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# Virchow Triad, but Not Use of an Aortic Connector Device, Predicts Early Graft Failure after Off-Pump Coronary Bypass

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## ABSTRACT

The risk of early thrombosis of coronary artery bypass (CAB) grafts may be increased after off-pump CAB, particularly after the use of an aortic connector device (ACD) to perform the proximal aortosaphenous anastomosis. We have been investigating tools that quantify the risk of early vein graft thrombosis after off-pump CAB on the basis of the Virchow triad of hypercoagulability, endothelial disease, and low conduit flow. These tools were applied in this prospective trial of a heterogeneous group of patients with varying degrees of aortic disease and who received the Symmetry ACD. After controlling for the Virchow risk factor triad, we hypothesized that the ACD does not independently influence graft thrombosis. There was no statistically significant difference in the early thrombosis rates of vein grafts connected with an ACD versus hand-sewn grafts (6.7% versus 6.5%). We found a wide range of graft flow measurements, platelet function, and vein endothelial phenotypes in patients with traditionally hand-sewn vein grafts and with grafts connected with an ACD in patients with a wide range of ascending aortic atherosclerosis. The perioperative combination of platelet hyperreactivity, marginal graft flow, and endothelial disease proved to be highly predictive of early graft failure as seen with postoperative computed tomographic angiography.

## INTRODUCTION

Early thrombosis of coronary artery bypass (CAB) grafts may be increased after off-pump CAB (OPCAB) [Gundry 1998, Khan 2004], particularly after the use of an aortic connector device (ACD) to perform the proximal aortosaphenous anastomosis [Traverse 2003, Cavendish 2004]. A causal relationship between early venous graft thrombosis and either OPCAB or the ACD is difficult to ascertain without an established mechanism. OPCAB has been said to promote thrombosis by means of a postoperative hypercoagulability that is not checked by the anticoagulating effect of cardiopulmonary bypass. Surprisingly little evidence supports this conventional wisdom. Plasma coagulation indices have been demonstrated to be elevated with OPCAB compared with on-pump CAB [Mariani 1999]. The superior efficacy of perioperative aspirin [Stein 1995] versus warfarin sodium (Coumadin) [POST CABG Investigators 1997] at improving venous bypass graft patency suggests that platelets play a more central pathogenic role than plasma coagulation factors. In contrast to the well-established link between platelet hyperreactivity and thrombosis of the native coronary artery or inside coronary stents, little data exist on the role of the platelet in bypass graft failure. A comparison of the ACD with a coronary stent has been invited by the requirement of intraluminal metal in both devices and by studies showing an increased risk of acute and subacute thrombosis of grafts connected with an ACD. However, these data are based on retrospective reports of symptomatic patients and are susceptible to reporting bias.

Ongoing randomized trials comparing the ACD to hand-sewn proximal anastomoses will provide some needed answers, but the exclusion of patients with severely diseased ascending aortas from these trials limits the relevance of their findings. We have been investigating tools that quantify the risk of early vein graft thrombosis after OPCAB on the basis of the Virchow triad of hypercoagulability, endothelial disease, and low conduit flow. These tools were applied in this prospective trial of a heterogeneous group of patients with aortic disease ranging from none to severe and who received the Symmetry ACD (St. Jude Medical, St. Paul, MN, USA). After controlling for the Virchow risk factor triad, we hypothesized that the ACD does not independently influence graft thrombosis.

## METHODS

These data were derived from 2 ongoing prospective trials performed at a single center (University of Maryland, Division of Cardiac Surgery). The patients in the group that received the Symmetry ACD were from a prospective cohort study initiated in October 2002. Patients were eligible if they were referred for isolated coronary artery surgery and their cases were deemed appropriate for an off-pump approach. The traditional criterion for the use of an ACD, ie, severe ascending aorta or aortic arch atherosclerosis, was not a requirement for enrollment in this study. The patients in the control group who received hand-sewn proximal anastomoses were obtained from an ongoing prospective randomized trial of aprotinin in OPCAB that was initiated in February 2003.

