Evaluation of a novel sutureless anastomotic connector: From endothelial function to mid-term clinical and angiographic follow-up

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Objectives: We evaluated the effect of the St Jude Medical sutureless anastomotic connector on endothelium-dependent and -independent saphenous vein graft relaxation, as well as on clinical outcomes and graft patency in patients.

Methods: Human saphenous vein grafts were assigned to control or connector groups (loaded for 1 or 5 minutes; n = 18). Isometric dose-response curves to endothelium-dependent and -independent (sodium nitroprusside) vasodilators were constructed in saphenous vein grafts precontracted with phenylephrine. Thrombin-mediated vasorelaxation, an early determinant of saphenous vein graft failure, was also evaluated. Percent maximum relaxation was compared between groups. Patients in whom the St Jude Medical connector was employed underwent clinical follow-up, stress tests, and angiography 6 to 12 months postoperatively.

Results: A23187-induced endothelium-mediated relaxation, sodium nitroprusside-induced endothelium-independent relaxation, and thrombin-mediated vasorelaxation did not differ between control and connector saphenous vein grafts at either time point studied. Twenty-seven patients received St Jude Medical connectors. There was no hospital mortality; patients were followed for 679 ± 241 days. There was 1 late death; the connector saphenous vein graft was patent at postmortem. All connector saphenous vein grafts were patent at follow-up angiography. Four grafts had stenoses (30%-60%), without symptoms or requirement for intervention. All hand-sewn saphenous vein grafts were also patent.

Conclusions: The St Jude Medical connector does not impair endothelium-dependent vasorelaxation. In patients, patency of the connector saphenous vein grafts 6 to 12 months postoperatively was 100% but 22% of grafts had non-flow-limiting stenoses at or near the connector. Further long-term studies are required to confirm the safety of the St Jude Medical connector with regards to endothelial function and restenosis.

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The development of a facile, reliable alternative to traditional hand-sutured proximal and distal coronary anastomoses has been pursued for some time. These devices may represent an enabling technology for minimal access surgery and a facilitating technology for off-pump surgery, where complete avoidance of aortic clamping may allow the potential neuropsychological benefits of this strategy¹⁻³ to become evident. However, it must first be demonstrated that these devices are safe both for the grafts and for the patients and that they will result in the same excellent outcomes as traditional hand suturing.

The St Jude Medical (SJM) anastomotic connector creates a rapid, sutureless anastomosis of a saphenous vein graft (SVG) to the aorta without aortic manipulation or clamping.¹⁻⁵ However, with this device, the saphenous vein segment must be loaded over the cylindrical delivery system, and potential for injury to the SVG endothelium therefore exists. Endothelial dysfunction could in turn facilitate the initiation and continuation of diverse prothrombotic and proatherosclerotic processes, resulting in accelerated graft failure, which could negate the advantages of this device.⁶⁻⁸ We therefore evaluated the effect of SVG loading onto the anastomotic connector system on endothelium-dependent and -independent function in human SVGs. We also report the clinical outcomes and angiographic graft patency in our initial clinical series of patients in whom this sutureless anastomotic connector was employed.

Methods

Assessment of Endothelial Function

Segments of saphenous veins ($n = 18$, 3-5 cm in length) were obtained intraoperatively. These veins had undergone careful limited-pressure manual distension with saline by the operating surgeon, as is our usual clinical practice. The segments were placed in oxygenated physiological salt solution and immediately transferred to the pharmacology laboratory. The vessels were cleaned of adherent tissue and cut into segments, with each segment being randomly and blindly assigned to either the connector or control group. Segments assigned to the connector group were loaded onto the SJM connector transfer rod (the portion of the delivery system with the maximum diameter and greatest potential for endothelial contact) for a period of 1 or 5 minutes, following which isometric responses were recorded as described below.

