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Off-Pump Coronary Artery Bypass Surgery May Produce a Hypercoagulable Patient

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ABSTRACT

Background: The incidence of thromboembolic events following traditional open heart surgery has not been clinically significant. However, with beating heart surgery, for which cardiopulmonary bypass (CPB) is not required, the incidence of spontaneous intravascular thrombosis may be similar to that encountered after general surgeries. Compounding this risk is that many cases of off-pump coronary artery bypass (OPCAB) surgery are reserved for the elderly patient with multiple comorbidities. The few studies to date that have assessed the coagulation profile in OPCAB patients have been limited to the first 24 hours after surgery.

Methods: We prospectively studied 17 OPCAB and 6 on-pump patients over 4 days (hospital course) with daily thromboelastography. A coagulation index (CI) (reflecting R and K times, α angle, and maximum amplitude [MA]) was calculated for the patients, who served as their own controls.

Results: The OPCAB patients demonstrated 3 days postoperatively a 17% increase in coagulation compared with the baseline. Specifically, the CI consistently revealed an elevation in the α angle and the MA, both of which reflect increased fibrinogen and platelet activity. On the other hand, 3 days following surgery the CI of the CPB group was tightly clustered around their respective baseline CI values, which had recovered from a significant decrease immediately after surgery.

Conclusion: A state of hypercoagulability, as measured by thromboelastography, exists in the OPCAB patient beyond the first postoperative day, and this finding suggests that prophylactic postoperative anticoagulation therapy targeting fibrinogen and platelet activity may be indicated for these patients.

INTRODUCTION

Historically, the incidence of thromboembolic events such as deep venous thrombosis and pulmonary embolus following conventional coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass (CPB) has been less than that seen in elective general surgeries (ie, orthopedic, urologic, gastrointestinal, and so on) [Shammas 2000]. Furthermore, nonembolic cerebrovascular accidents due to "sludging" or spontaneous thrombosis in the cerebral vasculature are very rare in this population of patients. The combination of CPB and hypothermia activate the coagulation, complement, and kallikrein/kinin systems to produce a relative state of hypocoagulation. Off-pump coronary artery bypass (OPCAB) surgery patients, who do not benefit from this documented anticoagulant effect of CPB (reduced platelet count and function, factor consumption and dilution, fibrinolytic activity, residual heparin levels, and so forth) [Kesteven 1990], may therefore be at similar risks for thromboembolic events as their general surgical counterparts. Nevertheless, most heart centers where beating heart surgery is performed have not yet altered their traditional postoperative anticoagulation regimens for their OPCAB patients [Hull 1998]. To date, there are no conclusive, dynamic studies in the literature that analyze the coagulation profile of the OPCAB patient beyond the first 24 hours after surgery [Mariani 1999, Cartier 2001].

Thromboelastography (TEG) provides a complete graphical representation of blood coagulation from initial procoagulant activation and fibrin formation through fibrin cross-linking and clot retraction to the eventual lysis of the clot [Whitten 2000]. Although TEG data are not correlated with any specific coagulation test, they do examine the process of whole blood coagulation, the interaction of the protein coagulation cascade, fibrinogen, and the platelet surface.

The purpose of this study was to determine whether TEG could be used to detect hypercoagulability in the OPCAB patient. We prospectively studied 17 patients undergoing OPCAB surgery and 6 patients for whom conventional CABG surgery with CPB was used. We chose not to prospectively randomize the patients for several reasons. We believe strongly that there exists a significant population of patients for whom CPB is absolutely or relatively contraindicated (ie, those with multiorgan dysfunction, significant neurologic history, severe aortic disease). We therefore did not feel that it was ethical or necessary to randomize the patients to fulfill our investigative purpose. The decision to use CPB for any given patient was made independently by the cardiac surgeon, and these choices explain the disparity in the 2 sample sizes.

