Bilateral internal mammary artery grafting reverses the negative influence of gender on outcomes of coronary artery bypass grafting surgery†

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Abstract

OBJECTIVES: Coronary artery bypass grafting (CABG) has historically demonstrated higher hospital mortality in women compared with men. The influence of gender on long-term outcomes has not been clearly defined.

METHODS: A retrospective analysis of 4584 consecutive CABG patients was conducted: 3647 men (1761 single internal mammary artery, [SIMA]; 1886 bilateral IMA, [BIMA]) and 937 women (608 SIMA and 329 BIMA). Propensity-score analysis and optimal matching algorithms were used to create matched groups for baseline risk factors between men and women (SIMA: 602 men and 602 women; BIMA: 328 men and 328 women). Cross-sectional follow-up (6 weeks to 32.1 years; mean 12.8 years) was 96.7% complete.

RESULTS: Hospital mortality was higher in unmatched female vs male patients (SIMA 36/608; 5.9 vs 72/1761; 4.1%; BIMA 11/329; 3.3 vs 47/1886; 2.5%; P = 0.010). However, in the matched groups the increased hospital mortality for females approached statistical significance in the SIMA but not in the BIMA patients. (SIMA male 21/602, 3.5%; female 35/602, 5.8%; P = 0.055; BIMA male 12/328; 3.7%; female 11/328; 3.4%; P = 0.832). When propensity matched for baseline variables, the female SIMA patients experienced prolonged survival compared with their male counterparts. (male vs female, 20-year survival 17.0 ± 2.0 vs 26.1 ± 2.3%; median 13.7 vs 11.4; P = 0.043.) However, long-term survival between the matched male and the female BIMA patients was comparable (male vs female, 20-year survival 31.3 ± 3.6 vs 30.1 ± 3.6%; median 13.7 vs 13.7; P = 0.790).

CONCLUSIONS: When liberally applied, BIMA grafting ameliorates both the increased perioperative mortality in female patients and the reduced long-term survival of male patients, effectively reversing the negative influence of gender on both short- and long-term outcomes of CABG surgery.

Keywords: Coronary artery bypass grafting • Women • Internal mammary artery • Arterial grafts • Propensity matching

INTRODUCTION

In 1992, Bernadine Healy, the first woman to direct the National Institutes of Health, convened an invitational conference, ‘Cardiovascular Health and Disease in Women’, to address the disparity between the high prevalence and mortality of cardiovascular disease in women and the relatively sparse information and research available for clinical application. Since then, there has been a wealth of knowledge gained regarding the impact of gender on the outcomes of coronary artery bypass grafting (CABG) surgery [1]. The observation that women experience a higher operative mortality compared with men undergoing CABG surgery is well documented, even though considerable controversy continues regarding the specific causes. Data on long-term survival are somewhat less robust and equally indeterminate [2–7].

The beneficial impact of bilateral internal mammary artery (BIMA) grafting on long-term survival in CABG patients is well documented [8]. However, sparse data exist regarding the impact of BIMA grafting on the influence of gender in CABG surgery patients [9, 10]. In fact, review of the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery database reveals that only 2.3% of female patients undergoing isolated CABG surgery from 2002 to 2005 received BIMA grafting (vs 4.7% of men) [11]. On the basis of these findings, we studied the short- and long-term impact of single internal mammary artery (SIMA) vs BIMA grafting on gender-related outcomes in a large cohort of patients, followed over a 30-year period, in which BIMA grafting was broadly applied.

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PATIENTS AND METHODS

Patient population
From February of 1972 through May of 1994, 4584 consecutive patients underwent isolated multivessel CABG, of whom 3646 (79.6%) were men and 937 (20.4%) women. Among the men, 1886 (51.7%) received BIMA and 1761 (48.3%) received SIMA grafts. In women, 329 (35.1%) received BIMA and 608 (64.9%) received SIMA grafts (P < 0.001). Excluded from this study were patients with concomitant procedures, those with only one distal anastomosis and patients who received only saphenous vein grafts (6.7% of the total isolated CABG population). This study was presented to the Institutional Review Board and a waiver of the requirement for informed patient consent was granted on the basis of its retrospective nature.

The coronary and perioperative risk factors as well as preoperative angiographic findings for male and female patients are summarized in Table 1. As can be seen, a number of risk factors are significantly different. In order to account for differences in patient risk factors between groups, propensity-score matching was performed to create comparable study groups.

