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Adaptive changes in autogenous vein grafts for arterial reconstruction: Clinical Implications

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Abstract

For patients with the most severe manifestations of lower extremity arterial occlusive disease, bypass surgery using autogenous vein has been the most durable reconstruction. However the incidence of bypass graft stenosis and graft failure remains substantial and wholesale improvements in patency are lacking. One potential explanation is that stenosis arises not only from over exuberant intimal hyperplasia but also due to insufficient adaptation or remodeling of the vein to the arterial environment. Although in vivo human studies are difficult to conduct, recent advances in imaging technology have made possible a more comprehensive structural examination of vein bypass maturation. This review summarizes recent translational efforts to understand the structural and functional properties of human vein grafts and places it within the context of the rich existing literature of vein graft failure.

Introduction

With the changing demographics of an aging population and a near-epidemic of diabetes mellitus, the prevalence of peripheral arterial disease (PAD) now approaches between 9–12 million Americans.[1,2] Among established treatments for advanced PAD, the autogenous vein bypass graft has been both the clinical standard and the most comprehensively studied revascularization strategy. Nevertheless, 30–50% of saphenous vein grafts fail during the intermediate period from 1–18 months postimplantation. This period is the most active from a biologic standpoint and the culprit lesion is intimal hyperplasia (IH). It is clear that IH is universal to all implanted vein grafts but why it becomes pernicious and progresses to clinical stenosis at some locations in some veins while others are relatively spared is not clear. In addition, all vein grafts undergo structural remodeling of the lumen and wall to some extent during this same time period. Long-term patency of the vein graft likely depends on adequate adaptation into the arterial environment as well as a relative moderation in the development of IH.

For well over 50 years surgeon-scientists have studied histopathological changes in the vein after implantation, developed animal models, documented efficacy of vein bypass, and with the aid of modern biology techniques, elucidated molecular signaling pathways involved in IH. With the later, came the potential of genetic engineering of the vein graft and the promise

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Competition of interest: none

of improving patency through novel therapeutics with specific molecular stratagies.[3–5] For example, the PRoject of Ex-Vivo graft ENgineering via Transfection III (PREVENT III) was a phase III study employing an anti-sense DNA decoy molecule to the transcription factor E2F. This randomized, placebo-controlled, double blinded, trial was specifically powered to detect a significant difference in vein graft patency in a cohort of over 1400 patients with critical limb ischemia (CLI). In this contemporary study, the overall one-year primary patency rate was 61% - a value that has not changed for the past several decades.[6] While this trial ultimately failed to meet its primary efficacy endpoint, it underscored our lack of understanding of the pathophysiology of vein graft failure perhaps by underestimating the complexity and redundancy in the molecular elements contributing to IH or neglecting other potential variables such as remodeling.[4,6]

Advances in imaging technology during the last decade such as high resolution ultrasound, 3-diminsional magnetic resonance imaging (3D-MRI), and intravascular ultrasound have greatly facilitated our ability to study human vein bypass grafts in vivo.[7,8] These modalities have the ability to reliably resolve sub millimeter structures.[8–10] Serial changes in the vein graft structure and function can be quantified and patterns of normal and abnormal adaptation be discerned. Beyond luminal changes, wall thickness can now be determined and mathematical models constructed building on the rich existing experimental data compiled from animal and histomorphological studies from the last 4 decades.

Herein, recent advances to better understand the pathogenesis and subsequent evolution of vein graft failure are outlined. Importantly, in vivo observations are emphasized and placed within a historical and a clinical context whenever possible.

The human saphenous vein and the universal response to injury

The normal in vivo appearance of the human saphenous vein is a light blue, thin walled structure that easily distends with minimal pressure. Unfortunately, many veins used in bypass grafting have pre-existing lesions such as endothelial damage, medial hypertrophy, or intimal thickening which may give them a slightly sclerotic appearance.[11,12] This creates considerable variability in the normal (useable) range of vein wall thickness from 180 to 650 μm.[13] While severe changes render the vein unusable, the impact of subtle pre-bypass morphological changes on the future development of vein graft stenosis is not known, though decreased compliance has been shown to be associated with early vein graft failure.[14] The focal nature of vein graft stenosis detected by surveillance ultrasound studies, suggests that predisposing lesions may exist in these areas.[15]

Intimal hyperplasia was first described in veins by the Nobel prize winning physician Alex Carrel in 1906 and is generally regarded as the universal injury response to a blood vessel: regardless of the injury or the vessel.[16] It is thought to be due to a proliferation of smooth muscle cells (SMC) which have undergone a phenotypic switch from a quiescent, contractile phenotype to that of a synthetic migratory phenotype. The source the SMCs which contribute to the intimal hyperplasia has long been thought to be from the media of the vessel wall but the identification of graft-extrinsic cells such as peri-adventitial fibroblast or circulating precursor cells has challenged this concept.[17–22] Production of extracellular fibrous matrix and ground substance by synthetic SMCs leads to a progressive increase in intimal and medial fibrosis, reduction in cellularity, and overall stiffening of the vein graft which may subsequently limit the graft's ability to properly remodel in the arterial circulation. The endothelial cells play a key role in regulation of intimal growth by a number of tonic growth-inhibitory mechanisms.[23,24] Endothelial cell loss or damage markedly attenuates these growth modulating effects.

