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Survival after bilateral internal mammary artery in coronary artery bypass grafting: Are women at risk?

Francisca A. Saraiva [a,1], Nicolas Girerd [b,1], Rui J. Cerqueira [a,c,1], João Pedro Ferreira [a,b,1], Noélia Vilas-Boas [a,1], Paulo Pinho [a,c,1], António Barros [a,1], Mário J. Amorim [a,c,1], André P. Lourenço [a,d,1], Adelino F. Leite-Moreira [a,c,*,1]

[a] Department of Surgery and Physiology, Cardiovascular Research and Development Unit, Faculty of Medicine, University of Porto, Porto, Portugal
[b] INSERM, Centre d'Investigations Cliniques Plurithématique 1433, INSERM U1116, Université de Lorraine, CHRU de Nancy, F-CRIN INI-CRCT, Nancy, France
[c] Department of Cardiothoracic Surgery, Centro Hospitalar São João, Porto, Portugal
[d] Department of Anesthesiology, Centro Hospitalar São João, Porto, Portugal

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ABSTRACT

Background: Most observational studies support long-term survival benefit after bilateral internal mammary artery (BIMA) compared with single internal mammary artery (SIMA) coronary artery bypass grafting (CABG) but data on females is scarce. We compared survival and safety of BIMA *versus* SIMA CABG between males and females at our tertiary care center.

Methods: Single-center retrospective cohort including consecutive patients with at least 2 left-coronary system (LCS) vessel disease who underwent isolated CABG with at least 1 IMA conduit and a minimum of 2 conduits targeting the LCS in 2004–2013. All-cause mortality was the primary outcome, secondary outcomes were early mortality and reoperation due to sternal wound complications (SWC). Kaplan-Meier analysis after inverse probability weighting using propensity score (IPW) was used to compare BIMA and SIMA CABG amongst genders. Results were confirmed in subgroup analysis.

Results: BIMA CABG was performed in 39% out of 2424 eligible procedures and in 27% of 460 females. No differences were found in survival after BIMA and SIMA CABG (median and maximum follow-up of 5.5 and 12 years, respectively) but a statistical interaction was observed with gender ($P < 0.001$). Females who underwent BIMA CABG showed higher mortality (weighted HR in females subset: 3.16; 95% CI: 1.56–6.29, $P = 0.001$). BIMA CABG showed a higher incidence of reoperation due to SWC (IPW adjusted model OR: 1.74; 95% CI: 1.16–2.60) that was mostly ascribable to males (weighted OR in males: 3.10; 95% CI: 1.74–5.51, $P < 0.001$).

Conclusions: Females may experience higher mortality after BIMA CABG which should be further explored.

1. Introduction

State-of-the-art coronary artery bypass grafting (CABG) involves anastomosis of an internal mammary artery (IMA) to the left anterior descending artery (LAD) because IMA has excellent long-term patency and survival benefit [1]. The choice of conduit for the remaining target vessels remains disputed. Most observational studies document better long-term survival after bilateral internal mammary artery (BIMA) compared with single internal mammary artery (SIMA) CABG [2–4]. Both North American and European guidelines endorse BIMA grafting to non-LAD coronary arteries in patients with reasonable life expectancy [5,6]. Importantly, whether BIMA CABG fares better than SIMA CABG in the female gender is poorly explored.

The Arterial Revascularization Trial (ART) was designed for 10-year survival comparison between BIMA and SIMA CABG. Interim analyses at 1 and 5 years did not show differences in survival and cardiovascular events but did show a higher rate of sternal wound complications (SWC) after BIMA CABG [7,8]. ART faced difficulties of implementation that may hamper generalization. Mostly low-risk patients were enrolled, only about 28% of the patients who met eligibility criteria were actually enrolled and 15.5% of patients in the BIMA group did not undergo BIMA CABG [8]. Therefore, it is unlikely that ART will solve the controversy regarding BIMA or SIMA CABG. Most importantly the issue of gender was not explored or reported.

Throughout the past years BIMA CABG procedures increased at our center and these have often been performed in females. Our aim was to address the role of gender in early postoperative outcomes and long-term survival after BIMA and SIMA CABG.

* Corresponding author at: Department of Surgery and Physiology, Faculty of Medicine, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal.
E-mail address: amoreira@med.up.pt (A.F. Leite-Moreira).

