Vascular Reactivity and Flow Characteristics of Radial Artery and Long Saphenous Vein Coronary Bypass Grafts
A 5-Year Follow-Up

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Background—Radial artery (RA) aortocoronary bypass grafts anastomosed to a branch of the circumflex coronary artery have significantly better patency rates than saphenous vein (SV) grafts at 5 years, but the physiological characteristics and mechanisms involved are not clearly defined. We compared RA and SV graft vasomotor and flow responses to endothelium-dependent and -independent stimuli 5 years after surgery in a subgroup of patients enrolled in the Radial artery versus Saphenous Vein Patency (RSVP) trial.

Methods and Results—Twenty-seven patients were included in the study (RA, n = 15; SV, n = 12). Graft blood flow was calculated from flow velocity, measured by intracoronary Doppler, and luminal diameter, measured by quantitative coronary angiography, before and after intragraft infusions of adenosine, acetylcholine, and isosorbide dinitrate. At rest, RA luminal diameters were significantly smaller than SV luminal diameters (P = 0.029), blood flow velocity was greater in RA than SV (P = 0.008), and volume blood flows were similar. RA but not SV dilated in response to adenosine and isosorbide dinitrate (all P < 0.05, RA versus SV, percent change from baseline), and there were no significant differences in the diameter responses to acetylcholine. Volume blood flow responses to adenosine, acetylcholine, and isosorbide dinitrate were comparable.

Conclusions—Five years after surgery, RA coronary bypass conduits grafted to a single coronary territory demonstrated preserved flow-mediated vasodilatation, whereas SV grafts did not. Our results may provide insight into the more favorable patency of RA grafts over SV grafts.


Key Words: arteries ■ blood flow ■ endothelium ■ revascularization

The morphological and physiological differences between arteries and veins should result in significant differences in their behavior when used as aortocoronary bypass grafts. These differences may partly explain the predisposition of veins used as coronary conduits to demonstrate accelerated atherosclerosis in comparison with arterial grafts. Early postoperative studies have shown no difference in flow-mediated dilatation between radial artery (RA) and internal mammary artery (IMA) grafts or blood flow between RA and saphenous vein (SV) grafts. However, we showed positive endothelium-dependent and -independent vasodilatation in RA grafts but not in SV grafts, with no differences in volume blood flow responses, at 3-month follow-up of the Radial artery versus Saphenous Vein Patency (RSVP) trial. Over time, however, changes in conduit physiological function may occur.

The endothelium is a key regulator of vascular physiology, and damaged or dysfunctional endothelium is an initiator of vascular atherosclerosis. Endothelial function is a predictor of coronary events in patients with coronary artery disease and is associated with short-term coronary graft performance. Greater endothelium-dependent relaxation occurs in vitro in precontracted IMA compared with SV after harvesting for coronary artery bypass surgery, and although exposure of vein grafts to arterial pressure might be expected to result in further dysfunction of the endothelium, heterogeneity in endothelium-dependent relaxation response, not related to duration of arterialization but to localized areas of intimal hyperplasia, has been
reported. Previous studies have shown preserved IMA graft vascular reactivity in vivo a number of years after surgery; however, at present there are few data describing the vascular function of the RA as an in vivo coronary conduit over the longer term.

We designed the present study to compare 5-year postsurgery diameter and blood flow responses of in vivo RA and SV grafts to endothelium-dependent and -independent stimuli, including patients who were enrolled in the RSVP trial. We hypothesized that RA grafts would have preserved vascular reactivity compared with SV grafts 5 years after surgery.

Methods

Patients
The RSVP trial was a prospective randomized trial to compare angiographic patency rates of RA and LSV grafts to the native left circumflex territory 3 months and 5 years after coronary artery bypass graft surgery. All patients returning for 5-year follow-up angiography for the RSVP trial were invited to participate in this substudy. Eligible patients had an unobstructed randomized graft at angiography, had no history of hypertension or asthma, and had not taken vasoactive medication for at least 24 hours before angiography.

Separate ethics approvals for the randomized trial and the substudy were obtained from the Royal Brompton Hospital Ethics Committee, and patients gave separate written informed consent before 5-year follow-up angiography.

