Long-term Morphofunctional Remodeling of Internal Thoracic Artery Grafts
A Frequency-Domain Optical Coherence Tomography Study

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Background—Internal thoracic arteries (ITAs) are frequently anastomosed to the coronary circulation for bypass grafting. The purpose of this research was to investigate in vivo the long-term morphofunctional changes of ITAs after their use as coronary artery bypass conduits, by comparing the morphological features and vasoreactivity of the grafted left ITA (LITA) with the native, nonharvested right ITA (RITA) in the same patient.

Methods and Results—At least 10 years after surgery, in 10 patients, LITA graft and nonharvested RITA were assessed by quantitative angiography and frequency-domain optical tomography. Endothelium-dependent and independent vasodilation was tested by selective infusion of acetylcholine and isosorbide dinitrate. Quantitative angiography showed that baseline mean diameter of LITA graft was significantly smaller than that of RITA (2.59 mm [2.29–3.04] versus 3.05 mm [2.75–3.32]; P=0.01). LITA showed a significant intimal thickening (P=0.05) and a nonsignificant medial thinning (P=0.22) compared with RITA, leading to an increased intima-media ratio (intima-media ratio, 0.72 [0.53–0.91] versus 0.23 [0.12–0.38]; P=0.02). The intima-media ratio correlated inversely with the vasodilator response in RITA (r=-0.68, P=0.03 for acetylcholine and r=-0.62, P=0.05 for isosorbide dinitrate) but not in LITA (r=-0.18, P=0.63 for acetylcholine and r=-0.11, P=0.75 for isosorbide dinitrate).

Conclusions—Ten years after implantation to the coronary circulation, LITA grafts show intimal thickening, increased intima/media ratio, and maintained endothelium-derived vasodilation. These changes are likely to be an adaptive answer to the different flow dynamics typical of coronary circulation. (Circ Cardiovasc Interv. 2013;6:269-276.)

Key Words: endothelium-dependent vasodilation • frequency-domain–optical coherence tomography • left internal thoracic artery • right internal thoracic artery

Internal thoracic arteries (ITAs) are commonly anastomosed to the coronary circulation for coronary artery bypass grafting (CABG), with excellent results.1 In particular, the left ITA (LITA) is widely considered the gold standard CABG conduit, with higher rates of long-term patency2 and a large survival impact compared with saphenous vein grafts.3 The characteristics of LITA, including its elastomuscular composition and its well-known resistance to atherosclerosis, are thought mainly to account for these results.2 The adaptation of the conduit to a different flow dynamics from that encountered while in situ is also considered essential for its long-term patency.5

While few data exist for radial artery grafts,6 information on long-term morphofunctional changes of successful LITA grafts is lacking.

Thus, we aimed to assess in vivo and at a long-term follow-up the morphological and functional changes occurred in the grafted LITA and in the in situ, nonharvested right ITA (RITA), by taking advantage of the recently available frequency-domain–optical coherence tomography (FD–OCT), a micrometric resolution intravascular technique.

Methods

Patient Selection and Perioperative Management
Patients were enrolled at the Department of Cardiovascular Sciences, Policlinico A. Gemelli, Catholic University of the Sacred Heart–Rome, Italy from June 2010 to June 2011. Elective patients with positive stress test or recurring effort angina or previous (>10 years) LITA grafting to the left anterior descending artery were screened before angiography. Patients with acute coronary syndrome were not included. Patients with previous angiographic documentation of LITA occlusion were excluded. Other exclusion criteria were severe...
WHAT IS KNOWN

- Left internal thoracic artery (ITA) is considered the gold standard coronary artery bypass graft due to its high rate of long-term patency.
- Despite being the most commonly used conduit, in vivo long-term morphofunctional changes of patent left ITA grafts are poorly known.

WHAT THE STUDY ADDS

- We analyzed anatomic-functional correlations in the grafted left ITA versus in situ right ITA, measuring intimal thickening through frequency-domain–optical coherence tomography, and analyzing endothelium-dependent and endothelium-independent vasodilation.
- More intimal thickening was observed in patent left ITA grafts as compared with in situ right ITA grafts in the same patient.
- In patent left ITA grafts, but not in right ITA grafts, a mismatch between acetylcholine-induced vasodilator response and intimal thickening was observed, suggesting that successful left ITA grafts are characterized by maintenance of endothelium-mediated vasodilation despite intimal hyperplasia induced by changes in flow dynamics associated with grafting to the coronary tree.

renal function impairment (creatinine clearance <30 mL/min), clinical signs of heart failure, or calculated left ventricular ejection fraction <50% and atrial fibrillation.

