Endoscopic Venous Harvesting by Inexperienced Operators Compromises Venous Graft Remodeling

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Background. Endoscopic vein harvesting (EVH) is the standard of care for coronary artery bypass grafting (CABG) in the United States, but recent comparisons with open harvesting suggest that conduit quality and outcomes may be compromised in EVH. To test the hypothesis that problems with EVH may relate to its learning curve and conduit quality, we analyzed the quality and early function of conduits procured by technicians with varying experience in EVH.

Methods. Experienced (more than 900 cases, n = 55 patients) and novice (less than 100 cases, n = 30 patients) technicians performed EVH during CABG. Subsequently, optical coherence tomography (OCT) was used to examine the conduits for vascular injury, with segments identified as injured being further examined for gene expression with an array of genes related to tissue injury. Conduit diameter was measured intra- and postoperatively (day 5 and 6 months, respectively) with OCT and computed tomographic angiography.

Results. Endoscopic vein harvesting by novice harvesters resulted in a greater number of discrete graft injuries and greater expression of tissue-injury genes than EVH done by experienced harvesters. Regression analysis revealed an association between shear stress and early dilation of engrafted vessels (positive remodeling) ($R^2 = 0.48$, $p < 0.01$). Injured veins showed blunted positive remodeling at 5 days after harvesting and a greater degree of late lumen loss at 6 months.

Conclusions. Under normal conditions, intraluminal shear stress leads to positive remodeling of vein grafts during the first postoperative week. Injury to conduits, a frequent sequela of the learning curve for EVH, was a predictor of early graft failure and of blunted positive remodeling and greater negative remodeling of endoscopically harvested vein grafts. Given the current annual volume of cases in which EVH is used, rigorous monitoring of the learning curve for this procedure represents an important and unrecognized issue in public health.

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After initial studies showed dramatically improved wound outcomes with its use, and comparable patency during its use in coronary artery bypass grafting (CABG) [1–4], endoscopic vein harvesting (EVH) rapidly became more popular than the open technique of vein harvesting. However, recent postmarketing data have suggested poorer graft patency and poor clinical outcomes within the first year after CABG done with EVH than with open harvesting [5–8]. Harvesters inexperienced with EVH show a tendency to more forcefully manipulate the vein being harvested in an effort to gain better endoscopic visualization and exposure of the vein. Technique in EVH improves with experience and follows a learning-curve process seen with other technically challenging procedures. A greater risk of endothelial injury to saphenous vein grafts (SVG) during this learning curve may help explain an associated risk of early graft thrombosis for patients undergoing EVH as a source of these grafts.

Saphenous vein grafts can also undergo a gradual loss of luminal caliber during the first 6 to 12 months after CABG, as a result of negative or constrictive remodeling and neointimal hyperplasia [9, 10]. Meticulous preservation of the tissue surrounding SVG through use of the so-called "no-touch" open harvesting technique avoids adventitial trauma and significantly improves SVG patency [11, 12]. This suggests that adventitial injury during

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Abbreviations and Acronyms

CABG = coronary artery bypass surgery
CT = computed tomography
Ct = cycle threshold
CTA = (cardiac) computed tomography angiogram
EVH = endoscopic vein harvest
NIH = National Institutes of Health
OCT = optical coherence tomography
PA = physician's assistant
PCR = polymerase chain reaction
SVG = saphenous vein graft

the procurement of SVG is a factor contributing to negative remodeling.

Our laboratory, the Division of Cardiac and Thoracic Surgery at the University of Arizona, has established the use of optical coherence tomography (OCT) and computed tomographic angiography (CTA) as high-resolution tools for identifying injury within the bypass conduit intraoperatively and monitoring the patency and luminal diameter of SVG after grafting. To test the hypothesis that problems with EVH may relate to its learning curve, we used these tools to analyze whether the degree of SVG injury after the procurement of these grafts influenced the patency and vascular function of the resulting conduits.

Material and Methods

Patient Enrollment

Approval was obtained from the institutional review boards at two institutions for a prospective observational study of patients undergoing isolated CABG. The inclusion criterion for this subset analysis was EVH during CABG. Exclusion criteria were the inability to obtain follow-up CTA because of a serum creatinine concentration above 2.0 mg/dL, allergy to radiographic contrast medium, CABG done on an emergency basis, or a prior bleeding diathesis. Demographic data, preoperative risk factors and medications, and intraoperative and postoperative data for the study patient population were imported prospectively into a relational database. All of the patients in the study provided prospective informed consent for their participation.

