Implantation in Coronary Circulation Induces Morphofunctional Transformation of Radial Grafts From Muscular to Elastomuscular

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Background—The purpose of this research was to investigate the in vivo morphofunctional changes induced in the radial artery (RA) by its use as coronary artery bypass conduit by comparing the morphological features and vasoreactivity of the native RA versus the coronary RA graft in the same patient.

Methods and Results—Ten years after surgery, 10 patients were submitted to intravascular ultrasound examination of the RA graft of the contralateral (in situ) RA and of the internal thoracic artery (ITA) graft and to vasoactive challenges with acetylcholine and serotonin. Quantitative angiographic assessment showed that the mean diameter of the RA coronary grafts was significantly larger than that of the in situ RA and of the ITA (2.89 ± 0.40 mm RA grafts, 2.14 ± 0.52 mm in situ RA, 2.25 ± 0.53 mm ITA grafts; P < 0.001). The in situ RA demonstrated a typical muscular architecture, whereas RA coronary grafts showed a clear reduction of the thickness of the medial layer and had a less well-defined muscular component of the media with interposition of elastic tissue. Serotonin endovascular infusion elicited a strong spastic reaction in in situ RAs; the same challenge induced only moderate constriction in RA and ITA coronary grafts.

Conclusions—Implantation in the coronary circulation leads to major anatomic and vasoreactive modifications of the RAs that tend to lose the morphofunctional features of a muscular conduit and assume those of an elastomuscular artery, such as the ITA. (Circulation. 2005;112[suppl 1]:I-208–I-211.)

Key Words: coronary disease ■ radial artery ■ surgery
Selective angiography of all grafts, native coronary arteries, and in situ RA were performed by percutaneous brachial or femoral approach.

Multiple angiographic views were obtained to detect significant stenosis at any level. The Thrombolysis in Myocardial Infarction Study flow grade was visually estimated separately by 2 different observers who were blinded to each other.

Pharmacologic internal thoracic artery (ITA) stimulation was then started with a 4-point protocol according to previously described methods:13 (1) serotonin; (2) isosorbide dinitrate; (3) acetylcholine; and (4) isosorbide dinitrate.

Serotonin hydrochloride at $10^{-5}$ mol/L (ICN Pharmaceuticals, Inc) was selectively injected into the conduits at a rate of 3 mL/min for 3 minutes. At the end of the serotonin challenge, 2 mg of isosorbide dinitrate was injected. After a 20-minute period, acetylcholine chloride $10^{-6}$ mol/L (Miovisin) was administered IV. Again, at the end of the infusion of acetylcholine, 2 mg of isosorbide dinitrate was injected. The 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).

**TABLE 1. Main Features of the Patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female ratio</td>
<td>6:4</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>59.5±3.2</td>
</tr>
<tr>
<td>Cardiac risk factors</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
</tr>
<tr>
<td>Smoking</td>
<td>4</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>4</td>
</tr>
<tr>
<td>Mean ejection fraction</td>
<td>0.67±0.22</td>
</tr>
<tr>
<td>Target RA vessel</td>
<td></td>
</tr>
<tr>
<td>Obtuse marginal</td>
<td>5</td>
</tr>
<tr>
<td>Diagonal</td>
<td>2</td>
</tr>
<tr>
<td>Posterior descending</td>
<td>3</td>
</tr>
</tbody>
</table>

**Figure 1.** Angiographic and IVUS imaging of in situ RA and RA used for coronary revascularization. Angiogram shows a patent RA graft (arrow bottom left). IVUS assessment confirms absence of atherosclerotic lesion and shows an altered vessel wall morphology without the tunica media echolucency, typical of muscular arteries (arrow bottom right). Conversely, angiography and IVUS show that the in situ RA is a widely patent artery with a well-preserved muscular layer (top left and arrow in the top right).

