Percutaneous Revascularization of Occluded Vein Grafts
Is It Still a Temptation to Be Resisted?

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Given the number of patients who have undergone coronary bypass surgery in which vein grafts were used, the increasing incidence of vein graft disease over time, and the reluctance of most patients to see a cardiovascular surgeon professionally again after the first go-around, there is continued need for development of approaches to treat such patients. There are many unique characteristics of patients treated for vein graft disease: they are older than when they had their initial procedure, and more importantly, their vein grafts are also older. Beyond 1 year and particularly >3 years after surgery, atherosclerosis of vein grafts becomes increasingly prevalent.1-3 It may coexist with intimal fibrovascular proliferation and, in patients with acute ischemic syndromes, thrombus of varying ages. Atherosclerotic plaques in vein grafts are often large compared with plaques in native coronary arteries and are usually soft and friable, rich in necrotic debris, cholesterol crystals, blood elements, and foam cells; this is often referred to as gruel. Thrombus has been documented by angioscopy in up to 70% of vein graft lesions undergoing treatment.6 This substrate is primarily responsible for the problems encountered during interventional procedures, which include distal embolization, inadequate dilatation, and increased restenosis rates.

Distal embolization is of the greatest concern because the treatment options for embolization are so limited. Saber et al7 assessed the histopathology of 6 vein grafts from 5 patients treated with balloon angioplasty. Two grafts were obtained during autopsy; the remainder were from surgical excision. The picture worth a thousand words (Figure) tells the compelling story of the underlying pathophysiology: a 59-year-old woman 6 years after CAGB surgery presented with an acute occluded vein graft and was treated with streptokinase and PTCA. The patient developed profound hypotension and subsequently died. At postmortem examination, there was extensive disruption of friable atheromatous plaque, extruded atheromatous debris, and acute thrombus formation. In the native coronary artery downstream from the vein graft insertion, there were obstructive atheromatous emboli with cholesterol clefts and fresh thrombus. In a subsequent study, Saber et al8 found that emboli are usually multiple and are associated with plaque rupture, plaque extrusion, and medial dissection, all of which commonly result from vein graft interventions.

In an attempt to improve the outcome of intervention in obstructed vein grafts, almost all of the newer nonballoon devices have been studied. Directional coronary atherectomy (DCA) was evaluated in 305 patients in the randomized CAVEAT-2 trial (Coronary Angioplasty Versus Excisional Atherectomy Trial-2).9 Although the initial angiographic success rate was improved with DCA (at 89.2% versus 79.0% for PTCA), the 6-month restenosis rates were similar (45.6% for DCA and 50.5% for PTCA; P=0.491). Distal embolization occurred more frequently with DCA (13.4% versus 5.1%; P=0.012), and non-Q-wave myocardial infarction was also increased (16.1% versus 11.5%). Lefkovits et al10 evaluated the predictors and sequelae of distal embolization in this trial. Independent predictors of embolization were the use of DCA (71% in distal embolization patients versus 47% in patients without embolization; OR=2.87 [1.26, 6.54]) and more importantly, the presence of thrombus (39% in distal embolization patients compared with 14% in patients without embolization; OR=3.95 [1.80, 8.66]). Of patients with distal embolization, 71% had an adverse clinical event during their index hospitalization versus 20% of patients without distal embolization (P<0.001). At 1 year, the composite endpoint of death, myocardial infarction, repeat interventions, or elective CAGB surgery remained worse in the group that had suffered distal embolization.

Transluminal extraction has also been studied in patients with vein graft disease. Dooris et al11 compared the transluminal extraction catheter in 175 patients with 183 stenotic vein grafts, including 59 with (32%) and 124 without (68%) thrombus. Grafts with thrombus were more likely to be occluded, to have diffuse disease, and to have reduced antegrade flow at baseline. Grafts containing thrombus also had a lower rate of clinical success (69% compared with 88% in grafts without thrombus; P=0.01). No reflow was seen in 19% of patients with thrombus and only 5% of patients without thrombus. Distal embolization occurred in 7% of all patients (8% of patients with and 6% of patients without thrombus). Angiographic follow-up was limited to 74% of lesions, but in these, late complete vessel occlusion was seen in 35% of patients with thrombus.