Biological mediators are also involved.[25] Liberated growth factors from platelets lining the injured vessel wall, infiltration of inflammatory cells through the permeable EC layer,

circulating inflammatory molecules, and endothelial dysfunction are likely operative.[26–28] The platelet-endothelium interaction is emphasized by the effectiveness of platelet inhibitors in preventing the early and late occlusion of vein grafts.[29,30]

The harvesting and preparation of the saphenous vein for bypass surgery affords ample opportunity to impart injury. Mechanical manipulation, valve lysis, pressure distension, ischemia/reperfusion, devascularization and denervation, and transposition into the arterial environment contribute to the injury of the vein.[31–33] A number of intra-operative techniques have been employed in an attempt to mitigate the venous injury. These include no-touch harvesting technique, various storage solutions such as the University of Wisconsin Solution, and placing veins in the in situ configuration to theoretically decrease manipulation and warm-ischemia time.[34–38] In general, it is felt that storage in a papaverine-treated, tissue culture solution, gentle harvesting, and the use of controlled distension decreases endothelial injury and possibly subsequent IH formation.[39]

The causal relationship between arterial hemodynamics and IH is well established and, in a sense, fulfills Koch's postulates. For example, Brody demonstrated that veins transposed into the arterial circulation developed IH whereas those dissected and re-anastomosed to the venous circulation did not.[40] Experimental vein grafts explanted from the arterial circulation and subsequently transferred back to the venous circulation demonstrated regression of IH.[41–44]Finally, vein grafts placed in a low flow, high resistance, environment developed an exuberant IH response that regressed once placed into a normal flow environment.[45] These experiments suggest that the cyclic mechanical forces of the arterial circulation are sufficient and necessary for the development IH rather than simply the injury of dissection.

Evidence from animal models consistently show that the IH thickness of a vein graft varies inversely proportional to the magnitude of shear stress across the endothelial cell surface.[45–53] In one study, vein grafts exposed to 50% less shear stress had a 63% thicker intimal layer after 4 weeks.[48] Vein grafts placed in conditions of high shear stress demonstrated more endothelium dependent relaxation suggesting that higher shear stress favorably improved endothelial function, possibly through increased nitric oxide (NO) production.[47,54,55]

The kinetics of IH development have also been studied in the rabbit and canine vein graft models.[22,56] There is an initial burst of endothelial and smooth muscle cell proliferation occurring within 1 week following implantation and a return to the baseline quiescent state by week 12. More recently, mathematical relationships of the temporal sequence of the development of IH as a function of shear stress and time, $h(t, \tau)=h_o+(R_L[1-e^{-A(t-t^*)}])/(1+B\tau^C)$, where h is the intimal thickness, t is time, τ is shear stress, h_o is the intimal thickness at the time of implantation, R_L is the initial lumen radius, and t* is the time when intimal thickness begins to change. A, B, C are experimentally derived constants and therefore unique to the model used.[57,58] The application of mathematical models of this type, validated in human vein grafts, would be of great benefit in the determination of efficacy of new therapeutics or biologics developed to inhibit IH.

The importance of vein graft caliber regulation

While much attention has been given to IH as the primary mode of failure for vein grafts, relatively limited information is available on the role remodeling plays in the failing vein graft.[6,7,10,59,60] Remodeling is defined as a dynamic structural and biochemical adaptation within the vein graft that results in long-term changes in lumen caliber, wall thickness, composition of matrix proteins, and endothelial cell reactivity.[7,61–67] Remodeling is dependent on an interaction between locally and remotely generated growth factors, vasoactive substances, and hemodynamic stimuli.[22,68]

It is well known that arteries undergo compensatory remodeling in response to hemodynamic forces.[69,70] [71] [72–74] [75] The resulting change in lumen caliber or wall thickness is thought to maintain these forces at a biologically preset value that promotes maximum efficiency of blood transport.[69,70] Between the predominant hemodynamic forces, wall tension and shear stress, the later appears to be the dominant of the two in regulating lumen caliber.[76] While blood flow is proportional to the product of the vessel's radius and the pressure gradient across the vessel, shear stress is proportional to the quotient of blood flow and lumen radius. Shear stress is the frictional force per unit area tangential to the vessel wall and therefore "sensed" by endothelial cells. Endothelial cells are the recognized biosensor of the vessel and align themselves along the direction of shear stress. Steady laminar shear stress has a healthy trophic effect on the endothelial cells by inhibiting leukocyte adhesion, promoting vasodilator production such as NO[77] and prostacyclin[78], limiting SMC hyperplasia[79], and decreasing platelet aggregation[80]. Conversely, low shear stress and turbulence associated with complex geometries such as anastomosis and valves, has the opposite effect. [81] Removal of the endothelium abolishes flow-dependent vasodilation.[82]

A vein implanted into the arterial circulation will experience a several-fold increase in both shear stress and wall tension and several lines of evidence argue that hemodynamic regulation of venous structures exists.[74,83–85] In a rabbit jugular vein – carotid artery interposition model, the lumen radius increased 57% over a 24 week study period: a magnitude sufficient to reduce the initially high shear stress down to that of a normal rabbit carotid artery.[56] The remarkable rapidity in which the vein remodels after implantation in the arterial circulation was exemplified in a canine model whereby maximal diameter was attained in just 7 days. [22]

The ability for human saphenous vein grafts to dilate substantially-and sometimes pathologically-after implantation has been known from autopsy studies for nearly 50 years. [86] Fillinger et al demonstrated that final lumen diameter attained at 12 months was a function of the initial lumen diameter and shear stress.[87] While vein grafts which had the highest initial shear stress tended to be smaller at the time of implantation, they underwent greater lumen dilation then those with lower initial shear stress. This observation is important to consider when choosing to use or discard a relatively small vein as it is well known that the luminal size of the vein is of primary importance for subsequent patency.[88,89] However a small vein, free of pre-existing pathology, that is compliant and distends easily will likely dilate and function well as a bypass graft.