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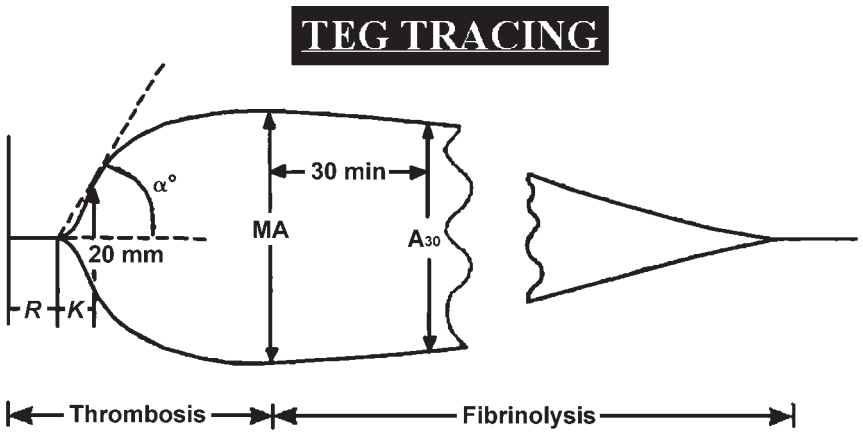

Figure 1. Normal thromboelastograph (TEG) tracing. MA indicates maximum amplitude.

Furthermore, the relative state of anticoagulation following CPB, as has already been mentioned, has been well documented by all accounts including TEG [Hull 1998, Mariani 1999].

MATERIALS AND METHODS

Thromboelastography

A thromboelastogram is a viscoelastic measure of the entire blood utilization process from the initial clot formation to the eventual lysis of the clot. It provides a graphical representation of the entire coagulation process, which can then be qualitatively and quantitatively analyzed (Figure 1).

Four coagulation parameters are determined from the TEG tracing: the R time, the K time, the α angle, and the maximum amplitude (MA). The R time is the time from the start of a sample run until the first significant levels of clot formation. The K time is the time from the measurement of R until a fixed level of clot firmness (strength) is reached. The α angle is the angle (measured in degrees) formed from R to the point on the TEG tracing where the clot amplitude reaches 20 mm and is a measure of the speed of fibrin build-up and cross-linking. The MA is a measure of the maximum strength or stiffness of the developing clot and depends on the dynamic properties of fibrin and platelet bonding. These 4 parameters are entered into a regression equation from which an overall coagulation index (CI) is generated. The expected normal range for the CI is 0.0 ± 3.0 SD units. Blood samples with a CI >3.0 are considered hypercoagulable, and samples with a CI <–3.0 are considered hypocoagulable.

Patients

Following institutional review board approval, 17 elective/urgent patients (as defined by the Society of Thoracic Surgeons) underwent OPCAB surgery and 6 underwent CABG with CPB. Exclusion criteria are listed in Table 1, and the epidemiologic data for the 23 patients are listed in Table 2.

All OPCAB surgeries were performed with the use of approved mechanical stabilizers, with or without the use of intracoronary shunts and occluders, through a median sternotomy. All patients were given a bolus of 3.5 mg/kg heparin on completion of the conduit harvest, and the activated clotting time was maintained above 400 seconds with a continuous heparin drip or a subsequent heparin bolus. On completion of each surgery, protamine sulfate was given to the patient to return the activated clotting time to the baseline level. Intraoperatively, pneumatic stockings were applied to the distal lower extremities of each OPCAB patient and removed on completion of the surgical procedure. Postoperatively, all patients received an oral dose of aspirin (325 mg) daily.

Sample Times and Techniques

Blood samples were obtained and analyzed as follows: preprocedure (after placement of the arterial line), postprocedure (15 min after protamine administration), postoperative day 1 (POD 1), POD 2, and POD 3. Blood samples were obtained by aseptic technique from indwelling catheters whenever possible and via direct venipuncture at all other times.

