A Randomized Trial of External Stenting for Saphenous Vein Grafts in Coronary Artery Bypass Grafting

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Background. **External stents inhibit saphenous vein graft (SVG) intimal hyperplasia in animal studies. We investigated whether external stenting inhibits SVG diffuse intimal hyperplasia 1 year after coronary artery bypass graft surgery.**

Methods. **Thirty patients with multivessel disease undergoing coronary artery bypass graft surgery were enrolled. In addition to an internal mammary artery graft, each patient received one external stent to a single SVG randomly allocated to either the right or left coronary territories; and one or more nonstented SVG served as the control. Graft patency was confirmed at the end of surgery in all patients. The primary endpoint was SVG intimal hyperplasia (mean area) assessed by intravascular ultrasonography at 1 year. Secondary endpoints were SVG failure, ectasia (>50% initial diameter), and overall uniformity as judged by Fitzgibbon classification.**

Results. **One-year follow-up angiography was completed in 29 patients (96.6%). All internal mammary artery grafts were patent. Overall SVG failure rates did not differ significantly between the two groups (30% stented versus 28.2% nonstented SVG, $p = 0.55$). The SVG mean intimal hyperplasia area, assessed in 43 SVGs, was significantly reduced in the stented group (4.37 ± 1.40 mm^2) versus nonstented group (5.12 ± 1.35 mm^2, $p = 0.04$). In addition, stented SVGs demonstrated marginally significant improvement in lumen uniformity ($p = 0.08$) and less ectasia (6.7% versus 28.2%, $p = 0.05$). There was some evidence that ligation of side branches with metallic clips increased SVG failure in the stented group.**

Conclusions. **External stenting has the potential to improve SVG lumen uniformity and reduce diffuse intimal hyperplasia 1 year after coronary artery bypass graft surgery.**

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Coronary artery bypass graft surgery (CABG) remains the gold standard treatment for patients with multivessel coronary artery disease [1]. Despite the proposed benefits of multiple arterial grafts [2], autologous saphenous vein graft (SVG) is still the most frequently used bypass conduit in CABG. However, progressive SVG failure remains a key limitation to the long-term success of CABG [3]. Although SVG failure soon after CABG is usually due to technical errors or trauma to the conduit, SVG disease after the first year is typically dominated by intimal hyperplasia, which predisposes the SVG to accelerated atherosclerosis [3]. Arterial pressure coupled with abnormal flow patterns generated mainly by luminal irregularities are the main contributors to both focal and diffuse intimal hyperplasia that develops in the SVG over time [4, 5]. In contemporary studies, SVG failure rate has been reported from 10% to 30% over the first year, whereas at 10 years, only 50% of vein grafts are patent, of which half have significant disease [6–8].

Attempts to mitigate intimal hyperplasia and SVG failure have been the focus of intense clinical research. To date, only persistent use of statin therapy and beta-blockers have been shown to reduce intimal hyperplasia in SVGs [9] whereas edifoligide [8] and aspirin plus clopidogrel [10] have both failed to do so, respectively, at

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12 and 18 months after CABG. Mechanical external stents for SVGs have shown considerable promise in preclinical testing with reduction of proliferative intimal hyperplasia by reducing wall tension, improving lumen uniformity, and creating a protective "neoadventitia" layer rich with microvasculature [11–13]. However, limited clinical data have been published to date with such devices. Murphy and colleagues [14] described 100% occlusion of externally stented SVGs at 6 months, and Schoettler and associates [15] reported a 72% occlusion rate at 9 months. Recently, Rescigno and colleagues [16] described 66.9% occlusion at 12 months of SVGs supported with nitinol mesh. All of these external stents required gluing or suturing, or both, to the vein graft during the implantation procedure, maneuvers that may have compromised SVG patency [17].

We present here the first-in-human use of a venous external stent, the VEST (Vascular Graft Solutions Ltd, Tel Aviv, Israel), a new cobalt-chromium external stent for SVGs. The VEST has previously shown promising preclinical results in a large animal CABG setting, reducing thrombotic occlusion of SVGs as well as significantly reducing the area of intimal hyperplasia [12]. Based on the preclinical data, a pilot clinical study was designed with a prespecified primary outcome measure of intimal hyperplasia area 12 months after CABG.