More recently, quantification of human vein graft lumen remodeling has been assessed using high resolution ultrasound. It has been shown that the vein graft lumen, on average, dilates about 22% over the first 6 months of implantation, Figure 1a.[10] The most pronounced period of luminal change was during the first 30 days. However, considerable variability existed in luminal dilation (range −31 to +64%) as evidence by the fact that a substantial minority (28%) of the vein grafts actually decreased in size during this time frame, Figure 1b. Importantly, loss of vein graft lumen size-negative remodeling- during the first month was associated with earlier loss of primary patency compared to those veins which underwent luminal dilation. Therefore it appears that the ability of vein grafts to adequately dilate in the early period of implantation is critical to ensure long-term patency. Not surprisingly, shear stress correlated with early vein graft lumen remodeling, Figure 1c.[10] Those with higher initial shear stress dilated to a greater extent than those with less.

Taken together, these data indicate that laminar shear stress acting through endothelium-dependent mechanisms, not only attenuates the development of over-exuberant IH, but also influences vein graft lumen caliber regulation; perhaps, through common mediators such as NO, prostanoids, or hyperpolarizing factors.[22,50,54,55,90]

The influence of inflammation

It has long been recognized that the implantation of a vein in the arterial circulation is accompanied by a local inflammatory response within the vein graft wall.[27,91] But the effects of systemic inflammation on the incidence of vein graft stenosis is unknown and has only recently been investigated in a cohort of patients undergoing lower extremity revascularization exclusively with autogenous constructs.[92,93] In this study, 3 biomarkers of inflammation, high sensitivity C reactive protein (hs-CRP), serum amyloid A (SAA), and fibrinogen, were examined. While all three were all associated with the severity of PAD at the time of presentation, diabetes, and renal failure, only hs-CRP was found to be independently associated with adverse events following bypass surgery, most of which were vein graft related.[92]

Among all inflammatory markers, the high sensitivity CRP test (hsCRP) is the most validated, most widely available, and the only test endorsed by the American Heart Association (AHA) and Center for Disease Control as a cardiovascular risk marker.[94] The AHA has determined the hs-CRP test is appropriate for patients with intermediate risk of cardiovascular events and that values of 0–1 mg/L, 1–3 mg/L, and >3 mg/L would place patients in low, medium and high risk categories respectively. However, PAD is considered to be a coronary heart disease equivalent and these patients are already considered high risk. Indeed, patients undergoing lower extremity bypass surgery have a median hsCRP was 3.25 mg/L and therefore the AHA guidelines would not appropriate for this population.[92] Rather, a cutoff value of hsCRP at 5 mg/L has more potent discriminating ability with respect to adverse outcomes then hsCRP placed in tertiles, according to the AHA recommendations, or another cutoff value.

It is still unclear whether CRP is simply a marker of inflammation or a biomodulator of vein graft biology. However, vein grafts in patients with high CRP do not dilate as much as would be expected to shear stress.[93] Dichotomizing patients undergoing bypass surgery with autogenous vein by preoperative plasma CRP concentration, individuals with high CRP levels (>5 mg/L) had significantly less vein graft luminal dilation in the first month after surgery compared to patients with CRP below 5 mg/L, 10% vs. 37%, Figure 2.[93] Further, the significant positive correlation between shear stress and vein graft luminal remodeling was no longer present in the individuals with higher levels of CRP. Hence, patients with high levels of systemic inflammation have impaired ability to positively remodel vein grafts, possibly by impairing endothelial function. These studies are ongoing and the contention that inflammation per se, can be used as a surrogate biomarker for graft-specific failure remains to be proven.

However, many lines of evidence suggest that systemic inflammation impairs endothelial function in patients with PAD with significant clinical consequences. C-reactive protein has been shown to be associated with impaired brachial artery flow mediated, endothelium dependent, vasodilation (FMD) in patients with PAD.[95][96][97] Further, in a cohort of patients undergoing vascular surgery, impaired FMD has been shown to be independently associated with adverse 30-day cardiovascular outcomes.[98,99] Whether or not intensive peri-operative reduction of inflammation such as with high-dose statin therapy would improve clinical outcomes in this population, remains to be studied.

Endothelial Function

Animal studies have demonstrated that veins are capable of relaxation and contraction to vasoactive mediators but to a lesser extent than a similarly sized arteries.[100–104]The thinner media or the histologic arrangement of SMCs and fibrous protein may be responsible. Vascular responses of the human GSV to vasoactive mediators has been studied using Acetylcholine (Ach) or the calcium ionophore A23187 to elicit endothelium-dependent vasodilation.[105–107] In general, the GSV can generate as much contractile force in response to phenylephrine

as the internal mammary artery-about 8–10 grams. However, precontracted GSVs exhibit variable relaxation with Ach and a more pronounced relaxation to A23187.[105,106]

However, the underlying hypothesis that vein graft endothelial function is a critical regulator of final luminal caliber, and ultimately patency, remains to be proven. Veins excised during redo coronary bypass grafting [108] or during revision of lower extremity vein graft stenosis [109] have demonstrated altered smooth muscle cell contractility and the absence of relaxation to Ach.[105,108,109] However, these were diseased specimens and the clinical relevance is uncertain. Ku et al studied functioning vein grafts with patent lumens that were 7 months to 12 years in age excised from patients undergoing heart transplantation.[110] Several important observations are noteworthy from this study. First, all vein grafts exhibited vasorelaxation to Ach though considerable variability, −9 to −65% of the pre-contracted state, existed between different grafts. Second, there was significant variability even within a single vein graft segment indicating local heterogeneity in NO production along the course of the vein graft. And third, vein grafts with the most pronounced IH exhibited the least amount of endothelium dependent relaxation. These observations suggest that a functional endothelial lining is regenerated in human vein grafts, that it is not constant along the length of the vein graft, and that IH is at least associated with endothelial impairment.[111]

