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REVIEW

Neointimal Hyperplasia in Coronary Vein Grafts: Pathophysiology and Prevention of a Significant Clinical Problem

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ABSTRACT

Neointimal hyperplasia in aortocoronary vein grafts represents a significant problem that, by itself or by development of vein graft atherosclerosis, leads to the return of symptoms and to major adverse cardiac events after coronary artery bypass grafting. The main causes of neointimal hyperplasia are surgical trauma, intraoperative ischemia reperfusion injury, and implantation of a vein into the arterial circulation. All these pathogenetic factors cause a loss of protective endothelial mediators. The initiating steps lead to the induction of a significant inflammatory response and to the production of mitogenic factors in the vascular wall. DNA synthesis in vascular smooth muscle cells is markedly up-regulated, and intracellular signal transduction leads to transcription of immediate early genes, which causes an intense proliferative response. Vascular smooth muscle cells proliferate, migrate through the internal elastic lamina with the support of proteases, and transform from contractile-type into secretory-type cells. A thick layer of neointima is formed. The prevention of neointimal hyperplasia includes meticulous surgical technique, the choice of a large target vessel, and adequate intraoperative storage of the vein graft. Local intraoperative therapy of the implanted graft has been successfully tested in the experimental setting with a variety of substances that tackle different steps in the pathologic mechanism. Systemic pharmacologic therapy in clinical use primarily consists of the use of platelet inhibitors and anticoagulants. The transfer of experimental knowledge to bedside application has been slow. Gene therapy represents a promising field for the improved management of vein graft neointimal hyperplasia.

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CLINICAL IMPORTANCE OF NEOINTIMAL HYPERPLASIA IN CORONARY VEIN GRAFTS

The success of coronary artery bypass grafting (CABG) is limited by degenerative changes that occur in saphenous vein grafts, which are still frequently used in combination with internal mammary artery (IMA) bypass conduits. Thrombotic occlusions are the major cause of vein graft failure during the first postoperative days. Throughout the first postoperative year after CABG, stenoses caused by neointimal hyperplasia (NIH) play a major role. This narrowing, together with development of atherosclerotic lesions, finally leads to complete graft occlusion. Vein graft degeneration represents a specific pathologic entity called saphenous vein bypass graft disease [Yang 1993b, Motwani 1998].

Vein graft occlusion also represents a significant clinical and economic burden. Twenty percent of all vein grafts are occluded at 1 year postoperatively, 50% are occluded at 10 years [Campeau 1984, Loop 1986, Bourassa 1991, Cataldo 1993, Rajah 1994, FitzGibbon 1996], and 20% of all CABG patients require surgical or catheter-based coronary reintervention during this period [Campeau 1984, Loop 1986, Bourassa 1991, Cataldo 1993, Rajah 1994, Weintraub 1994, FitzGibbon 1996]. Development of NIH is one of the key steps of a vein graft on its way to degeneration and occlusion. The aim of this review is to outline the pathophysiology of NIH in coronary artery vein grafts and to present current experimental and clinical aspects of treatment.

PATHOPHYSIOLOGY OF NIH

Structure of the Vein Graft Wall

An untreated vein graft wall of a small laboratory animal such as the mouse or the rat consists of a single layer of endothelial cells (ECs) or intima that is separated from a vascular smooth muscle cell (VSMC) layer (media) by the internal elastic lamina. This elastic membrane is produced and maintained by the ECs and is composed of collagen type IV, laminin, heparan sulfate, and proteoglycans [Murphy 1992]. The media consists of several VSMC layers surrounded by

collagen, ground substance (eg, fibronectin, dermatan sulfate, proteoglycans, and chondroitin), as well as elastic fibers [Murphy 1992]. In the outer layer of the vein wall (adventitia), bundles of collagen and scattered, longitudinally aligned smooth muscle cells can be found. The adventitia also carries the vasa vasorum.

Immediate Postoperative Changes in Arterialized Veins

Immediately after implantation, arterialized vein grafts exhibit wall edema, disruptions, and dissections. The vein wall is then infiltrated by inflammatory cells. All of these changes were described in Carrel's pioneering studies at the beginning of the 20th century [Carrel 1983].

Definitions and Models of NIH

NIH is characterized by excessive growth of special cell types of the vein wall, primarily media-derived VSMCs and adventitia-derived myofibroblasts [Kalra 2000, Otani 2000]. VSMCs proliferate under the stimulation of a variety of growth factors, such as platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF). These VSMCs penetrate the internal elastic lamina and migrate into the intima, where they further proliferate and secrete matrix substances such as collagen, elastin, and proteoglycan [Campeau 1978, Sottiurai 1983, Snow 1990, Cox 1991]. During this process of migration, VSMCs undergo a phenotypic change from a contractile to a secretory cell type [Quist 1992]. The continuing secretion of ground substance at last leads to an increased intimal fibrosis and a decreased intimal cell content [Cox 1991, Dilley 1992, Allaire 1997]. A scheme for the main pathophysiological processes that occur in NIH formation is shown in Figure 1.

A dog model of NIH developed in the early 1970s showed that the pathologic changes in the arterialized vein are due to an increased intraluminal pressure and an impaired supply by the vasa vasorum. Vein grafts with intact adventitia developed pure intimal fibrosis, whereas vein grafts with damaged adventitia developed both intimal and medial fibrosis. Veins without adventitia that were implanted into the venous circulation showed medial fibrosis [Brody 1972a, 1972b].

Another study with a dog model describes the course of NIH during the first postoperative months [Fonkalsrud 1978]. At 48 hours postoperatively, irregular VSMCs were noted, the endothelium was severely damaged in part, and inflammatory cells were stuck to the injured endothelium. At 1 week postoperatively, subendothelial proliferation as well as inflammatory cells could be seen in the media and the adventitia. At 2 weeks postoperatively, collagen accumulated in the subendothelial proliferations, and gaps and areas of necrosis and bleeding occurred in the media. Chronic inflammation developed. At 2 months after vein graft implantation, the inflammatory infiltrate was decreasing, and the subendothelial proliferation showed an increased density. After 5 months, the endothelial layer regenerated, the media appeared fibrotic and thickened, and the adventitia presented slight fibrotic changes.

Another classic model was described by Zwolak and coworkers [1987]. Following interposition of the rabbit jugular vein into the carotid artery, platelets and leukocytes became attached to endothelium-denuded areas. Two weeks later, the denuded areas were completely reendothelialized. At this point, intimal thickening started. Within the first 4 weeks, VSMCs accumulated and proliferated, and deposition of extracellular matrix followed the cessation of the proliferative response. The thickening of the vein wall showed a maximum at 12 weeks postoperatively. The proliferative process can be expected to terminate if the ratio of the vessel radius to the wall thickness of the interposed vein is similar to the corresponding ratio of the arteries [Kohler 1989, Allaire 1997].

