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Discussion

Dr Jack Boyd (Indianapolis, Ind). I have 3 questions for you, and it's more extrapolating from your study. The first one is, what do you contribute the higher rate of late RA occlusions to in nondiabetic patients? Although it wasn't statistically significant, it was more than double the percentage.

Dr Deb. The univariate analysis did show that. From a physiology standpoint, it didn't make sense. However, when you see the patency curves of the RA grafts between diabetic and nondiabetic patients, they're almost similar. A large portion

of that difference is probably because of the low number of events. So I don't think there is a scientific reasoning for this finding. I think it has to do with the numbers. But seeing the patency curves, we're more comforted by the fact that they're fairly similar.

Dr Boyd. My second question even goes a little bit further off topic from your study, but I'm interested in what your left ITA patency rates were on the angiographic data. Did you have that information available to you because I think that would be significant in the late MACE and the other graft patencies.

Dr Deb. We didn't present it here, but left ITA patency was greater than 94% overall.

Dr Boyd. Was there any difference between the diabetic and nondiabetic groups?

Dr Deb. We did not assess that.

Dr Boyd. How has this influenced the practice of your group? Do you not use RAs in nondiabetic patients because they have the same patency rate as an SV graft? How does that influence the practice at your institution?

Dr Deb. This is the first study from a clinical trial that actually looked at such long-term outcomes between arterial and venous grafts, and this is the first study that showed from a clinical trial standpoint that RAs were protective in diabetic patients. Two large observational studies also showed, using a propensity score match, that RAs did better in diabetic patients.

With respect to our center, we use RAs a lot. Hopefully, the 10-year results of the Radial Artery Patency and Clinical Outcomes trial and other large studies will further corroborate our findings and encourage others to use RA grafting in diabetic patients. In this whole conference, there has been a push toward RA grafting, especially evident in the last few sessions.

Dr Boyd. Yes, I thought you could have given your presentation upstairs at the plenary session earlier this afternoon.

Dr Deb. Bilateral ITAs and RAs were the highlights there, and I hope this encourages more RA grafting.

EDITORIAL COMMENTARY

Arterial grafting and the challenge of the patient with diabetes

Paul A. Kurlansky, MD

Diabetes currently affects 29.1 million Americans, approximately 9.3% of the population. The prevalence has more than doubled in the past decade, and current estimates predict an incidence between 1 in 5 and 1 in 3 by the year 2050.¹

Adults with diabetes are 2 to 4 times more likely to have cardiovascular disease than are those without it, and at least 65% will die of it. In an era when preventive and therapeutic measures have resulted in a progressive and dramatic decline in cardiovascular mortality, the scourge of diabetes,

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at least partially if not mostly related to obesity, sorely threatens these otherwise encouraging advances. As a systemic disease, diabetes impacts vascular physiology on multiple levels and thus tends to manifest in cardiovascular pathology with extensive and diffuse multivessel involvement.² It is perhaps for this reason that the more “vessel-directed” surgical rather than “lesion-directed” percutaneous coronary intervention (PCI) approach has proved more successful in this population. Although the BARI (Bypass Angioplasty Revascularization Investigation) results demonstrated a survival advantage for coronary artery bypass grafting (CABG) relative to PCI with balloon angioplasty for patients with diabetes, provided the left internal thoracic artery (ITA) was used,³ interventional approaches have developed rapidly, proving somewhat of a “moving target” for the comparative study of long-term outcomes. The introduction of coronary stents, and the subsequent development of drug-eluting stents (DESs), changed the landscape of interventional cardiology and greatly extended the indications for an interventional rather than surgical approach to revascularization. The experience with DESs in patients with diabetes has been complex, however, with reports documenting both an increased mortality⁴ and an improved survival⁵ with DES versus bare metal stenting in the diabetic population. The long-term comparative results of newer generation DESs in the diabetic population has yet to be well documented.⁶ Since the prospective randomized control FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial reported at 5 years significantly reduced mortality and infarction rate with CABG versus PCI with first-generation DESs,⁷ there have been a plethora of meta-analyses—some focusing only on randomized, controlled trials (RCTs)^{8,9} and others including both RCTs and observational studies¹⁰⁻¹³—all of which document a long-term benefit for CABG relative to PCI in the diabetic population. These findings have inspired the surgical community to seek the optimal approach for the care of these patients.

