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Is endoscopic harvesting bad for saphenous vein graft patency in coronary surgery?

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Abstract

Purpose of review—Endoscopic vein harvest (EVH) has quickly been adopted as standard-of-care for CABG. Despite clear advantages in terms of wound morbidity, healing, pain and patient satisfaction, data from recent large clinical trials have called its safety into question.

Recent findings—Post hoc analyses of a variety of prospective trials have suggested EVH is associated with decreased graft patency, and higher rates of cardiovascular complications (e.g. myocardial infarction, need for repeat revascularization) and mortality. Imaging studies of veins procured by EVH have revealed retained clot and vascular injury, particularly when technicians are during their “learning curve”. These findings may alter the quality of the conduit and therefore the outcome of the bypass graft. Elucidating the mechanisms that underlie any differences in results produced by the open and endoscopic procedures would help better inform clinical practice and the development of targeted strategies to improve EVH.

Summary—Clear clinical advantages over traditional open vein harvest have allowed EVH to rapidly become the standard-of-care for harvesting of one or more vein grafts during CABG. Conduit quality, suggested to be equivalent by early studies, has come into question as groups with varying levels of experience have adopted the endoscopic technique. Elucidating the principles of “best practice” for vein harvest will likely help shorten the learning curve and improve the safety of EVH.

Keywords

Saphenous Vein Graft (SVG); Endoscopic Vein Harvest (EVH); Coronary Artery Bypass Grafting (CABG); Patency

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Introduction

Endoscopic Vein Harvest (EVH) debuted in 1997 and over the next decade became the standard of care for CABG with >75% of procedures and 93% of centers utilizing this technique¹. The rapid adoption of EVH results from a dramatic reduction in invasiveness compared to the open, traditional vein harvesting (OVH) technique. Several studies have shown 2- and 3-fold improvements in the rate of wound-related complications and infections for EVH^{2,3}. The significant reduction in incision length when grafts are procured using EVH yields less wound-related pain (WMD=1.95, P=0.06; 95% CI: -0.10–4.01)⁴, and increased patient satisfaction⁵ compared to OVH. While the required disposable equipment costs are increased, a reduction in length of hospital stay compared OVH maintains the cost effectiveness of EVH⁴.

In contrast to the overt benefits of reducing surgical invasiveness, the quality and therefore patency of the conduit harvested by this technique have been more difficult to define. EVH deviates from the classic “no touch” principles that have represented the standard of care for surgical handling of vascular tissue. Despite differences in technique, meta-analyses of early clinical trials suggested that EVH was non-inferior to OVH with respect to short- and mid-term clinical outcomes such as in-hospital mortality, perioperative myocardial infarction (MI), and need for reoperation^{3,5}. However, these data were limited by the lack of angiographic follow-up of graft patency, minimal statistical power to define long-term outcomes and were not derived from prospectively designed trials.

Three recent *post hoc* analyses of large randomized controlled clinical trials with angiographic follow-up data^{6,7} create a more concerning picture about the safety of EVH. The PREVENT IV trial⁶ (n=3000 patients: 1753 undergoing EVH and 1247 undergoing OVH) demonstrated an increased rate of vein graft failure at 12-18 months after using EVH vs. OVH (46.7% vs. 38.0%, P<0.001)⁶. Additionally, EVH was associated with higher rates of the primary endpoints of death, myocardial infarction, or repeat revascularization (20.2% vs. 17.4%; adjusted hazard ratio, 1.22; 95% CI: 1.01 to 1.47; P=0.04), and death (7.4% vs. 5.8%; adjusted hazard ratio: 1.52; 95% CI: 1.13 to 2.04; P=0.005) after 3 years⁶. A secondary analysis of the randomized comparison of on- vs. off-pump CABG, the ROOBY trial (n=894 patients: 341 EVH and 553 OVH), corroborated that EVH was associated with a higher rate of graft failure (25.5% vs. 14.8%, P<0.0001), and repeat revascularization (6.7% vs. 3.4%, P<0.05) at one year. Data from the EPIC trial demonstrated lower graft patency rate at 9 months in EVH vs. OVH (79.2% vs. 90.8%)⁸. The limitation of each of these trials is that none were specifically designed with the purpose of comparing OVH and EVH, introducing the possibility of unadjusted confounding and other biases. On the other hand, these data were collected prospectively with the deliberate goal of defining whether EVH was a risk factor for compromised graft patency and/or clinical outcomes, thus reducing the risk of any substantial bias.