Yiping Zou of our research group has recently developed a mouse model of vein graft NIH. Significant cell loss and vessel wall degeneration in the vein graft are observed 1 week after implantation simultaneously with connective tissue deposition and mononuclear cell infiltration in the adventitia. By 2 weeks, mononuclear cells have infiltrated the vessel wall from both the lumen and adventitial sides. Vessel wall thickening occurs as early as 1 week after surgery and progresses to 4, 10, 15, and 18 times the original thickness of the grafted veins at 2, 4, 8, and 16 weeks, respectively, after surgery. The lumens of grafted veins are significantly narrowed. The 3 main processes that occur in this venous graft model are a marked loss of smooth muscle cells in vein segments at 1 and 2 weeks after grafting, a massive infiltration of $CD11b^{+}CD18^{+}$ mononuclear cells in the vessel wall between 2 weeks and 4 weeks following surgery, and a significant proliferation of VSMCs (α-$actin^{+}$) to constitute neointimal lesions between 4 weeks and 16 weeks after surgery [Zou 1998]. Figure 2 shows a typical mouse vein interposition graft with a marked neointima.

Davies and coworkers described wall changes that occurred when arterialized rabbit veins were reimplanted into the venous circulation. Vacuoles were noted in VSMCs at 3 days following reimplantation, and marked apoptotic changes were observed after 7 days. This landmark study demonstrated the reversibility of vein graft NIH [Davies 1999].

The restenosis after arterial catheter intervention exhibits a histologic pattern very similar to the changes observed in vein graft NIH. It is important, however, that these two pathophysiological processes be clearly distinguished. The classic pathologic course in the arterial model is as follows: A balloon catheter is rubbed over the intimal surface of an artery, usually the carotid artery, and the endothelium is denuded. Immediately thereafter, platelets adhere to the denuded area and degranulate. VSMC proliferation starts as early as 24 hours after injury and increases from 0.06%/day at baseline to 30%/day. Smooth muscle cells begin to migrate into the intima after 4 days. The VSMCs proliferate in the intima and secrete extracellular matrix. After 3 months, the cellular content of the intima is 20%, and the matrix content reaches 80% [Nikkari 1994].

Factors Predisposing for the Development of Vein Graft NIH

Clinical studies have demonstrated that saphenous vein grafts with reduced compliance, preexisting intimal

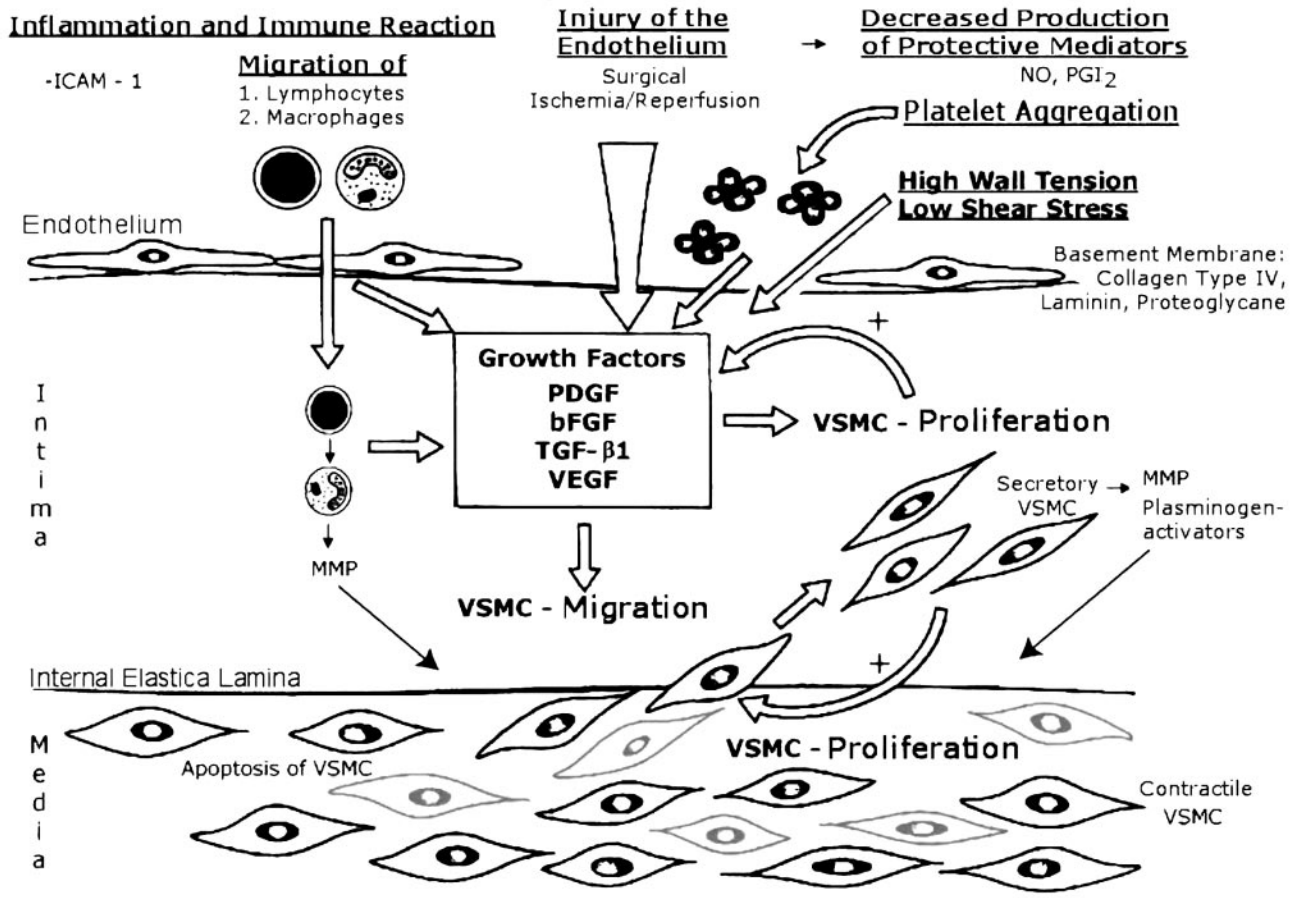

Figure 1. Scheme of the main mechanisms involved in the development of vein graft neointimal hyperplasia. NO indicates nitric oxide; PGI2, prostacyclin; PDGF, platelet-derived growth factor; bFGF, basic fibroblast growth factor; TGF-β1, transforming growth factor β1; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell; MMP, matrix metalloproteinase.

thickening, or other histologic abnormalities show an increased incidence of early and late bypass occlusion [Davies 1992, Marin 1993, Davies 1995]. A relatively high percentage of patients exhibit mild forms of saphenous vein intimal and medial fibrosis at implantation [Thiene 1980]. The degree of endothelial damage seems to be of paramount importance for the later fate of the vein graft [Waller 1985]. Ohki and coworkers investigated the role of vein graft valves on the development of NIH and found an increased wall thickness and neovascularization in the vein valve sinus compared with other sections of the vein graft [Ohki 1993].