Operative data
Details of the operative technique used in the present series, including internal mammary artery (IMA) mobilization, orientation and reconstruction in BIMA grafting have been previously discussed [12]. The IMA was dissected as an isolated vessel from the chest wall free from surrounding muscle and fascia. The vein was initially dissected but subsequently removed to allow maximal length and versatility. All side branches were cauterized carefully or clipped as necessary. Since 1989, combined antegrade and retrograde infusion methods of cardioplegia were implemented to enhance myocardial protection during the operation. Cardiopulmonary bypass was used in all operations. The left IMA, either as a sequential or as isolated graft was preferentially anastomosed to the left anterior descending coronary artery. The right IMA was used for grafting either the right or the left system, as previously discussed in detail [12].

Data sources
Perioperative data were entered prospectively in a standardized manner into a clinical database, according to the guidelines of the STS Adult Cardiac Surgery database. Follow-up information was obtained through comprehensive questionnaires and by telephone interview with surviving patients, family members or the patient’s personal physician and entered into the follow-up component of the database. Follow-up was 98.3% complete in the SIMA and 96.7% in the BIMA group. Similarly, a 97.5% follow-up was achieved in the male group, and 97.8% in the female group.

Statistical analysis
Demographic and clinical data are presented as frequency distributions and simple percentages. Values of continuous variables are expressed as mean ± standard deviation. Univariate analysis of selected preoperative and postoperative discrete variables was accomplished by χ² with the appropriate degrees of freedom or a Fisher’s exact test to discern the equality of proportions in the case of categorical variables. Two-sample t-tests were used to test for the equality of the means of continuous variables.

To control for baseline differences between treatment groups, a propensity score was generated from a multivariable logistic regression model based on 16 preoperative covariates as independent variables with treatment type (SIMA vs BIMA) used as a binary dependent variable for male and female cohorts. (see Supplementary Table 1 for list of variables used to generate the model).

The propensity score in the male cohort represented the probability that a patient underwent BIMA grafting in CABG. On the basis of the propensity score generated from the logistic regression, BIMA patients were then matched to SIMA patients in a 1:1 ratio using a Rosenbaum optimal matching algorithm [13]. This approach minimized the overall distance between observations and was conducted using Mahalanobis distance within propensity-score calipers (no matches outside the calipers). A similar approach was used to generate a propensity score for female patients. In addition, using the same baseline variables, propensity-score analysis with gender (male vs female) used as a binary dependent variable was used to create matched groups of male and female patients in both the SIMA and the BIMA cohorts. Following propensity-score matching, there were no significant differences in any of the covariates between matched groups for any of the preoperative risk factors.

To identify predictors of hospital mortality, a multivariable logistic regression model was developed using preoperative and intraoperative variables. An initial multivariable logistic regression was performed using 19 covariates. (see Supplementary Table 2 for variables used to predict hospital mortality). The final multivariate logistic regression included three covariates. Cox proportional hazards regression model using 21 covariates was performed to discern the influence of multiple perioperative clinical variables on late survival in unmatched male and female patients. Regression coefficients and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to determine the relative influence of each covariate on the survivor function. Coefficients were computed by the method of maximum likelihood (see Supplementary Table 3 for the list of variables used in the Cox regression model).

Actuarial survival estimates (including operative deaths) were calculated according to the method of Kaplan and Meier using time zero as the date of operation and late death as the endpoint. The equality of survival distribution was tested with the log-rank algorithm. All P-values reported are two-sided and are not adjusted for multiple testing. A significant difference between measurements was defined as P ≤ 0.050. All analyses were performed using the Number Cruncher Statistical Systems software (NCSS, Kaysville, UT, USA).

RESULTS

Hospital morbidity
The overall incidence of postoperative morbidity was low. No complications were experienced in 84.2% (3072/3647) of unmatched male patients or in 81.9% (767/937) of female patients (P = 0.079). In matched male SIMA and BIMA patients, the SIMA
patients. However, in unmatched female patients, a significant difference in sternal wound infection was observed (OR 0.6; 95% CI 0.4–0.8; P < 0.001). In addition, in matched male patients, the following six variables were associated with hospital mortality: age at operation (OR 1.1; 95% CI 1.0–1.1, P < 0.001), congestive heart failure (OR 3.0; 95% CI 1.7–5.2, P < 0.001), distal grafts (OR 0.6; 95% CI 0.4–0.8, P < 0.001), perfusion time (OR 1.0; 95% CI 1.0–1.0, P < 0.001), smoking history (OR 2.2; 95% CI 1.2–4.0, P = 0.009) and nonelective surgery (OR 2.3; 95% CI 1.3–3.9, P = 0.002).

