Flow patterns in externally stented saphenous vein grafts and development of intimal hyperplasia

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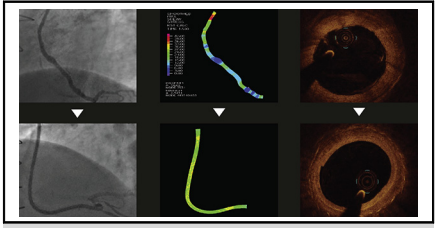
ABSTRACT

Background: Low and oscillatory wall shear stress promotes endothelial dysfunction and vascular disease. The aim of the study was to investigate the impact of an external stent on hemodynamic flow parameters in saphenous vein grafts (SVGs) and their correlation with the development of intimal hyperplasia.

Methods: We performed post hoc computational fluid dynamics analysis of the randomized Venous External Support Trial, in which angiography and intravascular ultrasound data were available for 29 patients, 1 year after coronary artery bypass grafting. Each patient received 1 external stent, to either the right or left coronary territories; ≥1 patients with nonstented SVGs served as control(s). Diffuse flow patterns were assessed using mean values of various hemodynamic parameters, including time-averaged wall shear stress and oscillatory shear index (OSI). Focal flow disturbances were characterized using percentile analysis of each parameter.

Results: Angiography and intravascular ultrasound data were available for 53 and 43 SVGs, respectively. The stented versus nonstented SVG failure rates were significantly lower in the left territory (17.6% vs 27.5%; $P = .02$), and significantly higher in the right territory (46.2% vs 13.4%; $P = .01$). In both diffuse and focal flow-pattern analyses, OSI was significantly lower in the stented versus nonstented SVG group ($P = .009$ and $P < .003$, respectively), whereas no significant differences were observed in time-averaged wall shear stress values. High OSI values were correlated with the development of intimal hyperplasia ($P = .01$).

Conclusions: External stenting affects SVG's hemodynamics 1 year after coronary artery bypass grafting and may mitigate the progression of intimal hyperplasia by reducing oscillatory shear stress. (J Thorac Cardiovasc Surg 2015;150:871-9)



Improved lumen uniformity → improved flow pattern → reduction of intimal hyperplasia.

Central Message

External stenting improves vein graft hemodynamics and may mitigate intimal hyperplasia by reducing oscillatory shear stress.

Perspective

Although susceptible to progressive failure, autologous SVGs remain the most frequently used bypass conduits in CABG. Strategies that minimize flow disturbances have the potential to mitigate SVG intimal hyperplasia, which is the foundation for development of graft atheroma. Improving SVG longevity can potentially affect clinical outcomes of CABG.

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Coronary artery bypass grafting (CABG) remains the gold standard of treatment for patients with multivessel coronary artery disease.[1] Although susceptible to progressive failure,[2] autologous saphenous vein grafts (SVGs) are still the most frequently used bypass conduits in CABG. Exposure to the hemodynamics of the arterial circulation, which involve high pressure and shear stress, results in SVG remodeling and the development of diffuse intimal hyperplasia along the entire graft, in the first months after implantation.

This process represents the foundation for development of graft atheroma, and its extent creates a diffuse atherosclerosis-prone region.[3] Focal aggressive intimal hyperplasia and stenotic atherosclerotic lesions are mostly "site specific," signifying an interaction between disease pathogenesis and disturbed flow that occurs in susceptible regions.[4] Laminar flow pattern, with physiologic wall shear stress (WSS) and minimal or no oscillation, has a protective effect against the development of vessel-wall injury and atherosclerosis. In contrast, areas with low and oscillatory WSS, such as the inner wall of curved segments and areas with lumen irregularities, are more prone to endothelial

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Abbreviations and Acronyms
CABG = coronary artery bypass grafting
OSI = oscillatory shear index
RRT = relative residence time
SVG = saphenous vein graft
TAWSS = time-averaged wall shear stress
WSS = wall shear stress

dysfunction, focal aggressive intimal hyperplasia, and vascular disease.[5-9]

Mechanical external stents for SVGs have shown significant reductions of proliferative intimal hyperplasia, foam cell deposition, and other vascular disease markers in preclinical testing.[10-13] This protective effect of external stents is attributed to the reduction in SVG wall tension, improvement of lumen uniformity, and formation of a ''neo-adventitia'' layer that is rich with microvasculature.[10-14] The VEST (Vascular Graft Solutions Ltd, Tel Aviv, Israel) is a kink-resistant cobalt-chromium braided mesh, applied externally to the vein graft during surgery. The VEST was evaluated in both preclinical testing and a randomized controlled clinical study, and was shown to significantly reduce SVG's diffuse intimal hyperplasia and to improve lumen uniformity.[14,15]

We report here the application of computational fluid dynamics analysis to geometric models of SVGs, based on angiographic imaging and quantitative analysis data from the Venous External Support Trial.[15] Coupled with imaging technologies, computational fluid dynamics has been employed to investigate blood flow patterns.[16] In this approach, numeric methods are used to approximate the flow fields in vessels, which are too complex for analytic solutions. To characterize the various flow patterns, several hemodynamic parameters have been developed and investigated. These parameters have been shown to strongly correlate with the development of vascular pathology, mainly in the arterial system.[17,18] The aim of the present study was to compare the flow pattern in externally stented and nonstented SVGs, and to analyze the relationship between various hemodynamic parameters and the development of intimal hyperplasia in venous grafts.