Study Design
All vasoactive medications were stopped at least 24 hours before study. After confirmation of patency of the randomized graft, patients were heparinized, and a 0.014-inch Doppler wire (Volcano, UK) was positioned in the proximal third of the randomized graft via a 5F to 7F diagnostic catheter. Average peak blood flow velocity, arterial blood pressure, heart rate, and ECG were continuously recorded. After equilibration, an intragraft bolus of the endothelium-independent vasodilator adenosine (30 μg) was given via the catheter, followed by two 2-minute infusions of the endothelium-dependent vasodilator acetylcholine (10⁻⁶ and 10⁻⁷ mol/L), and finally an intragraft bolus of nitrate (isosorbide dinitrate [ISDN] 300 μg). Blood flow velocity was measured at peak velocity response or at 2 minutes after commencement of infusion. Study graft angiograms were performed at baseline and at peak velocity response to each vasoactive substance with the use of Omnipaque contrast medium at an acquisition rate of 12.5 frames per second. There was a rest period of at least 1 minute between each infusion to allow all measured parameters to return to baseline.

Quantitative Coronary Angiography and Calculation of Blood Flow
Coronary angiograms were acquired digitally with a real-time digital image acquisition system (Siemens AG, Germany) and analyzed offline. Diameter was measured ∼4 mm distal to the tip of the Doppler wire with quantitative coronary angiography (MEDIS, Netherlands) and used to quantify volume flow as described previously.

Calculation of Coronary Flow Reserve and Coronary Resistance
Adenosine was infused to induce maximal hyperemic response. Coronary flow reserve was calculated as the quotient of maximal coronary velocity/baseline velocity and coronary blood flow/baseline coronary blood flow. Coronary resistance was calculated as the quotient of mean arterial pressure (mm Hg) and coronary blood flow (mL/min).

Statistics
Sample Size
The sample size was calculated with the use of data from a pilot study performed in 7 patients at the 3-month follow-up angiogram for the RSVP trial RA graft diameter increased in response to acetylcholine 10⁻⁶ mol/L (endothelium-dependent responses) by a mean of 0.12% and SV grafts by a mean of −0.01% with a standard deviation of 0.1, giving a standardized difference of 1.1. Power of 0.8 and significance level at 0.05 gave a sample size of 26 (13 each group). We sought to include 15 patients in each group to allow for patient dropout.

Statistical Analysis
Both absolute measurements and percent change from baseline data were analyzed. Statistical analyses were performed by an independent statistician using STATA software. Nominal data were compared between groups with the Fisher exact test. Continuous data were compared with unpaired Student t tests when assumptions were fulfilled; otherwise, the Mann-Whitney test was used. Adjustment for multiple comparisons was made with the Bonferroni method. Significance was set at 5%. Continuous data are expressed as mean±SD.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patients
Twenty-seven of the 103 patients who returned for 5-year angiography were included in the study (RA, n=15; SV, n=12). The main reasons for ineligibility were nonfulfillment of inclusion criteria or technical issues, such as difficulty with stable positioning of the catheter for the duration of the study. There were no significant differences in patient characteristics between groups (Table).

Endothelium-Dependent and -Independent Responses

Luminal Diameters
SV diameter was significantly greater than RA diameter at baseline. There was no difference in absolute diameter measurements in response to pharmacological challenge.
Compared with baseline, RA but not SV dilated in response to adenosine and ISDN (Figures 1 and 2), and there was a nonsignificant trend to an increase in diameter in response to acetylcholine in RA but not SV grafts ($P=0.092$ and $P=0.124$, acetylcholine $10^{-7}$ and $10^{-6}$ mol/L, respectively). Individual responses to acetylcholine in the RA and SV groups are presented in Figure 3. There was no difference in the target vessel diameter at surgery ($P=0.027$ and $P=0.029$, baseline to ISDN, respectively).

Figure 1. Coronary graft diameter at baseline (Base) and after infusions of adenosine (Ad), acetylcholine $10^{-7}$ to $10^{-6}$ mol/L (A7, A6), and ISDN in patients randomized to RA or SV (median and interquartile range). Bottom panel shows percent change from baseline (mean±SD) for RA and SV.

Figure 2. Coronary graft diameter for individual patients at baseline (Base) and after infusion of ISDN for the RA group (top) and the SV group (bottom). Dark line represents median.
between groups (1.7±0.3 mm for RA and 1.7±0.4 mm for SV; \(P=0.9\)).

