Platelet function tests predict bleeding and thrombotic events after off-pump coronary bypass grafting

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Abstract

Objective: A balanced coagulation system after cardiac surgery minimizes bleeding and thrombotic events. However, the best method to monitor this balance has not been established. We used a series of tests of coagulation and platelet function to define the risk of bleeding and thrombotic events after OPCAB.

Methods: In 76 patients, routine coagulation tests (i.e. prothrombin time, fibrinogen level, d-dimer, and platelet count), thrombelastography, and whole blood aggregometry were obtained perioperatively and on days 1 and 3 after OPCAB. Intra- and postoperative blood loss was determined. Early patency of venous bypass grafts was determined using CT angiography (Philips Medical, Corp.).

Results: Chest tube output and red cell volume loss at 24 h were 952 ± 475 and 190 ± 115 ml, respectively. Early graft failure developed in eight patients. Perioperative changes in routine coagulation tests showed no correlation with either bleeding or thrombosis. However, perioperative decline in platelet function as assessed by the area under the impedance curve for whole blood aggregometry correlated with intraoperative blood loss (R = 0.42, P < 0.05). A perioperative decline in the maximum amplitude of the thrombelastography trace showed a significant correlation with 24 h hemoglobin loss (R = 0.45, P < 0.05). Compared to those with all patent grafts, patients with early graft failure demonstrated a reduction in platelet sensitivity to aspirin by both thrombelastography and aggregometry on day 3.

Conclusions: In contrast to standard coagulation testing, platelet function predicted both bleeding and thrombosis after OPCAB. Titration of perioperative platelet function according to these tests may minimize thrombosis without increasing bleeding.

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1. Introduction

A postoperative hypercoagulable state that increases the risk for thrombotic events is well established after general surgical procedures [1]. An 'anticoagulating effect' of cardiopulmonary bypass (CPB) is thought to create a risk of bleeding that exceeds the tendency for postoperative hypercoagulability. Whether circumventing CPB during off-pump coronary artery bypass (OPCAB) alters the balance of coagulation and increases the risk for a postoperative hypercoagulable state after OPCAB is unclear [5,6]. Although transfusion requirements are reduced by OPCAB, postoperative bleeding has been found to be consistently the same between these two approaches [2–4]. Early graft thrombosis was increased after off- compared to on-pump CAB in one recent randomized trial [2] but not others [3].

The lack of an in vitro assay that is capable of confirming a hypercoagulable state also adds to the controversy. There is currently great variability in antiplatelet strategies after OPCAB [7]. The accurate prediction of adverse bleeding and thrombotic events would provide a more rational basis for therapy and reduce this variability. In this study, we tested the hypothesis that in vitro platelet function tests provide an accurate method for defining the risk of bleeding and graft thrombosis after OPCAB.

2. Methods

2.1. Patient enrollment and study design

This study was a prospective cohort trial of patients undergoing OPCAB at a single center. Local IRB approval was obtained (protocol #0303108) and all subjects provided informed consent prior to enrollment. From November 2002 until May 2004, 122 patients were screened. Forty patients were excluded due to creatinine > 2.0 mg/dl (n = 16), conversion to on-pump CAB (n = 12), refusal of consent...
(n=10) and the emergent nature of the surgery (n=2). The primary endpoint of this study was the correlation of in vitro platelet activity with both early graft thrombosis and bleeding.

