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Routine use of bilateral internal artery grafting in women does not increase in-hospital mortality and could improve long-term survival

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A B S T R A C T

Background: Bilateral internal thoracic artery (BITA) grafting is underused in women.
Methods: Outcomes of 798 consecutive women with multivessel coronary disease who underwent isolated coronary surgery (1999–2016) using BITA ($n = 530$, 66.4%) or single internal thoracic artery (SITA) grafting ($n = 268$, 33.6%) were reviewed retrospectively. Differences between BITA and SITA cohort were adjusted by propensity score matching. For both series, late survival was estimated with the Kaplan-Meier method.
Results: One-to-one propensity score matching resulted in 247 BITA/SITA pairs with similar baseline characteristics and risk profile. According to the propensity matching, BITA grafting was associated with a trend towards reduced in-hospital mortality (3.2% vs. 5.7%, $p = 0.19$). However, BITA women had an increased chest tube output ($p = 0.0076$) as well as higher rates of any (13% vs. 5.3%, $p = 0.003$) and deep sternal wound infections (9.3% vs. 4.9%, $p = 0.054$), this translating in a longer in-hospital stay (10 vs. 9 days, $p = 0.029$). Test for interaction showed that body mass index >30 kg/m^2 and extracardiac arteriopathy were associated with a higher risk of deep sternal wound infection in BITA than in SITA women (23.4% vs. 13.7%, $p < 0.001$ and 23.9% vs. 3.4%, $p = 0.001$, respectively). Freedom from all-cause death and cardiac or cerebrovascular death were improved in BITA cohort, even though the differences were not quite significant ($p = 0.16$ and 0.076, respectively).
Conclusions: When routinely performed, BITA grafting does not increase in-hospital mortality in women and could improve long-term survival. However, its use should be avoided in obese women with extracardiac arteriopathy because of increased risk of deep sternal wound infection.

1. Introduction

To date there is no conclusive evidence, which should be derived from randomized controlled trials, that supports long-term benefits of bilateral (BITA) versus single internal thoracic artery (SITA) grafting for coronary surgery patients. Actually, the interim analysis of clinical and safety outcomes of the ongoing Arterial Revascularization Trial has failed to show any superiority of BITA grafting at five years of follow-up, being significantly increased instead the risk of sternal wound infection (SWI) [1]. However, pooled analyses of observational studies suggest that, at 10 years, there are approximately 20% fewer deaths from any cause with BITA than with SITA grafting [2–7]. In most of these studies, BITA grafting is adopted for low-risk selected patients. In almost all of these studies, BITA grafting is underused in women because of concerns about increased risk of postoperative complications, primarily SWI [8–16]. Consequently, outcome of routine use of BITA grafting remains largely unexplored in female gender. This disparity in BITA use by sex should be addressed in the interest of expanding the still hypothetical benefits of BITA grafting to more large number of patients.

In this retrospective investigation, the authors have reviewed whole their experience in coronary surgery using internal thoracic artery (ITA) grafts in women. Early and late outcomes following BITA and SITA grafting were compared in a cohort of women who underwent BITA grafting on a routine basis (50% or more). The aim of the study was to show whether there are benefits that could derive from the extended use of BITA in female gender.

2. Patients and methods

From 1999 throughout 2016, 888 consecutive women with multivessel coronary artery disease underwent isolated coronary bypass surgery at the Cardio-Thoracic and Vascular Department of the University Hospital of Trieste, Italy. Their baseline characteristics, operative data and postoperative complications were prospectively recorded in a computerized database (FileMaker Pro 15; FileMaker Inc., Santa Clara, CA, USA). Radial artery and saphenous vein grafts (SVGs) alone were used in 39 and 51 patients, respectively, who were all ruled out from this study. Consequently, the present analysis involved a total

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of 798 women who underwent BITA grafting ($n = 530$, 66.4%), with or without SVGs in addition, or SITA grafting ($n = 268$, 33.6%), plus one or more SVGs.

Unless otherwise stated, the definitions and cut-off values of the preoperative variables were those used for the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) [17]. The risk profile of each patient was established according to EuroSCORE II. The definitions of postoperative complications were in accordance with the internationally agreed definitions of complications after cardiac surgery [18].

