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Institutional report - Coronary

Despite modern off-pump coronary artery bypass grafting women fare worse than men

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Abstract

Female gender is an established risk factor for worse outcomes after cardiac surgery. Avoiding cardiopulmonary bypass (CPB) for coronary bypass grafting has an unknown effect on gender differences. Herein, we evaluate if gender has an impact on outcomes after modern off-pump coronary artery bypass grafting (OPCAB). From 2002 to 2007, we analyzed 983 patients (male: n = 807; female: n = 176) who underwent OPCAB with symptomatic multi-vessel disease at our institution. The link between gender and outcome was assessed by multivariate analysis and logistic regression. A composite endpoint was constructed from: 30-day-mortality, renal failure, prolonged intensive care unit (ICU) stay, neurological complications, use of intra-aortic balloon pump (IABP) and conversion to CPB. Mortality was 3.2% in women vs. 1.8% in men (P = 0.15) and the EuroSCORE was significantly correlated to gender (6.8 vs. 5.2; P < 0.001), even after correction (P = 0.036). Significant more occurrence of the composite endpoint was noted in women (39.8% vs. 29.0%; P = 0.007) whereas for men the risk was much lower (odds ratio (OR) 0.65; 95% confidence interval (CI) 0.46–0.92; P = 0.015). For both genders the logistic regression revealed a risk increase of 15% per one-point-increase of EuroSCORE (corrected) (OR 1.15; 95% CI: 1.10–1.19; P < 0.0001). Women had more frequently a prolonged stay at ICU (P = 0.006) and had a higher stroke rate (2.3% vs. 1.2%; P = 0.29). Complete revascularization was achieved similarly (95% vs. 94%; P = 0.93). OPCAB offers low mortality and excellent clinical outcome. Women are more likely to experience postoperative complications. Even if partially neutralized by avoiding CPB, gender differences remain present with modern OPCAB strategies.

Keywords: Coronary heart disease; Gender differences; Off-pump surgery

1. Introduction

Coronary artery disease (CAD) is the leading cause of mortality in women [1] (American Heart Association/ www.women.americanheart.org). Surgical revascularisation for CAD remains the treatment of choice in patients with three-vessel disease, left-main-disease, associated decreased left ventricular function and diabetes mellitus [2–4]. Current data report the mortality rate after coronary artery bypass grafting (CABG) to be significantly increased in females [5, 6]. Possible causes may be related to later clinical presentation, worse hemodynamic impairment, higher age, more incidence of diabetes, more severe heart disease and particular anatomical considerations, such as smaller vessel diameter [1]. In addition to this, women seem to suffer from increased length of intensive care unit (ICU) stay due to more frequent cardiac low-output states [6]. Furthermore, especially younger women with myocardial infarction (MI) undergoing CABG represent a particular high-risk sub-group, as reported by a higher overall mortality [5]. The EuroSCORE (www.euroscore.org) is an established score system for preoperative risk stratification in patients undergoing cardiac surgery. In this risk stratification, female gender is an independent risk factor for worse outcomes after cardiac surgery [7]. Cardiopulmonary bypass (CPB) is associated with severe complications, such as stroke, renal dysfunction, low cardiac output, post-operative bleeding and systemic inflammatory response syndrome (SIRS). Minimally-invasive approaches to CABG have led to the development of off-pump coronary artery bypass grafting (OPCAB) which permits myocardial revascularisation while avoiding CPB. OPCAB remains limited as clinical acceptance has yet to be achieved. Current data demonstrate that OPCAB is associated with less complications and a decrease in mortality [8]. These reports have not assessed the role of female gender on these outcomes. Herein, we determine if gender differences remain present in a modern OPCAB setting.
2. Methods

From 2002 to 2007, a total of 983 patients underwent isolated OPCAB for symptomatic multi-vessel disease (MVD) at our teaching institution. Of these patients, 82% (n = 807) were male and 18% (n = 176) female and preoperative risk was calculated by use of the EuroSCORE risk stratification system. A database review was performed after approval by our institutional review board (including a waiver of signed informed consent). Tables 1–3 resume patients' demographics, including EuroSCORE, co-morbidities, medication and preoperative data.