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The exclusion criteria for both trials were an age less than 18 years, an indication for additional surgical procedures, an inability to provide written informed consent, a creatinine level >2.0 mg/dL, and a history of complications after diagnostic angiography. Both studies were approved by the University of Maryland institutional review board. Written informed consent was obtained from all patients.

### *Surgical and Perioperative Treatment*

In all patients, the heart was exposed through a median sternotomy incision. Intraoperative heparin was dosed to 3 mg/mL and reversed with protamine according to a heparin management system (Hepcon HMS Plus; Medtronic, Minneapolis, MN, USA). The Octopus stabilizer (Medtronic) was used to facilitate the hand-sewn distal anastomoses. Intracoronary shunts were not used routinely; indications for their use included poor visibility, ST-segment changes, and hemodynamic instability. Veins were harvested by means of an endoscopic method and stored in heparinized blood at 25°C. For every patient, the proximal vein-to-aorta anastomoses were performed first. Strict attention to technical detail was paid for appropriate sizing of the grafts and avoidance of proximal kinking.

All patients received preoperative, perioperative, and postoperative aspirin at 325 mg orally within 6 hours of surgery and daily thereafter. No other postoperative antiplatelet agents were employed. A standardized protocol for immediate postoperative care in the adult intensive care unit focused on avoiding secondary hypercoagulability, which can occur because of acute hyperglycemia or overtransfusion of empiric blood products. This complication was avoided by maintaining strict glucose control between 80 mg% and 120 mg% by means of insulin infusions. Blood product transfusions followed a standardized algorithm based on a physical examination of the operative field at the end of the case, chest tube output during the first postoperative hour, and perioperative thromboelastography (TEG) as reported previously [Shore-Lesserson 1999].

### *Study Procedures: Coagulation*

Perioperative platelet function was assessed at baseline (prior to skin incision), postoperatively (after skin closure), and on postoperative days 1 and 3. For each of the assays described below, the 95% reference interval was estimated from the results obtained from 10 healthy volunteers. Hypercoagulability was defined by finding a platelet function that was greater than the 95% reference interval for any of these tests at any time point.

**Thromboelastography.** We used 360 μL whole blood and the TEG system (Haemoscope Corporation, Niles, IL, USA) to monitor platelet reactivity as the maximum amplitude of the viscoelasticity trace of a blood clot activated by kaolin.

**Hemostatus (Medtronic).** The "channel 5 clot ratio" or the ratio of the activated clotting time seen after adding 12.5 nM platelet-activating factor versus that after no added platelet-activating factor (clot ratios of channel 5 versus channel 1) was used to assess hypercoagulability, given prior effectiveness in predicting bleeding.

**Whole Blood Aggregometry.** An aggregometer (Chronolog Corporation, Havertown, PA, USA) was used to assess impedance changes at 6 minutes following the addition of 1 μg/mL and 5 μg/mL collagen to blood samples containing 3.8% citrate.

**Serum Indices of Coagulation.** The activity of the coagulation cascade was screened by using the perioperative partial thromboplastin and TEG "*r*" times (intrinsic cascade) and fibrinogen and the international normalized ratio (extrinsic cascade). A quantitative D-dimer assay was used to assess fibrinolysis.