These findings may be one explanation of the focal nature of most vein graft lesions. While diffuse IH occlusive disease may occur in approximately 12% vein grafts, the majority of culprit lesions are focal and often perianastomotic, Figure 3.[15,16,35] A focal deficiency in NO from either pre-existing lesions, primary endothelial injury, or turbulent flow with altered shear stress, may result in an area of the graft that fails to sufficiently remodel.[31,33,112–114] The cumulative result of the relative deficiency of NO would be increased IH,[79,115] decreased remodeling,[116] and possibly an increase in collagen production[117,118] thereby stiffening the vein graft and further reducing the ability to dilate. Hence, the wall would thicken disproportionately to the lumen dilatation producing the clinically familiar focal stenosis within a segment of the vein graft, Figure 4.

Detection of the more physiologically relevant flow stimulated endothelial function has recently been tested in vivo in a cohort of patients with mature (>1 year since implantation) femoro-popliteal vein grafts that have not underwent revision. The technique was similar to the one employed to test brachial artery FMD which is known to be endothelium dependent and mediated by NO.[119] Assessment of endothelial function by brachial artery flow mediated dilation is a well established research tool which measures small changes in brachial artery diameter in response to an increase in blood flow. By applying an occlusive blood pressure cuff over the proximal calf for 5 minutes, a hyperemic response (increase in blood flow and shear stress) was stimulated in the leg upon its release, figure 5. High resolution ultrasound and post-processing imaging software was then used to carefully measure vein graft blood flow, shear stress, and lumen diameter before and after the hyperemic response and therefore calculate flow mediated dilation (FMD) in the vein graft. Hyperemia resulted in a 233% increase in volumetric flow through the vein graft above baseline in this experiment.[120] This study showed for the first time that vein grafts did dilate to an increase in blood flow. Vein graft FMD was 5.28% ± 3.1% (range 1.99–9.36%), for the entire cohort, Figure 5. The specificity of NO as the mediator of this response was established by intravenously administering the NO inhibitor N^G L-monomethyl arginine (LNMMA), during a subsequent test which abolished the FMD response in all vein grafts.

These studies demonstrate that vein grafts have a biologically active endothelial layer which can be assessed by non-invasive techniques. The relationship of endothelial cell function, the extent and timing of its recovery of function, and patency of the vein graft remains to be seen and is an area of ongoing investigation. It is provocative to speculate that pharmacologic

adjuncts, provided locally or remotely, to improve endothelial function and NO availability may decrease IH, improve remodeling, and increase vein graft patency.

The vein graft wall

While shear stress is the dominant regulator of lumen caliber, wall tension is the more critical determinant of wall thickness. Animal models indicate that there is a structurally optimal lumen radius/wall thickness ratio to support arterial pressure with minimal wall stress. Indeed, there is a remarkable consistency of tension per lamellar unit of the aortic media across diverse mammalian species from the mouse to man.[121] In a rabbit vein graft model the ratio of lumen radius to wall thickness (r_i/h), initially very high at the time of implantation, approached that of the normal carotid artery by 24 weeks.[56] In humans, vein graft lumen diameter to wall thickness ratio, about 9:1 at the time of implantation, is reduced to 7.4 at 6 months, a value close to that of the superficial femoral artery,Table 1.[122]

Until recently, accurate in vivo measurement of the vein graft wall has been elusive. However, high resolution, 3-D MRI with superior signal to noise ratio, is capable of resolving structures as small as 300 microns-within the range of the vein graft wall.[8] By simultaneously measuring wall thickness and lumen radius at 1 and 6 months post-implantation, a very strong correlation existed between luminal enlargement and total vessel enlargement.[120] The equation $\Delta LD = .62(\Delta OD) - .02$, where LD is lumen diameter and OD is total vein graft diameter, relates changes in luminal diameter to changes in total vessel diameter. This linear regression equation relates what should happen to the lumen of a normal patent bypass graft given a measurable change in the vein graft wall. For example, a 22% increase in the lumen diameter should be accompanied by a 35% increase in the outer diameter of the vein graft. A slope substantially less then .62 would indicate excessive thickening of the wall or insufficient lumen dilation.

Systematic studies of human vein grafts with aid of modern high resolution imaging technology provide insight into vein adaptation in the arterial environment. It has become clear that vein remodeling constitutes changes in luminal and total vessel diameter. The forces and flows responsible for these changes are becoming clear but other factors are involved as well. As can be seen in figure 4, segments of a vein graft with near occlusive IH also had a smaller total vessel diameter compared with a normal adjacent segment. Therefore, in this particular case, the stenosis was due to a combination of negative remodeling and IH. Further studies are needed in this important area.

