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REVIEW ARTICLE

Pathophysiology of Vein Graft Failure: A Review

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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.[1] 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[2] and in the same year, Lexer interposed a segment of great saphenous vein to bridge an arterial defect following excision of a post-traumatic axillary artery aneurysm.[3] 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[4] and Holden in 1950 reported the use of the saphenous vein to bypass an occluded superficial femoral artery.[5] By 1962, the development of selective coronary angiography allowed Sabiston to perform the first right coronary artery bypass procedure.[6] The art of coronary artery bypass grafting was further developed and refined by Garret and Favaloro.[7,8] 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 *in-situ* technique. 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

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Table 1. Mechanisms of vein graft failure

Intrinsic	Extrinsic
Poor vein quality	Anastomotic problems
Missed valve/branch (*in situ*)	Inflow tract stenosis or occlusion
Branch ligature placement	Outflow tract stenosis or occlusion
Intimal flaps	Thromboembolism
Intimal hyperplasia (anastomotic or intra-graft)	Graft sepsis
Accelerated atherosclerosis	Mechanical compression of the graft (entrapment or kinking)
Aneurysmal degeneration	

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). Generically the causes of these failures may be classified as either intrinsic or extrinsic (Table 1). Early failures are ascribed to either technical failures occurring at the anastomoses, the position of the graft, kinking of the graft or initial poor distal runoff and account for less than 5% of all vein graft occlusions. The number of occlusions due to technical difficulties or inappropriate graft placement into poor inflow/runoff tracts is unlikely to diminish further given the present level of vascular diagnosis and surgical expertise. 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.

Preoperative Period

The wall of a vein is traditionally divided into three anatomic layers: the intima, the media and the adventitia. The intima is composed of a thin layer of endothelial cells beneath which is a fenestrated basement membrane, a subendothelial matrix of glycoproteins and connective tissue elements, and occasional intimal cells. In the media, the smooth muscle cells are arranged in an inner longitudinal and an outer circumferential pattern with collagen and elastic fibrils interlaced. The elastic fibrils appear to be orientated predominantly in a longitudinal direction. The adventitia forms the outer layer of vein wall and is often

thicker than the media and consists of a loose network of longitudinally orientated collagen bundles and scattered fibroblasts through which the vasa vasorum of the vein pass. The vasa vasorum of veins form an anastomotic plexus that provides resistance to ischaemic injury when there is local interruption of these vessels.[23,24] On occasion, longitudinal or spirally arranged smooth muscle cells may appear in areas of the adventitia adjacent to the media. The endothelial cells appear as flat polygonal cells with large centrally placed nuclei surrounded by a thin cytoplasm with the usual organelles and large numbers of plasmalemmal vesicles.[25] The junctions between the cells are mainly of a long occluding type and are considered more permeable than those of the arterial circulation.[24,25] Numerous microvilli can be demonstrated on the luminal surface and lesser numbers of cytoplasmic processes penetrate the subendothelial matrix.[25,26] The smooth muscle cells contain contractile fibres with dense bodies, prominent subsurface vesicles and the usual organelles. Veins are highly compliant over the range of venous pressures and are relatively non-compliant at arterial pressures.[27] Veins have a high degree of lactic dehydrogenase activity with lesser amounts of the other oxidative enzymes.[28] In addition, veins appear to have a different metabolic profile and tissue content compared to arteries which may in part account for the distinct patterns of lipid accumulation found 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, dermatan sulfate is the dominant glycosaminoglycan.[33] In association with these structural and biochemical differences, there are differences in the vasomotor function of the saphenous 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 converting enzyme activity which converts angiotensin I to angiotensin II and degrades bradykinin (a potent mediator of nitric oxide release) is greater in the saphenous 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 discriminate those veins which should be rejected as grafts.[21,22] It is apparent that most saphenous veins excised have a degree of intimal thickening and show altered *in vitro* smooth muscle cell contractility which are not dependent on donor age but can be positively correlated with donor gender.[17,20,35–37] Endothelial mediated relaxation appears to be intact in the saphenous veins of patients undergoing peripheral vascular surgery, although there are suggestions that saphenous veins have a decreased ability to release intraluminal 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 solutions[48,51–54] and the control of distension pressures to ~100mmHg 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 (decreased prostacyclin and NO release) but appears to leave smooth muscle cell contractility intact.[58, 59] During this period of storage the vein grafts do not experience significant hypoxia.[60] Furthermore, injudicious distension of veins (> 100mmHg) 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.[66–73] 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 functional 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 techniques 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 angioscopic 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 α_i and α_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 hrs) 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 1965[85] 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 graft[86] 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-α, α-thrombin and interleukin-1β) and G-protein (angiotension 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-β 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 physiologically relevant agonists which are markedly reduced compared to fresh saphenous veins.[91–93]Grafting of saphenous veins appears to result in the loss of endothelium-dependent relaxation responses to the receptor-coupled agonists, but not to the receptor-independent agonists.[34, 92–95] It is also suggested that endothelium mediated relaxation is preserved in retrieved human coronary vein bypass grafts but that there are significant decreases in this response with increasing severity of the intimal lesions.[96] In addition to the decreased NO mediated responses, there is a decrease in prostacyclin mediated responses in retrieved vein grafts.[34] Associated with the decrease both NO and prostacyclin activity, the local intrinsic fibrinolytic activity of vein grafts is reduced compared to ungrafted veins.[97, 98] This combination of decreased anti-aggregatory potential and fibrinolytic activity results in an increased thrombogenic surface and it is notable that two-thirds of vein grafts removed during redo coronary artery bypass operation show evidence of mural or occlusive thrombus.[99]