The protective role of estrogens in NIH development is less clear than in the development of native coronary artery disease. Calcagno and coworkers demonstrated that incubation of canine and human veins with 17β-estradiol did not prevent NIH formation, and estrogen application in a rabbit vein graft interposition model failed to show a protective effect [Calcagno 1992].

Risk factors such as diabetes mellitus and hyperlipidemia seem to play a major role in vein graft degeneration, and smoking seems to promote saphenous vein graft disease, probably via nicotine-stimulated release of growth factors such as bFGF and transforming growth factor 1 (TGF-1) [Cucina 2000]. The role of lipoprotein(a), fibrinogen, and homocysteine has been the topic of recent investigations [Motwani 1998].

Distribution of the Disease along the Graft Course

Diffuse narrowing of the vein graft in the range of 30% occurs during the first postoperative year [Solymoss 1991]. On the other hand, localized intimal growth is possible at surgically traumatized sites. The anastomotic regions seem to be predisposed to NIH development [Bassiouny 1992, Cambria 1992, Davies 1994a]. Potential causes of this phenomenon are turbulent flow and increased wall stress to the vein at the anastomosis. Dilley et al noted pronounced arterial VSMC infiltration of the vein graft at the proximal anastomosis, and the investigators concluded that this infiltration was responsible in part for the predilection of this site for NIH formation [Berkowitz 1992, Dilley 1992, Hoch 1994]. Other investigators have not pointed out significant differences in neointimal growth along the graft course [Calcagno 1991].

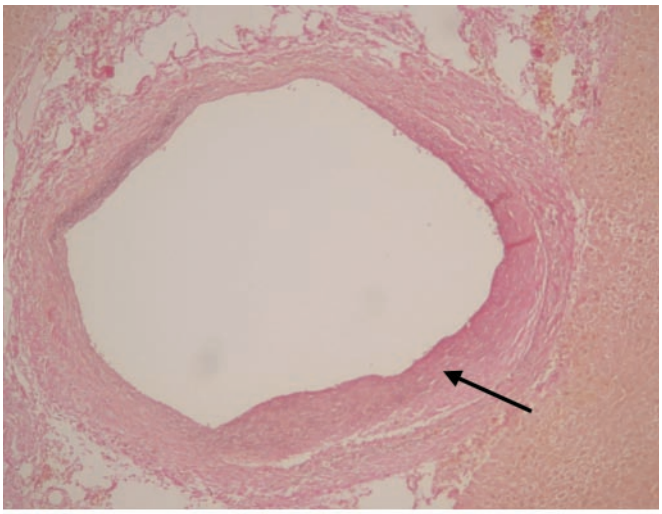

Figure 2. Neointimal hyperplasia in a mouse vein graft. The vein wall, which usually consists of a few cell layers, is thickened. A marked layer of neointima has formed (arrow). The medial and adventitial layers of the interposition graft are also thickened.

The Role of Surgical Preparation and Endothelial Damage

ECs steadily produce paracrine factors that inhibit VSMC proliferation. Any damage to these ECs can therefore promote NIH. Areas of endothelial damage are usually covered by platelets, which release PDGF and thereby stimulate VSMC ingrowth. The local platelet thrombus is organized systematically by VSMCs. The anastomotic suture line seems to be especially predisposed for platelet adherence [Lam 1991, Verrier 1996]. Intimal proliferation continues after endothelial regeneration and termination of platelet activation. EC- and VSMC-derived paracrine factors play a major role in this continuing process [Dilley 1992, Davies 1993]. The extent of neointimal proliferation probably does not correlate with the extent of endothelial damage in the implanted vein [Angelini 1992]. The data on the correlations between endothelial damage and EC repopulation are primarily derived from arterial injury models. Study with a rat model has demonstrated that isolated EC denudation with a fine nylon wire can promote NIH development. The degree of this injury is less pronounced than after balloon injury. After complete EC coverage of the defect, the intimal proliferative response is down-regulated [Fingerle 1990]. If an endothelial defect reaches 3 cm in diameter, repopulation by ECs from the defect borders becomes impossible [Clowes 1986]. The repopulating ECs show a decreased production rate of nitric oxide (NO, endothelium-derived relaxing factor) compared with native ECs [Niimi 1994]. This functional impairment has also been described by Wang and coworkers [1998].

In arteries, platelets adhering to EC defects can provoke NO release by the neighboring ECs. This causes vasodilation and inhibition of further platelet adherence. In vein grafts, however, local NO release is less pronounced than in arteries, and this lower level of NO release can even lead to vasoconstriction and increased platelet adherence.

Surgical preparation has been demonstrated to cause severe endothelial loss and functional impairment of the vein graft wall. Nonphysiological pressure dilation of human saphenous vein grafts decreases patency rates [Angelini 1990], and investigators have therefore suggested that vein grafts be dilated with physiological pressures via cannulae inserted into the aorta [Angelini 1989] or lines connected to the heart-lung machine [Waters 1993].

Intrinsic fibrinolytic activity in the human saphenous vein graft wall is also impaired by surgical preparation, particularly when dilating pressures in the range of 230 mm Hg are applied. Dilation pressures of 120 mm Hg seem to preserve intrinsic fibrinolytic activity [Underwood 1993, Shi 1997]. Surgically prepared vein grafts show an increased proliferative response in organ cultures compared with native veins [Soyombo 1993] and exhibit a high sensitivity for endogenous or exogenous vasoconstrictors [O'Neil 1994].

The Role of Arterialization

Vein grafts implanted into the arterial circulation encounter an unphysiological radial wall stress that is correlated with the ratio of vessel radius to the thickness of the vessel wall. The vein is maximally dilated, and blood flow velocity is reduced. The pulsatile nature of the arterial circulation seems to be a specific NIH-promoting factor [Predel 1992].

Berguer and coworkers demonstrated in a dog vein graft interposition model that a low blood flow leads to an increased wall thickness compared with a high blood flow [Berguer 1980].

