Long-Term Patency of Internal Mammary Artery Bypass Grafts

Relationship With Preoperative Severity of the Native Coronary Artery Stenosis

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Background—Internal mammary artery conduits (IMA) have an excellent long-term patency rate. Nevertheless, graft closure does occur and significantly limits future revascularization options. We sought to investigate the relationship between the long-term patency of IMA with clinical and angiographic parameters. Particularly, the preoperative degree of stenosis of the relevant bypassed coronary vessel was assessed to analyze the importance of chronic competitive flow on the arterial graft closure rate.

Methods and Results—Consecutive patients in whom occlusion of at least 1 IMA had been documented at angiography (OCC group) were compared with a group of patients with patent IMA grafts (PAT group). The degree of stenosis in the native coronary artery on which the IMA was placed was analyzed by off-line quantitative coronary angiography. Multivariate stepwise logistic regression was used to identify independent clinical and angiographic predictors of occlusion. The OCC group comprised 96 patients (67 ± 10 years) with 103 native bypassed arteries analyzed. The PAT group comprised 127 patients (69 ± 8 years) with 170 native bypassed arteries analyzed. Both groups were similar except for gender (42% versus 32% female; \( P = 0.04 \)), height (166 ± 8 versus 169 ± 8 cm; \( P = 0.006 \)), minimum lumen diameter (0.76 ± 0.7 versus 0.51 ± 0.5; \( P = 0.001 \)), and diameter stenosis of the native artery (73 ± 25% versus 84 ± 16%; \( P < 0.0001 \)) in OCC versus PAT, respectively. In the multivariate analysis, only percent diameter stenosis was an independent and statistically significant predictor for graft patency. Among IMA placed on coronary arteries with a diameter of stenosis \( < 50\% \) (n = 28), the occlusion rate was very high (79%).

Conclusion—The degree of stenosis in the native vessel is a major predictor of internal mammary artery bypass graft patency. The association between nonsignificant stenosis of the native artery and high occlusion rate of the arterial bypass conduit raises concerns about the use of IMA in the treatment of native vessels with only mild or moderate stenosis. (Circulation. 2004;110[suppl II]:II-36–II-40.)

Key Words: bypass ■ revascularization ■ stenosis ■ surgery

In contrast to saphenous vein grafts, the long-term patency rate of arterial bypass conduits is very high, with 85% to 95% of grafts free of significant stenosis at 7 to 10 years.\(^1\)\(^-\)\(^6\) This is supposed to be because of physiological, anatomic, and hemodynamic characteristics.\(^7\) Therefore, the use of arterial conduit is now unanimously accepted as the best choice for surgical revascularization. Although rare, occlusion of internal mammary artery conduits (IMA) significantly limits future revascularization options.

Causes of occlusion of the arterial bypass grafts remain controversial. Doppler studies suggested that a moderate stenosis in the target vessel is associated with competitive flow, thereby leading to a decreased anterograde flow in the arterial graft, which may lead to early failure (“disuse atrophy”).\(^8\) However, the clinical importance of this process remains controversial. Canine experiments have shown that arterial conduits grafted on fully patent native arteries remained patent.\(^9\)\(^,\)\(^10\) Yet in the latter studies, patency was assessed at a maximum of 2 months, which is not enough to predict the long-term effect of competitive flow. In humans studies on potential predictive factors of IMA occlusion, control angiograms were also obtained relatively soon after coronary artery bypass grafting (CABG).\(^11\)\(^-\)\(^14\)

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Accordingly, the purpose of our study was to evaluate the influence of clinical and angiographic parameters and particularly the influence of the degree of stenosis on the native vessel on the long-term arterial graft patency.

Methods

Patient Population
From 1985 to 2002, 12,969 patients underwent CABG at our center. Among 2,659 patients who underwent a postoperative coronary angiogram for clinical reasons, 96 (3.6%) were identified as having at least 1 IMA closure. Because closure of both IMA was observed in 7 patients, 103 internal mammary arterial graft closures were included (OCC group). One hundred twenty-seven patients undergoing operation during the same period and with an angiographically documented patent IMA were randomly selected and served as a control group (PAT group). One hundred seventy patent arterial grafts were included in this group. Graft closure was defined as diffuse and very pronounced (>95%) conduit narrowing ("string sign").

