Remodeling leads to distinctly more intimal hyperplasia in coronary than in infrainguinal vein grafts

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Background: **Flow patterns and shear forces in native coronary arteries are more protective against neointimal hyperplasia than those in femoral arteries. Yet, the caliber mismatch with their target arteries makes coronary artery bypass grafts more likely to encounter intimal hyperplasia than their infrainguinal counterparts due to the resultant slow flow velocity and decreased wall stress. To allow a site-specific, flow-related comparison of remodeling behavior, saphenous vein bypass grafts were simultaneously implanted in femoral and coronary positions.**

Methods: **Saphenous vein grafts were concomitantly implanted as coronary and femoral bypass grafts using a senescent nonhuman primate model. Duplex ultrasound-based blood flow velocity profiles and vein graft and target artery dimensions were correlated with dimensional and histomorphologic graft remodeling in large, senescent Chacma baboons (n = 8; 28.1 ± 4.9 kg) during a 24-week period.**

Results: **At implantation, the cross-sectional quotient (Q_c) between target arteries and vein grafts was 0.62 ± 0.10 for femoral grafts vs 0.17 ± 0.06 for coronary grafts, resulting in a dimensional graft-to-artery mismatch 3.6 times higher ($P < .0001$) in coronary grafts. Together with different velocity profiles, these site-specific dimensional discrepancies resulted in a 57.9% ± 19.4% lower maximum flow velocity ($P = .0048$), 48.1% ± 23.6% lower maximal cycling wall shear stress ($P = .012$), and 62.2% ± 21.2% lower mean velocity ($P = .007$) in coronary grafts. After 24 weeks, the luminal diameter of all coronary grafts had contracted by 63%, from an inner diameter of 4.49 ± 0.60 to 1.68 ± 0.63 mm ($P < .0001$; subintimal diameter: −41.5%; $P = .002$), whereas 57% of the femoral interposition grafts had dilated by 31%, from 4.21 ± 0.25 to 5.53 ±1.30 mm ($P = .020$). Neointimal tissue was 2.3 times thicker in coronary than in femoral grafts (561 ± 73 vs 240 ± 149 μm; $P = .001$). Overall, the luminal area of coronary grafts was an average of 4.1 times smaller than that of femoral grafts.**

Conclusions: **Although coronary and infrainguinal bypass surgery uses saphenous veins as conduits, they undergo significantly different remodeling processes in these two anatomic positions. (J Vasc Surg 2012;55:1734-41.)**

Clinical Relevance. **Saphenous vein grafts still represent the gold standard of bypass graft surgery. Although flow-dependent vein graft remodeling has been experimentally shown, there is limited clinical appreciation for the remodeling differences between coronary and infrainguinal vein grafts because the procedures are generally performed by two different clinical disciplines. Understanding the site-specific baseline response of vein grafts in both positions is a prerequisite for optimally strategizing therapeutic modalities aiming at the suppression of potentially detrimental remodeling processes such as neointimal hyperplasia or luminal encroachment.**

Despite the increasing importance of interventional and endovascular procedures, peripheral and coronary bypass graft surgery continue to be two of the most widely performed operations. For both procedures, the saphenous vein remains the most frequently used conduit. Once exposed to the arterial circulation, vein grafts undergo distinct remodeling processes. Although initially representing site-specific adaptation processes, some of the remodeling aspects, such as intimal hyperplasia, are seen as the "soil" for subsequent pathologic processes that lead to graft failure.[1]

The two main biomechanical forces responsible for triggering vein graft remodeling—wall stress and shear forces[2-4]—are determined by graft diameter, pressure, and flow. Whereas wall stress is predominantly determined by diameter and pressure, shear stress is defined through diameter and flow. Although diameter affects both remodeling forces, it affects wall tension linearly but shear stress with the third power. Therefore, diameter deviations from target arteries dramatically affect flow velocities and shear forces but only moderately affect wall tension.

Because the saphenous vein is a conduit of a given diameter,[5] the dimension of the run-off artery determines to what extent the vein graft deviates from the functionally

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"optimal" dimensions of an anatomic site. Although saphenous vein bypass grafts are usually more than three times larger in cross-sectional area than their bypassed coronary arteries,[6] they are only 0.36 to 0.77 times the size of popliteal arteries in femoropopliteal bypasses.[7] Therefore, independent of the additional effect of inflow patterns, downstream resistance, and disease, the resulting baseline flow deceleration in coronary bypass grafts and flow acceleration in femoropopliteal grafts is expected to be reflected in significant shear-force differences between the two anatomic sites and, as such, in a markedly different remodeling response favoring, for example, diffuse intimal hyperplasia formation in coronary grafts.

