Does Location of the Second Internal Thoracic Artery Graft Influence Outcome of Coronary Artery Bypass Grafting?

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Background—We sought to determine whether location of the second internal thoracic artery (ITA) graft used for bilateral ITA grafting affects mortality and morbidity of patients with 3-system coronary artery disease and to identify factors associated with second ITA location.

Methods and Results—From January 1972 to June 2006, 3611 patients with 3-system coronary artery disease underwent bilateral ITA grafting with one graft anastomosed to the left anterior descending system and the second to either the circumflex (n=2926) or right coronary artery (n=685) system. Follow-up was 9.2±7.2 years. Propensity score methodology was used to obtain risk-adjusted outcome comparisons between patients with the second ITA to circumflex versus right coronary artery. Hospital mortality (0.34% versus 0.58%; P=0.4), stroke (0.96% versus 0.88%; P=0.8), myocardial infarction (1.3% versus 0.73%; P=0.2), renal failure (0.44% versus 0.29%; P=0.6), respiratory insufficiency (3.5% versus 3.8%; P=0.7), and reoperation for bleeding (3.4% versus 3.2%; P=0.8) were similar in patients who received the second ITA to circumflex or right coronary artery and remained similar after propensity score adjustment. Late survival (86% versus 87% at 10 years) was also similar. Despite this, there was a gradual decline in ITA to right coronary artery grafting.

Conclusions—Contrary to prevailing wisdom that the second ITA graft should be anastomosed to the next most important left-sided coronary artery in 3-system coronary artery disease, it may be placed to either the circumflex or right coronary artery system with similar early and late outcomes. (Circulation. 2008;118[suppl 1]:S210–S215.)

Key Words: coronary disease ■ revascularization ■ risk factors ■ surgery ■ survival

Bilateral internal thoracic artery (ITA) grafting prolongs survival and decreases coronary reintervention for recurrent myocardial ischemia after coronary artery bypass grafting. One ITA is routinely used to bypass the left anterior descending coronary artery (LAD). Conventional wisdom is to use the second ITA to graft the circumflex (Cx) system. To determine if this revascularization strategy is more beneficial than using the second ITA to bypass the right coronary artery (RCA) system, we compared early and late outcomes in patients with 3-system disease undergoing bilateral ITA grafting who had the second graft used to bypass either the Cx or RCA system.

Patients and Methods

From January 1972 to June 2006, 3611 patients with 3-system coronary artery disease underwent isolated coronary artery bypass grafting using bilateral ITA grafting (with or without other vein or arterial grafts) at Cleveland Clinic, with one ITA used to bypass the LAD and the second used to bypass either the Cx or RCA system, according to surgeon preference. In 2926 (81%), the second ITA was used to graft the Cx system and in 685 (19%), the RCA system.

Variables and Definitions

Patient characteristics and operative techniques used were obtained by routine prospective data collection during the hospital admission for primary coronary artery bypass grafting. Left ventricular function was echocardiographically graded as normal (ejection fraction ≥60%), mild dysfunction (ejection fraction 40% to 59%), moderate dysfunction (ejection fraction 25% to 39%), or severe dysfunction (ejection fraction <25%). A coronary artery system was considered importantly stenotic if it contained a ≥50% diameter obstruction. Incomplete revascularization was defined as failure to graft any system containing ≥50% stenosis or both LAD and Cx systems for ≥50% left main trunk stenosis.

End Points

The primary end point of the study was long-term mortality. Late death was obtained from routine anniversary follow-up in the CVIR supplemented with the Social Security Death Index. Mean follow-up was 9.2±7.2 years (median, 9.0 years). A total of 33 307 patient-years of follow-up data were available for analysis.

From the Departments of Thoracic and Cardiovascular Surgery (J.F.S., A.S., E.R.N., E.H.B., B.W.L., F.D.L.) and Quantitative Health Sciences (E.H.B., P.L.H.), Cleveland Clinic, Cleveland, Ohio.

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The secondary end point was postoperative hospital outcomes, defined as for the Society of Thoracic Surgeons National Database (see www.ctsnet.org/file/rptDataSpecifications252_1_ForVendorsPGS.pdf).