To evaluate the suitability of both ITAs to be used as coronary grafts, all patients had undergone bilateral selective angiography of the subclavian artery during preoperative coronary angiography. All diabetic patients were treated during operation, and then in intensive care unit with a continuous intravenous insulin infusion. Prophylactic antibiotics were administered before surgical incision. A first-generation cephalosporin (cefazolin) was usually chosen. Vancomycin was used if there was allergy to β-lactam antibiotics, or in the event of mediastinal re-exploration; in the last case, the addition of an aminoglycoside was considered [11,19–26].

2.1. Surgery

Surgery was carried out via a median sternotomy either with cardiopulmonary bypass, with or without cross-clamping the aorta, or off-pump technique. When a period of myocardial ischaemia was used, myocardial protection was usually achieved with multidose cold blood cardioplegia. However, two crystalloid cardioplegic solutions were adopted as well, the St. Thomas' Hospital solution No. 2 (Plegisol®; Pfizer Inc., New York, NY, USA) [27], which was abandoned in November 2002, and the Custodiol® histidine-tryptophan-ketoglutarate solution (Essential Pharma, Newtown, PA, USA) [28], which was sometimes used from December 2009, especially when long ischemic times were expected. Both blood and crystalloid cardioplegia was delivered in both antegrade and retrograde mode. Off-pump and on-pump beating heart techniques were adopted only in the presence of a diseased (atherosclerotic) ascending aorta, which was demonstrated by epiaortic ultrasonography scan [29].

Both ITAs were harvested as skeletonized conduits with low-intensity bipolar coagulation forceps, extending from the inferior border of the subclavian vein distally to the bifurcation into the superior epigastric and musculophrenic arteries [30]. In BITA cohort, when both ITAs were used as in situ grafts, the right ITA was almost invariably directed to the left anterior descending coronary artery, and the left ITA to the posterolateral cardiac wall. The anteaortic crossover right ITA bypass graft was protected by means of a pedicled flap taken from the thymic remnants [31]. When the two ITAs were used as composite Y-graft, the right ITA was proximally transected and used as a free graft from the in situ left ITA. Very occasionally, the proximal (aortic) end of a SVG was used as take-off for the right ITA free graft. In SITA patients, either the in situ left or (exceptionally) right ITA was directed to the left anterior descending coronary artery. In both groups, additional coronary bypasses were performed with one or more SVGs. The aortic anastomosis of every venous graft was performed during cross-clamping of the ascending aorta in on-pump technique and during aortic side-clamping both in off-pump and on-pump beating heart technique.

Details of the techniques of perioperative management of sternal wounds and of postoperative treatment of SWI have been described in recent publications of the present authors [12,19–26,29,31].

2.2. Criteria of choice of BITA grafting

Criteria of choice of BITA (vs. SITA) grafting did not change significantly during the study period. Generally, all patients with multivessel coronary disease who required left-sided coronary revascularization were potential candidates for BITA grafting. The sole exceptions were: (1) the rare cases in which one or both ITAs were unsuitable as coronary grafts, (2) when there was an unexpected operative finding of severe cardiac dysfunction, or (3) when a rapid worsening of haemodynamics due to ischaemia required immediate institution of cardiopulmonary bypass, even though there have been some (exceptional) cases where a second ITA graft was harvested during cardiopulmonary bypass [12,19–26]. According to our institutional policy, in the presence of significantly stenotic (>50%) or even occluded subclavian artery, the corresponding ITA was not a priori rejected. It was harvested anyway and, if the flow was good, proximally transected and used as a free graft. In the case of a subclavian artery stenosis of 50% or lesser, the corresponding ITA was used as in situ, non-composite graft for one-single anastomosis with a coronary vessel other than the left anterior descending coronary artery.

2.3. Follow-up

An up-to-date clinical follow-up was obtained by a telephonic interview with the patients or their family. Post-discharge surveillance of the surgical wounds was performed for every patient in a specifically dedicated surgical outpatient clinic. The occurrence of at least one postoperative major adverse cardiac or cerebrovascular event (MACCE) – defined as any of the following complications from surgery to follow-up: cardiac death, recurrent angina, myocardial infarction, congestive heart failure needing hospital readmission, percutaneous coronary intervention, repeat operation, pulmonary embolism and cerebrovascular accidents – was recorded. For this study, follow-up was closed on September 30, 2017.

Approval to conduct the study was acquired from the hospital ethics committee based on retrospective data retrieval; the need for patients to provide individual written consent was waived.

