Thromboelastography Maximum Amplitude Predicts Postoperative Thrombotic Complications Including Myocardial Infarction

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Postoperative thrombotic complications increase hospital length of stay and health care costs. Given the potential for thrombotic complications to result from hypercoagulable states, we sought to determine whether postoperative blood analysis using thromboelastography could predict the occurrence of thrombotic complications, including myocardial infarction (MI). We prospectively enrolled 240 patients undergoing a wide variety of surgical procedures. A cardiac risk score was assigned to each patient using the established revised Goldman risk index. Thromboelastography was performed immediately after surgery and maximum amplitude (MA), representing clot strength, was determined. Postoperative thrombotic complications requiring confirmation by a diagnostic test were assessed by a blinded observer. Ten patients (4.2%) suffered a total of 12 postoperative thrombotic complications.

Postoperative thrombotic complications, including myocardial infarction (MI), ischemic stroke, deep vein thrombosis (DVT), and pulmonary embolism (PE), are recognized causes of postoperative morbidity and increased hospital costs and length of stay. In particular, perioperative MI in noncardiac surgery has been studied extensively. It has been estimated that the impact of

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The incidence of thrombotic complications with increased MA (8 of $95 = 8.4\%$) was significantly ($P =$ 0.0157) more frequent than that of patients with MA ≤ 68 (2 of 145 = 1.4%). Furthermore, the percentage suffering postoperative MI in the increased MA group (6 of 95 = 6.3%) was significantly larger than that in the MA ≤ 68 group (0 of 145 = 0%) (*P* = 0.0035). In a multivariate analysis, increased MA $(P = 0.013;$ odds ratio, 1.16; 95% confidence interval, 1.03–1.20) and Goldman risk score ($P = 0.046$; odds ratio, 2.39; 95% confidence interval, 1.02–5.61) both independently predicted postoperative MI. A postoperative hypercoagulable state as determined by thromboelastography is associated with postoperative thrombotic complications, including MI, in a diverse group of surgical patients.

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perioperative cardiac complications results in approximately \$20 billion in annual costs of hospital and long-term care. Large series of noncardiac surgical patients have shown the risk of postoperative MI to range between 1.2% and 18%. Perioperative stroke occurs in a range of ${<}1\%$ to approximately 2.5% of cases. DVT and PE are also recognized postoperative complications. Overall, 450,000 cases of DVT and 240,000 cases of fatal pulmonary embolus are diagnosed annually in the United States per year. The average cost of each DVT case is \$9,337 with an average length of stay of 6.3 days and each PE costs \$12,795 with an average length of stay of 7.4 days (1).

Hypercoagulability has been implicated in the pathogenesis of thrombotic complications, including MI, DVT, PE, ischemic stroke, and vascular graft thrombosis. It has been well known since the time of Virchow that a hypercoagulable state is a risk factor for venous thrombosis and PE, and current studies

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continue to support this concept (2,3). Hypercoagulable states, including both inherited and acquired conditions, have been shown to be a potential mechanism in postoperative ischemic stroke (4 –7).

Classically, in the medical (nonsurgical) setting, coronary atherosclerosis and plaque rupture are thought to be the main factors in the initial pathogenesis of the majority of MIs. The role of the coagulation system in acute coronary syndromes has been well recognized in the field of cardiology, hence the widespread use of prophylactic therapies, such as aspirin and heparin, in nonsurgical patients. The process of undergoing a major surgical procedure has been demonstrated to induce an acquired postoperative hypercoagulable state. Potential mechanisms for this prothrombotic state include increased platelet activation, decreased fibrinolysis, and decreased anticoagulants (antithrombin III). No studies have assessed the role of postoperative hypercoagulability on MI after major surgery.

Most assays of clotting (e.g., prothrombin time, activated partial thromboplastin time) can identify a specific factor deficiency; however, their performance in plasma (rather than whole blood) and the addition of buffered solutions limits their relevance to overall dynamic clot formation in whole blood. In contrast, thromboelastography (TEG®) was designed specifically to assess overall clotting kinetics and strength in whole blood. TEG[®] has been successfully used in clinical settings to detect hypercoagulable states. TEG® has been increasingly used in the assessment of postoperative hypercoagulability for a variety of surgical procedures $(8-13)$.

Therefore, we designed a prospective cohort study to test the hypothesis that a hypercoagulable state at the end of surgery as revealed by $TE\overline{G}^{\circledast}$ is associated with an increased incidence of postoperative thrombotic complications, including MI.