Changes in haemodynamic parameters have been shown to affect the structure of both normal and diseased vessels.[100] Haemodynamic alterations are implicated in the intimal response of vein grafts.[40, 101–112] 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.[113] Vein grafts with lower flows are associated with greater intimal thickening.[105] Similarly low shear stress is also associated with increased development of intimal hyperplasia in vein grafts.[106, 108] 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.[109, 111] Similarly, Morinaga reported that accelerated intimal thickening develops in vein grafts under low flow conditions (poor distal runoff) and is

reversed when these vessels are re-implanted into a system with normal parameters of flow.[110] Several studies have shown that rigid external support of a vein graft reduces intimal hyperplasia and can preserve endothelium dependent responses in vein grafts.[114–117] Other studies have suggested a role for increased wall tension in the development of intimal hyperplasia.[107, 112] In a recent study, it has been shown that rabbit arterial vein grafts removed from the arterial circulation after 2 weeks and returned to the venous circulation for a further 2 weeks demonstrate a significant regression of both intimal and medial thickening in the re-implanted grafts with restoration of endothelium dependent relaxation to all agonists.[118] A study by Fann using a similar procedure in a canine model has shown that vein graft intimal hyperplasia is not reduced when a graft implanted for 12 weeks is returned to the venous circulation and harvested after an additional 12 weeks.[119] However, the medial area regresses significantly in this study suggesting that circumferential deformation of the vessel wall is the dominant factor in the stimulation of medial thickening, while alterations in flow, are responsible for the decreases in intimal hyperplasia.

Diffuse dilatation or expansion of vein grafts is often seen when they are used as aortorenal bypass grafts.[16, 120, 121] 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 dilation or aneurysm formation has been reported in vein grafts irrespective of the site of insertion.[16, 122–126] Although these aneurysms may be associated with atherosclerotic changes, the tissue from many aneurysms often does not differ histologically from the non-aneurysmal 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.[127–130] Furthermore, it appears that hypertension is not associated with the later development of vein graft atherosclerosis.[127] 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.[127, 131, 132] Clinically, diabetes does not appear to impact significantly on vein graft patency but experimentally, it does increase short term intimal hyperplasia development.[127, 133] 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.[79]

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.[134] Under hyperlipidemic conditions, venous tissue has demonstrated an avidity for the uptake of serum lipid surpassing that of arterial tissue in the same species.[29, 135] 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.[131, 132, 136] Macrophages are one of the principal cells involved in the development of atherosclerosis through the oxidation of lipoproteins and the formation of lipid peroxides.[137–139] Oxygen free radicals and lipid peroxides also interfere with the vasomotor function of both endothelial and smooth muscle cells.[140–143] Reduction of both cholesterol and low density lipoproteins (LDL) is considered useful in slowing and preventing atherogenesis.[144] In experimental vein grafts, reduction in serum cholesterol by 20% in hypercholesterolemic rabbits with either lovostatin therapy or ileal bypass surgery has resulted in a significant decrease in total graft cholesterol content.[145] 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.[146] 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.[147] 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.[148] Other studies have suggested that platelet dysfunction, hyperfibrinogenemia and lipoprotein (a) may be associated with an increased risk of stenosis development.[149, 150] At present the association with smoking and vein graft stenosis is equivocal.[148, 150]

Vein grafts retrieved from patients with angiographic evidence of occlusive disease demonstrate histologic features of atherosclerosis.[128, 129, 151–154] 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".[82] 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.[155] 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.[156] The various class of compounds which have shown promise in experimental vein

Table 2. Therapeutic control in experimental models

Class	Compound	Outcome
Solutions	Warm iso-osmotic physiological solutions	Yes[43, 45]
Mechanical	PTFE support	Yes[116, 117]
Anti platelet	Aspirin/dipyridamole	Yes[157, 158]/No[159]
Antioxidant	Desferrioxamine manganese 21-aminosteroids	Yes[160] Yes[161]
Ca^{2+} channel Blocker	Verapamil	Yes[162]
Steroids	Prednisolone	Yes[163]/No[164]
Immunosuppression	Cyclosporine	Yes[158]
ACE inhibitors	Captopril Cilazapril	Yes[165] No[158]
Receptor Antagonists	Ketanserin Prazosin	Yes[166] No[167]
Heparins	Heparin LMW heparin	Yes[168, 169]/No[170] No[171]
Peptides	Angiopeptin	Yes[172]
Amino acids	L-arginine	Yes[173]
Ω-3 Polyunsaturated Fatty Acids	Eicosapentaenoic acid	Yes[174, 175]

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

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.

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 pathobiology of vein grafts will ultimately produce practical therapeutic strategies to enhance graft function and control intimal hyperplasia.