Surgical Technique

All patients underwent off-pump CABG via median sternotomy done by a single surgeon. All EVH procedures were performed concurrently with harvesting of the left internal mammary vein by physician assistants (PA) using standardized technique (VasoView 6.0, Maquet Corp, Wayne, NJ). A heparin bolus was given to each patient before insufflation with CO_2 at a pressure of 10 to 12 mm Hg in the perivenous tunnel created endoscopically using the dissection tip. Venous branches were divided with bipolar electrocautery at a setting of 20 W. Proximal ligation of the saphenous vein was performed through a separate stab incision. At the beginning of the study, the PAs performing EVH were separated into a novice group (n = 5) who had done EVH in fewer than 100 prior cases at a frequency of fewer than 3 cases per month and an expert group (n = 2) who had done EVH in more than 900 prior cases at a frequency of more than 30 cases per month.

After grafting, blood flow was measured in each SVG through the use of transit-time ultrasonography (Medistim, Oslo, Norway). Mean shear stress was calculated for each conduit according to the Hagen-Poiseuille formula, $Tw = 4\mu Q/\pi r^3$, where Tw is shear stress in dynes/cm^2; Q is the mean volumetric flow; μ is the viscosity of blood, which was assumed to be 0.035 poise [13]; and r is the luminal radius in centimeters, as measured through OCT imaging with the SVG distended to 100 mm Hg pressure.

Intraoperative Image Acquisition and Analysis

After being harvested, conduits were cannulated on a sterile back table with a Y-adapter of 0.118-inch ID (Gateway TM Plus Y-Adapter, Boston Scientific, Natick, MA) to allow flushing with a Plasma-Lyte solution (Baxter International, Deerfield, IL) containing heparin, glyceryl trinitrate, and verapamil at a controlled pressure of 100 mm Hg. A size 1F OCT catheter (Image Wire, Light Lab Imaging, Westford, MA) was inserted into the lumen of the SVG and images were acquired during a manual pullback of the catheter at a rate of 1mm/s. Because the OCT wire emits a red light that was easily visualized through the vessel wall, the location of the wire can be identified in real time so that portions of the conduit identified as abnormal can be registered to the portions chosen (or excluded) from grafting.

A technician in the operating room acquired the OCT data, which were also used for intraoperative image-guided biopsy. Two separate technicians, who were blinded to their group assignment, analyzed each OCT image independently after the CABG operation. Conduit injury during procurement was categorized as isolated to the intima and minor when the resulting abnormality was restricted to the ostium of branch points, or as severe when the intimal injury involved the luminal surface. Deep-vessel injury was diagnosed with OCT when a separation of the intimal layer from the medial or adventitial layer of the harvested vessel was noted (with or without an intimal tear). Adventitial injury was diagnosed as discontinuity in the external elastic lamina. A composite injury score was calculated as the sum of all discrete injuries noted within each conduit.

Image-guided biopsy specimens were obtained from the affected vessel segments, frozen in cutting compound (Tissue-Tek O.C.T., Redding, CA), and sectioned at 5 μm. The specimens were stained with a mouse monoclonal antibody to CD31 (anti-CD31/PECAM-1 MAb, mouse IgG1, R&D Systems, Minneapolis, MN) to determine endothelial integrity using previously described histochemical techniques [14], or with Verhoeff's stain to assess vascular architecture. The external elastic lamina was identified as a thick layer of elastic fibers immediately adjacent to the media. Adventitia was defined as the loose connective tissue external to the external elastic lamina.

Analysis of Graft Function

Cardiac CTA was done with a 64-multidetector computed tomographic (MDCT) scanner (Philips Medical Systems, Andover, MA) on postoperative day 5, and was interpreted by a thoracic radiologist using axial and reconstructed curved planar images. Saphenous vein graft patency was defined as any blood flow through the length of the graft regardless of the presence of stenosis [15]. Conduit diameter was calculated intraoperatively (with OCT) and on postoperative day 5 and at 6 months (with CTA) after CABG by obtaining the mean of three separate measurements made on the proximal, middle, and distal segments of the portion of conduit used for grafting. Positive and negative remodeling were defined as a postoperative mean SVG diameter that was greater or smaller, respectively, than the baseline diameter of the respective graft as determined with intraoperative OCT.

RNA Extraction and Reverse Transcription

Total RNA was extracted from image-guided biopsies of SVG using the miRNeasy Mini kit (Qiagen, Valencia, CA). Genomic DNA was removed on a column with the RNase-Free DNase Set (Catalogue #7924, Qiagen, Valencia, CA) by treatment with ribonuclease-free deoxyribonuclease I (Qiagen). The samples of total RNA were quantified through Nanodrop spectrophotometry using the ND-1000 (Thermo Scientific, Wilmington, DE), and the quality of each RNA sample was validated by measuring the ratio of its absorbance at 260 nm to that at 280 nm (A260/A280) with the Nanodrop spectrophotometer. The integrity of the RNA in each sample was measured with an Agilent-1000 Bioanalyzer (Agilent, Santa Clara, CA). Complementary DNA was synthesized with the High Capacity RNA-to-cDNA Master Mix With No RT Control Kit using the (Applied Biosystems, Foster City, CA).