[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Material and methods

2.1. Ethics statement

This study was approved by the Ethics Committee of *Centro Hospitalar de São João*, as well as by the National Data Protection Committee (*Comissão Nacional de Proteção de Dados*). Patient consent was waived since the study was observational and retrospective, and all data processing was anonymous.

2.2. Sample selection

Unlike previous observational studies not all patients that underwent CABG were analyzed but strictly those whose anatomic lesions and planned interventions were comparable. We selected cases from the Database of the Department of Cardiothoracic Surgery of *Centro Hospitalar São João* that could have underwent either BIMA or SIMA CABG in whom surgical decision was the main determinant of having chosen either one or the other procedure. Patients who first underwent isolated CABG between 2004 and 2013 in whom pre-operative assessment showed significant coronary artery disease involving both main branches of left coronary system (LCS): left anterior descendent (LAD) and circumflex (CX) or their branches (diagonal and marginal, respectively) or any of these and an intermediate coronary vessel (variant found in nearly 20% of individuals) were selected if at least 2 different conduits (2 IMA or 1 IMA and at least 1 supplemental graft) had been implanted in both main branches of the LCS. Cases of BIMA in which 1 IMA targeted the right coronary artery (RCA) territory were excluded. Supplemental grafts could be either saphenous veins, or radial and gastroepiploic arteries. All possible configurations of IMA grafts were considered (Y-graft, *in-situ* or free grafts) as well as on-pump or off-pump techniques. Emergent or salvage surgeries or emergent conversions from off-pump to on-pump CABG were excluded.

2.3. Study design and setting

Clinical and demographic data were collected retrospectively from clinical files in paper and digital format. Surgical data included number and site of implantation of grafts, on-pump or off-pump technique, surgeon and date of surgery. Because a large period was spanned (from 2004 to 2013), date of surgery (timing of CABG) was recoded in years as time passed from the first surgery included in the database. Various surgeons performed the procedures with variable preference for BIMA CABG, we tried to define surgeon profiles according to the rate of BIMA CABG, as high (≥50%), intermediate (25–49%) and low-usage groups (<25%). Main outcome was death for any cause evaluated as of January 2016 through *Registo Nacional de Utentes* (Portuguese Health System Database). Secondary outcomes obtained were early mortality (in-hospital or until 30 days after surgery), duration of mechanical ventilation (prolonged if >24 h), need of inotropic support or intra-aortic balloon pump (IABP), re-exploration for bleeding, reoperation due to SWC, need of redo-CABG and post-operative atrial fibrillation (POAF). POAF was defined as new electrocardiography evidence of AF, amiodarone administration or electric cardioversion recorded in clinical files after the surgical period.

2.4. Statistical methods

Categorical and continuous data are presented as count (percentage) and mean ± standard deviation, respectively. Statistical analysis was carried out with the aid of IBM SPSS Statistics version 23.0 and R version 3.2.3 software. Statistical significance was set at two-tailed $P < 0.05$. Chi-square test, Mann-Whitney and unpaired *t*-test were employed to compare groups for categorical, ordinal and continuous variables, respectively. Bonferroni adjustment was used to correct for multiple testing. Propensity score analysis was used to account for selection bias between SIMA and BIMA CABG. A non-parsimonious multivariate logistic regression model (model 1) based on 24 covariates (defined in Supplementary table 1) estimated the propensity score (PS). Known confounders related to gender such as hemoglobin levels and body surface area (BSA) were included in the model. Because we wanted to assess the influence of gender, a second model (model 2) taking into account 4 relevant interaction terms, particularly those concerning gender was also evaluated. Models were checked for robustness. A detailed statistical methodological section is presented as supplementary material. Main effect and interaction analysis consisted of inverse probability of treatment weighting (IPW) using stabilized weights to minimize the influence of large weights [9]. Covariate balance was assessed by absolute standardized mean differences (ASMD) (Supplementary Fig. 1), C-statistic after weighting (Supplementary Fig. 2) and graphical comparisons of the distribution of continuous covariates (Supplementary Fig. 3). Since model 2 performed better than model 1 and it carried relevant gender interactions into the PS, all further analyses were based on model 2. Truncated weight analysis was also performed using the 99th percentile as threshold (Supplementary Fig. 4). The model was further adjusted for surgeon profile. Survival was analyzed by Kaplan-Meier curves and Cox proportional hazards model using a robust variance estimator. Since a significant interaction was found between intervention (BIMA *vs* SIMA) and gender, we carried out subgroup analysis for each gender. Due to reduced sample size we performed simple PS adjustment. For such purpose a new PS was derived for each separate gender (further details in Supplementary statistical methods). Secondary outcome measures were assessed by logistic regression and factorial logistic regression for interaction assessment.

