Session 4

Future improvements in graft performance

The Impact of Drug Therapy on Surgical Bypass

BY RUSSELL H. SAMSON, MD, FACS, RVT

Infrainguinal arterial bypass grafts are prone to early and late failure. This is irrespective of whether they are constructed from autologous vein or prosthetic, nonautogenous material such as expanded polytetrafluoroethylene (ePTFE). Early graft failures (< 30 days) are typically technical failures, so most adjuvant medications will not be effective during the first 30 days. Failures after 30 days are likely due to a confluence of factors that may differ depending upon the conduit used. These factors include intimal hyperplasia, spontaneous graft thrombosis, and the development of proximal or distal atherosclerosis. Further, atherosclerotic disease can also occur within vein grafts. These factors are all interrelated and reflect ongoing disease processes. Although graft thrombosis is often idiopathic, it can also be associated with hypercoagulable states or external compression.

Adjuvant agents prescribed to help prevent graft failure may target intimal hyperplasia, graft thrombosis, atherosclerosis, or all factors concurrently. For the most part, current adjuvant medications include antiplatelet agents, antithrombotics, and statins. Beta-blockers, cilostazol, and the transcription factor decoy edifoligide have also been explored as adjuvants. Currently, there is no ongoing trial to compare the efficacy of these drugs in preventing graft failure. The largest study to evaluate any of these adjuvant agents was the PREVENT III trial of edifoligide.[1] Edifoligide targets E2F, which is a transcription factor that plays a critical role in coordinating the expression of several genes that regulate cell-cycle progression, thus potentially preventing the development of hyperplastic intimal thickening. However, ex vivo treatment of lower extremity vein grafts with edifoligide was unable to protect graft failure.[1]

ANTIPLATELET AGENTS

Antiplatelet agents are typically prescribed to help prevent platelet aggregation that leads to hyperplastic intimal thickening. They may also prevent platelet agglutination and subsequent spontaneous thrombosis. Activated platelets aggregate on injured endothelial cells in denuded areas and fibrin is deposited. The deposited fibrin acts with platelets to form an adhesive surface that binds circulating leukocytes. The leukocytes then become the central modulators in the development of hyperplastic intimal thickening.

There are multiple antiplatelet agents including ASPIRIN® (acetylsalicylic acid) (ASA), clopidogrel bisulfate, and ticagrelor. The field becomes even more complex with the addition of a new drug (eg, vorapaxar). Vorapaxar is unique in that it is the first antiplatelet agent approved by the US Food and Drug Administration (FDA) specifically for the treatment of peripheral artery disease. However, there are no current data to support its use in preventing graft failure.

In 1994, the Antiplatelet Trialists' Collaboration studied approximately 3,000 patients who underwent peripheral artery procedures.[2] The procedures included vein grafts and nonautologous grafts. The study found that antiplatelet therapy (primarily ASA) resulted in 38% fewer graft occlusions when compared with placebo. This study was seminal in the consideration of adjuvant therapy for improving vascular graft failure rates.

In 1999, Tangelder et al[3] reviewed trials comparing ASA versus anticoagulation versus placebo. The investigators found a 22% relative reduction (RR) with ASA, a 44% RR with warfarin, and a 62% RR with combined ASA and warfarin. However, patients who received ASA combined with warfarin had a higher incidence of bleeding.

A subgroup analysis of the CASPAR trial suggested a benefit for dual-antiplatelet agents (eg, ASA, clopidogrel) in prosthetic grafts (not vein grafts) without an increase in bleeding risk.[4] However, as a post hoc analysis this result may be suspect. Furthermore, the CASCADE trial failed to show any benefit for clopidogrel over ASA in the prevention of coronary artery graft intimal hyperplasia.[5,6]

ANTICOAGULANTS

Although there are many new novel anticoagulants, the only anticoagulants currently studied to prevent graft thrombosis have been heparin, low-molecular-weight heparin, and warfarin.

The Cochrane Review examined the effectiveness of low-molecular-weight heparin compared to unfractionated heparin and found no difference in graft patency between the two therapies.[7]

In 1998, Sarac et al examined the effects of warfarin and other vitamin K antagonists in a randomized trial.[8] The investigators reported a patency of 74% at 3 years in the high-risk group randomized to warfarin and ASA. Patency was significantly higher in the patients who received warfarin and ASA when compared to the patients who received only ASA. However, bleeding was more common in the group receiving warfarin.

The Dutch Bypass Oral Anticoagulants or ASPIRIN study compared oral anticoagulants to ASA in a large randomized trial that included vein grafts and prosthetic grafts.[9] The investigators found that ASA at a dose of 80 mg significantly reduced occlusion in prosthetic grafts when compared with warfarin. Patients who received ASA also experienced fewer bleeding episodes. This study from 2000 likely has had the largest influence on subsequent guidelines.