After native coronary and venous graft angiography, the operator performed LITA graft angiography. If LITA was perfectly patent (grade A according to Fitz–Gibbon classification) with optimal distal flow, with no significant stenoses distal to the anastomosis, and no percutaneous intervention was deemed necessary in any vessel, vasoreactivity test and FD–OCT assessment were performed. Then the in situ RITA was engaged and, after angiographic assessment, pharmacological challenges and FD–OCT assessment were undertaken. Figure 1 summarizes the study flow (Figure 1).

Local Ethics Committee approved the study, all patients signed an informed consent before the enrollment, and all procedures were performed in accordance with the ethical standards on human experimentation and with the Helsinki Declaration.

Graft Angiography

Angiography of ITAs was performed in 9 cases by bilateral radial approach, whereas in 1 case a femoral approach was used. Unfractionated heparin was administered with a target activated clotting time of >250 seconds. After selective cannulation of ITA, a baseline angiogram was acquired at a frame rate of 25 frames per second. No intracoronary nitrates were given during this part of the procedure.

Pharmacological Challenges: Endothelium-Dependent and Endothelium-Independent Vasodilatory Capacity of LITA and RITA Grafts

Drugs with potential effects on vasomotor response, including nitrates, calcium channel blockers, and β-blockers were discontinued ≥24 hours before cardiac catheterization. To assess endothelium-dependent vasoreactivity, once baseline angiogram was obtained, a stepwise infusion of incremental doses of acetylcholine (Ach) chloride (10, 30, and 100 μg during 1 minute) was performed. A 3-minute interval between each concentration was allowed. Each step was followed by an angiography. Finally, to test endothelium-independent vasoreactivity, a final angiogram was repeated after a bolus of 500 μg isosorbide dinitrate (ISDN).

Ach was infused until the maximal dose was reached or until the appearance of any adverse reaction requiring cessation of the infusion, such as typical chest pain, evidence of ischemia on the 12 lead ECG, dyspnea, arrhythmias, conduction abnormalities, or severe spasm. Spasm was defined as a focal lumen reduction of >50%, or as a diffuse lumen reduction and flow reduction (thrombolysis in myocardial infarction flow <3).

Quantitative Coronary Angiographic Analysis and Quantitative Coronary Angiography-FD–OCT Matching

Quantitative analysis of grafts was performed using automated coronary analysis software with edge contour detection (CASS QCA 5.9, Pie Medical, Imaging BV, Maastricht, The Netherlands).

Quantitative coronary angiography (QCA) analysis was targeted to the mean lumen diameter (mLD) site along LITA and RITA measured in diastolic frames according to validated protocols. QCA analysis was performed considering the portion of graft included between the ostium (chosen as proximal reference) and the intersection point between the graft itself and the superior margin of the second rib (chosen as distal reference; Figure 2). Vasodilator response at maximum dose of Ach and after ISDN was assessed as percentage increase of mL (ΔAch-mLD increase and ΔISDN-mLD increase) compared with baseline.

FD–OCT Analysis

After completion of angiography and pharmacological challenges, a 0.014-mm guide wire was placed distally in the ITAs. FD–OCT images were acquired with a commercially available system (C7 System; LightLab Imaging Inc/St Jude Medical, Westford, MA) after the OCT catheter (C7 Dragonfly; LightLab Imaging Inc/St Jude Medical, Westford, MA) was advanced distally in the target graft. The same segment of both LITA and RITA used for QCA assessment (from the ostium to the intersection with the superior margin of the second costa) was analyzed (Figure 2). The graft was scanned using the integrated automated pullback device at 20 mm/s. During image acquisition, coronary blood flow was displaced by continuous flushing of contrast media directly from the guiding catheter at a rate of 4 mL/s with a power injector (Medrad Avanta, Siemens, Germany). All images were recorded digitally, stored, and analyzed by 2 independent investigators who were blinded to clinical and laboratory data. Offline analysis was performed with proprietary software (LightLab Imaging) after confirming proper calibration settings of the Z-offset.