Patients and Methods

Study Design and Population

The VEST trial, conducted from October 2011 to September 2013, was a prospective, multicenter, randomized and self-controlled study. The study was approved by a UK Research Ethics Committee, and all subjects gave informed consent. Patients were eligible if they were scheduled for on-pump multivessel CABG including a left internal mammary artery to the left anterior descending coronary artery and SVGs to right and circumflex territories. Eligibility required a target vessel diameter of 1.5 mm or greater with a coronary stenosis greater than 75% and with an adequate distal vascular bed, as assessed by preoperative angiography. Each patient received one external stent device to a single SVG, randomly assigned intraoperatively, to either the right or the circumflex coronary territories. One or more SVG remained nonstented and served as the control group. The primary safety endpoint was the composite occurrence at 6 weeks after surgery of all-cause mortality, stroke, myocardial infarction, and coronary revascularization. The primary effectiveness endpoint compared intimal hyperplasia area as assessed by intravascular ultrasonography (IVUS) at 12 months, between stented and nonstented SVG groups.

Procedure and Follow-Up

All SVGs were harvested by an open technique, and surgery was performed with use of cardiopulmonary bypass. Randomization to either stent deployment to the circumflex or stent deployment to the right coronary artery took place intraoperatively, by the opening of a sealed envelope, only after all distal anastomoses were performed. An adequate device size was selected from 12 available models based on the graft's diameter and length. The device was threaded over the randomized SVG, the proximal anastomoses were subsequently performed, and finally the device, which combines radial elasticity and axial plasticity, was expanded along the entire vein graft length and simultaneously reduced its diameter to mildly constrict the SVG. Once shaped to its final configuration, taking into consideration the specific SVG anatomy, the device maintains its position, and there is no need for further fixation. Although uncalled for by the protocol or the instructions for use, in 9 cases, the study device was fixated to the proximal or distal anastomoses or both using sutures. Procedural steps are depicted in Figure 1. Transit time flow measurement was applied to all grafts. Contrast angiography of all grafts and IVUS of SVG to the right and the circumflex territories were attempted at the 12 months visit, as described in Figure 2. All patients were prescribed statins and aspirin for 12 months postoperatively.

Quantitative Angiography Analysis

Contrast angiography was attempted for all grafts and quantitative coronary angiography (QCA [QAngio XA, Medis, Netherlands]) was performed for all patent vein grafts. Analysis was performed by an independent observer. Mean diameters were measured for all patent SVG and averaged for every 10 mm segment, as previously described [18] using an angiographic frame showing the worst appearance [7]. Vein graft failure was defined as more than 50% stenosis [6, 7], and ectasia was defined as segmental dilation that exceeded the diameter of normal adjacent segments by 50% [19]. Blood flow and velocity were assessed using the Thrombolysis In Myocardial Infarction frame count [20]. Graft uniformity was graded by an independent observer using the Fitzgibbon classification: I, uniform graft; II, nonuniformity that involves less than 50% of the graft length; and III, nonuniformity that involves more than 50% of the graft length [7].

Intravascular Ultrasonography

A 40 MHz IVUS catheter (Boston Scientific, Hemel Hempstead, UK) was advanced beyond the distal anastomosis of all patent vein grafts and then pulled back using a motorized pullback device at a rate of 1.0 mm/s to and including the proximal anastomosis in a series of as many as three pullbacks per graft. Images were analyzed using QIVUS software (Medis, Netherlands), and the lumen and the external elastic membrane (EEM) were identified and marked by an independent observer according to American College of Cardiology guidelines [21]. To assess the extent of diffuse intimal hyperplasia, measurements of each vessel's EEM, and lumen cross-sectional area were made approximately every 10 mm along the graft from the distal to the proximal anastomosis. The area of intimal and medial hyperplasia was calculated as the EEM area minus the lumen area. The

