Endothelial injury and acquired aspirin resistance as promoters of regional thrombin formation and early vein graft failure after coronary artery bypass grafting

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Objective: The predominant mechanism of early graft failure after coronary artery bypass grafting remains in doubt. Aspirin administered in the initial hours after coronary artery bypass grafting improves graft patency, implicating prostanoid synthesis in the pathogenesis. We hypothesized that synergy between endothelial disruption in the venous conduit and aspirin resistance would cause vein graft failure.

Methods: Aspirin resistance, defined by diagnostic findings on at least two of three separate assays, was serially assessed in 225 patients undergoing off-pump coronary artery bypass grafting. Endothelial cell integrity was determined in surplus segments obtained from 408 vein grafts. The deposition of intraluminal thrombin within the vein was determined by comparing serum F1.2 levels between the coronary sinus and the aorta after grafting. Intraoperative blood flow in the grafts was measured with transit-time technology, and patency was assessed with electrocardiographically gated multichannel computed tomographic coronary angiography on day 5. Aspirin was the sole antithrombotic agent used during the study.

Results: Thrombosed grafts (16/408) showed more endothelial cell loss at the time of grafting than did those grafts that remained patent (10.8% ± 21.5% vs 51.4% ± 39.1% integrity, $P < .01$). Aspirin resistance occurred in 67 patients (30%). Graft thrombosis was associated with aspirin resistance ($P < .04$) and reduced endothelial integrity ($P < .01$). These factors coexisted in 14 of 16 grafts that failed and were associated with elevated coronary sinus F1.2 levels.

Conclusion: Aspirin resistance and relatively compromised venous endothelial cell integrity together marked patients whose vein grafts failed within days after off-pump coronary artery bypass grafting. These observations form a basis for identifying patients at risk and developing approaches to prevent vein injury or to selectively intervene in high-risk circumstances.

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Conditions that create nonlaminar or sluggish flow within the saphenous vein graft (SVG)—such as a large size mismatch between the conduit and coronary target,[1] intrinsic disease in the outflow bed, or an abnormal anastomotic angle[3]—influence SVG thrombosis after coronary artery bypass grafting (CABG). The most important cause of early attrition is thought to be inaccurate microvascular technique, particularly for grafts performed during off-pump CABG (OPCAB).[4] However, randomized trials have shown no consistent influence of OPCAB on SVG thrombosis.[5-7] In fact, we have found that SVG grafts still fail despite careful intraoperative screening for problems in technique with transit-time flow measurements.[8] These observations implicate alternative features in the pathogenesis of graft thrombosis, such as conduit quality and systemic thrombogenicity.

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CS = coronary sinus
CT = computed tomography
EC = endothelial cell
MA = maximum amplitude
OPCAB = off-pump coronary artery bypass grafting
PFA-100 = platelet function analyzer
SVG = saphenous vein graft
TEG = thromboelastography
WBA = whole-blood aggregometry

Endothelial cell (EC) integrity is known to be frequently impaired in veins used for bypass,[9] and the proportion of denuded surface area correlates directly with reduced graft patency.[10] Aspirin, a well known therapy for preventing graft failure,[11] insufficiently inhibits platelets in many patients after cardiac surgery.[12] These risk factors have rarely been evaluated in a systematic way after CABG and never for how they influence SVG patency in aggregate.

SVG thrombosis, variously reported at between 5%[6] and 40%[7] at 1 year, accounts for a substantial proportion of the well-known limitations of long-term patency associated with this conduit. Because of this demographically important opportunity for practice improvement, we initiated a prospective investigation of the mechanism of SVG thrombosis in patients undergoing OPCAB at a single institution. Preliminary analysis of this data set revealed that aspirin resistance[13] and EC disruption[10] were each associated with an increased risk of acute SVG failure. The hypothesis of this more current analysis of 250 unselected patients undergoing OPCAB was that these two risk factors interact to promote rapid thrombin formation within the SVG, synergistically increasing the risk of early thrombosis.

