Early vasoreactive profile of skeletonized versus pedicled internal thoracic artery grafts

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Background: No data are available on the early vasoreactive profile of skeletonized internal thoracic artery grafts.

Methods: Fifteen patients undergoing primary isolated coronary artery bypass grafting were randomly assigned to receive a skeletonized or pedicled internal thoracic artery graft. On the second postoperative day all patients were subjected to follow-up angiography and endovascular infusion of serotonin, acetylcholine, and isosorbide dinitrate.

Results: Internal thoracic artery grafts were widely patent in all cases. Mean diameters of the internal thoracic artery were 1.95 ± 0.17 mm in the pedicled group and 2.26 ± 0.40 mm in the skeletonized group. After serotonin challenge, mean internal thoracic artery diameters were reduced to 1.44 ± 0.34 mm and 1.64 ± 0.14 mm, respectively; acetylcholine challenge lead to a moderate degree of vasoconstriction (1.55 ± 0.59 mm in the pedicled group and 1.84 ± 0.15 mm in the skeletonized group). No statistically significant difference was evident between the two groups at any step.

Conclusion: Skeletonization does not affect the early vasoreactive profile of internal thoracic artery grafts used for surgical myocardial revascularization.

Skeletonization of the internal thoracic artery (ITA) allows the preparation of longer conduits with a superior free flow and can reduce the incidence of postoperative pulmonary and sternal complications.¹⁻⁴ However, to date no study has compared the vasoreactivity of pedicled and skeletonized ITA grafts and the functional consequences of the surgical trauma, and possible loss of innervation and vasa vasorum perfusion in the skeletonized conduits have not been yet elucidated. This study was conceived to characterize the vasoreactive profiles of skeletonized and pedicled ITA grafts in a period in which the functional consequences of the different type of surgical harvesting should be maximized, the first postoperative days.

Material and Methods

Study Population

This investigation received approval by the local ethics Committee, and written informed consent was obtained from each patient. The study included 15 patients subjected to primary isolated coronary artery bypass grafting (CABG) between March and September 2001 at our institution.

Before the operation, inclusion criteria for enrollment were as follows:

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- Absence of cardiac or noncardiac associate pathologic conditions
- Ejection fraction of at least 0.50
- Normal renal function (preoperative creatinine level not higher than 1.2 mg/dL)
- Angiographic evidence of good collateral flow to the left anterior descending coronary artery (LAD) to avoid severe anterior ischemia in case of marked vasospastic reaction of the ITA to the vasoactive stimuli
- Willingness of the patient to undergo the early angiographic control

After enrollment, patients were randomly assigned to receive a skeletonized ($n = 8$) or pedicled ($n = 7$) ITA graft. The main preoperative and intraoperative characteristics of the entire series of patients and of the two subgroups are summarized in Table 1.

Surgical Technique

All the procedures were performed by the same surgeon with a standardized technique. When the ITA was harvested as a pedicled conduit, the left pleura was opened for all its length and the internal thoracic vessels were visualized; a longitudinal incision of the internal thoracic fascia (parallel and medial to the medial thoracic vein) was then performed along the entire course of the vessel. The ITA branches were clipped proximally and transected with the electrocautery, and the artery and its pedicle were isolated from the origin to the epigastric bifurcation.

When the ITA was isolated in a skeletonized fashion, the pleura was left intact. The longitudinal incision of the fascia was performed as for the pedicled ITA. With the distal end of the electrocautery as a blunt dissector, the branches of the ITA were exposed, clipped distally and proximally, and transected with Potts forceps; the artery was then isolated alone, without any other surrounding structure. A bipolar electrocautery was always used for ITA harvesting.

The CABG procedure was then performed in standard fashion with cardiopulmonary bypass, aortic cross clamping, and cardioplegic arrest. The left ITA was always used to graft the LAD, and complementary venous grafts were used for the non-LAD target vessels. At the end of the procedure, the normal functioning of the anastomosis was assessed with an intraoperative flowmeter.

Angiographic Protocol

Postoperative angiography was performed on the second postoperative day. All patients did not receive vasoactive medications during the 24 hours before the procedure. Patients were studied in a fasting state after medication with diazepam (10 mg orally). Selective left ITA angiography was performed by percutaneous left radial ($n = 11$) or right femoral approach ($n = 4$). Internal thoracic 5F or 6F catheters (Boston Scientific Corporation, Boston, Mass) were used as appropriate to obtain optimal ITA visualization and selective contrast medium injection.

Multiple angiographic views were obtained to detect significant stenosis at any ITA or LAD level. Thrombolysis in Myocardial Infarction study (TIMI) flow grade was visually estimated separately by two different observers who were blinded to ITA harvesting technique.