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References

1 Carrel A, Guthrie CC. Anastomosis of blood vessels by the patching method and transplantation of the kidney. *JAMA* 1906; **47**: 1648–1651.
2 Goyanes DJ. Substitution Plastica de las Arterias por Pas Vena o Arterioplastica Venosa, Aplicado Como Naevo Metodica Tratamiento de los Anemismas. *El Siglo Medico* 1906 Sept; **1**: 346–362.
3 Lexer F. Die ideale Operation des Arteriellen und des Arteriennen-venosen aneurysma. *Archiv Klin Chir* 1907; **83**: 459–460.
4 Kunlin J. Le traitment de l'arterite obliterante par la greffe veineuse. *Arch Mal Coeur* 1949; **42**: 371–372.
5 Holden WD. Reconstruction of the femoral artery for atherosclerotic thrombosis. *Surgery* 1950; **27**: 417.
6 Sabiston DC Jr. The Coronary Circulation: The William F. Reinhoff, Jr. Lecture. *John Hopkins Med J* 1974; **134**: 314–320.
7 Garrett HE, Dennis EW, DeBakey ME. Aortocoronary bypass with saphenous vein graft: Seven year follow up. *JAMA* 1973; **223**: 792–794.
8 Favaloro RG. Saphenous vein autograft replacement of severe sequential coronary artery occlusion. Operative technique. *Ann Thorac Surg* 1968; **5**: 334–339.
9 Rob CG. Discussion following Szilagyi DE, Smith RF, Elliott JP. Venous autografts in femoropopliteal arterioplasty. Observations in treatment of occlusive disease. *Arch Surg* 1964; **89**: 113–125.
10 Hall K. The great saphenous vein used *in situ* as an arterial shunt after extirpation of the vein valves. A preliminary report. *Surgery* 1962; **51**: 492–495.
11 Leather RP, Powers SB, Karmody AM. A reappraisal of the *in situ* saphenous vein arterial bypass: its use in limb salvage. *Surgery* 1979; **86**: 453–461.
12 Leather RR, Shah DM, Buchbinder D, Annest SJ, Karmody AM. Further experience with the saphenous vein used *in situ* for arterial bypass. *Am J Surg* 1981; **1981**: 142–144.
13 Mills JL, Fujitani RM, Taylor SM. The characteristics and anatomic distribution of lesions that cause reversed vein graft failure: a five year prospective study. *J Vasc Surg* 1993; **17**: 195–204.
14 Whittemore AD, Clowes AW, Couch NP, Mannick JA. Secondary femoropopliteal reconstruction. *Ann Surg* 1980; **193**: 35–42.
15 Green RM, Ouriel K, Ricotta JJ, deWeese JA. Revision of failed infrainguinal bypass graft: principles of management. *Surgery* 1986; **100**: 646–653.
16 Stanley JC, Ernst CB, Fry WJ. Fate of 100 aortorenal vein grafts: characteristics of late graft expansion. Aneurysmal dilatation and stenosis. *Surgery* 1973; **74**: 931–944.
17 Thiene G, Miazzi P, Valsecchi M, *et al.* Histological survey of the saphenous vein before its use as autologous aortocoronary bypass graft. *Thorax* 1980; **35**: 519–522.
18 Milroy CM, Scott DJA, Beard JD, Horrocks M, Bradfield JWB. Histological appearance of the long saphenous vein. *J Pathol* 1989; **159**: 311–316.
19 Schwartz LB, Radic ZS, O'Donohoe MK, McCann RL, Hagen P-O. Saphenous vein endothelium dependent relaxation in patients with peripheral vascular disease. *Ann Vasc Surg* 1992; **6**: 425–432.
20 Davies MG, Brockbank KGM, Hagen P-O. The relationship of human saphenous vein intimal area to age and gender. *Vasc Surg* 1992; **26**: 700–704.
21 Panetta TF, Marin ML, Veith FJ, *et al.* Unsuspected preexisting saphenous vein disease: an unrecognized cause of vein bypass failure. *J Vasc Surg* 1992; **15**: 102–112.
22 Varty K, Allen KE, Bell PRF, London NJM. Infrainguinal vein graft stenosis. *Br J Surg* 1993; **80**; 825–833.
23 Cheanveshi C, Effier DB, Hooper JR. The structural study of the saphenous vein. *Ann Thorac Surg* 1976; **20**: 636–645.
24 Cox JL, Chaisson DA, Gotlieb AI. Stranger in a strange land: the pathogenesis of saphenous vein graft stenosis with emphasis on structural and functional differences between veins and arteries. *Prog Cardiovasc Dis* 1991; **34**: 45–68.
25 Simionescu M, Simionescu M. *Endothelial Cell Biology in Health and Disease.* (1st ed.) New York: Plenum Press, 1988.
26 Merrilees MJ, Sheppherd AJ, Robinson MC. Structural features of saphenous vein and internal thoracic artery endothelium: correlates with susceptibility and resistance to graft atherosclerosis. *J Cardiovasc Surg* 1988; **29**: 639–646.

27 Wesly RLR, Vaishnau RN, Fuchs JCA, *et al.* Static linear and nonlinear elastic properties of normal and arterialized venous tissue. *Circ Res* 1975; **37**: 509–520.

28 McCabe M, Cunningham J, Wyatt AP, Rothnie NG, Taylor GW. A histological and histochemical examination of autogenous vein grafts. *Br J Surg* 1967; **54**: 147–155.

29 Fuchs JCA, Hagen P-O, Oldham HNJ, Sabiston DC. Lipid composition in venous arterial bypass grafts. *Surg Forum* 1972; **23**: 139–141.

30 Larson RM, Hagen P-O, Fuchs JCA. Lipid biosynthesis in arteries, veins and venous grafts (abstract). *Circulation* 1974; **30** (Suppl III): 139.

31 Hasegawa M. Rheological properties and wall structure of large veins. *Biorheology* 1983; **20**: 531–545.

32 Shafi S, Palinski W, Born GVR. Comparison of uptake and degradation of low density lipoproteins by arteres and veins of rabbits. *Atherosclerosis* 1987; **66**: 131–138.

33 Siisto T, Yla-Herttualla S, Luoma J, Rickkinen H, Nikkari T. Biochemical composition of human internal mammary artery and saphenous vein. *J Vasc Surg* 1990; **11**: 418–422.

34 Lüscher TF. Vascular biology of coronary bypass grafts. *Coronary Artery Disease* 1992; **3**: 157–165.

35 Bouissou H, Julian M, Pierraggi MT, *et al.* Vein morphology. *Phlebology* 1988; **3**: 1–11.

36 Lowell RC, Gloviczki P, Miller VM. *In vitro* evaluation of endothelial and smooth muscle function of primary varicose veins. *J Vasc Surg* 1992; **16**: 679–686.

37 Brockbank KGM, Davies MG, Fields SM, Pallos LL, Hagen P-O. The relationship of human saphenous vein smooth muscle cell contractile responses to donor age. *Vasc Surg* 1994; **28**: in press.

38 Higman DJ, Greenhalgh RM, Powell JT. Smoking impairs endothelium dependent relaxation of saphenous vein. *Br J Surg* 1993; **80**: 1242–1245.

39 Davies AH, Magee TR, Baird RN, Sheffield E, Horrocks M. Pre-bypass morphological changes in vein grafts. *Eur J Vasc Surg* 1993; **7**: 642–647.

40 Davies AH, Magee TR, Baird RN, Sheffield E, Horrocks M. Vein compliance: a preoperative indicator of vein morphology and of veins at risk of vascular graft stenosis. *Br J Surg* 1992; **79**: 1019–1021.