2.2. Surgical technique and patient management

Four surgeons, experienced in OPCAB, enrolled patients during the study. After a full median sternotomy, the left internal thoracic artery (ITA) was used as a bypass conduit in all patients; the great saphenous vein was harvested using an endoscopic (n=105 venous conduits) (VasoView Endoscopic Vessel Harvesting System, Guidant Systems, Inc., Minneapolis, MN) or open (n=23 venous conduits) approach, based on anatomical considerations. Radial arteries were harvested (n=8) using a 'no touch' technique. Other types of arterial conduits were not used during the course of this study. Conduits were stored in dilute heparinized blood until use. Prior to distal ligation of ITA pedicle, intravenous heparin was given at a dose calculated by the Hecon instrument (Medtronic, Inc., Minneapolis, MN) as sufficient to obtain a kaolin based ACT of greater than 300 s. Further heparin doses were given as required every 30 min to maintain the heparin level at >2 IU/ml and ACT >300 s. Suction-based exposure and stabilizing devices (Octopus 4.3, Tissue Stabilizer & Urchin, Heart Positioner, Medtronic, Inc., Minneapolis, MN) were used for creating all distal anastomosis. To minimize coagulation variability in study subjects, patients requiring conversion to a standard, on-pump CAB technique were excluded from analysis. At the end of surgery, the heparin effect was reversed by half the dose of protamine calculated by the Hecon device. Preoperative aspirin was continued throughout the date of surgery. Postoperative aspirin (325 mg p.o. qd)—given within 6 h of arrival to the ICU—was the sole platelet inhibitor used in all patients. Postoperative use of blood products followed a TEG-based algorithm as previously described [8].

2.3. Perioperative bleeding

Shed mediastinal blood was collected intraoperatively using a cellsera device (Cobe BRAT 2, Cobe Cardiovascular, Inc., Arvada, CO), processed and retransfused. The volume retrieved intraoperatively was measured along with the amount of postoperative shed blood after 24 h. The red blood cell volume lost after 24 h was calculated by the hematocrit of the contents in the water seal chest drainage system (Atrium Medical Corp., Hudson, NH) multiplied by the total volume. The chest drain contents were mixed thoroughly to obtain an average hematocrit over the 24 h observation period.

2.4. Intraoperative graft analysis

Blood flow and flow waveform were measured in each graft using transit time ultrasound (Transonic, Inc., Ithica, NY), a routinely available technology shown to predict bypass graft failure on follow-up angiography [9]. Waveforms were stored on a laptop computer using digital data acquisition software (WinDaq®, DATAQ Instruments, Inc., Dayton, OH). Discarded vein segments were procured intraoperatively from each bypass graft for analysis of endothelial integrity by immunohistochemistry. A portion was snap frozen in OCT compound and stored at −80 °C. Sections (~5 µm thick) were stained with CD31 monoclonal antibody (R&D System, Inc.) for calculating percentage endothelial integrity using image analysis software (Bioquant Nova Prime ver.6™, Nashville, TN).

2.5. Routine coagulation assays

Routine tests of coagulation (INR, activated partial thromboplastin time, fibrinogen, platelet count, and quantitative d-dimer levels) were performed at baseline (prior to skin incision), postoperatively (immediately after skin closure), postoperative day 1 and postoperative day 3 by the institution’s clinical laboratory using standard techniques.

2.6. Assays for platelet activity

At the same perioperative time points described above, citrated (3.8%) whole blood was collected for the following in vitro assays of platelet function.

- TEG®. Using 360 µl whole blood per assay, the following parameters were obtained from the TEG trace: R time—period of time from initiation of the test to the start of the trace and represents initial fibrin formation; α—an angle between the line in the middle of the TEG tracing and the line tangential to the developing TEG tracing and represents the kinetics of fibrin cross-linking; MAkolin—maximum amplitude reflects strength of a clot which is dependent on number and function of platelets and its interaction with fibrin but is insensitive to the aspirin effect [10]; LY30—measures the rate of amplitude reduction 30 min after MA and represents the stability of the clot. Given that all subjects were maintained on perioperative aspirin, additional TEG assays were performed to improve the detection of an aspirin effect. A heparinized (>2 U/ml) sample was treated using a direct fibrinogen activator (factor XIIa 5 U/ml and reptilase 0.2 U/ml ± arachidonic acid (0.14 mg/ml) and the resulting MA generated from arachidonic acid (MAAA) or fibrin formation alone (MAF) were recorded. The aspirin effect (MAAA,MAF) was calculated as follows: [(MAAA,MAF)/(MAkolin − MAF)] × 100% [10].

Whole blood aggregometry (model 592A, Chronolog, Havertown, Pennsylvania). Whole blood diluted 1:1 with saline was stimulated with either low (1 µg/ml) or high (5 µg/ml) dose collagen. Impedance changes were then measured across two electrodes immersed in the sample. The area under the developing impedance curve (AUC) and the maximum impedance changes (2) were assessed after 6 min. The aspirin effect was determined by comparing the impedance change resulting from low vs. high dose collagen as described [11].