Clinical science

Translational advances notwithstanding, there has been much improvement in the clinical sciences of vein graft outcomes. Hypothesis-driven, multi-centered trials[6], national data bases with quality measures,[123] and comparative effectiveness trials[124] have replaced single-center retrospective studies and promise to be more reflective of real world practice. These trials, when carefully conducted, can potentially bridge the bench to bedside translational gulf and careful observations of the results can often be hypothesis-generating. For example, PREVENT III alone has resulted in 10 published manuscripts of outcomes in patients with CLI examining quality measures, resource utilization, racial disparities, technical considerations, and risk estimation scores.[6,89,125–132]

Long-term results from the BASIL trial emphasize that the more durable reconstruction with a vein graft translates into improved outcomes compared to less invasive alternatives.[124, 133] However, technical factors such as smaller diameter and longer bypass grafts experience more graft related events (GRE) and GREs result in decreased quality of life (QoL) and increased resource utilization emphasizing the importance of patency as an outcome measure. [89,128] A priori identification of vulnerable grafts through the use of biochemical and imaging

biomarkers may provide an opportunity for targeted therapy or at the very least identify patients who would benefit from a more intensive surveillance program. Surrogate endpoints such as novel methods of detection of vein endothelial health (function), IH kinetics, and normal and abnormal remodeling patterns will improve our understanding of the mechanisms of action for the next biologic or new clinical entity to emerge to improve vein graft patency.

Results from clinical trials may have significant biologic implications. For example, gender and racial disparity, often overlooked in single-centered studies due to small sample size, can be examined in multi-centered cohorts. While it is well known that PAD disproportionately affects black patients, less is known about graft specific outcomes. In the PREVENT III database, patients with black race and female gender were at increased risk of graft occlusion and had inferior limb salvage but there were no differences in primary patency compared with white patients.[125] This finding suggests that the disease process is more aggressive, possibly more diffuse, and therefore lower rates of graft salvage by revisions once IH stenosis developed or surgeons were quicker to abandon the graft. An altered biologic healing response to the implanted graft, possibly through increased inflammation, altered thrombogenicity, or differential endothelial cell responses may be responsible.[134–138] Thus observations from clinical trials such as these can directly stimulate basic scientific efforts.

Conclusion

Beyond the risk of limb loss, decreased graft patency results in increased resource utilization [128] and significantly impacts quality of life.[127] Our current pharmacopoeia has not made any significant impact on the natural history of vein graft stenosis emphasizing the need for a better mechanistic understanding of graft failure.[139] Animal models and mathematical constructs should incorporate structural as well as functional changes of the maturing vein graft. Understanding the relative contributions of IH and remodeling are not simply academic as molecular therapeutics targeted at IH will likely not improve remodeling. Multidisciplinary translational research programs leveraging recent advances in biomedical imaging, molecular technology, and genetic engineering will likely dramatically increase our understanding of this vexing problem.

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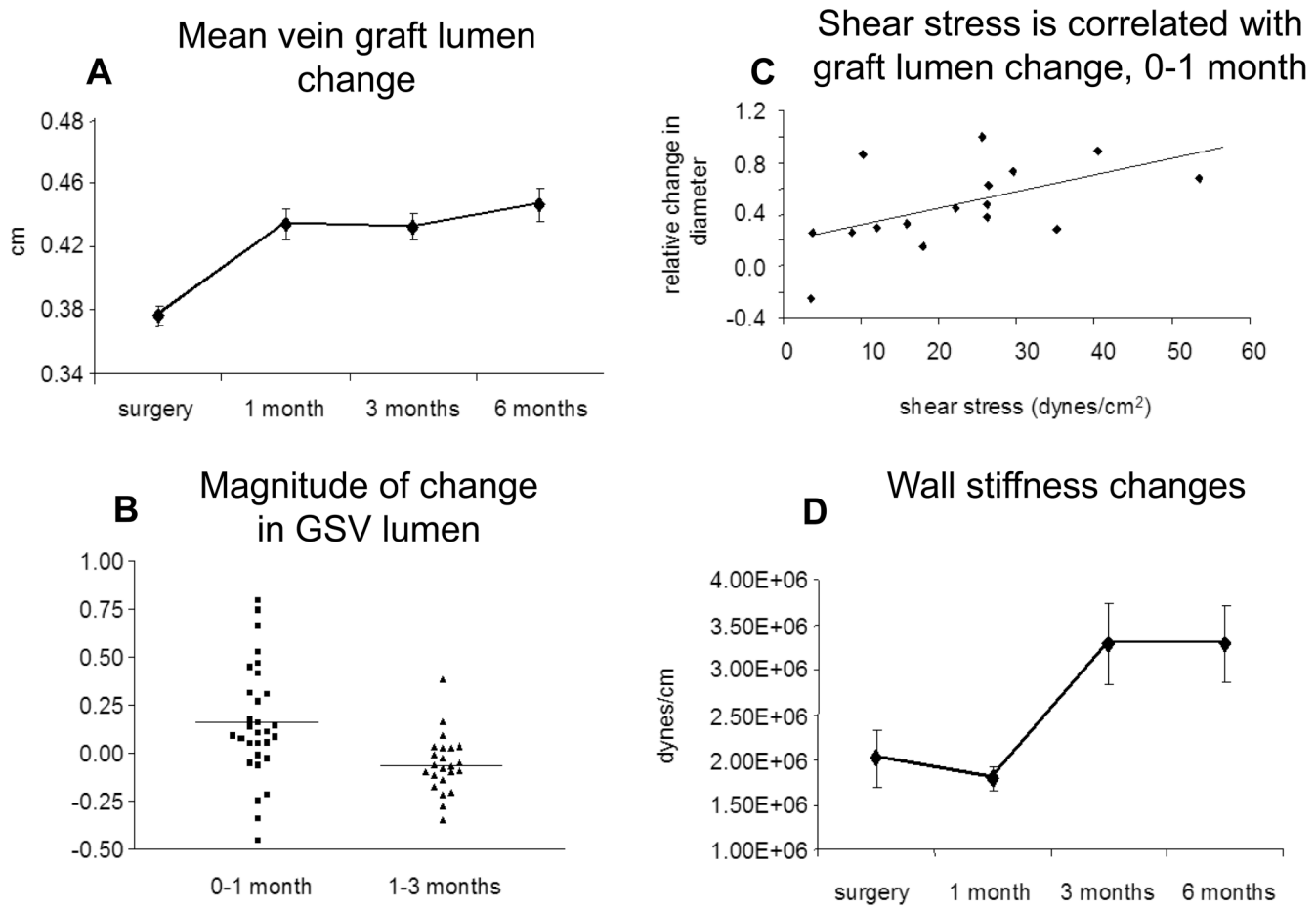

Figure 1.