41 Munro EN, Chan P, Patel M, *et al.* Intimal hyperplasia: the variable response of the human smooth muscle cell (abstract). *XXI World Congress of the International Society for Cardiovasculara Surgery.* Lisbon Portugal: 1993: 107.

42 Adcock GD. Vein grafts: implantation injury. *J Vasc Surg* 1989; **10**: 587–589.

43 Quist WC, LoGerfo FW. Prevention of smooth muscle cell phenotypic modulation in vein grafts: a histomorphometric study. *J Vasc Surg* 1992; **16**: 225–231.

44 Cavaliari N, Abebe W, Hunter WJ, *et al.* University of Wisconsin solution prevents intimal proliferation in canine autogenous vein grafts (abstract). *VIIth Annual Meeting of the European Society for Vascular Surgery.* Barcelona, Spain: 1993: 44.

45 Davies MG, Hagen P-O. Influence of perioperative storage solutions on long term vein graft function and morphology. *Ann Vasc Surg* 1994; **8**: 150–157.

46 Gottlob R. The preservation of the venous endothelium by a dissection without touching and by an atraumatic technique of vascular anastomosis. *Min Chir* 1977; **32**: 693–700.

47 Haudenschild CC, Gould KE, Quist WC, LoGerfo FW. Protection of endothelium in vessel segments excised for grafting *Circulation* 1981; **64**: 101–107.

48 LoGerfo FW, Quist WC, Cranshaw HM, Haudenschild CC. An improved technique for preservation of endothelial morphology in vein grafts. *Surgery* 1981; **90**: 115–124.

49 LoGerfo FW, Quist WC, Cantelmo NL, Haudenschild CC. Integrity of vein grafts as a function of initial intimal and media preservation. *Circulation* 1983; **68** (Suppl): 117–124.

50 LoGerfo FW, Haudenschild CC, Quist WC. A clinical technique for prevention of spasm of endothelium in saphenous vein grafts. *Arch Surg* 1984; **119**: 1212–1214.

51 Karnsz M, Christman EW, Derrick JR, *et al.* Use of cardioplegic solution for vein graft distension and preservation: a light and scanning electron microscopic study. *Ann Thorac Surg* 1981; **32**: 68–74.

52 Souttiurai V, Stanley FC, Fry WJ. Ultrastructure of human and transplanted canine veins: effects of different preparation media. *Surgery* 1983; **93**: 28–38.

53 Bush HL, McCabe ME, Nabseth DC. Functional injury of vein graft endothelium: role of hypothermia and distension. *Arch Surg* 1984; **119**: 770–774.

54 Solberg S, Larsen T, Jorgensen L, *et al.* Cold induced endothelial cell detachment in human saphenous vein grafts. *J Cardiovasc Surg* 1987; **28**: 571–575.

55 Adcock GLD, Adcock OT, Wheeler JR, Gregory RT, Snyder SOJ, Goyle RC. Optimal techniques for harvesting and preparation of reversed autogenous vein grafts for use as an arterial substitute. *Surgery* 1984; **96**: 886–894.

56 Angelini GD, Passani SR, Breckenridge IM, *et al.* Nature and pressure dependence of damage induced by distension of human saphenous vein coronary artery bypass grafts. *Cardiovasc Res* 1987; **21**: 902–907.

57 Dries D, Mohammad SF, Woodward SC, Nelson RM. The influence of harvesting technique on endothelial preservation in saphenous veins. *J Surg Res* 1992; **52**: 219–225.

58 Angelini GD, Christi MI, Bryan AJ, *et al.* Preparation of human saphenous vein for coronary artery bypass grafting impairs its capacity to release of endothelium-derived relaxing factor. *Ann Thorac Surg* 1989; **48**: 417–421.

59 Schwartz LB, Radic ZS, O'Donohoe MK, McCann RL, Mikat EM, Hagen P-O. Functional and morphologic endothelial damage in rabbit external jugular veins stored in heparinized normal saline. *Blood Vessels* 1991; **28**: 511–519.

60 Dregelid E, Svendsen E, Sandberg S. Hypoxia does not occur during temporary storage of vein grafts in air equilibrated solutions. *J Cardiovasc Surg* 1992; **33**: 143–149.

61 Malone JM, Kischer CW, Moore WS. Changes in venous endothelial fibrinolytic activity and histology with *in vitro* distension and arterial implantation. *Am J Surg* 1981; **142**: 178–182.

62 Kennedy JH, Lever MJ, Addis BJ, *et al.* Changes in vein interstitium following distension for aortocoronary bypass. *J Cardiovasc Surg* 1989; **30**: 992–995.

63 Angelini GD, Bryan AJ, Williams HMJ, *et al.* Distension promotes platelet and leukocyte adhesion and reduces short-term patency in pig arteriovenous bypass grafts. *J Thorac Cardiovasc Surg* 1990; **99**: 433–439.

64 Schwartz LB, Massey MF, Davies MG, Klyachkin ML, Hagen P-O, McCann RL. Effect of *in vitro* pressurization on human saphenous vein vasoreactivity (abstract). *FASEB J* 1992; **6**: A1041.

65 Underwood MJ, More R, Weeresena N, Firmin RK, DeBono DP. The effect of surgical preparation and *in vitro* distension on the intrinsic fibrinolytic activity of human saphenous veins. *Eur J Vasc Surg* 1993; **7**: 518–522.

66 Bush HL, Jakubowski JA, Curl R, Deykin D, Nasbeth DC. The natural history of endothelial structure and function in arterialized vein grafts. *J Vasc Surg* 1986; **3**: 204–215.

67 Boyd JM, Stevens R, Harvey A, Silver D. Intimal integrity and fibrinolytic potential of reversed and *in situ* vein grafts. *J Vasc Surg* 1987; **5**: 614–621.

68 Cambria RP, Megerman J, Abbott WM. Endothelial preservation in reversed and *in situ* autogenous vein grafts. A quantitative experimental study. *Ann Surg* 1985; **202**: 50–55.