METHODS

As previously described, the Venous External Support Trial[15] randomized 30 patients in a prospective, multicenter study. The study was approved by a United Kingdom research ethics committee (NRES Committee East of England-Cambridge Central), and all subjects gave informed consent. All SVGs were harvested using an open technique, and surgery was performed with use of cardiopulmonary bypass. During surgery, and after completion of all distal anastomoses, 1 SVG was randomized to receive an external stent, and ≥1 SVGs remained nonstented and served as the control group.

An adequate device size was selected based on the graft's diameter and length. The device was threaded over the randomized SVG and expanded along the entire vein graft length; its diameter was simultaneously reduced to mildly constrict the SVG. Because of its axial plasticity, after being expanded over the entire SVG, the device maintains its length and diameter, and no glue or sutures are required to affix it to the SVG (Figure 1).

Baseline parameters that have the potential to affect SVG hemodynamics, and the development of intimal hyperplasia, were recorded. These included the severity of the proximal stenosis in the coronary artery and its diameter, as well as transit time flow measurement and the pulsatility index, which were evaluated in each SVG before chest closure (Table 1). Contrast angiography of all SVGs was attempted 12 months after CABG, along with intravascular ultrasound of patent SVG to the right and the circumflex territories, to assess intimal hyperplasia area, which was the prespecified primary endpoint of the trial.

Quantitative Angiography Analysis and Intravascular Ultrasound

As previously described,[15] quantitative coronary angiography was performed for all patent SVGs. Analysis was performed by an independent observer using an angiographic frame showing the worst appearance for each SVG.[3] Blood flow and velocity were assessed using the thrombolysis in myocardial infarction frame count.[19] The total number of frames was counted, from the initial complete opacification of the proximal anastomosis of the graft, to the frame where dye first enters the native coronary artery at the distal anastomosis. Graft uniformity was graded by an independent observer, using the Fitzgibbon classification: I = uniform graft; II = nonuniformity that involves <50% graft length; III = nonuniformity that involves >50% graft length.[2]

Intravascular ultrasound was performed for all patent SVGs to the right and the circumflex territories. Images were analyzed, and the lumen and the external elastic membrane were identified and marked by an independent observer according to American College of Cardiology guidelines.[20] The area of intimal hyperplasia was calculated as the external elastic membrane area minus the lumen area. Cross-sectional intimal area analysis was performed approximately every 10 mm along the graft, from the distal to the proximal anastomosis, and a mean value was calculated for each SVG, representing the diffuse burden of intimal hyperplasia.

Geometry Reconstruction and Computational Fluid Dynamics

The geometric reconstruction of individual grafts was performed using their respective singular angiographic images from the 12-month visit. Based on each SVG centerline, boundaries and cross-sections were generated, and 3-dimensional models were created using the commercial software SOLIDWORKS (Dassault Systèmes Americas Corp, Waltham Mass). Lumen dimensions of SVGs were calibrated using the external diameter of the angiography catheter. Each cardiac cycle was divided into 100 equally spaced time steps of 10 ms; 3 cycles were computed to obtain results that are independent of any transient effects.

The inlet velocity of each SVG was calculated from the thrombolysis in myocardial infarction frame count average velocity provided by the core-lab analysis and the inlet cross-sectional area. The incompressible Navier-Stokes equations were solved numerically (ABAQUS FEA [Dassault Systemes Americas Corp, Waltham, Mass]), using the finite-element scheme under pulsatile flow conditions, assuming Newtonian fluid (viscosity: 0.0035 N·second/m^2; density: 1056 kg/cm^3), 3-dimensional, time-dependent, laminar, and isothermal flow. The numeric mesh consisted of approximately 1 million tetrahedral fluid elements, with an element edge length of 0.15 cm.

Hemodynamic Parameters

Three hemodynamic parameters of the externally stented and nonstented groups were calculated and compared: time-averaged wall