Vascular rings (~6 to 9 mm in length) were suspended in isolated tissue baths (volume 25 mL) containing oxygenated Krebs-Ringer bicarbonate buffer as described previously.^{9,10} A progressive resting tension of 2 to 2.5 g was applied (determined by preliminary experiments to afford the optimum tension-length relationship). Following equilibration for 90 minutes, isometric dose response curves (DRC) were recorded using the following protocol: (1) cumulative DRC to phenylephrine (10^{-8} to 10^{-4} mol/L), (2) cumulative DRC to A23187 (10^{-9} to 10^{-6} mol/L) in rings precontracted with the effective dose causing 75% of maximum phenylephrine (PE)-induced contraction (ED_{75}), (3) cumu-

lative DRC to sodium nitroprusside (SNP; 10^{-8} to 10^{-5} mol/L) in rings precontracted with the ED_{75} of PE. In a separate series of experiments, we evaluated thrombin (0.1 U/mL)-mediated vasorelaxation in PE precontracted veins, as a marker of potential early graft failure. Vascular rings were allowed to equilibrate between each DRC for 60 to 90 minutes. All drugs and chemicals were obtained from Sigma (St Louis, Mo, USA). For all experiments, isometric force was measured with transducers coupled to MP100 data acquisition software. Data were analyzed off-line and expressed as mean $\pm$ SEM. Percent maximum relaxation ($\%E_{max}$) and agonist sensitivity (pEC_{50}) were compared between interventions. pEC_{50} values were calculated as the negative log of molar ED_{50} . Nonlinear analysis of the individual dose-response curves was performed, and the obtained pEC_{50} values were averaged. Dose-response curves were compared by means of repeated-measures analysis of variance. Differences between mean values were considered statistically significant when $P < .05$.

Clinical Evaluation

Patients undergoing isolated primary coronary artery bypass grafting (CABG), whether on-pump or off-pump, were eligible to participate in this study. All patients gave informed consent to a clinical investigational protocol approved by our institutional Research Ethics Board. The SJM connector was employed primarily in SVGs to the right coronary artery (RCA) territory and was loaded and deployed as per manufacturer's specifications. Patients underwent standard clinical follow-up in addition to exercise stress tests at 6 weeks and 3 months and angiography of all SVGs 6 to 12 months postoperatively. Left internal thoracic artery grafts were not injected at the time of angiography except in patients with suggestive symptoms or positive stress tests to minimize the risk of internal thoracic artery graft injury during angiography.

Results

Endothelial Function

SVGs from 18 patients were evaluated. The internal diameter was similar between groups [control 3.0 ± 0.04 mm; connector (1-minute loading) 3.1 ± 0.6 mm; connector (5-minute loading) 3.3 ± 0.1 mm; $P = .6$]. Figure 1 depicts the effects of the SJM connector on endothelium-dependent and -independent vascular responses to A23187 and SNP, respectively. A23187 and SNP caused dose-dependent vasorelaxation in all vessels studied; vascular responses remained unaffected by intraluminal exposure to the connector for either 1 or 5 minutes [A23187: control ($\%E_{max}$ 24% $\pm$ 3%; pEC_{50} 6.8 $\pm$ 0.07); connector, 1-minute loading ($\%E_{max}$ 19% $\pm$ 4%; pEC_{50} 7.0 $\pm$ 0.05); connector, 5-minute loading ($\%E_{max}$ 16% $\pm$ 6%; pEC_{50} 7.1 $\pm$ 0.12); $P = .5$]. Figure 2 depicts the effects of thrombin on percent maximum relaxation in PE precontracted vascular rings. Thrombin-mediated vasorelaxation, a surrogate marker of early endothelial damage and thrombogenicity, remained unchanged in SVGs exposed to the connector for either 1 or 5 minutes [$\%E_{max}$ control 35% $\pm$ 5%; connector (1-minute loading) 25% $\pm$ 7%; connector (5-minute loading) 24% $\pm$ 5%; $P = .2$].

Figure 1. Vascular responses in segments of saphenous vein grafts exposed to the aortic anastomotic connector (AAC). **A**, Endothelium-dependent vasodilation to A23187 in saphenous vein grafts exposed to the AAC for 1 minute (AAC 1) or 5 minutes (AAC 5) versus control. Maximum relaxation was evaluated in veins precontracted with the ED₇₅ of phenylephrine (see Methods). A23187 caused dose-dependent vasorelaxation; this effect was similar between groups ($P = .53$). **B**, Endothelium-independent vasorelaxation to sodium-nitroprusside was also similar between groups ($P = .47$). The use of the AAC for up to 5 minutes does not impair endothelium-dependent or -independent vascular responses.