### *Endothelial Disease/Damage*

Discarded segments from each bypass graft were procured in the operating room and immediately processed for further analysis of endothelial phenotype. For immunohistochemical analyses, segments were frozen in liquid nitrogen in O.C.T. compound (Sakura Finetek USA, Torrance, CA, USA) or fixed in 10% formalin prior to paraffin embedding. Thrombomodulin and tissue factor were assessed with monoclonal antibodies. For enzyme-linked immunosorbent assay (ELISA) analysis, the endothelial layer was isolated from the vein segment and homogenized. Plasminogen activator inhibitor 1 (PAI-1), CD31, and tissue plasminogen activator (tPA) levels were detected by means of ELISA kits. Endothelial disease was defined by an increase in prothrombotic antigen (PAI-1 and tissue factor) and a decrease in fibrinolytic antigen (thrombomodulin and tPA) levels normalized against the level of CD31 expression. Immunohistochemistry results were evaluated on a scale of 0 to 3. The percentage of endothelial integrity was determined by immunohistochemical analysis for CD31 using an image analysis system (AxioVision 3.0, Axioskop Imaging System; Carl Zeiss, Göttingen, Germany).

### *Graft Flow*

After the proximal aortosaphenous anastomosis was created, an objective assessment of graft inflow was provided by a timed release of the occluding clamp placed on each vein graft as flow was monitored. After the distal saphenocoronary anastomosis, further flow measurements were obtained for quality control and to quantify other nontechnical graft defects. Marginal flow was defined as <20 mL/min. Poor outflow was defined by a graft flow of <20 mL, a pulsatility index >5, and a percent diastolic flow of <50% with the native coronary artery occluded. Competitive flow was defined by a graft flow that decreased by >10 mL/min and to <20 mL/min in the absence of native coronary artery occlusion. Grafts with flow rates <10 mL/min that did not improve after anastomotic revision (n = 2) were excluded from analysis.

### *Graft Patency Follow-up*

On postoperative day 5, native coronary and bypass graft angiography analysis was obtained with a noninvasive, 16 detector–row, spiral computed tomography (CT) scanner (420 ms rotation, 100-150 mL contrast agent IV at 5 mL/s). Retrospective electrocardiographic gating was performed for image reconstruction to minimize cardiac motion artifacts. Volumetric reconstruction provided a 3-dimensional display

Vein Bypass Graft Patency on Postoperative Day 5

| Group | Grafts, n | Grafts Evaluated, n (%) | Thrombosed Grafts, n (%) |
|---|---|---|---|
| Symmetry aortic connector device | 81 | 75 (93) | 5 (6.7) |
| Hand-sewn proximal | 93 | 93 (100) | 6 (6.5) |

of the coronary bypass grafts for the assessment of early patency by a single blinded expert reviewer (C.W.). Patency was defined as any flow through the 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 on the CT angiogram.

Clinically, graft patency was assessed by a daily assessment of electrocardiograms, hemodynamics, and troponin levels. Troponin I levels were measured at baseline (during the induction of anesthesia), after protamine administration at the end of the surgery, and at 24 and 72 hours. Samples were spun and frozen to –80°C within 30 minutes after collection and were analyzed in batches.

### *Statistical Analysis*

Means (±SD) were used to describe the continuous variables, and frequencies were calculated for categorical variables. Differences between treatment groups were compared for continuous variables by using a 2-sided, type I error Student *t* test or the Mann-Whitney *U* test. The Fisher exact test was used for the analysis of categorical variables. To analyze data from serially collected tests of coagulation and troponin I levels, we used the trapezoidal method to calculate the area under the concentration-time curve for each patient, and treatment-related differences in the area under the curve were then compared by means of the Student *t* test. All reported *P* values are the results of 2-sided tests.

## RESULTS

### *Early Graft Patency and Clinical Course*

The ACD was used for 83 venous bypass grafts placed in 41 patients. Two grafts were excluded from further analysis because of intraoperative flows of <10 mL/min that did not improve with revision. Postoperative CT angiographic follow-up was obtained for 37 patients (93%). Three patients were excluded because of elevated creatinine levels, and 1 patient refused angiography. Early (ie, postoperative day 5) graft thrombosis was demonstrated by CT angiography in 5 of 75 grafts (4 of 37 patients). The control group (hand-sewn proximal anastomoses) consisted of 93 venous grafts placed in 50 patients with CT angiographic follow-up data obtained for all patients. Thrombosis was seen in 6 of 93 grafts (5 of 50 patients). There was no significant difference in the early thrombosis rates of vein grafts connected with an ACD versus hand-sewn grafts (6.7% versus 6.5%; not significantly different by the Fisher exact test) (Table). None of the 4 patients with thrombosed ACD grafts or the 5 patients with hand-sewn grafts had evidence of ischemia by electrocardiography, anginal recurrence, or abnormal hemodynamics. There was no statistically significant difference (comparison of the area under the curve with the Student *t* test) in the postoperative levels of troponin I between the patients who developed thrombosis and the patients with all patent grafts.