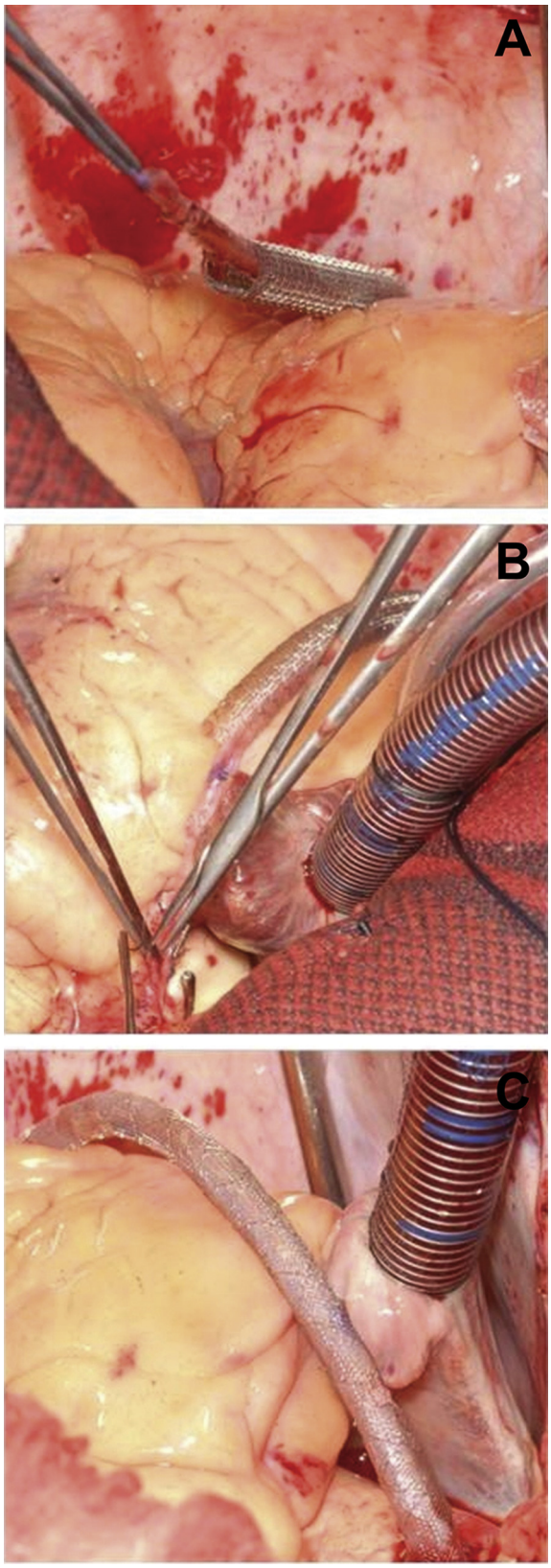

Fig 1. Venous external stent (VEST) implantation procedure. (A) Threading on saphenous vein graft (SVG). (B) Suturing SVG proximal anastomosis. (C) Expanding VEST over the entire SVG length.

average intimal-medial thickness was calculated by subtracting the average lumen diameter from the average EEM diameter and dividing by two. The effect of external stenting was further analyzed to evaluate the influence of side branches ligation method (metallic clips/sutures) on the primary endpoint.

Statistical Analysis

To evaluate the effect of VEST on continuous variables (plaque area and thickness), a linear mixed model with subject random effect and presence of VEST as a fixed factor was used. To evaluate the effect of VEST on categoric variables, a generalized mixed model (for binomial and multinomial distributions) with subject random effect and presence of VEST as a fixed factor was used. A mixed model with random subject effect was used also to compare baseline characteristics between stented and nonstented SVGs. Significance was set at 5%. Continuous data are presented as mean ± SD.