**Statistical Analysis**

**Selection Differences**

Because selection bias may influence outcomes, we used balancing score methods developed for producing what might be termed pseudo-randomized comparisons.5,6 For this, we first characterized differences in preoperative characteristics of patients having the second ITA used to bypass either the Cx or RCA system and then used this information to adjust assessment of outcomes. Multivariable logistic regression was used to identify factors associated with placing the second ITA to the RCA. Initially, variables were selected (Supplemental Appendix) using bootstrap aggregation (bagging) with automated analysis of 1000 resampled data sets and a criterion of $P \leq 0.05$ for variable retention.7 Factors appearing in $\geq 50\%$ of the models (median rule) were retained to create a final parsimonious model. The percentage of times each variable appeared in these bootstrap models is represented as “reliability,” specifically, the reliability that $P \leq 0.05$. This parsimonious model was then augmented into a saturated propensity model by including patient characteristics that were not statistically significantly different between groups, but represented demographic, cardiac, and noncardiac comorbidities.5,6 From this, a propensity score was calculated for each patient and incorporated into analyses of outcome.8

**Time-Related Mortality**

Survival after coronary artery bypass grafting was estimated non-parametrically using the Kaplan-Meier method9 and parametrically using the Cox proportional hazards model10 (SAS 9.2; SAS Institute, Cary, NC). All analyses were performed using SAS 9.2.

**Table 1. Patient Characteristics Stratified by Second ITA Group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cx (n=2926)</th>
<th>RCA (n=685)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>2926</td>
<td>685</td>
</tr>
<tr>
<td>Female</td>
<td>2926</td>
<td>685</td>
</tr>
<tr>
<td>Preoperative New York Heart Association class</td>
<td>2926</td>
<td>684</td>
</tr>
<tr>
<td>I</td>
<td>611 (21)</td>
<td>162 (24)</td>
</tr>
<tr>
<td>II</td>
<td>1373 (47)</td>
<td>298 (44)</td>
</tr>
<tr>
<td>III</td>
<td>261 (8.9)</td>
<td>65 (9.5)</td>
</tr>
<tr>
<td>IV</td>
<td>681 (23)</td>
<td>159 (23)</td>
</tr>
<tr>
<td>Cardiac comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>2920</td>
<td>682</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2926</td>
<td>685</td>
</tr>
<tr>
<td>Maximum RCA system stenosis, %</td>
<td>2926</td>
<td>685</td>
</tr>
<tr>
<td>&lt;70</td>
<td>369 (13)</td>
<td>104 (15)</td>
</tr>
<tr>
<td>70–90</td>
<td>1037 (35)</td>
<td>375 (55)</td>
</tr>
<tr>
<td>&gt;90</td>
<td>1520 (52)</td>
<td>206 (30)</td>
</tr>
<tr>
<td>RCA segment stenosis ≥50%</td>
<td>2926</td>
<td>685</td>
</tr>
<tr>
<td>Middle RCA</td>
<td>1057 (36)</td>
<td>272 (40)</td>
</tr>
<tr>
<td>Distal RCA</td>
<td>534 (18)</td>
<td>99 (14)</td>
</tr>
<tr>
<td>Right posterior descending</td>
<td>497 (17)</td>
<td>70 (10)</td>
</tr>
<tr>
<td>Posterolateral segment</td>
<td>310 (11)</td>
<td>54 (7.9)</td>
</tr>
<tr>
<td>Maximum Cx system stenosis, %</td>
<td>2926</td>
<td>685</td>
</tr>
<tr>
<td>&lt;70</td>
<td>555 (19)</td>
<td>171 (25)</td>
</tr>
<tr>
<td>70–90</td>
<td>1445 (49)</td>
<td>268 (39)</td>
</tr>
<tr>
<td>&gt;90</td>
<td>924 (32)</td>
<td>246 (36)</td>
</tr>
<tr>
<td>Noncardiac comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>2828</td>
<td>656</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2756</td>
<td>641</td>
</tr>
<tr>
<td>Treated diabetes</td>
<td>2751</td>
<td>642</td>
</tr>
<tr>
<td>Stroke</td>
<td>2926</td>
<td>685</td>
</tr>
<tr>
<td>Preoperative creatinine, mg/dL</td>
<td>1777</td>
<td>357</td>
</tr>
<tr>
<td>Preoperative cholesterol, mg/dL</td>
<td>2192</td>
<td>532</td>
</tr>
<tr>
<td>Preoperative HDL cholesterol, mg/dL</td>
<td>1750</td>
<td>419</td>
</tr>
<tr>
<td>Preoperative LDL cholesterol, mg/dL</td>
<td>1343</td>
<td>277</td>
</tr>
<tr>
<td>Preoperative triglycerides, mg/dL</td>
<td>2016</td>
<td>489</td>
</tr>
</tbody>
</table>

*No. of patients with data available.
MI indicates myocardial infarction; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
using multiphase hazard methodology. The latter involved determining number of hazard phases, appropriate form of equation for each phase, and parameters characterizing distribution of times to death. (For additional details, see www.clevelandclinic.org/heartcenter/hazard).