High flow and high shear stress to the vein graft wall are the predominant stimulators for the release of the vasodilating and antiproliferative mediators NO and prostacyclin. The trigger for NO release, according to reports by Noris and coworkers, is an alternative organization of the cytoskeleton [Noris 1995]. The low shear stress in vein grafts can only insufficiently promote NO and prostacyclin release, and the production of mitogenic factors, such as PDGF, bFGF, and endothelin-1, is predominant [Grondin 1971, Bartlett 1987, Cox 1991, Allaire 1997]. An increased radial vein wall stress in the dog model also leads to up-regulation of bFGF receptors in the intima [Nguyen 1994]. Other studies have demonstrated that the deformation of VSMCs by arterial hemodynamics leads to protein tyrosine kinase activation, which can lead directly to increased proliferation [Yang 1992]. If venous VSMCs are exposed to a pulsatile stimulus of 60 cycles/min, cell growth is much more pronounced than if arterial VSMCs undergo a uniform stress [Predel 1992].

The Role of Ischemia-Reperfusion Injury

From the point of harvesting until flow is reestablished in the arterial circulation, vein grafts undergo a period of ischemia that is followed by reperfusion injury [Holt 1993]. All of the previously mentioned forms of damage to the vein graft wall are aggravated by this ischemia-reperfusion injury, which is characterized by a functional impairment of ECs with a subsequent decrease in the release of the antiproliferative mediators NO, prostacyclin, and adenosine. In addition, oxygen free radicals that promote proto-oncogene expression

are produced [Rao 1992, Holt 1993]. Hydrogen peroxide has been demonstrated to significantly increase the levels of the immediate early genes c-myc and c-fos [Rao 1992].

Veins are much more dependent on the circulation supplied by the vasa vasorum than are arteries. Harvesting a vein graft can theoretically lead to sustained ischemia with subsequent fibrotic changes in the graft wall [Yang 1997].

The Role of Inflammation

An early infiltration of a vein graft by inflammatory cells (monocytes, macrophages) is one obvious sign of the importance of inflammation in the process of NIH development [Angelini 1990]. Significant expression of monocyte chemotactic protein during NIH formation has been demonstrated in an animal model [Stark 1997].

The intercellular adhesion molecule ICAM-1, which is responsible for leukocyte adhesion and transmigration, seems to play a major role in the inflammatory process. Members of our research group have demonstrated that wall thickening is reduced by 30% to 50% in ICAM-1–deficient mice [Zou 2000].

Cherian and coworkers found increased amounts of S-100–positive cells (dendritic cells), $CD3^+$ cells (T-cells), and $CD68^+$ cells (macrophages) in areas of NIH in the human saphenous vein [Cherian 1999]. The specimens were obtained from patients who underwent coronary bypass reoperation after an average of 11.5 years. The inflammatory cells were unevenly distributed in the vein wall media with local accumulations in atherosclerotic plaques. Native human veins contained no S-100–positive cells.

The Role of Platelets

In a sheep arterial injury model, a reduction of platelet count with antiplatelet serum led to significant reduction of NIH [Moore 1976]. Such an effect has not yet been demonstrated for the arterialized vein. Platelets seem to play a major role by releasing growth factors.

The Role of Growth Factors

VSMC growth factors are predominately released by platelets, ECs, and macrophages. Macrophages seem to release these factors, especially under hypoxic conditions [Nguyen 1994, Shi 1997].

Platelet-Derived Growth Factor. PDGF is a polypeptide that was the first mitogenic substance found to stimulate NIH development [Ross 1974]. PDGF is stored in the α granules of platelets and can stimulate proliferation in veins but not in arteries [Yang 1993b]. PDGF has been observed to have a monocyte and macrophage chemotactic action that can potentiate the proliferative response [Newby 1993]. In cell cultures, PDGF has also shown a pronounced antiapoptotic action [Bennett 1995].

The proliferation of VSMCs continues in the neointimal area [Clowes 1986]. Growth factors, such as PDGF, TGF-β, insulin-like growth factor 1, and angiotensin II receptor, are massively present in this region [Hansson 1988, Cercek 1990, Majesky 1990, Daemen 1991, Majesky 1991, Nunokawa 1992, Viswanathan 1992, Schwartz 1995].

Francis et al cultured porcine venous bypass grafts in a serum-free medium at 1 and 4 weeks after implantation into the arterial circulation [Francis 1994]. Cellular proliferation in the neointimal and media layer was found, and endogenously produced PDGF in the vessel wall was suspected as the cause of ongoing proliferation in the neointima. The continued presence of PDGF in the neointimal layer after endothelial regeneration may be due to its secretion by ECs and VSMCs, which are stimulated by shear stress [Hsieh 1992]. This finding points out the role of PDGF in the late phase of NIH in vein grafts.

Basic Fibroblast Growth Factor. The activity of FGF is determined by two proteins, acidic FGF and bFGF. Both factors represent potent mitogens for a variety of cells, including ECs and VSMCs [DiCorleto 1986, Limanni 1988, Hughes 1993]. FGF is produced by ECs, VSMCs, and monocytes. The primary stimulus for release is injury to the vascular wall [Newby 1993], eg, vascular injury by nicotine [Hughes 1993, Cucina 2000]. Another stimulus of bFGF release is serine elastase. O'Blenes and coworkers demonstrated in a rabbit vein interposition graft model that a marked inflammatory response with significantly elevated levels of serine elastase can be noted 48 hours following implantation. Blockade of this enzyme results in a reduction of the inflammation [O'Blenes 2000].

In the presence of endothelial injury, exogenous bFGF causes VSMC proliferation [Walker 1986, Libby 1988, Hughes 1993], and antibodies against bFGF can inhibit this proliferative response. Already existing NIH, however, cannot be reduced with anti-bFGF antibodies [Olson 1992]. bFGF gene transfer promotes neointimal growth in porcine arteries, and inhibition of transcription by antisense oligonucleotides blocks this growth [Hanna 2000]. Both findings underline the significant role that this mitogenic protein plays in the pathologic mechanism [Nabel 1993].

Transforming Growth Factor β1. Dattilo and coworkers demonstrated in a dog model of venous CABG an increased expression of TGF-β1 as early as 2 hours after grafting. The elevated levels did not return to normal until the seventh postoperative day [Dattilo 1997].

Vascular Endothelial Growth Factor. Vascular endothelial growth factor (VEGF) is a cytokine that up-regulates the permeability and integrin expression of ECs. Additionally, VEGF modulates fibrinolytic as well as procoagulant factors [Pepper 1991, Senger 1997, Bobryshev 2001]. A prerequisite for VEGF activity is the expression of VEGF receptors 1 and 2 on the wall of the target cell.