Gene Array for Quantitative Polymerase Chain Reaction

The tissue stress-response array test was done with the ABI 7500 Fast Real-Time PCR system (Applied Biosystems, Foster City, CA) according to the manufacturer's instructions (Qiagen, Valencia, CA; Lonza, Walkersville, MD). Raw data on tissue stress-response were collected as cycle threshold (Ct) values that were then normalized with housekeeping genes used as the expression background. Subgroup analysis was done on the basis of whether the vessel from which the biopsy was derived showed evidence of positive or negative remodeling, and according to the severity of injury noted in other portions of the vessel with OCT. Regression analysis was also done, to determine the correlations between the endpoints described above and the expression levels of each gene studied.

Statistical Analysis

The primary endpoint of the study was to establish a level of injury during graft procurement with EVH that was likely to have a significant effect on the vascular function of patent bypass conduits. Baseline and perioperative variables for patients assigned to the two study groups were compared with the use of Student's *t* test for continuous variables and the χ^2 test for categorical variables. On the basis of findings in previous studies of early vein remodeling, we included shear [16], serum lipids [17], endothelial integrity [18], and the expression of tissue-injury marker genes as candidate predictors of such remodeling. Single and multivariate binary and logistic regression analyses were done to determine predictive relationships among variables.

The accuracy of OCT-based diagnoses of vascular injury was validated through histopathologic analysis of corresponding regions of interest based on OCT examinations, and by determining interobserver agreement through the use of Cohen's kappa coefficient. Statistical analysis was done with SPSS version 17.0 (SPSS, Chicago, IL); significance was set at $p < 0.05$.

Results

Experience With Endoscopic Venous Harvesting

Whether performed by the novice group (n = 30 SVG) or the expert group (n = 55 SVG) of PAs, EVH was completed in all cases without the need for open conversion. Conduits from the novice and expert groups had similar total lengths (33 vs 34 cm, respectively, $p = 0.880$), and required similar harvesting times (32.4 vs 31.8 minutes, respectively, $p = 0.640$) and an equivalent number of repair sutures (0.5 vs 0.7 sutures per vein, $p = 0.750$). Patients who received SVG harvested by the novice and expert groups had similar baseline characteristics, comorbidities, and early and late postoperative outcomes (data not shown), with the exception of the incidence of unstable angina, which was greater among patients whose SVG were harvested by the expert group (68.09% vs 26.67%, expert vs novice group, respectively, $p < 0.001$). Notably, the rate of graft attrition was similar for SVG harvested by the novice and expert groups (6.45% vs 4.34% loss at 5 days, novice vs expert group, respectively, $p = 0.552$).

Conduit Injury

Intimal injury around the ostia of conduit branch points (2.48 vs 1.76 injuries per conduit, novice vs expert group, respectively, $p = 0.02$) and disruption of the external elastic lamina (5.37 vs 3.31 injuries per conduit, novice vs expert group, respectively, $p = 0.014$) were more frequent findings with SVG harvested by the novice group than with those harvested by the expert group. This resulted in a significantly higher composite injury score for the novice than for the expert group (injuries per conduit, 7.77 ± 5.28 vs 5.11 ± 3.71, mean ± standard deviation, $p = 0.009$) as well as significantly higher numbers of adventitial injuries (5.37 ± 4.33 vs 3.31 ± 3.13, $p = 0.014$).

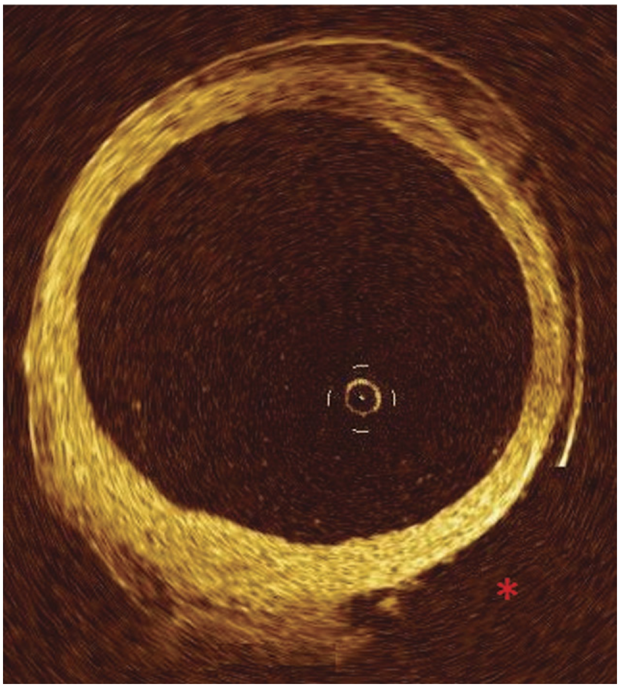

Fig 1. Representation of adventitial tear as seen on optical coherence tomographic imaging of a saphenous vein graft with a significant adventitial tear (red asterisk) with associated denudation of adventitia from the deeper vessel wall.