Quantitative Angiographic Measurement
Quantitative coronary angiographic measurements of the stenoses in the native coronary artery was performed as described by Reiber et al. The projection in which the stenotic segment was best visible was studied to calculate the interpolated reference diameter (mm), which corresponds to the normal vessel diameter at the level of the stenosis, the minimal luminal diameter (mm), and the percent diameter stenosis (DS; %). The angiography catheter was used as the scaling device. Global left ventricular ejection fraction (LVEF; %) was calculated from the right anterior oblique projection using Simpson rule. The regional wall motion in the myocardial region depending on the IMA was assessed visually.

Statistical Analysis
Because this study evaluates potential predictors of the patency of arterial bypass grafts, the statistical analysis was performed per arterial conduit (n = 103 in the OCC group and 170 in the PAT group) and not per patient (n = 96 in the OCC and 127 in the PAT group). In univariate tests, clinical and angiographic variables were compared between both groups. The χ² and Fisher exact test were used for categorical variables, and Student t test or U test was used for continuous variables. Multivariate stepwise logistic regression was performed to identify independent predictors for patency. In all tests, differences were considered nonsignificant when P ≥ 0.05.

Results

Clinical Characteristics
Clinical characteristics of the 2 groups are given in Table 1. The proportion of female patients, height, and the time interval between CABG and angiographic control were slightly but statistically smaller in the OCC group than in the PAT group. The control (postoperative) angiograms in both groups were indicated for clinical reasons. Time from operation to angiogram is shown in Table 1 (graft age). The difference in this time interval between the 2 groups may result from bias introduced by patients with patent IMA being investigated later, in contrast to patients with occluded IMA who would conceivably become symptomatic earlier.

There were slightly more patients with a history of previous myocardial infarction in the OCC group than in the PAT group (nonsignificant). Table 2 gives the number and type of bypass grafts used as well as the recipient arteries of the IMA.

| TABLE 1. Clinical Characteristics of the 2 Patients Groups |
|------------------|------------------|------|
|                  | OCC Group (n=103) | PAT Group (n=170) | P     |
| Female           | 43 (42%)          | 55 (32%)         | 0.04  |
| Age, y           | 67±10             | 69±8             | NS    |
| Weight, kg       | 71±11             | 75±13            | NS    |
| Height, cm       | 166±8             | 169±8            | 0.006 |
| No risk factor   | 7 (7%)            | 18 (10%)         | NS    |
| Diabetes         | 21 (20%)          | 33 (19%)         | NS    |
| Hypertension     | 45 (44%)          | 78 (46%)         | NS    |
| Smoking          | 52 (50%)          | 77 (45%)         | NS    |
| Hypercholesterolemia | 60 (58%)   | 100 (58%)       | NS    |
| Family history   | 21 (20%)          | 32 (19%)         | NS    |
| Graft age, y     | 4±4               | 5±4              | 0.04  |
| History of previous AMI | 34 (33%) | 48 (28%) | NS    |

OCC indicates group of occluded arterial grafts; PAT, group of patent arterial grafts; NS, nonsignificant; AMI, acute myocardial infarction.

Angiographic Characteristics
As shown in Table 3, LVEF was similar in both groups: 78 (76%) patients in the OCC group had a normal LVEF (EF ≥ 50%) versus 148 (87%) patients in the PAT group (P = NS). Twenty-five (24%) patients of the OCC group had a baseline LVEF < 50% versus 22 (13%) in the PAT group (P = 0.06). The minimal luminal diameter was significantly greater in the OCC group than in the PAT group (0.76±0.75 versus 0.51±0.51, P = 0.001). Accordingly, the DS is smaller in the OCC group than in the PAT group (73±25% versus 84±16%, P < 0.0001). Yet there was no difference in the reference diameter of the grafted arteries. After withdrawal of the totally occluded native arteries in both groups, the average DS was 58±2% (n = 65) in the OCC group versus 74±1% (n = 106) in the patent group (P < 0.0001). As shown in the Figure, 28 IMA were placed on target coronary arteries with a narrowing ≤ 50% DS. Of these 28 IMA, 22 (79%) were
TABLE 3. Angiographic Characteristics of the 2 Groups