**IVUS Assessment**

**Image Acquisition**

IVUS images were obtained with the use of mechanical ultrasound imaging catheters at 40 MHz (2.9 F, Atlantis, Cardiovascular Imaging Systems/Boston Scientific). IVUS assessment was performed in RA and ITA grafts and in the in situ RA. Patients were given 7000 U of heparin in the arterial sheath and 300 μg of nitroglycerin into arterial grafts and in situ RA to prevent possible vasospasm. The imaging probe was positioned distally and withdrawn at a constant speed of 1 mm/s by using a motorized pullback device. IVUS studies were recorded on high-resolution S-VHS tapes for off-line analysis.

**Qualitative and Quantitative IVUS Analysis**

Cross-sections were analyzed for every second of videotape with commercially available software (Tape Measure, INDEC Co.). The adoption of an automated (1 mm/s) modality of acquisition permitted us to match IVUS and angiographic images. Qualitative assessment of vessel wall anatomy was performed both in situ artery and coronary bypass conduits.

Based on previous reports IVUS qualitative assessment of tunica media was performed. In particular, a distinct sonolucent layer was considered as indicative of tunica media.14,15 In the IVUS cross-section corresponding with the site of maximal angiographic lumen narrowing,
the following measurements were obtained: lumen area, total vessel area delimited by the external elastic membrane area, and plaque area.

**Statistical Analysis**

Quantitative angiographic data, expressed in millimeters, were normally distributed and are expressed as mean±SD. ANOVA 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 2 groups. Relative (percentage) changes in diameter were compared by Fisher exact test. Analysis was conducted with the software STATISTICA for Windows 4.1 (StatSoft Inc.).

**Results**

Angiographic controls were performed at a mean follow-up time of 124±11 months.

**Angiographic Study**

All of the RA and ITA grafts were found to be perfectly patent and free from appreciable atherosclerotic disease or intimal hyperplasia; in 2 cases, minimal irregularities were appreciated in the proximal segment of the RA graft. Similarly, perfect patency and absence of disease was found in all of the investigated in situ RAs.

Quantitative angiographic assessment showed that the mean diameter of the RA coronary grafts was significantly larger to that of the in situ RA and the ITA (2.89±0.40 mm RA grafts, 2.14±0.52 mm in situ RA, 2.25±0.53 mm ITA grafts; *P*<0.001).

**IVUS Assessment**

IVUS confirmed the absence of significant atherosclerotic disease in all of the RA and ITA grafts and in the in situ artery. The in situ RA demonstrated a well-delimited media presence of a prominent muscular layer (Figure 1). In contrast, in none of the RA and ITA coronary grafts was the 3-layer composition, which is indicative of muscular media, revealed by IVUS (Figures 1 and 2).

**Vasoactive Challenges**

Detailed results of the in vivo pharmacological challenges are given in Table 2. Serotonin endovascular infusion elicited a strong spastic reaction in in situ RAs; the same challenge induced only moderate constriction in RA and ITA coronary grafts. Vasoconstriction was more evident in RA grafts with a more abundant muscular component. Acetylcholine administration showed an appreciable capacity of endothelium-dependent vasodilatation in all of the investigated conduits.

**Discussion**

In contrast with the gold standard ITA (which is an elastomuscular artery), the RA is characterized by a thick medium composed mainly of smooth muscle tissue.14,15 The abundant muscular component of the medium is the histological background of the well-described RA hyperreactivity and the spastic tendency of the in situ artery and RA coronary grafts in the early postoperative period.

Indeed, at the time of its reintroduction in coronary surgery, several authors expressed major conceptual concerns related to the peculiar vasoactive features of this conduit,16,17 and a chronic antispastic therapy has always been considered mandatory for patients carrying a RA graft.1 However, serial angiographic studies and in vivo pharmacologic challenges have recently showed how the spastic tendency of the artery tend to reduce after implantation in the coronary circulation, and 5 years after surgery, the vasoreactive profile of the RA has became similar to that of the ITA.10

Our group has reported how coronary RA grafts undergo a progressive remodeling characterized by an increase in the luminal diameter, maintained endothelium-mediated vasodilator capacity, and reduced spastic reaction to vasoactive stimulation.8 However, no data are available on the modifications of the arterial wall that accompany the RA graft remodeling and the morphofunctional differences that exist between the RA used as coronary graft and the in situ artery.

