Clinical and Angiographic Effects of Chronic Calcium Channel Blocker Therapy Continued Beyond First Postoperative Year in Patients With Radial Artery Grafts

Results of a Prospective Randomized Investigation

Mario Gaudino, MD; Franco Glieca, MD; Nicola Luciani, MD; Francesco Alessandrini, MD; Gianfederico Possati, MD

Background — This study was conceived to elucidate the clinical and angiographic effects of chronic calcium channel blocker therapy (CCCBT) continued after the first postoperative year in patients in whom the radial artery (RA) was used for myocardial revascularization.

Methods and Results — Patients who received RA grafts at our institution and who at 1 year had no scintigraphic evidence of ischemia in the RA territory or angiographic evidence of RA malfunction (n = 120) were randomly assigned to continue (n = 63) or suspend (n = 57) the CCCBT with diltiazem (120 mg/d). After 5 years, all patients were reassessed clinically and by stress myocardial scintigraphy, and 87 of them (45 from the continued group that continued CCCBT and 42 from the group that suspended CCCBT) were restudied angiographically. No differences regarding either the clinical and scintigraphic results or the RA angiographic status were demonstrated between the 2 groups.

Conclusions — After the first postoperative year, the continuation of CCCBT does not affect RA graft patency or clinical and scintigraphic results. (Circulation. 2001;104[suppl I]:I-64-I-67.)

Key Words: arteries ■ coronary disease ■ surgery

Ever since the reintroduction of radial artery (RA) grafts in coronary surgery in the mid 1990s, a chronic antispastic therapy (usually with the use of calcium channel blockers) has traditionally been considered necessary.

Indeed, the superior early and midterm patency rates of the RA in the current era (in contrast to the unacceptably high incidence of failure in the 1970s) have usually been attributed to the less traumatic harvesting technique and, most of all, to the systematic use of vasodilators in the postoperative period.

However, to date, no objective data on the optimal duration of the postoperative chronic calcium channel blocker therapy (CCCBT) or on its real benefits in terms of RA graft patency and clinical results have been published, so that the modalities of the antispastic therapy are actually empirically established by the single centers.

The present study was conceived to clarify the clinical and angiographic effects of CCCBT beyond the first postoperative year in patients with an RA graft.

Methods

Our experience with the RA started in January 1993 and, until January 2000, 619 patients received an RA graft for surgical myocardial revascularization. Ever since the beginning of our series, the antispastic therapy consisted of oral diltiazem (120 mg/d) started in the early postoperative period and continued indefinitely.1

The follow-up protocol included a clinical assessment and a 201Tl stress myocardial scintigraphy 1 and 6 months after surgery and then every year thereafter and an angiographic control at 1, 5, and 10 years for those patients who had a recurrence of ischemia or who had consented to undergo angiography for study purposes.

The early and midterm clinical and angiographic results and the early and midterm alterations of the forearm circulation and the midterm vasodilatory profile of the RA grafts have been the object of previous reports.1–5

The present study was designed to elucidate the clinical and angiographic effects of CCCBT after the first postoperative year.

For this purpose, after institutional approval and with the consent of every participating patient, the first 120 RA graft patients who at 1 year demonstrated scintigraphic evidence of normal perfusion in the RA territory or angiographic evidence of a perfectly functioning RA graft were randomly assigned to continue (n = 63, continued group) or suspend (n = 57, suspended group) the CCCBT. Patients were then followed up according to the previously described protocol, and 5 years after surgery, they were reassessed clinically and scintigraphically; 87 of them (45 from the continued group and 42 from the suspended group) also underwent midterm control repeat angiography.

Moreover, to verify the effect of the CCCBT therapy on the spastic response of the RA grafts, we evaluated the response of the RA to the endovascular infusion of serotonin in 15 of the patients...
TABLE 1. Preoperative Characteristics of Patients in the 2 Groups

<table>
<thead>
<tr>
<th></th>
<th>Continued Group</th>
<th>Suspended Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>63</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Mean age, y</td>
<td>62.3±8.1</td>
<td>61.9±7.7</td>
<td>0.78</td>
</tr>
<tr>
<td>Male/female, n</td>
<td>49/14</td>
<td>45/12</td>
<td>0.95</td>
</tr>
<tr>
<td>Cardiac risk factors, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>27</td>
<td>19</td>
<td>0.38</td>
</tr>
<tr>
<td>Smoking</td>
<td>32</td>
<td>23</td>
<td>0.33</td>
</tr>
<tr>
<td>Dyslipemia</td>
<td>19</td>
<td>29</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23</td>
<td>21</td>
<td>0.88</td>
</tr>
<tr>
<td>Previous myocardial infarction, n</td>
<td>19</td>
<td>15</td>
<td>0.79</td>
</tr>
<tr>
<td>Three-vessel disease, n</td>
<td>51</td>
<td>48</td>
<td>0.82</td>
</tr>
<tr>
<td>Left main disease, n</td>
<td>8</td>
<td>5</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Radial artery target vessel, n

OM 29 23 0.66
PDA 17 19 0.58
RCA 14 14 0.93
Diag 3 1 0.68

OM indicates obtuse marginal branch; PDA, posterior descending artery; RCA, right coronary artery; and Diag, diagonal branch. Age is shown as mean±SD, and other values are numbers of patients.

