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REMODELING LEADS TO DISTINCTLY MORE INTIMAL HYPERPLASIA IN CORONARY THAN IN INFRA-INGUINAL VEIN GRAFTS

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Word Count excluding abstracts and citations: 3,354

ABSTRACT

Background

Flow patterns and shear forces in native coronary arteries are more protective against neo-intimal hyperplasia than those in femoral arteries. Yet, the calibre mismatch with their target arteries makes coronary artery bypass grafts (CABGs) more likely to encounter intimal hyperplasia than their infra-inguinal counterparts due to the resultant slow flow velocity and increased wall stress. In order to allow a site-specific, flow-related comparison of remodeling behavior, saphenous vein bypass grafts were simultaneously implanted in femoral and coronary position.

Methods

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

Results

At implantation, the cross sectional quotient between target arteries and vein grafts was Q_c=0.62±0.10 for femoral grafts versus 0.17±0.06 for coronary grafts and as such the dimensional graft-to-artery mismatch was 3.6 times higher ($p<0.0001$) 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=0.0048); 48.1±23.6% lower maximal cycling wall shear stress (p=0.012) and 62.2±21.2% lower mean velocity (p=0.007) in coronary grafts. After 24 weeks, the luminal diameter of all coronary grafts had contracted by 63% (from ID 4.49±0.60 to 1.68±0.63mm; $p<0.0001$) [sub-intimal diameter: -41.5%, p=0.002] while 57% of

the femoral interposition grafts had dilated by 31% (from ID 4.21±0.25 to 5.53±1.30mm; p=0.020). Neo-intimal tissue was 2.3 times thicker in coronary than in femoral grafts (561±73μm versus 240±149μm ; p=0.001). Overall, the luminal area of coronary grafts was, on average, 4.1 times smaller than that of femoral grafts.

Conclusion

Although coronary and infra-inguinal bypass surgery uses saphenous veins as conduits they undergo significantly different remodeling processes in these two anatomical positions.

Word Count: 305

CLINICAL RELEVANCE

Saphenous vein grafts still represent the gold standard of bypass surgery. Although flow-dependent vein graft remodeling has been experimentally shown, there is limited clinical appreciation for the remodeling differences between coronary and infra-inguinal vein grafts as the procedures are generally performed by two different clinical disciplines. Understanding the site specific base-line 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 neo-intimal hyperplasia or luminal encroachment.

Word Count: 82

INTRODUCTION

Despite the increasing importance of interventional and endovascular procedures, peripheral and coronary bypass 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 pathological 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.

While 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 while only moderately affecting wall tension. Because the saphenous vein is a conduit of a given diameter[5], it is the dimension of the run-off artery that determines to what extent the vein graft deviates from the functionally 'optimal' dimensions of an anatomical site. While saphenous vein bypass grafts are usually more than 3 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 femoro-popliteal bypasses[7]. Therefore – independent of the additional effect of inflow-patterns, down stream resistance and disease - the resulting base-line flow deceleration in coronary bypasses and flow-acceleration in femoro-popliteal grafts is expected to be reflected in significant shear-force differences between the two anatomical sites and as such in a markedly different remodeling response favoring diffuse intimal hyperplasia formation in coronary grafts.

In order to be able to compare the base-line remodeling response of saphenous vein grafts in these two clinically most relevant anatomical locations, we correlated the flow dynamics with the remodeling processes in concurrently implanted coronary and infra-inguinal 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].