Table 1: Comparison of preoperative variables and risk factors for unmatched single internal mammary artery and bilateral internal mammary artery grafting by gender

<table>
<thead>
<tr>
<th>Variable</th>
<th>Single internal mammary artery patients</th>
<th>Bilateral internal mammary artery patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (P-value)</td>
<td>Female (P-value)</td>
</tr>
<tr>
<td>No. of patients</td>
<td>1761 (100.0)</td>
<td>608 (100.0)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>66.6 ± 9.7 &lt; 0.001</td>
<td>70.2 ± 8.2</td>
</tr>
<tr>
<td>Age groups (year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>98 (5.6)</td>
<td>11 (1.8)</td>
</tr>
<tr>
<td>50–59</td>
<td>290 (16.5)</td>
<td>49 (8.1)</td>
</tr>
<tr>
<td>60–69</td>
<td>638 (36.2)</td>
<td>199 (32.7)</td>
</tr>
<tr>
<td>≥80</td>
<td>104 (5.9)</td>
<td>100 (100.0)</td>
</tr>
<tr>
<td>Preoperative coronary risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>891 (50.6)</td>
<td>306 (50.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>613 (34.8)</td>
<td>260 (42.8) &lt; 0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>229 (13.6)</td>
<td>111 (18.3) 0.005</td>
</tr>
<tr>
<td>Smoking history</td>
<td>1109 (63.0)</td>
<td>251 (41.3) &lt; 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>195 (32.1)</td>
<td>451 (25.6) 0.002</td>
</tr>
<tr>
<td>Perioperative risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>90 (5.1)</td>
<td>16 (2.6) 0.011</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>101 (5.7)</td>
<td>42 (6.9) 0.295</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>101 (5.7)</td>
<td>37 (6.1) 0.751</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>1055 (59.9)</td>
<td>314 (51.6) &lt; 0.001</td>
</tr>
<tr>
<td>History of chronic heart failure</td>
<td>239 (13.6)</td>
<td>105 (17.3) 0.026</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1161 (65.9)</td>
<td>475 (78.1) &lt; 0.001</td>
</tr>
<tr>
<td>Preoperative coronary angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>1473 (83.6)</td>
<td>478 (78.6) 0.005</td>
</tr>
<tr>
<td>Impaired ejection fraction (&lt;50)</td>
<td>644 (37.1)</td>
<td>158 (26.2) &lt; 0.001</td>
</tr>
</tbody>
</table>

*Numbers in parentheses are percentages. SD: standard deviation; CAD: coronary artery disease.

Hospital mortality

Hospital mortality rate was defined as death that occurred during the operation or the hospitalization in which the procedure was performed or after discharge from the hospital but within 30 days of the surgical procedure, unless the cause was unrelated to the operation. Hospital mortality was increased in unmatched women vs men: SIMA, 36/608 (5.9%) vs 72/1761 (4.1%), P = 0.062; BIMA, 11/329 (3.3%) vs 47/1886 (2.5%), P = 0.793; total 47/937 (5.0%) vs 119/3647 (3.3%), P = 0.010.

Multivariable logistic regression in unmatched males confirmed four variables associated with increased risk in hospital mortality: age at operation (OR 1.1; 95% CI 1.0–1.1, P < 0.001), smoking history (OR 1.7; 95% CI 1.1–2.7, P = 0.012), distal grafts (OR 0.6, 95% CI 0.5–0.8, P < 0.001) and perfusion time (OR 1.0, 95% CI 1.0–1.0, P < 0.001). In addition, in matched male patients, the following six variables were associated with hospital mortality: age at operation (OR 1.1; 95% CI 1.0–1.1, P < 0.001), congestive heart failure (OR 3.0; 95% CI 1.7–5.2, P < 0.001), distal grafts (OR 0.6; 95% CI 0.4–0.8, P < 0.001), perfusion time (OR 1.0; 95% CI 1.0–1.0, P < 0.001), smoking history (OR 2.2; 95% CI 1.2–4.0, P = 0.009) and nonelective surgery (OR 2.3; 95% CI 1.3–3.9, P = 0.002).