69 Buchbinder D, Singh JK, Karmody AM, Leather RP, Shah DM. Comparison of patency rate and structural changes of *in situ* and reversed vein arterial bypass. *J Surg Res* 1981; **30**: 213–322.

70 Magnant JG, Walsh DB, Schneider JR, James TW, Wagner RJ, Cronenwett JL. Differences in vasoreactivity of *in situ* and reversed vein grafts (abstract). *J Vasc Surg* 1992; **15**: 1068.

71 Miller VM, Bower TC, McCullough JL, Gloviczki P, Vanhoutte PM. Endothelium-dependent responses in non-reversed (*in situ*) vein grafts. *J Vasc Med Biol* 1990; **2**: 155–162.

72 O'Donohoe MK, Murchan PM, Marks P, Feeley J, Feeley TM. Endothelium derived relaxing factor is absent in experimental *in situ* vein grafts. *Eur J Vasc Surg* 1993; **7**: 144–150.

73 Davies MG, Klyachkin ML, Massey MF, Svendsen E, Hagen P-O. A comparative study of EDRF-mediated relaxation and smooth muscle cell function in arterial and venous vein bypass grafts. *Cardiovasc Surg* 1994; **2**: in press.

74 Sayers RD, Watt PAC, Muller S, Bell PRF, Thurston H. Structural and functional muscle injury after surgical preparation of reversed and non-reversed (*in situ*) saphenous vein bypass grafts. *Br J Surg* 1991; **78**: 1256–1258.

75 Sayers RD, Watt PAC, Muller S, Bell PRF, Thurston H. Endothelial cell injury secondary to surgical preparation of reversed and *in situ* saphenous vein bypass grafts. *Eur J Vasc Surg* 1992; **6**: 354–361.

76 Davies MG, Klyachkin ML, Dalen H, Massey M, Svendsen E, Hagen P-O. The integrity of experimental vein graft endothelium: implications on the etiology of early graft failure. *Eur J Vasc Surg* 1993; **7**: 156–165.

77 Schwartz LB, Pence JC, Kerns BJ, Iglehart JD, McCann RL, Hagen P-O. Kinetics of vein graft cell division and function. *Surgical Forum* 1991; **47**: 362–365.

78 Zwolak RM, Adams MC, Clowes AW. Kinetics of vein graft hyperplasia: association with tangential stress. *J Vasc Surg* 1987; **5**: 126–136.

79 Davies MG, Hagen P-O. Modelling the pathophysiology of vein graft failure. *J Vasc Surg* 1994; **20**: 139–141.

80 Svendsen E, Dalen H, Moland J, Engedal H. A quantitative study of endothelial cell injury in aortocoronary vein grafts. *J Cardiovasc Surg* 1986; **27**: 65–67.

81 Chervu A, Moore WS. An overview of intimal hyperplasia. *Surg Gynecol Obstet* 1990; **171**: 433–447.

82 Ip JH, Fuster V, Badimon L, Taubman MB, Chesebro JH. Syndromes of accelerated atherosclerosis: role of vascular injury and smooth muscle cell proliferation. *J Am Coll Cardiol* 1990; **15**: 1667–1687.

83 Sayers RD, Jones L, Varty K, *et al.* The histopathology of infrainguinal vein graft stenoses. *Eur J Vasc Surg* 1993; **7**: 16–20.

84 Berkowitz HD, Fox AD, Deaton DH. Reversed vein graft stenosis: early diagnosis and management. *J Vasc Surg* 1992; **15**: 130–142.

85 Breslau RC, DeWeese JA. Successful endophlebectomy of autogenous venous bypass grafts. *Ann Surg* 1965; **162**: 251–254.

86 Grondin CM, Meere C, Castonguey Y, *et al.* Progressive and late obstruction of an aortocoronary venous bypass graft. *Circulation* 1971; **43**: 698–702.

87 Clowes AW, Clowes MM, Fingerle J, Reidy MA. Regulation of smooth muscle cell growth in injured artery. *J Cardiovasc Pharmacol* 1989; **14** (Suppl 6): S12–S15.

88 Clowes AW. Intimal hyperplasia and graft failure. *Cardiovasc Pathol* 1993; **2** (Suppl): 179S–186S.

89 Kuntz RE, Piana R, Schnitt SJ, Johnson RG, Safian RD, Baim DS. Early ostial vein graft stenosis: management by athrectomy. *Cath Cardiovasc Diag* 1991; **24**: 41–44.

90 Chan P, Munro E, Patel M, *et al.* Cellular biology of human intimal hyperplastic stenosis. *Eur J Vasc Surg* 1993; **7**: 129–135.

91 Hanet C, Robert A, Wijns W. Vasomotor response to ergometrine and nitrates of saphenous vein grafts, internal mammary artery grafts and grafted coronary arteries late after bypass surgery. *Circulation* 1992; **86** (Suppl II): 210–216.

92 Park TC, Harker CT, Edwards JM, Moneta GL, Taylor LM, Porter JM. Human saphenous veins grafted into arterial circulation demonstrate altered smooth muscle and endothelial response. *J Vasc Surg* 1993; **18**: 61–69.

93 Cross KS, Davies MG, ElSanadiki MN, Murray JJ, Mikat EM, Hagen P-O. Long-term human vein graft contractility and morphology: A functional and histopathological study of retrieved coronary vein grafts. *Br J Surg* 1994; **81**: 699–705.

94 Miller VM, Reigel MM, Hollier LH, Vanhoutte PM. Endothelium-dependent responses in autogenous femoral veins grafted into the arterial circulation of the dog. *J Clin Invest* 1987; **80**: 1350–1357.

95 Lüscher TF, Diederich D, Siebenmann R, *et al.* Differences between endothelium-dependent relaxation in arterial and in venous coronary bypass grafts. *N Engl J Med* 1988; **319**: 462–467.