MATERIALS AND METHODS

A functional, dimension-associated starting point was related to a patho-morphological end point. As pressure-controlled perfusion-fixation for accurate morphological micro-analysis[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 (n=8; 28.1±4.9kg) strictly following a no-touch technique. The distal vein was canulated early and gently injected with heparinised papaverin-containing blood (1mg/ml; near body temperature). After storage in heparinised blood at environmental temperatures routie surgical distension without the use of pressure controlling syringes was applied to identify leaks. Vein grafts were concomitantly implanted as bypasses from superficial femoral to supra-popliteal artery and aorta to left anterior descending coronary artery [LAD] 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 (HD11 XE ultrasound system with L15-7io transducer and Vascular software, HD11 XE, Philips Healthcare, Best, The Netherlands). Vessel diameters were obtained from pre-grafted target arteries at the expected sites of the distal anastomoses and at mid-grafts at three 1cm 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 Qc[11]. Blood flow velocity was recorded in pre-grafting target arteries at the sites of grafting and in mid-graft location in the sagittal plane using Duplex ultrasound 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 $\bar{v}$ was expressed as the arithmetic mean considering changes in flow direction: $\bar{v} = 1/n \sum_{i=1}^{n} v_i$, 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 figure 1. The mean wall shear stress (WSS) 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 $\overline{WSS} = 1/n \sum_{i=1}^{n} |WSS_i|$ where $\overline{WSS}$ 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 at120mm Hg and analyzed as previously described[11]. Luminal dimensions were assessed by macroscopic image analysis of mid-graft cross sections 1cm apart. Detailed morphometric assessments were based on composite images of series of mid-graft sections from digital single-frames captured at 4x and 10x magnification (Nikon Eclipse 90i and Nikon Coolscope) using Eclipse Net software (Laboratory Imaging, Prague, Czech Republic). Surface endothelialization was assessed by a

JEOL JSM 5200 (Jeol, 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 mid-graft sections (QWinPro V2.5; Leica Microsystems Imaging Solutions) with histological cross sections.

STATISTICAL ANALYSIS

Comparison of patency between the coronary and femoral grafts was performed using the two-tailed Fisher's Exact test. Linear standard least squares modeling of the effect of shear stress parameters maximum shear stress, peak systolic shear stress and maximum cyclic shear stress on intimal hyperplasia thickness was performed. Continuous numerical data were expressed as means ± standard deviation. Post-hoc comparisons between groups represented by continuous numerical data were performed using unpaired, 2-tailed Student’s t-tests, with p-values less than 0.05 regarded as significant.

RESULTS

There was no statistically significant difference in the 180-day patency (87% [7/8] femoral grafts; 63% [5/8] coronary grafts; p=0.57).

LUMENAL DIMENSIONS AND FLOW DYNAMICS AT IMPLANT

At graft insertion no signs of irregularities were detectible in the mid graft portions investigated by ultrasound. The IDs of the saphenous vein grafts were almost identical in coronary and femoral position (Table I)(N.S.) with the cross sectional quotient between target artery and vein graft being 3.6 times lower ($p<0.0001$) in coronary grafts. Accordingly, flow velocities and shear stress were distinctly more damped in coronary than in femoral grafts *(Figure 1; Table II)* resulting in a 57.9±19.4% lower maximum velocity (p=0.005); 48.1±23.6% lower maximal cycling wall shear stress (p=0.012) and 62.2±21.2% lower mean velocity (p=0.007). Modeling shear stress parameters against intimal hyperplasia thickness confirmed significant associations with this outcome variable for all shear stress maxima: maximum (p=0.007), peak systolic (p=0.003) and maximum cyclic shear stress (p=0.012) but not for mean or peak diastolic shear stress.

GRAFT PATHOLOGY AT EXPLANT

All coronary grafts appeared shrunken with a thick whitish wall whereas a majority of femoral grafts looked dilated with a distinctly thinner wall *(Figure. 2)*. Neo-intimal tissue was 2.3 times thicker in coronary than in femoral grafts (p=0.001) *(Table I and Figure 3)*. Within femoral grafts inward remodeling was associated with 2.5 times thicker neo-intimal tissue than outward remodeling (145±108μm vrs 368±82μm ; p=0.030). Reflecting diameter changes, the intimal area differed less distinctly between femoral and coronary grafts than thickness (2,335±1,631x10^3μm^2 vrs 4,126±2,196x10^3μ$m^{2;}$ 1.8x; N.S.). Media thickness increased by a factor 3.1 [from 133±50μm to 407±182μm; p=0.002] in femoral grafts and 2.4 [to 319±113μm;

p=0.006] in coronary grafts. At the same time 'muscularity' decreased from 65.9±24.9% to 32.9±9.9% (p=0.007) in the femoral grafts and from 65.5±30.5% to 33.8±6.8% (p=0.021) in the coronary grafts, respectively *(Figure 4)*. Yet, total muscle mass increased by 182% (from 1.01±0.72 $x10^6\mu m^2$ to1.75±0.65$x10^6\mu m^2$; N.S.) and 74% (from 0.93±0.41$x10^6\mu m^2$ to 1.23±0.54 $x10^6\mu m^2$; p=0.030). In both coronary and femoral grafts identical, near-complete endothelialization was found with only small patches of pre-confluent or non-endothelialized surface [91.8±11.1% (fem) and 91.3±12.0% (cor) N.S.].