To adjust for confounding of the comparison of location of second ITA on mortality, multivariable analysis was performed in the hazard function domain using variables listed in the Supplemental Appendix. This method was chosen over more commonly used proportional hazards semiparametric modeling because it is well known that factors influencing risk after coronary artery bypass grafting change over time, resulting in nonproportional hazards. To accomplish this, the method decomposes instantaneous risk of death (hazard function) into up to 3 additive phases, each characterized by a low-order simple equation whose form is determined from the data. Each phase is scaled by its own unique set of risk factors simultaneously identified for all phases. Bootstrap bagging using the median rule was used for this variable selection, including appropriate transformations of continuous and ordinal variables with a criterion for variable selection. The indicator for second ITA to RCA was thereafter forced into each model as was propensity score.

A subgroup analysis was also performed of patients having equal stenosis in both Cx and RCA systems to examine the effect of ITA grafting independent of differing degrees of coronary system stenosis.

**Presentation**

Categorical variables are summarized by frequencies and percentages and continuous variables by means and SDs. To consistently express degree of uncertainty and variation, medians are accompanied by 15th and 85th percentiles, equivalent to $1\text{ SD}$, and survival estimates are enclosed within 68% asymmetrical confidence limits equivalent to $1\text{ SE}$.

**Statement of Author Responsibility**

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

### Table 2. Factors Related to Having Second ITA Grafted to RCA System

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate ± SE</th>
<th>$P$</th>
<th>Reliability, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCA disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum RCA stenosis &gt;90%</td>
<td>−1.12±0.099</td>
<td>&lt;0.0001</td>
<td>100</td>
</tr>
<tr>
<td>Maximum RCA stenosis &lt;70%</td>
<td>−0.36±0.129</td>
<td>0.006</td>
<td>100</td>
</tr>
<tr>
<td>Right distal segment stenosis ≥90%</td>
<td>−0.38±0.123</td>
<td>0.002</td>
<td>84</td>
</tr>
<tr>
<td>Right posterior descending artery stenosis ≥50%</td>
<td>−0.83±0.140</td>
<td>&lt;0.0001</td>
<td>100</td>
</tr>
<tr>
<td><strong>Cx disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum Cx stenosis &lt;70%</td>
<td>0.44±0.113</td>
<td>&lt;0.0001</td>
<td>93</td>
</tr>
<tr>
<td>Maximum Cx stenosis ≥90%</td>
<td>0.42±0.101</td>
<td>&lt;0.0001</td>
<td>93</td>
</tr>
<tr>
<td>Earlier date of operation</td>
<td>−0.029±0.0066</td>
<td>&lt;0.0001</td>
<td>94</td>
</tr>
<tr>
<td>Intercept</td>
<td>−0.404±0.166</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

*Percent of times factor appeared in 1000 bootstrap analyses.

### Table 3. Preoperative Coronary System Stenosis and the Likelihood of Using Second ITA to Graft RCA System

<table>
<thead>
<tr>
<th>RCA Stenosis</th>
<th>Cx Stenosis</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70%</td>
<td>&lt;70%</td>
<td>0.01</td>
</tr>
<tr>
<td>70%–90%</td>
<td>70%–90%</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Figure 1. Temporal trend of grafting second ITA to RCA system. Each closed circle is a yearly proportion and solid line the trend.