The Veteran Affairs Cooperative trial in 2002 included 665 patients undergoing femoropopliteal bypass.[10] Patients were randomized to 325 mg ASA and warfarin, or ASA alone. The investigators found no significant difference in patency rates between the treatment groups in the 8-mm bypass subgroup; however, they did find a difference in the 6-mm bypass subgroups (71.4% in the warfarin-plus-ASA group vs 57.9% in the ASA-only group; $P = .02$). However, again, warfarin nearly doubled the risk of major bleeding episodes when compared to patients who received ASA alone.

Guidelines published in 2004 recommend ASA for all patients undergoing prosthetic infrainguinal bypass.[11] Warfarin was not recommended due to an increased risk of bleeding. The guidelines suggest that patients who are at a high risk for occlusion should receive combination therapy with warfarin and ASA. However, these guidelines changed in 2008 with only ASA being recommended for all grafts (unless a patient has the rare ASA allergy).

Despite these published findings, the Vascular Study Group of New England reported that patients receiving prosthetic conduit were more likely to be treated with warfarin than those receiving a saphenous vein conduit (57% vs 24%; $P < .001$).[12]

STATINS

Although statins are primarily prescribed to prevent atherosclerotic disease, they are also effective in reducing inflammation.

In vitro studies have demonstrated that statins increase endothelial progenitor cells and promote smooth muscle apoptosis.[13] This suggests that statins may be helpful in bypass surgery through a mechanism of action that is distinct from lowering low-density lipoprotein (LDL) cholesterol.[14] A 2004 study found that the risk of graft failure was 3.2-fold higher in a control group when compared to patients who received statins.[15] The investigators reported that the levels of cholesterol were not statistically different between the two groups, suggesting that the mechanism behind the protective effect was distinct from the LDL-lowering effect of the statins. Statin therapy in the CASCADE trial[16] achieved an LDL level < 100 mg, which was associated with improved graft patency. On the other hand, PREVENT III[1] found that statins had no effect on patency at 1 year and no effect on perioperative mortality. However, patients who received statins did have decreased mortality at 1 year. Similarly, the Vascular Study Group of New England found that statin therapy was not associated with 1-year rates of major amputation or graft occlusion.[17]

SUMMARY

Current treatment guidelines are controversial. The American College of Chest Physicians recommends only ASA for prosthetic and vein grafts.[18] In 2011, the Cochrane Review suggested that all patients receiving a prosthetic graft benefit would benefit from platelet inhibitors, whereas vein grafts would more likely benefit from a vitamin K antagonist.[7] The consensus is that statins should be prescribed because even if they do not improve patency, they do appear to prolong life. Patients who receive high-risk prosthetic grafts may benefit from a vitamin K antagonist or dual-antiplatelet agents. ■

Russell H. Samson, MD, FACS, RVT, is Clinical Professor of Surgery at Florida State University Medical School and is an attending surgeon with Sarasota Vascular Specialists in Sarasota, Florida. He has disclosed that he has received compensation from Gore for participating in the Summit and has received honoraria from Gore for writing this article. Dr. Samson may be reached at rsamson@veinsandarteries.com.

1. Conte MS, Bandyk DF, Clowes AW, et al. Results of PREVENT III: a multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery. J Vasc Surg. 2006;43:742-751; discussion 751.
2. Collaborative overview of randomised trials of antiplatelet therapy--II: maintenance of vascular graft or arterial patency by antiplatelet therapy. Antiplatelet Trialists' Collaboration. Br Med J. 1994;308:159-168.
3. Tangelder MJ, Lawson JA, Algra A, et al. Systematic review of randomized controlled trials of ASPIRIN and oral anticoagulants in the prevention of graft occlusion and ischemic events after infrainguinal bypass surgery. J Vasc Surg. 1999;30:701-709.
4. Belch JJ, Dormandy J, Committee CW, et al. Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial. J Vasc Surg. 2010;52:825-833, e821-822.
5. Kulik A, Le May MR, Voisine P, et al. ASPIRIN plus clopidogrel versus ASPIRIN alone after coronary artery bypass grafting: the clopidogrel after surgery for coronary artery disease (CASCADE) Trial. Circulation. 2010;122:2680-2687.
6. Une D, Kulik A, Voisine P, et al. Correlates of saphenous vein graft hyperplasia and occlusion 1 year after coronary artery bypass grafting: analysis from the CASCADE randomized trial. Circulation. 2013;128(Suppl 1):S213-218.