To be able to compare the baseline remodeling response of saphenous vein grafts in these two clinically most relevant anatomic locations, we correlated flow dynamics with the remodeling processes in concurrently implanted coronary and infrainguinal reversed saphenous vein bypass grafts. As our animal model we chose senescent Chacma baboons, whose anatomy and vascular healing response have been shown to come closest to man.[8]

METHODS

A functional, dimension-associated starting point was related to a pathomorphologic end point. Because pressure-controlled perfusion-fixation for accurate morphologic microanalysis[9-11] depended on explantation, dimensional assessments were based on ultrasound measurements at the time of implantation. Congruency of vessel dimensions has previously been shown between the two methods.[12]

Graft implantation. After approval by the Animal Ethics Committee of the University of Cape Town, the right-sided saphenous vein was harvested from eight large senescent Chacma baboons (28.1 ± 4.9 kg) strictly following a no-touch technique. The distal vein was cannulated early and gently injected with heparinized papaverine-containing blood (1 mg/mL at near-body temperature).

After storage in heparinized blood at environmental temperatures, routine surgical distension, without the use of pressure-controlling syringes, was applied to identify leaks. Vein grafts were concomitantly implanted as bypasses from the superficial femoral to the suprapopliteal artery and from the aorta to the left anterior descending (LAD) coronary artery using extracorporeal circulation. Bypass procedures alternately commenced with the femoral or coronary position. Bypassed arteries were ligated proximal to the distal anastomosis.

Vessel dimensions and flow dynamics. Vessel dimensions and blood flow were measured by duplex ultrasound imaging (HD11 XE ultrasound system with L15-7io transducer) and vascular software (HD11 XE, Philips Healthcare, Best, The Netherlands). Vessel diameters were obtained from pregrafted target arteries at the expected sites of the distal anastomoses and at midgrafts at three 1-cm intervals during four consecutive cardiac cycles using linear measurements in M-mode in the orthogonal plane.

Dimensional mismatch between vein grafts and target arteries was expressed as the quotient of cross-sectional areas (Q_c).[11] Blood flow velocity was recorded in pregrafting target arteries at the sites of grafting and in the midgraft location in the sagittal plane using duplex ultrasound imaging combining pulsed-wave Doppler with B-mode imaging. The Doppler spectral display of two consecutive cardiac cycles was digitized (DigitizeIt 1.5.8b, Digital River, Cologne, Germany) with 250 time increments per cardiac cycle to obtain data for flow velocity profiles.

The mean velocity (V_{mean}) was expressed as the arithmetic mean considering changes in flow direction:

$$V_{mean} = 1/n \sum_{i=1}^{n} v_i$$

where v_i is the velocity measured at a time increment i, n is the total number of time increments during the two cardiac cycles, and

$$\sum_{i=1}^{n} v_i$$

is the sum of all 500 velocity data points. Wall shear stress (WSS) was calculated for each time increment from the flow velocity data according to the equation $WSS = 4\mu Q/\pi r^3$ where μ is the blood viscosity, Q is the volumetric flow rate $Q = 2rv$, and r is the vessel radius. The WSS data provided WSS curves throughout two cardiac cycles as presented in Fig 1. The mean WSS (WSS_{mean}) was calculated from these data as arithmetic mean value in the same way as for the flow velocity, without accounting for changes in direction of the stress using the formula