The findings of these large and well-publicized trials prompted other groups routinely utilizing EVH to examine long-term outcomes in their practices. Three recent studies with a combined total of more than 16,000 CABG patients each independently found that EVH was not associated with increased harm in terms of reduced survival or need for repeat

revascularization⁹. Of note, these results were derived from high-volume centers that were early adopters of EVH and therefore had surgical technicians that were highly experienced in the endoscopic technique. As a result, the impact of the learning curve on the results was likely minimal. A weakness of these studies was the lack of graft patency data. In a pooled meta-analysis of all data to date that have analyzed graft patency with EVH and OVH, there was a significant increase risk of graft failure with EVH with an OR of 1.26 (95% CI=1.07-1.49, p=0.0039, with no significant bias, heterogeneity demonstrated)⁴.

Mechanism of Graft Failure Using EVH

The question whether long-term outcomes after CABG are compromised by EVH is most definitively answered by a multi-center trial for a randomized comparison against OVH. However, an appropriately powered study to test this relationship would require the enrollment and angiographic follow-up of more than 4000 CABG patients. Moreover, many centers have confidence in their own ability to safely use this technique and might not accept the external validity of a trial where the requisite technical skills may not be available at all study sites. It is possible that clinical practice might not substantially change even if EVH was demonstrated to produce inferior outcomes in this type of trial.

An alternative study design would be to incorporate an analysis of conduit quality as a surrogate of patency and clinical outcome. A sensitive and direct analysis of injury to the harvested conduit would more effectively address the mechanism of how graft failure might be increased by EVH. As a result, targeted strategies for improvement could be developed. The quality of the graft was defined in the PREVENT IV trial by visual inspection by the operative surgeon. In fact, if a graft was determined to be “poor,” or “fair,” quality, graft failure was significantly more likely when compared to a “good,” quality graft if the surgery was done off-pump (OR 1.90, 95% CI: 1.27-2.84)¹⁰. However, this technique is not adequate for demonstrating luminal injury to conduits that might otherwise look normal based on their gross external appearance.

Despite obvious differences in how the vein is handled for EVH, multiple prior comparisons with OVH have failed to demonstrate measurable differences in endothelial integrity or other markers of conduit integrity and/or quality^{3,11-13}. These investigations have been limited to discarded specimens of the vein with the assumption that intimal loss observed histochemically from these graft segments closely reflects the overall status of the endothelium within the graft proper. The inherent sampling error caused by this technique limits its utility to test the hypothesis about the importance of trauma during EVH because this process usually presents as focal disruption of the vein. Focal injury is critically important to diagnose because it can provoke an occlusive thrombus and loss of the graft even when the remainder of the vessel is pristine.

Our lab has established a catheter based imaging technique, optical coherence tomography (OCT), as method for identifying luminal abnormalities, intimal or deep vessel injury in the vein (Figure 1). Given an imaging resolution of 10 microns, this modality is able to detect injury anywhere within a conduit in real time with unsurpassed sensitivity (Figure 2). Therefore, OCT is the only technique reported to date with the adequate sensitivity to be

able to compare the quality of conduits procured using EVH vs. OVH. Systematic analysis of conduits before and after harvest may help to characterize mechanisms of injury that possibly underlie compromised outcomes and lead to targeted improvements in the technique and/or technology.

Retained Luminal Clot

Intraoperative use of OCT has shown using that EVH is commonly associated with luminal clot strands that are retained within the SVG^{14,15}. We have shown that saline flushing does not sufficiently reduce this clot burden and, in fact, may increase thrombogenicity of the SVG by causing secondary endothelial injury¹⁶. Instead, low dose heparinization (2500-5000 IU bolus) administered prior to initiating EVH has been a more effective way to decrease, though not eliminate, this clot burden¹⁵. Although a direct link to graft outcomes has not been established, it is reasonable to assume that retained clot may provoke graft thrombogenicity and contribute, at least in part, to compromised outcomes in EVH. Systemic heparinization before harvest is a benign change in practice that significantly lessens this complication.