The excimer laser has also been tested in vein graft disease.12 In a clinical series of 495 patients, the success rate ranged from 84% to 96% and appeared to be related to a number of clinical and angiographic variables.12 Embolization occurred in 3.3% and Q-wave myocardial infarction in...
2.4% of patients. In other laser studies, thrombus-containing lesions have been found to be associated with increased potential of embolization, leading some authors to conclude that a large amount of thrombus should be considered a relative contraindication to excimer laser angioplasty.\textsuperscript{13}

Finally, stents have been widely used.\textsuperscript{14–16} Typically, they have not been deployed as primary treatment of lesions with a large thrombus burden because of concern about distal embolization and/or subacute closures. Stents are, however, widely used as an adjunctive treatment after debulking or attempted thrombus removal. They have been tested and compared with PTCA in 1 randomized clinical trial.\textsuperscript{16} That trial focused on very select lesions that were short, focal, and nonocclusive, did not contain thrombus, and had not been associated with myocardial infarction within 1 week. In that study, no information concerning no reflow or distal embolization was reported, but by virtue of patient and lesion selection criteria, these complications could have been expected to be relatively low. Indeed, the incidence of non–Q-wave myocardial infarction was only 2% in the stent group and 7% in the PTCA limb. Angiographic restenosis was not statistically different between the 2 limbs, although a strong trend (9% absolute difference) favored stent placement (37% restenosis for stents and 46% for PTCA; \(P=0.24\)). Nonrandomized studies also strongly support stent use for lesions in stenotic vein grafts.\textsuperscript{14,15}

Adjunctive medical therapy has also been studied in patients undergoing percutaneous revascularization of stenotic vein grafts. Abciximab was studied in 101 patients in the EPIC trial (Evaluation of IIb/IIIa Platelet receptor antagonist 7E3 in preventing Ischemic Complications).\textsuperscript{17} In the patients treated with a bolus and infusion, distal embolization occurred in only 2% versus 18% who received a placebo (\(P=0.017\)). There was no difference, however, in 30-day or 6-month clinical outcomes. At 6 months, the composite end point of death, nonfatal infarction, or repeat revascularization occurred in 31% of patients who received a placebo and 35% of patients who received a bolus plus infusion of abciximab. More recently, local administration of abciximab has been tested in the EDGE pilot study of 58 patients undergoing treatment of 9.0 year old vein grafts.\textsuperscript{18} Primary end points for this trial were changes in percent diameter stenosis, TIMI (Thrombolysis In Myocardial Infarction) thrombus grade, and TIMI flow grade after local drug delivery. Before local drug delivery, 68% of grafts had angiographic evidence of thrombus; after treatment, only 34% had evidence of thrombus. At the end of the procedure, in which 90% of cases received stents after local drug delivery, 89% had no evidence of thrombus. There was no change in TIMI flow rate after local

Pathological specimens obtained from vein graft (A and B) and native coronary artery downstream from the vein graft insertion (C and D). Thrombus (Thr) and atheromatous plaque are present in the body of the vein graft (A and B). The coronary artery is obstructed with atheromatous emboli and thrombus that originated in the occluded vein graft.
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treatment, however, and 7 patients developed an acute myocardial infarction in association with the treatment.

The highest-risk groups of patients are those with occluded vein grafts. Such patients have the potential to benefit from revascularization attempts but also the potential to “crash and burn.” This is a situation in which the patient with an occluded conduit who is relatively stable can be rendered much worse when distal embolization occurs. It was this complication among others that led to the article by de Feyter et al in 1989 subtitled “A Challenge That Should Be Resisted.” In these high-risk patients, there have been more recent series that again have documented that the short- and longer-term outcomes remain poor.

Berger et al analyzed 77 consecutive patients in whom an occluded vein graft was treated. In this clinical series, stents were used in 9%, laser in 30%, DCA in 16%, and thrombolytic therapy in 23%. The angioplasty success rate was 71%. Thirty-day events included death in 5.2%, Q-wave myocardial infarction in 1.3%, and repeat CABG surgery in 7.8%. Distal embolization occurred in 11.7%, and creatine phosphokinase elevation was documented in 43%. During follow-up for 3 years, there were no differences in survival, recurrent infarction, or recurrent severe angina between patients in whom the initial procedure was successful and those in whom it was not; 1 of these adverse events occurred in ≈80% of patients in both groups. Kahn et al similarly evaluated the outcomes of 83 patients after PTCA of occluded bypass grafts. Angiographic success was obtained in only 73%; distal embolization occurred in 11%. Angiographic follow-up was available in only 61% of the patients. In these patients, recocclusion was seen in 46%, and freedom from repeat angioplasty or CABG surgery at 3 years was only 34%.