$$WSS_{mean} = 1/n \sum_{i=1}^{n} |WSS_i|$$

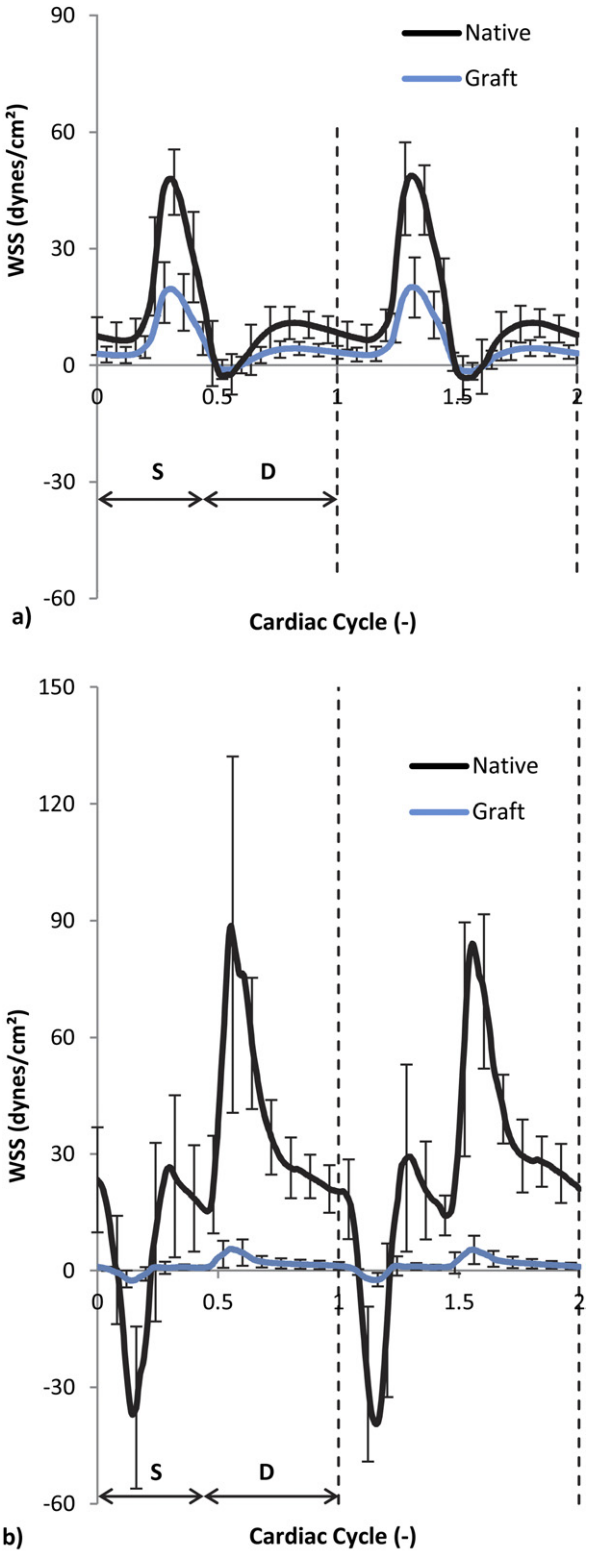
where WSS_{mean} is the mean value, $|WSS_i|$ is the absolute value of WSS measured at a time point i during a cardiac cycle, with n being the total number of measurement time points during two cardiac cycles and

$$\sum_{i=1}^{n} |WSS_i|$$

the sum of all n WSS measurements.

Graft retrieval and microscopy. After 180 days of implantation, grafts were perfusion-fixed at 120 mm Hg and analyzed as previously described.[11] Luminal dimensions were assessed by macroscopic image analysis of midgraft cross sections 1 cm apart. Detailed morphometric assessments were based on composite images of series of midgraft sections from digital single-frames captured at original magnification ×4 and ×10 (Nikon Eclipse 90i and Nikon Coolscope, Melville, NY) using Eclipse Net software (Laboratory Imaging, Prague, Czech Republic). Surface endothelialization was assessed by a JEOL JSM 5200 (Japan Electron Optics Laboratory Co, Tokyo, Japan) scanning electron microscope. Media muscularity was defined as the partial cross-sectional area of smooth muscle cells within the boundaries of the media using Azan/actin-stained double sections, as previously described.[10,11]

Fixation-related tissue shrinkage was 9.9% ± 3.9% based on the comparison of macroscopic image analysis of midgraft sections (QwinPro v 2.5; Leica Microsystems Imaging Solutions, Cambridge, UK) with histologic cross sections.



Statistical analysis. Comparison of patency between the coronary and femoral grafts was performed using the two-tailed Fisher exact test. Linear standard least-squares modeling of the effect of the shear stress parameters maximum shear stress, peak systolic shear stress, and maximum cyclic shear stress on intimal hyperplasia thickness was performed. Continuous data are expressed as means ± standard deviation. Post hoc comparisons between groups represented by continuous data were performed using unpaired, two-tailed Student *t* tests, with *P* values $< .05$ regarded as significant.

RESULTS

The difference in the 180-day patency rates for femoral grafts (87% [7 of 8]) compared with coronary grafts (63% [5 of 8]) was not statistically significant ($P = .57$).

Luminal dimensions and flow dynamics at implant. At graft insertion, no signs of irregularities were detectible in the midgraft portions investigated by ultrasound imaging. The inner diameters (IDs) of the saphenous vein grafts were almost identical in the coronary and femoral positions (Table I; NS), with the cross-sectional quotient between target artery and vein graft being 3.6 times lower ($P < .0001$) in coronary grafts. Accordingly, flow velocities and shear stress were distinctly more damped in coronary than in femoral grafts (Fig 1, Table II), resulting in a 57.9% ± 19.4% lower maximum velocity ($P = .005$), 48.1% ± 23.6% lower maximal cycling wall shear stress ($P = .012$), and 62.2% ± 21.2% lower mean velocity ($P = .007$). Modeling shear stress parameters against intimal hyperplasia thickness confirmed significant associations with this outcome variable for all shear stress maxima: maximum ($P = .007$), peak systolic ($P = .003$), and maximum cyclic shear stress ($P = .012$), but not for mean or peak diastolic shear stress.

