Reprinted Article “Pathophysiology of Vein Graft Failure: A Review”

M.G. Davies, P.-O. Hagen*

Vascular Biology and Atherosclerosis Research Laboratory, Department of Surgery, Duke University Medical Center, Durham, North Carolina, USA

Abstract  Vein bypass grafting is an integral component of cardiovascular surgical practice for both arterial and venous diseases. However, many of these grafts will eventually fail due to either intrinsic or extrinsic causes. This review examines the current understanding and knowledge of venous histology, vein graft pathology and the associated endothelial and smooth muscle cell physiology and pharmacology. In addition, the status of research on the therapeutic control of vein graft intimal hyperplasia and accelerated atherosclerosis is assessed.

Key Words  Vein; Vein graft; Intimal hyperplasia; Atherosclerosis; Failure; Smooth muscle cell endothelium

Introduction
Cardiovascular surgery as a surgical discipline is less than a century old. Its birth coincided with a change in the prevailing philosophy of surgical practice from removal to repair. The earliest experiments with venous autografts were those of Gluck, Exner and Hopfner. However, these vein grafts all failed. Carrel and Guthrie successfully pioneered experimental autogenous vein bypass grafting. In 1906, Goyanes inserted the first autogenous vein graft into a human, using a popliteal vein as an interposition graft to bridge an arterial defect, following excision of a syphilitic popliteal aneurysm and in the same year, Lexer interposed a segment of great saphenous vein to bridge an arterial defect following excision of a posttraumatic axillary artery aneurysm. However, this patient died shortly thereafter and at autopsy, a clamp induced, non-occluding thrombus on the inner wall of the axillary artery was observed. This was the first description of the consequences of intimal injury. In the following two decades, vascular procedures did not gain popular acceptance because of inaccurate preoperative diagnoses and frequent perioperative distal thrombotic events. The development of contrast angiography and the introduction of heparin resolved these major impediments to such an extent that the risk to benefit ratio for bypass procedures became acceptable. Kunlin in 1949 described the modern popliteal bypass and Holden in 1950 reported the use of the saphenous vein to bypass an occluded superficial femoral artery. By 1962, the development of selective coronary angiography allowed Sabiston to perform the first right coronary artery bypass procedure. The art of coronary artery bypass grafting was further developed and refined by Garret and Favaloro. Although refinements in techniques and suture materials continue to occur, the guiding principles of the early surgeons are still applicable. Further advance in peripheral arterial vein bypassing came with the introduction of the

* Corresponding author. Per-Otto Hagen, Duke University Medical Centre, Box 3473, Durham, NC 27710, USA.

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The impetus for the development of this technique was the belief that explantation of the vein produced considerable endothelial and mural injury that was contributing to the high failure rates. Although Rob performed the first modern successful *in-situ* bypass in 1959,9 it was Hall who pioneered the principle, introduced technical modifications and developed a valvulotome.10 The *in-situ* technique did not enter into widespread use until the reports of Leather and Karmody appeared, detailing impressive short- and long-term patency results.11,12 The debate on the advantages of the *in-situ* technique compared to the reversed vein grafts is ongoing and at present it appears that there are equivalent patency rates for both types of grafts in all positions.

Clinical graft patency of autogenous saphenous vein grafts in the arterial circulation can be divided into three temporal categories: early (0 to 30 days), short-term (30 days to 2 years) or long-term (greater than 2 years). Generally, short-term failures are due predominantly to the development of intimal hyperplasia within the graft. Generally, short-term patency rates range from 80-90% with a subsequent annual failure rate of 2 to 5%. Up to 30% of vein grafts will require intervention within two years due to the development of haemodynamically significant intimal hyperplastic lesions (graft stenoses).13 The etiology of long-term failure is still unclear but a combination of progression of the host’s underlying disease, increased graft intimal hyperplasia and the development of atherosclerosis-like lesions within the vein graft appear to be the principal causes.

The concept of the “failing graft”, is one of a patent graft, whose patency is threatened by a haemodynamically significant lesion in the inflow/outflow tracts or within the body of the graft. Salvage of “failing” and failed bypass grafts remains an important clinical and technical challenge. As many as 80% of patients who present with recurrent limb ischaemia have an occluded graft and the patency of these occluded vein grafts after revision is often extremely poor.14,15 This bleak outcome with occlusion has led to the evolution of graft surveillance programs to detect “failing” grafts and has spurred research on means to control the development of intimal hyperplasia.