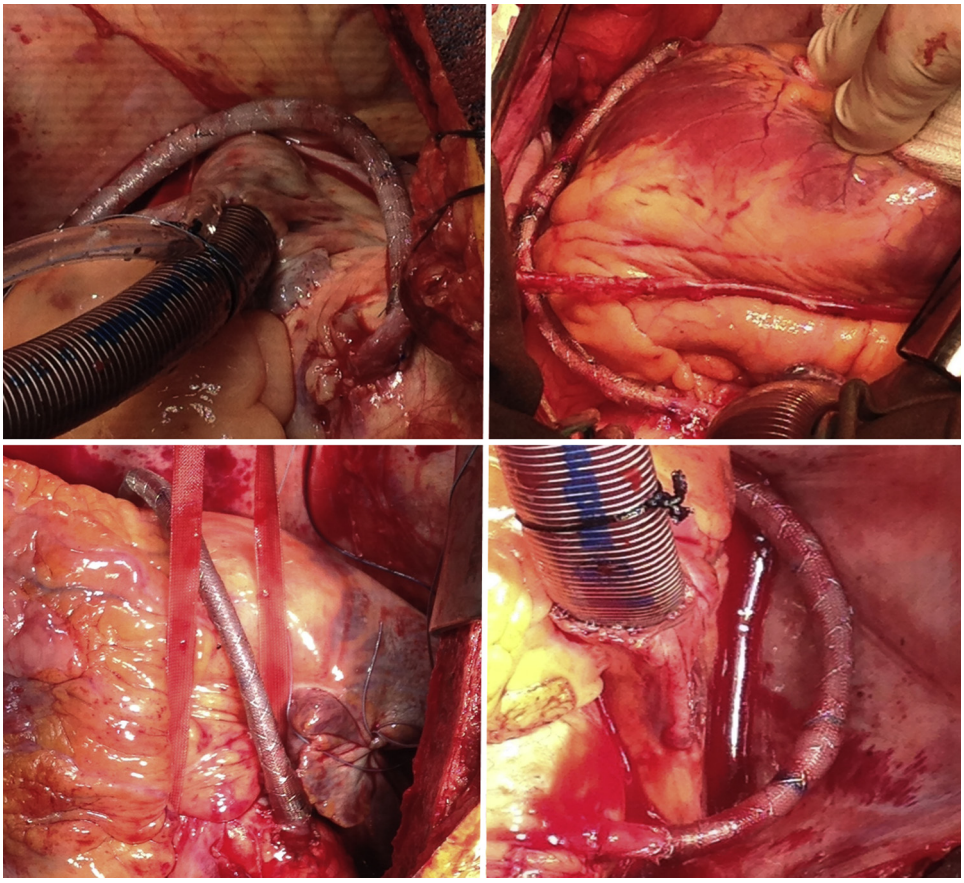

FIGURE 1. External stent (VEST [Vascular Graft Solutions Ltd, Tel Aviv, Israel]) deployed on saphenous vein graft, grafted to the obtuse marginal artery and the right coronary artery.

shear stress (TAWSS); oscillatory shear index (OSI); and relative residence time (RRT). Wall shear stress, expressed in units of force per unit area, quantifies the tangential friction force exerted by flowing blood on the vessel wall. When the flow is pulsatile and time dependent, the time average of WSS is calculated by integrating the magnitude of WSS over the cardiac cycle, as

$$TAWSS = \frac{1}{T}\int_0^T |wss_i|dt,$$

where wss_i is the instantaneous shear stress vector, and T is the duration of the cycle.

The OSI is a nondimensional parameter (ranging from 0 to 0.5) that measures the degree of deviation of WSS from the antegrade flow direction. High OSI values reflect large variations in the WSS vector, which means that during some periods of time, flow is stopped or reversed.[21] The OSI is computed as:

$$OSI = \frac{1}{2}\left\{1 - \frac{\left|\int_0^T wss_i dt\right|}{\int_0^T |wss_i|dt}\right\},$$

where wss_i is the instantaneous WSS vector, and T is the duration of the cardiac cycle.

Relative residence time. Vascular disease is accelerated in areas at which the blood elements have high residence times near the endothelium.[22] The RRT quantifies the relative duration that blood elements reside near the vessel wall; it is inversely proportional to TAWSS.

TABLE 1. Characteristics of saphenous vein graft groups

Characteristic	Stented (n = 30)	Nonstented (n = 30)	*P* value
Host coronary artery stenosis (%)	86.9 ± 12.7	86.6 ± 10	.63
Host coronary artery diameter (mm)	1.8 ± 0.2	1.9 ± 0.3	.14
Graft length (cm)	15.4 ± 2.5	15 ± 2.4	.45
Systolic pressure at TTFM (mm Hg)	109.1 ± 15.2	109.7 ± 15.9	.57
Final TTFM flow (mL/min)	67 ± 27.8	66.2 ± 33.4	.89
Final TTFM pulsatility index	2.2 ± 1.1	2.2 ± 1.0	1.0
Anatomic and physiologic parameters of SVG, based on 12 mo of QCA analysis	(n = 21)	(n = 31)	
Mean lumen diameter (mm)	2.8 ± 0.5	2.7 ± 0.6	.72
Average blood flow (mL/s)	94.7 ± 49.5	94.3 ± 46.6	.970
Average blood velocity (cm/s)	15.8 ± 6.5	15.5 ± 7.2	.900
Inlet cross-sectional area (mm^2)	6.36 ± 2.00	7.75 ± 4.46	.187
Inlet blood velocity (cm/s)	17.50 ± 7.11	17.05 ± 8.59	.846

Data are expressed as mean ± SD, unless otherwise indicated. Average blood flow and average blood velocity are thrombolysis in myocardial infarction estimations. From the Venous External Support Trial.[15] *TTFM*, Transit time flow measurement; *SVG*, saphenous vein graft; *QCA*, quantitative coronary angiography.