As compared with a normal SVG, in which the adventitia constitutes the bulk of the vascular wall, there was complete removal of a segment of adventitia extending for 7 cm along the most severely injured conduit in an SVG harvested by the novice group (Fig 1). Less severe instances of adventitial injury included minor separations of the adventitia from the media, associated with focal disruption of the external elastic lamina.

Regions of injury identified by OCT imaging of SVG showed an increased expression of several genes relevant to tissue stress. The composite vessel injury score showed significant correlation with *CXCL2* ($R = 0.748$, $p = 0.053$) and *PDGFA* ($R = 0.784$, $p = 0.037$). The degree of adventitial injury was significantly correlated with the expression of *EGF*, *HSP90AA1*, and *ITGAV* ($R = 0.766$, $p = 0.045$; $R = 0.828$, $p = 0.042$; and $R = 0.773$, $p = 0.042$, respectively). The degree of intimal injury was significantly correlated with the expression of *IL-1B* ($R = 0.881$, $p = 0.020$) and *IL-7* ($R = 0.855$, $p = 0.030$).

Validation of OCT Findings

There was strong interobserver agreement for the diagnosis through OCT of ostial branch injuries (kappa = 0.81), intimal injuries (kappa = 0.89), and deep injuries (kappa = 0.82) of conduits derived from SVG. Histologic analyses of surplus segments of SVG showed a significant correlation between the number of intimal abnormalities detected with OCT and percent endothelial integrity ($R = -0.5$, $p = 0.02$). There was no difference in the degree of endothelial disruption found on histologic examination in areas identified through OCT as having either minor or severe intimal abnormalities.

Relationship Between Shear and Early Dilation

There was a strong relationship between the magnitude of shear force at the time of anastomosis in CABG and the change in vessel diameter (positive remodeling) at 5 days postoperatively ($R^2 = 0.48$, $p < 0.001$) (Fig 2).

Relationship Between Graft Injury and Function

We demonstrated injury scores of 4 or more for the SVG of 16 patients. The baseline clinical parameters of this group were similar to those of the remaining patients who received SVG but had fewer than 4 discrete injuries (Table 1). The serum lipid profiles of the two subgroups with differing SVG injury scores were similar. After distension at 100 mm Hg with a venodilator solution, the baseline diameter of the SVG procured from both subgroups was similar (3.09 ± 0.98 mm vs 2.88 ± 0.72 mm, $p = 0.249$). At 5 days after grafting, the percentage change in diameter of the conduits created with the SVG was strongly associated with shear stress in the subgroup with fewer than 4 injuries ($R = 0.686$, $p < 0.001$). However, this association between early positive remodeling and shear stress was not present in the subgroup with conduits created from SVG having 4 or more injuries ($R = 0.383$, $p = 0.396$). The association between shear stress and early positive remodeling was also stronger for the expert harvester group than for the novice group ($R = 0.718$, $p < 0.001$; $R = 0.531$, $p = 0.028$, respectively). Reduction in luminal diameter at 6 months after CABG

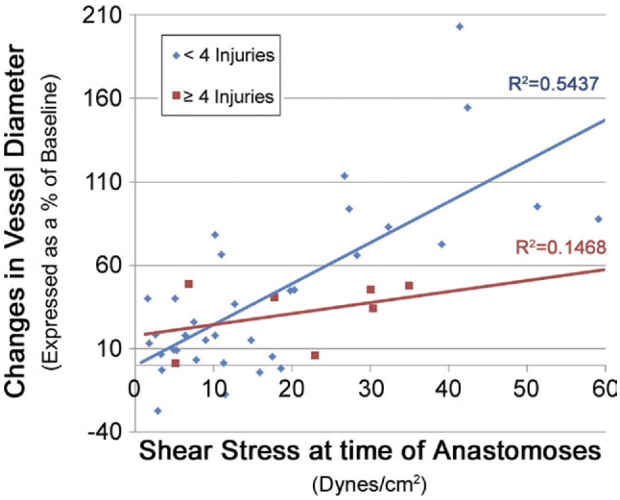

Fig 2. Early relationship (ie, day 5) between shear stress (dynes/cm^2) and positive remodeling of saphenous vein conduits stratified according to the number of injuries found on intraoperative optical coherence tomography. The plots illustrate that luminal shear stress showed a significant relationship to the degree of diameter change noted in conduits with <4 injuries ($R^2 = 0.5437$, $p < 0.0001$; blue line and squares). In comparison, conduits with ≥ 4 injuries ($R^2 = 0.1468$, $p = 0.396$; red line and diamonds) had a blunted dilation response to shear stress.

