative FFP	2	3	NS
Postoperative PC	1	2	NS
Reoperation (n)	1	1	NS
ICU stay (days)	1.0 (1, 1)	1.1 (1–3)	NS
Total length of stay (days)	11.1 (6–24)	10.2 (6–27)	NS

Data are presented as mean (range), otherwise indicated. CPB, cardiopulmonary bypass; NS, not significant; RBC, red blood cells; FFP, fresh frozen plasma; PC, platelet concentrate; ICU, intensive care unit.



**Figure 1.** TEG-MA was measured preoperatively and days 1 and 4 postoperatively on 29 patients undergoing OPCAB and 24 patients undergoing conventional CABG. Data are presented as mean  $\pm$  SD. \* $p < .05$ , \*\* $p < .0001$ , Wilcoxon rank-sum test.

however, between-group analysis showed a significantly lower POD1 TEG-MA in the CABG group compared with the OPCAB patients ( $66.3 \pm 5.47$  vs.  $62.2 \pm 4.10$  mm,  $p < .05$ ; Figure 1). By POD4, there was a significant increase in the TEG-MA in both groups compared with the preoperative values. The TEG-MA values for CABG patients increased 12% ( $p < .0001$ ) and for OPCAB patients increased 9% ( $p < .0001$ ; Figure 1). There was no difference in the magnitude of TEG-MA increase at POD4 between groups.

A total of 23% (12/53) presented with a preoperative TEG-MA value above the normal reference range of 69 mm, but, by POD4, 88% (46/53) had a TEG-MA  $> 69$  mm. Data for the TEG-MA at POD30 were collected in 30 of the 53 patients. In this group, six of the eight patients (75%) with a high TEG-MA ( $> 69$  mm) preoperatively also presented with high platelet reactivity at POD30 compared with only 1 of the 22 patients (4.5%) presenting with normal platelet reactivity (TEG-MA  $< 69$  mm and  $> 51$  mm) preoperatively ( $p > .0001$ ).

## DISCUSSION

The primary findings of this study are that 23% of OPCAB and CABG patients present with hypercoagulability preoperatively, as evaluated by TEG-MA, and that 88% of OPCAB and CABG patients become hypercoagulable during the early postoperative period. Furthermore, the majority (75%) of those patients expressing platelet hyperreactivity before surgery, as defined as a TEG-MA above the upper reference level, remain hyperactive 1 month after surgery. Moreover, it seemed that patients showing a TEG-MA within the reference range preoperatively return to this level 1 month after surgery.

It is widely accepted that platelets play a pivotal role in the development of thrombosis (10–12). The TEG-MA parameter reflects the ultimate physical strength of the clot including the fibrin network and especially the

contribution of platelets to clot strength (13). Consequently, the TEG-MA provides a measurement mainly of platelet function and hence offers a measure of the maximal platelet reactivity, i.e., the platelets' ability to become activated, as discussed by Samama et al. (14). The TEG-MA parameter has previously been shown to correlate with development of both thrombotic and ischemic complications. McCrath et al. (15) showed, in a cohort of 219 patients undergoing major non-cardiac surgery, that the TEG-MA value, evaluated 2 hours postoperatively, correlated with the development of thrombotic complications and acute MI. As mentioned, the results of this study showed that 23% of all patients undergoing elective CAB surgery preoperatively present with a TEG-MA above the upper reference level of 69 mm, validated in a population of healthy blood donors (16). This is in alignment with Gurbel et al. (17), who identified a subpopulation of patients (25%) who presented with a TEG-MA above the normal reference range among a population of 175 patients undergoing elective percutaneous coronary intervention (PCI) with stent implantation. It should be noted that the normal reference range of TEG in this study differs from that in the PCI study because citrated blood was used in this study compared with native samples in the study of Gurbel et al. (17). Furthermore, Gurbel et al. (17) also found that an increased TEG-MA value, both before and after intervention, was associated with an increased development of ischemic events. Because patients undergoing PCI and CAB grafting have the same disease as patients undergoing CABG surgery, albeit to a lesser extent, we hypothesize that the patients identified in this study as being hypercoagulable with regard to TEG-MA are at increased risk of developing a thromboembolic complication compared with those presenting with a normal TEG-MA.