96 Ku DD, Caufield JB, Kirklin JK. Endothelium-dependent responses in longterm human coronary artery bypass grafts. *Circulation* 1991; **83**: 402–411.

97 Yao JST, Bergan JJ, Kwaan HC. Quantification of fibrinolytic activity in venous and prosthetic arterial grafts. *Arch Surg* 1974; **109**: 163–167.

98 Riseberg B. Fibrinolysis in grafted arteries and veins. *Hemostas* 1978; **40**: 512–517.

99 Solymoss BC, Nadeau P, Millette D, Campeau L. Late thrombosis of saphenous vein coronary bypass graft related to risk factors (abstract). *Circulation* 1988; **78** (Suppl II): 140.

100 Glagov S, Zarins CK, Masawa N, Xu CP, Bassiouny H, Giddens DP. Mechanical and functional role of non-atherosclerotic intimal thickening. *Frontiers of Medical and Biological Engineering* 1993; **5**: 37–43.

101 Brody WR, Kosek JG, Angell WV. Changes in vein grafts following aortocoronary bypass induced by pressure and ischemia. *J Thorac Cardiovasc Surg* 1972; **64**: 847–854.

102 Kennedy JH, Wieting DW, Hwang NHC, *et al.* Hydraulic and morphologic study of fibrous intimal hyperplasia in autogenous saphenous vein bypass grafts. *J Thorac Cardiovasc Surg* 1974; **67**: 805–813.

103 Faulkner SL, Fischer RD, Conkle DM, *et al.* Effect of blood flow rate on subendothelial proliferation in venous autografts used as arterial substitutes (abstract). *Circulation* 1975; **52** (Suppl I): 163.

104 Rittgers SE, Karayannacos PE, Guy JF, *et al.* Velocity distribution and intimal proliferation in autologous vein grafts in dogs. *Circ Res* 1978; **42**: 792–801.

105 Berguer R, Higgins RF, Reddy DJ. Intimal hyperplasia: an experimental study. *Arch Surg* 1980; **115**: 332–338.

106 Kamiya A, Togawa T. Adaptive regulation of wall shear stress on intimal thickening of arterially transplanted autogenous veins in dogs. *Am J Physiol* 1980; **239**: 14–21.

107 Karayannacos PE, Rittgers SE, Kakos GS, Williams TE, Meckstroth CV, Vasko JS. Potential role of velocity and wall tension in vein graft failure. *J Cardiovasc Surg* 1980; **21**: 171–178.

108 Morinaga K, Okadome K, Ohtsuka K, *et al.* Effect of wall shear stress on intimal thickening of arterially transplanted autologous veins in dogs. *J Vasc Surg* 1985; **2**: 430–433.

109 Dobrin PB, Littooy FN, Golan J, *et al.* Mechanical and histologic changes in canine vein grafts. *J Surg Res* 1988; **14**: 259–260.

110 Morinaga K, Eguchi H, Miyazaki T, Okadome K, Sugimachi K. Development and regression of intimal thickening of arterially transplanted autologous vein grafts in dogs. *J Vasc Surg* 1987; **5**: 19–30.

111 Dobrin PB, Littooy FN, Endean ED. Mechanical factors predisposing to intimal hyperplasia and medial thickening in autogenous vein grafts. *Surgery* 1989; **105**: 393–400.

112 Schwartz LB, O'Donohoe MK, Purut CM, Mikat EM, Hagen P-O, McCann RL. Myointimal thickening in experimental vein grafts is dependent on wall tension. *J Vasc Surg* 1992; **15**: 176–186.

113 Yang Z, VonSegesser L, Stulz P, Turina M, Luscher TF. Pulsatile stretch and Platelet-derived Growth Factor (PDGF): important mechanisms for coronary venous graft disease (abstract), *Circulation* 1992; **86** (Suppl I): 1–84.

114 KARAYANNACOS PE, GEER J, GAST M, HODGES R, BOND G, VASKO, JS. Wall strain in arterial vein grafts (abstract). *Clin Res* 1973; **21** 813.

115 BARRA JA, VOLANT A, LEROY JP, *et al.* Constrictive perivenous mesh prosthesis for preservation of vein integrity. *J Thorac Cardiovasc Surg* 1986; **92**: 330–336.

116 KOHLER TR, KIRKMAN TR, CLOWES AW. The effect of rigid external support on vein graft adaptation to the arterial circulation. *J Vasc Surg* 1989; **9**: 277–285.

117 HOPSON SB, LUST RM, ZERI RS, *et al.* The effects of wall tension on the development of intimal development of intimal hyperplasia in vein grafts. XXIst World Congress of the International Society for Cardiovascular Surgery. Lisbon, Portugal: 1993: 106.

118 DAVIES MG, KLYACHKIN ML, DALEN H, SVENDSEN E, HAGEN P-O. Regression of intimal hyperplasia with restoration of EDRF-mediated relaxation in experimental vein grafts. *Surgery* 1993; **114**: 258–271.

119 FANN JL, SOKOLOFF MH, SARRIS GE, YUN KL, KOSEK JC, MILLAR DC. The reversibility of canine vein graft arterialization. *Circulation* 1990; **82** (Suppl IV): 9–18.

120 DEAN RH, WILSON JP, BURKO H, FOSTER JH. Saphenous vein aortorenal bypass grafts: serial arteriographic study. *Ann Surg* 1974; **180**: 469–470.

121 FOSTER JH, DEAN RH, PINKERTON JA, RHAMY RK. Ten years experience with the surgical management of renovascular hypertension. *Ann Surg* 1973; **177**: 755.

122 DAVIDSON ED, DEPALMA RG. Atherosclerotic aneurysm occurring in an autogenous vein graft. *Am J Surg* 1972; **124**: 112–114.

123 DELAROCHA AG, PEIXOTO RS, BAIRD RJ. Atherosclerosis and aneurysm formation in a saphenous vein graft. *Br J Surg* 1973; **60**: 72–73.