2.7. Postoperative graft follow-up

The patency of bypass grafts was determined by blinded review by a single expert reviewer (CW) of 16 detector row, spiral computed tomography examinations (420 ms rotation, 100–150 ml contrast agent IV at 5 cm³/s). Retrospective ECG
gating was performed for image reconstruction to minimize cardiac motion artifact. Patency was defined as any flow through the entire graft regardless of the presence of stenosis. The graft was said to be nonpatent if a stump was seen or if there was no flow by CT angiography (CTA) as previously described [12].

2.8. Statistics

Assumptions for the power analysis were based on prior studies by our group showing a 6.5% rate of early graft failure after OPCAB [13] and by others demonstrating the strong correlations between platelet function testing and hemorrhage [8,14,18]. In addition, aspirin has been shown to reduce graft thrombosis by 50% relative to placebo [15], suggesting an equally strong relationship between platelet function and graft thrombosis. On the basis of these data, enrollment of 75 patients was required to demonstrate a correlation of platelet function with bleeding and thrombosis at \( P = 0.05 \) and power = 80% (http://calculators.stat.ucla.edu/powercalc/).

Platelet hyperactivity was defined for each assay as platelet responsive at any point of analysis \( > 1 \) SD above the mean ‘normal’ value determined from 20 healthy volunteers [11]. Correlations were performed using Fischer exact test for categorical variables and linear regression for continuous variables. The predictive value of each platelet function test at predicting bleeding was determined by determining the area under the curve (AUC) for Receiver Operating Characteristics curves, using \( > 800 \text{ml} \) bleeding per 24 h for the definition of a ‘bleeding’ vs. ‘nonbleeding’ patient. Calculations were performed using the InStat™ statistical package (GraphPad Software, San Diego, CA).

3. Results

3.1. Early thrombosis vs. patent vein grafts

Of the 82 OPCAB patients with 156 venous grafts that completed the protocol, 19 venous grafts from six patients were not included in the early graft patency assessment due to prospectively determined exclusion criteria: (1) inability to obtain postoperative angiography due to creatinine \( > 2.0 \text{mg/dl} \) (\( n = 3 \)); (2) patient refusal (\( n = 2 \)); and (3) graft blood flow \( < 10 \text{cm}^3/\text{min} \) despite revision (\( n = 2 \)). Patency of arterial grafts was not included in this analysis, but was 100%. CTA was obtained in 97% of study subjects before hospital discharge. Of the 137 vein grafts analyzed, eight grafts (5.8%) in eight patients were found to be thrombosed by CTA (Fig. 1). Four of these patients underwent further follow-up by conventional, catheter based angiography which confirmed the diagnosis of graft thrombosis in each case.

No significant differences were noted between patients with thrombosed vs. all patent grafts in demographics/preoperative risk factors or medication use (Table 1). Intraoperatively collected data such as ejection fraction, conduit diameter, and target size and quality and inotropic requirements were also similar (Table 2). Intraoperative blood loss was similar but chest tube output at 24 h was significantly reduced in those patients that developed early graft thrombosis (Fig. 2).

3.2. Conduit quality

Grafts that developed early failure by POD5 had less blood flow measured intraoperatively than grafts that remained patent (36.5 ± 29.3 vs. 46.9 ± 32.3 cm³/min), but the differences were minimal and did not reach statistical
significance. Pulsatility index (2.6 ± 1.9 vs. 2.1 ± 0.8) and percentage diastolic flow (51 ± 15 vs. 58 ± 11%) were also similar between groups that developed thrombosis vs. no graft thrombosis, respectively. The percentage of endothelial integrity was 16.7 ± 21.5% in eight vein grafts that failed early compared to 55.2 ± 35.7% in grafts remaining patent (P = 0.047) (Fig. 3).