3. Results

3.1. Study sample and baseline characteristics

From 3437 patients undergoing first isolated CABG at our institution from 2004 to 2013, we included 2513 patients undergoing either SIMA or BIMA CABG, 1544 and 969, respectively. Only 55 patients were excluded because the second IMA targeted the right coronary artery. From the included patients, 4 met exclusion criteria and another 85 were excluded due to missing data in any of the variables under evaluation. Five of these patients had missing follow-up data (0.2%). No significant differences were observed between missing data or exclusion criteria between SIMA and BIMA. The final sample was composed of 2424 patients undergoing either SIMA or BIMA, 1488 and 936, respectively. A study flowchart is outlined in Fig. 1. Sample baseline characteristics are given in Table 1. BIMA patients were younger, more commonly male, had a higher pre-operative hemoglobin level and higher proportion of hypercholesterolemia and smoking history whereas SIMA patients had more history of neoplasia, diabetes, hypertension, cerebrovascular disease, moderate to severe LV dysfunction, atrial fibrillation, and severe renal function impairment. Regarding surgical features, BIMA interventions were on average done later in time and were predominantly performed with an off-pump technique. SIMA and BIMA CABG patients received a similar number of grafts (2.9 ± 0.7 *vs* 2.9 ± 0.8). Of note the number of CABG procedures and the relative proportion of BIMA CABG increased throughout the period from 2004 to 2013 as well as the number of females receiving BIMA (Supplementary Fig. 5, panel A). A description of the population according to gender is provided in Supplemental Table 2. Females were older and showed higher prevalence of comorbidities, systemic hypertension, diabetes mellitus and chronic kidney disease as well as higher New York Heart Association class than men, their BSA was lower, as well as their preoperative hemoglobin concentrations whereas men had higher prevalence of smoking. The total number of grafts performed in females and males was similar (2.8 ± 0.8 *vs* 2.9 ± 0.8). Overall, 124 female patients (27% of females) underwent BIMA CABG. Throughout this period 12 surgeons performed CABG surgeries at our center, and the proportion of BIMA CABG was highly variable between surgeons (Supplementary Fig. 5, panel B). The rate of use of radial or gastroepiploic arteries as grafts was low (0.7% and 0.5%, respectively).

3.2. Survival analysis

Median follow-up was 5.5 years (4.6 and 6.2 years for BIMA and SIMA, respectively; 5.8 and 5.5 years for female and male, respectively) and maximum follow-up was 12 years. Overall mortality was 16.2% (392 patients). Although a lower proportion of BIMA patients died, 9.6% compared with 20.3% of SIMA patients (Fig. 2, panel A; HR = 0.61; 95% CI = 0.48–0.77, $P < 0.001$) differences were no longer observed after IPW (Fig. 2, panel B; HR = 1.1; 95% CI = 0.68–1.8).

Survival curves stratified by gender in a cox proportional hazards model revealed that while BIMA CABG tended to improve survival in males it did not change survival in females (Fig. 2, Panel C). Interestingly, the interaction between gender and BIMA CABG was strengthened in IPW survival analysis (Fig. 2, Panel D); in the weighted analysis women undergoing BIMA CABG showed considerably worse survival and remained significant after further adjusting for surgical profile or truncating extreme IPW weights (Supplementary Fig. 6). In gender subgroup analysis (see Supplementary Statistical Methods section), females showed worse survival rates for BIMA CABG in the PS covariate-adjusted analysis (HR = 2.00; 95% CI: 1.03–3.89 with SIMA as reference; $P = 0.039$) whereas no difference was found for males (HR = 0.91; 95% CI: 0.65–1.27) as illustrated in panels E and F of Fig. 2, respectively.