### *Effect of Coagulation*

Of the 87 study patients who underwent angiographic follow-up (37 ACD and 50 control patients), a cohort of 42 patients was identified to have hypercoagulability as determined by postoperative in vitro platelet hyperreactivity (Figure 1). This hyperreactivity was seen in 8 (88%) of the 9 patients who developed early vein graft thrombosis and in 33 (42.3%) of the 78 patients with all patent grafts (not significantly different by the Fisher exact test).

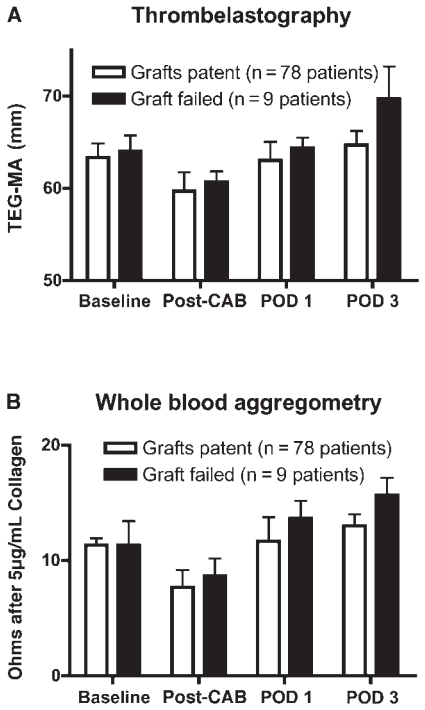


Figure 1. Platelet function was monitored perioperatively by using the maximum amplitude of the thromboelastography trace (TEG-MA) (A) and the resistance developed during impedance aggregometry after the administration of high-dose collagen (B). These panels summarize the data from the Symmetry aortic connector device and hand-sewn anastomosis groups. Even though each case was completed off-pump, a drop in MA and in ohms was seen immediately after coronary artery bypass (CAB). Those patients found to have graft thrombosis on postoperative day (POD) 5 by computed tomographic angiography showed increased platelet reactivity, with statistical significance reached on POD 3.