Early Clinical Outcomes

Of the 44 patients who consented to the clinical study, 17 were excluded intraoperatively. In 16 of these excluded patients, the saphenous vein segment was found to be of inadequate caliber (measured by external diameter, OD) for the connector delivery systems available. Early in our experience, only systems for vein grafts with external diameters of 5.0 to 5.5 mm and 5.5 to 6.0 mm were available; intraoperative exclusions declined significantly when the delivery system for veins with OD 4.5 to 5.0 mm became available. One patient was excluded intraoperatively after median sternotomy was performed and matted mediastinal lymph nodes were found. A previously clinically and radiographically undetected primary lung carcinoma was identified in this patient, who was withdrawn from the protocol at that time.

Twenty-seven patients received anastomotic connectors. The mean diameter of the connector SVGs was 5.2 ± 0.3 mm, and mean diameter of the target coronary arteries was 1.6 ± 0.3 mm. The SVG segments were loaded onto the delivery system by the operating surgeon, requiring 5 ± 3 minutes.

In this series, there were 2 deployment failures. In 1 patient, a connector was deployed without problems but the proximal anastomosis was noted to be leaking at 1 pinpoint site. In accordance with manufacturer's recommendations, the connector was manually removed and the aortotomy enlarged slightly with a standard aortic punch. The proximal end of the vein graft, to which the connector was affixed, was amputated and a hand-sewn anastomosis was created without problems. In a second patient, the connector was

Figure 2. Percent maximum relaxation to thrombin (0.1 u/mL), in saphenous vein grafts precontracted with the ED₇₅ of phenylephrine. Thrombin-mediated vasorelaxation, an early marker of vein graft thrombogenicity, remained unchanged following exposure to the aortic anastomotic connector (AAC) for a period of 1 or 5 minutes (AAC 1 and AAC 5, respectively; $P = .21$).

fired without incident but was not retained within the aorta on withdrawal of the delivery system. A hand-sewn anastomosis was also performed without difficulty. The manufacturer's quality control department evaluated both of the explanted connectors and no device-related issues were identified.

There was no hospital mortality in this series. No patient suffered a perioperative myocardial infarction, stroke, or required reexploration for bleeding.

Mid-Term Clinical Outcomes

Patients were followed for 679 ± 241 days (median 778 days) and clinical follow-up was complete. There was 1 late death, in a patient who had an 80% left main stenosis,

Figure 3. Angiographic appearance of (A) a widely patent connector graft and (B) a graft with a stenosis at the level of the connector, possibly due to intimal hyperplasia.

diffuse triple vessel disease, and peripheral vascular disease precluding the use of an internal thoracic artery graft. At the time of surgery, he was found to have an atherosclerotic aorta and ungraftable coronaries save for a left anterior descending (LAD) coronary artery. A single vein graft was constructed to the LAD using the anastomotic connector. His postoperative course in hospital was uneventful but he died during the follow-up period. A postmortem was obtained and the connector SVG was found to be patent.

No patient had recurrent or persistent angina during follow-up, and none required repeat revascularization procedures.

Angiographic Outcomes

Two patients, both of whom were free of angina postoperatively, declined to return for angiography. In addition, 2 elderly patients residing in nursing homes who had significant renal failure were felt not to be candidates for postoperative study angiography. Neither has had angina or a positive stress test.

The 18 other patients underwent graft angiography 6 to 12 months postoperatively. The patency of the connector SVGs was 100% (18/18 grafts). Four grafts (22%), however, had stenoses (30%, 50%, 50%, 60%), without symptoms or requirement for further intervention. All stenoses occurred at or within 3 cm of the proximal anastomosis (Figure 3).

The patency of hand-sutured SVGs was also 100% (24/24 grafts). No stenoses were observed in the proximal portions of the hand-sewn grafts. Three patients had their

left internal thoracic artery grafts injected at angiography; all were patent.