The increasing use of autogenous vein grafting procedures and the heightened awareness of its pathological sequelae has stimulated interest in venous biology and the biological consequences upon the vein of being placed in the arterial system. Studies of human veins harvested for bypass procedures have revealed that many have abnormal histologic and physiologic attributes.16–20 Furthermore, the quality of the saphenous vein can have significant clinical consequences.21,22 Vein grafts in the arterial circulation, must be considered as a viable, constantly adapting and evolving conduit. This review examines the physiology, pharmacology and pathology of veins and vein grafts in the preoperative, perioperative and postoperative periods. Better definition and understanding of the biological events during these periods should allow an accurate definition of the pathophysiology of vein graft failure and the development of new interventional therapies.

**Table 1** Mechanisms of vein graft failure.

<table>
<thead>
<tr>
<th>Intrinsic</th>
<th>Extrinsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor vein quality</td>
<td>Anastomotic problems</td>
</tr>
<tr>
<td>Missed valve/branch (in-situ)</td>
<td>Inflow tract stenosis or occlusion</td>
</tr>
<tr>
<td>Branch ligature placement</td>
<td>Outflow tract stenosis or occlusion</td>
</tr>
<tr>
<td>Intimal flaps</td>
<td>Thromboembolism</td>
</tr>
<tr>
<td>Intimal hyperplasia (anastomotic or intra-graft)</td>
<td>Graft sepsis</td>
</tr>
<tr>
<td>Accelerated atherosclerosis</td>
<td>Mechanical compression of the graft (entrapment or kinking)</td>
</tr>
<tr>
<td>Aneurysmal degeneration</td>
<td></td>
</tr>
</tbody>
</table>
responses.19,34,38 A recent study of the morphological
ations that saphenous veins have a decreased ability to
peripheral vascular surgery, although there are sugges-
who may in part account for the distinct patterns of lipid
between veins and arteries.29–33 Although there is no difference in total protein content, the amount of collagen appears to be greater in the saphenous veins.33 The total content of glycosaminoglycans is also similar in the saphenous veins and internal mammary arteries, although the major component present in the internal mammary artery is heparan sulfate while in the saphenous vein, derma-
veins compared to the internal mammary arteries. Nitric oxide and prostacyclin mediated relaxation responses of saphenous veins are much less and the maximal contractile forces generated are much greater than the internal mammary artery.34 In addition, local angiotensin con-
vein compared to the internal mammary artery.34 Saphenous veins demonstrate a spectrum of pre-existing pathological conditions ranging from significantly thickened walls to post phlebitic changes and varicosities at the time of harvest. Between 2 and 5% of these veins are unusable and up to 12% can be considered "diseased".21 These "diseased" veins have a patency rate one half that of "non-diseased" controls. The etiology of the venous diseases observed are multifactorial in origin and at the present time without gross morphological evidence of disease there is no clear prognostic indicator to discrimi-
the saphenous veins have a decreased ability to release
intra luminal nitric oxide and that smoking can impair both nitric oxide and prostacyclin mediated responses.19,34,38 A recent study of the morphological features of veins which have been used for bypass has shown intimal thickening and histological evidence of early atheromatous changes in the intima;39 additionally, the compliance of the vein wall can be correlated with the intimal thickness of the vessel.40 Primary cultures from saphenous veins of patients undergoing venous bypass reconstruction suggest that the smooth muscle cell
phenotypes present demonstrate a spectrum of sensitivity to growth inhibition by heparin.41