Table 1. Baseline Characteristics of Groups With and Without Severe Saphenous Vein Graft Injury

Demographic	4 or More Injuries (n = 16)	Fewer Than 4 Injuries (n = 66)	*p* Value
Age (years)	67.1 ± 11.4	65.2 ± 10.9	0.542
Male sex	81.25% (13/16)	83.33% (55/66)	1.00
Number of diseased vessels	3.00 ± 0.00	2.94 ± 0.39	0.208
BMI (kg/m^2)	29.7 ± 6.7	30.0 ± 6.1	0.819
Hypertension	81.25% (13/16)	89.39% (59/66)	0.401
Diabetes mellitus	43.75% (7/16)	45.45% (30/66)	1.00
Dyslipidemia	87.50% (14/16)	78.78% (52/66)	0.726
Active tobacco smoking	31.25% (5/16)	28.78% (19/66)	1.00
Existing renal failure	6.25% (1/16)	1.52% (1/66)	0.354
Prior CVA	6.25% (1/16)	10.61% (7/66)	1.00
PVD	6.25% (1/16)	12.12% (8/66)	0.681
Family history of CAD	25.00% (4/16)	40.91% (27/66)	0.269
Active therapy with ASA	100.00% (16/16)	87.88% (58/66)	0.344
EF (<35%)	31.25% (5/16)	34.85% (23/66)	1.00
Unstable angina	25.00% (4/16)	37.88% (25/66)	0.054

ASA = acetylsalicylic acid; BMI = body mass index; CAD = coronary artery disease; CVA = cerebral vascular accident; EF = ejection fraction; PVD = peripheral vascular disease.

was greater in the subgroup of patients whose grafts demonstrated 4 or more injuries, trending toward significance (Table 2).

Predictors of the luminal diameter of SVG at 6 months included the degree of intimal injury noted intraoperatively ($R = -0.744$, $p = 0.041$), the baseline intimal thickness of a graft on histologic examination ($R = -0.58$, $p = 0.002$), and the degree of positive remodeling on postoperative day 5 ($R = 0.940$, $p = 0.005$) (Fig 3).

Comment

Prior studies have demonstrated a variety of histopathologic abnormalities in SVG harvested through EVH [19], but have failed to address whether these abnormalities influence the performance of the harvested vessel as a bypass graft. Our study utilized high-resolution OCT and CTA imaging to identify graft injury within the grafted portion of SVG and to postoperatively follow serial changes in the diameter of the conduit created with the graft. The design of the study allowed a link to be established between severe vascular injury (ie, 4 or more discrete injuries) and abnormal positive remodeling of grafts over the first 5 days after CABG. Saphenous vein grafts spared from injury showed a strong correlation between the calculated intraluminal shear and the degree of graft dilation measured on day 5. In contrast, injured SVG showed little or no vasodilatory response to shear and showed a strong trend toward a greater risk of late lumen loss, or negative remodeling, at 6 months. Lumen loss of grafts within the first year after CABG is critical, because grafts with smaller luminal diameters are more prone to late graft failure [20].

Early positive remodeling occurs in SVG when nitric oxide, prostacyclins, and matrix metalloproteinases are produced locally in response to a chronic increase in intraluminal shear stress in the graft [16, 21]. Animal and clinical studies demonstrate that positive remodeling requires intact endothelium [18, 22] and correlates with improved long-term SVG patency [13]. Impairment of this remodeling response has been attributed to trauma as well as to biochemical and morphologic changes within the graft [16]. To increase their elastic modulus in response to an increase in wall tension, SVG develop wall thickening and stiffening [13, 23]. However, narrowing of the SVG lumen within the first year after CABG is predominantly caused by negative remodeling of the entire vessel rather than by changes in wall thickness and stiffness [10]. Evidence suggests that adventitial injury and the subsequent fibrotic scar response at the site of injury are critical steps in the pathogenesis of negative remodeling of grafts after CABG [24–26]. We documented that the vascular and adventitial injury noted in our SVG were associated with the increased expression

Table 2. Comparison of Outcomes of Saphenous Vein Grafting in Study Groups as Stratified by Injury

Parameter	4 or More Injuries (n = 16)	Fewer Than 4 Injuries (n = 66)	*p* Value[a]
Baseline luminal diameter (mm), mean ± standard deviation	2.77 ± 0.81	2.97 ± 0.84	0.41
Change in luminal diameter vs shear (Pearson's R^2 value)	0.147[b]	0.544	N/A
Mean change in luminal diameter at 6 months (% of baseline diameter)	−30.70 (5.79)	−12.4 (13.82)	0.06

[a] Significance was set at $p < 0.05$. [b] Correlation is nonsignificant.

of genes linked to tissue injury and to a remodeling response (Table 3), corroborating the importance of adventitial injury and a fibrotic scar response in the negative postoperative remodeling of grafts.