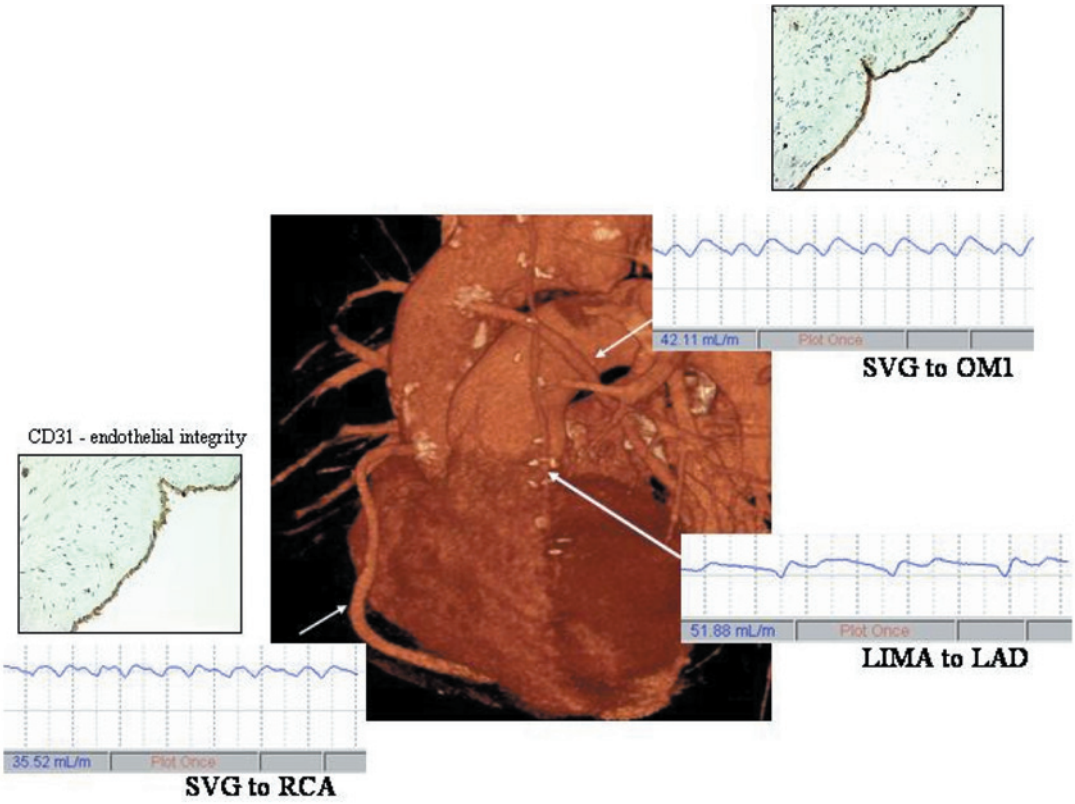


Figure 2. Representative example of data collection for each case. Intraoperatively, conduit blood flow was assessed with a transit-time flowmeter (Transonic Systems, Ithaca, NY, USA). Endothelial integrity was determined just after the proximal anastomosis in the discarded segments of each vein graft by means of immunohistochemical analysis for CD31, an endothelial marker. As illustrated in this example, the use of the Symmetry device did not affect endothelial integrity compared with hand-sewn grafts. Computed tomographic angiograms were obtained on postoperative day 5. SVG indicates saphenous vein graft; OM1, obtuse marginal artery 1; LIMA, left internal mammary artery; LAD, left anterior descending coronary artery; RCA, right coronary artery.

### *Effect of Graft Flow*

Intraoperative flow analyses revealed that none of the grafts that developed thrombosis had evidence of poor conduit inflow or competitive flow. Compared with the 157 patent grafts, the 11 grafts found to be thrombosed on postoperative day 5 showed worse intraoperative blood flows (26.7 ± 5.6 mL/min versus 42.1 ± 4.2 mL/min; $P < .01$) and a higher incidence of grafts meeting the definition of "marginal flow" (85% versus 46%; $P < .03$) (Figure 2).

### *Effect of Endothelial Disease/Disruption*

Venous endothelial disease was quantified by assessing an increase in the expression of prothrombotic marker PAI-1 and/or a decrease in tPA level. Grafts that thrombosed showed no significant difference in PAI-1 expression or in tPA level versus those grafts that remained patent (PAI-1, 3.4 ± 2.1 ng/mL versus 2.3 ± 1.1 ng/mL; tPA, 4.3 ± 2.2 ng/mL versus 5.6 ± 4.3 ng/mL) (Figure 3). The results of immunohistochemical analyses of abnormal expression of tissue factor (ie, >1+ on the endothelial layer) and thrombomodulin (ie, expression absent on the endothelium) were also not significantly different between the groups (71% versus 48% of grafts). A prothrombotic phenotype was seen in 6 of the 9 grafts that failed, compared with 33 of the 157 patent grafts (difference not statistically significant). According to CD31 staining, endothelial disruption was similar in thrombosed and patent grafts (31% ± 20% versus 22% ± 11% disruption; difference not statistically significant). No increase in endothelial disruption was seen after vein loading onto the ACD, as evidenced by comparison with hand-sewn vein segments (25% ± 15% versus 20% ± 14% disruption; difference not statistically significant) (Figure 4).