Methods

After IRB approval and informed consent, 240 patients undergoing major elective noncardiac surgery at Columbia-Presbyterian Medical Center between July and October 2002 were enrolled in a prospective blinded cohort study. Patients were identified for enrollment in the study based on the severity of the surgical procedure to be performed; only patients undergoing surgery requiring inpatient admission were selected for enrollment. No patients undergoing ambulatory or emergency surgery were included in the study.

Patients providing informed consent underwent preoperative evaluations including detailed medical histories, physical examinations, and laboratory testing. A cardiac risk score was assigned to each patient using the established Revised Goldman cardiac risk

index, which has been shown to be predictive in assessing risk of major cardiac complications, including MI, after noncardiac surgery (14). Risk factors included in this risk scoring system are high-risk type of surgery, presence of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative use of insulin therapy for diabetes, and preoperative serum creatinine more than 2.0 mg/dL.

Study patients received routine surgical and anesthetic care for their procedures. Patients received standard postoperative care including routine postoperative thromboprophylaxis with lower extremity pneumatic compression devices or subcutaneous (SQ) heparin administration. Orthopedic surgical patients received standard postoperative warfarin dosing. During each patient's postoperative course until discharge from the hospital, study personnel blinded as to the TEG^{\otimes} results assessed the patient for the presence of thrombotic complications. These complications included DVT, PE, ischemic stroke, and MI. New onset MI was assessed using the Joint European Society of Cardiology/American College of Cardiology definition (15). DVT was diagnosed based on new clinical findings resulting in changes in treatment and positive venous duplex ultrasound scanning. PE was diagnosed based on clinical findings along with ventilation/perfusion scanning or pulmonary computed tomography (CT) angiography. Ischemic stroke was confirmed after clinical findings with head CT.

Within 2 h after completion of a procedure, 0.5 mL of whole blood was sampled from an indwelling intravascular catheter. According to the manufacturer's guidelines, celite-activated TEG^{\circledast} using a Thromboelastograph Coagulation Analyzer (TEG®; Haemoscope Corporation, Skokie, IL) was performed on the blood samples within 4 min of collection, obviating the need for citrated blood. Maximum amplitude (MA) from the TEG® tracing, representing clot strength, was recorded for each patient. MA is a direct function of the maximum dynamic properties of fibrin and platelet bonding via GPIIb/IIIa and represents the ultimate strength of the fibrin clot. The upper limit of normal for MA in celite-activated TEG[®] is $\overline{68}$ mm (16). No relevant reference standard exists for dynamic clotting of whole blood.

The objective of this study was to test the hypothesis that a postoperative hypercoagulable state as determined by TEG^{\otimes} is associated with an increased likelihood of postoperative thrombotic complications including MI. Patients were divided into control and hypercoagulable (MA >68 mm) groups based on TEG® MA values, and the incidence of thrombotic complications were recorded for each group. A Fisher's exact test was conducted to test the significance of differences between groups. This analysis was also

conducted examining the occurrence of new postoperative MI. For all analyses a significance level of *P* 0.05, two-tailed, was assumed.

Given the observed association between the TEG^{ω} variable MA and postoperative MI and the availability of an established risk score for MI (14), a multivariate analysis was performed to determine if MA predicted postoperative MI independent of known risk factors using the Revised Goldman Risk Index. The independent variables included MA and Revised Goldman Risk Index, and the dependent variable was postoperative MI. In addition, use of a dichotomous cutpoint for MA was analyzed using a cutpoint of 68 mm, which is the test's upper limit of normal.

Results

Overall, 240 patients participated in the study. Twelve postoperative thrombotic complications occurred in 10 patients (MI, $n = 6$; DVT, $n = 2$; PE, $n = 2$; cerebrovascular accident, $n = 2$). Perioperative variables are shown (Table 1) for patients with ($n = 95$) and without ($n = 145$) increased MA at the end of surgery. Of note, age, gender, body mass index, Goldman Cardiac Risk score, type of anesthetic, and surgical procedure type were similar between groups. Postoperative prophylactic anticoagulation management was also similar between groups. The incidence of thrombotic complications was significantly more frequent in patients in the increased MA group (Fig. 1). Moreover, all postoperative MIs were observed in patients with a hypercoagulable state as manifested by increased MA (Fig. 2). The sensitivity and specificity of the increased TEG® MA value for all thrombotic complications included was 80% and 62%, respectively, whereas for MI alone the sensitivity and specificity were 100% and 61%, respectively. The positive predictive value and negative predictive value of the increased TEG® MA value for all thrombotic complications included were 8% and 99%, respectively, whereas for MI alone these were 6% and 100%, respectively.