One-level quality control was performed daily for each channel of the thromboelastograph used. Quality control values were accepted when 3 of the 4 coagulation parameters (R, K, α angle, and MA) were within the ranges specified by the manufacturer. All samples were processed per the manufacturer's instructions. After the first 3 samples (preprocedure, postprocedure, and POD 1) were obtained, 1 mL of whole blood was added to a vial containing 1% infusorial earth (Celite). Next, 0.36 mL of the blood/Celite mixture was

Table 1. Thromboelastography Study Exclusion Criteria

- Failure to obtain informed consent
- Placement of intra-aortic balloon pump (preoperative, perioperative, postoperative)
- Operation not limited to coronary artery bypass grafting
- Administration of platelets, cryoprecipitate, or fresh-frozen plasma
- Patients started postoperatively on anticoagulation therapy (including subcutaneous heparin)
- Intraoperative use of aprotinin
- Thromboelastography samples not obtained through postoperative day 3
- Surgical procedure performed emergently

Table 2. Epidemiologic Data*

	OPCAB	CPB
Male, n	14 (82.4%)	5 (83.3%)
Female, n	3 (17.6%)	1 (16.7%)
Age (range), y	68.5 (50-82)	60.8 (33-81)
Grafts (range), n	2.65 (1-5)	4.17 (3-5)
Pump time (range), min	Not applicable	110.0 (82-134)

*OPCAB indicates off-pump coronary artery bypass; CPB, cardiopulmonary bypass.

added to a heparinase-impregnated TEG sample cup and analyzed for 30 minutes (or until all 4 coagulation parameters were determined). All later samples (POD 2 and thereafter) were added to a blood sample tube containing 3.8% buffered citrate sodium (0.129 M). After a wait of at least 15 minutes but not longer than 90 minutes, 1 mL of citrated whole blood was added to a vial containing 1% Celite. Next, 0.34 mL of the citrated/Celite blood sample was added to an unmodified sample cup containing 0.02 mL of 0.2 M calcium chloride, and the sample was analyzed for 30 minutes.

Data Analysis

The TEG data for each study patient were entered into the SPSS 10.1 statistical software program (SPSS, Chicago, IL, USA). The mean, range, and SD for each of the 5 sample times were calculated for the 17 OPCAB patients and the 6 CPB patients. The preprocedure TEG sample for each patient provided a coagulation baseline with which subsequent samples could be compared. In this way, the patients served both as their own controls and as participants in their respective surgical groups. The preprocedure CI value for each study patient was compared with the same patient's CI at 2 standard reference points: postprocedure and POD 3. The comparison with the postprocedure sample provides early information on how the procedure itself affected coagulation, and the POD 3 comparison looked at the late impact on the patient's coagulation status.

RESULTS

TEG was performed during this investigation on 85 blood samples from 17 patients undergoing OPCAB and 30 samples from 6 CPB patients. The mean CI at each sample time for the OPCAB and CPB patients are presented in Figure 2.

OPCAB Patients

The mean CI for the OPCAB patients decreased by 0.30 units immediately following the surgical procedure. Compared with their preprocedure CI, 7 (41%) of 17 OPCAB patients experienced an increase in their CI postprocedure, a finding consistent with greater coagulability, whereas the CI fell in 10 (59%) of 17 patients, a result indicative of lower coagulability. The mean CI on POD 3 for the OPCAB patients was 2.32 units higher than the mean CI for the preprocedure sample. Only 1 (6%) of 17 OPCAB patients demonstrated a lower CI on POD 3 compared with the preprocedure CI, and 16 (94%) of 17 patients experienced an increase in their CI, which is consistent with greater coagulability. The largest 1-day change in the CI, +1.35 units, occurred in the 24-hour period immediately following the OPCAB procedure (postprocedure sample to POD 1 sample). The smallest change in the CI following the OPCAB procedure occurred between POD 1 and POD 2 (+0.45 units). Following the OPCAB procedure, the CI peaked on POD 3 for 13 (76%) of 17 OPCAB patients, 3 (18%) peaked on POD 2, and only 1 (6%) peaked on POD 1.