In brief, surgery was performed through a median sternotomy and heparin was administered to obtain active clotting time in excess of 300 s. Epicardial atrial and sometimes ventricular pacemaker wires were applied. An octopus 4 Tissue-Stabilizer, Medtronic, Minneapolis, USA) was used to properly expose the target vessel. A mister blower (Guidant, Indianapolis, USA) was used to clear the opening field during anastomosis. Coronary arteriotomy was performed with a beaver blade and shunt insertion (ClearView™ Intracoronary-Shunt, Medtronic, Minneapolis, USA) was attempted in all. Proximal anastomosis was performed in a clamp-less fashion using a heartstring-device (HEARTSTRING™ Seal-System, Guidant, Indianapolis, USA). Revascularization was commenced by left anterior descending-left internal mammary artery (LAD-LIMA) grafting, after which the right coronary system was approached, and finally the circumflex territory was done. Hemodynamic optimization was attempted by fluid resuscitation, Trendelenburg positioning, atrial pacing and catecholamine administration as a last measure. When still insufficient an intra-aortic balloon pump (IABP) was placed intra-operatively (n = 10, 1%). As an ultimate action, or if necessary, conversion to CPB was done (n = 57, 6%). A beating-heart procedure was attempted; only in difficult cases cardioplegic arrest was performed.

Continuous data are presented as mean ± standard deviation (S.D.) and are compared using the Mann–Whitney test. Categorical data are presented as number and percentage and are compared using the χ²-test or Fisher's exact test where appropriate. A ‘Completeness of Revascularization Index’ (CRI) was calculated for each patient and was defined as the total number of distal grafts divided by the number of the affected coronary vessels reported on the preoperative coronary angiogram. A composite endpoint was constructed from: 30-day-mortality, postoperative renal failure, ICU length of stay (LOS) (> 2 days), neurological complications, use of IABP and conversion to CPB.
bivariate logistic regression with gender and a gender-corrected EuroSCORE as covariates was performed to analyze whether gender is an independent predictor of the composite endpoint. All analyses were performed using SPSS13 (SPSS Inc, Chicago, IL, USA). Two-sided P-values <0.05 are considered statistically significant.

3. Results

The mortality was 2% for all-comers. Females were more likely to die during the first 30 days when compared to males (3.4% vs. 1.7%; P = 0.15). Women appeared to have a higher occurrence of stroke than men (2.3% vs. 1.2%; P = 0.29) whereas the rate of peripheral neurological complications was similar in both groups (0.6% vs. 0.9%; P = 1.00). Furthermore, the frequency of re-operation for bleeding was higher in women, although this did not reach statistical significance (4.5% vs. 3.3%; P = 0.50). In contrast to this, it appeared that women experienced a significantly longer stay in the ICU when compared to males (2.7±4.9 days vs. 2.1±3.5 days; P = 0.011), whereas the length of hospital stay was quite similar (10.1±5.2 days vs. 10.2±5.3 days; P = 0.12). Additionally, it became apparent that women had a significantly lower level of platelets than men (164±87 vs. 182±111; P = 0.037) at the first postoperative day (Table 4).

Intra-operative insertion of an IABP was necessary in (0.6% vs. 1.1%; P = 0.44). The rate of conversion to CPB during the procedure was 5.1% vs. 5.9%; P = 0.86, after conversion 78% vs. 75% were performed beating heart, while 22% vs. 25% underwent aortic cross-clamping. The number of the diseased coronary vessels were well comparable (2.76±0.49 vs. 2.79±0.50; P = 0.64). Next, the number of arterial grafts per patient (1.76±1.05 vs. 1.69±0.94; P = 0.52), the number of saphenous vein grafts (SVG) per patient (1.87±1.25 vs. 1.97±1.27; P = 0.29) and the total number of used grafts per patient were similar among both genders (3.63±1.03 vs. 3.66±0.96; P = 0.75). In addition to this, completeness of revascularization was achieved in 95% of women vs. 94% of men (P = 0.93) and the CRI revealed no significant differences (1.39±0.67 vs. 1.40±0.63; P = 0.90) (Table 5).

The EuroSCORE for women was significantly higher than in men (6.8±3.4 vs. 5.2±3.5; P < 0.001). Even the corrected EuroSCORE (EuroSCORE −1) for female gender was still significantly higher than in men (5.8±3.4 vs. 5.2±3.5; P = 0.036).

Significantly more occurrence of the composite endpoint was noted in 40% vs. 29% for women and men (P = 0.007). These results were mainly driven by the significant longer stay (>2 days) at the ICU (27% vs. 18%; P = 0.006). Although the mortality rate (3.4%), the number of central neurological complications (2.3%) and the frequency of re-thoracotomy (4.5%) were higher in women, these components failed to reach statistical significance (Table 4). Mean EuroSCORE (corrected −1) of the affected women was 7.3±3.8 (median: 7; range: 0–17) vs. 6.3±4.0 (median: 5; range: 0–18) in men. In the non-affected the EuroSCORE was similar: 4.8±3.0 (median: 4; range: 0–20) vs. 4.7±3.1 (median: 4; range: 0–18) (Fig. 1).