Flow Velocity
Flow velocity was significantly greater in the RA than SV at baseline (16.9±5.2 versus 10.8±3.5 cm/s; \(P=0.01\)) and after acetylcholine \(10^{-7}\) mol/L (20.6±5.9 versus 13.3±3.7 cm/s; \(P=0.0045\)) but not after adenosine (38.5±13.6 versus 16.2±5.6 cm/s; \(P=0.065\)), and ISDN (30.3±8.9 versus 23.3±7.3 cm/s; \(P=0.195\)).

Volume Flow
Volume flow was similar in the RA and SV groups at baseline, and volume flow responses to adenosine, acetylcholine, and ISDN were similar (Figure 4). Percent change from baseline tended to be greater in RA grafts but was not significantly different (Figure 4).

Coronary Flow Reserve and Resistance
Coronary flow reserve was not significantly different between groups with the use of velocity measurements (2.3±0.58 versus 2.6±0.4, RA versus SV; \(P=0.11\)) or volume flow measurements (2.71±0.93 versus 2.42±0.52, RA versus SV; \(P=0.34\)). Resistance in the RA group was 4.16±2.19 mm Hg/mL per minute and in the SV group was 3.92±1.51 mm Hg/mL per minute at baseline (\(P=0.76\)). Although resistance decreased after each pharmacological challenge within groups compared with baseline for RA and SV (\(P<0.01\) for all except after acetylcholine \(10^{-7}\) mol/L in the SV group, where \(P=0.15\)), the difference between groups did not change after any pharmacological challenge.

Systemic Hemodynamics
Mean arterial pressure and heart rate did not change significantly from baseline throughout the study procedure in either the RA (100±13 mm Hg and 62±10 bpm, respectively) or SV group (102±14 mm Hg and 66±14 bpm, respectively). There was no difference between groups.

Discussion
Five years after surgery, RA and SV aortocoronary bypass conduits grafted to a single coronary territory in a randomized trial had similar absolute volume blood flow at rest and after pharmacological stimulation. RA grafts demonstrated preserved flow-mediated vasodilatation, whereas SV grafts did not. Dilator responses to adenosine and ISDN suggest a more physiological response in the RA grafts that is absent at 5 years in the SV grafts, which appear to act as inert conduits of blood flow. Our data provide novel information on vasomotor and blood flow responses in human surgical conduits in vivo in the longer term. Previous observational studies have either focused on measurement of diameter and have not considered flow, have not been randomized, and/or have had shorter follow-up periods.\(^{2,3,15}\)

Many factors determine graft patency, including patient characteristics, target vessel and conduit selection,\(^{18}\) surgical technique,\(^{18}\) postoperative medical therapy, and risk factor management.\(^{19}\) The endothelium modulates vascular reactivity via a number of factors that include nitric oxide, endothelium-derived hyperpolarizing factor, and endothe- lin and also has antiproliferative and antithrombotic properties.\(^{20}\) In our study, endothelial function was tested with acetylcholine. This caused a trend to an increase in
diameter in RA grafts but not in SV grafts, with no difference in flow velocity or absolute volume blood flow. Acetylcholine is known indirectly to cause vasodilatation via interaction with muscarinic receptors on the endothelial cell plasma membrane with subsequent stimulated release of nitric oxide. However, when there is endothelial damage or dysfunction, acetylcholine may couple with muscarinic receptors on the vascular smooth muscle, resulting in vasoconstriction. Indeed, there was variation in vasomotor response to acetylcholine within groups in our study, even though the medians were not significantly different (Figure 3). Ciszewski and colleagues21 found that preserved vascular function was found in one third of SV grafts at 54-month follow-up and that a dilatory response was associated with a smaller graft to native coronary artery diameter difference. Previously, we showed reduced dilatation to acetylcholine but preserved dilator response to nitrate in SV grafts 3 months after surgery.4 Now we have shown loss of the dilator response to both acetylcholine and nitrate. The reason for lack of response of SV grafts to acetylcholine could be due to (1) the loss of the ability to react to acetylcholine, (2) the fact that they are fully vasodilated, or (3) the fact that the vascular smooth muscle cells have totally lost reactivity to any agent. The latter 2 possibilities are supported by the fact that only 3 SV grafts dilated to ISDN by >5%. Previous studies have reported a similar lack of vascular reactivity in SV grafts in the longer term.12,22 The evolution of loss of vasoreactivity over time in SV grafts, so that they become passive conduits, may be one of the mechanisms that may contribute to the less favorable patency rate in SV compared with RA aortocoronary conduits in the longer term.16

