Coronary vein graft disease: Pathogenesis and prevention

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Not long after coronary artery bypass grafting surgery was described, several reports presented follow-up angiographic data on large cohorts of patients, demonstrating that approximately one-half of saphenous vein grafts fail within 10 to 15 years of surgery and that graft failure is associated with worse clinical outcomes. Three processes are responsible for vein graft failure. Thrombosis, intimal hyperplasia and accelerated atherosclerosis contribute to graft failure in the acute, subacute and late postoperative periods, respectively. Studies have shown that perioperative antiplatelet therapy can reduce early thrombosis and graft failure. As in native coronaries, intensive lipid lowering can attenuate the process of atherosclerosis in vein grafts. Intimal hyperplasia in the vein graft is thought to be an adaptation of the vein to higher pressures in the arterial circulation. This process is further promoted by the loss of inhibition from the endothelial layer, which is injured during surgery. A new 'no-touch' technique for harvesting grafts may be effective in preventing disruption to the endothelial layer, and subsequent intimal hyperplasia and graft loss. Off-pump surgery and endoscopic vein harvesting, which are known to reduce surgical morbidity, have been shown to be no worse than on-pump surgery and open vein harvesting, respectively, in terms of vein graft patency. Various gene therapies can prevent intimal hyperplasia in animal models, but human data obtained so far have been disappointing. Placing an external stent around a vein graft may reduce tangential wall stress and subsequent intimal hyperplasia.

Key Words: *Coronary artery bypass surgery; Endoscopic vein harvesting; External stenting; Gene therapy; No-touch technique; Off-pump bypass surgery; Vein graft disease*

La pathogenèse et la prévention de la maladie du greffon veineux coronaire

Peu après la description du pontage aortocoronarien, plusieurs rapports ont porté sur les données angiographiques de suivi de vastes cohortes de patients, démontrant qu'environ la moitié des greffons veineux saphènes échouent dans les dix à 15 ans suivant l'opération et que l'échec des greffons s'associe à des issues cliniques encore plus négatives. Trois processus sont responsables de l'échec des greffons veineux. La thrombose, l'hyperplasie intimale et l'athérosclérose accélérée contribuent à l'échec du greffon pendant les périodes postopératoires aiguë, subaiguë et tardive, respectivement. Les études démontrent qu'une thérapie antiplaquettaire périopératoire peut réduire le risque de thrombose précoce et d'échec du greffon. Tout comme dans les artères coronaires originales, une diminution lipidique intensive peut atténuer le processus d'athérosclérose dans les greffons veineux. On pense que l'hyperplasie intimale dans le greffon veineux est une adaptation de la veine à de plus fortes pressions de la circulation artérielle. Ce processus est favorisé par la perte d'inhibition de la couche endothéliale, blessé pendant l'opération. Une nouvelle méthode sans contact de prélèvement du greffon pourrait être efficace pour prévenir la perturbation de la couche endothéliale, l'hyperplasie intimale qui s'ensuit et la perte du greffon. Il est démontré que le pontage à cœur battant et le prélèvement veineux par endoscopie, dont l'effet sur la réduction de la morbidité chirurgicale est connu, ne sont pas plus néfastes que le pontage avec circulation extracorporelle et le prélèvement veineux ouvert, respectivement, pour ce qui est de la perméabilité du greffon veineux. Plusieurs thérapies géniques peuvent prévenir l'hyperplasie intimale dans les modèles animaux, mais les données humaines obtenues jusqu'à présent sont décevantes. L'installation d'une endoprothèse externe autour d'un greffon veineux peut réduire la contrainte tangentielle exercée sur la paroi et l'hyperplasie intimale qui s'ensuit.

Coronary artery bypass grafting (CABG) is a highly effective method of relieving signs and symptoms of ischemic heart disease. However, its effectiveness is impeded by the limited life expectancy of saphenous vein grafts, which are the most common types of conduits used. The present paper reviews the studies that established our current understanding of the pathogenesis of saphenous vein graft failure, and strategies that have been shown to improve the lifespan of these grafts (Table 1). Studies cited in the present article were identified through a MEDLINE search and, for the sake of brevity, only frequently cited articles are reviewed here.