Results

Patients, Procedure, and Follow-Up

Thirty-five patients were enrolled, and 30 were randomly assigned to the VEST trial between October 2011 and September 2012. Demographic characteristics for the randomized patients are shown in Table 1. During surgery, 4 patients were deemed ineligible due either to inadequate vein quality or target coronary artery calcification, and 1 patient was not randomized for administrative reasons. Thirty grafts, 1 per patient, were successfully stented with the study device and compared with 39 nonstented SVGs. Baseline grafting variables were well balanced between the two study groups, with no significant difference, as shown in Table 2. All 30 patients were seen at 6 weeks with no complications, as defined in the primary safety endpoint. Twenty-nine randomized patients completed 12 months of follow-up, including angiography. One patient died 11 months postoperatively; this death occurred 8 months after repeat revascularization by percutaneous coronary intervention to two nonstented SVG territories.

Angiography, QCA, and IVUS

One-year follow-up angiography and IVUS were completed in 29 patients (96.6%). The IVUS data were available for analysis for a total of 43 SVG (20 of 30 stented [66.6%] and 23 of 30 [76.6%] nonstented SVG). Intravascular ultrasonography was not performed in occluded SVG (n = 12), or in diseased SVG in which cannulation for the IVUS was not considered safe (n = 3), or SVG that were not bypassed to the right or circumflex territory as indicated in the protocol (n = 9). In 1 patient, IVUS data of both the stented and nonstented SVG could not be analyzed owing to incompatibility of the IVUS software that was used. All patent SVGs (n = 53, 76.8%) were analyzed by QCA, including 21 of 30 stented SVGs (70%) and 32 of 39 nonstented SVGs (82%). In 1 patient, QCA analysis of