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OCC Group (n=103)</th>
<th>PAT Group (n=170)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>62±16</td>
<td>65±13</td>
<td>NS</td>
</tr>
<tr>
<td>Normal regular wall motion</td>
<td>69 (64%)</td>
<td>122 (72%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>21 (20%)</td>
<td>38 (22%)</td>
<td>NS</td>
</tr>
<tr>
<td>Akinetia</td>
<td>13 (13%)</td>
<td>10 (6%)</td>
<td>NS</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>0.76±0.75</td>
<td>0.51±0.51</td>
<td>0.001</td>
</tr>
<tr>
<td>DS, %</td>
<td>73±25</td>
<td>84±16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RD, mm</td>
<td>2.9±0.7</td>
<td>2.9±0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

DS indicates percent diameter stenosis; LVEF, left ventricular ejection fraction; MLD, minimal lumen diameter; NS, nonsignificant; RD, reference diameter; OCC, occluded arterial graft group; PAT, patent arterial graft group.

occluded after a mean follow-up of 57±56 months. In contrast, after withdrawal of the target native artery with a narrowing ≤50%, there was no difference in DS between the OCC and the PAT group (83±2% versus 85±2%, respectively; NS). When only IMA were grafted on the left anterior descending (LAD) coronary artery with a stenosis ≤50% DS (n=20), the occlusion rate was 80%. The Figure shows overlap between the groups, particularly those with stenosis >50%, and we sought to establish other factors (in addition to angiographic parameters) that contribute to graft closure by performing multivariate analysis.

Predictors of IMA Occlusion by Multivariate Analysis (Table 4)

In the stepwise multivariate logistic regression analysis including all angiographic and clinical variable listed in Tables 1 and 3, DS percent diameter (P=0.001), LVEF (P=0.011), and height (P=0.001) were the only independent parameters that predicted graft patency. DS <50% had an odds ratio of 21.5, which was even higher than the crude (unadjusted) odds ratio of 14.2.

Discussion

The present study investigates the influence of the stenosis severity in the recipient native coronary artery on the long-term patency of IMA bypass grafts in humans. The data indicate that the occlusion rate of IMA is very high (79%) when they are placed on coronary arteries without an angiographically significant stenosis. This high occlusion rate was also observed when only the IMA grafted on the LAD were considered.

Arterial Versus Venous Graft

Because arterial grafts have a better long-term patency than venous grafts, the use of IMA instead of saphenous vein grafts is considered preferable whenever possible. The 2 types of conduits behave in different ways. Arteries show a larger response to vasoactive substances with a larger production of relaxing factors such as nitric oxide by the endothelium. The structure of the wall of the arterial conduit is better-adapted to high pressures and high flow rates after coronary artery bypass surgery. These anatomic and physiological differences may account for the possible differences in postoperative graft function and long-term patency rates. It is generally accepted that the progression of atherosclerosis in the native artery is accelerated after bypass of the latter. Moreover, some data suggest that the degeneration and occlusion rate of saphenous vein grafts is inversely proportional to the severity of the stenosis in the native coronary artery. The present data indicate that a similar relationship exists for arterial bypass conduits: when the native artery does not create any significant resistance to flow, the occlusion rate of the IMA bypass is particularly high.

Mechanisms of Closure of IMA

Despite a low incidence of atherosclerosis in the IMA, a late closure rate of 10% has been identified after 10 to 15 years. Several causes for this phenomenon have been proposed. Spasm and inflammation of the IMA from a postpericardiotomy syndrome has not been confirmed by clinical data. Damage to the IMA during surgery can cause a focal narrowing, but this does not explain the diffuse pattern of the string phenomenon. The most likely hypothesis to explain late closures of IMA grafts is that of flow competition between the bypass and the native artery. Accordingly, Barner introduced the term of “disuse atrophy” to describe the shrinkage of arterial conduits grafted on unobstructed coronary arteries. The “distal thread phenomenon” or the “string sign phenomenon” were terms used to describe the angiographic appearance of the occluded arterial conduit. However, the data from animal experiments regarding this competitive flow hypothesis are conflicting. A series of canine experiments showed that when grafted on fully patent LAD coronary arteries, the flow in the IMA was at least as high as that when left in situ, suggesting that a decrease in flow was not the cause of arterial closure. Using the same model, Lust et al further demonstrated that the flow through the IMA did not decrease even after 8 weeks of competitive