Discussion

The technology employed in the current generation of aortic anastomotic connectors poses the theoretical concern of causing endothelial damage with resultant endothelial cell dysfunction. Endothelial dysfunction is a broad term that implies diminished production/availability of nitric oxide and/or an imbalance in the relative contribution of endothelium-derived relaxing and contracting factors (such as endothelin-1, angiotensin, and oxidants).¹¹⁻¹³ It is well accepted that endothelial dysfunction precedes the development of atherosclerosis. Endothelial dysfunction actively partakes in the process of lesion formation by promoting the early and late mechanisms of atherosclerosis. These include up-regulation of adhesion molecules, increased chemokine secretion and leukocyte adherence, increased cell permeability, enhanced low-density lipoprotein oxidation, platelet activation, cytokine elaboration, and finally vascular smooth muscle cell proliferation and migration. In addition to participating in the development of atherosclerosis, endothelial dysfunction plays an important role in the clinical course of the disease. Impaired endothelium-dependent vasodilatation in atherosclerotic vessels results in paradoxical vasoconstriction, which may result in reduced myocardial perfusion and myocardial ischemia. Hence, disruption of normal endothelial function results in diverse effects including vasoconstriction, leukocyte adher-

ence, platelet activation, mitogenesis, pro-oxidation, thrombosis, impaired coagulation, vascular inflammation, and atherosclerosis.

Given the importance of endothelial function to short- and long-term vascular homeostasis, any effect of the connector to cause endothelial dysfunction might negate its potential benefits. Our data suggest that loading SVGs on the connector for up to 5 minutes under the conditions employed does not result in changes in endothelium-dependent or -independent vascular responses over and above those observed merely due to the standard clinical practice of careful, low-pressure manual distension. Importantly, thrombin-mediated vasorelaxation, a marker of early thrombogenicity, also remained unaltered in SVGs subjected to the SJM connector for 5 minutes. The 5-minute time point coincides with the mean loading time in the clinical experience presented in this series. Because acutely measured endothelial function predicts long-term atherosclerotic vascular disease,¹⁴ these data suggest that short-term exposure of SVGs to the connector may have limited effect on graft atherosclerosis. Whether longer exposure times may result in endothelial dysfunction remains to be determined.

The SJM anastomotic connector can be used to rapidly and reproducibly create proximal anastomoses for SVGs. The current generation of this technology requires the implanting surgeon to pay close attention to a number of issues. These proximal anastomoses are constructed at 90° angles from the aorta, and in our series, connectors were therefore generally employed for grafts to the RCA territory. Connectors can also be employed for left-sided grafts, but positioning of the anastomosis on the lateral wall of the ascending aorta is critical to avoid kinking of the graft either by the pulmonary artery or by the pericardium. Sizing of the vein, avoidance of excessively thick-walled segments, and careful loading are key.

One of the most important aspects of this technology is the availability of an easy “bailout” procedure should the device fail to perform as desired. With this connector, nonhemostatic anastomoses that cannot be repaired can be resolved simply by manual traction on the connector graft until the connector is dislodged from the aorta. In our experience, this was easily performed and did not result in visible trauma to the aortotomy. Reuse of the previously loaded vein segment can be accomplished either with a hand-sewn anastomosis or reloading and deployment of another anastomotic connector. In our series, early in the worldwide clinical experience with this device, we followed the manufacturer’s recommendations to revert to hand-sewn anastomoses in the case of any deployment failure. Currently, a connector that was leaking at a single point would be repaired with a simple suture, and a vein that was not retained in the aorta on deployment would simply be reloaded onto another system and redeployed.

The 100% patency rate of the connector grafts (and the hand-sewn grafts) is reassuring, although there are insufficient numbers to make meaningful comparisons to the anticipated 85% to 90% patency of SVGs in historical series. If there is any inference that can be drawn from the 100% patency of both the connector and the hand-sutured vein grafts observed in this study, it may be that current antiplatelet and lipid-lowering therapies have favorably impacted early graft patency compared with historical controls.