CPB Patients

The mean CI for the CPB patients decreased significantly by 2.61 units immediately following surgery. Compared with their preprocedure CI, all 6 patients (100%) experienced a decrease in their postprocedure CI, which is consistent with reduced coagulability. The mean CI on POD 3 for CPB patients was essentially unchanged (0.04 units higher), compared with the mean CI of the preprocedure sample. Two (33%) of the 6 CPB patients demonstrated an elevated CI on POD 3 compared with the preprocedure CI, and 4 (67%) of the 6 experienced a decrease in their CI, which is consistent with a reduced coagulability. The largest 1-day change in CI occurred in the 24-hour period immediately following the procedure (+1.89 units). The smallest change in the CI following the surgical procedure occurred between POD 2 and POD 3 (+0.10 units). Following the surgical procedure, the CI peaked on POD 2 for 3 (50%) of the 6 CPB patients, 2 patients (33%) peaked on POD 1, and only 1 (17%) peaked on POD 3.

DISCUSSION

This study demonstrates that patients undergoing OPCAB surgery exhibit increases in their coagulation status, as indicated by TEG, through the third POD. Three days postoperatively, the typical OPCAB patient had a CI more than 2.3 units higher than that of the preprocedure baseline. Our TEG data suggest that during this same period CPB patients typically returned to their preprocedure baseline CI value. Specifically, the 6 patients who underwent CABG with CPB demonstrated the predicted decrease in their coagulation status after exposure to the extracorporeal circuit (postprocedure sample), followed by a gradual return to baseline by POD 3.

Although our cohort of patients is small and there may be bias in the OPCAB group (increased age) influencing the TEG results, the consistent, reproducible state of hypercoagulability is of obvious concern, particularly because OPCAB surgery is reserved in many centers for the elderly and the high-risk patient [Koutlas 2000]. These same patients have multiple comorbidities and are already at risk for thromboembolic events. Furthermore, such states may actually increase the risk of proximal stenosis of saphenous vein conduits that have been anastomosed to the aorta with connector devices. These devices, which avoid aortic manipulation, create an intravascular foreign body (nitinol) surface capable of activating the coagulation cascade.