VEGF plays a major role in embryonic development, wound healing, menstruation, and tumor growth. VEGF acts as a strong vasodilator in part due to the release of NO synthase (NOS), and VEGF stimulates cell migration and inhibits apoptosis [Malone 1981]. It has been demonstrated recently that the IMA releases more NO after VEGF stimulation than the saphenous vein [Broeders 2001].

The following stimuli can increase VEGF release and activity: hypoxia [Hata 1995], bFGF [Stavri 1995b], PDGF [Stavri 1995a], TGF-β [Pertovaara 1994], and tumor necrosis factors α and β [Jackson 2001].

High rates of neovascularization have been demonstrated in areas of NIH [Cherian 1999]. Bobryshev and coworkers investigated saphenous vein grafts from patients who underwent coronary redo operation and noticed neovascularization in the atherosclerotic lesions of the vein grafts. There was no new vascularization without VEGF expression. Macrophages, T-cells, mast cells, and dendritic cells were found between the newly formed vessels [Bobryshev 2001]. Macrophages were VEGF positive at a significant frequency.

Other Growth Factors. Other growth factors and their corresponding receptors have been identified: insulin-like growth factors [Sidawy 1993], epidermal growth factor, and connective tissue growth factor [Foegh 1994].

Vasoconstrictors also seem to play a role in the mitogenic response. Endothelin-1 stimulates VSMC proliferation, neutrophil adhesion, and the induction of growth factors in VSMCs. Endothelin-1 receptor blockade was successful in inhibiting intimal hyperplasia in an arterial balloon injury model [Dashwood 1998], but no such effects have been investigated in models of vein graft NIH.

The Role of Proteinases

Proteinases are very important factors that enable the growth and migration of cells through the surrounding matrix. Two classes of proteinases, plasminogen activators and metalloproteinases, exhibit increased activity during NIH development.

Matrix metalloproteinases (MMPs) can degrade the extracellular matrix, including collagen and elastin. Besides their action in NIH formation, MMPs show increased activity during tumor formation and in rheumatoid arthritis. MMPs are secreted by ECs, macrophages, and VSMCs (especially if these cells have undergone transformation into the secretory type).

MMP2 production and activity is higher in veins than in arteries [Guarda 1996].

The Role of the Adventitia

Recent porcine experiments have demonstrated that perivascular fibroblasts can transform into myofibroblasts and then migrate into the intima [Shi 1997]. According to Otani and coworkers, most cells in areas of NIH are not typical VSMCs but are myofibroblasts that have become α-actin$^+$ cells after migrating into the intima [Otani 2000]. This phenomenon is similarly described by Kalra and Miller [2000].

Intracellular Signal Transduction

During the first week after the implantation of a vein graft into the arterial circulation, the DNA content of ECs and VSMCs rises significantly and decreases thereafter. After the stimulation of these cells by growth factors, so-called immediate early genes become expressed. The primary immediate early genes are c-fos, c-myc, and c-jun, and their major role is to stimulate further gene transcription and to promote the transition of the cell into the cell cycle. The increased levels of expressed immediate early genes are lowered after 4 to 10 hours (c-fos, c-myc) [Mannion 1998a, 1998b, Suggs 1999].

The Role of Cardiovascular Risk Factors

Not all of the known risk factors for coronary atherosclerosis increase the risk of vein graft NIH and graft atherosclerosis. During the first postoperative year after clinical aortocoronary vein grafting, there is a known stimulating effect of smoking on NIH development [Motwani 1998]. Hypercholesterolemia seems to promote vein graft atherosclerosis after the third postoperative year, rather than the NIH that occurs during the early postoperative period. Diabetes mellitus and hypertension seem to play a minor role in the pathogenesis of NIH [Motwani 1998].

Clinical Diagnosis of NIH

Clinical diagnosis of the disease during the early postoperative months is difficult. At present, noninvasive imaging techniques such as ultrafast computed tomography scans and magnetic resonance imaging angiography lack the requisite sensitivity and specificity. Coronary angiography can detect stenoses of aortocoronary vein grafts, but the differential diagnosis of NIH and graft atherosclerosis is a problem. An attractive method for accurate detection of the disease is intravascular ultrasound. The problem of restenosis after catheter-based coronary interventions has been evaluated in a large number of studies [Gorge 1998]. Intravascular ultrasound has been much less frequently applied in the diagnosis of aortocoronary vein graft NIH despite the well-documented interest in this technique [Willard 1992]. In peripheral venous bypass grafting, intravascular ultrasound also represents a highly sensitive method [Gunen 1999]. A noninvasive tool for evaluating aortocoronary vein graft intimal hyperplasia is desirable for efficacy control of new therapeutics in clinical trials.

The Transition of NIH into Vein Graft Atherosclerosis

The transition of NIH into atherosclerotic lesions has only partly been clarified. Because atherosclerosis can develop in areas of vein graft NIH, these lesions have been called atherosclerosis-prone lesions [Stary 1992]. Atherosclerosis in vein grafts differs substantially from that in native coronary arteries. The distribution is diffuse and concentric, and the fibrous cap is very thin [Lam 1991, Solymoss 1991]. The basic morphologic changes, such as lipid deposition, calcium deposition, plaque rupture, and local thrombosis, are, however, the same in both forms of atherosclerosis. Lipid deposition into vein grafts seems to correlate with the degree of NIH, and experimental inhibition of NIH has been demonstrated to reduce lipid deposition into the vascular wall [Mann 1995, Guarda 1996].

PREVENTION AND THERAPY OF VEIN GRAFT NIH

Choice of Bypass Material: Advantages of Arterial Grafts versus Saphenous Vein Grafts

A variety of biologic advantages of arterial bypass grafts, especially with the IMA, over saphenous vein grafts have been observed in clinical as well as laboratory studies. Blood flow models have demonstrated higher flow rates and maximal shear stress in arterial grafts [Bach 1993]. The human

saphenous vein in culture exhibits much more marked NIH than the cultured IMA [Holt 1993], and PDGF stimulates VSMC proliferation in the saphenous veins but not in the IMA [Yang 1993b].

From the anatomical point of view, the IMA shows a perfect conformity of the lumen with that of target coronary arteries. Even in patients with generalized atherosclerosis, the IMA is rarely affected by the atherosclerotic process. The reason for this phenomenon is not clearly understood. A protective action of the musculature of the inner thoracic wall in reducing radial wall stress has been proposed. One of the major causes, however, may be an intense release of vasoactive and protective mediators from the IMA's vascular wall.