If needed, 2 FD–OCT runs were performed to ensure the coverage of the interested segment. The 2 pullbacks were matched to obtain the entire image length using landmarks, such as vasa vasorum or small side branches. Only 1 analysis was performed for those regions imaged twice.

LITA and RITA were imaged as a 3-layer structure by FD–OCT. The intima layer appeared as a bright area, whereas the media layer appeared as a lower intensity signal area. These 2 layers were separated by internal elastic lamina. The adventitia was imaged as a bright area surrounding the media layer. The external elastic lamina was the line between the media and the adventitia layers. Both the areas and the maximum thickness were measured for intima and media. Intimal hyperplasia indexes were calculated as intimal thickness index (intimal thickness indexes; intimal area/medial area), intima-media ratio (IMR; maximum intimal thickness/maximum medial thickness), and percentage of luminal narrowing (%LN; [intimal area+medial area]/external elastic membrane area×100). IMR, intimal thickness indexes, and %LN were measured in every other cross-section (0.4 mm interval), and a mean value was calculated (Figure 3).

WHAT THE STUDY ADDS

- We analyzed anatomic-functional correlations in the grafted left ITA versus in situ right ITA, measuring intimal thickening through frequency-domain–optical coherence tomography, and analyzing endothelium-dependent and endothelium-independent vasodilation.
- More intimal thickening was observed in patent left ITA grafts as compared with in situ right ITA grafts in the same patient.
- In patent left ITA grafts, but not in right ITA grafts, a mismatch between acetylcholine-induced vasodilator response and intimal thickening was observed, suggesting that successful left ITA grafts are characterized by maintenance of endothelium-mediated vasodilation despite intimal hyperplasia induced by changes in flow dynamics associated with grafting to the coronary tree.
FD–OCT analysis of LITA and RITA was also extended to atherosclerotic plaque identification and characterization. Cumulative occurrence of atherosclerosis was defined as the presence of ≥1 lipid or fibrotic plaque. Thin-cap fibroatheroma was defined as a lipid-rich plaque (with a lipid core of >2 quadrants) with a fibrous cap thickness of ≤565 μm. Thrombus was identified as a mass protruding into the vessel lumen discontinuous from the surface of the vessel wall.

**Statistical Analysis**

QCA and FD–OCT data are shown as median and interquartile range, because Shapiro–Wilk test showed that the data were not normally distributed. Frequencies were compared with Fisher test. Paired samples Wilcoxon test was used to compare QCA and FD–OCT data between LITA and RITA in each patient. The relationship between FD–OCT data and vasodilatatory response in each patient was evaluated using Spearman correlation coefficient. A P value <0.05 was considered for statistical significance. Statistical analysis was performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL).

**Results**

Ten patients were submitted to angiographic and FD–OCT examination and to vasoactive challenges of LITA and RITA. No LITA or RITA spasm was observed, although asymptomatic coronary spasm was observed in 4 patients in the coronary bed distal to LITA at the maximum Ach dose (100 μg), without overt signs or symptoms of ischemia. No significant systemic adverse reactions were seen, whereas 5 patients reported significant burning sensation in the upper right thoracic region during contrast injection in the RITA. Angiographic and FD–OCT characteristics are summarized in Table 2. Of note, both QCA and FD–OCT showed that at baseline, LITA mLd was significantly smaller than that of RITA. At FD–OCT, no thrombus, thin-cap fibroatheroma, or ruptured plaques were observed. Percentage area stenosis was always <20%. LITA showed a larger mean intimal area (0.50 mm² [0.37–1.02] versus 0.30 mm² [0.20–0.45]; P=0.05) and maximal intimal thickness (156.5 [77.7–186.2] μm versus 45.0 [29.0–70.3] μm; P<0.01) and, albeit not significantly, a thinner medial layer (1.70 mm² [1.40–1.85] versus 1.80 mm² [1.40–3.00]; P=0.22) as compared with RITA. No difference was observed between LITA and RITA in terms of total wall thickness expressed as intima+media area (2.35 mm² [1.80–2.72] versus 2.15 mm² [1.67–3.72]; P=0.61).