DIMENSIONAL GRAFT REMODELING

While the ID of all patent coronary grafts had contracted by 63% (p<0.0001), a majority of the patent femoral interposition grafts (4/7) had actually dilated by 31% or factor 1.3x (from 4.21±0.25 to 5.53±1.30mm;p=0.020) *(Figure 5)*. Overall, all narrowed grafts showed distinct luminal midgraft irregularities at explantation whereby the inner diameter (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 sub-intimal diameters, all coronary grafts had distinctly constricted by 41.5% (p=0.002) whereas a majority of patent femoral grafts (4/7) showed outward remodeling by 35.3% (p=0.005). The remaining femoral grafts (3/7) displayed an equal degree of 35.2% inward remodeling (p=0.020) *(Figure 5)*. At the time of implantation the two femoral subgroups neither differed regarding the weight of the animals (29.4±6.3 vrs 30.6±0.8kg; p>0.9 N.S.) nor the ID or flow-conditions of the run-off supra-popliteal arteries (3.04±0.26mm vrs 3.30±0.36mm p>0.5 N.S.) nor were there any signs of luminal irregularities. Distinct neo-intimal proliferation and a 2.4-3.1 times increase in media thickness – together with an increase in adventitial collagen – led to a distinct thickening of the vein graft wall (Femoral: from 214±67μm to 797±382μm; 3.7 times; p=0.002 and Coronary: from 208±69 to 1062±79; 5.2 times; p<0.0001) resulting in a dramatic decrease in the ratio of wall thickness to luminal

radius (from 10.2±0.6 to 3.9±4.8;p=0.015 in femoral grafts and 11.6±5.8 to 0.9±0.3;p=0.002 in coronary grafts).

DISCUSSION

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

- All coronary grafts showed a sub-intimal diameter constriction of 42% as opposed to a majority of femoral grafts showing a sub-intimal diameter expansion of 31%.
- Neo-intimal tissue was 2.3 times thicker in coronary than in femoral grafts.
- The luminal area of coronary grafts was in average 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 the time of termination with vessel dimensions and shear forces at implantation made accurate measurements of vessel dimensions a sine qua non. As the functional effect of flow-dynamics at implantation were related to patho-morphological changes at the time of explantation, two different assessment modes for vessel dimensions were applied at the two time points potentially raising concerns regarding direct comparability. Although minor inter-measurement deviations have been previously reported[13] diameter measurement showed virtually no differences between ultra sound and angiography[14] and ultra sound and macro-morphology[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 down-stream 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 in and outflow conditions - coronary grafts would experience a 4-9 fold lower blood flow than

femoro-popliteal 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 preripheral resistance. As a result of these more favourable flow conditions in coronaries, the dimensional bias in our study was diministed 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 down-stream disease would disproportionately affect infra-infuingal grafts as far as run-off resistance is concerned. This would explain why the actual flow in clinical infra-inguinal 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 IH. However, Okadome et al[3] showed at a high flow of 80ml/min but low shear variation (36dynes/cm^2) significantly more neointimal hyperplasia than at a low flow of only 6ml/min but a high shear variation of 174 dynes/cm^2. Given a shear variation of less than 25 dynes/cm^2 in our femoral grafts together with a high-flow volume of >80ml/min the control of intimal hyperplasia in a majority of grafts rather confirms Keynton et al's conclusion that the mean shear forces correlated more strongly with IH than either peak or pulse-amplitude shear forces[2]. The mean shear stress of 5.8dynes/cm^2 in the group that showed little IH lies well above the value of <2 dynes/cm^2 from which downwards IH accelerates non-linearly[16] and also above the 5dynes/cm^2 that were reported as a threshold for the development of neointimal hyperplasia[17]. In our correlation of shear forces with intimal hyperplasia, it was maximum-, peak systolic- and cyclic shear stress rather than mean and peak diastolic SS that correlated highly significantly with intimal hyperplasia.