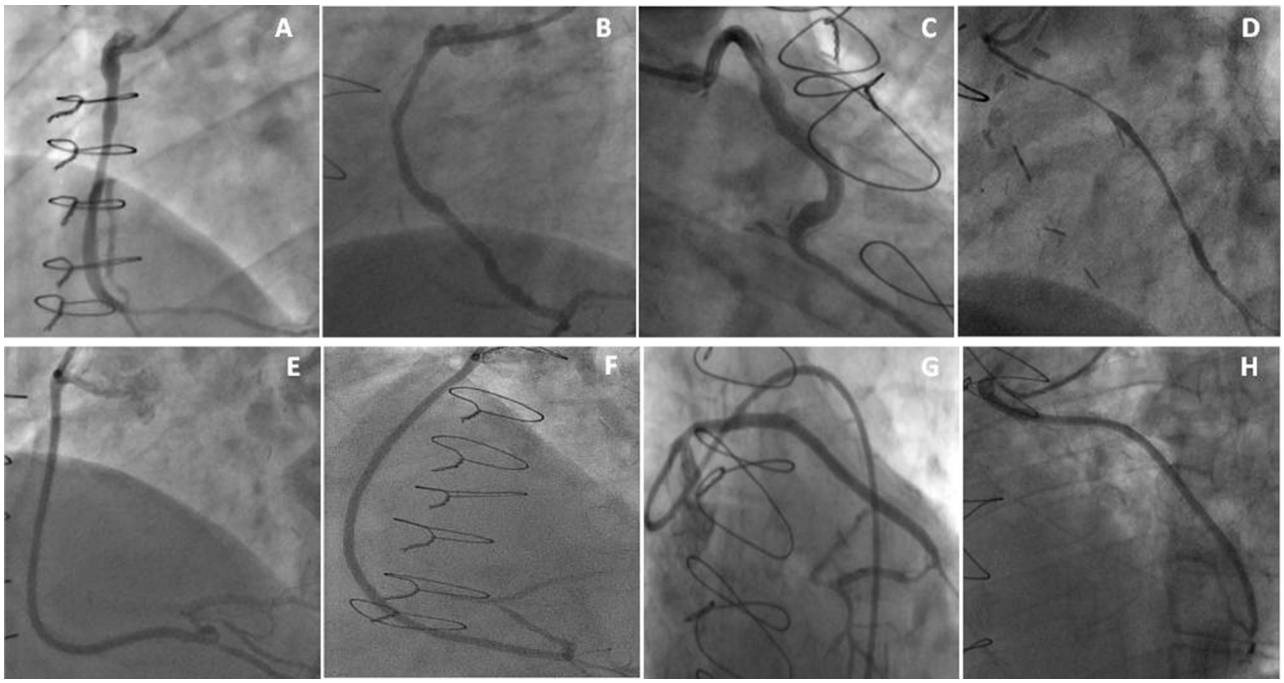

Fig 2. Contrast angiography at 12 months of nonstented saphenous vein graft (SVG) to the (A, B) right territories and (C, D) left territories, and stented SVG to the (E, F) right territories and (G, H) left territories.

Table 1. Patient Demographics

Characteristic (n = 30)	Mean (±SD) or n (%)
Age, years	65.3 ± 8.1
Male	90%
Height, cm	173 ± 7.2
Weight, kg	84.7 ± 9.6
Smoking status	
Current	3 (10)
Former smoker	22 (73.3)
Never	5 (16.7)
Diabetes mellitus	
Insulin dependent	5 (17)
Noninsulin dependent	6 (20)
No history	19 (63)
Hypertension	20 (66.7)
Hyperlipidemia	29 (96.7)
Prior stroke (nondebilitating)	1 (3.3)
Chronic obstructive pulmonary disease	1 (3.3)
New York Heart Association class	
I	11 (36.7)
II	13 (43.3)
III	4 (13.3)
IV	2 (6.7)
Left ventricular ejection fraction, %	56.4 ± 9.8
Creatinine, μmol/L	85 ± 18.9
Preoperative logistic EuroSCORE, %	1.58 ± 1.29

EuroSCORE = European System for Cardiac Operative Risk Evaluation.

all SVGs was based on angiography that was performed 3 months after CABG as part of revascularization treatment, as described above. All 30 of the left internal mammary artery grafts were patent but were not analyzed as part of the study.

The primary outcome measure (Table 3), SVG mean intimal-medial area, differed significantly between the stented group and nonstented group (4.37 ± 1.40 mm^2 versus 5.12 ± 1.35 mm^2, respectively; $p = 0.04$). External stenting also led to reduction in intimal thickness with marginal significance (0.37 ± 0.1 mm stented versus 0.42 ± 0.1 mm nonstented SVG, $p = 0.06$). Comparing stented and nonstented SVGs, ligating SVGs side branches with sutures rather than metallic clips was associated with a marginally significant reduction in both plaque area (27.4%, $p = 0.05$) and plaque thickness (23.8%, $p = 0.04$), unlike ligation with metallic clips, which resulted in a nonsignificant reduction in both plaque area (4.6%, $p = 0.33$) and thickness (2.4%, $p = 0.60$). As shown in Table 4, there was no significant difference in overall SVG failure rates at 12 months between the two groups (30% stented versus 28.2% nonstented SVG, $p = 0.55$). However, the stented versus nonstented SVG failure rates, respectively, were significantly lower in the circumflex territory (17.6% versus 27.5%, $p = 0.02$) and significantly higher in the right territory (46.2% versus 13.4%, $p = 0.01$). Mean lumen diameter, overall blood flow, and blood velocities were similar in both the stented group and nonstented group. With regard to lumen regularity, however, using the Fitzgibbon classification a higher proportion of stented SVGs were in Fitzgibbon class I (62% versus 39%, $p =$

Table 2. Baseline Characteristics of Saphenous Vein Graft Groups

Variable	Stented (n = 30)	Nonstented (n = 30)	*p* Value
Host coronary artery stenosis, %	86.9 ± 12.7	86.6 ± 10	0.63
Host coronary artery diameter, mm	1.8 ± 0.2	1.9 ± 0.3	0.14
Graft length, cm	15.4 ± 2.5	15 ± 2.4	0.45
Systolic pressure at TTFM, mm Hg	109.1 ± 15.2	109.7 ± 15.9	0.57
Final TTFM flow, mL/min	67 ± 27.8	66.2 ± 33.4	0.89
Final TTFM pulsatility index	2.2 ± 1.1	2.2 ± 1.0	1.0

Values are mean ± SD.