3.3. Platelet hyperactivity

Prior to surgery, platelet hyperreactivity (i.e. > 1 SD above the normal value for either test) was noted in only two patients (3%). Nearly all patients developed a significant decrease in platelet function according to TEG and WBA during the immediate postoperative assessment (Fig. 4). In most patients, platelet function returned to baseline. However, the function exceeded baseline by > 1 SD on POD#3 in 10 patients (Fig. 4 and Table 2). Only one in 10 of this hyperreactive subgroup developed early graft thrombosis (10 vs. 5.8% of the remaining patients who maintained normal postoperative platelet function, P = NS).

No consistent differences in platelet function were noted for the eight patients with graft thrombosis (n = 8 grafts) vs. the 67 patients with all patent grafts (n = 129 grafts) on either test and at any time point. However, analyzing platelet function according to aspirin responsiveness improved the value of these tests. A significant increase in platelet resistance to the aspirin effect was noted in those patients that developed early graft thrombosis (Table 2).

Table 1
Preoperative demographics and postoperative course

<table>
<thead>
<tr>
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<th>Thrombosis</th>
<th>No thrombosis</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>67 ± 10</td>
<td>69 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>62</td>
<td>65</td>
<td>NS</td>
</tr>
<tr>
<td>Active smoker (%)</td>
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<td>25</td>
<td>NS</td>
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<tr>
<td>Hypertension (%)</td>
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<td>84</td>
<td>NS</td>
</tr>
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<td>NS</td>
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<tr>
<td>Diabetes (%)</td>
<td>45</td>
<td>42</td>
<td>NS</td>
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<tr>
<td>EF &lt; 40% (%)</td>
<td>20</td>
<td>18</td>
<td>NS</td>
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Preoperative medications

<table>
<thead>
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<th>Thrombosis</th>
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</tr>
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<tbody>
<tr>
<td>Beta-blocker (%)</td>
<td>90</td>
<td>88</td>
<td>NS</td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>91</td>
<td>94</td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitor (%)</td>
<td>60</td>
<td>54</td>
<td>NS</td>
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<tr>
<td>Length of intubation (h)</td>
<td>15 ± 12</td>
<td>16 ± 16</td>
<td>NS</td>
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<td>Postop low CI (%)</td>
<td>9</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Postop LOS (days)</td>
<td>6.1 ± 1.2</td>
<td>6.2 ± 1.8</td>
<td>NS</td>
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</table>

EF, ejection fraction determined on intraoperative transesophageal echocardiography; low CI, cardiac index < 2.0 l/min/m²; LOS, length of stay.

Table 2
Aspirin resistance predicts graft thrombosis

<table>
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<th>P</th>
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<tr>
<td>Peak PT change (s)</td>
<td>1.7 ± 1.0</td>
<td>1.4 ± 1.4</td>
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</tr>
<tr>
<td>Peak fibrinogen (mg/dl)</td>
<td>595 ± 185</td>
<td>579 ± 186</td>
<td>NS</td>
</tr>
<tr>
<td>Peak d-dimer (mg/dl)</td>
<td>2133 ± 1602</td>
<td>1703 ± 1037</td>
<td>NS</td>
</tr>
<tr>
<td>Peak platelet count (&gt;100 cells/mm³)</td>
<td>282 ± 144</td>
<td>291 ± 108</td>
<td>NS</td>
</tr>
<tr>
<td>TEG-MA (mm)</td>
<td>71.1 ± 5.1</td>
<td>70.4 ± 3.7</td>
<td>NS</td>
</tr>
<tr>
<td>U6 min—high dose collagen</td>
<td>13.2 ± 3.9</td>
<td>14.1 ± 3.3</td>
<td>NS</td>
</tr>
<tr>
<td>% MAAS</td>
<td>55.2 ± 22.1</td>
<td>22.4 ± 16.9</td>
<td>0.05</td>
</tr>
<tr>
<td>% U6 min—low vs. high dose collagen</td>
<td>69.3 ± 23.4</td>
<td>35.3 ± 19.9</td>
<td>0.05</td>
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Fig. 2. Blood loss during surgery (i.e. intraoperative) and over the first 24 h (i.e. postoperative) was determined by the volume collected by the cellsaver and chest drainage devices, respectively. Although intraoperative bleeding was similar, patients that developed early graft failure showed preserved hemostasis over the first postoperative day as evidenced by reduced blood loss.