Perioperative variables for patients with and without a thrombotic complication (Table 2) and MI (Table 3) are shown. Of note, postoperative hospital length of stay was significantly longer in patients with a thrombotic complication or MI. Patients who experienced a thrombotic complication or MI were just as likely to have received SQ heparin or coumadin postoperatively for thromboprophylaxis. Interestingly, none of the patients who suffered a postoperative MI had received aspirin in the postoperative period (Table 3).

This study was not designed to rigorously develop and validate a predictive model of postoperative MI. Nevertheless, we were interested in ascertaining whether the TEG[®] variable MA at the end of surgery was an independent predictor of postoperative MI or merely closely linked to known predictors of MI in this

setting. Both the TEG^{\circledast} variable MA at the end of surgery (odds ratio [OR], 1.14; 95% confidence interval [CI], 1.03– 1.27; $P = 0.014$) and the established Goldman Risk Score (OR, 2.47; 95%CI, 1.01–6.04; *P* = 0.047) were univariate predictors of postoperative MI. The association between age and postoperative MI did not achieve significance (*P* $= 0.1028$). In a multivariate analysis, MA at the end of surgery independently predicted postoperative MI (OR, 1.16; 95%CI, 1.03–1.20; $P = 0.013$) over and above the effects of Goldman Risk Score (OR, 2.39; 95%CI, 1.02– $5.61; P = 0.046$). This overall model was significant at the $P = 0.008$ level (model χ^2 9.784; *df* = 2). Forcing the independent variable age into this model still resulted in statistical significance ($P = 0.0158$) for the variable MA at predicting MI. In addition, use of a dichotomous cutpoint for MA was also analyzed using a cutpoint of 68 mm, which is the test's upper limit of normal. This analysis revealed a robust effect corresponding with an OR of 6.6 ($P < 0.01$).

Discussion

Little attention has been focussed on characterizing the incidence and clinical relevance of a hypercoagulable state on patient outcome in the perioperative period. We have completed a prospective study of 240 patients undergoing a diverse group of surgical procedures and found that a hypercoagulable state, as manifested by increased MA at the end of surgery, is associated with postoperative thrombotic complications, including MI.

It is increasingly recognized that postoperative thrombotic complications are common and consume considerable amounts of health care resources. Indeed, the significant incidences of postoperative MI and other thrombotic complications occurring in our study are consistent with the rates documented in the literature (1,14,17–23). Hypercoagulable states, such as those shown to be induced by surgery, have been cited as a factor in the development of the thrombotic complications we studied, including ischemic stroke $(4-6)$, MI (7,24), DVT, and venous thromboembolism (2,3). Despite these well-known links, studies developing preoperative risk stratification or assessment systems typically do not include information concerning coagulation and, specifically, hypercoagulable states, as a risk factor for perioperative morbidity and mortality. Given the infrequent occurrence of heritable or acquired hypercoagulable states existing without previous clinical manifestations, screening for such states in the clinical or perioperative setting is rarely recommended. This is a result of the small yield and resultant poor cost-effectiveness of the extensive battery of tests for cases such as Factor V Leiden mutation, protein C, protein S, and antithrombin III deficiencies, or antiphospholipid antibodies and hyperhomocystinemia (25). However, TEG[®] has shown a promising

Table 1. Perioperative Variables in Patients with End of Surgery Maximum Amplitude (MA) ≤ 68 Versus MA > 68

Values are mean \pm sp and median in parenthesis or n (%) where applicable.

LR = lactated Ringer's solution; SQ = subcutaneous; Postoperative any coag. = received SQ heparin, coumadin, or aspirin postoperatively; MI = myocardial infarction; $ENT = ear$, nose, throat.

 $* P = 0.0157$ compared with the MA ≤ 68 group; $\dagger P = 0.0035$ compared with the MA ≤ 68 group.