### *Virchow Triad*

A combination of hypercoagulability, marginal graft flow, and endothelial disease/disruption was seen in 5 of the 9 grafts that thrombosed versus 29 of the 157 patent grafts ($P < .03$, Fisher exact test).

## DISCUSSION

Initially described in the 1800s, the Virchow triad remains the theoretical framework for understanding any intravascular thrombotic event. We found a wide range of graft flow measurements, platelet function, and vein endothelial phenotypes in patients with traditionally hand-sewn vein grafts and

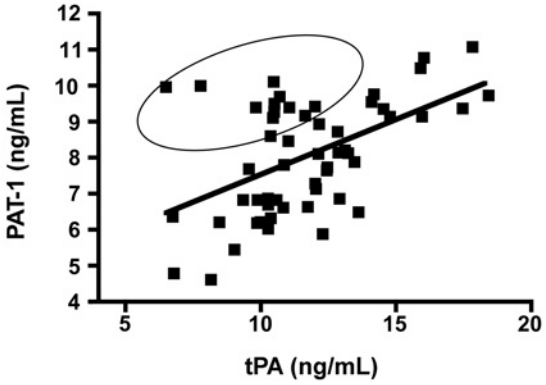


Figure 3. In addition to immunohistochemistry, discarded saphenous vein segments from each graft were homogenized for enzyme immunosorbent assay analysis of tissue plasminogen activator (tPA) and plasminogen activator inhibitor 1 (PAI-1). Twelve vein grafts had an increased ratio of PAI-1 to tPA, 5 of which developed early thrombosis ($P$ = .08, Fisher exact test).

with grafts connected by an ACD in patients with a wide range of ascending aortic atherosclerosis. The perioperative combination of platelet hyperreactivity, marginal graft flow, and endothelial disease proved to be highly predictive of early graft failure as seen with postoperative CT angiography.

The risk of stroke is avoided by typically focusing OPCAB and ACD use on patients with high-grade aortic atherosclerosis [van der Linden 2001, Scarborough 2003]. A severe atherosclerotic burden is an established marker of hypercoagulability [Stehbens 1992, FitzGerald 1997], systemic endothelial disease, and diffuse coronary disease that is often associated with poor coronary targets [Nihoyannopoulos 1993] and poor conduit runoff after aortocoronary bypass. Furthermore, patients with severe vascular disease have also been shown to be at an increased risk of deep venous thrombosis [Prandoni 2003]. The presence of thrombus within the saphenous vein significantly alters endothelial viability [Kawai 2003]. In our study, use of the ACD did not influence early graft patency. Prior reports of reduced early patency after ACD use are likely best explained by the strong association of aortic atherosclerosis and this triad. However, without the data on these variables from these studies, our assertion remains speculative.

An additional concern based on the stent analogy is the possibility of a delayed "restenosis" of the ACD at 4 to 6 months. The recurrent nature of this finding has led some investigators to initiate systemic rapamycin therapy [Traverse 2003]. Although supported by autopsy analyses showing neointimal hyperplasia at the ACD sites, these data are again derived from retrospective reports of symptomatic patients. Another more plausible explanation for delayed graft problems is the technical difficulty in creating an ACD anastomosis with the required 90° angle off the aorta, increasing the chance for graft kinking or turbulent flow (Figure 4). In addition to being linked with early thrombosis, platelet function is thought to be central in coronary stent restenosis. A planned 6-month follow-up study of the ACD patients with early patency will allow the assessment of a correlation between early perioperative Virchow triad and delayed graft problems.