PATHOGENESIS AND MODELS OF VEIN GRAFT DISEASE

There are three main causes of vein graft failure. In the early (less than one month) postoperative period, acute thrombosis is the dominant etiology. This is related to technical factors such as small size of the target vessel resulting in poor distal runoff, size mismatch between the graft and the target vessel creating turbulent flow, graft ischemia, and disruption of the endothelial layer as a result of mechanical trauma and manual distention. The loss of the endothelial layer can promote platelet adhesion and thrombosis as well as vasospasm resulting from decreased nitric oxide levels. In the subacute period (one to 12 months), intimal hyperplasia is the main etiology. This results from the graft's adaptation to higher arterial pressures and loss of inhibition from the endothelial layer. Smooth muscle cells proliferate and then migrate into the intima, where proliferation continues. During the late period (more than 12 months), atherosclerosis becomes the major reason for graft stenosis and occlusion. As in native coronary arteries, vein graft atheromas can rupture and cause thrombotic occlusion of the graft (1). Vein graft atheromas are more diffuse and concentric, less calcified and have poorly developed or absent fibrous caps (2).

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TABLE 1
Strategies shown to be effective in extending the life of saphenous vein grafts

Intervention	Evidence
Antiplatelet therapy	Shown in randomized human trials to be superior to placebo (17-24)
Aggressive lipid-lowering therapy	Shown in randomized human trials to be superior to placebo or less aggressive lipid-lowering therapy (29-32)
No-touch technique	Shown in randomized human trials to be superior to the traditional technique (35,36)
Off-pump surgery	With an experienced surgeon, no worse than on-pump surgery in terms of graft patency (40-43)
Endoscopic vein harvesting	No worse than traditional technique (44,45)
Gene therapy	Shown to be effective in animal trials and human trials of peripheral bypass. Trial in coronary artery bypass graft patients did not show any benefit (57,58)
External stent	Preliminary data in animal studies indicate benefit in preventing intimal hyperplasia. Human data lacking (59-61)

Zwolak et al (3) transplanted rabbits' jugular veins in the carotid artery circulation. The veins were explanted and examined at 1 h, two weeks, four weeks and 24 weeks. At 1 h, there was loss of endothelium at the sites of anastamosis. Denuded areas were covered with platelets, microthrombi and leukocytes. The endothelium was restored within two weeks, although there was already a large increase in smooth muscle proliferation, which resulted in vessel wall thickening. Maximal wall thickness was reached by 12 weeks. The authors hypothesized that the vessel wall thickening was a response of the vein to the increased arterial pressure. This was based on the observation that the tangential wall stress, calculated as the ratio of lumen radius to wall thickness, is constant across a wide range of arteries in different species. In the transplanted jugular vein, the vessel wall thickened until the above ratio reached the normal value for the carotid artery (3).

Vein graft failure is associated with worse clinical outcomes. Halabi et al (4) identified 1243 patients from the Duke cardiovascular databank who had had CABG surgery between 1986 and 2003, and had a coronary angiogram within 18 months of surgery. Follow-up data were obtained for a median of 6.7 years. The primary end point of death, nonfatal myocardial infarction (MI) or revascularization was reached significantly more often in patients who had critical or occlusive vein graft disease on angiography compared with patients who had noncritical or no vein graft disease. Although it included a large number of patients, the study was limited by being a retrospective analysis (4).