Pharmacologic ITA stimulation was then started with a 4-point protocol:

TABLE 1. Preoperative characteristics of the patients

	Total	Skeletonized	Pedicled	P value
Male/female ratio	12:3	7:1	5:2	.42
Mean age (y, mean $\pm$ SD)	67.1 $\pm$ 7.2	65.3 $\pm$ 7.7	69.1 $\pm$ 6.7	.33
Hypertension	11	6	5	.55
Diabetes	6	3	3	.70
Smoking	12	7	5	.33
Dyslipidemia	7	4	3	.44
Familial history of coronary artery disease	8	5	3	.22
Previous acute myocardial infarction	8	4	4	.70
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I	3	1	2	.42
II	3	2	1	.28
III	9	5	4	.53

- Serotonin
- Isosorbide dinitrate
- Acetylcholine
- Isosorbide dinitrate

Serotonin hydrochloride at 10^{-5} mol/L (ICN Pharmaceuticals, Incorporated, Costa Mesa, Calif) was selectively injected into the ITA graft at a rate of 3 mL/min for 3 minutes. At the end of the serotonin challenge, 2 mg of isosorbide dinitrate was injected into the conduit. After a 20-minute period, acetylcholine chloride at 10^{-6} mol/L (Miovisin, Farmigee, Italy) was selectively injected into the ITA at a rate of 1.5 mL/min for 3 minutes. Again, at the end of the acetylcholine infusion, 2 mg of isosorbide dinitrate was injected into the graft. Drug infusion was always performed under electrocardiographic and invasive blood pressure monitoring.

At the end of each step of the protocol, a cineangiographic run was performed, keeping a fixed angiographic view. Digital angiograms were then analyzed with computerized quantitative angiography (Medis, Neuen, The Netherlands). For each step of the protocol, four vascular segments were measured in end-diastolic frames after proper catheter calibration: proximal left ITA (just distal to the ostium), preanastomosis left ITA, LAD 5 to 10 mm distal to anastomosis, and LAD 5 to 10 mm proximal to anastomosis.

Statistical Analysis

Quantitative angiographic data, expressed in millimeters, were normally distributed and are expressed as mean $\pm$ SD. Analysis of variance for repeated measures was used to test differences between steps; post hoc comparison was performed by Neumann-Keuls test. The Student *t* test was used to compare the two groups. Relative (percentage) changes in diameter between the skeletonized and pedicled groups were compared by Fisher exact test. Analysis was conducted with the software STATISTICA for Windows 4.1 (StatSoft Inc, Tulsa, Okla).

TABLE 2. ITA and LAD response to vasoactive challenges in the skeletonized and pedicled graft groups

	ITA proximal		ITA before anastomosis		LAD after anastomosis		LAD before anastomosis	
	Pedicled	Skeletonized	Pedicled	Skeletonized	Pedicled	Skeletonized	Pedicled	Skeletonized
Basal	2.69 ± 0.21	2.72 ± 0.31	1.95 ± 0.17	2.26 ± 0.40	1.69 ± 0.49	1.71 ± 0.26	1.63 ± 0.32	1.73 ± 0.28
Serotonin	2.16 ± 0.59	2.31 ± 0.45	1.44 ± 0.34	1.64 ± 0.14	0.98 ± 0.42	0.47 ± 0.17	0.96 ± 0.69	0.93 ± 0.32
Isosorbide dinitrate	2.43 ± 0.45	2.60 ± 0.37	1.85 ± 0.24	2.02 ± 0.36	1.49 ± 0.31	1.64 ± 0.30	1.31 ± 0.36	1.46 ± 0.60
Acetylcholine	2.57 ± 0.21	2.48 ± 0.45	1.55 ± 0.59	1.84 ± 0.15	1.61 ± 0.33	1.65 ± 0.22	1.56 ± 0.58	1.64 ± 0.42
Isosorbide dinitrate	2.74 ± 0.23	2.52 ± 0.35	1.92 ± 0.19	1.94 ± 0.25	1.71 ± 0.38	1.63 ± 0.13	1.37 ± 0.60	1.60 ± 0.27

Measures (all in millimeters) are reported as mean ± SD for each step of the protocol. No statistically significant difference was evident between groups at any step, regardless of the vascular segment considered.

Results

The two patients subgroups were comparable in terms of preoperative clinical and angiographic characteristics (Table 1). Intraoperative flowmetric assessment demonstrated normal function in all the performed grafts. The postoperative recovery in all cases was uneventful. Early postoperative angiography demonstrated a widely patent ITA graft in all patients. However, in 2 cases (1 in each group) the pharmacologic protocol could not be performed because of the technical difficulties in achieving satisfactory selective ITA ostium engagement.

The results of the vasoactive challenges on the different part of the ITA and the LAD in the two subgroups are summarized in Table 2. The ITA reacted to the serotonin challenge with a significant vasoconstriction, which was only partially relieved by isosorbide dinitrate administration. In contrast, the acetylcholine challenge led to a weak vasoconstriction of ITA grafts that tended to disappear after nitrate infusion. The LAD paralleled the ITA response, although the vasoconstriction after serotonin was markedly increased (leading to the complete disappearance of the artery in some instances).