The production of vasodilating substances such as NO [Luscher 1988], prostacyclin [Chaikhouni 1986, Subramanian 1986, Bonatti 1998b], endothelium-derived hyperpolarizing factor [Liu 2000], and adenosine [Holt 1993] is much more pronounced in the IMA than in the saphenous vein. All of these mediators prevent spasm, platelet aggregation, and VSMC proliferation. NO is produced by NOS, which is present as constitutive and inducible forms in ECs. The second NO messenger is cyclic guanosine monophosphate (cGMP), which induces the vasodilating, platelet-inhibiting, cytoprotective, and antiproliferative action of NO. Our research group has demonstrated another highly potent mode of cGMP activation in human coronary artery bypass grafts. The natriuretic peptides atrial natriuretic peptide, brain natriuretic peptide, and urodilatin can stimulate a marked cGMP release in the IMA, whereas C-type natriuretic peptide seems to exert a specific cGMP-stimulating effect on the saphenous vein [Bonatti 1998a, 2000].

Endothelin-1 is one of the most potent vasoconstrictors and has a high sensitivity for veins, especially surgically prepared or damaged veins [Verrier 1996].

These findings prompt the question of whether heart surgeons should avoid vein grafts entirely and aim for totally arterial revascularization in every case. A variety of arterial grafts is available (both IMAs, radial arteries, right gastroepiploic artery, inferior epigastric artery), and clinical data have shown that bilateral IMA grafting definitely has long-term benefits [Ascione 2001, Taggart 2001]. Definite proof of the superiority of arterial grafting, however, is lacking [Sergeant 1997]. Arterial bypass conduits other than the IMA seem to achieve better patency rates than saphenous veins, but the acceptance of these bypass grafts varies among surgeons. Therefore, vein grafts are still an integral part of surgical coronary revascularization strategy. A major advantage of venous conduits compared with arterial conduits is that the harvesting of veins and their surgical handling are much easier.

Surgical Technique and the Role of Storage Solutions

Because of the extraordinary role of endothelial damage in the pathogenesis of NIH, it is of utmost importance that the vein graft be handled very gently throughout the whole procedure [Angelini 1989, Waters 1993].

The composition of the storage solutions used for vein grafts is a matter of ongoing debate [Chester 1993, Santoli 1993, Zerkowski 1993, Zilla 1993]. Normal saline solutions and whole blood are frequently used but may lead to functional disturbance of the vessels [Gundry 1980, LoGerfo 1983, Barner 1990]. In addition, storage at 4°C, which is often recommended, can damage rather than protect the endothelium [Solberg 1987], whereas a reduction in endothelial damage has been demonstrated by the use of warmer (20°C) solutions. Conflicting data are available for UW (University of Wisconsin) solution, which is normally used in transplantation surgery [Anastasiou 1997]. Balanced electrolyte solutions such as Plasma-Lyte (Baxter Healthcare, Glendale, CA, USA) also exhibit protective effects on vein graft function in vitro [Sanchez 1994].

Surgical experience has long shown that vein grafts should be anastomosed to an adequately large target vessel to guarantee long-term patency [Kalan 1990]. In an angiographic study of 218 grafts in 66 CABG patients, Roth and coworkers observed a 1-year patency rate of 90% for grafts anastomosed to target vessels >1.5 mm in diameter. The patency rate was only 69% for smaller vessels [Roth 1979]. Low flow rates in vein grafts to small-caliber target coronary arteries is the best explanation for this phenomenon.

Local Intraoperative Pharmacotherapy

Local intraoperative application of drugs to vein grafts has so far gained little clinical acceptance despite the fact that local therapy is broadly tested in the experimental setting. In the experimental treatment of vein graft disease, therapeutic agents are applied as solutions or as mixtures in gel-like carriers. Pluronic gel (BASF Corporation, Mount Olive, NJ, USA) is such a carrier. This gel is a liquid at 4°C and forms a gel at 20°C, allowing the release of drugs over a period of up to 3 days.

Target: Increase of Local NO Release. A significant reduction in vein graft NIH in a rabbit model was demonstrated by the application of the NO donor, spermine/NO [Chaux 1998]. A challenging finding in this study was that spermine alone led to a significant reduction in NIH. The carrier polymer also provoked a significant inflammatory response in the surrounding connective tissue.

Kown and coworkers have found a dose-dependent reduction in vein graft NIH in a rabbit model by the intraluminal application of an L-arginine polymer [Kown 2001].

A local increase in the concentration of the NO second messenger, cGMP, can significantly inhibit NIH in cultured human saphenous veins. Soyombo and coworkers reduced NIH in these vein cultures by applying isobutylmethylxanthine, a phosphodiesterase inhibitor, and 8-Br-cGMP, a stable cGMP analogue [Soyombo 1995].

Target: Growth Factors. VEGF usually promotes angiogenesis, but it also functions in the repair of vein graft intima. In a rabbit model, vein grafts were incubated with a solution containing 500 μg VEGF, and a 30% reduction in NIH was achieved [Luo 1998]. Hu and coworkers locally applied suramin, a PDGF receptor blocker, in a mouse model of vein graft NIH and reduced intimal hyperplasia by 70% [Hu 1999]. In the rabbit, the periadventitial application of β-cyclodextrin, a substance that can neutralize heparin-binding growth factors, also led to a significant reduction of NIH [Toes 1996].

Target: Ischemia-Reperfusion Injury. An oxygen free radical scavenger, desferrioxamine manganese, was used as a local agent by Hagen and coworkers. A significant reduction in NIH was demonstrated in 3 different segments of a vein interposition graft in the rabbit [Hagen 1992].

Target: Intracellular Signal Transduction. Tyrosine kinase plays a central role in signal transduction during the proliferative response of vascular tissue, and tyrphostin effectively inhibits this enzyme. Its application led to a 49% inhibition of NIH in a study with a rabbit model. In this study, tyrphostin was applied in dimethyl sulfoxide. Dimethyl sulfoxide alone also reduced vein graft NIH by 28%, a result that may be due to the free radical–scavenging properties of this substance [Huynh 1998].

Target: Cell Cycle Regulation, Transcriptional, and Translational Control. Rapamycin (sirolimus) has gained significant interest in the interventional cardiology community, because this substance delivered by stents has been shown to dramatically reduce restenosis after coronary balloon angioplasty [Suzuki 2001]. We recently applied rapamycin in a mouse model of vein graft NIH and noted a significant reduction in the proliferative response of vein grafts [Schachner 2004].