Figure 2. Mortality after bilateral ITA grafting. A, Survival. Solid line is parametric estimate enclosed within 68% confidence limits equivalent to $1\text{ SE}$. Symbols at 5-year intervals are Kaplan–Meier estimates for comparison, vertical bars represent 68% confidence limits, and numbers in parentheses represent patients remaining at risk. B, Hazard. Solid line is parametric estimate enclosed within dashed 68% confidence limits.
Table 4. Risk Factors for Death in Patients With Second ITA to RCA (Compared With ITA to Cx)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Coefficient ± SE</th>
<th>Hazard Ratio (68% CL)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early hazard phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITA–RCA</td>
<td>0.27±0.55</td>
<td>1.31 (0.74–2.32)</td>
<td>0.6</td>
</tr>
<tr>
<td>Constant hazard phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITA–RCA</td>
<td>−0.19±0.36</td>
<td>0.83 (0.58–1.17)</td>
<td>0.6</td>
</tr>
<tr>
<td>Late hazard phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITA–RCA</td>
<td>−0.054±0.19</td>
<td>0.95 (0.78–1.14)</td>
<td>0.8</td>
</tr>
<tr>
<td>Adjusted*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early hazard phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITA–RCA</td>
<td>0.113±0.71</td>
<td>1.12 (0.55–2.27)</td>
<td>0.9</td>
</tr>
<tr>
<td>Constant hazard phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITA–RCA</td>
<td>−0.092±0.32</td>
<td>0.91 (0.66–1.26)</td>
<td>0.8</td>
</tr>
<tr>
<td>Late hazard phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITA–RCA</td>
<td>−0.084±0.16</td>
<td>0.92 (0.78–1.08)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*Analysis adjusted for age, native vessel stenosis, left ventricular dysfunction, comorbidities, and propensity score. CL indicates confidence limits.

Results

Preoperative Group Differences

Preoperative characteristics of patients with the second ITA graft to either the Cx or RCA system were similar except for distribution and degree of coronary artery stenosis in the Cx and RCA systems (Table 1). For both Cx and RCA, the probability of second ITA grafting was highest when stenosis was in the 70% to 90% range and decreased for <70% and >90% stenosis. RCA stenosis <70% and distal RCA disease were associated with grafting the second ITA to the Cx; Cx stenosis <70% was associated with grafting it to the RCA (Table 2). Severe (70% to 90%) stenosis of the RCA and Cx was associated with using the ITA to graft to that artery (Table 3), but >90% stenosis or occlusion was associated with using the ITA to graft the opposite artery. Greater than 90% Cx stenosis and occlusion were associated with inferior segmental wall motion abnormalities and >90% Cx stenosis and occlusion with lateral segmental wall motion abnormalities (Table 2; \( P < .0001 \)). Multivariable logistic regression analysis also demonstrated that earlier date of operation was associated with grafting the second ITA to the Cx system (Table 2; Figure 1).

Unadjusted Survival

Overall unadjusted estimated survival at 1, 5, 10, 15, and 20 years was 98%, 95%, 86%, 74%, and 59%, respectively (Figure 2A). A 3-phase hazard model was identified (see “Time-Related Mortality” under “Patients and Methods”) consisting of a small early phase lasting approximately 1 month, a constant phase, and then a dominating late phase beginning approximately 5 years after revascularization (Figure 2B).

Unadjusted survival was similar in patients having the second ITA graft to either the Cx or RCA system (Table 4). The 1-, 5-, 10-, 15-, and 20-year unadjusted survival estimates for patients having the second ITA used to bypass the Cx system were 98%, 94%, 86%, 74%, and 59%, respectively, and for those having the second ITA used to bypass the RCA system 98%, 95%, 87%, 76%, and 61%, respectively (Figure 3, \( P [\text{log rank}]=0.4 \)).

For the subgroup of patients with equal stenosis of Cx and RCA systems, unadjusted survival after ITA grafting to either was similar (Table 5; Figure 4).

Adjusted Survival

After risk adjustment, survival between patients with the second ITA graft used to bypass the Cx or RCA system was similar (Table 4), as it was for the subgroup of patients having equal stenosis of Cx and RCA systems (Table 5).

Confounders for mortality included right marginal stenosis >50% during the early phase and greater left ventricular dysfunction, history of peripheral arterial disease, and history of hypertension during the constant phase. Those associated with mortality during the late hazard phase were older age, greater left ventricular dysfunction, a family history of coronary artery disease, greater RCA stenosis, a history of smoking, and medically treated diabetes mellitus.