The IMA was the first successful arterial conduit adopted to routine coronary artery bypass surgery and has been shown to have better preserved endothelial integrity compared with SV both in vitro9 and in vivo.14 Comparison of in vivo endothelial function of the IMA and RA showed similar vasodilatation in response to acetylcholine 5 years postoperatively.15 This is despite conflicting in vitro data showing greater nitric oxide–dependent relaxation to acetylcholine in RA versus IMA in 1 study, which is proposed to be due to increased endothelial nitric oxide production and/or vessel sensitivity.10 Another study reported reduced basal and stimulated nitric oxide and endothelium-derived hyperpolarizing factor–mediated hyperpolarization in the RA compared with the IMA.23 Most patients in the RSVP trial had an IMA graft to the left anterior descending coronary artery; however, we did not image the IMA at follow-up angiography because it was beyond the limit of the ethics approval for the present study (for radiation exposure reasons). Conduit harvesting is known to damage the endothelium and may reduce endothelial nitric oxide synthase and nitric oxide release24,25; however, careful surgical technique may minimize endothelial damage of coronary conduits.26,27 Shear stress is also known to affect graft endothelial function, and reducing shear stress during graft preparation may preserve endothelial integrity.24,28 Details of the harvesting techniques used in the RSVP trial have been published previously.16

Endogenous adenosine is a local regulator of blood flow that acts via A1 and A2 receptors, which inhibit and stimulate adenylate cyclase, respectively, thus reducing and increasing intracellular cAMP formation, resulting in vasoconstriction and vasodilatation, respectively.29 Exogenous adeno-
sine administration causes vasodilatation, resulting in fast-onset hyperemia via flow-mediated dilatation. In the present study, an intracoronary bolus of adenosine caused dilatation in RA but not SV grafts compared with baseline (Figure 1), indicating preserved flow-mediated dilatation in RA but not SV conduits. In addition, there was a nonsignificant trend toward an increased change in flow velocity compared with baseline in SV conduits compared with RA conduits ($P=0.11$). Taken together, these responses of SV conduits to adenosine might lead to an elevation in shear stress with a resulting increased risk of graft atherosclerosis; however, further investigation would be required to clarify this.

At 5-year angiographic follow-up for the RSVP trial, the patency rate was 98.3% for RA and 86.4% for SV grafts ($P=0.04$). Whether our results explain the more favorable patency of RA grafts over SV grafts in the RSVP trial cannot be directly determined by the present study because all patients had to have a patent graft to be included in the study. Because only 1 woman was studied, the results can only be extrapolated to the male population, as discussed previously.

Conclusions

Five years after surgery, RA coronary bypass conduits grafted to a single coronary territory demonstrated preserved flow-mediated vasodilatation, whereas SV grafts did not. Preserved vascular reactivity of RA conduits compared with SV conduits, despite similar blood flow responses, may at least partly explain the more favorable patency of RA grafts over SV grafts in aortic coronary bypass surgery.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

We have demonstrated, in a randomized clinical trial (the Radial Artery Versus Saphenous Vein Patency [RSVP] trial), that radial artery (RA) aortocoronary bypass grafts anastomosed to a branch of the circumflex coronary artery have significantly better patency rates than saphenous vein (SV) grafts at 5 years. The reasons for this are relatively unexplored. In a substudy from this trial, we now report preserved vascular function in RA but not SV grafts 5 years after surgery, which may at least in part explain the patency results of the RSVP trial. The primary finding from this study is that RA aortocoronary bypass grafts are living conduits at 5 years, with the ability to autoregulate their diameter in response to changes in myocardial flow physiology, similar to that which has been observed and reported for the pedicle left internal mammary artery graft. The SV grafts, devoid of their vascular autoregulatory function, are merely passive conduits at 5 years. This may result in the SV grafts being subjected to extreme flow stresses, resulting in repeated cycles of injury and repair, and this may be one of the mechanisms that may contribute to the less favorable patency rate in SV compared with RA aortocoronary conduits in the longer term. Our clinical trial results, with the use of excellent surgical technique, support the use of the RA in aortocoronary bypass graft surgery, which we hope will result in the more widespread and acceptable use of the RA as an aortocoronary conduit.
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