Perioperative Period

Perioperative manipulations of veins prior to their insertion have been shown to produce significant tissue damage. Such implantation injury leads to endothelial dysfunction, endothelial cell injury, endothelial denudation and smooth muscle cell injury each of which are important factors in the initiation of intimal hyperplasia. It is now recognised that every effort should be made to reduce the degree of implantation injury that a vein graft suffers.42–45 The basic principles of optimal saphenous vein procurement have been established by many studies and include as strict as possible adherence to the "no touch" technique, where there should be minimum manual and instrumental contact with the vessel,46 the use of papaverine as a smooth muscle cell relaxant,47–50 the use of an appropriate physiological storage solution, the avoidance of cold procurement solu-
tions48,51–54 and the control of distension pressures to ~100 mmHg during vein perfusion.53,55–57 Storage of vein grafts in non-physiological solutions (i.e. solutions which do not have an electrolyte composition, pH, osmolarity and temperature close to serum) leads to morphological damage, loss of endothelium dependent vasomotor function, increased smooth muscle cells of the vein graft.33,34 Saphenous veins in-situ >100 mmHg can produce both morphological and functional injuries to the endothelial and smooth muscle cells of the vein graft.53,56,57,61–65 The use of physiological solutions containing papaverine with osmotic and pH characteristics closer to serum or the use of whole blood to store vein grafts has improved the quality of the harvested vein graft, as assessed by functional, biochemical and histological studies. There appears to be a direct relationship between the morphological integrity of the vein graft prior to grafting and its later histopathological appearance and function.43,45 Poorly prepared vein grafts develop significantly greater intimal hyperplasia and increased smooth muscle cell contractility compared to carefully prepared vein grafts.43,45

The in-situ technique is considered to prevent many of the problems associated with implantation injury particularly with regard to the body of the vein graft. In-situ vein bypass grafts appear to have a greater degree of endothelial preservation and superior endothelial cell function compared to reversed vein grafts.56–73 Two recent articles have suggested that the use of a valvutome in the in-situ vein results in near total endothelial cell loss with an associated endothelial and smooth muscle cell function deficit implying that this particular type of in-situ technique is not beneficial.74,75 It is to be expected that the passage of a valvutome along the length of the vein which is akin to the passage of an embolectomy catheter along an artery would result in significant vessel wall injuries. However, not all in-situ techniques require the full length passage of a valvutome and studies using different tech-
niques would suggest that there is a significant morphologic
and functional benefit to the technique in the perioperative period.66–73

Postoperative Period

The preservation of the endothelial cell layer during harvest has changed the sequence of histological changes observed after implantation. It is now apparent from experimental and angiographic studies that the endothelium is preserved after implantation into the arterial circulation. Current studies have demonstrated that following exposure to the arterial environment, the cells experience severe stretching and increased tangential stress both of which contribute to endothelial cell damage.24,76 Within 24 hours, the endothelial cells are sandwiched between adherent luminal and infiltrating subendothelial polymorphonucleocytes with platelet deposition on the endothelial surface. In addition, there is extensive subendothelial oedema which reflects a combination of increased transmural flux and stretch damage due to the vein graft’s distension by arterial blood pressure. In experimental vein grafts smooth muscle cell proliferation occurs within the first 72 hours and continues for at least 7 days after insertion.77,78 Associated with the onset of proliferation, there are changes in specific membrane G-protein subunit expression in the smooth muscle cells with the de novo expression of $\alpha_{i}$ and $\alpha_{s}$ subunits. Microscopic development of intimal hyperplasia occurs later, from day 3 to 5 and increases rapidly between 7 to 14 days. There is a loss of contractile function with the onset of smooth muscle cell proliferation in the vein grafts. This contractile function returns with time after day 7. The pattern of smooth muscle cell contractility is markedly different to the control vein and is associated with additional changes in the functional coupling of receptors to G-proteins in vein grafts.79

Histological surveys of human saphenous vein grafts have been derived from specimens obtained at autopsy or at re-operation.24,80 Vein grafts obtained in the early postoperative period (<24 hours) show focal loss of endothelial cells particularly at the perianastomotic areas and fibrin deposition on the intima. An increased permeability of the endothelium has been observed with polymorphonucleocytes and platelet adherence to denuded areas within one day postoperatively. In the following four days, the deposition of intimal fibrin and the accumulation of various blood cell elements on the endothelial surface become more prominent. In addition, focal areas of denuded endothelium due to cells sloughing are also observed. By days 7 to 14, the endothelial cell layer in these grafts can be redefined and at this time intimal smooth muscle cells can be identified.24