TABLE 4. Results From Multivariate Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Predictors</th>
<th>P</th>
<th>Odds Ratio</th>
<th>95% CI Lower/Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter stenosis &lt;50%</td>
<td>0.000</td>
<td>21.5</td>
<td>5.18/64.38</td>
</tr>
<tr>
<td>Height, cm</td>
<td>0.000</td>
<td>0.95</td>
<td>0.94/9.80</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.02</td>
<td>0.42</td>
<td>0.97/80.22</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction.
flow. In contrast, Pagni et al. observed a 70% decrease in the IMA flow after grafting on normal LAD artery. These studies have limited clinical implications because of the short-term follow-up. In human studies, conflicting observations were also reported. Using intravascular Doppler crystal-tipped guide wires, Shimizu et al. and Nasu et al. observed a major reduction in IMA flow in patients with mild-to-moderate stenoses in the LAD coronary artery as compared with patients with a tight stenosis. In contrast, Kawasui et al. did not find that competitive flow predisposed to graft closure.

Previous Clinical Studies
Controversial data exist with respect to the relation between occlusion rate of the arterial bypass conduits and the severity of the stenosis in the native vessels. Hashimoto et al. showed that when the stenosis in the recipient artery is <60%, the occlusion rate was high. The data of Villareal et al. appeared to confirm the importance of competitive flow in 28 cases of arterial graft closure (35±35 months). In 81% of patients whose arterial conduits were occluded, evidence of competitive flow was observed. Two studies demonstrated that radial arteries used as coronary bypass conduits were also sensitive to the severity of the stenosis in the native artery. The patency rate of the grafts was poor when 70% or less stenosis was found in the native coronary arteries. Moran et al. showed that patent radial artery grafts had a significantly greater degree of stenosis on the bypassed vessel than their occluded counterparts (73±14% versus 40±24%). In contrast to these results, some authors have not confirmed the relationship between arterial graft closure and competitive flow because of nonsignificant stenosis on the recipient artery. Angiographic predictors of graft patency were studied by Manninen et al., with a mean follow-up of 2 years, and by Gaudino et al. during an average of 53±13 months. Both studies concluded that the severity of the stenosis in the native vessel did not influence the patency rate of IMA bypasses. These conflicting results may be, however, largely explained by methodological differences.

Limitations
Patients in the present study underwent a control angiogram only because of clinical reasons (recurrent angina or other indicators of ischemia). It is thus likely that patients in whom the recipient vessel was only moderately stenosed remained asymptomatic even in the presence of a string phenomenon. Therefore, it is also likely that the incidence of occlusion of IMA grafts of moderately stenosed recipient arteries is underestimated.

A retrospective study such as this may have some degree of selection bias with respect to the decision-making process of the surgeon in terms of appropriateness of IMA use and target vessel characteristics. There may also be discrepancies in surgical technique, although some of these factors would affect both OCC and PAT groups equally.

Coronary angiography, albeit quantitative, remains a relatively weak tool to determine the functional repercussion of a stenosis. Therefore, it is likely that some lesions with a DS of <50% were actually hemodynamically significant and, conversely, that stenoses with a DS of >50% were not. Fractional flow reserve (FFR) is a guide wire-based index derived from intracoronary pressure measurements that has been shown to assess the functional significance of a coronary stenosis much more accurately than angiography. FFR has been shown to be a predictable surrogate for noninvasive stress testing and is therefore a useful tool in determining the appropriateness of revascularization. It is likely that in the present study, FFR measurements would have provided us with a better predictor of long-term patency of IMA grafts.

Another limitation of coronary angiography is its poor ability to establish the true functional nature of an IMA graft demonstrating the “string sign.” It is possible that some of these grafts remain functional and would have the capacity to increase in size as the native vessel stenosis worsened, and there are sporadic reports of this occurring in the literature.

Conclusion and Clinical Implications
Even though the overall patency rate of IMA grafts is high, the present data indicate that the long-term patency rate of IMA grafts is low when the recipient vessel is only moderately stenosed. Practically, these findings imply that the decision to use an IMA should be carefully considered in light of the hemodynamic severity of the stenosis in the recipient vessel. When angiography is ambiguous, more reliable—albeit simple—measurements, like pressure-derived FFR, should be advocated. The latter might avoid the inappropriate use of an IMA as a graft to a recipient artery that does not need to be revascularized.

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