Graft pathology at explant. All coronary grafts appeared shrunken, with a thick whitish wall, whereas most femoral grafts looked dilated, with a distinctly thinner wall (Fig 2). Neointimal tissue was 2.3 times thicker in coronary than in femoral grafts ($P = .001$; Table I, Fig 3). Within femoral grafts, inward remodeling was associated with 2.5 times thicker neointimal tissue than outward remodeling (145 ± 108 vs 368 ± 82 μm; $P = .030$).

Fig 1. Mean wall shear stress (*WSS*) in the native femoral and left anterior descending coronary arteries before grafting (*black*) and in their vein grafts. In femoral arteries (*top*) the peak shear stress occurs during the main forward flow phase during systole, followed by a brief second peak during the reverse-flow period. As a result of moderately larger luminal dimension, shear forces in femoral vein grafts mirror those of the femoral artery in a mildly damped fashion. In left anterior descending coronary arteries (*bottom*), a consistent biphasic pattern was seen with a predominant early diastolic peak. The early systolic flow reversal precedes a mild late-systolic second peak in WSS. The distinct caliber mismatch between coronary bypass grafts and their target arteries causes a dramatic "flattening" of WSS in the vein grafts. The *range bars* show the standard deviation.

Table I. Dimensional comparisons between target arteries and saphenous vein grafts at implantation and at termination after 24 weeks

Variable[a]	*ID*	*LA*	*SID*	Q_c	*IT*	*WT*	*R/WT*
Femoral grafts							
SFA	3.23 ± 0.32	8.56 ± 1.34					
SVG							
Implant	4.07 ± 0.44	13.02 ± 2.75	4.11 ± 0.44	0.62 ± 0.11		214 ± 67	10.2 ± 0.58
Explant	3.81 ± 2.02	12.03 ± 7.18	4.28 ± 1.44	1.47 ± 1.53	240 ± 149	797 ± 314	3.9 ± 4.8
Coronary grafts							
LAD	1.84 ± 0.23	2.69 ± 0.66					
SVG							
Implant	4.49 ± 0.60	16.18 ± 5.67	4.79 ± 0.23	0.17 ± 0.06		208 ± 69	11.6 ± 5.8
Explant	1.68 ± 0.63	2.97 ± 1.36	2.80 ± 0.51	1.11 ± 0.79	561 ± 73	1062 ± 79	0.9 ± 0.3

ID, Inner diameter; *IT,* intimal thickness; *LA,* luminal area; *LAD,* left anterior descending artery; Q_c, cross-sectional quotient; *R/WT,* radius-to-wall thickness ratio; *SFA,* superficial femoral artery; *SID,* subintimal diameter; *SVG,* saphenous vein graft; *WT,* wall thickness.
[a]Data are reported as mean ± standard deviation.

Table II. Comparison of flow dynamics in the target arteries before grafting and in the vein grafts after grafting

	Femoral position		*Coronary position*	
Variable[a]	*Artery*	*Graft*	*Artery*	*Graft*
Velocities, cm/s				
Mean	15.7 ± 4.3	8.6 ± 3.3	16.4 ± 2.6	3.1 ± 1.5
Maximal	61.4 ± 12.8	34.0 ± 11.5	72.6 ± 15.9	13.4 ± 5.7
Peak systolic (S)	60.9 ± 12.5	33.6 ± 11.2	27.0 ± 8.1	5.1 ± 3.2
Peak diastolic (D)	14.2 ± 40	7.7 ± 2.7	65.4 ± 18.6	11.9 ± 5.2
Peak velocity ratio (D/S) (–)	0.24 ± 0.08		2.75 ± 1.46	
Wall sheer stress, dynes/cm^2				
Mean	14.5 ± 3.2	5.8 ± 2.1	34.4 ± 6.4	2.4 ± 1.2
Maximal	51.8 ± 8.3	21.1 ± 7.1	107.5 ± 32.7	8.3 ± 3.5
Peak systolic	51.3 ± 8.1	20.9 ± 7.0	42.9 ± 14.3	3.2 ± 2.0
Peak diastolic	12.1 ± 3.5	4.8 ± 1.7	104.7 ± 38.2	7.42 ± 3.2
Maximal cyclic	60.2 ± 9.2	24.4 ± 7.4	166.0 ± 59.4	12.0 ± 5.2
Systolic acceleration time, sec	0.21 ± 0.02		0.12 ± 0.11	
Diastolic acceleration time, sec	0.55 ± 0.07		0.39 ± 0.04	
Q_c at implant (–)	0.54 ± 0.08		0.21 ± 0.08	
Volumetric flow rate, mL/min	82.3 ± 31.5		29.5 ± 14.0	

[a]Data are reported as mean ± standard deviation.