In contrast to our findings, Poston et al. (18), using the TEG-MA, found only 2 of 78 (3%) OPCAB patients presenting with hypercoagulability preoperatively and 10/78 (13%) as being hypercoagulable postoperatively. It is difficult to explain the conflicting data because Poston et al. also used citrate stabilized whole blood, although it is not described in detail whether their TEG analysis included initiation with kaolin. Their sampling time points were similar to ours: preoperatively and postoperative measurements at days 1 and 3 after surgery. There seems to be no apparent differences in the patient demographics compared with this study population, but it cannot be excluded that our patients had more advanced disease and hence presented with higher TEG-MA preoperatively. However, it is surprising that only 3% of OPCAB patients but 25% of PCI patients, all from the Baltimore area, had a high baseline TEG-MA (17,18).

Controversy exists regarding whether or not the OPCAB technique results in a hypercoagulable state per se and therefore an increased risk of early graft failure

compared with conventional bypass surgery and whether OPCAB patients should be more aggressively treated with additional antithrombotic drugs postoperatively. Several studies evaluating the hemostatic response to the OPCAB vs. CABG procedure have focused on the first 24-hour period postoperatively (5–8). These studies have shown that OPCAB patients are more hypercoagulable compared with CABG patients. This study found that OPCAB surgery did not increase platelet reactivity, in terms of TEG-MA, during the first 24 hours postoperatively; however, by POD4, a significant increase in platelet reactivity was shown (TEG-MA > 69 mm). Patients undergoing CABG surgery, on the other hand, showed a decrease in platelet reactivity (TEG-MA) at POD1 compared with OPCAB patients, but by POD4, platelet reactivity increased to the same level as OPCAB patients. Güden et al. (7) found no differences in TEG between pre- and postoperative measurements immediately after arrival in the ICU, in alignment with the findings of this study not showing any TEG-MA differences at day 1 compared with preoperative values.

Our results showed a significant increase in platelet reactivity for both CABG and OPCAB patients by POD4. These results are in alignment with that of a study by Paparella et al. (11) showing that both OPCAB and CABG patients had preserved platelet function as determined by *in vitro* bleeding time and increased thrombin formation at patient discharge compared with preoperative values.

Considerable variability in the thrombotic prophylaxis after OPCAB procedures exists. In a Nordic survey of 26 Nordic units performing OPCAB procedures, 22% administered aspirin alone postoperatively, 52% administered aspirin and LMWH, 9% administered aspirin and clopidogrel, and 17% administered a combination of the three (1). At our institution, OPCAB patients receive life-long aspirin plus LMWH for the first 4 days postoperatively, whereas CABG patients only receive lifelong aspirin therapy. The results of this study suggest that platelets from both OPCAB and CABG patients are equally prone to hyperreactivity by POD4. Early graft failure is hypothesized to be related to thrombus development, of which platelet reactivity may be an important component (19). The data from this study suggest that there is a trend toward platelet-mediated hypercoagulability after cardiac surgery, which in turn may be related to graft failure. We therefore suggest that both OPCAB and CABG patients presenting with a preoperative TEG-MA above the upper reference range should be considered at high risk for developing thrombotic complications after surgery. Additionally, our data showed that the majority of patients presenting with high platelet reactivity returned to the same TEG-MA level by 1 month postoperatively, suggesting that these patients should not be at particular risk of bleeding, and consequently, we find it reasonable to

introduce a more aggressive antithrombotic approach, not only for OPCAB patients but for all CAB surgical patients with high platelet reactivity. Based on our data supporting that atherosclerotic patients have hyperreactive platelets, the use of LMWH as additional thromboprophylaxis may not be the optimal strategy, because LMWH does not inhibit platelet function *per se*.