Figure 1. Patients with a confirmed thrombotic complication (deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accident) by presence or absence of increased maximum amplitude. Crosshatched bar $=$ control group; solid bar $= MA$ >68 group. $*P = 0.0157$.

ability to detect known or established hypercoagulable states during pregnancy and postpartum (26–28) or during the presence of cancer (29 –32). Furthermore, a study by Handa et al. (33) suggested that TEG[®] could play a valuable role in screening patients with suspected prothrombotic states. In this study of 103 patients, 49 were found to have hypercoagulable or borderline TEG^{ω} results. Of these 49 patients, 31 (63%) were then identified as having a defined prothrombotic abnormality by conventional testing for acquired or heritable hypercoagulable states. Furthermore, 100% of the study's 31 patients found to have normal

TEG® results were also normal on conventional testing.

Although a larger formal investigation is needed to establish TEG^{\circledast} as a widespread screening test for prothrombotic states, TEG^{\circledcirc} clearly shows an ability to detect hypercoagulable states produced by surgery. Potential causes for this hypercoagulable state include surgical trauma, systemic inflammation, tissue factor expression, platelet activation, and crystalloid administration.

Despite the limitation that TEG^{\circledR} cannot specify the mechanism for hypercoagulable states, it is nonetheless a valuable tool for assessing the presence of these

Table 2. Perioperative Variables in Patients *with* and *without* a Postoperative Thrombotic Complication (DVT, PE, MI, and/or CVA)

Values are mean \pm sp and median in parenthesis where applicable.

 $LR =$ lactated Ringer's solution; $SQ =$ subcutaneous; Postoperative any coag. = received SQ heparin, coumadin, or aspirin postoperatively; MA = thrombolestographic variable maximum amplitude; $R =$ thrombolestographic variable R; $DVT =$ deep vein thrombosis; $PE =$ pulmonary embolism; $MI =$ myocardial infarction; $CVA =$ cerebrovascular accident; $ENT =$ ear, nose, throat.

states. The utility of TEG^{\circledast} in the measurement of postoperative hypercoagulability is evident in many studies within a variety of noncardiac surgical specialty fields including neurosurgery (13), orthopedic surgery (8), abdominal surgery (9,34), and vascular surgery (35). Indeed, our study included a variety of the aforementioned noncardiac surgical specialties and documented 95 of the 240 study patients (40%) as exhibiting a postoperative hypercoagulable state.

Despite the established link between the occurrence of thrombotic complications and the induction of hypercoagulability by major surgery and the ability of TEG^{\otimes} to measure hypercoagulable states and specifically postoperative hypercoagulability, no large, well designed studies have assessed the association between postoperative hypercoagulability as measured by TEG^{ω} and the occurrence of a multitude of thrombotic complications in a diverse group of surgical patients. Caprini et al. (34) attempted to study the association of TEG® and postoperative DVT in a series of 100 patients undergoing laparoscopic cholecystectomy. TEG® measurements were measured postoperatively and patients were followed for the occurrence of DVT; however, only one DVT complication was observed and thus no statistical association could be demonstrated. Abrahams et al. (13) studied 46 patients undergoing neurosurgery with TEG® measurements

and lower extremity Doppler sonography postoperatively and, again, limited occurrence of postoperative complications prevented significant statistical analysis. In addition, a study by Traverso et al. (36) included 100 patients undergoing elective abdominal surgery, and in the patients randomized to receive no postoperative heparin thromboprophylaxis, TEG® MA value showed the ability to predict the occurrence of DVT with a sensitivity of 72.2% and specificity of 69% (37). Finally, Wilson et al. (8) performed TEG® every other day in 250 patients having undergone proximal femoral fracture repair and showed that patients suffering from postoperative DVT had a significantly higher level of hypercoagulability as measured by TEG^{ω} than did those who did not suffer DVT.

Our study is the first to demonstrate an association between hypercoagulability as measured by $\mathrm{TEG}^{\circledast}$ and postoperative thrombotic complications in patients undergoing a diverse set of surgical procedures. The aforementioned previous studies were limited by power or methodological limitations, including focus on a single type of surgical procedure (e.g., orthopedic) and limiting thrombotic complications to DVT only. Our study included 240 patients undergoing a variety of major noncardiac surgical procedures who were followed postoperatively until discharge. Several

Table 3. Perioperative Variables in Patients *with* and *without* a Postoperative Myocardial Infarction

Values are mean \pm sp and median in parenthesis where applicable.