124 RIAHI M, VASU CM, TOMATIS LA, SCHLOSSER RJ, ZIMMERMAN E. Aneurysm of saphenous vein bypass graft to coronary artery. *J Thorac Cardiovasc Surg* 1975; **70**: 358–359.

125 STORM FK, GIERSON ED, SPARKS FC, BARKER WF. Autogenous vein bypass grafts: biological effects of mechanical dilatation and adventitial stripping in dogs. *Surgery* 1975; **77**: 261–267.

126 SZILAGYI DE, ELLIOTT JP, HAGEMAN JH, SMITH RF, SALLOLMO CA. Biologic fate of autogenous vein implants as arterial substitutes: clinical angiographic and histopathologic observations in femoropopliteal operations for atherosclerosis. *Ann Surg* 1973; **78**: 232–246.

127 NEITZEL GF, BARBORIAK JJ, PINTAR K, QUERSHI L. Atherosclerosis in aortocoronary bypass grafts. Morphologic study and risk factor analysis 6 to 12 years after surgery. *Arteriosclerosis* 1986; **6**: 594–600.

128 ATKINSON JB, FORMAN MB, VAUGHAN WK, *et al.* Morphologic changes in longterm saphenous vein bypass grafts. *Chest* 1985; **88**: 341–348.

129 VIRAMI R, ATKINSON JB, FORMAN MB. Aortocoronary saphenous vein bypass grafts. *Cardiovasc Clin* 1988; **18**: 41–59.

130 O'DONOHOE MK, RADIC ZS, SCHWARTZ LB, MIKAT EM, MCCANN RL, HAGEN P-O. Systemic hypertension alters vasomotor function in experimental vein grafts. *J Vasc Surg* 1991; **14**: 30–39.

131 LANDYMORE RW, KINLEY CE, CAMERON CA. Intimal hyperplasia in autogenous vein grafts used for arterial bypass: a canine model. *Cardiovasc Res* 1985; **19**: 589–592.

132 KLYACHKIN ML, DAVIES MG, SVENDSEN E, *et al.* Hypercholesterolemia and experimental vein grafts. Accelerated development of intimal hyperplasia and abnormal vasomotor function. *J Surg Res* 1993; **54**: 451–468.

133 ROSENBLATT MS, QUIST WC, SIDAWY AN, PANISZYN CC, LOGERFO FW. Results of vein graft reconstruction of the lower extremity in diabetic and non-diabetic patients. *Surg Gynecol Obstet* 1990; **171**: 331–335.

134 AMANO J, SUZUKI A, SUNAMORI M, TSUKADA T, NUMANO F. Cytokinetic study of aortocoronary bypass vein grafts in place for less than six months. *Am J Cardiol* 1991; **67**: 1234–1236.

135 SCOTT HWJ, MORGAN CV, BOLASNY BL, *et al.* Experimental atherosclerosis in autogenous venous grafts. *Arch Surg* 1970; **101**: 677.

136 ZWOLAK RM, KIRKMAN TR, CLOWES AW. Atherosclerosis in rabbit vein grafts. *Arteriosclerosis* 1989; **9**: 374–379.

137 LENZ M, HUGHES H, RAYA J, TAYLOR A, GUYTON J. Vascular smooth muscle cell-mediated LDL oxidation; Loss of polyunsaturated fatty acids and formation of specific lipid peroxidation products (abstract). *FASEB J* 1992; **6**: A1323.

138 TAPPEL A. Measurement of and protection from *in vivo* lipid peroxidation. In: PRYOR WA, ed. *Free Radicals in Biology.* San Diego: Academic Press, 1980; 1–47.

139 PIOTROWSKI JJ, HUNTER GC, ESKELSON CD, *et al.* Lipid peroxidation: A possible factor in late graft failure of coronary artery bypass grafts. *J Vasc Surg* 1991; **13**: 652–657.

140 BECKMAN JS, BECKMAN TW, CHEN J, MARSHALL PA, FREEMAN BA. Apparent hydroxyl radical production of peroxynitrite: implications for endothelial injury from nitric oxide and superoxide. *Proc Natl Acad Sci USA* 1990; **87**: 1620–1624.

141 RUBANYI G. Vascular effects of oxygen derived free radicals. *Free Radic Biol Med* 1988; **4**: 107–120.

142 GALLE J, BASSANGE E, BUSSE R. Oxidized low density lipoproteins potentiate vasoconstrictions to various agonists by direct interaction with vascular smooth muscle. *Cir Res* 1990; **66**: 1287–1293.

143 SACHINIDOS A, MENGDEN T, LOCHER R, BRUNNER C, VETTER W. Novel cellular activities for low density lipoproteins in vascular smooth muscle cells. *Hypertension* 1990; **15**: 704–711.

144 FUSTER V. Progression-regression of atherosclerosis: molecular, cellular and clinical bases. *Circulation* 1992; **86** (Suppl III): 1–123.

145 MENCHACA HJ, MORRIS TJ, BOURDAGES H, NEFF T, MICHALEK VN, BUCHWALD H. Role of the mechanism of cholesterol reduction on vein graft atherosclerosis. *Surgical Forum* 1992; **XLIII**: 351–352.

146 KLYACHKIN ML, DAVIES MG, KIM JH, *et al.* Post-operative reduction of high serum cholesterol concentrations and experimental vein bypass grafts: Effect on the development of intimal hyperplasia and abnormal vasomotor function. *J Thorac Cardiovasc Surg* 1994; **107**: 556–566.

147 BLANKENHORN DH, NESSIM SA, JOHNSON RL, SANMARCO ME, AZEN SP, CASHIN-HEMPHILL L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987; **257**: 3233–3240.

148 SLADEN JG, GILMOUR JL. Vein graft stenosis: characteristics and effect of treatment. *Am J Surg* 1981; **141**: 549–553.

149 HOFF HF, BECK GJ, SKIBINSKI CJ, *et al.* Serum Lp(a) level as a predictor of vein graft stenosis after coronary artery bypass surgery in patients. *Circulation* 1988; **77**: 1238–1244.