7. Geraghty AJ, Welch K. Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery. Cochrane Database Syst Rev. 2011(6):CD000536.
8. Sarac TP, Huber TS, Back MR, et al. Warfarin improves the outcome of infrainguinal vein bypass grafting at high risk for failure. J Vasc Surg. 1998;28:446-457.
9. Tangelder MJ, Algra A, Lawson JA, et al. Risk factors for occlusion of infrainguinal bypass grafts. Eur J Vasc Endovasc Surg. 2000;20:118-124.
10. Johnson WC, Williford WO. Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. J Vasc Surg. 2002;35:413-421.
11. Clagett GP, Sobel M, Jackson MR, et al. Antithrombotic therapy in peripheral arterial occlusive disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):609S-626S.
12. Suckow BD, Kraiss LW, Stone DH, et al. Comparison of graft patency, limb salvage, and antithrombotic therapy between prosthetic and autogenous below-knee bypass for critical limb ischemia. Ann Vasc Surg. 2013;27:1134-1145.
13. Erl W, Hristov M, Neureuter M, et al. HMG-CoA reductase inhibitors induce apoptosis in neointima-derived vascular smooth muscle cells. Atherosclerosis. 2003;169:251-258.
14. LaMuraglia GM, Stoner MC, Brewster DC, et al. Determinants of carotid endarterectomy anatomic durability: effects of serum lipids and lipid-lowering drugs. J Vasc Surg. 2005;41:762-768.
15. Kulik A, Voisine P, Mathieu P, et al. Statin therapy and saphenous vein graft disease after coronary bypass surgery: analysis from the CASCADE randomized trial. Ann Thorac Surg. 2011;92:1284-1290; discussion 1290-1281.
16. Abbruzzese TA, Havens J, Belkin M, et al. Statin therapy is associated with improved patency of autogenous infrainguinal bypass grafts. J Vasc Surg. 2004;39:1178-1185.
17. Suckow BD, Kraiss LW, Schanzer A, et al. Statin therapy after infrainguinal bypass surgery for critical limb ischemia is associated with improved 5-year survival. J Vasc Surg. 2015;61:126-133 e121.
18. Sobel M, Verhaeghe R, American College of Chest P, et al. Antithrombotic therapy for peripheral artery occlusive disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):815S-843S.

Sequential Bypass

An option for the tibials.

BY JEAN BISMUTH, MD

The first randomized trial to compare the GORE® PROPATEN® Vascular Graft (Gore & Associates) to expanded polytetrafluoroethylene (ePTFE) found that the GORE® PROPATEN® Vascular Graft significantly decreased the relative risk of losing primary and secondary patency by 36% and 40%, respectively.[1] The study joins a number of trials that have demonstrated the efficacy of prosthetic grafts.[2-5] A comparison of tibial bypass with saphenous vein graft to tibial bypass with heparin-bonded PTFE performed with autologous vein patch found comparable 1-year primary patency between the two groups: 86% for saphenous vein graft and 75.4% for heparin-bonded PTFE.[2] A prospective randomized trial evaluated spliced vein versus PTFE plus patch; the investigators concluded that both spliced vein bypass grafting and PTFE bypass grafting with a distal vein cuff produced acceptable limb salvage rates.[3] The Vascular Study Group of New England evaluated their experience with 1,227 patients from 2003 to 2009[5] who received a prosthetic graft to a below-the-knee target (70%) or more distal target (30%), and concluded that patients who receive below-the-knee prosthetic bypass grafting can have similar 1-year outcomes as patients who receive greater saphenous vein conduit.[5]

Sequential bypass is indicated for patients with multiple failed bypasses, critical ischemia, and adequate inflow, who are fit enough to undergo a lengthy procedure. Two different techniques are frequently used for sequential bypass configurations: composite sequencing and modified configuration of the prosthetic-vein anastomosis for composite sequential bypass.[6] Patients may receive sequential bypasses with PTFE and autologous vein if they do not have the required length of autologous vein. A series of six such procedures were performed at Houston Methodist Hospital over 18 months; of the six cases, four remained patent for 1 to 3 years with no intervention. The small series is consistent with results from published studies of sequential bypass. An analysis of patency rates of sequential bypass revealed 1-year patency rates of 91% with composite sequential, 73% with distal arteriovenous fistulae, and 52% with a disadvantaged vein.[7] A separate trial found a small benefit from sequential bypass for patients who have a single vein.[8]

Although trials typically measure patency rates and limb salvage rates, surgical outcomes can also be evaluated via visualization of muscle perfusion of the leg and foot using magnetic resonance imaging (MRI) with gadolinium contrast. We used the technique to image a series of patients who received open surgery and endovascular therapy. MRI was performed both before the intervention and at 6 months after revascularization. MRI revealed that patients who were healthy had well-defined muscle. As patients began to show symptoms, such as a decrease in ankle-brachial index, the muscles changed and collagen fibers replaced muscle. Collagen fibers continued to become more pronounced as ischemia increased. MRI also revealed a correlation between worsening scar tissue and worsening outcomes. A closer analysis by muscle group, as well as symptomatic and asymptomatic leg, should allow for further visualization of the changes effected by revascularization.