Mechanisms of Vein Graft Failure

Intimal hyperplasia is the universal response of a vein graft to insertion into the arterial circulation and is considered to result from both the migration of smooth muscle cells out of the media into the intima and proliferation of these smooth muscle cells; later the smooth muscle cells deposit an extracellular matrix. Macroscopically, intimal hyperplastic lesions appear pale, smooth, firm and homogenous; they are uniformly located between the endothelium and the medial smooth muscle cell layer of a vein graft.81,82 Due to the lack of a well defined internal elastic lamina in veins, the separation between intimal and medial layers may be delineated by identification of the demarcation between the criss-cross orientation of the intimal hyperplastic smooth muscle cells and circular smooth muscle cells of the media; the outer limit of the media was defined by the interface between the circular smooth muscle cells of the media and the connective tissue of the adventitia. In general, intimal hyperplasia is a self-limiting process which does not produce luminal compromise and usually becomes quiescent within 2 years of graft insertion. However, in focal areas, the intimal hyperplastic process can proceed to significant stenosis.81–84 The first report of a vein graft stenosis was in 196585 but it was not until 1971 that the first report appeared citing intimal hyperplasia as the cause of the late occlusion in an aorto-coronary vein bypass graft86 but recent studies of peripheral vein grafts have documented that the majority of stenotic lesions which develop in a graft are composed of intimal hyperplastic tissue.83,84

The precise initiating stimuli for intimal hyperplasia have not been fully defined but it appears to be the response of the vascular smooth muscle cells to a combination of physical, cellular and humoral factors accompanied by dysfunctional endothelial regulation.81,82,87,88 Fibroblast growth factors contribute significantly to the medial proliferation of smooth muscle cells while the presence of either endogenous or exogenous platelet derived growth factors promote the migration of smooth muscle cells from the media to the intima. Several other mediators of both the tyrosine kinase (IGF-1, TGF-$\alpha$, $\alpha$-thrombin and interleukin-1$\beta$) and G-protein (angiotensin II, endothelin-1, serotonin) coupled membrane receptors have been shown to participate in these initial events. The mediators of the intimal proliferative response which occurs after migration from the media are unclear as are the factors which induce smooth muscle cell proliferation to wane and the synthesis of extracellular matrix to begin; however, there are suggestions that the activity of transforming growth factor-$\beta$ isoforms and endothelial cells are important in this transition from an “activated” state to a relative “quiescent” state.81,82,87

The majority of vein graft stenoses from human peripheral bypass grafts can be classified as intimal hyperplasia being highly cellular consisting predominantly of smooth muscle cells with a variable amount of connective tissue features similar to the intimal hyperplasia of animal models. During the initial perioperative period after saphenous vein coronary grafting, early stenosis and occlusions occurs in 5–8% of grafts due to intimal hyperplasia.13,22,83,84,89 Primary cultures from these stenotic lesions have suggested that the smooth muscle cell phenotype present is more resistant to the action of growth inhibitors such as heparin than other areas of the graft.90 Saphenous vein grafts excised from patients undergoing revision surgery continue to exhibit dose-dependent contractile responses to the
A role for increased wall tension in the development of intimal hyperplasia has been suggested. Growth factors, such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β), are implicated in the intimal response of vein grafts. These factors promote smooth muscle cell proliferation and migration, which are key components of the hyperplastic response.

Recent evidence suggests that deformation of smooth muscle cells by arterial haemodynamics can lead to activation of protein tyrosine kinases and thereby initiate smooth muscle cell proliferation. Vein grafts with lower flows are associated with greater intimal thickening. Similarly, low shear stress is also associated with increased development of intimal hyperplasia in vein grafts. Dobrin has shown in vein grafts that blood flow (closely associated with shear stress) is best associated with the formation of intimal hyperplasia and that deformation of the vessel wall in a circumferential direction is best associated with medial thickening.

Changes in haemodynamic parameters have been shown to affect the structure of both normal and diseased vessels. Haemodynamic alterations are implicated in the intimal response of vein grafts. Recent evidence suggests that smooth muscle cells are critical for the development of vein graft disease. Studies in animal models and clinical trials have shown an association of hyperlipidemia with the development of intimal hyperplasia. Hyperlipidemia has a significant additive effect on the formation of intimal hyperplasia compared to hyperlipidemia alone. In cases of combined hypertension and hyperlipidemia, there appears to be no additive effects on intimal hyperplasia development in vein grafts compared to hyperlipidemia alone. In contrast, however, the combined presence of diabetes and hyperlipidemia has a significant additive effect on the formation of intimal hyperplasia in experimental vein grafts. Interestingly, the profile of vasomotor function of vein grafts, in situations where more than one atherogenic risk factor is present, is attenuated compared to the comparative situation where only one disease state is present and the observed profiles are very similar to those observed in retrieved human vein grafts.