In unmatched female patients, three preoperative and intraoperative variables were found to be associated with hospital mortality. These include age at operation (OR 1.1; 95% CI 1.0–1.1, P = 0.014), impaired ejection fraction (OR 2.4; 95% CI 1.3–4.5, P = 0.008) and perfusion time (OR 1.0; 95% CI 1.0–1.0, P < 0.001). In matched female patients, two preoperative and intraoperative variables were associated with hospital mortality. These include perfusion time (OR 1.0; 95% CI 1.0–1.0, P < 0.001) and prior myocardial infarction (OR 2.7; 95% CI 1.1–6.8, P = 0.027).

In none of the multivariable logistic regression analyses was choice of conduit (SIMA vs BIMA) associated with hospital mortality in either matched or unmatched men or women. However, when male and female patients were propensity matched for preoperative variables, the increased hospital mortality for women approached statistical significance in the SIMA but not in the BIMA patients: SIMA men 21/602 (3.5%) vs women 35/602 (5.8%), P = 0.055; BIMA men 12/328 (3.7%) vs women 11/328 (3.4%), P = 0.832. Therefore, among comparable groups of patients, when comparing SIMA with BIMA grafting, it appears that BIMA grafting tends to reduce the impact of female gender on perioperative mortality.
Long-term follow-up

The average duration of follow-up for hospital survivors was 12.1 years (range, 6 weeks to 32.1 years) in the male group, and 11.3 years (range 6 weeks to 31.1 years) in the female group. Cumulative patient follow-up was 42527.0 patient-years in male patients, and 10041.2 patient-years in female patients.

To identify independent predictors of late death, a Cox proportional hazards regression model was created to measure the effects of various prognostic factors on time-to-response (operation to late death). Among the unmatched SIMA and BIMA males, there were 14 covariates associated with late mortality: nine preoperative, two intraoperative and three postoperative variables (Table 4). Choice of conduit (SIMA vs BIMA) was identified as a predictor of late mortality among males. In the unmatched female group, there were 10 covariates associated with late mortality, five reoperative, one intraoperative and four postoperative (Table 5). Choice of conduit (SIMA vs BIMA) was not associated with late mortality among female patients.

The actuarial survival data for unmatched SIMA and BIMA male patients are shown in Fig. 1A. The median survival for SIMA was 11.3 years (95% CI, 10.8–11.9) compared with 16.6 years (95% CI, 15.8–17.5) for BIMA patients. The equality of survival distribution for the two unmatched male patient groups demonstrated a significant difference (P < 0.001).

In the propensity-matched male groups (Fig. 1B), the median survival for SIMA patients was 14.2 years (95% CI, 13.2–15.2) compared with 15.8 years (95% CI, 15.0–16.8) for BIMA patients. The equality of survival distribution for these two groups of male patients demonstrated a significant difference (P < 0.001). These results provide further evidence of the survival benefits achieved in male patients with BIMA grafting.

In female patients, the median survival for unmatched SIMA patients was 11.3 years (CI, 10.6–12.3) while that for unmatched BIMA patients was 13.9 years (CI, 12.8–14.7) (Fig. 2A). The equality of survival distribution for the two unmatched female groups demonstrated a significant difference (P = 0.004). In propensity-matched female groups (Fig. 2B), however, the median survival
was liberally applied, the use of BIMA grafting appeared to
that of female patients. Male BIMA patients did appear to achieve longevity equal to
that of female patients. However, when propensity matched,
median survival was 13.7 years (95% CI, 12.8–14.7) for male
patients, median survival was 11.4 years (95% CI, 10.6–12.4) (Fig. 3A) for
female patients. The equality of survival distribution for matched
male and female patients demonstrated a significant difference
(P = 0.043). On the other hand, among the BIMA patients,
median survival was 13.7 years (95% CI, 12.5–14.5) for male
patients and 13.7 years (95% CI, 12.8–14.7) for female patients,
with no significant difference in survival distribution (P = 0.790)
(Fig. 3B). Therefore, when matched for preoperative variables,
male SIMA patients did not appear to achieve longevity equal to
that of female patients. However, when propensity matched,
BIMA patients did appear to achieve longevity equal to
that of female patients.