Deb and colleagues,¹⁴ in this issue of *The Journal of Thoracic and Cardiovascular Surgery*,¹⁴ address the issue of optimal grafting for patients with diabetes directly with their report of the late angiographic and clinical findings of the RAPS (Radial Artery Patency Study) trial. This prospective RCT enrolled 529 patients undergoing elective 3-vessel CABG, all of whom received a left ITA to the left anterior descending coronary artery and underwent within-patient randomization to receive a radial artery (RA) or a saphenous vein graft (SVG) to either the right or circumflex coronary system. This ingenious approach permitted control for patient-specific factors by permitting each patient to serve as his or her own control. There were 148 (28.0%) patients with diabetes in the study

population. Of the 358 patients eligible for longer than 5-year follow-up, 269 (75.1%) underwent angiographic evaluation, 234 with coronary angiography and 35 with computed tomographic angiography. Primary angiographic outcome was graft occlusion by Thrombolysis In Myocardial Infarction criteria. At a mean of 7.7 ± 1.5 years, the proportion of graft occlusion among the diabetic population was significantly lower in the RA group (4/83 [4.8%]) than in the SVG group (21/83 [25.3%]; $P = .0004$). Through a 10-year period, freedom from graft occlusion was equivalent for the RA in patients both with and without diabetes, whereas the cumulative patency of SVGs was significantly worse in patients with diabetes than in patients without diabetes ($P = .03$). Interestingly, occlusion of the ITA grafts appeared to be similar to that of the RA grafts (7.8% in patients with diabetes and 5.1% in patients without diabetes). Clinically, major adverse cardiac events were higher in the diabetic population. Because every patient received both RA and SVG placement, this study was not designed to distinguish clinical outcomes between the 2 conduits.

Deb and colleagues¹⁴ are to be congratulated for a well-conceived and conducted RCT in a surgical population. Although considered the criterion standard of experimental evidence, the RCT is always a challenging affair in the surgical realm for the simple fact that, unlike the fixed dosage of a specific medication, surgical procedures can neither be blinded nor strictly standardized, but rather will inevitably vary somewhat according to surgical skill and style, patient anatomy, and clinical scenario. Deb and colleagues¹⁴ therefore made considerable effort to standardize the technique of RA harvest, as well as the construction of grafts (no sequential grafts) and the conduct of the operation (all operations were performed with the aid of cardiopulmonary bypass). Although angiographic assessment involved both classical angiography and computed tomographic angiography, use of the rather maximal end point of graft occlusion, rather than the more nuanced approach of the Fitzgibbon scale, considerably decreased the likelihood of discrepant findings between the 2 approaches. Those who refused angiography were clinically similar to those who did not, and the angiographic findings were similar for those who had clinically driven studies and those who had routine follow-up. If anything, we might expect the graft occlusion rate to be higher among those studied than among those who refused, because patients with possible concerns regarding symptoms might be more likely to agree to the procedure. In brief, RAPS provides compelling evidence that the RA is a reliable long-term conduit in patients with diabetes, and the saphenous vein is not.

How then can we use this information to synthesize the optimal surgical strategy for revascularization of the patient with diabetes who has extensive coronary artery disease?

Simple logic might dictate that we adopt the left ITA to left anterior descending coronary artery, RA to most severely stenotic secondary distribution, and SVGs for the rest. Progress in the use of bilateral ITAs (BITA grafting) for patients with diabetes, however, cannot be disregarded. Although surgeons were originally reluctant to perform BITA grafting in patients with diabetes because of the increased risk of sternal wound infection, improvements in the management of this complication, as well as advances in the technique of ITA harvest, have shifted this paradigm. Considerable evidence now exists that a “skeletonized” approach to ITA harvest provides better preservation of sternal perfusion and diminishes the risk of infection. Large registry experience has documented improved long-term survival in patients with diabetes undergoing BITA versus single ITA grafting, without an associated increased risk of sternal wound infection.^{15,16} These findings bring the question into sharper focus—given the superior performance of arterial conduits in patients with diabetes, what is the most appropriate secondary conduit?