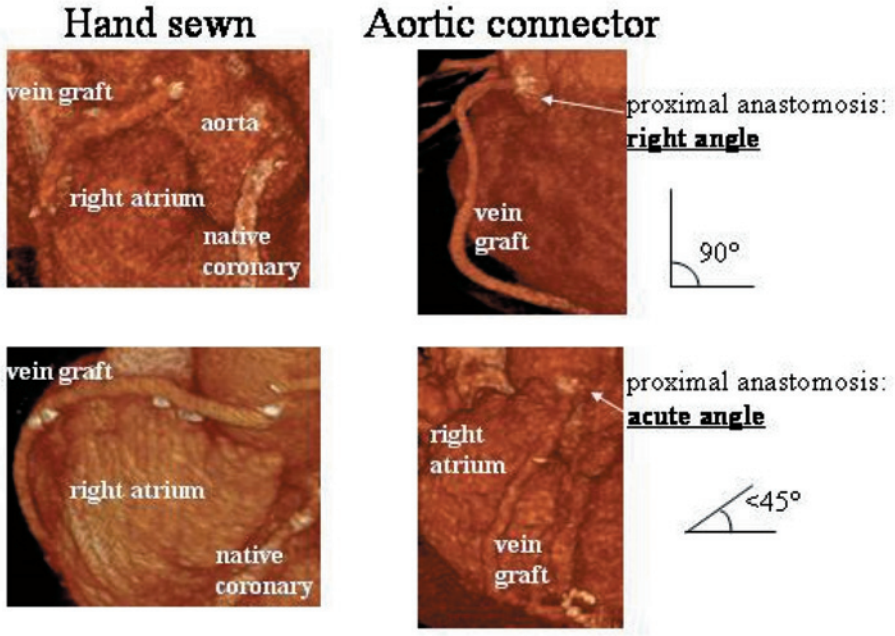


Figure 4. Examples of the difficulty in creating a 90° anastomosis with the Symmetry device to a right-sided coronary target. The hand-sewn grafts take an acute angle off the aorta and are typically placed behind the right atrium to protect against kinking after chest closure. However, the device grafts must take a course in the right atrioventricular groove. The top right example demonstrates the recommended course. The bottom right case illustrates a device graft that is patent on postoperative day 5 but takes an acute angle at the aortosaphenous anastomosis. This orientation may affect graft patency during midterm follow-up.

Multichannel CT angiography is particularly well suited to perform this follow-up evaluation. Recent advances in cardiac software eliminate the metallic artifact produced by the Symmetry ACD and enable reconstruction of data in any angle desired. Unlike conventional angiography, CT angiography has the ability to display the vessel wall as well as the lumen. This capability may differentiate proximal graft kinking from intimal hyperplasia. Standard angiography is insensitive to this hyperplasia because of a well-known compensatory vasodilation that grafts develop during the initial disease phases.

A growing understanding of the role of hypercoagulability in early (and potentially delayed) graft problems provides a rationale to develop new postoperative anticoagulation regimens. In this study, patients were given only aspirin. Clopidogrel when added to aspirin prior to coronary stent implantation has reduced the incidence of acute stent thrombosis to ⅒ of the former value. Many surgeons add clopidogrel to the postoperative regimen of OPCAB patients, particularly those who have been treated with an ACD, on the belief that a similar protective effect might be expected against vein graft thrombosis [D'Ancona 2001]. However, increasing anticoagulation therapy is not harmless in postoperative patients. A preoperative regimen of aspirin and clopidogrel provokes a significant risk of bleeding and a need for reexploration [Yende 2001, Hongo 2002]. Delaying the initiation of clopidogrel until after OPCAB to reduce its influence on bleeding (ie, desired hemostasis) is likely to be balanced by a decrease in effectiveness against graft thrombus formation (ie, undesired hemostasis). One way to address this dilemma is by targeting more aggressive perioperative antiplatelet agents solely to those patients who demonstrate overreactive platelets and by withholding this regimen from those at low risk. Identifying hypercoagulability or resistance to antiplatelet therapies will focus anticoagulation strategies toward optimizing graft patency without increasing the risk of postoperative hemorrhage for the population as a whole.

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