LR = lactated Ringer's solution; SQ = subcutaneous; Postoperative any coag. = received SQ heparin, coumadin, or aspirin postoperatively; MA = thrombolestographic variable maximum amplitude; $R =$ thrombolestographic variable R; ENT = ear, nose, throat.

conclusions can be drawn from our results. First, postoperative TEG® MA values in the hypercoagulable range are associated with a higher risk of postoperative thrombotic complications including PE, DVT, MI, and ischemic stroke. These findings, along with the aforementioned research linking thrombotic complications with hypercoagulability, suggest that surgical patients are at high risk for hypercoagulability and that this plays an important role in the pathogenesis of thrombotic complications. Second, patients with increased MA values in the postoperative setting are at particularly higher risk for postoperative MI. Despite preoperative risk adjustment based on an established cardiac risk index for noncardiac surgery, patients with hypercoagulable TEG^{\circledast} MA values had a significantly more frequent incidence of postoperative MI. Given the morbidity and mortality of postoperative MI, patients identified with hypercoagulable TEG^{ω} MA values postoperatively may benefit from aspirin in the immediate perioperative period. Although postoperative aspirin has been shown to decrease the incidence of postoperative MI and stroke after coronary bypass (38), it is typically held in the immediate perioperative period to improve hemostasis. In light of Mangano et al.'s report (38) involving cardiac surgical patients, it is interesting to note that none of the patients with postoperative MI in our study received aspirin postoperatively. The high sensitivity of increased TEG® MA values validates it as a tool for

identifying patients at high risk for thrombotic complications. It is interesting to speculate that individuals affected with hypercoagulable states postoperatively might benefit from a more intensive anticoagulation treatment, perhaps involving platelet-specific drugs.

A potential limitation of our study is the lack of a preoperative TEG® measurement for comparison with the postoperative TEG[®] values. The goal of our study, however, was to show that a postoperative hypercoagulable state as manifested by TEG^{ω} is associated with the occurrence of thrombotic complications, regardless of whether or not the postoperative hypercoagulable state is a result of the surgery itself or to a preexisting heritable or acquired prothrombotic condition.

Our study was not designed or powered to compare the associations between TEG^{\circledast} MA and thrombotic complications between subgroups of patients undergoing specific surgical procedures. This could be considered a limitation of the study. However, the incidence of thrombotic complications including MI alone were not localized to a specific procedure type, suggesting applicability of these results to most patients undergoing major surgery.

A significant consideration in any study assessing postoperative complications is proper risk stratification and adjustment of patients to minimize the likelihood that patients suffering postoperative complications simply had increased preoperative morbidities. We used the

revised Goldman cardiac risk index for noncardiac surgery to risk-adjust for the presence of postoperative MI. There is no well-established risk index for the occurrence of postoperative DVT, PE, and stroke in the setting of noncardiac surgery. The focus of proposed risk indices for DVT and venous thromboembolism have focused on prophylactic treatments to be used with given risk factors rather than the incidence of events associated with these risk factors.

The length of postoperative TEG^{\circledast} monitoring has been scrutinized by previous studies examining postoperative hypercoagulability measured by TEG®. In studies measuring TEG® values from the immediate postoperative period to between 3 and 7 days postoperatively, TEG[®] MA levels were increased immediately after surgery and remained increased over the subsequent measurement days (8,9,39). Therefore, it is possible that little benefit is gained from the repeated measurement of TEG® over a prolonged postoperative period. Our results strongly suggest that most (if not all) hypercoagulable states associated with MI can be diagnosed with a simple diagnostic test at the end of surgery. If this holds true in subsequent studies, it would obviate the need for more complex and lengthy screening procedures. Of note, the MIs in our study were observed on postoperative days 1 ($n = 4$), 2 ($n =$ 1), and 4 $(n = 1)$, which argues for the relevance of measurements obtained immediately after surgery.

Finally, we did not perform screening diagnostic tests on all patients for the thrombotic complications we included in the study, including MI, so we cannot exclude the occurrence of clinically occult complications that could have been revealed by diagnostic tests alone. Although we do not know the overall relevance of these occult complications, length of stay was consistently longer among those patients we found to have complications, demonstrating the potential clinical relevance of the complications we did diagnose.

In summary, increased postoperative TEG® MA values immediately after surgery were associated with a higher risk of postoperative thrombotic complications, including MI. On the basis of our findings, a randomized clinical trial is being planned to assess the utility of TEG^{ω} to improve the safety and efficacy of antithrombotic strategies in patients undergoing major surgery.

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