While the mean bypass graft lumen increases about 22% over the first 6 months following implantation, A, considerable variability exists between individual grafts, B. Early luminal remodeling is correlated with initial shear stress at the time of implantation, C. Temporally distinct from luminal remodeling, the vein graft significantly stiffens between 1 and 3 months following implantation, D. Adapted from reference [10].

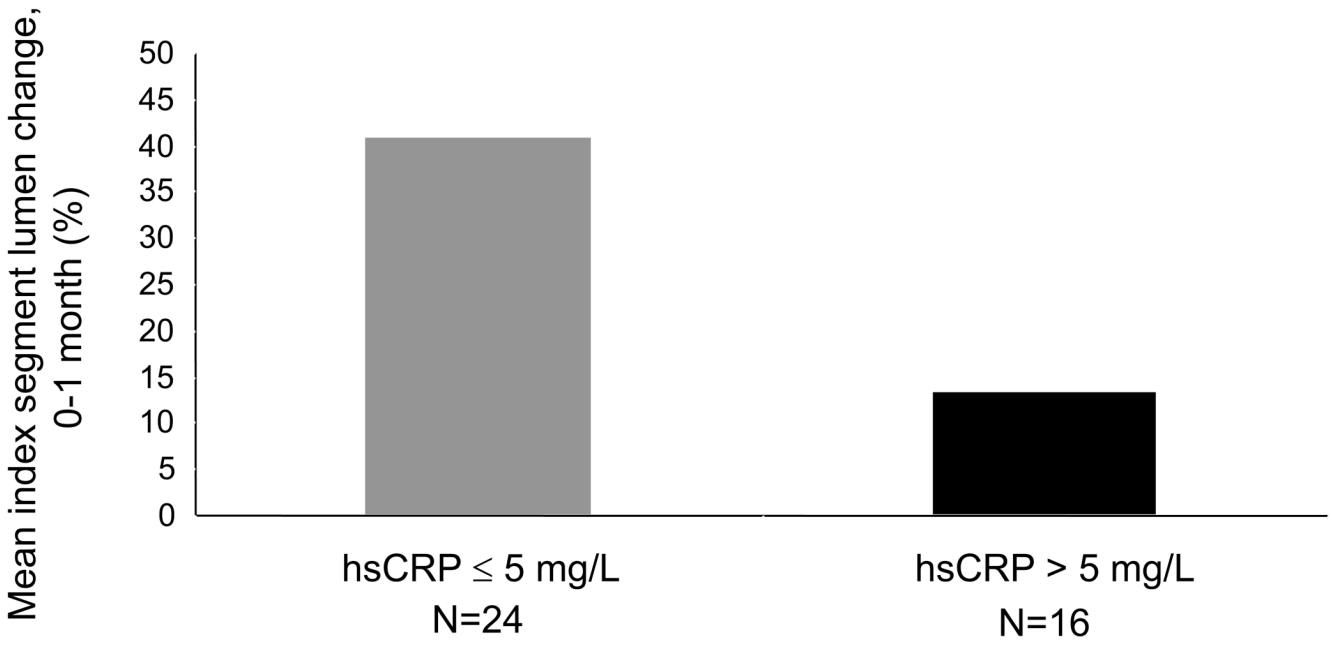

Figure 2.
Vein graft lumen change (percent) from implantation to 1 month in a population undergoing lower extremity bypass grafting for arterial occlusive disease. Luminal measurements were made with high resolution M-mode ultrasound at the same location of the vein graft for the operative and the 1 month assessment. By dichotomizing the population by baseline plasma CRP levels above and below 5 mg/L, disparate early luminal remodeling patterns of the vein graft become apparent, 37% vs 10 %, P=.0072. Thus, patients with high levels of systemic inflammation have impaired ability to positively remodel vein grafts, adapted from reference [93].