IMR (0.72 [0.53–0.91] versus 0.23 [0.12–0.38]; P=0.02) and intimal thickness indexes (0.29 [0.27–0.59] versus 0.16 [0.13–0.28]; P=0.03) were greater in LITA as compared with RITA. No significant difference was observed between LITA and RITA with regard to %LN (28.37% [19.56–33.67] versus 23.04 [15.67–30.89], respectively; P=0.11). Neither cumulative occurrence of atherosclerosis nor indexes of intimal thickening (IMR, intimal thickness indexes, and %LN) were significantly related to the presence of typical cardiovascular risk factors of atherosclerosis.

Vasodilator response to drug challenge was similar in LITA and RITA: %Ach-mLD increase was 10.30% (7.55–13.04) versus 7.14% (4.64–10.97), P=0.26, respectively, whereas %ISDN-mLD increase was 15.48% (9.15–21.29) versus 12.12% (9.56–15.12), P=0.10, respectively.

IMR was inversely related with the vasodilatatory response in RITA (r=−0.68, P=0.03 for %Ach-mLD increase and r=−0.62, P=0.05 for %ISDN-mLD increase).
but not in LITA ($r=-0.18, P=0.63$ for $\%$Ach-mLD increase and $r=-0.11, P=0.75$ for $\%$ISDN-mLD increase; Figure 3). Conversely, a positive relationship was observed between $\%$LN and vasodilatory response in RITA ($r=0.80, P=0.005$ for $\%$Ach-mLD increase and $r=0.65, P=0.04$ for $\%$ISDN-mLD increase) but not in LITA, ($r=-0.56, P=0.10$ for $\%$Ach-mLD increase and $r=-0.46, P=0.17$ for $\%$ISDN-mLD increase; Figure 4). No relationship was observed between intima+media area and vasodilatory response both in LITA ($r=-0.52, P=0.12$ for $\%$Ach-mLD increase

Figure 2. Definition of left internal thoracic artery (LITA) and right internal thoracic artery (RITA) segment used for quantitative coronary angiography (QCA) and frequency-domain–optical coherence tomography (FD-OCT) analysis. The figure shows the segment of LITA and RITA undergoing QCA and FD-OCT analysis. The analysis was targeted on the segment included between the ostium vessel (chosen as proximal reference) and the intersection point between the vessel itself and the superior margin of the second rib (chosen as distal reference). Minimal diameter, maximum diameter, mean diameter, and length of the segment analyzed are visualized in the left inferior part of each panel. As an example, 3 FD–OCT cross-sections (proximal, mid, and distal) of both LITA and RITA are visualized. D indicates distal reference; and P, proximal reference.

Figure 3. Definition of intima-media ratio (IMR), intimal thickness index, and percentage of luminal narrowing ($\%$LN). An example of detection of lumen border (white line in right internal thoracic artery [RITA] panel and blue line in left internal thoracic artery [LITA] panel), internal elastic lamina (IEL; pink line in both panels), and external elastic lamina (EEL; yellow line in both panels). Intima area was calculated as IEL area minus lumen area, whereas medial area was calculated as EEL area minus the sum of IEL area and lumen area. Maximum intimal and media thickness were also detected. Intimal thickness indexes, IMR, and $\%$LN were calculated according to the reported formulas.
Discussion

In the present study, morphological changes and functional status of LITA were assessed at long-term follow-up in patients with CABG and compared with in situ, nonharvested RITA in the same patient. We took advantage of the excellent spatial resolution of last-generation FD–OCT, which allows in vivo histology with differentiation of intimal and media layer. We observed in the grafted LITA a 65% greater intimal thickness as compared with RITA.

Several models suggest that a condition of increased flow is related to intimal thickening. In a previous study by our group, a similar increase in intimal thickness was observed in the ulnar artery when it became the only forearm artery because of the removal of radial artery used as free graft for coronary revascularization. A similar trend toward intimal hyperplasia has been described on the arterial side of arteriovenous fistulas and related to the higher blood flow. The intimal thickening observed in LITA likely represents an adaptive response to higher flow conditions, thus, differing from that observed in the early stages of atherosclerosis in native coronary arteries, which is related to endothelial dysfunction. Indeed, the intimal thickening observed in the harvested LITA was associated to normal endothelium–mediated vasoreactivity, different from that observed in native coronary arteries.

Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Age, y, median (IQR)</th>
<th>63.5 (53.7–68.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n</td>
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<tr>
<td>Diabetes mellitus, n</td>
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<tr>
<td>Hypertension, n</td>
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<tr>
<td>Smoker, n</td>
<td>2</td>
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<tr>
<td>Dyslipidemia, n</td>
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<tr>
<td>Family history, n</td>
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</tr>
<tr>
<td>Previous ACS, n</td>
<td>4</td>
</tr>
<tr>
<td>Previous PCI, n</td>
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<tr>
<td>Chronic stable angina on admission, n</td>
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</tr>
<tr>
<td>Impaired ejection fraction, n</td>
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<tr>
<td>Renal failure, n</td>
<td>0</td>
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<tr>
<td>One vessel disease, n</td>
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<tr>
<td>Two vessels disease, n</td>
<td>2</td>
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<tr>
<td>Three vessels disease, n</td>
<td>8</td>
</tr>
<tr>
<td>Number grafts per patient, median (IQR)</td>
<td>3.0 (2.70–4.0)</td>
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</tbody>
</table>

ACS indicates acute coronary syndrome; IQR, interquartile range; and PCI, percutaneous coronary intervention.

and \( r = 0.56, P = 0.10 \) for %ISDN-mLD increase and in RITA (\( r = -0.55, P = 0.10 \) for %Ach-mLD increase and \( r = -0.41, P = 0.24 \) for %ISDN-mLD increase).

Table 2. QCA and FD–OCT Data

<table>
<thead>
<tr>
<th>QCA</th>
<th>LITA (10 Pts)</th>
<th>In Situ RITA (10 Pts)</th>
<th>P Value</th>
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<tr>
<td>Baseline mLD, mm, median (IQR)</td>
<td>2.59 (2.29–3.04)</td>
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<td>mLD after Ach, mm, median (IQR)</td>
<td>2.87 (2.50–3.38)</td>
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<td>mLD after ISDN, mm, median (IQR)</td>
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<td>%ISDN-mLD increase, median (IQR)</td>
<td>15.48 (9.15–21.29)</td>
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<td>FD–OCT</td>
<td></td>
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<td>Lumen area, mm², median (IQR)</td>
<td>6.10 (5.15–6.82)</td>
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<td>0.005</td>
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<td>EEL area, mm², median (IQR)</td>
<td>6.95 (5.77–7.45)</td>
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<td>Internal area, mm², median (IQR)</td>
<td>8.50 (7.47–9.07)</td>
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<td>Max media thickness, µm, median (IQR)</td>
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QCA indicates quantitative coronary angiography; IQR, interquartile range; and PCI, percutaneous coronary intervention.

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%Ach-mLD increase, percentage of mLD increase after acetylcholine; %LN, percentage of luminal narrowing; %ISDN-mLD increase, percentage of mLD increase after isosorbide dinitrate; Ach, acetylcholin; EEL, external elastic lamina; FD–OCT, frequency-domain–optical coherence tomography; IEL, internal elastic lamina; IMR, intimal-media ratio; IQR, interquartile range; ISDN, isosorbide dinitrate; ITI, intimal thickness index; LITA, left internal thoracic artery; mLD, mean lumen diameter; QCA, quantitative coronary angiography; RITA, right internal thoracic artery; and TCFA, thin-cap fibroatheroma.
We also observed a trend toward a reduction in thickness of the media layer in LITA as compared with RITA. In a similar way, we previously described a progressive remodeling of the radial artery when used as graft, with significant reduction of the medial layer, increased luminal diameter, and preserved endothelium-dependent vasodilatory capacity. The loss of vasa vasorum because of artery manipulation during CABG procedure and the new flow condition after the anastomosis to coronary circulation could potentially explain the medial thinning observed in LITA and in radial artery.

Importantly, no differences were observed in our study in terms of both endothelium-dependent and endothelium-independent vasodilatory response between LITA and RITA. Thus, we report a mismatch between intimal thickening and vasodilatory response in LITA, but not in RITA, because of a preserved vasodilatory response in LITA despite intimal thickening.