Table 4: Multivariate analysis of demographic and
perioperative clinical variables influencing late mortality
by Cox regression analysis for unmatched single internal
mammary artery and bilateral internal mammary artery
male patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>β-estimate</th>
<th>SE</th>
<th>HR (95% CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at operation</td>
<td>0.0642</td>
<td>0.0027</td>
<td>1.1 (1.1–1.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.4623</td>
<td>0.0680</td>
<td>1.6 (1.4–1.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0.3045</td>
<td>0.1029</td>
<td>1.4 (1.1–1.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.4548</td>
<td>0.0516</td>
<td>1.6 (1.4–1.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Impaired ejection fraction</td>
<td>0.2629</td>
<td>0.0496</td>
<td>1.3 (1.2–1.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.2085</td>
<td>0.0481</td>
<td>1.2 (1.1–1.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>0.4344</td>
<td>0.0941</td>
<td>1.5 (1.3–1.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Renal disease</td>
<td>0.3263</td>
<td>0.1019</td>
<td>1.4 (1.1–1.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Nonelective surgery</td>
<td>0.1288</td>
<td>0.0461</td>
<td>1.1 (1.0–1.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Intraoperative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIMA used</td>
<td>-0.2439</td>
<td>0.0469</td>
<td>0.8 (0.7–0.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Perfusion time</td>
<td>0.0023</td>
<td>0.0006</td>
<td>1.0 (1.0–1.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Postoperative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>0.4487</td>
<td>0.1556</td>
<td>1.6 (1.1–2.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.2888</td>
<td>0.0991</td>
<td>1.3 (1.1–1.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>Pulmonary insufficiency</td>
<td>0.3458</td>
<td>0.0994</td>
<td>1.4 (1.2–1.7)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Only significant variables (P < 0.050) are listed.
SE: standard error; HR: hazard ratio; CI: confidence interval; SIMA:
single internal mammary artery.

for SIMA patients was 14.0 years (95% CI, 12.8–15.4) and that for
BIMA patients was 13.7 (95% CI, 12.8–14.7), with no significant
difference in survival distribution (P = 0.571). Therefore, BIMA
grafting appears to confer an incremental survival benefit relative
to SIMA grafting in men but not in women.

In order to further define the impact of gender on survival in
CABG patients relative to the surgical grafting strategy applied,
we compared the actuarial survival of propensity-matched male
and female patients on preoperative variables. Among SIMA
patients, median survival was 10.4 years (95% CI, 9.7–11.4) for
male patients and 11.4 years (95% CI, 10.6–12.4) (Fig. 3A) for
female patients. The equality of survival distribution for matched
male and female patients demonstrated a significant difference
(P = 0.043). On the other hand, among the BIMA patients,
median survival was 13.7 years (95% CI, 12.5–14.5) for male
patients and 13.7 years (95% CI, 12.8–14.7) for female patients,
with no significant difference in survival distribution (P = 0.790)
(Fig. 3B). Therefore, when matched for preoperative variables,
male SIMA patients did not appear to achieve longevity equal to
that of female patients. However, when propensity matched,
BIMA patients did appear to achieve longevity equal to
that of female patients.

In summary, in this cohort of patients in which BIMA grafting
was liberally applied, the use of BIMA grafting appeared to
diminish the relative disadvantage that women have in hospital
mortality, while eliminating the relative disadvantage that men
have in long-term survival.

DISCUSSION

Heart disease is the leading killer of women in this country,
accounting for more deaths than the next three leading causes
combined. Since 1984, more women than men die of cardiovascular
disease every year. It is, therefore, somewhat curious that the
universal experience with CABG surgery demonstrates a preponderance
of male patients. In 2009, only 27.3% of isolated CABG
operations recorded in the STS Adult Cardiac Surgery database
were performed on women. [http://www.sts.org/sites/default/files/
documents/pdf/ndb2010/Isolated_CAB_Data_Summary_92
pdf (30 August 2012, date last accessed)]

Extensive epidemiological, physiological and basic science re-
search has identified numerous factors that distinguish women
from men in the development and manifestation of ischaemic
heart disease [14]. Unfortunately, identification of pertinent
factors that link this information to optimal revascularization
strategies that specifically address these differences has not yet
been reported. As a result, the weight of empirical evidence
must drive clinical decision-making. The controversy that persists
in the literature regarding risk factor vs gender as an explanation
for increased perioperative mortality in women remains
unresolved.