While 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 intima hyperplasia themselves may augment the occurrence of focal stenoses.

In contrast to luminal diameters, subintimal diameters disregard the contribution of intimal hyperplasia to luminal dimensions and as such 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 while more than half of the femoral grafts showed distinct dilatation confirmed clinical studies where at midterm most patent CABG grafts were uniformly narrowed by at least a third of their inner diameter[6] while femoral grafts showed a mixed picture with predominant dilatation. In a study comprising 92 patients who received femoro-popliteal 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].

While flow and shear stress were recognized as the dominant regulators of luminal dimensions and calibre, wall tension was identified as the more critical determinant of wall thickness. Accordingly, the endpoint 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 infra-inguinal vein grafts, this ratio was shown to decrease from about 9:1 at the time of implantation to 7.4:1 at six 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 Alexander Clowes' group the wall-ratio decreased from 8.2 to 3.2 in jugular interposition grafts[20]. Given a cross sectional quotient of Q_c=0.17 in the coronary bypass grafts of our current study, the stimulus towards 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.

While wall tension partly explains overall wall thickening, the actual layer-specific events remain vaguely described. Even as some investigators describe a gradually occurring fibrous scarring process whereby SMCs 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'.

Thus, 60 years after bypass surgery became a modality for the treatment of occlusive arterial disease, the remodeling process occurring in vein grafts at different anatomical 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 anatomical sites, however, is a prerequisite for any differentiated therapeutic intervention. Given the manifold longer graft lengths clinically used for infra-inguinal 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 infra-inguinal bypass grafts does not contradict the distinctly better remodeling behavior we saw in the direct comparison.

ACKNOWLEDGEMENTS

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LEGENDS

Table I: Dimensional comparisons between target arteries and saphenous vein grafts at the time of implantation and at termination after 24 weeks (ID=inner diameter; LA=luminal area; SID=sub-intimal diameter; Qc=Cross sectional quotient; IT=intimal thickness; WT=wall thickness; R:WT=ratio of radius to wall thickness).

Table II: Comparison of flow dynamics in the target arteries prior to grafting and in the vein grafts post grafting.

Figure 1: Mean wall shear stress (WSS) in the native femoral and left anterior descending coronary arteries prior to 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 coronary arteries (LAD/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 calibre mismatch between coronary bypass grafts and their target arteries causes a dramatic 'flattening' of WSS in the vein grafts.

Figure 2: Saphenous vein grafts in coronary (a,b) and infra-inguinal (c,d) position at implantation (a,c) and after 6 months (b,d). The femoral grafts represent the two subgroups of dilation and constriction. The ruler displays millimeters.

Figure 3: Significantly thicker neo-intimal tissue in coronary bypass grafts (a,b) than in infra-inguinal grafts (c,d). While coronary grafts regularly showed a massive concentric layer of neo-intimal tissue (a,b), femoral grafts often had one half of the luminal circumference lacking neo-

intimal tissue and the other half covered by a modest, excentric layer of crescent-shaped neo-intima (c,d). [Masson's Trichrome x 12 (b,c) and Azan (a,c) x40]. The high magnifications show both sites (d). The neo-intimal layers are delineated with triangles.

Figure 4: Media development over 6 months of implantation (coronary grafts solid lines; 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).

Figure 5: Dimensional remodeling of saphenous vein grafts in coronary (cor) and femoral (fem) position over 6 months of implantation. Independent from neointimal tissue, subintimal diameters (dashed red lines) significantly decreased in all coronary grafts while they increased in a majority of femoral grafts. The true luminal diameter (solid green line) of coronary grafts even decreased by 63% as opposed to a 31% increase in more than half of the femoral grafts.