Reflecting diameter changes, the intimal area differed less distinctly between femoral and coronary grafts than thickness (2335 ± 1631 × 103 μm^2 vs 4126 ± 2196 × 103 μm^2; 1.8 times; NS). Media thickness increased by a factor of 3.1, from 133 ± 50 to 407 ± 182 μm ($P = .002$) in femoral grafts and from 2.4 to 319 ± 113 μm ($P = .006$) in coronary grafts. At the same time "muscularity" decreased from 65.9% ± 24.9% to 32.9% ± 9.9% ($P = .007$) in the femoral grafts and from 65.5% ± 30.5% to 33.8% ± 6.8% ($P = .021$) in the coronary grafts (Fig 4); yet, total muscle mass increased, respectively, by 182% (1.01 ± 0.72 × 106 μm^2 to 1.75 ± 0.65 × 106 μm^2; NS) and by 74% (0.93 ± 0.41 × 106 μm^2 to 1.23 ± 0.54 × 106 μm^2; $P = .030$). In both coronary and femoral grafts, identical, nearly complete endothelialization was found, with only small patches of preconfluent or nonendothelialized surface (91.8% ± 11.1%, femoral; 91.3% ± 12.0% coronary; NS).

Dimensional graft remodeling. The IDs of all patent coronary grafts had contracted by 63% ($P < .0001$), but most of the patent femoral interposition grafts (4 of 7) had actually dilated by 31% or a factor of 1.3 times (4.21 ± 0.25 to 5.53 ± 1.30 mm; $P = .020$; Fig 5). Overall, all narrowed grafts showed distinct luminal midgraft irregularities at explantation whereby the ID at the narrowest and the widest segment differed by as much as 86.4% ± 53.5%. Diameter fluctuations were almost absent in the dilated grafts (11.1% ± 4.2%). Comparing subintimal diameters, all coronary grafts had distinctly constricted by 41.5% ($P = .002$), whereas most of the patent femoral grafts (4 of 7) showed outward remodeling by 35.3% ($P = .005$). The remaining femoral grafts (3 of 7) displayed an equal degree of 35.2% inward remodeling ($P = .020$; Fig 5). At implantation, the two femoral subgroups did not differ regarding animal weights (29.4 ± 6.3 vs 30.6 ± 0.8 kg; $P > .9$), the ID, or flow-conditions of the run-off suprapopliteal arteries (3.04 ± 0.26 vs 3.30 ± 0.36 mm; $P > .5$), nor were there any signs of luminal irregularities.

Distinct neointimal proliferation and a 2.4 to 3.1 times increase in media thickness, together with an increase in

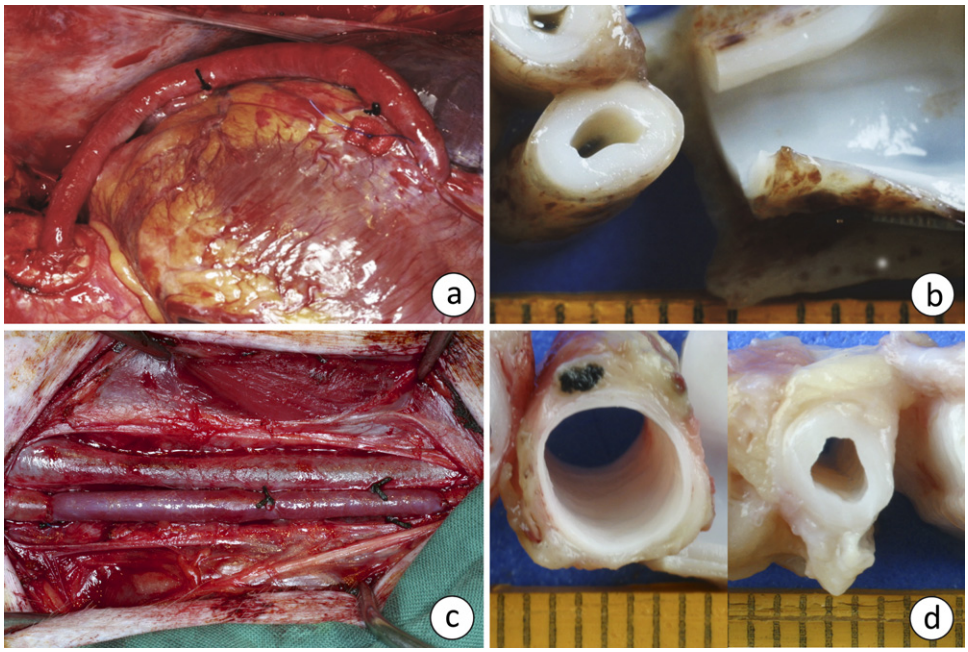


Fig 2. Saphenous vein grafts in (**a** and **b**) coronary and (**c** and **d**) infrainguinal position at (**a** and **c**) implantation and (**b** and **d**) after 6 months. The femoral grafts represent the two subgroups of dilation and constriction. The ruler displays millimeters.