Fig. 3. A discarded segment of each vein graft was procured intraoperatively for immunohistochemical analysis of CD31, an endothelial marker that is constitutively expressed. Endothelial integrity was determined by positive CD31 staining (red arrows) and disruption depicted by the lack of staining on the luminal surface (blue arrows). Using image analysis software, graft attrition was found to be significantly associated with lesser endothelial integrity compared to those grafts that remained patent (P < 0.04 for thrombosed vs. patent grafts) (For interpretation of the reference to colour in this legend, the reader is referred to the web version of this article.).
3.4 Bleeding

Although intraoperative blood loss did not differ, the thrombosed group was noted to have a significant reduction in the volume retrieved in chest drainage device (632 ± 366 vs. 1106 ± 741 ml, P < 0.01) and in the amount of red blood cell volume lost (80.8 ± 92 vs. 192 ± 120 ml blood for thrombosed vs. patent group, respectively, P < 0.01) over the initial 24 h after OPCAB (Fig. 3). Despite a reduction in bleeding, no differences were noted in the use of blood products or % receiving products between groups. Intraoperative bleeding was found to significantly correlate with the decrease in the pre- vs. postoperative platelet count (R = 0.54, P < 0.001) and function according to the area under the impedance curve for WBA (R = 0.42, P < 0.05) but not for the MA of the TEG trace (R = 0.34, P = NS). Perioperative coagulation assessed by routinely available testing (INR, fibrinogen, platelet count) showed no correlation with blood loss at 24 h (R = 0.10, 0.25 and 0.26, respectively, P = NS). Of all the coagulation tests obtained, a significant correlation with 24 h hemoglobin loss was seen only with a perioperative decline in the maximum amplitude of the TEG trace (R = 0.45, P < 0.05) and fibrinogen levels (R = 0.43, P < 0.05). ROC analysis confirmed that only the MA demonstrated an AUC that was > 0.75, the generally accepted cutoff for an appropriately predictive test (Fig. 5).

4. Discussion

In this study, 'point of care' platelet function tests showed a significant correlation with perioperative hemorrhage and graft thrombosis. The current standard of care for perioperative coagulation monitoring consists of a platelet count, prothrombin (PT) and activated partial thromboplastin (aPTT) times. Neither these routine tests nor other isolated indices of coagulation such as fibrinogen and d-dimer levels have been shown to correlate with bleeding or arterial thrombotic events after CAB [16–18]. We confirm the findings of others regarding the value of platelet function testing using WBA [19] and TEG [8,18] as a means of predicting intra- and postoperative bleeding after cardiac surgery. When modified to detect aspirin responsiveness, these platelet function tests also predicted early graft failure after OPCAB. Given the dual benefit for predicting bleeding and thrombosis, our findings challenge the standard of care for perioperative coagulation monitoring which typically omits platelet function monitoring.

Transfusion protocols incorporating platelet count, fibrinogen level and INR have been shown to reduce the requirement for transfusions after cardiac surgery compared to an empiric strategy [20]. However, these routine tests are insensitive predictors of bleeding [16–18] and changes in perioperative platelet counts show poor correlation with changes in platelet function [21]. Therefore, the mechanism of benefit for protocols based on these assays is unclear. Monitoring coagulation during surgery with the TEG-MA reduces the rate of subsequent reoperation for bleeding in part by helping the surgeon to differentiate ‘surgical’ from ‘nonsurgical’ bleeding [18]. Postoperative TEG monitoring also provides a rational guide for transfusions that has been shown to minimize the rate of unnecessary transfusions [8]. In our study, we were not able to duplicate the work of others [19] demonstrating a role for WBA as a predictor of postoperative bleeding.