TABLES AND FIGURES

Table I:

	Femoral Grafts						
	ID	LA	SID	Qc	IT	WT	R:WT
SFA	3.23±0.32	8.56±1.34					
SVG Impl	4.07±0.44	13.02±2.75	4.11±0.44	0.62±0.11		214±67	10.2±0.58
SVG Expl	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						
	ID	LA	SID	Qc	IT	WT	R:WT
LAD	1.84±0.23	2.69±0.66					
SVG Impl	4.49±0.60	16.18±5.67	4.79±0.23	0.17±0.06		208±69	11.6±5.8
SVG Expl	1.68±0.63	2.97±1.36	2.80±0.51	1.11±0.79	561±73	1062±79	0.9±0.3

Table II:

	Femoral Position		**Coronary Position**	
	Artery	**Graft**	**Artery**	**Graft**
Velocities				
Mean Velocity (cm/s)	15.7±4.3	8.6±3.3	16.4±2.6	3.1±1.5
Maximal Velocity (cm/s)	61.4±12.8	34.0±11.5	72.6±15.9	13.4±5.7
Peak Systolic Velocity (cm/s)	60.9±12.5	33.6±11.2	27.0±8.1	5.1±3.2
Peak Diastolic Velocity (cm/s)	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 Shear Stress (WSS)				
Mean WSS (dynes/cm^2)	14.5±3.2	5.8±2.1	34.4±6.4	2.4±1.2
Maximal WSS (dynes/cm^2)	51.8±8.3	21.1±7.1	107.5±32.7	8.3±3.5
Peak Systolic WSS (dynes/cm^2)	51.3±8.1	20.9±7.0	42.9±14.3	3.2±2.0
Peak Diastolic WSS (dynes/cm^2)	12.1±3.5	4.8±1.7	104.7±38.2	7.42±3.2
Maximal Cyclic WSS (dynes/cm^2)	60.2±9.2	24.4±7.4	166.0±59.4	12.0±5.2
Systolic Acceleration Time (s)	0.21±0.02		0.12±0.11	
Diastolic Acceleration Time(s)	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	

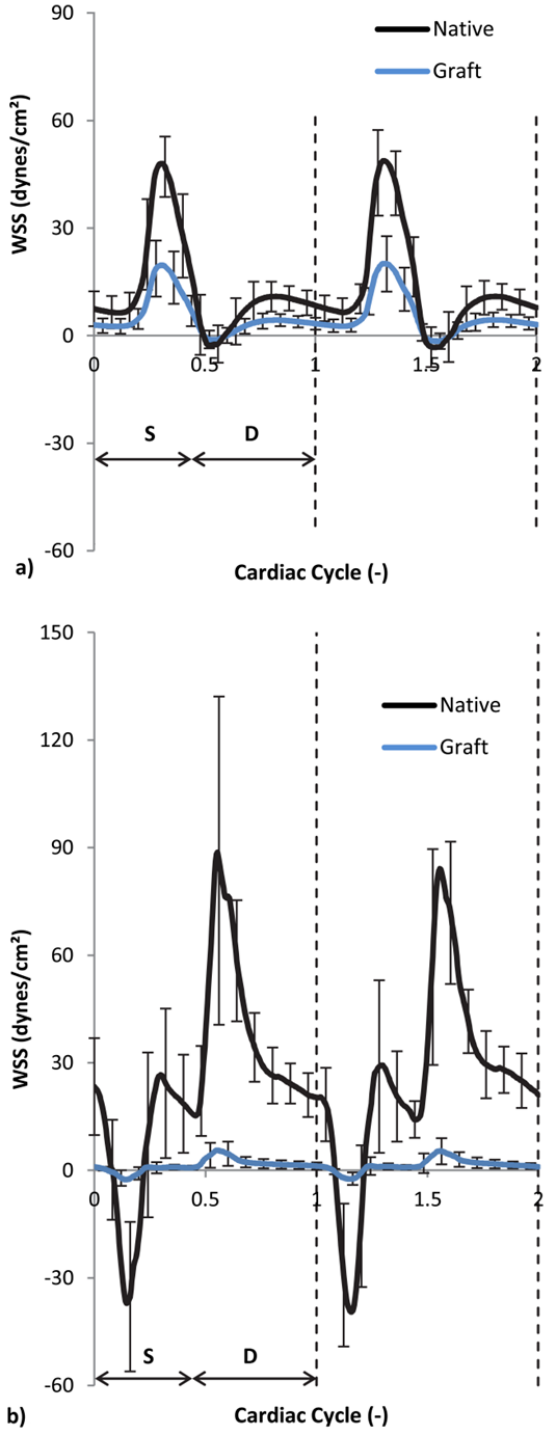
Native
Graft
WSS (dynes/cm²)
90
60
30
0
-30
-60
0
0.5
1
1.5
2
S
D
a)
Cardiac Cycle (-)
150
120
90
60
30
0
-30
-60
b)