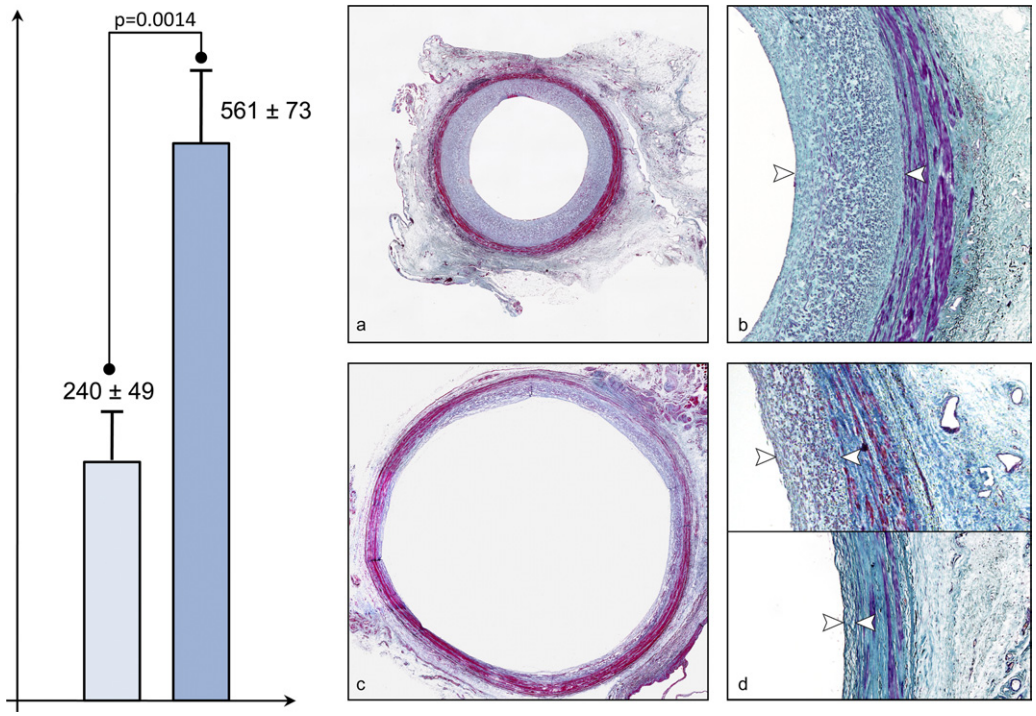


Fig 3. Neointimal tissue was significantly thicker in (**a** and **b**) coronary bypass grafts than in (**c** and **d**) infrainguinal grafts. Whereas (**a** and **b**) coronary grafts regularly showed a massive concentric layer of neointimal tissue, (**c** and **d**) femoral grafts often had one-half of the luminal circumference lacking neointimal tissue and the other half covered by a modest, excentric layer of crescent-shaped neointima (**a** and **c**, Azan, original magnification, ×12; **b** and **d**, Masson's trichrome, original magnification, ×40). The (**d**) high magnifications show both sites. The neointimal layers are delineated with *triangles*.

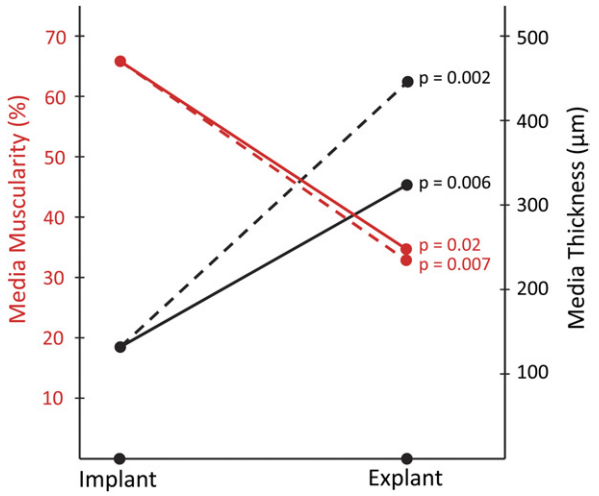


Fig 4. Media development during 6 months of implantation in coronary grafts (*solid lines*) and femoral grafts (*dashed lines*). Rather than "arterialization," media remodeling represents a fibrotic process where an increase in media thickness (*black lines*) is accompanied by a mirror-image decrease in muscle content (*red lines*).