In fact, RRT is a single marker of "low and oscillatory" shear, and is computed as:

$$RRT = \frac{1}{TAWSS \times (1 - 2 \times OSI)}.$$

Mean values of each hemodynamic parameter were calculated for each SVG. These mean values included all fluid elements along the SVG from the distal to the proximal anastomosis. For each SVG, the mean value of every hemodynamic parameter was analyzed with respect to the mean value of the intimal area assessed by intravascular ultrasound. Group analysis, of both the stented and nonstented groups, was performed to study the relationship between a mean value of each hemodynamic parameter and the development of diffuse intimal hyperplasia.[15]

Given the "site-specific" pattern of stenotic atherosclerotic disease, we additionally investigated segmental flow disturbances in each SVG. Robust data regarding pathologic threshold values of each hemodynamic parameter, based on extensive in vivo studies, have not been documented. Consequently, and as an alternative, we decided to compare equal percentile values as a threshold from which the most-disturbed pattern was observed for each hemodynamic parameter.

The 80th, 90th, and 95th percentiles for OSI and RRT values, and for the 20th, 10th, and 5th percentiles for TAWSS values, were calculated for each SVG. All fluid elements with values above (for OSI and RRT) or below (for TAWSS) these percentiles represent SVG segments with average length between 0.75 cm (for the 95th/5th percentiles) and 3 cm (for 80th/20th percentiles), in which the most-disturbed flow pattern was observed (Figure 2).

Mean values for each percentile were calculated, and a comparison was made between the stented and the nonstented groups. In addition, qualitative analysis of areas with visible velocity vortices was performed for all vein graft models by a single observer, and the number of these areas per graft was noted. Velocity vortices, defined as nonuniform flow with recirculation eddy (Figure 3) were counted during maximal flow (peak diastole). Very small areas with flow discrepancies were not counted.

Statistical Analysis

To evaluate the effect of VEST on continuous parameters, a linear mixed model was used, with subject random effect, and presence of VEST as a fixed factor. In addition, a mixed model with random subject effect was used to compare baseline characteristics between stented and nonstented SVGs. Significance was set at 5%. Continuous data are presented as mean ± SD. To assess whether intimal hyperplasia area is affected by the hemodynamic parameter, an analysis of variance with repeated measurements was conducted, where plaque area was treated as a dependent variable, and a single hemodynamic parameter was treated as a predictor.

RESULTS

Thirty patients were randomized into the study between October 2011 and September 2012. Thirty SVGs, 1 per patient, were externally stented with the study device, and 9 additional grafts were performed for a total of 39 nonstented SVGs. Baseline grafting parameters were all well balanced between the 2 study groups, with no significant differences (Table 1).

One-year follow up angiography was completed in 29 patients (96.6%). All patent SVGs (n = 53; 76.8%) were analyzed by quantitative coronary angiography. Due to technical errors of angiographic data acquisition and recording, thrombolysis in myocardial infarction flow and velocity could not be calculated for 3 nonstented SVGs, and these grafts were excluded from the hemodynamic analysis. Average SVG diameter, thrombolysis in myocardial infarction velocity and flow at 12 months, and inlet parameters, were similar in the stented and nonstented groups (Table 1). Intravascular ultrasound data were available for analysis, for a total of 43 SVG—20 of 30 stented (66.6%), and 23 of 30 (76.6%) nonstented. As previously reported,[15] the SVG mean intimal-medial area differed significantly between the stented and nonstented groups (4.37 ± 1.40 mm^2 vs 5.12 ± 1.35 mm^2; relative reduction: 14.6%; $P = .04$). Angiographic and quantitative coronary angiography findings, including SVG failure rates, uniformity, and ectasia are summarized in Table 2. Using the Fitzgibbon classification,[2] a higher proportion of stented SVGs were in Fitzgibbon Class I (62% vs 39%; $P = .08$), and a lower incidence of SVG ectasia defined as segmental dilatation >50% (6.7% vs 28.2%; $P = .05$).

Geometry Reconstruction and Computational Fluid Dynamics

The TAWSS, OSI, and RRT fields were calculated for 21 stented SVGs and 29 nonstented SVGs. Figure 2 depicts sample angiography images and resulting hemodynamic parameter distributions for 2 stented and 2 nonstented SVGs. Mean OSI was significantly lower in the stented versus nonstented SVG group ($P = .009$), whereas mean TAWSS and RRT did not differ significantly (Table 3).

Both OSI and RRT values were significantly lower in the stented group, at all percentile levels ($P = .003$, $P = .001$, and $P < .001$ for the OSI 80th, 90th, and 95th percentiles, respectively, and $P = .019$, $P = .011$, and $P = .007$ for the 80th, 90th, and 95th RRT percentiles, respectively), whereas no significant difference was observed in TAWSS values. The average number of vortices per SVG was significantly lower in the stented group (Table 2). Mean OSI values were shown to be correlated with the development of diffuse intimal hyperplasia ($P = .01$; n = 43), unlike mean values of TAWSS ($P = .432$; n = 43) and RRT ($P = .113$; n = 43).