As for institutional policy, we never performed bilateral RA harvesting when we had the possibility of comparing the anatomic and vasoactive features of the conduit in the 2 different conditions in the same patient. Our data show that the RA, when exposed to the different hemodynamic and rheologic conditions of the coronary circulation, undergo major morphological modifications.

In fact, angiographic and IVUS studies demonstrated that 10 years after the operation, coronary RA grafts have a luminal
coronary arteries with a medial thickness tissue, and proteoglycans. As shown in previous studies, only smaller amount of other components, such as collagen, elastic limits long-term angiographic controls6,10 can be explained on the basis of calcium channel blocker therapy and the reduction in the incidence show, in fact, a significantly reduced spastic tendency and tend to major differences in the vasoactive properties: coronary RA grafts (Figures 1 and 2). These anatomic modifications are reflected by closely resembles that of an elastomuscular artery, such as the ITA.

In concomitance with the increase in diameter, coronary RA grafts undergo major morphological modifications of their vascular wall architecture: the well-delimited and represented muscular medium typical of the in situ artery becomes far less evident and closely resembles that of an elastomuscular artery, such as the ITA (Figures 1 and 2). These anatomic modifications are reflected by major differences in the vasoactive properties: coronary RA grafts show, in fact, a significantly reduced spastic tendency and tend to react to the endovascular infusion of a vasoconstrictive agent in a manner more similar to that of the ITA than of the in situ RA (Table 2). It seems plausible that even the reported lack of efficacy of the calcium channel blocker therapy and the reduction in the incidence of catheter-induced RA graft spasm between the early and the long-term angiographic controls6-10 can be explained on the basis of our present findings.

In conclusion, implantation in the coronary circulation leads to major anatomic and vasoreactive modifications of the RA that tend to lose the morphofunctional features of a muscular conduit and assume instead those of an elastomuscular artery. On these basis the conceptual perplexities on the use of the RAs can be appreciated by IVUS. However, because the thickness of the muscular layer is slightly greater than the resolution of IVUS, a quantitative evaluation could not be attempted.

Limits

The finding of a 3-layer morphology of the coronary artery walls at IVUS is not consistent. The muscular media of coronary arteries is mainly composed of smooth muscle cells with a smaller amount of other components, such as collagen, elastic tissue, and proteoglycans. As shown in previous studies, only coronary arteries with a medial thickness >178 µm exhibit a 3-layer appearance.14,15 Yet, unlike the coronaries, the radial arteries have a prominent muscular layer, which can be easily appreciated by IVUS. However, because the thickness of the muscular layer is slightly greater than the resolution of IVUS, a quantitative evaluation could not be attempted.

References


TABLE 2. Results of the Endovascular Vasoactive Challenges

<table>
<thead>
<tr>
<th>Variables</th>
<th>RA Grafts</th>
<th>In Situ RA</th>
<th>ITA Grafts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.89±0.40 mm</td>
<td>2.14±0.52 mm</td>
<td>2.25±0.53 mm</td>
</tr>
<tr>
<td>Serotonin</td>
<td>2.58±0.18 mm*</td>
<td>1.55±0.21 mm</td>
<td>2.18±0.16 mm</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>2.99±0.30 mm</td>
<td>2.44±0.15 mm</td>
<td>2.41±0.11 mm</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>2.95±0.26 mm</td>
<td>2.33±0.19 mm</td>
<td>2.30±0.22 mm</td>
</tr>
</tbody>
</table>

P value is not significant vs ITA grafts. *P=0.001 vs in situ RA.
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