Review of large multicenter databases weigh in on both sides
of the issue [15, 16]. Even sophisticated propensity-score match-
ing models in various large surgical experiences arrive at

Table 5: Multivariate analysis of demographic and
perioperative clinical variables influencing late mortality
by Cox regression analysis for unmatched single internal
mammary artery and bilateral internal mammary artery
female patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>β-estimate</th>
<th>SE</th>
<th>HR (95% CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at operation</td>
<td>0.0612</td>
<td>0.0058</td>
<td>1.1 (1.1–1.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0.4739</td>
<td>0.1623</td>
<td>1.6 (1.2–2.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Impaired ejection fraction</td>
<td>0.4208</td>
<td>0.0947</td>
<td>1.5 (1.3–1.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>0.4094</td>
<td>0.1194</td>
<td>1.5 (1.2–1.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Renal disease</td>
<td>0.6208</td>
<td>0.2593</td>
<td>1.9 (1.1–3.1)</td>
<td>0.028</td>
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<td>Intraoperative</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Perfusion time</td>
<td>0.0024</td>
<td>0.0008</td>
<td>1.0 (1.0–1.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Postoperative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>1.3182</td>
<td>0.2169</td>
<td>3.7 (2.4–5.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.8868</td>
<td>0.2752</td>
<td>2.4 (1.4–4.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>0.9912</td>
<td>0.2034</td>
<td>2.7 (1.8–4.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.6485</td>
<td>0.1622</td>
<td>1.9 (1.4–2.6)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Only significant variables (P < 0.050) are listed.
SE: standard error; HR: hazard ratio; CI: confidence interval; SIMA:
single internal mammary artery.
conflicting conclusions [17, 18]. Both STS and EuroSCORE II include gender in their risk models. However, neither accounts for such factors in the risk model as the use of the IMA, preoperative haematocrit, coronary artery size or other factors that may directly influence outcome. Numerous authors have emphasized the importance of IMA grafting in reducing CABG mortality in women [19], although not all have concurred with its importance [15]. Nonetheless, the current STS guidelines for CABG surgery in women include use of a single IMA as a Class I indication. The issue of a second IMA graft is, however, not addressed.

It is certainly reasonable to carefully explore the incremental benefit of a second IMA graft in women. Women have been documented to have smaller calibre of coronary arteries, even independent of body surface area [20]. Saphenous vein graft patency is lower but IMA graft patency is equivalent in women compared with men [21]. Women have an increased tendency for thrombosis [22] which may impact long-term graft patency. Microvascular disease is more clinically prominent in women, and the IMA graft has been shown to supply distal circulation with enhanced NO [23]. Nonetheless, studies demonstrating the long-term survival benefit of BIMA grafting have been predominantly comprised of male patients.

From the wealth of data currently available regarding the impact of gender on the outcomes of CABG surgery, two trends emerge: first, women have increased perioperative mortality, and secondly, women tend to outlive men [4–7]. Even the CASS data reported improved long-term survival for older women—a population more clearly reflective of current surgical experience [3]. Perhaps the latter phenomenon relates to the fact that women in America live 5 years longer than men, although the exact reason(s) for this phenomenon and how it relates to cardiovascular disease and surgical mortality is still somewhat obscure.

Nonetheless, the key findings of the current analysis are 2-fold: first, use of BIMA grafting appears to reverse the tendency for increased perioperative mortality in women, and secondly, BIMA grafting tends to reverse the diminished long-term survival in men. In short, BIMA grafting appears to ‘level the playing field’ and reverse the impact of gender on short- and long-term mortality. Whether these findings are due to enhanced graft patency, improved downstream microvascular

Figure 1: (A) Survival analysis of single internal mammary artery (SIMA) vs bilateral internal mammary artery (BIMA) in unmatched male patients. (B) Survival analysis of single internal mammary artery (SIMA) vs bilateral internal mammary artery (BIMA) in matched male patients.
and endothelial function, better accommodation to flow demand or some other constellation of these and other phenomena is purely speculative at present. Unfortunately, our data do not include information regarding coronary artery size, fractional flow reserve or graft patency. At the very least, these observations are sufficiently provocative to warrant exploration with larger databases incorporating multiple sites and greater patient experience.