SUMMARY

Patients who do not have adequate saphenous vein can successfully receive a GORE® PROPATEN® Vascular Graft with a distal vein patch. An analysis of muscle perfusions suggests the perfusion effect is greater when several vessels are targeted for revascularization compared to a single vessel. We have attempted to harness this effect in a small series of sequential bypass, but this technique is best reserved as a potential last resort effort in patients fit enough to undergo a lengthy procedure. ■

Jean Bismuth, MD, is from the Methodist DeBakey Heart & Vascular Center in Houston, Texas. He has disclosed

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1. Lindholt JS, Gottschalksen B, Johannesen N, et al. The Scandinavian Propaten(R) trial--1-year patency of PTFE vascular prostheses with heparin-bonded luminal surfaces compared to ordinary pure PTFE vascular prostheses: a randomised clinical controlled multi-centre trial. Eur J Vasc Endovasc Surg. 2011;41:668-673.
2. Neville RF, Capone A, Amdur R, et al. A comparison of tibial artery bypass performed with heparin-bonded expanded polytetrafluoroethylene and great saphenous vein to treat critical limb ischemia. J Vasc Surg. 2012;56:1008-1014.
3. Kreienberg PB, Darling RC 3rd, Chang BB, et al. Early results of a prospective randomized trial of spliced vein versus polytetrafluoroethylene graft with a distal vein cuff for limb-threatening ischemia. J Vasc Surg. 2002;35:299-306.
4. Calligaro KD, Syrek JR, Dougherty MJ, et al. Use of arm and lesser saphenous vein compared with prosthetic grafts for infrapopliteal arterial bypass: are they worth the effort? J Vasc Surg. 1997;26:919-924; discussion 925-917.
5. Suckow BD, Kraiss LW, Stone DH, et al. Comparison of graft patency, limb salvage, and antithrombotic therapy between prosthetic and autogenous below-knee bypass for critical limb ischemia. Ann Vasc Surg. 2013;27:1134-1145.
6. Gargiulo NJ 3rd, Veith FJ, O'Connor DJ, et al. Experience with a modified composite sequential bypass technique for limb-threatening ischemia. Ann Vasc Surg. 2010;24:1000-1004.
7. Roddy SP, Darling RC 3rd, Ozsvath KJ, et al. Composite sequential arterial reconstruction for limb salvage. J Vasc Surg. 2002;36:325-329.
8. Mahmood A, Garnham A, Sintler M, et al. Composite sequential grafts for femorocrural bypass reconstruction: experience with a modified technique. J Vasc Surg. 2002;36:772-778.

TAKE HOME POINTS

RUSSELL H. SAMSON, MD, FACS, RVT

Original studies on drug therapy were performed in the era of ASA, at a time when clopidogrel was only beginning to be investigated. Data from more recent trials suggest that patients who receive ePTFE grafts should receive an antiplatelet agent. However, there are no current data to support clopidogrel over ASA, and dual-antiplatelet agents are not recommended for uncomplicated ePTFE bypasses. Patients who receive an ePTFE graft and appear to be at high risk for thrombosis may require dual-antiplatelet agents or warfarin. Patients who receive vein grafts may benefit from warfarin. Although statins have not been shown to prevent graft failure, they are important adjuvants to prevent cardiovascular mortality.

JEAN BISMUTH, MD

Evidence clearly supports the GORE® PROPATEN® Vascular Graft as the preferred conduit for below-the-knee bypasses in the absence of a suitable autologous vein graft. To further qualify this, it would seem that support for a suitable vein conduit is really only significantly better in single segment veins. Spliced veins have been shown to have only marginally better outcomes, with the consequence of increased operative times, blood loss, and mortality. Like many groups, when using PTFE below the knee, we also advocate for adjuncts such as a patch angioplasty or, in patients with multiple failed bypasses, a sequential bypass procedure. We have limited experience with sequential bypasses as a last resort for limb salvage and, in our experience, the procedures are generally time consuming and result in a greater burden to patients. Patients also have to be selected carefully, but the procedure is a valuable tool in the spectrum of limb salvage surgery and has acceptable outcomes.