Patients and Methods

Patient Enrollment and Data Management

After institutional review board approval was obtained, all subjects provided informed consent before enrollment. From November 2002 until December 2004, a total of 410 patients were screened, and 133 patients excluded from the study for creatinine level 2.0 mg/dL (n = 43), requirement for cardiopulmonary bypass (n = 37), refusal of consent (n = 32), and inability to obtain valid consent because of patient condition or emergency nature of surgery (n = 21). After enrollment, computed tomographic (CT) angiography was not performed in 52 patients because of heart rate greater than 100 beats/min or creatinine level greater than 2.0 mg/dL (n = 28), patient withdrawal of consent (n = 12), unavailability for follow-up (n = 10), and patient death without an autopsy to confirm bypass graft patency (n = 2).

Demographic data, preoperative risk factors and medications, and intraoperative and postoperative data were prospectively recorded onto Teleform case report forms (TELEform Elite; Cardiff Software Ltd, Vista, Calif), electronically scanned, and imported into a relational database.

Surgical Technique

Four surgeons (R.P., J.B., J.G. and B.G.), experienced in OPCAB, enrolled patients. After median sternotomy, the left internal thoracic artery was used in all patients; the saphenous vein was harvested with an endoscopic (n = 363 venous conduits; VasoView5; Guidant Systems, Inc, Minneapolis, Minn) or open (n = 45 venous conduits) approach, according to anatomic considerations. Conduits were flushed with heparinized saline solution after harvest, with no methods used to control the distending pressure. The anastomoses were performed first proximally with a partial occluding aortic clamp and then distally with suction-based exposure and stabilizing devices (Octopus 4.3; Medtronic, Inc, Minneapolis, Minn). Because of this protocol, little variation was present in the length of time from when each SVG was initially placed in solution saline storage until the proximal anastomosis was completed and the graft was reperfused with oxygenated blood (i.e. ischemic times similar). It was reperfused with oxygenated blood (proximal anastomosis completed). Heparin was given initially and every 30 minutes at a dose calculated to obtain an activated clotting time longer than 300 seconds and a heparin level of 2 IU/mL according to protamine titration (HMS heparin assay cartridges; Medtronic). Heparin was reversed by half the dose of protamine calculated by heparin-protamine titration. Preoperative aspirin (325 mg/d orally) was continued and given within 6 hours of surgery as the sole antithrombotic agent used in the study.

Intraoperative Blood Flow Analysis

Blood flow and flow waveform were measured in each graft with transit time ultrasonography (Transonic Systems, Inc, Ithaca, NY). Waveforms were analyzed for pulsatility index ([maximum blood flow − minimum blood flow]/mean blood flow) and percentage diastolic flow with data acquisition software (WinDaq; DATAQ Instruments, Inc, Akron, Ohio). Grafts with flow less than 10 mL/min and pulsatility index greater than 5 despite anastomotic revision were excluded from analysis (n = 2).

Immunohistochemical Staining and Enzyme-Linked Immunosorbent Assay

Surplus segments obtained from each bypass conduit just before the distal anastomosis were stored in Hanks balanced salt solution, embedded in cutting compound (Tissue-Tek O.C.T., Electron Microscopy Sciences, Hatfield, Pa) and then frozen in liquid nitrogen. The percentages of the luminal circumference staining for the endothelial marker CD31 (R&D Systems, Minneapolis, Minn) and tissue factor (United States Biological, Swampscott, Mass) were analyzed as described previously[10] (Figure 1).

Assays for Coagulation

Tests of coagulation (international normalized ratio, partial thromboplastin time, levels of fibrinogen and the peptide fragment F1.2, and quantitative D-dimer levels) were obtained from citrated blood samples drawn just before skin incision (baseline), just after protamine administration, and on postoperative days 1, 3, and 30. Platelet-poor plasma was obtained from a coronary sinus (CS) blood sample drawn by direct puncture with a 21-gauge needle

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