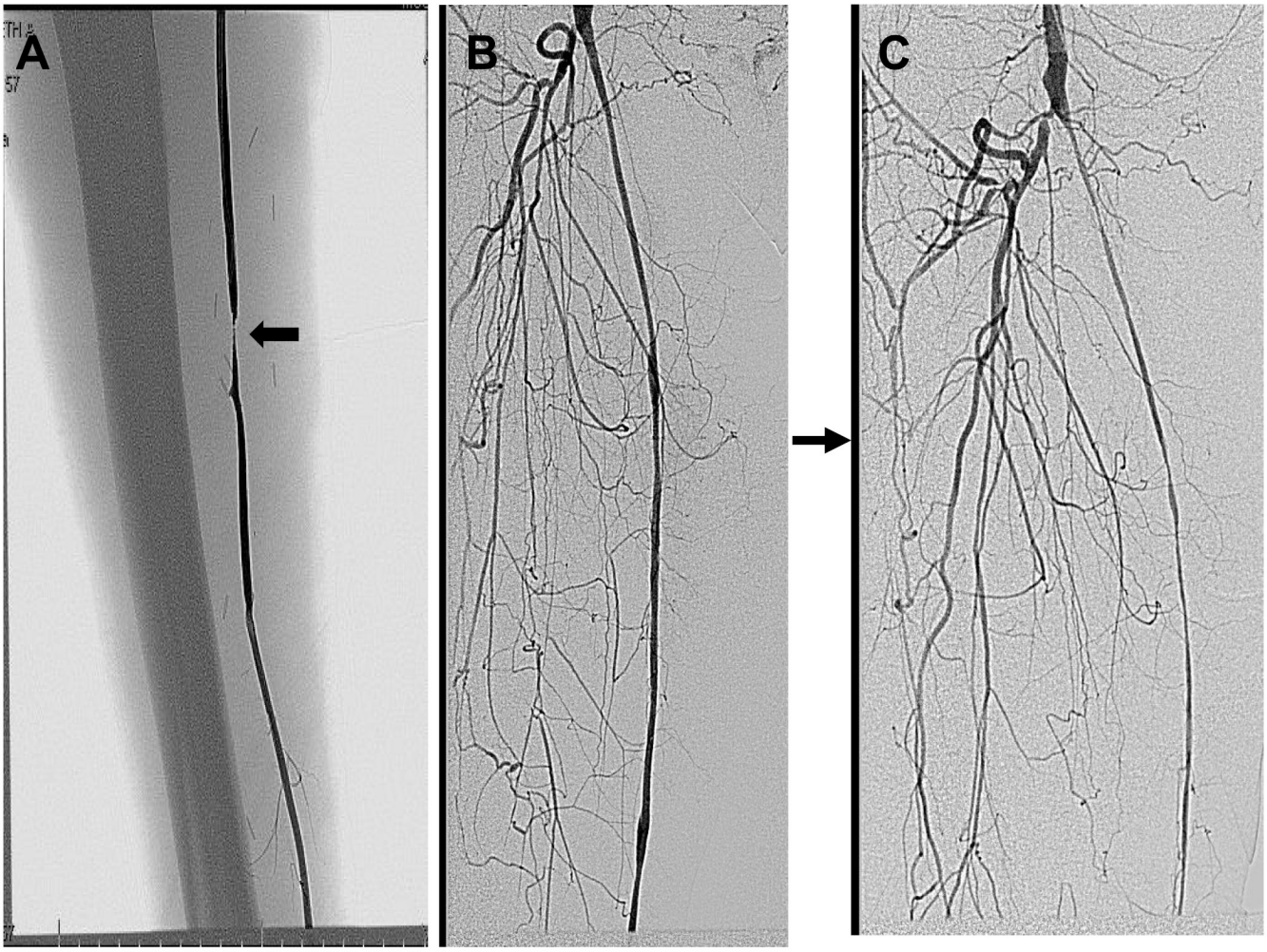

Figure 3.
Modes of vein graft failure. While the majority of intimal hyperplasia in vein grafts is focal, a substantial minority (12%) is diffuse. Panel A represents a 6 month old vein graft in a 67 year old white man that developed a mid graft stenosis (arrow) that was successfully treated with a vein patch angioplasty. Panel B represents a 4 month old vein graft in a 77 year Black women undergoing angiography for contralateral limb ischemia. Three months later, she developed diffuse intimal hyperplasia which progressed to vein graft occlusion.