Although we were able to demonstrate that BIMA grafting can be accomplished in both men and women without an increased incidence of sternal wound infection or other postoperative complications, the finding of an increased rate of reoperation for bleeding in the SIMA men, both unmatched and matched, was somewhat unexpected. Although early reports suggested increased bleeding with the use of BIMA grafting, this has not been uniformly observed. The number of patients observed makes chance occurrence unlikely. It is not impossible that, even though the propensity-score matching accounted well for critical preoperative variables, it may not have accounted well for those specifically associated with bleeding. For example, preoperative haemoglobin levels, coagulation parameters and the number of blood products transfused were not values available in our database, and, given the general proclivity for the SIMA group to represent a sicker group of patients, these unmeasured factors may have accounted for the differences observed. In any event, it is important to note that, even when broadly applied to over half of the male population, there does not appear to be any measureable increased morbidity that results from the use of BIMA grafting.

It is interesting that in this study, in patients appropriately matched for preoperative risk factors, the incremental benefit of BIMA grafting did not result in an improved long-term survival over SIMA grafting in women. Although consistent with our previous report [12], the current study involves a larger patient cohort, followed for a longer period of time and matched with more sophisticated techniques. Although this represents the largest experience in the current literature which specifically addresses long-term survival of BIMA grafting in women, it may be that 329 patients—compared with the male cohorts of more than 1000 patients—is just not sufficient to demonstrate a survival advantage (Type II error).

Figure 2: (A) Survival analysis of single internal mammary artery (SIMA) vs bilateral internal mammary artery (BIMA) in unmatched female patients. (B) Survival analysis of single internal mammary artery (SIMA) vs bilateral internal mammary artery (BIMA) in matched female patients.
It is also notable that BIMA grafting in this surgical experience was considerably less frequent in female than in male patients (35.1% vs 51.7%); perhaps those patients not receiving BIMA grafting in women may have been more likely to receive an enhanced survival benefit. It is also possible that given the known relative discrepancy between symptoms and the extent of coronary artery disease manifested in women vs men, and the greater proclivity of women for an acute manifestation of disease, revascularization in the acute phase may be more predictive of long-term outcome in women than in men. It is also not unlikely that whatever factors determine a long-term survival benefit for women in general may be more powerful predictors of long-term survival than the incremental benefit derived from a second IMA graft in the female population.

Limitations of the study

Although stimulating, this study is not without limitations. As a retrospective investigation, it is certainly prone to bias in patient selection and procedures—a factor that may be only partially accountable for, even given the most refined statistical techniques. Efforts to correct for baseline differences in risk are capable of addressing only available data and may therefore overlook important but unrecognized clinical factors.

Secondly, this study represents a historical surgical experience. The benefit of this approach is that it permits a very long-term follow-up. The conundrum of longitudinal studies is that in order to truly understand the impact of a major therapeutic intervention such as CABG surgery, one must follow patients for long enough to observe what occurs over time. However, by the time such information becomes readily available, surgical techniques and patient care may have dramatically changed. Whether or not we would arrive at the same conclusions in the modern era of off-pump bypass surgery, blood conservation, glucose control, ‘fast-track’ intensivist care and considerably lower surgical mortality requires further study from a more contemporary surgical experience. A recent report has confirmed the long-term survival benefits of BIMA grafting; however, it involved an 89.0% male population [24].

Thirdly, how to interpret the results herein in the current medical milieu of statins, modern antiplatelet therapy and more aggressive and informed risk factor control is not clearly known. Despite these limitations, given the clear beneficial impact that
BIMA grafting appears to have on ameliorating the short- and long-term negative impact of gender on outcomes of CABG surgery, it seems clear that the evidence justifies an expanded role for BIMA grafting in both men and women.

CONCLUSION

That data presented herein support the conclusion that when liberally applied, BIMA grafting ameliorates both the increased perioperative mortality in female patients and the reduced long-term survival of male patients, effectively reversing the negative influence of gender on both short- and long-term outcomes of CABG.

SUPPLEMENTARY MATERIAL

Supplementary material is available at EJCTS online.