DISCUSSION

To our knowledge, this study is the first to investigate the relationship between various flow patterns and the development of intimal hyperplasia in vein grafts. Its novelty stems from the accuracy of the combined anatomic and physiologic data from the Venous External Support Trial, used in the computational fluid dynamics simulations. The high sensitivity of the various hemodynamic parameters to SVG geometry and flow rates makes these baseline parameters critical when investigating flow patterns. Systematic methodology was developed for 3-dimensional reconstruction of the worst-case angiography views of all SVGs; in addition, velocity parameters

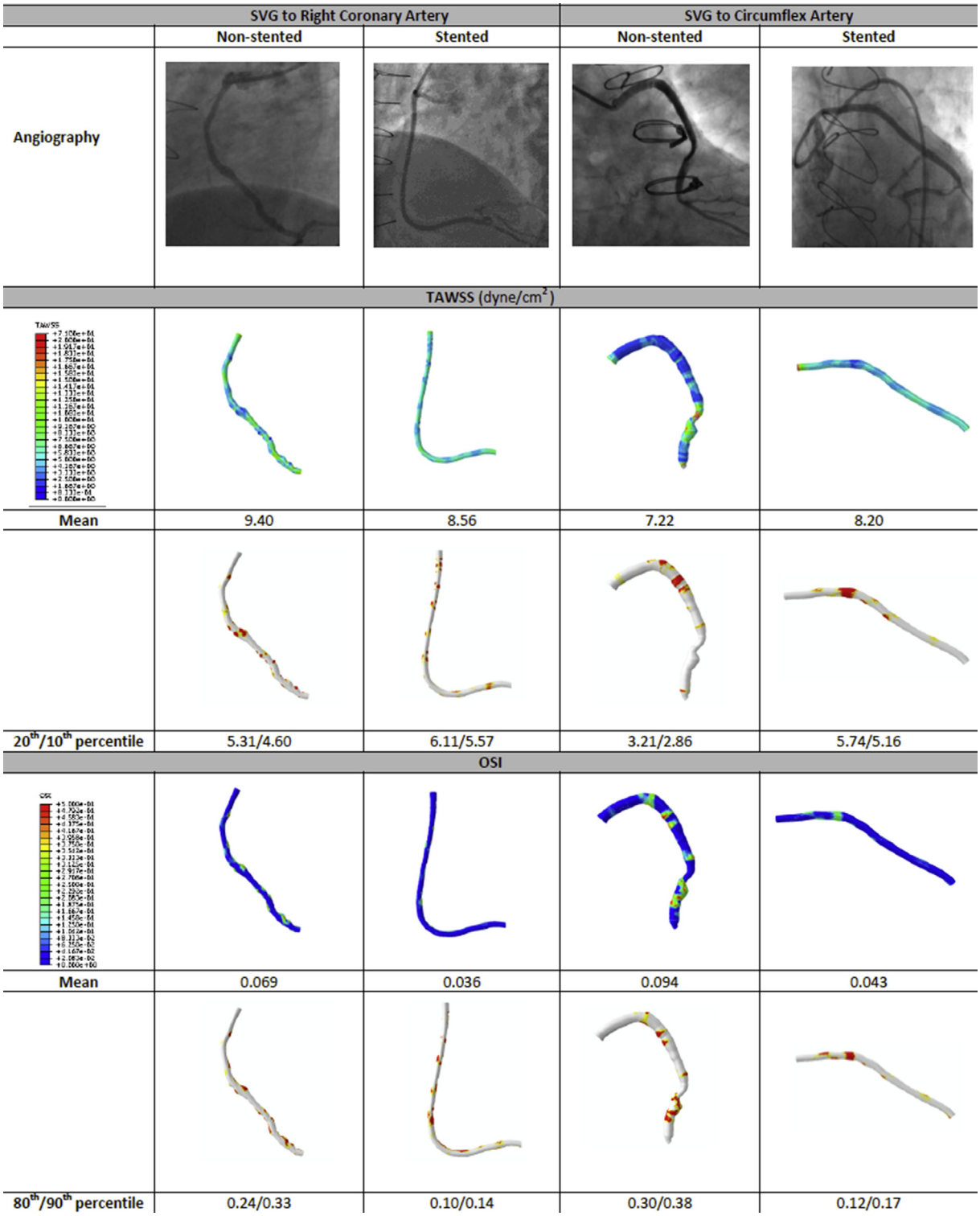

FIGURE 2. Stented and nonstented SVGs grafted to the right coronary and circumflex arteries. Although demonstrating equivalent time-averaged wall shear stress (*TAWSS*) values, oscillatory shear index (*OSI*) values differ significantly between the 2 groups. *SVG*, Saphenous vein graft.

were based on SVG-specific thrombolysis in myocardial infarction analysis reflecting the variance in vascular beds to which the various SVGs were grafted.

