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 controlateral (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

The radial artery (RA) is gaining widespread acceptance as a complementary arterial conduit for surgical myocardial revascularization, and several groups have reported excellent midterm to long-term angiographic patency.1–6 However, since the introduction of this conduit in clinical practice, major theoretical concerns were expressed by different authors because of the muscular architecture of this artery and its enhanced vasoreactivity and propensity to spasm.1,7,8 Recently, our group has shown that in the years after surgery, coronary RA grafts undergo a morphofunctional remodeling characterized by a progressive increase in luminal diameter and loss of the early spastic tendency.9 However, no data are currently available on the morphological modifications of the arterial wall that accompany these changes and on the anatomic consequences of RA implantation in the coronary circulation. The present study protocol was conceived to investigate the in vivo morphofunctional changes induced in the RA by its use as a coronary artery bypass conduit.

For this purpose, we adopted the imaging technique of the arterial wall with the highest spatial resolution (intravascular ultrasound, IVUS) and a series of pharmacological challenges and compared the vascular architecture and response to endovascular stimulation of the native RA versus the coronary RA graft in the same patient.

Methods

Patient Population and Perioperative Management

Our institutional experience with the use of the RA as a coronary artery bypass conduit started in 1993; a detailed description of the operative technique used at surgery, perioperative management, follow-up methodology, and midterm to long-term clinical and angiographic results have been published previously.7–13 Bilateral RA harvesting was never performed in our series, and the artery was always harvested from the nondominant arm.7

This investigation was approved by the local institutional board, and written informed consent was given by every patient. The study includes the first 10 cases that have reached the 10-year follow-up at the time of enrolment and accepted to undergo the IVUS examination and pharmacological vasoactive challenges. The main clinical data of these 10 cases are described in Table 1.

Angiographic Protocol

Angiographic Control and Vasoactive Challenges

Patients were studied in a fasting state after medication with diazepam (10 mg orally). All of the patients did not receive vasoactive medications during the 24 hours before the procedure.
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).

**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 in situ artery and coronary bypass conduits.

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).
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 elasto-muscular 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
diameter significantly larger than that of the in situ artery. For institutional policy, the RA was always harvested from the non-dominant arm (where the RA is of smaller size; Ref. 18), so the reported difference must be considered even more significant.

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 antispastic therapy for patients carrying a RA graft.

In conclusion, implantation in the coronary circulation leads to major anatomic and vasoactive 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 of the in situ artery do not seem substantiated. These data also challenge (at least theoretically) the necessity of a chronic antispastic therapy for patients carrying a RA graft.

**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. 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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