Figure 1

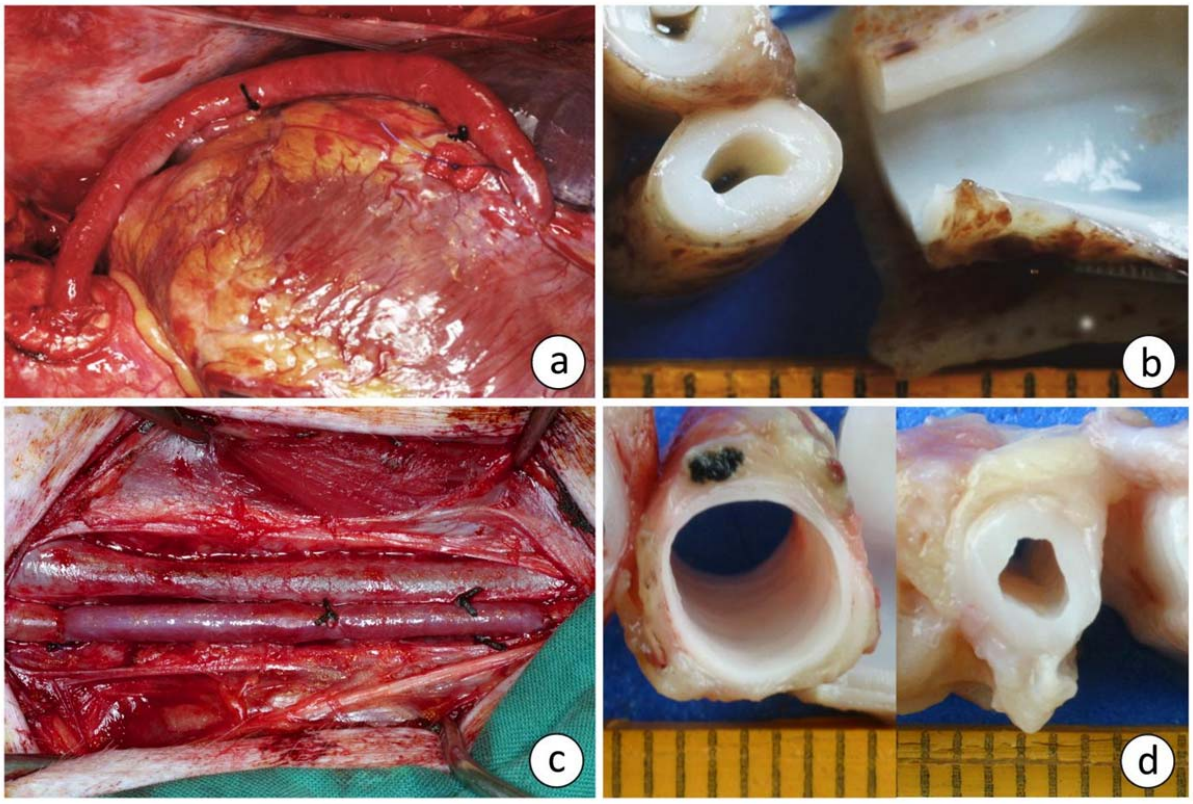

Figure 2

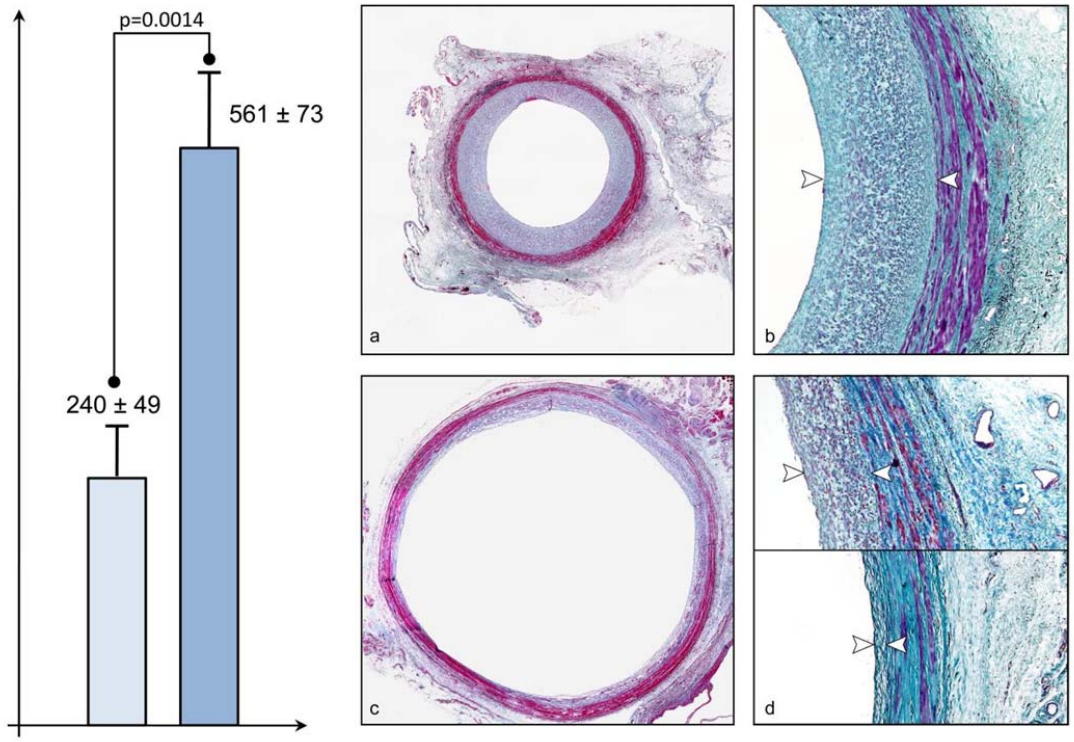

Figure 3

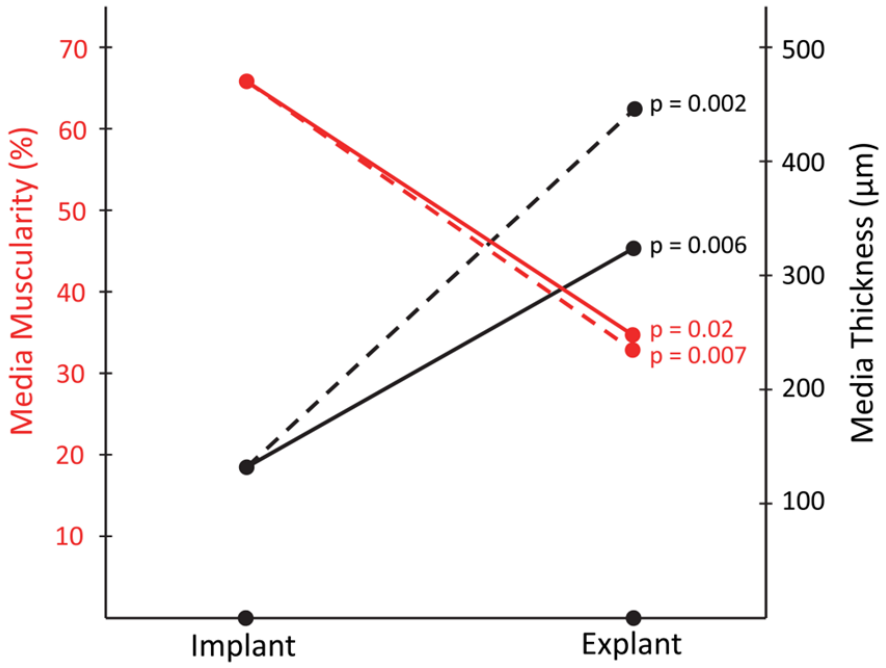
70
60
50
40
30
20
10
Media Muscularity (%)
500
400
300
200
100
Media Thickness (µm)
p = 0.002
p = 0.006
p = 0.02
p = 0.007
Implant
Explant