As the outermost layer of the vein, the adventitia is exposed to injury by EVH, particularly when novice technicians perform the initial blunt dissection step in this procedure. The ability to insure that the perivascular and adventitial tissues are fully preserved with EVH stands in stark contrast to the open, "no touch" technique of harvesting espoused by Souza and colleagues [11, 12]. Their technique describes the procurement of a full pedicle of fatty tissue completely encircling the vein without dissection of the vessel wall itself. With this as the gold standard for comparison, it is clear that the use of EVH to minimize graft injury so as to procure venous conduits with normal postoperative function requires that the technicians doing the harvesting acquire a higher degree of technical mastery than previously estimated.

Table 3. Summary of Functions of Genes Found to Be Associated With Saphenous Vein Graft Injury

Gene	Function
PDGFA	Angiogenesis Induction of neointimal hyperplasia Possible role in vascular sclerosis
EGF	Stimulation of wound healing at endothelium Smooth-muscle–cell proliferation and invasion
CXCL2	Leukocyte recruitment/chemotaxis Angiogenesis
ITGAV	Mediation of cell-to-cell adhesive interactions Interaction with MMP1 (ITGA2)
HSP90AA1	Protective functions in context of cellular stress Positive modulation of eNOS
IL-1B	Proinflammatory activity Mediates intimal hyperplasia
IL-7	Lymphangiogenesis

CXCL2 = chemokine (C–X–C motif) ligand 2; *ITGAV* = integrin alpha V; *EGF* = epithelial growth factor; eNOS = endothelial nitric oxide synthase; *HSP90AA1* = heat shock protein (HSP) 90 kDa alpha (cytosolic) class A member 1; *IL-1B* = interleukin 1-beta; *IL-7* = Interleukin 7; MMP = matrix metalloproteinase; *PDGFA* = platelet-derived growth factor subunit A.

Indeed, we confirm that technician inexperience increased the risk of abnormalities in the quality and function of vascular conduits procured by EVH. As compared with those harvested by the expert group of PAs in our study, veins harvested by the novice group had significantly more tears identified in their intimal and deep vascular layers. Moreover, the positive remodeling response induced by shear was significantly blunted in veins procured by novices as compared with those procured by the experienced group of PAs in our study. We have demonstrated that the degree of injury sustained by a graft affects its function and early patency [27]. These findings support our hypothesis that the learning curve for EVH influences the quality and function of bypass conduits, and warrant further study to more fully characterize this learning curve.

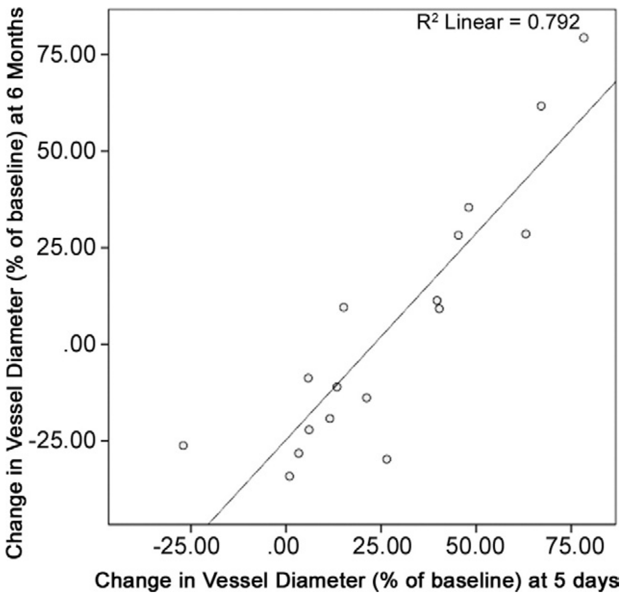

Fig 3. Relationship between change in graft diameter early (day 5) and late (6 months post) as compared to the diameter of the conduit measured intraoperatively (day 0). (post operative day 5) Plot demonstrates a significant relationship (R^2 = 0.792, p = 0.005) of the ability of the conduit to undergo positive remodeling at day 5 and maintain luminal diameter at 6 months.

The strengths of our study were that unlike all prior analyses of the effect of EVH on conduit quality, it quantified injury within the portion of conduit that was chosen for grafting. Previous studies have used sampling of discarded graft material for histologic and microscopic analysis. However, such studies are limited in their ability to permit conclusions that can be generalized to the rest of the graft because they use only a small portion of vessel, and presumably one that is disproportionately poor in quality as compared with the rest of the graft. By comparison, we noted no differences in our two study groups as assessed with the standard learning-curve metrics of the time needed to complete EVH, the number of sutures required for repair of the harvested vein, and the need to convert from EVH to an open harvesting technique. Additionally, our analysis of messenger RNA expression provided evidence that the injury observed in SVG was associated with changes in the cellular biology of the vessel and was not simply an incidental finding.