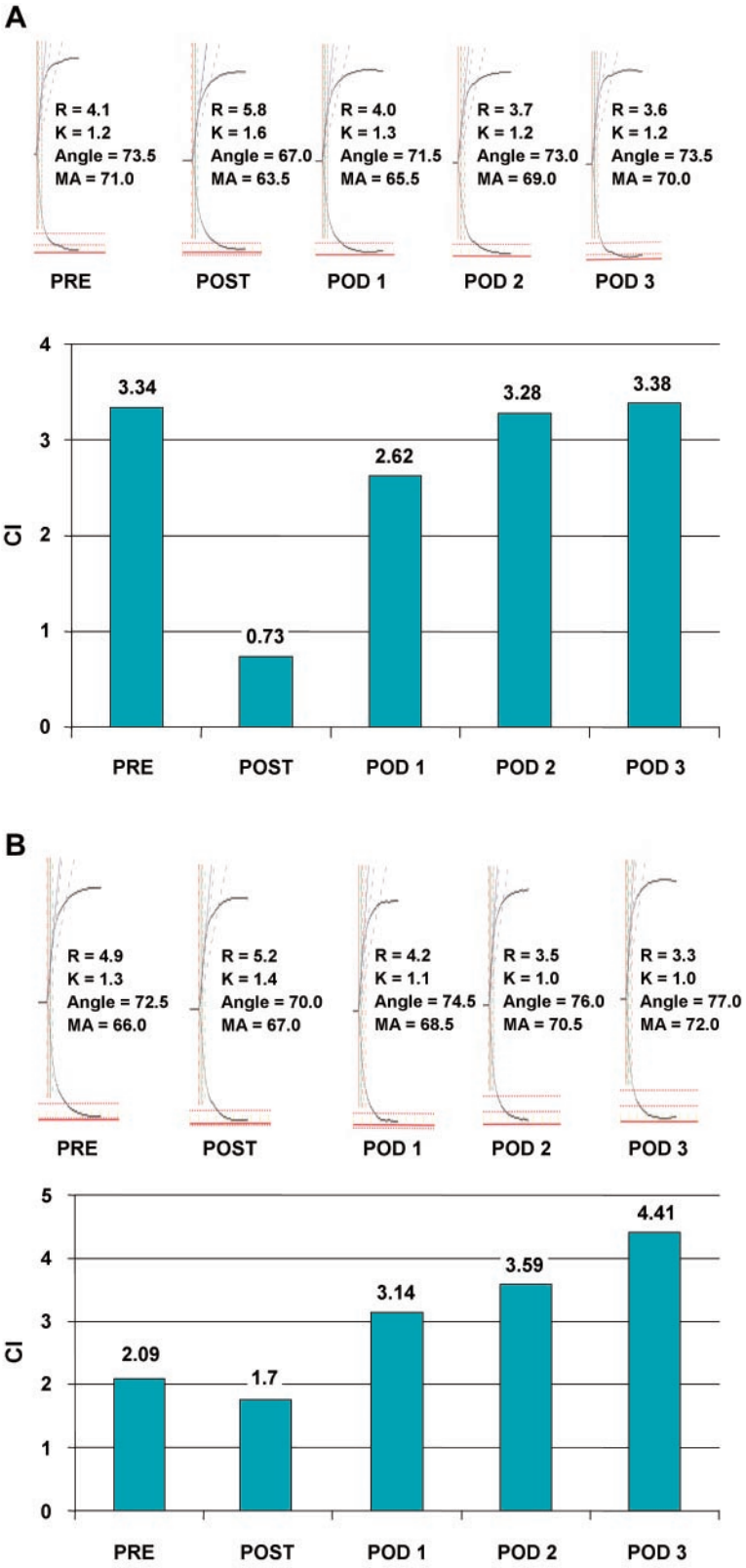

Figure 2. Representative thromboelastograph tracings and mean coagulation indices (CI) for cardiopulmonary bypass (A) and off-pump coronary artery bypass (B) surgeries for each sample time: preprocedure (PRE), postprocedure (POST), postoperative day 1 (POD 1), POD 2, and POD 3. MA indicates maximum amplitude.

Because we did not have complete data beyond POD 3 (owing to patient discharge), it is unclear what happens to the coagulation status of these patients beyond this time. However, we believe that by this postoperative time these patients are ambulatory, and therefore such a state may be of less clinical consequence.

It has previously been reported that mild-to-moderate surgical blood loss with hemodilution is associated with the development of hypercoagulability as measured by TEG [Ng 1996]. The OPCAB patients in our study received an average of 3860 mL of crystalloid (2000-8000 mL) and 580 mL of autologous packed cells (200-2000 mL) in the operating room. Presently, we do not have enough data to determine whether this effect of hemodilution on coagulation is additive with that seen for OPCAB surgery alone.

Mariani and colleagues have reported that OPCAB patients have a clearly demonstrable procoagulant activity in the first 24 hours (the extent of their study) [Mariani 1999]. This activity was characterized by increases in prothrombin factor I/II, fibrin degradation products, and von Willebrand factor and by a decrease in factor VII. These data correspond well with our own findings that the greatest 1-day change in CI occurred in the 24-hour period immediately following the OPCAB procedure (+1.35 units). Cartier and colleagues suggest that a median sternotomy, in which bone marrow is damaged, results in the generation of both local and systemic procoagulant factors [Cartier 2001]. Although they noted a higher incidence of thromboembolic complications in their OPCAB patients, this trend was not statistically significant when the results were compared with those of a cohort of CPB patients.

With the recent evidence of long-term cognitive dysfunction following CPB, it is imperative that any potential adverse effects of OPCAB surgery be addressed [Newman 2001]. Our data suggest that a state of relative hypercoagulability is present in the OPCAB population 72 hours after surgery. Because of patient "fast-tracking" and early discharge, we do not have complete TEG data after POD 3. We believe that our study demonstrates the need for further investigation to answer many fundamental questions. We acknowledge, however, that the study is neither randomized nor prospective, and this fact may limit our ability to draw such conclusions. A larger outcome study is necessary to determine whether the elevation we measured in the CI of the OPCAB patient is causally associated with an increased risk of thrombosis and thromboembolism that can result in deep venous thrombosis, pulmonary embolus, cerebrovascular accidents, and so on. Before the prophylactic use of postoperative anticoagulation therapy can be considered for these patients, it is necessary to dissect the pathway and mechanism of hypercoagulation in the OPCAB patient to determine the proper target for anticoagulation.

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