150 CHESHIRE NJ, WOLFE JH, BARRADAS M, *et al.* Smoking and platelet activity predict infrainguinal graft stenosis. *Br J Surg* 1993; **80**: 520.

151 BUCKLEY BH, HUTCHINS GM. Accelerated atherosclerosis: a morphological study of 97 saphenous vein coronary artery bypass grafts. *Circulation* 1977; **50**: 163–169.

152 LORENZ RL, WEBER M, KOTZUR J, *et al.* Improved aortocoronary bypass patency by low dose aspirin: effect on platelet aggregation and thromboxane formation. *Lancet* 1984; **i**: 1261–1264.

153 BOURASSA MG, CAMPEAU L, LESPERANCE J, GRONDIN CM. Changes in grafts and coronary arteries after saphenous vein aortocoronary bypass surgery: results at repeat angiography. *Circulation* 1982; **65** (Supple II): 90–97.

154 CAMPEAU L, ENJALBERT M, LESPERANCE J, BAISLIC C, GRONDIN CM, BOURASSA MG. Atherosclerosis and late closure of aortocoronary saphenous vein grafts: sequential angiographic studies at 2 weeks, 1 year, 5 to 7 years and 10 to 12 years after surgery. *Circulation* 1983; **68** (Suppl I): 1–7.

155 MANNICK JA. Improved limb salvage from modern infrainguinal artery bypass techniques. *Surgery* 1992; **111**: 361–362.

156 Fuster V, Dyken ML, Vokonas PS, *et al.* AHA Medical/scientific statement: aspirin as a therapeutic agent in cardiovascular disease. *Circulation* 1993; **87**: 659–675.
157 McCann RL, Hagen P-O, Fuchs JCA. Aspirin and dipyridamole decrease intimal hyperplasia in experimental vein grafts. *Ann Surg* 1980; **191**: 238–243.
158 Hirko MK, McShannic JR, Schmidt SP, *et al.* Pharmacologic modulation of intimal hyperplasia in canine vein grafts. *J Vasc Surg* 1993; **17**: 877–887.
159 Boerboom LE, Olinger GN, Liu TZ, Rodriguez ER, Ferrans VJ, Kisselbah AH. Histologic, morphometric and biochemical evaluation of vein grafts in a nonhuman primate model. II modification of early changes by platelet inhibition with aspirin and dipyridamole. *J Thorac Cardiovasc Surg* 1990; **99**: 107–112.
160 Hagen P-O, Davies MG, Schuman RW, Murray JJ. Reduction of vein graft intimal area by ex-vivo treatment with desferroxamine manganese. *J Vasc Res* 1992; **29**: 405–409.
161 Davies MG, Barber L, Dalen H, Svendsen E, Hagen P-O. Pharmacologic control of the structural and functional consequences of vein graft intimal hyperplasia by a 21-aminosteroid (U74389G). *Eur J Vasc Surg* 1994; **8**: 448–456.
162 ElSanadiki MN, Cross KS, Murray JJ, *et al.* Reduction of intimal hyperplasia and enhanced reactivity of experimental vein bypass grafts with verapamil treatment. *Ann Surg* 1990; **212**: 87–96.
163 Pearce JE, Dujovny M, Ho KL, *et al.* Acute inflammation and endothelial injury in vein grafts. *Neurosurgery* 1985; **17**: 626–634.
164 Brody WR, Brown JW, Reitz BA, Fry DL, Michaelis DL. Effects of dipyridamole and methylprednisolone on intimal thickening in vein grafts. *J Thorac Cardiovasc Surg* 1977; **73**: 602–604.
165 O'Donohoe MK, Schwartz LB, Radic ZS, Mikat EM, McCann RL, Hagen P-O. Chronic ACE inhibition reduces intimal hyperplasia in experimental vein grafts. *Ann Surg* 1991; **214**: 727–732.
166 Massey MF, Davies MG, Svendsen E, Klyachkin ML, Barber L, Hagen P-O. Ketanserin inhibits experimental vein graft intimal hyperplasia. *J Surg Res* 1993; **54**: 530–538.
167 Norman PE, House AK. Influence of prazosin on experimental vein graft intimal thickening. *Br J Surg* 1992; **79**: 276–279.
168 Makhoul RG, Davis WS, McCann RL, Hagen P-O. Heparin decreases intimal hyperplasia in experimental vein bypass grafts (abstract). *Circulation* 1986; **74** (Supple II): II–26.
169 Kohler TR, Kirkman T, Clowes AW. Effect of heparin on adaptation of vein grafts to arterial circulation. *Arteriosclerosis* 1989; **9**: 523–528.
170 Cambria RP, Ivarsson BL, Fallon JT, Abbott WM. Heparin fails to suppress intimal proliferation in experimental vein grafts. *Surgery* 1992; **111**: 424–429.
171 Wilson NV, Salisbury JR, Kakkar VV. The effect of low molecular weight heparin on intimal hyperplasia in vein grafts. *Eur J Vasc Surg* 1994; **8**: 60–64.
172 Calcagno D, Conte JV, Howell MH, Foegh ML. Peptide inhibition of neointimal hyperplasia in vein grafts. *J Vasc Surg* 1991; **13**: 475–479.
173 Davies MG, Kim JH, Makhoul RG, Dalen H, Svendsen E, Hagen P-O. Reduction of intimal hyperplasia and preservation of Nitric Oxide (NO)-mediated relaxation by the NO precursor: L-arginine. *Surgery* 1994; **116**: 557–568.
174 Cahill PD, Sarris GE, Cooper AD, *et al.* Inhibition of vein graft intimal thickening by eicosapentaenoic acid: Reduced thromboxane production without changes in lipoprotein levels or low density lipoprotein receptors density. *J Vasc Surg* 1988; **7**: 108–117.
175 Landymore RW, Manku MS, Tan M, MacAulay MA, Sheridan B. Effects of low dose marine oils on intimal hyperplasia in autologous vein grafts. *J Thorac Cardiovasc Surg* 1989; **98**: 788–791.