Vascular Injury and Graft Compromise

Consistent with another recent analysis¹⁶, we have found that abnormalities within the intimal and deeper layers are common in veins harvested by EVH¹⁷. Focal areas in the vein suggested to be injured on OCT imaging were found to have denuded endothelium and heightened activity of tissue factor, indicators that thrombogenicity might be altered¹⁷. In fact, when portion of conduit used for grafting had 4 or more discrete injuries detected by OCT, the rate of early graft failure (likely thrombosis) approached 35%¹⁷.

Vein injury during EVH also appears to alter the physiologic function of the graft. Changes in velocity of blood flow within a vein grafted into the arterial circulation causes gradual venodilation¹⁸, a response referred to as “positive remodeling”. The severity of vein injury, quantified by the number of discrete injuries detected by OCT, was a significant predictor of blunted positive remodeling in the graft over the first week. The analysis of gene expression in veins procured by EVH showed a correlation of vascular injury detected by OCT and markers of injury and inflammation such as *CXCL2*, *PDGFA*, *HSP90AA1* and *EGF*. Prior evidence suggests that inflammation within the vein prevents the positive remodeling response^{18,19}.

There is also evidence that early inflammation induced by EVH aggravates the risk of “negative remodeling” in the graft, a process characterized by smooth muscle cell proliferation, adventitial scarring and contraction, leading to gradual lumen loss. We noted that severe injury diagnosed intraoperatively by OCT was correlated to the risk of the graft developing a loss of lumen diameter over the next 6 months. Others have also shown that meticulous handling of veins during harvest can have a long-term benefit for the graft^{20,21}. Vein procurement using an open “no touch” technique helps to preserve the perivascular tissues as a pedicle surrounding the harvested vein. In a randomized comparison against conventional vein harvesting, the no touch technique demonstrated significantly improved graft patency 5 years after CABG²¹.

Learning Curve

EVH requires forces to be applied to the vein that are usually avoided in open harvest, including traction, adventitial stripping, and venous compression. Depending on the level of experience of technician performing the harvest, these forces can compromise the safety of this technique. In a prospective study utilizing OCT imaging, it was noted that veins procured from novice EVH harvesters (i.e. less than 100 cases of experience) had nearly 50% more discrete injuries than veins procured by harvesters with extensive EVH experience¹⁷. Moreover, the positive remodeling response noted in vein grafts procured by the experienced group was significantly blunted in veins from the novice group.

This potential relationship of the quality and function of EVH grafts to level of technician experience may reflect a tendency among harvesters who are less experienced with this technique to more forcefully manipulate the vein in an effort to gain better endoscopic vision or exposure. This stands in stark contrast to the open “no touch” technique espoused by Souza^{21,22}. Most of the recent CABG studies that reported adverse outcomes after EVH were enrolling patients while this technique was relatively new and being rapidly adopted^{8,9,23,24}. Although not reported in these studies, it is likely that a minority of the harvesters had more than 100 cases of experience during this timeframe. Differences in graft patency and clinical outcomes vs. the open technique may regress towards the mean over time if inexperience is the only cause of problems. However, many institutions are continually training new physician assistants to perform this technique. This means that that inexperience with EVH can continue to impact outcomes even at institutions that have extensive familiarity.

Conclusions

Available evidence does not suggest that EVH is an inherently bad method for procuring vascular conduits. However, 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. Given the ongoing annual volume of CABG procedures that utilize EVH, the learning curve for this procedure represents an important and under-recognized public health issue.

Recent recommendations for practitioners in Europe indicate judicious use and rigorous documentation of EVH²⁵. This reflects concern that this technique has yet to be fully characterized and that there is compelling evidence that unidentified technical errors are occurring that may be compromising grafts, and therefore patients. Several authors have demonstrated that the time required to complete the harvest and the need to convert to an open technique or place external repair stitches in the vein are higher during the early adoption of EVH. However, these metrics of the learning curve do not elucidate the more important issue of whether the integrity and thrombogenicity of the procured vein are altered during the learning curve. A high resolution imaging technique such as OCT is a far more sensitive method for monitoring progress through the learning curve.