ACKNOWLEDGEMENT

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Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr V. Mendes (Solingen, Germany): Your presentation reports impressive research with a large cohort of patients, 4,500 or more, over a long follow-up period of over 30 years. Your investigations underline the benefit of BIMA versus SIMA in both male and female patients. And we have heard a lot about BIMA here during our meeting and probably by now all of us are convinced that BIMA is the future in most CABB patients. In our institution in Wuppertal, we treat 85% of cases with bilateral mammarys using the skeletonized technique and we see very few patients who come back for reoperation after having had BIMA at the first operation.

I also would like to underline one issue which could possibly cause problems for women and, that is vessel mismatch; you mentioned that in your paper as well.
I have two questions. In your study, female patients in the matched group did much better when having bilateral mammarys but, on the other hand, the male patients did not. In fact, they did a little bit worse while having BIMA instead of single mammarys. And I am a bit disappointed about this finding and I would like to ask you to please explain this to us.

And my second question is, how are these results going to change your practice and what are your thoughts on bilateral or total arterial grafting using bilateral mammarys to supply the left coronary system in a no-touch aortic technique, and possibly applying the off-pump technique in order to achieve even better outcome for both male and female patients?

Dr. Kurlansky: First, as regards perioperative mortality, the difference between SIMA and BIMA was not significant in the male patients. But the conundrum of doing research in something like heart surgery and trying to figure out the impact that it’s going to have on patients is that you really need to follow patients for long enough in order to see what you’ve done. As regards the incremental benefit of SIMA grafting, we show that the curves don’t really start to diverge until five years. In our data we see a difference a little bit earlier than the Cleveland Clinic, but you really need about 10 years’ follow-up to start to see a significant difference. The problem is that by the time you have that information, everything has already changed. Anaesthetic techniques are different, surgical techniques are different. So you wonder whether it’s still relevant.

The way to rephrase your question might be not ‘why do men do worse’, because they don’t really do worse with BIMA grafting, but ‘why do women appear to do better’ perioperatively when men don’t. And I think the reason for that may be, and this is purely speculative, but you mentioned coronary artery size. Certainly we know that coronary size, even matched for body surface area, is smaller in women. We also know that saphenous vein grafts have less patency in women than they do in men. So perhaps the perioperative revascularization is actually less secure in female patients if they don’t undergo arterial revascularization.

As to how this is going to potentially affect the future, the more recent studies with off-pump surgery—there was no off-pump surgery in this particular study—but more recent studies (Grau from New Jersey, and others) have shown that use of bilateral internal mammary arteries is certainly adaptable to the off-pump technique, and I think it really presents sort of a bright future for cardiac surgeons in a field which has previously seemed very dim.

Dr. Mendes: Do you think using both mammarys for the left coronary system is going to be an advantage for both female and male patients?

Dr. Kurlansky: Well, we didn’t look at it with regard to gender, but we did look at our results right versus left, and we presented this at the Southern Thoracic meeting about two years ago and published in the Annals, and found exactly what the Cleveland Clinic found, much to our surprise, that there was absolutely no difference in short- or long-term mortality or quality of life whether we used the second internal mammary artery for the right system or the left system. I think probably part of that may be technical in that we tended to use the right mammary for the distal right system where perhaps it has a better long-term patency. And we also used a skeletonized approach, which perhaps is why we don’t see an increased incidence of sternal wound infection, but it also permits us to use the internal mammary through the transverse sinus to vascularize the left system, which actually ultimately became our procedure of greatest choice, but we couldn’t demonstrate that it had a long-term impact.

Dr. M. Zembala (Zabrze, Poland): Can you give us advice regarding what type of female patient you would not accept for bilateral revascularization from your large perspective? Please give us your personal surgical opinion.

Dr. Kurlansky: Actually, if you asked this question to Bruce Lytle and most cardiac surgeons, they’ll tell you it’s the very obese diabetic women.

Dr. Zembala: I would like your view.

Dr. Kurlansky: Actually, the one that scares me is the very frail woman. The woman who is sort of perhaps a cardiac cachectic, has a very low body mass index and a very frail sternum, and I think they don’t heal as well and they don’t do as well.

Dr. Zembala: Cachectic as well?

Dr. Kurlansky: Cachectic as well. These would be the ones that really scare me the most.