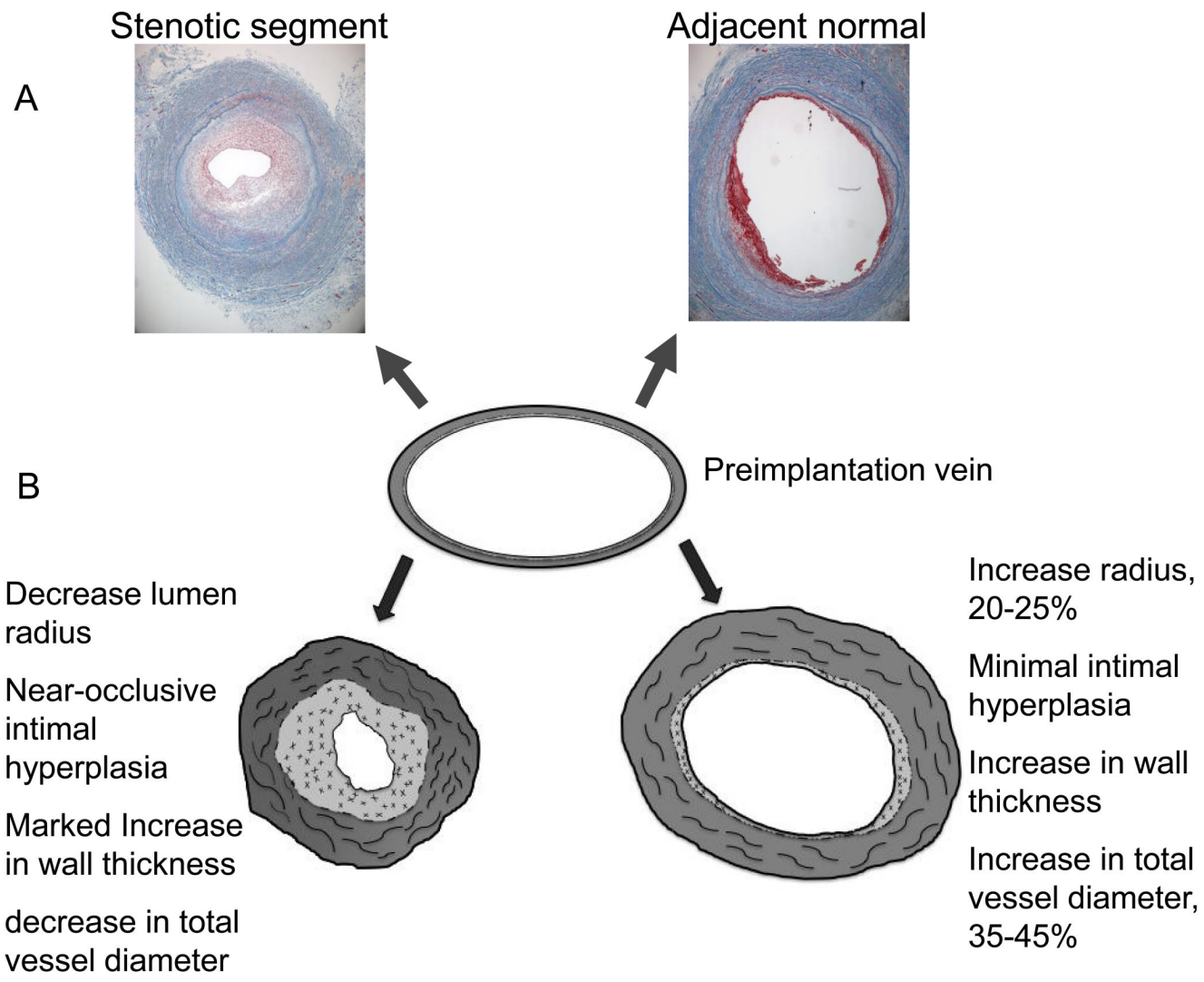

Figure 4.

Histologic sections (10X) of an 8 month old vein graft which developed a focal mid-graft stenosis and underwent open revision with a short interposition graft. The vein was of uniform size and caliber at the time of implantation. The sections were taken approximately 2 cm from one another. The area of stenosis has developed marked intimal hyperplasia and has a smaller area circumscribed by the internal elastic laminae as well as decreased total vessel diameter indicative of negative remodeling of the entire vein graft, A. Theoretical normal and abnormal adaptation patterns of a human lower extremity vein grafts, B. Normally the lumen and wall area increase in the early post-implantation period to produce a lumen diameter to wall thickness ratio of about 7.

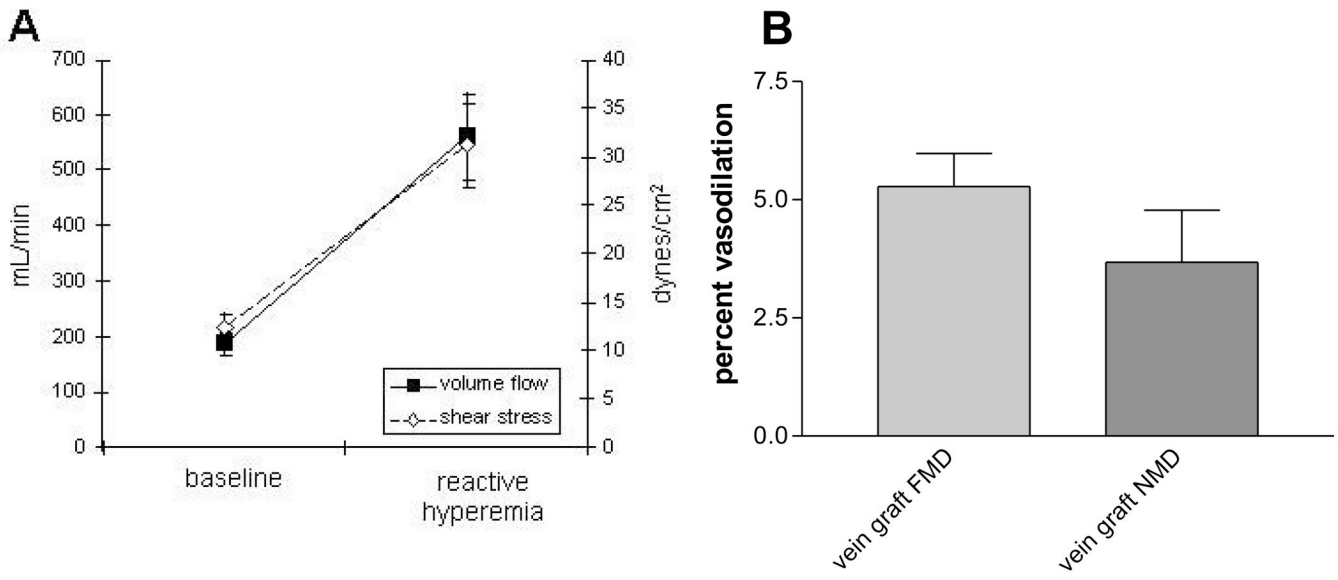

Figure 5.

Flow mediated vasodilation in mature human saphenous vein grafts demonstrates a functional endothelium. Application of an occlusive blood pressure cuff (220 mmHg) to the proximal calf of a cohort of patients undergoing femoro-popliteal bypass grafts for 5 minutes produces an increase in blood flow and shear stress within the graft, A. In this cohort, flow mediated, endothelium dependent vasodilation was 5.3% and nitroglycerin mediated, endothelium independent (0.4 mg sublingual nitroglycerin) dilation was 3.7%.

Table 1

Remodeling of Human Saphenous Vein Graft, 0–6 months

	Implantation	**6 mo.**	**SFA**
LD (mm)	3.7	4.5	6.8
Stiffness (Mdynes/cm)	2.0	3.3	1.7
Wall thickness (μm)	410	610	870
LD/WT	9.0	7.4	7.8

LD lumen diameter, WT wall thickness