It is common to identify unforeseen pitfalls as the adoption of any new technology becomes more widespread. This is not a unique finding of EVH. A key principle for improvement is

to rigorously monitor outcomes while adopting change so that errors in technique and training can be identified and changed. Given the well-established relationship between endothelial disruption and the risk of thrombosis, monitoring the quality of the intima of grafts procured by EVH is the most effective way to the safety of this approach.

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ROOBY and PREVENT IV were interpreted, and have led to changes in clinical practice, in Europe. [PubMed: 21148577]

Key Points

- While the endoscopic method utilizes less meticulous technique for handling vascular tissue, there is no evidence that EVH is an inherently bad technique for vein harvesting; however, recent evidence suggests that veins procured by EVH may be compromised.
- Poor conduit quality is a common sequela of the lengthy learning curve for EVH. Problems with conduit quality detected by intraoperative graft imaging have been shown to be a predictor of early graft failure, blunted positive remodeling and greater tendency to develop negative remodeling.
- Metrics that are sensitive at detecting conduit quality should be utilized in ongoing evaluations of EVG to document progress through the learning curve of harvesters, as a key principle for improvement is to rigorously monitor outcomes so that errors in technique and training can be identified and changed.
- Given the well-established relationship between endothelial disruption and the risk of thrombosis, monitoring the quality of the intima of grafts using high-resolution imaging is the most effective way to the safety of EVH.