Results

The mean preoperative clinical and angiographic characteristics of patients of the continued and suspended groups, as well as the RA target vessels, are summarized in Table 1; the 2 groups were similar regarding all the examined variables, with the only exception being dyslipemia, which was more frequent in the suspended group.

Follow-up was 100% complete; mean follow-up time was 58.2±4.6 months in the continued group and 58.6±3.1 months in the suspended group (P=0.58).

As detailed in Table 2, during this period, 3 patients died (2 from the continued group and 1 from the suspended group, P=0.93); 1 of the deaths in the continued group was cardiac-related (large posterolateral myocardial infarction in the territory of distribution of a saphenous vein graft 5.5 years after surgery), whereas the other 2 deaths were noncardiac (respectively, from a traffic accident and a lung tumor).

Symptomatic angina was reported by 6 of the patients who continued the CCCBT and 7 of the patients who suspended the CCCBT (9.5% and 12.2%, respectively; P=0.85), whereas scintigraphic demonstration of residual ischemia was present in 11 patients from the continued group and 10 patients from the suspended group (including all the symptomatic patients) (P=0.82). All the patients with angina and/or scintigraphic evidence of ischemia recurrence were submitted to repeat angiography; RA malfunction was the cause of the ischemia recurrence in only 5 patients (3 from the continued group and 2 from the suspended group, P=0.91).

A 5-year angiographic control study was performed in 87 patients (45 from the continued group and 42 from the suspended group). The angiographic results are summarized in Table 3; the 5-year patency and perfect patency rates of the RA were 97.7% and 93.3%, respectively, in the continued group and 97.6% and 95.2%, respectively, in the suspended group, without statistically significant difference in RA angiographic status between the 2 cohorts of patients.

Finally, in the subgroup of patients who underwent endovascular serotonin infusion at 5-year angiography, the RA exhibited only a slight contraction in response to the vasoconspastic challenge, and the spastic response of the artery was similar between patients who continued or suspended the CCCBT (see Table 4).

Discussion

Since the early days of its reintroduction in coronary surgery, the RA propensity for vasospasm has been worrisome.

In fact, in contrast to almost all conduits used for surgical myocardial revascularization and, in particular, the gold-standard internal thoracic artery, the RA has a thick muscular wall and only limited amount of elastic tissue in its media. This abundant muscular component is the anatomic background of the hyperspastic response of the artery, which has been well documented both in vivo and in vitro: in a classic organ-bath study, Chardigny et al reported that the contrac-

TABLE 2. Five-Year Clinical and Scintigraphic Results in the 2 Groups of Patients

<table>
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<tbody>
<tr>
<td>No. of patients</td>
<td>63</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Mean follow-up, mo</td>
<td>58.2±4.6</td>
<td>58.6±3.1</td>
<td>0.58</td>
</tr>
<tr>
<td>Deaths, n</td>
<td>2</td>
<td>1</td>
<td>0.93</td>
</tr>
<tr>
<td>Cardiac deaths, n</td>
<td>1</td>
<td>0</td>
<td>0.96</td>
</tr>
<tr>
<td>Angina recurrence, n</td>
<td>6</td>
<td>7</td>
<td>0.85</td>
</tr>
<tr>
<td>Scintigraphic evidence of residual ischemia, n</td>
<td>11</td>
<td>10</td>
<td>0.82</td>
</tr>
<tr>
<td>RA-related residual ischemia, n</td>
<td>3</td>
<td>2</td>
<td>0.91</td>
</tr>
</tbody>
</table>

RA indicates radial artery. Follow-up is given as mean±SD, and other values are numbers of patients.