A hypercoagulable state after OPCAB provokes concern about compromised patency of vein grafts. Evidence of such a state is based mainly on plasma markers of coagulation [5]. However, heightened activity of this enzymatic cascade or its inhibition with coumadin seems to have little influence on either postoperative bleeding...
the validity of CTA to determine early patency [12]. Although overall platelet reactivity was not significantly different in those with early graft failure, a hypercoagulable state is nevertheless suggested in these patients. First, perioperative hemostasis (i.e. hemorrhage over the first 24 h) was better preserved compared to those with all patent grafts. Second, a significant correlation of these assays with early graft failure was uncovered after substituting agonists shown to be more effective at determining the aspirin effect [18,19]. These data point to a novel role for platelet function testing as a means of defining the therapeutic window for antiplatelet medications.

Clopidogrel is used after OPCAB [7] based on concerns of a hypercoagulable state. However, this more aggressive antiplatelet strategy increases the risk of bleeding. The low incidence of generalized platelet hyperactivity that we detected after OPCAB suggests that routine clopidogrel use is likely to be associated with an unfavorable the risk-benefit ratio in patients with preserved aspirin sensitivity. Perioperative determination of aspirin sensitivity provides a rational way to titrate antiplatelet medications by establishing an individual patient’s postoperative risks. Antiplatelet strategies other than aspirin monotherapy can be safely avoided in those at high bleeding/low thrombosis risk such as those with reduced platelet function or preserved aspirin sensitivity.

The current study has several limitations. First, although TEG and WBA predict bleeding, their sensitivity to detect changes in platelet reactivity is not unchallenged. We have recently incorporated flow cytometry, a more established in vitro platelet assay, into our study to address this concern. Second, the delay in the diagnosis of aspirin resistance until POD#3 in most patients limits the clinical utility of our efforts. We archived patient leukocyte samples during this trial to allow for genetic profiling of subjects with and without graft failure. Expanding our mechanistic understanding from phenotype to genotype may provide the best avenue to prospectively prevent thrombosis before hypercoagulability occurs. Third, several different surgeons enrolled patients in this study which potentially confounded our graft patency and postoperative bleeding results. However, bypass grafts with inadequate blood flow (<10 cm³/min) and waveform (Pl>5) were excluded from analysis and those that developed early failure had no difference in blood flow vs. those that remained patent. While this does not rule out an influence of technique on patency, it suggests that the quality of distal anastomoses of grafts that developed early thrombosis was similar to those that remained patent [9]. Adherence to a strict protocol for coagulation monitoring and blood product use likely minimized the surgeon’s influence on postoperative bleeding. Finally, wide variations in the integrity of the conduit endothelium were found to correlate with graft thrombosis and may have hidden a more subtle effect of platelet function. Elucidating interactions between conduit blood flow, hypercoagulability, and endothelial disruption awaits future analysis of larger numbers of subjects enrolled in our ongoing trial.

In conclusion, serial assessment of platelet function using point of care assays was found to predict both bleeding and thrombotic events after OPCAB. In contrast, routine coagulation tests were unable to discriminate the risk for either of these outcomes. An analysis on platelet function that focused on the aspirin effect was able to identify a cohort of hyperresponsive patients that developed early graft failure despite apparently normal conduits. Titration of perioperative platelet function using clopidogrel and/or other agents may minimize thrombosis in these patients without increasing bleeding risk in the population as a whole. Future efforts to analyze genetic polymorphisms in this cohort may provide further avenues to prospectively intervene at the most optimal time point in these patients.

Acknowledgements

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References

be at risk for stent thrombosis should the agents be discontinued. This finding would suggest that it is safest to continue aggressive antiplatelet agents (e.g. aspirin and plavix) through surgery. On the other hand, if the patient that is treated with an aggressive antiplatelet therapy to prevent stent thrombosis is found to have a low TEG-MA, discontinuing the plavix may be important to avoid the risk of excessive bleeding.

Dr R. van Eps (Maastricht, Netherlands): A couple of studies showed that in off-pump CAB there is, for example, more thrombin generation after like 24 h, and I was wondering if you did measurements of thrombin generation as a function of coagulation and whether this correlated with the platelet function test and thrombotic risk?

Dr Poston: Yes, that is a plan of future studies. We have saved serum samples every time we have done platelet function testing, and plan on looking at fibrinogen and thrombin levels. The coagulation cascade also plays a role in platelet activation. Their assessment could potentially have some additional value at predicting thrombosis as well.