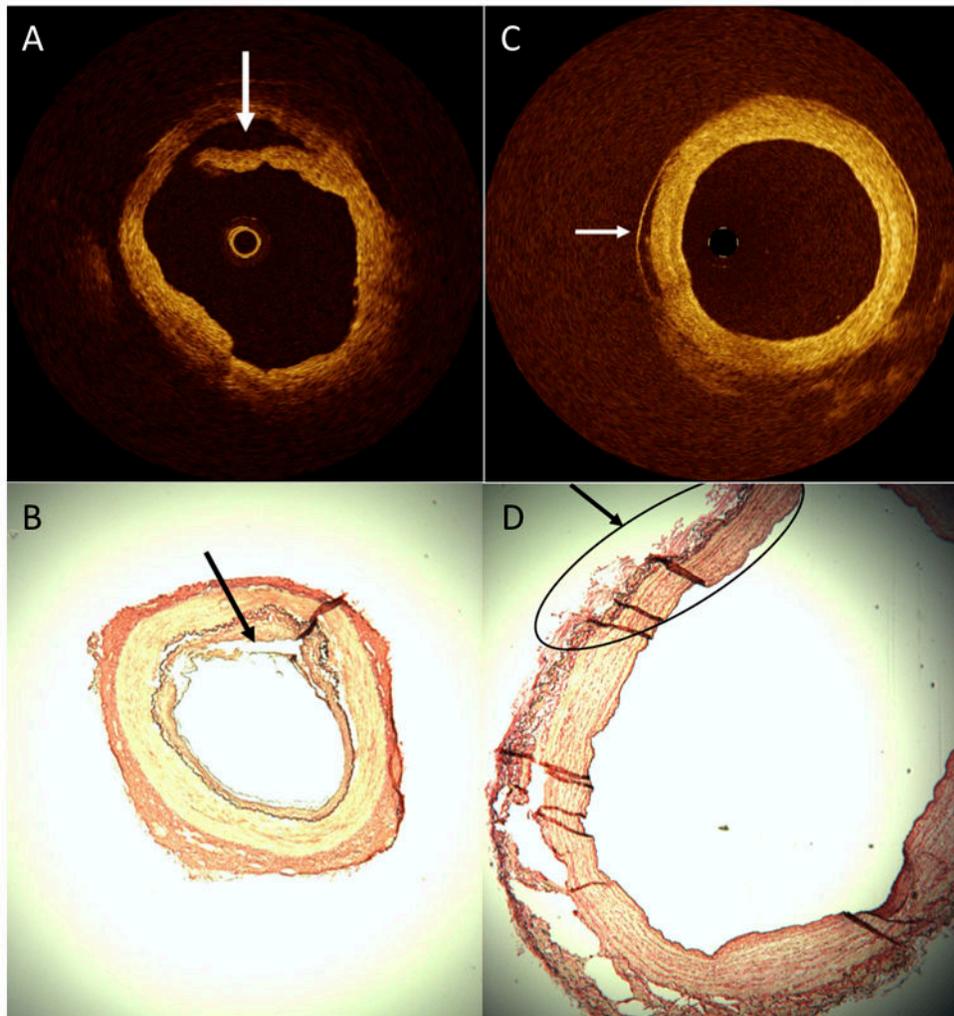


Figure 1. Representative OCT images of SVG injuries acquired during EVH

Legend: Depicted above are representative optical coherence tomography (OCT) images of intraluminal and deep vessel injuries. (A) Large intimal injury (white arrow) seen on OCT and (B) corresponding intimal injury seen on histology (black arrow); (C) Adventitial tear (white arrow) as seen on OCT and (D) corresponding injury (black arrow and black circle) seen on histology (D).

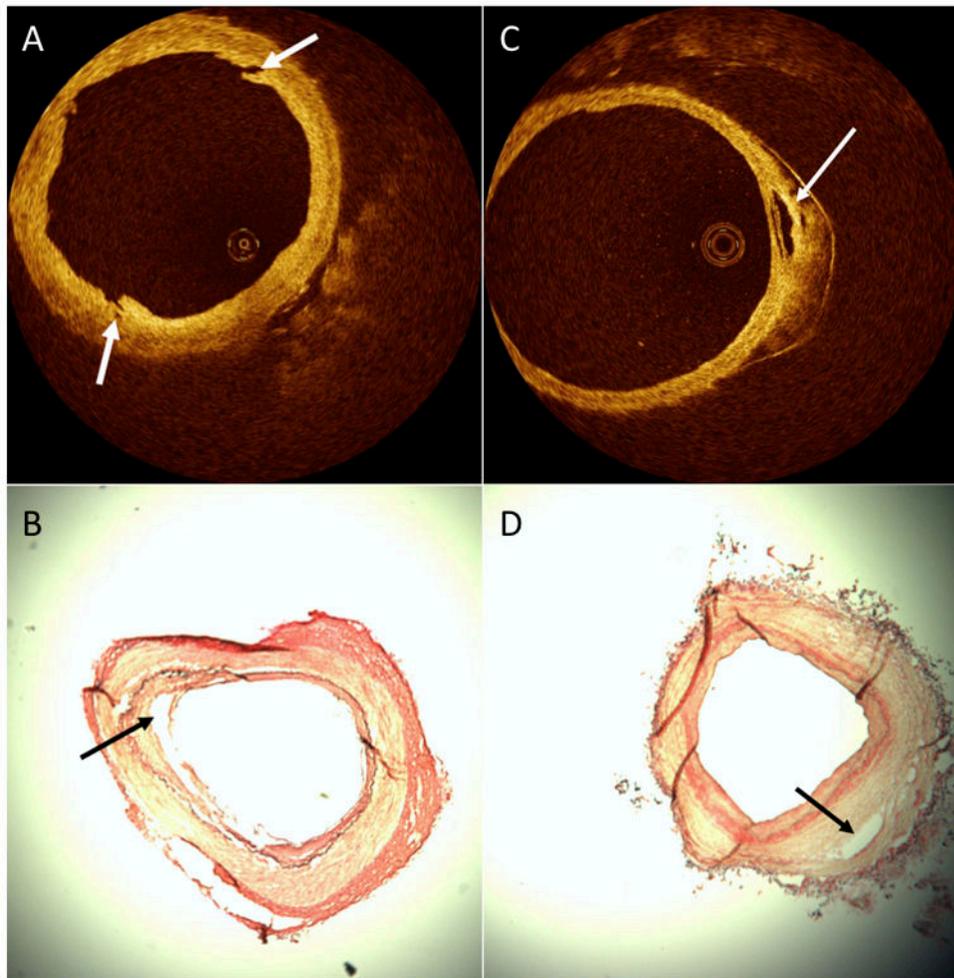


Figure 2. Representative OCT images of small SVG injuries acquired during EVH

Legend: Depicted above are optical coherence tomography (OCT) images that demonstrate the sensitivity of OCT for small injuries to the vessel. (A) Small intimal tears (white arrows) are seen on OCT with (B) corresponding histology (black arrow); (C) Intimal-medial dehiscence as seen on OCT (white arrow) with (D) corresponding injury on histology (black arrow).