Our study was limited by its small cohort size and lack of use of conventional angiography for confirming our perioperative findings with OCT and CTA. Without this gold standard we consider the results of our work to be a proof of concept rather than an exhaustive validation of our study protocol. However, defining the natural history and clinical importance of early SVG injury has remained elusive, largely because of the inconvenience of performing serial invasive angiography. In view of the variety of clinical advantages of serial imaging with OCT and CTA, future clinical research that incorporates their use may provide a renewed opportunity to make progress with this type of analysis.

In conclusion, intraluminal shear stress leads to positive remodeling of normal vein grafts during the first week after CABG. Poor conduit quality, a sequela of the learning curve for EVH, was a predictor of early graft failure, blunted positive remodeling, and greater negative remodeling of SVG after CABG. Given the large annual volume of use of EVH, rigorous monitoring of the learning curve for this procedure represents an important and under-recognized public health issue.

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References

1. Yun KL, Wu Y, Aharonian V, et al. Randomized trial of endoscopic versus open vein harvest for coronary artery bypass grafting: six-month patency rates. J Thorac Cardiovasc Surg 2005;129:496–503.
2. Bitondo JM, Daggett WM, Torchiana DF, et al. Endoscopic versus open saphenous vein harvest: a comparison of postoperative wound complications. Ann Thorac Surg 2002;73:523–8.
3. Davis Z, Jacobs HK, Zhang M, Thomas C, Castellanos Y. Endoscopic vein harvest for coronary artery bypass grafting: technique and outcomes. J Thorac Cardiovasc Surg 1998;116:228–35.
4. Puskas JD, Wright CE, Miller PK, et al. A randomized trial of endoscopic versus open saphenous vein harvest in coronary bypass surgery. Ann Thorac Surg 1999;68:1509–12.
5. Shroyer AL, Grover FL, Hattler B, et al. On-pump versus off-pump coronary-artery bypass surgery. N Engl J Med 2009;361:1827–37.
6. Lopes RD, Hafley GE, Allen KB, et al. Endoscopic versus open vein-graft harvesting in coronary-artery bypass surgery. N Engl J Med 2009;361:235–44.
7. Brener SJ, Barr LA, Burchenal JEB, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. Circulation 1998;98:734–41.
8. Alexander JH, Hafley G, Harrington RA, et al. Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. JAMA 2005;294:2446–54.
9. Kaneda H, Terashima M, Takahashi T, et al. Mechanisms of lumen narrowing of saphenous vein bypass grafts 12 months after implantation: an intravascular ultrasound study. Am Heart J 2006;151:726–9.
10. Lau GT, Ridley LJ, Bannon PG, et al. Lumen loss in the first year in saphenous vein grafts is predominantly a result of negative remodeling of the whole vessel rather than a result of changes in wall thickness. Circulation 2006;114(1 Suppl):I435–40.
11. Souza DSR, Dashwood MR, Tsui JCS, et al. Improved patency in vein grafts harvested with surrounding tissue: results of a randomized study using three harvesting techniques. Ann Thorac Surg 2002;73:1189–95.
12. Souza DSR, Johansson B, Boj L, et al. Harvesting the saphenous vein with surrounding tissue for CABG provides long-term graft patency comparable to the left internal thoracic artery: results of a randomized longitudinal trial. J Thorac Cardiovasc Surg 2006;132:373–8.
13. Owens CD, Wake N, Jacot JG, et al. Early biomechanical changes in lower extremity vein grafts—distinct temporal phases of remodeling and wall stiffness. J Vasc Surg 2006;44:740–6.
14. Manchio JV, Gu J, Romar L, et al. Disruption of graft endothelium correlates with early failure after off-pump coronary artery bypass surgery. Ann Thorac Surg 2005;79:1991–8.
15. Frazier AA, Qureshi F, Read KM, Gilkeson RC, Poston RS, White CS. Coronary artery bypass grafts: assessment with multidetector CT in the early and late postoperative s ettings. Radiographics 2005;25:881–96.
16. Owens CD, Ho KJ, Conte MS. Lower extremity vein graft failure: a translational approach. Vasc Med 2008;13:63–74.
17. RodÈs-Cabau J, Facta A, Larose E, et al. Predictors of aorto-saphenous vein bypass narrowing late after coronary artery bypass grafting. Am J Cardiol 2007;100:640–5.
18. Muto A, Model L, Ziegler K, Eghbalieh SD, Dardik A. Mechanisms of vein graft adaptation to the arterial circulation: insights into the neointimal algorithm and management strategies. Circ J 2010;74:1501–12.
19. Allen K, Cheng D, Cohn W, et al. Endoscopic vascular harvest in coronary artery bypass grafting surgery: a consensus statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2005. Innovations 2005;1:51–60 10.1097/1001.gim.0000196315.0000132179.0000196382.
20. Canos DA, Mintz GS, Berzingi CO, et al. Clinical, angiographic, and intravascular ultrasound characteristics of early saphenous vein graft failure. J Am Coll Cardiol 2004;44(1):53–6.
21. Vita JA, Holbrook M, Palmisano J, et al. Flow-induced arterial remodeling relates to endothelial function in the human forearm. Circulation 2008;117:3126–33.
22. Ohta S, Komori K, Yonemitsu Y, Onohara T, Matsumoto T, Sugimachi K. Intraluminal gene transfer of endothelial cell-nitric oxide synthase suppresses intimal hyperplasia of vein grafts in cholesterol-fed rabbit: a limited biological effect as a result of the loss of medial smooth muscle cells. Surgery 2002;131:644–53.
23. Jacot JG, Abdullah I, Belkin M, et al. Early adaptation of human lower extremity vein grafts: wall stiffness changes accompany geometric remodeling. J Vasc Surg 2004;39:547–55.
24. Shi Y, Pieniek M, Fard A, O'Brien J, Mannion JD, Zalewski A. Adventitial remodeling after coronary arterial injury. Circulation 1996;93:340–8.
25. Josiah NW, Ron W, Spencer BK, Neal AS. The role of the adventitia in the arterial response to angioplasty: the effect of intravascular radiation. Int J Radiat Oncol Biol Phys 1996;36:789–96.
26. Wilensky RL, March KL, Gradus-Pizlo I, Sandusky G, Fineberg N, Hathaway DR. Vascular injury, repair, and restenosis after percutaneous transluminal angioplasty in the atherosclerotic rabbit. Circulation 1995;92:2995–3005.
27. Desai P, Kiani S, Thiruvanthan N, et al. Impact of the learning curve for endoscopic vein harvest on conduit quality and early graft patency. Ann Thorac Surg 2011;91:1385–92.