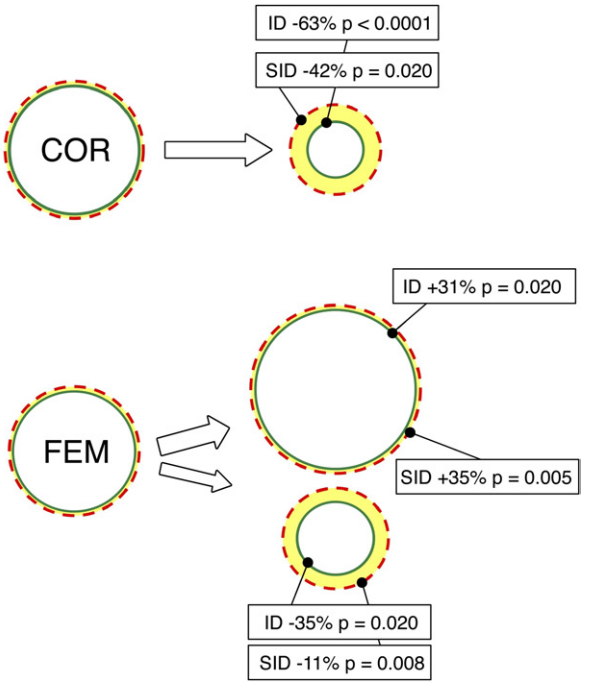


Fig 5. Dimensional remodeling of saphenous vein grafts in the coronary (*COR*) and femoral (*FEM*) positions during 6 months of implantation. Independent from neointimal tissue, subintimal diameters (*SID, dashed red lines*) significantly decreased in all coronary grafts but increased in most femoral grafts. The true luminal inner diameter (*ID, solid green line*) of coronary grafts even decreased by 63% vs a 31% increase in more than half of the femoral grafts.

adventitial collagen, led to a distinct thickening of the vein graft wall from 214 ± 67 to 797 ± 382 μm (3.7 times; $P = .002$) for the femoral and from 208 ± 69 to 1062 ± 79 μm; (5.2 times; $P < .0001$) for the coronary graft, resulting in a dramatic decrease in the wall thickness-to-luminal radius ratio from 10.2 ± 0.6 to 3.9 ± 4.8 ($P = .015$) in femoral grafts and from 11.6 ± 5.8 to 0.9 ± 0.3 ($P = .002$) in coronary grafts.

DISCUSSION

Although our model did not take the flow-limiting effect of downstream disease into account, distinct site-specific remodeling trends emerged for coronary and femoral vein grafts:

- All coronary grafts showed a subintimal diameter constriction of 42% compared with most femoral grafts showing a subintimal diameter expansion of 31%.
- Neointimal tissue was 2.3 times thicker in coronary than in femoral grafts.
- The luminal area of coronary grafts was an average of 4.1 times smaller than that of femoral grafts.
- A dramatic 13-fold decrease in the ratio of wall thickness to lumen radius in coronaries was opposed by a less than 3-fold decrease in femoral grafts.

The correlation of these remodeling trends at termination with vessel dimensions and shear forces at implantation made accurate measurements of vessel dimensions a sine qua non. Because the functional effect of flow dynamics at implantation were related to pathomorphologic changes at explantation, two different assessment modes for vessel dimensions were applied at the two intervals, potentially raising concerns regarding direct comparability. Although minor intermeasurement deviations have been previously reported,[13] diameter measurements showed virtually no differences between ultrasound imaging and angiography[14] and ultrasound imaging and macromorphology,[12] as applied in the current study. Moreover, by using M-mode, we were able to determine systolic vessel dimensions at implantation corresponding with perfusion-fixed dimensions at explantation that represented vessels arrested in systole.

By relating downstream remodeling to initial hemodynamic forces, we could confirm size mismatch between vein grafts and their target arteries as an over-riding determinant. Merely on the basis of size difference between the target arteries—otherwise presuming identical inflow and outflow conditions—coronary grafts would experience a fourfold to ninefold lower blood flow than femoropopliteal bypass grafts. However, native coronary arteries are perfused during both cardiac cycles with a moderate systolic and a predominant diastolic component, often showing an early systolic reverse flow.[15] Femoral arteries, in contrast, experience predominantly systolic flow and a relatively high peripheral resistance. As a result of these more favorable flow conditions in the coronaries, the dimensional bias in our study was diminished to a factor 2.8 in favor of femoral flow. Furthermore, the unique extent to which coronary

arteries are capable of forming collaterals suggests that under clinical conditions, downstream disease would disproportionately affect infrainguinal grafts as far as runoff resistance is concerned. This would explain why the actual flow in clinical infrainguinal bypass grafts is only twice as high as that in coronary grafts.[4,6]