TABLE 3. Five-Year Angiographic Results in the 2 Groups of Patients

<table>
<thead>
<tr>
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<th>Continued Group</th>
<th>Suspended Group</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>45</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Perfect RA, n</td>
<td>42</td>
<td>40</td>
<td>0.94</td>
</tr>
<tr>
<td>Stringed RA, n</td>
<td>1</td>
<td>1</td>
<td>0.50</td>
</tr>
<tr>
<td>Irregular RA, n</td>
<td>1</td>
<td>0</td>
<td>0.97</td>
</tr>
<tr>
<td>Occluded RA, n</td>
<td>1</td>
<td>1</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Values are numbers of patients.
TABLE 4. Five-Year RA Response to Endovascular Serotonin Infusion in the 2 Groups of Patients

<table>
<thead>
<tr>
<th></th>
<th>Continued Group</th>
<th>Suspended Group</th>
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</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Baseline RA diameter, mm</td>
<td>2.60±0.41</td>
<td>2.57±0.35</td>
<td>0.88</td>
</tr>
<tr>
<td>RA diameter after serotonin, mm</td>
<td>2.45±0.69</td>
<td>2.47±0.73</td>
<td>0.95</td>
</tr>
<tr>
<td>Mean diameter reduction, mm</td>
<td>0.15±0.28</td>
<td>0.10±0.38</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Values are number of patients or mean±SD.

The tile response elicited on RA rings by a variety of vasoconstricting stimuli is markedly superior to that exhibited by both the internal thoracic artery and gastroepiploic artery, and our group confirmed this finding in vivo; furthermore, almost all of the series of early angiography of RA grafts yielded instances of catheter-induced artery spasm.

For this reason, the necessity for pharmacological intervention to prevent RA spasm when this artery is used as a coronary artery bypass conduit has been emphasized by many authors, and the good patency rates obtained in the current era (opposed to the alarming incidence of graft failure in the 1970s) are often explained by the systematic adoption of vasodilating agents.

However, no convincing clinical evidence on the optimal modalities and duration of the antispastic therapy is actually available, and the type of drug and the duration of the treatment are usually established on an empirical basis by each investigator (although many groups decided to adopt the calcium channel blocker diltiazem, which was administered for variable periods of time).

The present study was designed with the aim of providing objective clinical and angiographic data regarding the effect of CCCBT beyond the first postoperative year in patients with RA grafts: after 5 years of follow-up and with a consistent percentage of our patients restudied angiographically, we were able to demonstrate that the prosecution of the antispastic therapy after the first 12 months after surgery does not produce any advantage in terms of clinical results or RA angiographic status. Furthermore, the data derived from the subset of patients submitted to endovascular serotonin challenge indicate that the CCCBT has no effect on the vasoreactive profile of the RA.

These observations are in accordance with the morpho-functional remodeling of RA grafts in the years after surgery that we have described in previous publications; indeed, it now seems evident that during the 5 years after surgery, the RA changes its morpho-functional characteristics, adapting them to the new hemodynamic situation. As a result of this process, the conduit tends to lose its peculiar hyperreactivity (as demonstrated by the increase in perfect patency rate and the reduction in the spastic response to vasoactive stimuli that we have described in those patients who underwent a serial angiographic control study) and to increase its luminal diameter, while maintaining a good capacity for endothelium-dependent vasodilatation.

Although the subtle physiological mechanisms for this adaptation are unknown at present, 2 main explanations can be hypothesized: (1) The augmented shear stress consequent to the implantation in the coronary circulation can lead to an augmented local production of NO; the well-known vasodilating and antimitotic effects of NO (to which the RA is particularly sensitive; see Shapiro et al) can then have induced the described morpho-physiological remodeling of the artery. (2) Alternatively, the histological architecture of the RA (with a considerable part of the outer muscular media nourished by the vasa vasorum and probably ischemic after conduit harvesting and preparation; see Van Son et al) renders plausible the hypothesis that progressive ischemic medial myocyte loss can be the explanation for the reduction of the RA hypervasospastic response in the years after surgery.

The described morpho-functional remodeling obviously implies that the importance of the CCCBT is high only in the first months after surgery (when the RA is still a highly reactive conduit) and tends to decrease with time, which offers a solid theoretical explanation for our present clinical and angiographic observations. Because the CCCBT is costly and can be associated with not negligible negative inotropic and chronotropic side effects and, possibly, with an increase risk of neoplastic pathologies, its use after the first postoperative year in patients with RA grafts should be abandoned.

In recent years, several authors have suggested the inappropriateness of diltiazem to prevent RA graft spasm and have suggested the use of different vasodilators (including nitroglycerin, isosorbide dinitrate, nicorandil, nifedipine, verapamil, and amiodipine) although the majority of these studies were conducted in vitro or had a limited follow-up period, the research of the ideal antispastic drug for RA graft seems worthwhile in view of the growing use of this artery in coronary surgery and the paucity of scientific data to support the use of diltiazem.

References


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