No statistically significant differences were noted between the skeletonized and pedicled groups at any step, regardless of the vascular segment considered (Table 2). Of note, skeletonized ITAs and LADs had superior luminal diameters both proximally and distally, although this difference never reached statistical significance.

Discussion

Skeletonization of the ITA, although technically more demanding and time-consuming, is associated with several technical and clinical advantages. The skeletonized ITA is in fact longer and can reach even distal target coronary vessels, extending the possibility of arterial revascularization. In addition, once freed from the constraining action of thoracic fascia and the surrounding tissue, the ITA has a superior free flow³ and allows an easier construction of sequential or composite thoracic grafts.¹

Moreover, skeletonization reduces the surgical damage to the chest wall and allows maintenance of the integrity of

the left pleura in most cases, with objective advantages in terms of postoperative pulmonary function and avoidance of complications.⁴ A further advantage is related to the superior preservation of the sternal vascularity (which is severely compromised after harvesting of the pedicled ITA),² with consequent reductions in the incidences of postoperative mediastinitis and mechanical sternal dehiscence.⁵

Technically, skeletonization is more delicate and takes somewhat longer than the classical pedicled ITA harvesting. Early concerns about a possible increase in incidence of endothelial damage for the skeletonized ITA have been refuted in several animal and clinical studies (although we have reported an increased number of microthrombi in skeletonized vessels).⁶ In the only published series on this issue, even the midterm angiographic results of skeletonized ITA grafts were reported to be comparable to those of the pedicled grafts.⁷

Despite the advantages, the great majority of surgical teams routinely harvest the ITA as a pedicle and reserve skeletonization for a minority of their CABG cases. A probable explanation for this attitude is the lack of data on the vasoreactive profile of the skeletonized ITA and the consequent concerns about a possible early spastic tendency of a conduit subjected to an higher degree of surgical manipulation and probably deprived of part of its innervation and vasa vasorum perfusion.

Our data testify that skeletonized thoracic grafts have a vasoreactive profile that is not different from that of the criterion standard pedicled ITA, even in the early postoperative period (when the effect of the surgical trauma and denervation should be maximal). Skeletonized grafts in fact showed a contractile response to endovascular serotonin infusion similar to that of pedicled ITAs, with a comparable vasodilatory reserve (Table 2). These data are concordant with the observations of Kushwaha and colleagues,⁸ who found no difference in the endothelial function of the free versus in situ ITA graft, showing how denervation and loss of vasa vasorum and lymphatics do not affect ITA vasoreactivity at least in the long term.

As in every in vivo study on the vasoreactivity of coronary artery bypass conduits, it is not possible to rule out the

possibility that the observed ITA diameter changes after vasoactive drug administration were the consequences of modifications of the resistance of the grafted coronary artery (and indeed the LAD showed significant vasodilatory and spastic response in response to the different stimuli). If this is the case, however, this adaptive effect was observed equally in the skeletonized and pedicled groups (LAD responses to the different vasoactive stimuli were similar in the two series; Table 2) and thus did not affect the reliability of our observations.

Another possible limitation of our protocol is related to its statistical power. Although with 15 cases the possibility of a type II statistical error cannot be excluded, all *P* values were far from statistical significance and the observations were reproducible in the different patients, findings that seem to reduce to a minimum the possibility of this type of bias.

A collateral but interesting finding of our study was the demonstration of a vasoconstrictive response of the ITA to acetylcholine challenge in the very early days after surgery, in marked contrast with the described vasodilatory reaction to acetylcholine of thoracic grafts in the midterm and long-term follow-up periods.^{9,10} To the best of our knowledge, all the previous studies that investigated in vivo the reactivity of the ITA to acetylcholine challenge were performed several months after surgery, and no data on the early vasoreactive profile of the ITA have been published. In this regard our data are new and cannot be directly compared with those previously reported. Once the possibility of a drug interaction has been excluded (because the same pharmacologic protocol has already been used by our group on ITA grafts at mid-term follow-up and confirmed the vasodilatory effect of acetylcholine on “old” thoracic conduits),¹¹ a possible explanation for our observations is that in the very early days after the operation ITA grafts (independently of the techniques used for harvesting) show an “inevitable” degree of endothelial dysfunction caused by the surgical trauma or the systemic inflammatory reaction to cardiopulmonary bypass. This early dysfunction disappears in the months after the operation, presumably as a result of the endothelial healing process. This transient endothelial impairment of the ITA may explain the early vasoconstrictive and late vasodilatory response to the administration of an

endothelium-mediated vasorelaxant agent such as acetylcholine.

In conclusion, our data furnish the first objective evidence that skeletonization does not affect the early vasoreactive profile of ITA grafts used for surgical myocardial revascularization. On this basis, concerns about a possible hyperreactive response of skeletonized ITA grafts do not seem to be justified. These data, coupled with the recognized clinical and technical advantages offered by skeletonized grafts, should probably lead to a more frequent adoption of the skeletonized ITA for CABG procedures.

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