Not all grafts in which the connector was employed were perfect, however. Four grafts demonstrated mild to moderate stenoses, all at or within 3 cm of the proximal anastomosis. In one graft, a stenosis 2 to 3 cm distal to the connector may have been due to partial kinking after its 90° origin. In the other 3 stenotic grafts, intimal hyperplasia appeared to be the most likely cause. During the process of loading, the segment of vein closest to the aorta may undergo the most manipulation and consequent contact of the endothelium with the delivery system. If this is a significant factor, intimal hyperplasia may be expected to be most marked in the proximal segment of the vein graft, where the stenoses were observed in this series. Our laboratory data did not suggest, however, that intraluminal exposure of the vein graft to the connector delivery system was associated with detectable endothelial injury under the experimental conditions employed. More traumatic loading conditions might have been associated with demonstrable endothelial injury.

These graft stenoses did not appear, at the time of postoperative angiography, to be significantly flow-limiting in nature. However, no physiologic studies of the grafts were performed, and their late significance therefore remains unknown. In this study, at a median duration of follow-up of more than 2 years, none of these patients, and specifically none of the patients with stenotic connector grafts, had had any recurrence of angina. Ongoing follow-up will clarify whether the stenoses observed are stable in behavior or whether they may progress to become hemodynamically significant lesions.

Limitations of This Study

Endothelial function can be adversely influenced by a number of factors, including patient comorbidities and intraoperative technique. The primary purpose of this study was to evaluate the effects of the aortic anastomotic connector on endothelial function when used in the conventional setting, which includes loading of a vein segment, after careful low-pressure manual distension, onto the transfer rod. Although loading of a nondistended vein may impair endothelium-dependent vasorelaxation compared with baseline, this experimental model does not correspond to the clinical scenario of loading following careful manual distension.

Therefore, our results suggest that the aortic anastomotic connector does not impair endothelial function over and above standard intraoperative distension. Although we did not observe any difference in functional endothelial capacity between vein segments loaded onto the connector system and control segments, our current data cannot exclude the possibility of changes in endothelial morphology and orientation microscopically. Our findings, however, do suggest that there is no additional damage to endothelial "function" when veins that have been carefully distended as per standard clinical practice are loaded onto the St Jude aortic anastomotic connector. We have corrected the responses in terms of grams of tension per cross-sectional area (mm^2). This correction allows us to carefully evaluate the effects of tension evoked as a function of vascular smooth muscle content and demonstrated no difference between groups (tension at maximum A23187 control 2.03 g/mm^2 vs aortic anastomotic connector 1.94 g/mm^2 , $P = \text{NS}$). It is important to recognize that the experimental conditions employed did not exactly mimic the piercing, rolling, and pressing on the vein segment that occurs intraoperatively as it is being loaded. However, our protocol did evaluate the effects of radial stretching by introduction of the loading device on endothelial functional reserve. Lastly, conclusive evidence of endothelial safety can only be determined by evaluating the long-term effects of the connector on endothelial function in a chronic animal model of vein graft interposition. Such further studies will be required to carefully define endothelial safety.

Future Developments

This anastomotic technology is likely to find the greatest application in patients undergoing off-pump CABG, in whom the availability of such a device makes application of a partial occlusion clamp on the aorta unnecessary.¹⁻³ If there is a benefit of avoidance of cardiopulmonary bypass on neuropsychological sequelae in patients, it may well be demonstrable only when the aorta is never clamped, and particulate emboli from an atherosclerotic aorta do not contribute to neuropsychological deficits. These connectors also are ideal for minimal-access surgery and may facilitate the ongoing development of these less-invasive approaches. Finally, these devices may reduce the mediastinal dissection

and aortic access required in patients undergoing reoperative CABG.

As this technology evolves, the next generations of these devices are likely to be significantly easier and quicker to load and deploy, to permit construction of distal anastomoses prior to proximals, and to be safe to use on arterial conduits.¹⁵ However, ongoing studies to evaluate the mid-term and late effects of these devices on graft patency will be required to fully document their advantages and limitations.

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