Other Targets. The actions of angiopeptin have been only slightly clarified. Most probably, angiopeptin reduces the number of angiotensin II receptors. The successful treatment of vein graft NIH in the rabbit by the local application of angiopeptin has been described by Calcagno and coworkers [1991].

Perioperative Systemic Pharmacotherapy

Target: Platelet Aggregation and Anticoagulation. The positive effect of platelet inhibitors for preventing NIH in arterialized veins has been proven in many experimental and clinical studies. Bilateral vein grafts were implanted in rhesus monkeys, and the animals were treated systemically twice a day with 165 mg aspirin and 25 mg dipyridamole. A significant reduction in NIH was noted at 16 weeks postoperatively following this treatment [McCann 1980].

The results of clinical studies of aspirin in inhibiting NIH seem clear; however, controversy exists regarding the appropriate aspirin dosage. Most studies have demonstrated that an early application of aspirin a few hours postoperatively is critical for achieving the inhibitory effects. Guidelines regularly published by the Consensus Conference of the American College of Chest Physicians currently recommend the clinical application of 325 mg aspirin from 6 hours to 1 year postoperatively [Stein 2001].

A question that increasingly arises is whether platelet inhibitors stronger than aspirin are more effective in the prevention of NIH. Ticlopidine and clopidogrel are two such substances that are indicated for patients who are allergic to aspirin or do not respond to aspirin [Motwani 1998]. Recent clinical data for clopidogrel and aspirin show that treatment with clopidogrel leads to a significantly reduced rate of long-term adverse events after CABG [Bhatt 2001]. It remains unclear, however, whether NIH development or atherogenesis in the vein grafts is the main target of clopidogrel.

According to several clinical studies, anticoagulants of the warfarin (Coumadin) group are also effective in preventing vein graft disease. They are indicated if operations in addition to CABG (eg, mechanical valve replacement) are performed that require postoperative anticoagulation treatment [Stein 2001].

Heparin as an anticoagulant has no proven effect on the development of vein graft NIH. Heparin did show an inhibitory effect on VSMCs in vitro [Weissberg 1993], but this effect could not be demonstrated in venous organ cultures or in animal models of vein graft NIH [Cambria 1992, Francis 1992, Wilson 1994].

Target: Increase of Local NO Release. Systemic application of the NO precursor L-arginine in rabbit experiments by Davies et al led to a 47% reduction in NIH by 4 weeks postoperatively. The substance was given from 7 days preoperatively until the veins were harvested [Davies 1994b].

Target: Inhibition of Inflammation and Immunosuppression. Studies of direct anti-inflammatory therapy have so far shown conflicting results. Steroids significantly inhibited NIH in studies with two animal models [Chervu 1989] but promoted an NIH response in a study with another model [Brody 1977]. A positive action in anti-inflammatory and immunosuppressive therapy has been described for cyclosporine [Hirko 1993], and cyclophosphamide and azathioprine have demonstrated a negative influence on the disease [Chervu 1990].

Target: Calcium Channel. Reports of successful therapy for vein graft disease with calcium channel blockers remain unconfirmed [Cambria 1992], even though calcium channel blockers can significantly reduce the proliferation of VSMCs in response to PDGF [Limet 1987, Dregelid 1992, Yang 1993a].

Target: Angiotensin-Converting Enzyme. Inhibitors of angiotensin-converting enzyme also show conflicting effects on the development of NIH. According to O'Donohoe and coworkers, captopril inhibits vein graft NIH [O'Donohoe 1991], but cilazapril promotes the disease, according to Hirko et al [1993].

Target: Ischemia-Reperfusion Injury. Lazaroids can neutralize oxygen free radicals via the formation of iron chelates. Davies and coworkers applied the lazaroid U74389G systemically in a rabbit model and effectively inhibited NIH development [Davies 1996].

Target: Inhibition of Proteinase Activity. The critical role of MMPs in the pathogenesis of NIH has already been elucidated. Porter et al investigated the MMP inhibitor marimastat in organ cultures of the human saphenous vein. A significant dose-dependent inhibition of NIH was noted [Porter 1998]. Doxycycline, another potent MMP inhibitor, achieved a 70% reduction in vein graft NIH in the same experimental setting [Porter 1999]. All-*trans*-retinoic acid can lead to reduced MMP production and activity in cell cultures [Clark 1987, Guerin 1997] and inhibits the proliferation and migration of mitogen-stimulated VSMCs [Hayashi 1995, Chen 1998]. This substance also significantly reduced NIH in a rabbit model of vein graft NIH when it was applied orally from 4 to 10 days postoperatively. A decrease in cell

proliferation and increased apoptosis were the primary responses noted in this model [Leville 2000a, 2000b].

Reduction of Wall Stress by External Support

Radial stress plays a highly significant role in the pathogenesis of vein graft NIH. A reduction in the development of the disease by providing external support has been demonstrated in the rabbit model [Kohler 1989, Izzat 1996]. Zweep and coworkers achieved therapeutic effects by using a bioprosthesis [Zweep 1993], and Batellier and his group successfully applied a polytetrafluoroethylene stent [Batellier 1993].

So-called biocompound grafts (vein grafts covered by a metal mesh) have been tested in animals and in clinical studies of patients from whom varicose veins were taken for CABG. According to these studies [Zurbrugg 2000], the medium-term patency rates of biocompound-modified varicose veins can compete with the patency rates of native saphenous veins.

Photodynamic Therapy

Photodynamic therapy takes advantage of substances that can cause injury to target cells if they are activated by specific wavelengths of light. This method showed inhibitory effects on cultured VSMCs [March 1993] and in an animal model of NIH [Ortu 1992]. In the animal model, the photosensitive compound motexafin lutetium was injected intravenously and activated with photodynamic therapy 24 hours later. A significant reduction in NIH was noted, but the effects were achieved only at 4 weeks postoperatively. At 12 weeks, the therapeutic action was absent, perhaps because the therapy depends on activated macrophages in the tissue [Yamaguchi 2000].

Gene Therapy

Potential Advantages of Gene Therapy for Vein Graft NIH. Gene therapy represents a very promising form of therapy for treating vein graft NIH. Theoretically, the vein graft is ideally suited for adequate vector exposure, because the vein structure is relatively simple and the vein can be completely harvested and incubated with the vector for a relatively long time before implantation into the aortocoronary circulation [Mann 1999a]. With this ex vivo approach, gene transfer can be concentrated to the target vascular tissue, and systemic spreading of vector material can be kept to a minimum [Schwartz 1999]. Because the key pathophysiological mechanisms of NIH occur during the first postoperative days, the transient expression of the vector may be an advantage rather than a disadvantage.