Diffuse dilatation or expansion of vein grafts is often seen when they are used as aorto-coronary bypass grafts. Approximately half of the vein grafts show a nonprogressive, uniform enlargement of the graft which is often as much as a 20% increase in the graft original transverse diameter. The factors responsible for this early dilatation may be a high flow rate and/or the expanding influence of the arterial pressure in tissue relatively unsupported by surrounding tissue. It has been suggested that the degree of dilation is most probably controlled by the concomitant development of intimal hyperplasia. Focal dilatation or aneurysm formation has been reported in vein grafts irrespective of the site of insertion. Although these aneurysms may be associated with atherosclerotic changes, the tissue from many aneurysms often does not differ histologically from the nonaneurysmal portion of the patent vein grafts.

With few exceptions, patients who undergo vein bypass grafting have a significant degree of arteriopathy, and concomitantly have one or more atherogenic risk factors present. Hypertension in both human and experimental models does not affect the development of intimal hyperplasia in the short or long term. Furthermore, it appears that hypertension is not associated with the later development of vein graft atherosclerosis. In contrast, both experimental and clinical studies have shown an association of hyperlipidemia with the development of intimal hyperplasia/atherosclerosis and with higher vein graft failure rates. Clinically, diabetes does not appear to impact significantly on vein graft patency but experimentally, it does increase short term intimal hyperplasia development. In cases of combined hypertension and hyperlipidemia, there appears to be no additive effects on intimal hyperplasia development in vein grafts compared to hyperlipidemia alone. In contrast, however, the combined presence of diabetes and hyperlipidemia has a significant additive effect on the formation of intimal hyperplasia in experimental vein grafts. Interestingly, the profile of vasomotor function of vein grafts, in situations where more than one atherogenic risk factor is present, is attenuated compared to the comparative situation where only one disease state is present and the observed profiles are very similar to those observed in retrieved human vein grafts.

The intimal hyperplastic lesions of vein grafts retrieved one month after aorto-coronary bypass in humans have been shown to consist of proliferating smooth muscle cells with only scattered macrophages in the subendothelium. Under hyperlipidemic conditions, venous tissue has demonstrated an avvity for the uptake of serum lipid surpassing that of arterial tissue in the same species. Intimal hyperplastic lesions of experimental hypercholesterolemic vein grafts are composed predominantly of lipid-laden smooth muscle cells with macrophages in various stages of foam cell formation interspersed between these cells. Macrophages are one of the principal cells involved in the development of atherosclerosis through the oxidation of lipoproteins and the formation of lipid peroxides. Oxygen free radicals and lipid peroxides also interfere with the vasomotor function of both endothelial and smooth muscle cells.
lipoproteins (LDL) is considered useful in slowing and preventing atherogenesis. In experimental vein grafts, reduction in serum cholesterol by 20% in hypercholesterolemic rabbits with either lovastatin therapy or ileal bypass surgery has resulted in a significant decrease in total graft cholesterol content. In rabbits, a 74% reduction in serum cholesterol concentrations over the first 28 postoperative days is associated with a 26% reduction in graft intimal thickness and the macroscopic absence of atheromatous lesions in the graft wall compared to untreated controls. A reduction of 26% in serum cholesterol in patients at 4 years after aorto-coronary bypass surgery using a combined cholestipol and niacin therapy for two years reduced the occurrence of stenotic and occlusive lesions in the vein bypass grafts of 16% of the patients suggesting that reduction of serum cholesterol may improve long term vein graft patency.

With particular regard to peripheral vein graft stenoses, no association has been found with patient age, sex, presenting symptoms, hypertension, diabetes or the condition of the outflow vessel. The incidence of stenosis appears higher the longer (i.e. the more distal) the insertion. Other studies have suggested that platelet dysfunction, hyperfibrinogenemia and lipoprotein (a) may be associated with an increased risk of stenosis development. At present the association with smoking and vein graft stenosis is equivocal.