LIFE EXPECTANCY OF VEIN GRAFTS AND RISK FACTORS FOR VEIN GRAFT DISEASE

Not long after the widespread adoption of CABG surgery, it was realized that vein grafts are prone to stenosis and closure. This was confirmed by angiographic data on several large cohorts of patients who had undergone bypass grafting. Loop et al (5) published data on the first 20,524 patients who had undergone CABG at the Cleveland Clinic (Cleveland, Ohio, USA) from 1967 to 1981. The mean time to catheterization was approximately two years. In women, 72.8% of grafts were patent compared with 79.2% in men. Campeau et al (6,7) published angiographic data on a group of 82 patients who were among the first 500 patients to receive CABG at the Montreal Heart Institute (Montreal, Quebec). The yearly occlusion rates were calculated to be 2.1% per year between years 1 and 5 to 7, and 5.2% per year between years 5 to 7 and 10 to 12. Higher low-density lipoprotein (LDL) (apolipoprotein B) and lower high-density lipoprotein (HDL) were associated with vein graft disease progression, but age, hypertension and smoking were not. Grondin et al (8) published data on a cohort of patients who had undergone CABG from 1968 to 1972. The patency rates at one month, one year and 10 years were 89.1%, 76.4% and 56.3%, respectively. Data from the Coronary Artery Surgery Study (CASS) registry (9) showed 90% patency at 60 days, 82% at 18 months and 82% at five years. Left anterior descending coronary artery grafts had higher patency rates than left circumflex or right coronary artery grafts.

Lytle et al (10) selected a group of patients who had undergone CABG at the Cleveland Clinic and had at least two subsequent angiograms, the first within five years of the operation and the second five years after the operation. Presence of angina and the native coronary artery grafted correlated (left anterior descending correlated better than right coronary or left circumflex) with graft occlusion on the first angiogram. On the second angiogram, increasing postoperative interval, interval MI, angina, diabetes and hyperlipidemia were correlated with graft closure. Therefore, risk factors for atherosclerosis were a factor in late graft closure but not early closure.

Fitzgibbon et al (11-13) reported data from two series of patients who had CABG at the Canadian National Defence Medical Centre (Ottawa, Ontario) and the University of Ottawa Heart Institute (Ottawa). All subjects were men and tended to be relatively young (mean age at surgery was 45 years in the first group and 49 years in the second group). The cumulative occlusion rate in the first group of 353 patients was 8% early after the operation, 13% at one year, 20% at five years, 41% at 7.5 years, 41% at 10 years and 45% at more than 11.5 years. The patency rates for the second group were 88% early after the operation, 81% at one year, 71% at 2.5 years, 75% at five years, 60% at 7.5 years, 60% at 10 years, 49% at 12.5 years and 50% at more than 15 years.

Goldman et al (14) reported data on patency rates of vein grafts from a series of patients who underwent CABG from 1983 to 1988. Patency rates were reported as 95% at one week, 84% at one year, 80% at three years, 69% at six years and 61% at 10 years after the operation. Grafts to the left anterior descending artery had significantly higher patency rates. Larger target vessel size, older age, aspirin use, lower serum cholesterol and better Canadian Cardiovascular Society Functional Class were also associated with higher patency rates. Smoking status and insulin-requiring diabetes were not associated with graft patency (14). More recent reports show that saphenous vein graft occlusion rates have not improved despite our better understanding of its pathophysiology and preventive strategies. In a series of patients who had CABG from 1996 to 2001, the saphenous graft occlusion rate at one year was 13.6% (15). Cho et al (16) reported one- and five-year patency rates of 82.4% and 80.2%, respectively, in patients who had CABG between 1995 and 1997.

Angiographic follow-up studies such as the ones cited above, despite including large numbers of patients, are limited by varying degrees of patient follow-up. Subjects who have occluded grafts may have higher mortality rates and, because angiograms can only be done on living patients, the patency rates may be falsely elevated. On the other hand, patients who have patent grafts will be less symptomatic and are more likely to refuse invasive follow-up angiograms, making the patency rates appear lower.

PREVENTION

Antiplatelet therapy

Chesebro et al (17,18) studied a group of patients undergoing CABG at the Mayo Clinic (Rochester, Minnesota) from 1977 to 1981. All patients received dipyridamole two days before the operation. At 7 h postoperatively, patients were randomly assigned to placebo or aspirin groups. Within one month of the operation, 3% of distal anastamoses in the aspirin group and 10% in the placebo group were occluded. The two groups were similar in blood loss, transfusions and reoperation for bleeding. The benefit of aspirin treatment persisted beyond the early postoperative period. Patients were re-evaluated at a mean of one year after bypass. The rate of new occlusions on the follow-up angiogram was 9% in the aspirin group and 14% in the placebo group.