Experience with Gene Therapy of Vein Grafts in Animal Models. The proliferating neointimal cells are well suited for gene transfer. The principal transfectability of these cells by reporter genes is well documented by data from Takeshita et al [1994] and Guzman [1993].

One of the first experiments with gene therapy for preventing NIH was published by Victor Dzau's group. Liposomes and the hemagglutinating virus of Japan (HVJ) as a vector were used to transfer antisense oligonucleotides against cdc2 kinase and proliferating cell nuclear antigen (PCNA) into vein grafts in a rabbit model. A significant reduction of NIH was achieved by this approach [Mann 1995]. In a pig model, Mannion and coworkers observed a significant reduction of macrophage infiltration, vascular wall edema, and VSMC content after the application of c-myc antisense oligonucleotides [Mannion 1998a].

The NOS gene is one of the most promising candidates for a therapeutic gene for gene transfer in the prevention of NIH. A liposome-HVJ–mediated gene transfer of the endothelial cell NOS gene into dog veins led to a 60% reduction of intimal thickness [Matsumoto 1998]. Kibbe and coworkers investigated an adenovirus-mediated gene transfer of the inducible NOS gene in the pig model. The intima/media ratio was reduced by 30%, and NO production was increased by 5 times compared with the control [Kibbe 2001].

Successful adenovirus-mediated transfection of rabbit jugular veins with a nonphosphorylated form of the retinoblastoma protein was reported in 1999. Gene expression was noted in the endothelium and in the media of the veins, and a 22% reduction of NIH was seen after 4 weeks [Schwartz 1999]. Bai et al overexpressed the senescent cell–derived inhibitor protein (sdi-1, p21) in the rabbit jugular vein–carotid artery interposition graft. A highly significant reduction of NIH was noted. The investigators discussed the transformation of the VSMC phenotype from the embryonic to the adult form as a possible mechanism for the promising therapeutic effect [Bai 1998].

Transfection of rabbit jugular veins with the gene for elafin, a selective inhibitor of serine elastase, achieved a 70% inhibition of elastase activity, a 60% reduction in inflammatory cells, and a 50% reduction in intimal thickness [O'Blenes 2000].

The application of E2F transcription factor decoys in a rabbit model also showed a promising 90% reduction in NIH at 6 months. An interesting aspect of this model was the development of medial hypertrophy in the hypercholesterolemic rabbits, which seemed to achieve an increased mechanical stability of the transfected vessel [Ehsan 2001].

Fulton and coworkers demonstrated that application of c-myb antisense oligonucleotides can lead to a significant reduction of vein graft NIH [Fulton 1997]. Inhibition of the immediate early genes c-jun and c-fos by the antisense oligonucleotide approach can also reduce neointimal growth [Suggs 1999].

Experience with Gene Therapy of Human Vein Grafts. The transfer of the NOS gene into human saphenous vein specimens has been demonstrated [Cable 1999]. Cable and coworkers used an adenovirus vector encoding bovine endothelial NOS. The maximum of gene expression was located in the intima and in the adventitia, and NO generation by the transfected veins after stimulation with L-arginine and calcium ionophore was significantly increased compared with the controls. Functional studies in the organ bath demonstrated a significantly increased maximal relaxation of the transfected vessels after calcium ionophore stimulation.

Another promising approach for gene therapy of vein graft disease is transfection with natural inhibitors of MMPs (tissue inhibitors of MMP [TIMP]). Successful adenovirus-

mediated gene transfer of TIMP-1 into human saphenous veins was reported by Fernandez and coworkers [Fernandez 1998]. Using adenovirus, George and colleagues transfected human saphenous veins in culture with the TIMP-2 gene. After 14 days, the neointimal cell count was reduced by 71%, and neointimal thickness decreased by 79% [George 1998]. The most significant effect so far has been achieved by adenovirus-mediated transfer of the TIMP-3 gene. Besides its inhibitory action against MMPs, TIMP-3 can induce apoptosis in VSMCs. In the pig model, TIMP-3 gene transfer reduced neointimal thickness by 58%, and NIH reduction in cultured human saphenous veins reached 84% with this approach [George 2000].

Hypothesizing that increased soluble vascular cell adhesion molecule 1 (VCAM1) prevents the adhesion of monocytes to vascular tissue, Chen et al transfected porcine jugular veins and human saphenous veins with the VCAM1 gene. This adenovirus-mediated gene transfer was performed by intraluminal application of the vector. Marked expression of the gene was noted in the intima [Chen 1994].

The cell cycle regulatory protein p53 inhibits VSMC proliferation and leads to increased apoptosis. According to experiments by George and coworkers [2001], adenovirus-mediated transfer of p53 into cultured human saphenous veins can significantly reduce the proliferative response in the veins.

Clinical Gene Therapy on the Human Saphenous Vein. Experimental work by Matsumoto, Morishita, and their colleagues was the basis for the first applications of gene therapy in a clinical trial [Morishita 1995, Matsumoto 1998]. In the PREVENT trial, an E2F transcription factor decoy was used to prevent NIH development in infrainguinal vein grafts in the treatment of peripheral vascular disease. The first results demonstrated E2F inhibition and significantly decreased c-myc and PCNA levels in transfected veins. The patency rate of treated veins was 69% at 60 weeks, whereas the patency rate in the control group was 29%. A continued decrease in patency was noted in the control vein grafts. In the treatment group, however, patency remained stable during the last 35 weeks. Adverse clinical effects of the gene therapy approach were not observed in this trial [Mann 1997, 1999b, Mangi 2001].

FUTURE ASPECTS

Understanding the process of NIH in aortocoronary vein grafts and finding new ways of treatment will remain an important issue through the coming years, because vein grafts will probably remain an integral part of surgical coronary artery revascularization strategy. The transfer into the clinical environment of knowledge that has been accumulating in the experimental setting will be one of the major challenges. Although groups at risk have already been well evaluated, other specific risk groups for the development of NIH need to be defined. There will be questions in the field of vein graft NIH as new anastomotic connector devices are developed for coronary surgery. Surgeons and cardiologists will have to deal with new intraoperative and postoperative pharmacologic approaches to the treatment of the disease. Local pharmacotherapy will require adequate modes of drug delivery. New diagnostic tools that enable accurate visualization of NIH development in implanted grafts may become available. Finally, the aortocoronary vein graft represents an ideal biologic structure for first steps in human gene therapy. Because of the relatively primitive structure of the saphenous vein and because intraoperative ex vivo treatment is possible, vein graft NIH may become one of the first diseases to be treated by gene therapy on a broader basis.

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