Vein grafts retrieved from patients with angiographic evidence of occlusive disease demonstrate histologic features of atherosclerosis. The earliest these lesions have been seen is six months after implantation. Thus, it appears that these late occlusions of vein bypass grafts are due to the development of a rapidly progressive and structurally distinct form of atherosclerosis which has been termed "accelerated atherosclerosis" in order to distinguish it from "spontaneous atherosclerosis". Accelerated atherosclerosis is morphologically different to spontaneous atherosclerosis in that its lesions appear to be diffuse, more concentric and have a greater cellularity with varying degrees of lipid accumulation and mononuclear cell infiltration. The syndrome of accelerated atherosclerosis shares many of the pathophysiological features of intimal hyperplasia, however, the prime mediators of this type of atherosclerosis are likely to be the macrophage. In addition the endothelium overlying accelerated atherosclerotic lesions expresses the class II antigens which are not observed in spontaneous atherosclerosis.

**Therapeutic control of Intimal Hyperplasia**

Intimal hyperplasia remains one of the major obstacles to long term graft patency. Minimising the degree of implantation injury appears to be a simple and effective first step. Therapies to limit its development in vein grafts continues to attract considerable attention; however, no effective clinical regimen is presently available to counter the intimal hyperplastic response found in vein grafts. The use of aspirin is associated with a decrease in early thrombotic events in vein grafts but has not been documented to reduce the incidence of restenosis or the development of atherosclerosis. The various class of compounds which have shown promise in experimental vein bypass models are shown in Table 2. However, few have successfully been transferred to the clinical arena. Furthermore, one must be cautious in interpreting the results of clinical trials which have attempted to pharmacologically reduce the development of angioplasty induced hyperplastic restenosis, because in many respects, vein graft intimal hyperplasia is a distinct entity.

**Table 2  Therapeutic control in experimental models.**

<table>
<thead>
<tr>
<th>Class</th>
<th>Compound</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solutions</td>
<td>Warm iso-osmotic physiological solutions</td>
<td>Yes43,45</td>
</tr>
<tr>
<td>Mechanical</td>
<td>PTFE support</td>
<td></td>
</tr>
<tr>
<td>Anti platelet</td>
<td>Aspirin/dipyridamole</td>
<td>Yes157,158/No159</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>Desferrioxamine manganese</td>
<td>Yes161</td>
</tr>
<tr>
<td>Calcium channel Blocker</td>
<td>Verapamil</td>
<td>Yes162</td>
</tr>
<tr>
<td>Steroids</td>
<td>Prednisolone</td>
<td>Yes163/No164</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Cyclosporine</td>
<td>Yes158</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Captopril</td>
<td>Yes165</td>
</tr>
<tr>
<td>Receptor Antagonists</td>
<td>Ketanserin</td>
<td>Yes166</td>
</tr>
<tr>
<td>Heparins</td>
<td>Heparin</td>
<td>No167</td>
</tr>
<tr>
<td>Peptides</td>
<td>Angiopeptin</td>
<td>Yes168,169/No170</td>
</tr>
<tr>
<td>Amino acids</td>
<td>L-arginine</td>
<td>No171</td>
</tr>
<tr>
<td>ω-3 Polyunsaturated Fatty Acids</td>
<td>Eicosapentaenoic acid</td>
<td>Yes174,175</td>
</tr>
</tbody>
</table>

Yes: Intimal hyperplasia reduced by more than 25% of control.
No: No reduction in intimal hyperplasia or a reduction of less than 25% of control.
Conclusion

The saphenous vein remains a mainstay of surgical therapy for arterial occlusive disease. As a biologic conduit, it has distinctive native properties and a degree of intrinsic degeneration which can impact on subsequent performance. The greater understanding of the sequence of events in the preoperative, perioperative and postoperative phases of vein grafting which have been gleaned from experimental and clinical studies has allowed a clearer definition of vein graft pathophysiology. Vein grafts are living, constantly evolving conduits that adapt to the arterial circulation with the development of intimal hyperplasia but subsequently develop accelerated atherosclerosis each of which compromises patency. At present, intimal hyperplasia is the principal impediment to more durable grafts. The growing understanding of the pathology of vein grafts will ultimately produce practical therapeutic strategies to enhance graft function and control intimal hyperplasia.

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