2.4. Statistical methods

Continuous variables with normal distribution were expressed as mean ± standard deviation and those without normal distribution as median and the range between the first and the third quartiles. Discrete variables were expressed as frequencies and percentages. Statistical comparison of baseline patient characteristics, operative data and postoperative complications was performed using the Chi-square or the Fisher's exact test for categorical variables, and the Student's *t*-test or the Mann-Whitney *U* test for continuous variables. Independent predictors of all-cause death, cardiac or cerebrovascular death, and MACCEs during the follow-up period were found with the Cox proportional-hazards regression analysis. Study patients were divided in two cohorts according to the use of one or both ITAs. Since the study groups significantly differed in a number of preoperative characteristics, a multivariable analysis was performed using the backward stepwise logistic regression. The area under the receiver-operating characteristic curve, with 95% confidence interval (CI), was used to represent the regression probabilities. To estimate the probability of being assigned either to the one or the other group, a propensity score (PS) was calculated in a non-parsimonious way including the following preoperative patient characteristics: age, hypertension, body mass index, haemoglobin, diabetes on oral hypoglycaemic agent, diabetes on insulin, glycaemia on hospital admission, poor mobility, prior stroke, chronic lung disease, estimated glomerular filtration rate, chronic dialysis, extracardiac arteriopathy, diseased ascending aorta, New York Heart Association (NYHA) functional classes III–IV, Canadian Cardiovascular Society class 4 of angina, recent myocardial infarction, left main coronary artery disease, number of diseased coronary vessels, left ventricular ejection fraction, pulmonary hypertension, prior percutaneous coronary intervention, prior coronary surgery, critical state, out-of-hospital cardiac arrest, ventricular arrhythmias, intra-aortic balloon pump use, surgical priority and EuroSCORE II. One-to-one PS matching was performed employing the nearest neighbour method and a caliper of 0.2 of the standard deviation of the logit of the PS. To evaluate the balance between the matched groups, the Student's *t*-test for paired samples for continuous variables, the McNemar test for dichotomous variables, and the analysis of the standardized differences after matching were used. Standardized difference < 10% was considered an acceptable imbalance between the treatment groups. The same tests were adopted to test differences in operative data and postoperative complications of matched groups. Tests for interaction for in-hospital mortality and deep SWI were performed for relevant baseline characteristics among PS matched pairs. In case of discordant classification of patients within a pair, due to residual variation in baseline variables, we gave precedence to the characteristics of the patients undergoing BITA grafting. All tests were two-sided and *p*-value <0.05 was set for statistical significance. Non-parametric estimates and curves of freedom from all-cause death, cardiac or cerebrovascular death, and MACCEs were generated with the Kaplan-Meier method, both for overall and matched series. Comparison between survival curves was made by the log-rank test. Statistical analysis was performed by the SPSS program for Windows, version 13.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

Throughout the study period, the rate of BITA use in the study patients changed from 55.4% between 1999 and 2004, to 68.1% between 2005 and 2010, up to 81.3%, between 2011 and 2016. Thus, there has been increasing indication to BITA use across the years (Supplementary Fig. S1). In effect, since 2005 the rate of BITA use increased in women older than 80 years ($p = 0.025$) or with body mass index >30 kg/m^2 ($p = 0.066$). At the same time, the rate of deep SWI increased significantly ($p = 0.0018$), while there was a decrease in expected ($p = 0.2$) and actual in-hospital mortality ($p = 0.16$). (Supplementary Figs. S2 and S3).

3.1. The overall series, early outcomes

The risk profile of patients in SITA cohort was higher than in BITA cohort (median EuroSCORE II, 4.2% vs. 3.3%, $p = 0.0067$) owing to the greater prevalence of octogenarians and higher rates of severe renal impairment, moderate left ventricular dysfunction and emergency surgical priority. In BITA patients, there was a higher prevalence of three-vessel coronary artery disease and a higher number of coronary anastomoses. Because of this fact and the time needed for harvesting of the second ITA, the length of operation was longer of about 20 min in BITA series. Cold blood cardioplegia was used more frequently in BITA women, while the St. Thomas' Hospital solution No. 2 was adopted more often for SITA patients. In-hospital and 30-day mortality were higher in SITA than in BITA women (5.6% vs. 2.8%, $p = 0.052$ and 5.2% vs. 1.7%, $p = 0.0049$, respectively). Although chest tube output was higher in BITA cohort, both number of transfused red blood cell units and rate of mediastinal re-exploration for bleeding or