DISCUSSION

DR KEITH B. ALLEN (Kansas City, MO): I congratulate you on your study. I've spent 15 years promoting the benefits of endoscopic vein harvesting with regard to decreasing wound complications. I am somewhat concerned, though, when I look at your data, that even in the hands of an experienced harvester, you still have a composite injury score of more than five. I am concerned that over the last 10 years, which have seen an explosion in the use of endoscopic vein harvesting (EVH), it was primarily driven by the abandonment of some of the early EVH techniques in which blunt dissection was not used in favor of the much easier technique that currently essentially involves blunt stripping of the vein. I think we need to be very cautious with some of the long-term data that are coming out about the negative influence of EVH and look very carefully at the harvesting devices that we use.

DR KIANI: Thank you for that comment.

DR MICHAEL NOWAK (Rochester, MN): I just wanted to ask which harvesting device was used in your study.

DR KIANI: I will defer that to the primary surgeon, Dr. Poston; however, I believe it was the VasoView.

DR POSTON: It was the VasoView.

MR LEONARD BAKLARZ (Bethesda, MD): Thank you for your study. It is very important to me. I have been harvesting vein for about 14 years and teaching it for about 10 years, and it is important to note that the learning curve is significant. Although I do believe in the technique that I have been performing, we do have to focus on how to shorten that learning curve. The procedure is difficult to perform, as most people who have done it can attest to.

Some of the things I have a concern with include the shortfalls of the *New England Journal of Medicine* article (the article about EVH by Lopes et al in the July 16, 2009 issue of *The New England Journal of Medicine*), especially with randomizing to vein harvesting, and there are two other articles, one of which is the Nova Scotia article (the article regarding endoscopic vein harvest by Ouzounian et al. in the February 2009 issue of *The Annals of Thoracic Surgery*) and the other the recent article from the Inova Fairfax Hospital dealing with long-term results in thousands of patients, which showed no difference between the two groups that had open and endoscopic vein harvesting, respectively.

How would you proceed with shortening the learning curve, and what was your definition of a novice harvester?

DR KIANI: Thank you for that question. I will answer your second question first. The novice harvesters were harvesters that we defined at our institution as physician assistants (PA) that had fewer than 100 cases of experience, and the expert harvesters were those that had over 900 or close to 1,000 cases.

In terms of shortening the learning curve for EVH, our study is a cross-sectional analysis of what is happening with the learning curve: a snapshot in time. I think the first thing that would be interesting and useful to do would be to study the actual learning curve so as to be able to describe it further; perhaps through a longitudinal study that follows novice PA through their learning curve and therefore enables us to characterize it further before we make any specific recommendations about the pedagogy.

I do think that the one conclusion that we at our institution have been able to draw is that although conventional wisdom tells us that about 20 or 30 cases is enough to get a harvester through the novice phase, at least 100 cases are needed to attain proficiency in harvesting. However, I think that to really define this, we need to look at a larger number of harvesters throughout the course of their learning curves, and perhaps use a cumulative sum control chart analysis to characterize the outcomes.