The mean TAWSS values were similar in the 2 groups. This finding is not surprising, because TAWSS is mainly affected by the mean diameter of the SVG and its flow

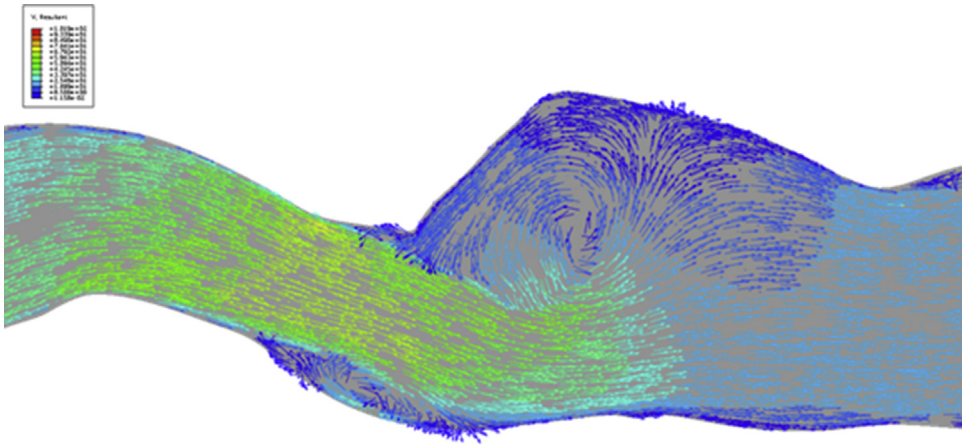

FIGURE 3. Visible velocity vortices demonstrating nonuniform flow with recirculation eddy.

rate, and these were well balanced between the stented and nonstented groups, both during the procedure and at the 12-month follow-up. In contrast, the stented SVGs had significantly lower mean OSI values, indicating less oscillation and reciprocation throughout the cardiac cycle. Although TAWSS values are highly affected by the flow rate inside the SVG, the OSI represents the direction of the shear, and it can differ between a unidirectional and multidirectional flow pattern, even in SVGs with similar average flow rate (Figure 2).

Unlike high OSI values, which were shown to be correlated with the development of diffuse intimal hyperplasia, mean values of TAWSS and RRT had no correlation with extent of the disease. This finding is consistent with studies reporting that the relationship between intimal thickness and OSI is much stronger than that between intimal thickness and mean shear stress.[23] Although low TAWSS is a well investigated promoter of vascular pathology in arteries,[5-9] little is known about its correlation to venous disease, and specifically, to disease progression in venous bypass grafts.

Arterial and venous endothelial cells are derived from separate sets of embryonic precursor cells, have distinct gene expression profiles, and respond differentially to various flow patterns and shear stress ranges.[24,25] In addition, the natural hemodynamic environments of

TABLE 2. Angiography and QCA data: SVG failure, ectaia, and lumen uniformity

Variable	Vein grafts (% [n]) Stented (n = 30)	Nonstented (n = 39)	*P* value
All territories			.55
SVG disease (50%-99% stenosis)	0 (0)	10.3 (4)	
SVG occlusion	30 (9)	17.9 (7)	
Total SVG failure (>50% stenosis)	30 (9)	28.2 (11)	
Left territory	(n = 17)	(n = 24)	.02
SVG disease (50%-99% stenosis)	0 (0)	12.5 (3)	
SVG occlusion	17.6 (3)	25 (6)	
Total SVG failure (>50% stenosis)	17.6 (3)	27.5 (9)	
Right territory	(n = 13)	(n = 15)	.01
SVG disease (50%-99% stenosis)	0 (0)	6.7 (1)	
SVG occlusion	46.2 (6)	6.7 (1)	
Total SVG failure (>50% stenosis)	46.2 (6)	13.4 (2)	
Lumen uniformity	(n = 21)	(n = 31)	.08
Fitzgibbon I classification (%)	61.9	38.7	
Fitzgibbon II + III classification (%)	38.1	61.3	
SVG ectasia (%)	6.7	28.2	.05

From the Venous External Support Trial.[15] *SVG*, Saphenous vein graft.

TABLE 3. Hemodynamic parameters calculated using computational fluid dynamics analysis

Parameter	Stented (n = 21)	Nonstented (n = 29)	*P* value
TAWSS (dyne/cm^2)			
Mean	8.72 ± 4.11	9.29 ± 4.64	.651
Percentile			
20th	5.54 ± 2.57	5.28 ± 2.63	.732
10th	5.04 ± 2.34	4.63 ± 2.36	.546
5th	4.64 ± 2.14	4.13 ± 2.13	.411
OSI			
Mean	0.05 ± 0.02	0.07 ± 0.02	.009
Percentile			
80th	0.16 ± 0.07	0.22 ± 0.07	.003
90th	0.21 ± 0.09	0.29 ± 0.08	.001
95th	0.26 ± 0.09	0.35 ± 0.07	<.001
RRT			
Mean	0.20 ± 0.09	0.25 ± 0.13	.147
Percentile			
80th	0.39 ± 0.25	0.62 ± 0.38	.019
90th	0.53 ± 0.41	0.92 ± 0.58	.011
95th	0.72 ± 0.66	1.37 ± 0.88	.007
Number of vortices	1.19 ± 1.66	4.76 ± 3.85	<.001

Data are expressed as mean ± SD, unless otherwise indicated. *TAWSS*, Time-averaged wall shear stress; *OSI*, oscillatory shear index; *RRT*, relative residence time.

veins versus arteries differ. In vivo, human saphenous veins are exposed to steady flow, with average shear of 2.2 dyne/cm^2, whereas the flow in the coronary system is pulsatile, with average shear[4] of 17 dyne/cm^2. In our study, the average shear stress in SVG was approximately 9 dyne/cm^2 in both the stented and the nonstented groups. This average shear is much higher than the physiologic shear in the venous system and may explain the lack of correlation between the relatively low TAWSS and the development of intimal hyperplasia in SVG.

