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

Tomer Meirson, BS,[a] Eyal Orion, MD, MBA,[b] Carlo Di Mario, MD, PhD,[c] Carolyn Webb, PhD,[c,d] Niket Patel, MD,[e] Keith M. Channon, MD,[e] Yanai Ben Gal, MD,[f] and David P. Taggart, MD, PhD[g]

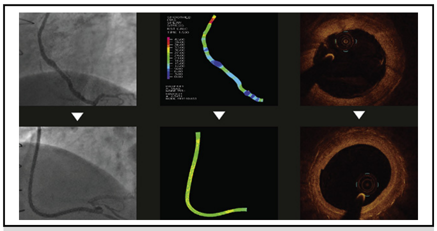
ABSTRACT

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.

See Editorial page 774.

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

From the [a]Department of Bio-Medical Engineering, Afeka Academic College of Engineering, Tel Aviv; [b]Vascular Graft Solutions, Ltd, Tel Aviv, Israel; [c]Department of Cardiology, Royal Brompton Hospital, London; [d]National Heart & Lung Institute, Imperial College London, London; [e]Department of Cardiovascular Medicine, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom; [f]Department of Cardiothoracic Surgery, Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel; and [g]Nuffield Department of Surgery, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom.

Read at the 95th Annual Meeting of the American Association for Thoracic Surgery, Seattle, Washington, April 25-29, 2015.

Received for publication Feb 5, 2015; revisions received April 8, 2015; accepted for publication April 11, 2015; available ahead of print Aug 1, 2015.

Address for reprints: Eyal Orion, MD, MBA, Vascular Graft Solutions, Ltd, 24 Raoul Wallenberg St, Tel Aviv 6971921, Israel (E-mail: eyal@graftsolutions.com).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2015.04.061

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 $\geq$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

ACD