TTFM = transit time flow measurement.

0.08) and with a lower incidence of SVG ectasia (6.7% versus 28.2%, $p = 0.05$). Ligation of side branches with sutures rather than metallic clips resulted also in more uniform SVG lumen in the stented group. When sutures were used, 88% of the stented SVGs showed perfectly uniform lumen (Fitzgibbon I) compared with 41% in the nonstented group ($p = 0.04$).

Comment

The key finding in the current study is that a mechanical external stent has the potential to reduce the process of diffuse intimal hyperplasia in SVG 1 year after CABG. External stenting of SVG resulted in a statistically significant reduction of this area by approximately 15% ($p = 0.04$). Several studies have previously reported comparable plaque areas in SVG 12 months after implantation [9, 22], and to date, only statins and beta-blockers have been shown to reduce the process [10].

A particular strength of the trial was the paired study design. In effect, patients acted as their own control, thereby eliminating many of the potential factors that could affect SVG disease progression. Accordingly, the stented and nonstented groups were well balanced with respect to baseline anatomic and physiologic factors that might contribute to the development of intimal hyperplasia, including the diameter of the native coronary artery and the severity of the proximal coronary artery stenosis. That was also evidenced by the similarity of measured graft flows in both the stented and nonstented SVGs during surgery and at 1-year angiography. As shown in Table 3, the ability of the external stent to mitigate intimal hyperplasia was affected by whether metallic clips or sutures were used to ligate SVG side branches. When sutures were used, the stented SVGs showed greater reduction in both plaque area and thickness (27%, $p = 0.05$, and 24%, $p = 0.04$, respectively) compared with a minor, nonsignificant effect that was observed when metallic clips were used (4.6%, $p = 0.33$, and 2.4%, $p = 0.60$, respectively). That could be explained by the use of metallic clips that compromised the optimal alignment between the stent and the SVG and resulted in more lumen irregularities (as reflected by the Fitzgibbon classification in Table 5) and flow disturbances, which accelerated the development of intimal hyperplasia.

Early vein graft failure, defined by occlusion or stenosis greater than 50%, was not reduced by the VEST. In contrast to nonstented SVGs, the failure rate of stented SVGs was significantly lower in the left territory but significantly higher in the right territory. In the right territory, a higher failure rate of stented SVGs was observed when either metallic clips, rather than sutures, were used to ligate side branches of SVGs (62% versus 20%, respectively) or when the stent was sutured and fixated to the proximal or distal anastomoses (75% versus 33.3%, respectively). The use of metal clips to ligate SVG side branches does not usually deform the vessel wall. However, it appears that when constrained within the stent, metallic clips may locally deform the vessel, causing stenosis and interruptions to flow that may trigger the conduit's occlusion. That is especially true in

Table 3. Intravascular Ultrasonography Data

Variable	Stented (n = 21)	Nonstented (n = 23)	Percent Difference	*p* Value
All saphenous vein grafts				
Plaque area, mm^2	4.37 ± 1.40	5.12 ± 1.35	−14.6	0.04
Plaque thickness, mm	0.37 ± 0.10	0.42 ± 0.10	−11.9	0.06
Average lumen diameter, mm	3.36 ± 0.57	3.42 ± 0.53	−1.0	0.60
Effect of SB ligation method on intimal hyperplasia				
Plaque area, mm^2				
SB ligated with metal clips	5.01 ± 1.23 (n = 11)	5.25 ± 1.42 (n = 13)	−4.6	0.33
SB ligated with sutures	3.59 ± 1.22 (n = 9)	4.95 ± 1.32 (n = 10)	−27.4	0.05
Plaque thickness, mm				
SB ligated with metal clips	0.41 ± 0.10 (n = 11)	0.42 ± 0.10 (n = 13)	−2.4	0.60
SB ligated with sutures	0.32 ± 0.09 (n = 9)	0.42 ± 0.10 (n = 10)	−23.8	0.04

Values are mean ± SD.