To assess focal flow disturbances, which in turn may trigger focal and more-aggressive vascular disease,[26-29] areas with the most-disturbed flow patterns in each SVG were analyzed, and the stented and nonstented groups were compared. In the percentile analysis, both the OSI and RRT values of the 80th, 90th, and 95th percentiles were found to be significantly higher in the nonstented group. The vortex count of areas with visibly complex flow was significantly higher in the nonstented group. Because local turbulence is generated mainly by lumen irregularities, these findings coincide with the fact that the stented SVGs demonstrate more-uniform lumens and have fewer ectatic segments.[15]

Several studies applied various methodologies in an effort to set a pathologic threshold value for TAWSS.[17,18,30] Values <4 dyne/cm^2 are considered to indicate disturbed flow that promotes vascular disease.[4] This TAWSS threshold value coincides with the TAWSS findings in our percentile analysis. The 20th and 10th TAWSS percentile values were 5.54 dyne/cm^2 and 5.04 dyne/cm^2, respectively, in the stented group, and 5.28 dyne/cm^2 and 4.63 dyne/cm^2 in the nonstented group.

Compared with nonstented SVGs, the failure rate of stented SVGs was significantly lower in the left territory but significantly higher in the right territory. As previously described,[15] the high failure rate in the right territory was observed when either metallic clips, rather than sutures, were used to ligate side branches (62% vs 20%, respectively) or when the stent was fixated to the proximal and/or distal anastomoses, even though contraindicated by the protocol (75% vs 33.3%, respectively). It seems that when constrained within the stent, metallic clips may locally deform the vessel, causing stenosis and interruptions to flow that may trigger vascular response and the conduit's occlusion.[15] The interaction of the device with metallic clips is riskier in grafts to the right territory, where the angulation of the graft is more acute and susceptible to kinking. Fixation of the external stent to the anastomosis may have led to high tension and SVG damage at the anastomoses site when the heart filled with blood pressure and regained its original dimensions. This risk is higher in the right territory in which the SVGs ''wrap'' the heart as part of their path from the aorta to the distal anastomosis.

Limitations

The 3-dimensional geometric reconstruction was based on 2-dimensional angiographic images, and future computational fluid dynamics investigations may be better served using 3-dimensional images derived from computed tomography or magnetic resonance angiography. Furthermore, the current study investigated SVG flow pattern 12 months after implantation, when some of the SVGs had already demonstrated major lumen irregularities that directly affect the computed hemodynamic parameters. No information is available on baseline lumen geometry, initiation of the disease, or disease progression over time.

Valves were not included in 3-dimensional SVG reconstruction and/or computational fluid dynamics analysis. Although valves may have a local effect on flow pattern, studies that investigated flow dynamics around SVG valves showed that when mean flow is >60 mL/minute, the valves are always open and fuse with the wall.[31] In our study, the mean flow was >93 mL/minute, so it is very reasonable to assume that the valves are completely open all the time and have no major effect on flow pattern.

CONCLUSIONS

The methodology of this study presents a novel combination of numeric analysis and clinical data. Our results provide further insight into the hemodynamics of SVGs and the pathogenesis of vein graft disease. Strategies that improve flow pattern may have the potential to mitigate SVG progressive disease, improve longevity of SVGs, and affect long-term clinical outcomes of CABG. Longitudinal studies are required to validate the correlation between flow disturbances and the progression of vein graft disease. In addition, research is required to illuminate the role of SVG external stenting in the clinical setting, and whether it affects long-term patency of vein grafts.

Conflict of Interest Statement

David Taggart is a consultant to, has stock-option ownership in, and receives consulting fees from Vascular Graft Solutions. Eyal Orion is a co-inventor of VEST, and is the Chief Executive Officer and a board member of Vascular Graft Solutions, in which he has stock ownership. Yanai Ben Gal is a co-inventor of VEST; he is a consultant to, has stock-option ownership in, and receives royalties from Vascular Graft Solutions. All other authors have nothing to disclose with regard to commercial support. The Venous External Support Trial was funded by Vascular Graft Solutions Ltd (Tel Aviv, Israel).

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Key Words: coronary artery bypass graft surgery, saphenous vein graft, external stent, intimal hyperplasia, flow pattern

Discussion

Dr J. Fann *(Stanford, Calif)*. Dr Orion—you and your colleagues present an elegant analysis of the impact of an external stent on the hemodynamic flow parameters in saphenous vein grafts (SVGs), and the development of intimal hyperplasia. Using computational fluid dynamics simulations derived from angiographic data and intravascular ultrasounds, at 1-year follow-up, you evaluated average wall shear stress, oscillatory shear index (OSI), and relative residence time (RRT). Impressively, both OSI and RRT values were lower in the externally stented group. Also, a high OSI correlated with the development of intimal hyperplasia.