Figure 4

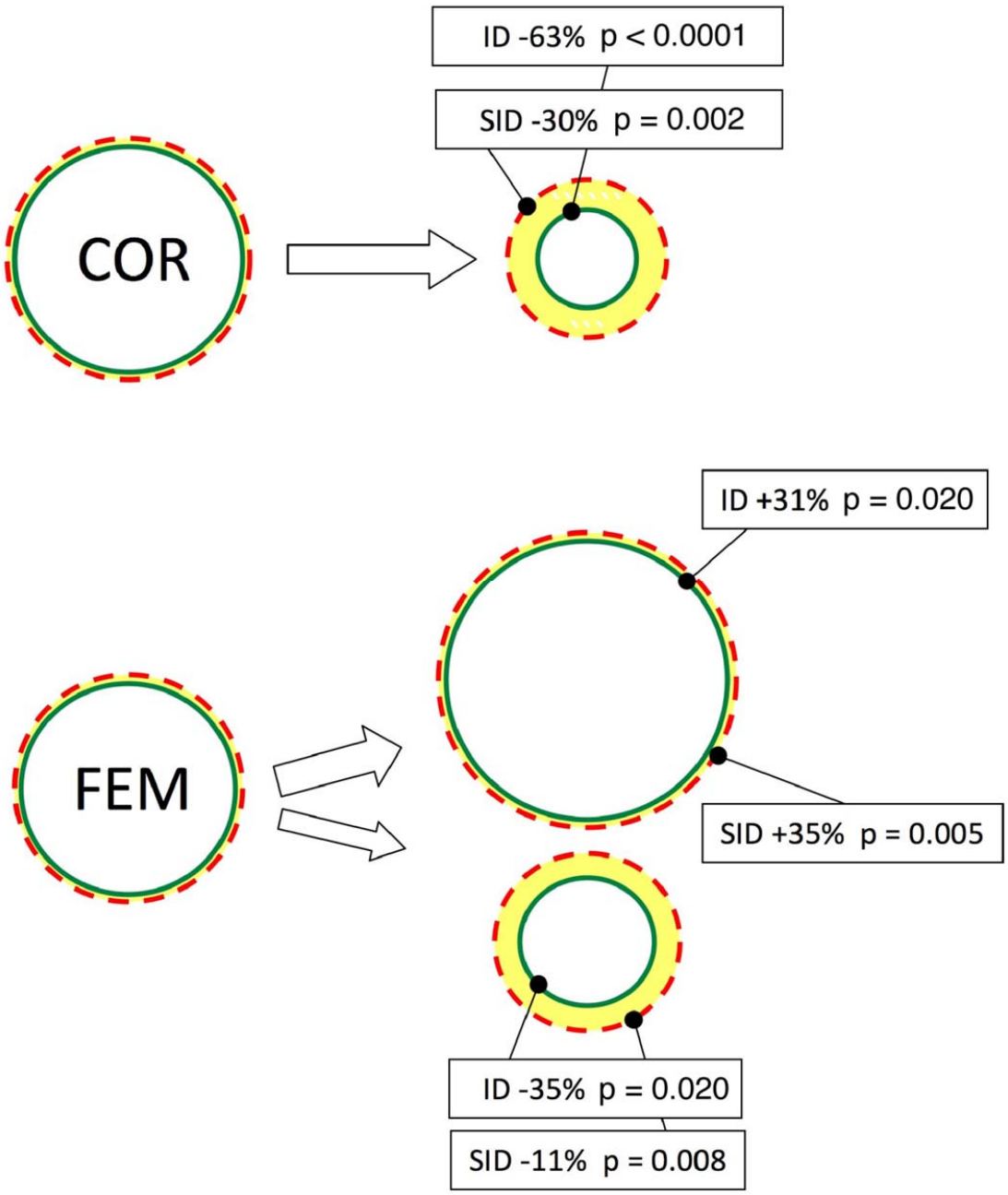
ID -63% p < 0.0001
SID -30% p = 0.002
COR
ID +31% p = 0.020
FEM
SID +35% p = 0.005
ID -35% p = 0.020
SID -11% p = 0.008

Figure 5

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