Other approaches for totally occluded vein grafts have included prolonged infusion of urokinase followed by balloon angioplasty. Hartmann et al, in a series of 47 occluded vein grafts, infused 0.7 to 9.8 million units of urokinase over a mean of 31 hours. Recanalization was achieved in 79%. During follow-up, 35% reoccluded. A subsequent multicenter trial evaluated this approach in 107 patients. After urokinase infusion for an average of 25 hours, patency was achieved in 69%, but the overall mortality rate was 6.5%, and distal embolization occurred in 17% of grafts. Although angiographic follow-up data were incomplete, the treated vessel was patent in only 40% of patients at the time of angiographic follow-up. Some investigators have termed this approach long, painful, and expensive. It is now infrequently used. Accordingly, the search for improved approaches for percutaneous treatment of vein graft disease goes on.

There are 2 promising new devices used for thrombectomy. One of these is described by Rosenschein et al, who in this issue of Circulation describe the first use of ultrasound thrombolysis in a 20-patient cohort, of whom 15 had occluded saphenous vein grafts. The device described by Rosenschein et al is a novel one that uses ultrasonic energy to fragment the clot. The median age of clot in this series was 6 days (ranging from 0 to 100 days). There was device success in 70%, with a residual stenosis of 65±28%. After initial success with the device, definitive treatment was required, and all patients were then treated with either balloon angioplasty or stent implantation. Final procedural success was obtained in 65% of patients, with a residual stenosis of 5±8%. One patient had distal embolization. There were 2 patients who had successful catheter ultrasound thrombolysis in which subsequent stenting nonetheless resulted in no reflow and procedural failure.

These results in a very small but difficult-to-treat group of patients are promising. There are issues in this report that are relevant for comparison with other series and other approaches. The preciseness of definitions is essential: how accurately can we define or distinguish no reflow, which occurred in 2 patients (10%), from distal embolization, which occurred in 1 (5%)? What, if any, is the effect of ReoPro when administered after no reflow has occurred, and what is its role in preventing the occurrence of no reflow? This is a major issue for which few data exist. Distal embolization may be the result of platelet emboli, but in the case of vein graft disease, it may also be related to atheromatous debris or vasoconstriction from vasoactive substances. Our ability to discern the mechanism is unclear, but it has major implications for practice.

Yet another issue relates to the 2 patients in whom catheter ultrasound thrombolysis was successful but in whom no reflow and procedural failure still occurred during subsequent stent implantation. By merely removing angiographically evident thrombus, we may not have adequately treated lesser amounts of thrombus or the problem of atheromatous debris. Covered stents may play a role in preventing this problem.

An important issue for any of these devices is the fact that when one is dealing with occluded vein grafts, a guidewire has to be passed through the occlusion into the distal vessel for the procedure to be successful. The authors do not report how frequently the patient was prepared to receive the device but did not because the occlusion could not be traversed.

A final issue relates to the distal vascular bed. In patients in whom the vein graft is occluded, there may be no details as to the size and function of the distal vascular bed. An occluded vein graft that goes to a very small vessel should probably not cause any problems and might best be left occluded. However, an occluded vein graft that goes to a very large distal vessel might be a very important target for either catheter-based intervention or repeat surgery.

What can we say based on this initial experience? (1) It is promising and is currently being tested in a randomized clinical trial against ReoPro and adjunctive mechanical therapy. (2) Documenting long-term benefit remains an issue; patients must be carefully monitored to determine whether any such benefit exists. (3) It must be remembered that patients with degenerating vein grafts may best be treated with repeat coronary bypass surgery. This is particularly the case in patients who did not have internal mammary grafts placed to their left anterior descending coronary artery. In these patients, an operation, with the use of ≥1 arterial grafts, may even be safer and result in better longer-term success than catheter-based treatment of degenerating vein grafts.

In summary, ultrasound thrombolysis is promising. To be sure, many questions remain about the role of this therapy. With recent advances in pharmacological therapy and new treatment devices, it may be too early to tell whether occluded
vein grafts remain a temptation to be resisted or a challenge to be met. At the present time, our answer to that question all too often depends on the outcome of the last such patient we treated. In the future, the outcome of randomized trials comparing many of these new therapies will be a better guide.

References


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