The first question is in regard to the region of the vein graft near the anastomosis, both proximally and distally where the stent stops and where there is an intervening portion of the uncovered SVG. Even though you have seen no increase in intimal hyperplasia in these intervening areas at 1-year follow-up, are these areas subject to the same shear stress compared with the nonstented grafts in the other group? Have you calculated, mathematically, the shear stress in these noncovered areas of the externally supported cohort?

Dr Orion. Thank you for the question. In the inlet of each graft, we have seen increased shear stress, compared with the body and the distal anastomosis, in both the supported and unsupported vein grafts. As you mentioned, the

intravascular ultrasound analysis at 1 year did not demonstrate a higher degree of intimal hyperplasia at the proximal or distal uncovered portions.

Our computational fluid dynamics analysis was based on 3-dimensional models derived from the 12-month angiographies. One limitation of this method is that we could simulate only the lumen of the graft, not the entire wall. In our simulations, we could not differentiate accurately between supported and unsupported regions in the same graft, and therefore, we could not analyze the differences in shear stress among these regions.

Dr Fann. In this study, you used rigid wall simulations; I agree with this approach, in that once the vein graft is placed in the arterial system, it becomes noncompliant after a number of weeks. I think that is a reasonable assumption, because what we see is a noncompliant vein graft, even when there is no external stent. So this development begs the question: If the uncovered or unstented vein graft becomes rigid, then what does the external stent provide? Therefore, is it a uniformity issue rather than a compliance mechanism? That is, if we take the time to fashion a more uniform graft, assuming that we remove the abnormal sinuses and perform an end-to-end veno-venous anastomosis, would you expect the modified graft to have better patency than it would with the way we prepare vein grafts currently?

Dr Orion. Thank you for the questions. I would like to start from the last question. Yes, I strongly believe that if you take more-uniform segments, you may improve the long-term patency of the vein graft. There is some evidence that veins grafts harvested from below the knee, which usually are more uniform than those taken from the thigh, have better long-term patency. In addition, a post hoc analysis of our clinical study demonstrated a correlation between vein graft uniformity and the development of intimal hyperplasia at 1 year.

For your first question, if you look at the pressure diameter curve of a human SVG, you can see that after 50 to 70 mm Hg, the curve becomes a plateau. That means that even if you increase the pressure to 200 mm Hg, the vein would not dilate any more. What I am saying is that in the arterial circulation, with an average pressure of 120 mm Hg, the vein is a rigid tube—it is a noncompliant vessel. After a few months, when the vein undergoes what we call arterialization, it becomes even much stiffer. So vein grafts are not a compliant vessel in the arterial circulation pressure, and external stenting does not make them more or less compliant.

For the first question—the way the external stenting affects vein graft biology, according to the extensive animal work that we and others have done, is first of all, by reducing the wall tension of the vein, not letting the wall feel the high arterial pressure. In addition, external stenting results in a more-uniform lumen, prevents vein graft dilatation, reduces the diameter mismatch between the vein and the coronary artery, and improves the flow pattern within the graft.

Dr Fann. Just one final thought. Based on the data regarding the right coronary artery bypass grafts, the patency rate was better in the non-externally stented group. In the left-sided grafts, the patency rate was better with the stented grafts.

So are there geometric differences between the two sides that could account for the patency differences? That is, can the lack of improvement with the right-sided externally stented graft be caused by the vein graft in this region being shorter and perhaps more uniform?

Dr Orion. Thank you very much, Dr Fann. Yes, in our first study in humans, we saw a lower patency rate in the right compared with the left territory. The average graft length was similar in the right and the left territories, and the randomization method ensured that the graft quality was also balanced. In the right territory, a higher failure rate of stented SVGs was observed either when metallic clips, rather than sutures, were used to ligate the side branches of the graft, or when the stent was sutured and affixed to the proximal and/or distal anastomoses. It seems that, when they are constrained within the stent, metallic clips may locally deform the vessel and cause stenosis. This is especially true in grafts to the right territory, where there is a more acute angulation of the graft around the acute margin of the heart. In addition, grafts to the right territory ''wrap'' the heart as part of their path from the aorta to the distal anastomosis in the inferior wall. As a result, more tension can be applied on the anastomoses sites when the heart inflates and recovers its original dimensions with physiological blood pressures. For this reason, affixing the external stent to the anastomosis may have led to high tension at the anastomosis site, and SVG failure.

Dr J. Lawton *(St. Louis, Mo)*. If we alter our vein grafts as Dr Fann suggested, or asked about, I think we need to be cautious regarding the role of the endothelium in neointimal hyperplasia. You are proposing an external type of support, and I think the endothelium has a huge role in neointimal hyperplasia over time. So we do not really know all of what is going on. Thank you very much—very nice.