Hospital Outcomes

Unadjusted hospital outcomes were similar after ITA grafting to either the Cx or RCA system, with hospital mortality of 0.34%
and 0.58%, respectively (Table 6). These outcomes compare favorably with those reported from The Society of Thoracic Surgeons National Database.13

Discussion
Background
One of the greatest achievements in coronary artery bypass surgery is use of ITAs as bypass grafts.14,15 When used to graft the LAD, ITAs have been shown to be better than saphenous veins in prolonging survival and decreasing recurrent angina, myocardial infarction, hospitalization for ischemic events, and coronary reintervention.16,17 These clinical benefits of ITA grafts are due to their better long-term patency compared with saphenous vein grafts.18

Because of the success of single ITA grafting to the LAD, logic dictates that adding a second ITA graft during coronary revascularization should further improve outcomes. We and many others have reported better survival and less reintervention for recurrent ischemia in patients undergoing bilateral versus single ITA grafting.1,2,19-24 However, a few studies have reported similar outcomes for both strategies.25,26

A possible explanation for these different observations is that all bilateral ITA revascularization strategies are not equally effective. In bilateral ITA grafting, one ITA is routinely used to bypass the LAD, and the second may be used to graft either the Cx or RCA system. However, the coronary artery grafted with the second ITA may be important in determining the incremental benefit over single ITA grafting to the LAD. Several studies have suggested that for bilateral ITA grafting to improve long-term outcomes over single ITA-to-LAD grafting, the second ITA should bypass the Cx rather than the RCA system.27-29 To test whether location of the second ITA graft is important in determining outcome, we compared long-term survival of patients undergoing bilateral ITA revascularization with one ITA graft used to bypass the LAD and the second to bypass either the Cx or RCA system.

Principal Findings
Unlike previous reports,27-29 we found that both non–risk-adjusted and extensively risk-adjusted long-term survival was similar for patients undergoing bilateral ITA grafting regardless of whether the second ITA was used to graft the Cx or RCA system in patients independent of degree of coronary system stenosis. Similar to short- and long-term survival, early in-hospital morbidity was also similar between the 2 patient groups, although distribution of hospital stay was different, but with similar median length of stay.

Our findings contrast with those of others. Schmidt and colleagues observed better long-term survival when both ITAs were used to bypass left-sided coronary arteries.27 At 9.6 years, survival was 93% when the second ITA was grafted to the Cx system, but only 70% when grafted to the RCA system (P=0.02). Similarly, Nauheim reported that using the second ITA to graft the RCA system offered no survival advantage over single ITA grafting, and Carrel and Pick have separately reported that using both ITAs to graft left-sided coronaries may increase survival over single ITA revascularization.26,28,29 These observations may reflect the lower patency of ITA grafts when used to bypass the RCA system compared with left-sided coronary arteries. ITA graft patency to the RCA is particularly dependent on degree of proximal coronary artery stenosis or native coronary competitive flow.18,30 ITA grafts to the RCA are less likely than saphe-
nous vein grafts to remain patent if proximal RCA coronary artery stenosis is <70%. Therefore, bilateral ITA revascularization strategies are unlikely to be any more effective than single ITA revascularization strategies when the second ITA is used to graft a RCA with only moderate stenosis.

Our findings of similar survival in patients after bilateral ITA grafting independent of whether the second ITA is used to bypass the RCA or Cx system may be attributable to careful patient selection. The second ITA was used to graft the RCA in fewer than 20% of our bilateral ITA operations. Two important factors used in selecting the RCA as the site for the second ITA were (1) RCA stenosis 70% to 90% with viable myocardium in its distribution; and (2) freedom from distal RCA stenosis (Table 2). These are important observations. We were likely to graft a RCA with an ITA only when the likelihood of the ITA graft remaining patent, and therefore effective, was high.

Limitations
This was a nonrandomized, nonprotocol-driven observational study, so surgeon bias may play an important role in our findings. Although the 2 patient groups were similar in most preoperative characteristics, to adjust for surgeon bias, we used propensity scores in our multivariable models. Important bias related to coronary artery stenosis degree and location. However, these observations may be beneficial in bilateral ITA revascularization strategies.

Conclusions
In bilateral ITA coronary revascularization, when one ITA is used to bypass the LAD and the second to bypass a coronary artery system in which the ITA is likely to remain patent, long-term survival is similar regardless of whether the second ITA is used to graft the RCA or Cx system.

Clinical Inferences
In bilateral ITA grafting, the second ITA should be used to bypass the coronary artery system that will maximize ITA patency and effectiveness. The system grafted should (1) have severe enough proximal stenosis to minimize the effect of native coronary competitive flow on ITA patency; (2) be free of distal stenosis; and (3) have viable myocardium in its distribution.

Source of Support
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Disclosures
None.

References
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