The existence of an inverse relationship between intimal thickening and endothelial function in the coronary circulation is well known. For instance, in patients with a transplanted heart, Martí et al observed an inverse relationship between intimal thickness indexes and endothelial function assessed as response to Ach in the left anterior descending artery. In contrast, a mismatch between endothelium-dependent vasodilation and anatomic changes in LITA grafts has never been documented before. We can only make inferences to explain this novel result. It is likely that the described morphofunctional remodeling of LITA represents an adaptive response to the different flow conditions encountered in the artery after CABG. Indeed, in situ LITA is a resistance conduit with a prevalent systolic flow, but after CABG it is attached to a low resistance vascular bed characterized by prevalent diastolic flow. The increased flow leads to higher peak and time-averaged flow velocities and thus to higher shear stress, known to favor NO production. Moreover, a high intrinsic production of NO in the LITA has already been described. Importantly, NO-mediated vasodilation was shown to be preserved even in patients with diabetes mellitus, characterized by high prevalence of endothelial dysfunction, and a dilatation response of LITA to Ach despite coronary endothelial constriction has been widely documented, both in situ arteries and in LITA grafts. The preserved capacity for NO-mediated vasodilatation might thus potentially explain the morphofunctional dissociation observed in this study.

Another important insight into the complex anatomic-functional alterations induced by grafting in the LITA derives from the relationship between %LN (a parameter mostly reflecting the artery vascular tone when measured in vivo) and Ach-induced vasodilation. Indeed, a direct relationship was observed in RITA, indicating that endothelium-dependent vasodilation was effective in reversing the basal tone of the artery, in the same way as endothelium-independent vasodilation obtained by ISDN. In the grafted LITA, in contrast, the increase in lumen diameter induced

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**Figure 4.** Relationship between intimal thickening and endothelium-dependent and endothelium-independent vasodilatory capacity in left internal thoracic artery (LITA) and in right internal thoracic artery (RITA). Scatter plots report the significant relationships between intima-media ratio (IMR; inverse, top left panels) and percentage of luminal narrowing (%LN; direct, bottom left panels) and both percentage of mean lumen diameter increase after acetylcholine (%Ach-mLD increase) and percentage of mLD increase after isosorbide dinitrate (%ISDN-mLD) for the in situ, nonharvested RITA. On the contrary, no significant relationships were observed in LITA (right panels). r indicates Spearman r coefficient.
by Ach (and by ISDN) was independent of %LN. Complex interactions have indeed been described between LITA and its downstream coronary vascular bed, profoundly affecting endothelin and NO production, and impacting on blood flow and vascular tone.25

Limitations

The first and main limitation of this study is represented by its small sample size, although several other published studies have reported inferences from similar populations,6 and the inrasubject nature of the comparisons reduces possible bias. Second, our study relies on the hypothesis that LITA and RITA morphofunctional characteristics are comparable before LITA grafting to the coronary circulation, an assumption largely, but not entirely, true.26 Third, the observational nature of our study, although reporting evidence of significant morphofunctional changes in LITA compared with in situ RITA, does not provide mechanistic insights. Thus, our data must be considered as merely hypothesis-generating, and further studies are warranted to explain the mechanisms of the morphofunctional remodeling observed in grafted LITA.

Conclusions

We report for the first time the application of FD–OCT in vivo for the analysis of the grafted LITA, compared with the in situ nonharvested RITA in CABG patients at long-term follow-up. Importantly, FD–OCT confirmed the low occurrence of atherosclerosis in LITA, although reported a higher intimal thickening compared with RITA. Both endothelium-dependent and endothelium-independent vasodilatory response were preserved at follow-up in LITA and in RITA; however, only in LITA, a mismatch between vasodilatory response and intimal thickening was observed, probably because of the different flow pattern encountered in LITA after CABG.

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Disclosures

None.

References


Long-term Morphofunctional Remodeling of Internal Thoracic Artery Grafts: A Frequency-Domain Optical Coherence Tomography Study

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**What is known**

- Left internal thoracic artery (ITA) is considered the “gold standard” coronary artery bypass graft thanks to its high rate of long-term patency.
- Despite being the most commonly used conduit, *in vivo* long-term morphofunctional changes of patent ITA grafts are poorly known.

**What the study adds**

- We analyzed anatomical-functional correlations in the grafted left ITA vs. *in situ* right ITA, measuring intimal thickening through frequency-domain optical coherence tomography (FD-OCT), and analyzing endothelium-dependent and independent vasodilation.
- More intimal thickening was observed in patent left ITA grafts as compared to *in situ* right ITAs in the same patient.
- In patent left ITA grafts but not in right ITAs, a mismatch between acetylcholine-induced vasodilatatory response and intimal thickening was observed, suggesting that successful left ITA grafts are characterized by maintenance of endothelium-mediated vasodilation despite intimal hyperplasia induced by changes in flow dynamics associated with grafting to the coronary tree.