Theoretically, total arterial revascularization with use of both ITAs and the RA might provide the optimal approach. The incremental clinical benefit of a third arterial conduit, however, is awaiting evidentiary support. Moreover, given the incredibly low penetration of the BITA technique in current clinical practice (<5% of isolated CABG operations in the Society of Thoracic Surgeons database) despite copious compelling registry evidence of clinical benefit, it seems highly unlikely that the tedious and technically demanding approach of complete arterial grafting will be readily adopted anytime soon. Within this construct, the decision then becomes, for a patient with diabetes who is theoretically a candidate for either approach, is it better to use a second ITA or to use the RA?

Introduced by Carpentier and colleagues in 1974, use of the RA for CABG has had an interesting evolution. Although the RA was initially abandoned soon after its introduction because of high failure rates,¹⁷ advances in the techniques of harvesting and the perioperative management have repopularized this conduit, with considerable clinical success. Structurally, the RA has a continuous intima, a relatively thick media of tightly-packed smooth muscle cells (which predispose toward spasm), and an increased intimal hyperplasia distally relative to more proximal segments. There is a low but notable incidence of medial calcification and atherosclerotic changes (~6%).¹⁸

Well known for its excellent long-term patency, the ITA has minimal proclivity for atherosclerotic change and is notable for a discontinuous internal elastic lamina and a relatively thin media with multiple elastic laminae and the absence of significant muscular component. Physiologically, the ITA has significantly increased rates of nitric oxide production in both basal and stimulated states. This

may account for the remarkable ability of the original Vineberg grafts to “violate” the simple laws of graft patency and remain patent despite high outflow resistance, as well as their ability to induce collateral circulation (most likely through a nitric oxide and vascular endothelial growth factor mechanism). Theoretically, as a conduit to deliver nitric oxide, ITA grafts have been hypothesized to alter the physiologic milieu of endothelial function and may therefore be specifically well suited to patients with diabetes.¹⁹ Moreover, as a living conduit with well-described adaptive mechanisms, the in situ ITA is well suited to adjust to variations in outflow resistance and flow demand.²⁰ Free ITA grafts, although structurally identical, do not share the same physiologic benefits and can be expected to have a commensurately diminished long-term patency.²¹

Hypothetical considerations aside, the RA in recent years in experienced hands has enjoyed an impressive clinical performance. Long-term patency has been demonstrated to be superior to that of SVGs²² and comparable to that of the free ITA.²³ Moreover, clinical results have documented improved long-term survival in patients with diabetes who undergo an ITA with RA versus an ITA with SVG approach, although this was confined to the non-insulin-dependent group.²⁴ Comparison with the free right ITA in patients with diabetes receiving a left ITA to the left anterior descending coronary artery demonstrated similar survival and reduced major adverse events relative to the RA in a 2-center comparison, although the ability to control for site- or surgeon-specific factors was limited.²⁵ Direct evaluation of the RA versus the in situ right ITA in patients with diabetes awaits further research.

If the art of medicine is the ability to make the right decision in the face of incomplete evidence, then the challenge for surgeons is clear. The optimal therapy for patients with diabetes who have extensive coronary artery disease is surgical revascularization. The use of 2 arterial conduits is clearly preferable to 1. Whether this second conduit is an ITA or a RA at this point appears to be a matter of surgical preference and expertise awaiting more definitive evidence to explore whether hypothetical considerations actually manifest in clinical performance. Perhaps clinical logic dictates that patient-specific factors should guide surgical decision making—a high-grade stenosis of a dominant right coronary artery may be more suitable for RA conduit use, whereas a diffusely diseased circumflex coronary artery might be more suitably bypassed with a skeletonized right ITA to the obtuse marginal coronary artery. It is specifically in this range of uncertainty that Deb and colleagues’ contribution¹⁴ is so valuable. With angiographic confirmation of the long-term freedom from graft occlusion of the RA in patients with diabetes, surgeons choosing this route can be confident of the validity of their approach.

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