There is still controversy whether flow itself, maximum cycling shear stress,[3] or mean shear stress[2] determine the extent of intimal hyperplasia. Normally, shear stress increases with flow, and as such, high flow has been assumed to be required for the suppression of intimal hyperplasia (IH). However, Okadome et al[3] showed at a high flow of 80 mL/min but low shear variation (36 dyne/cm^2) significantly more neo-IH than at a low flow of only 6 mL/min but a high shear variation of 174 dyne/cm^2. Given a shear variation of <25 dyne/cm^2 in our femoral grafts together with a high-flow volume of >80 mL/min, the almost complete suppression of IH in most femoral grafts rather confirms the conclusion by Keynton et al[2] that the mean shear forces correlated more strongly with IH than peak or pulse-amplitude shear forces. The mean shear stress of 5.8 dyne/cm^2 in the group that showed little IH lies well above the value of <2 dyne/cm^2 from which downwards IH accelerates nonlinearly[16] and also above the 5 dyne/cm^2 that was reported as a threshold for the development of neointimal hyperplasia.[17] In our correlation of shear forces with intimal hyperplasia, maximum, peak systolic, and cyclic shear stress rather than mean and peak diastolic shear stress were correlated highly significantly with intimal hyperplasia.

Whereas these considerations relate to the overall hemodynamic forces regulating adaptive remodeling, including diffuse intimal hyperplasia, the luminal diameter fluctuations observed in the narrowed grafts indicate the superimposition of focal events. The lack of such irregularities in the dilated grafts suggests that downward remodeling and diffuse IH may augment the occurrence of focal stenoses.

In contrast to luminal diameters, subintimal diameters disregard the contribution of IH to luminal dimensions and thus represent the net wall remodeling process of a vein graft in response to fluid dynamics. Our observation that all coronary grafts showed subintimal diameter constriction, whereas more than half of the femoral grafts showed distinct dilatation, confirmed clinical studies where at midterm most patent coronary artery bypass grafts were uniformly narrowed by at least one-third of their inner diameter,[6] but femoral grafts showed a mixed picture with predominant dilatation. In a study of 92 patients who received femoropopliteal bypass grafts, approximately one-third showed constriction and two-thirds dilation.[18] Again, shear stress seemed to be a major determinant in this development.[18]

Whereas flow and shear stress were recognized as the dominant regulators of luminal dimensions and caliber, wall tension was identified as the more critical determinant of wall thickness. Accordingly, the end point of vein graft remodeling is supposed to be a structurally optimal ratio of luminal radius to wall thickness that supports arterial pressure with minimal wall stress. In clinical infrainguinal vein grafts, this ratio decreased from about 9:1 at the time of implantation to 7.4:1 at 6 months, a value close to that of the native superficial femoral artery.[19] Given the moderately lower flow in the femoral grafts of our model, a decrease from 10.2 to 3.9 seems realistic. In a study from Zwolak et al,[20] the wall ratio decreased from 8.2 to 3.2 in jugular interposition grafts. Given a cross-sectional quotient of Q_c = 0.17 in the coronary bypass grafts of our current study, the stimulus toward narrowing of the lumen and thickening of the wall was significantly more pronounced, and therefore, an even lower ratio between inner diameter and wall thickness seems reasonable.

Wall tension partly explains overall wall thickening, but the actual layer-specific events remain vaguely described. Even as some investigators describe a gradually occurring fibrous scarring process whereby smooth muscle cells are replaced by thick bundles of collagen,[21] others describe a net increase in the muscle mass of the media[22] which they call "arterialization." In the present study, the thickness of the media did increase by a factor 3.1 (coronaries) and 2.4 (femorals), but concomitantly, the percentage of muscle tissue within the media decreased from 66% to 33%, clearly challenging the term "arterialization."

CONCLUSIONS

Sixty years after bypass surgery became a treatment for occlusive arterial disease, the remodeling process occurring in vein grafts at different anatomic locations remains only partially appreciated. However, the ability to relate different remodeling responses of one and the same saphenous vein to the site-specific fluid dynamics of the two clinically most relevant anatomic sites is a prerequisite for any differentiated therapeutic intervention. Given the manifold longer graft lengths clinically used for infrainguinal than for coronary bypasses, their exposure to bending and the presence of irregular segments that would be excised in coronary grafts, the mildly worse clinical performance of infrainguinal bypass grafts does not contradict the distinctly better remodeling behavior we saw in the direct comparison.

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AUTHOR CONTRIBUTIONS

Analysis and interpretation: PZ, HK, JK, PH, MW, TF
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Writing the article: PZ
Critical revision of the article: PZ, PH, TF
Final approval of the article: PZ, LM, JS, HK, JK, PH, MW, TF
Statistical analysis: PZ, PH
Obtained funding: PZ
Overall responsibility: PZ

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