Our study contained no randomization, and the scope of this study was not to identify the event rate of thromboembolic complications nor to determine whether the upper normal reference range of TEG-MA is the proper cut-off value for thromboembolic risk stratification of patients undergoing CAB grafting, although these issues deserve further attention with more patients. It is a weakness that the groups do not match completely in respect to number of grafts, BMI, and number of patients treated with cyclo-oxygenase inhibitors. Despite the limitations of this study, we have no reason to believe that patients undergoing CAB surgery should be less prone to developing thromboembolic complications compared with PCI patients because of platelet hypercoagulability (17). Our data presumably identify a subgroup of patients with increased platelet reactivity (TEG-MA) undergoing CABG and OPCAB who may be at increased risk for developing thromboembolic complications. These patients could potentially benefit from a more aggressive antithrombotic treatment regimen. This approach needs further study in a large population, and the benefit of such a treatment regimen is currently being investigated.

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## REFERENCES

1. Hansen KH, Hughes P, Steinbruchel DA. Antithrombotic- and anticoagulation regimens in OPCAB surgery. A Nordic survey. *Scand Cardiovasc J*. 2005;39:369–74.
2. Khan NE, De SA, Mister R, et al. A randomized comparison of off-pump and on-pump multivessel coronary-artery bypass surgery. *N Engl J Med*. 2004;350:21–8.
3. Puskas JD, Williams WH, Duke PG, et al. Off-pump coronary artery bypass grafting provides complete revascularization with reduced myocardial injury, transfusion requirements, and length of stay: a prospective randomized comparison of two hundred unselected patients undergoing off-pump versus conventional coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2003;125:797–808.
4. Widimsky P, Straka Z, Stros P, et al. One-year coronary bypass graft patency: a randomized comparison between off-pump and on-pump surgery angiographic results of the PRAGUE-4 trial. *Circulation*. 2004;110:3418–23.



5. 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.
6. 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.
7. Güden M, Sanisoglu I, Sagbas E, Ergenoglu MU, Ozbek U, Akpınar B. Hemodilution during off-pump coronary artery bypass grafting: can we improve flow and reduce hypercoagulability? *Heart Surg Forum*. 2003;6:399–402.
8. Moller CH, Steinbruchel DA. Platelet function after coronary artery bypass grafting: is there a procoagulant activity after off-pump compared with on-pump surgery? *Scand Cardiovasc J*. 2003;37:149–53.
9. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg*. 1999;16:9–13.
10. Kurlansky PA. Is there a hypercoagulable state after off-pump coronary artery bypass surgery? What do we know and what can we do? *J Thorac Cardiovasc Surg*. 2003;126:7–10.
11. 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.
12. Moor E, Blomback M, Silveira A, et al. Haemostatic function in patients undergoing coronary artery bypass grafting: perioperative perturbations and relations to saphenous vein graft closure. *Thromb Res*. 2000;98:39–49.
13. Lang T, von Depka M. Possibilities and limitations of thromboelastometry/thromboelastography. *Hamostaseologie*. 2007;26(Suppl 1):S21–9.
14. Samama CM, Thiry D, Elalamy I, et al. Perioperative activation of hemostasis in vascular surgery patients. *Anesthesiology*. 2001;94:74–8.
15. McCrath DJ, Cerboni E, Frumento RJ, Hirsh AL, Bennett-Guerrero E. Thromboelastography maximum amplitude predicts postoperative thrombotic complications including myocardial infarction. *Anesth Analg*. 2005;100:1576–83.
16. Bochsén L, Wiinberg B, Kjelgaard-Hansen M, Steinbruchel DA, Johansson PI. Evaluation of the TEG(R) platelet mapping assay in blood donors. *Thromb J*. 2007;5:3.
17. Gurbel PA, Bliden KP, Guyer K, et al. Platelet reactivity in patients and recurrent events post-stenting: results of the PREPARE POST-STENTING Study. *J Am Coll Cardiol*. 2005;46:1820–6.
18. Poston R, Gu J, Brown J, et al. Hypercoagulability affecting early vein graft patency does not exist after off-pump coronary artery bypass. *J Cardiothorac Vasc Anesth*. 2005;19:11–8.
19. Rocca B, Patrono C. Determinants of the interindividual variability in response to antiplatelet drugs. *J Thromb Haemost*. 2005;3:1597–602.