SB = side branch.

Table 4. Angiography and Quantitative Coronary Angiography Data, Occlusion and Disease

Variable	Vein Grafts, % (n)		
	Stented (n = 30)	Nonstented (n = 39)	*p* Value
All territories			
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)	0.55
Left territory	(n = 17)	(n = 24)	
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)	0.02
Right territory	(n = 13)	(n = 15)	
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)	0.01
Lumen uniformity, %	(n = 21)	(n = 31)	
All SVGs			
Fitzgibbon I classification	61.9	38.7	
Fitzgibbon II+III classification	38.1	61.3	0.08
SB ligated with metal clips, %	(n = 12)	(n = 19)	
Fitzgibbon I classification	41.6	36.8	
Fitzgibbon II+III classification	58.4	63.2	0.48
SB ligated with sutures, %	(n = 9)	(n = 12)	
Fitzgibbon I classification	88.8	41.6	0.04
Fitzgibbon II+III classification	11.2	58.4	
SVG ectasia, %	6.7 (n = 21)	28.2 (n = 31)	0.05
Blood flow and velocity	(n = 21)	(n = 29)	
Blood flow in SVG, mL/s	94.7 ± 49.5	94.3 ± 46.6	0.97
Blood velocity in SVG, cm/s	15.8 ± 6.5	15.5 ± 7.2	0.90

SB = side branch; SVG = saphenous vein graft.

grafts to the right territory where there is a more acute angulation of the graft around the acute margin of the heart, and an example of this is shown in Figure 3. Unlike SVGs to the left territory, SVGs 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 physiologic blood pressures. For this reason, as previously reported by Schoettler and associates [15], fixation of the external stent to the anastomosis may have led to high tension at the anastomosis site and SVG failure.

Together with the small sample size, a notable limitation of this study was the lack of very early patency data

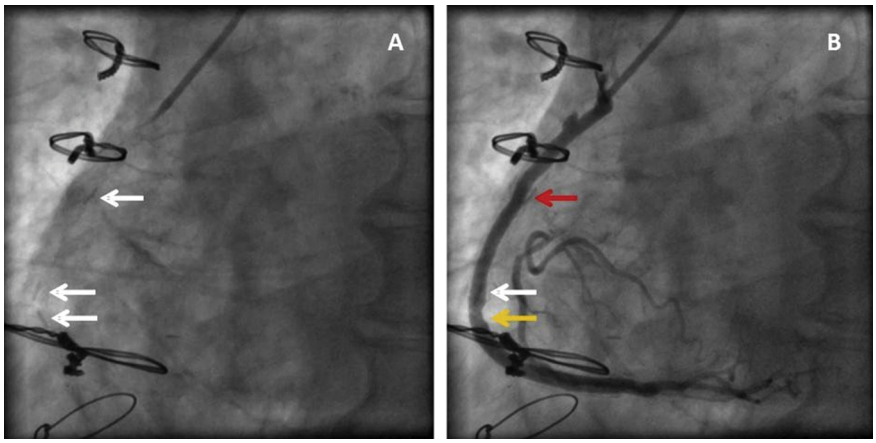

Fig 3. Stented saphenous vein graft (SVG) to the right coronary artery. (A) Metal clips (white arrows) were used to ligate the SVG side branches. (B) Contrast angiography demonstrates SVG displacement (red arrow) and stenosis at the SVG acute angulation (yellow arrow) where metal clips are present.

to enable more precise timing of vein graft occlusion. In addition, the long-term effect of external stent on vein graft pathophysiology could not be determined owing to the short follow-up period. However, the preliminary findings from this first-in-human study demonstrate that external stent has the potential to mitigate intimal hyperplasia progression in SVGs implanted during CABG. If maintained over the longer term, this has a potential to change the natural history of vein graft failure and to improve the outcomes of surgical revascularization. Large clinical studies with long-term follow-up are required to determine whether external stenting of vein grafts is associated with a continuing reduction in the progression of intimal hyperplasia and any associated potential clinical benefits.

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