Female gender was an independent risk factor, as men had a significantly lower risk for the occurrence of our composite endpoint. The odds ratio (OR) was 0.65 (95% confidence interval (CI): 0.46–0.92; P = 0.015). The logistic regression for both genders revealed a significant risk increase of 15% per one-point-increase of EuroSCORE (corrected). The OR was 1.15 (95% CI: 1.10–1.19; P < 0.0001).

Taken together, these data suggest that a male with a EuroSCORE of four points might roughly correlate with a
female having a EuroSCORE (corrected) of two points in regard to the occurrence of our composite endpoint.

4. Discussion

In our series, it appears that OPCAB offers low mortality and excellent clinical outcomes for patients requiring myocardial revascularization. However, despite the elimination of CPB, gender differences in regard to clinical outcomes remain present and cannot be completely compensated by the avoidance of CPB. When compared to men, women are significantly more likely to experience postoperative complications, such as mortality, ICU LOS, neurological complications, re-operation for bleeding and conversion to CPB. We believe the significantly decreased postoperative level of platelets among women might be a plausible explanation when considering the higher incidence of re-operation for bleeding. In addition, these findings are clearly confirmed by a significant lower OR of 0.65 (P=0.015) for the occurrence of our composite endpoint in men.

When taking the EuroSCORE into account we found it impressive, as even after correction (EuroSCORE –1) women had a significantly higher EuroSCORE than men (P=0.036). We, and others, believe that this highlights the fact that women may actually suffer from more severe CAD and worse associated co-morbidities [9]. These co-morbidities include: age, renal function, pulmonary conditions, peripheral vascular disease, neurological dysfunction and impaired ejection fraction (EF). Furthermore, women have smaller coronary arteries adding to the operative challenge when performing OPCAB [1].

Parallel to this, attention has recently shifted towards genetic factors which may contribute to worse outcomes in women. Schuit et al. conducted a prospective cohort study on postmenopausal women. They looked at MI and ischemic heart disease (IHD) and analysed the prevalence of a specific estrogen receptor. Female heterozygous carriers of haplotype-1 had an increased risk of MI (event rate: 2.8%; relative ratio (RR) 2.23) compared with non-carriers (event rate: 1.3%), whereas homozygous carriers had an increased risk (event-rate: 3.2%; RR: 2.48). For IHD events, they observed a similar association. In women, the effect of haplotype-1 on fatal IHD was larger than on non-fatal IHD. In men, the ESR1 haplotypes were not associated with an increased risk of MI or IHD. The authors concluded that postmenopausal women who carry the gene have not only an increased risk of having an IHD event but also an increased risk of death from such an event [10]. Regardless of the surgical approach, these results clearly indicate that women seem to have a genetic component for worse outcomes after cardiac surgery and might explain the significantly increased occurrence of our composite endpoint.

In contrast to this, Cartier and colleagues prospectively followed up 1000 OPCAB patients and found that particularly incomplete revascularization (hazard ratio (HR) 2.35),
multiple internal thoracic artery (MITA) (HR: 0.61), left ventricular EF (HR: 0.19) and cerebral vascular disease (HR: 1.50) but not female sex (P=0.89) were significant predictors of long-term mortality. They concluded that a lower survival rate especially observed in younger women was mostly related to a higher prevalence of preoperative co-morbidity and a lesser use of MITA grafts than gender itself [5]. In regard to the long-term outcome the report also highlights the importance of completeness of revascularization which has often been reported to be limited in OPCAB [4, 11]. By help of our constructed CRI, we were able to demonstrate completeness of revascularization for both genders and could successfully exclude this important risk factor. This is in line with Puskas et al. who recently demonstrated feasibility of completeness of revascularization in OPCAB [12]. Our results may be explained by our 100% standardized OPCAB approach and especially by the fact that we perform 95% of all cases in OPCAB fashion which is far above the international average [11].

In regard to outcomes when comparing on-pump vs. off-pump CABG in women, numerous reports are available [13, 14]. Mack et al. reported outcomes on 21,902 consecutive female patients at 82 institutions undergoing isolated CABG. Propensity scoring was performed on 7376 women demonstrating 73% higher mortality (P=0.002) and a 47% higher risk of bleeding complications (P=0.019) in patients undergoing on-pump CABG. It remains unclear if the avoidance of CPB is the only mechanism involved decreasing mortality, as the risk profile is essentially the same between the matched groups reported [13].

This report clearly indicates a benefit for women undergoing OPCAB and is in line with our overall results that OPCAB offer lower mortality and an excellent clinical outcome. In comparison, we focussed on the important question, if off-pump procedures do also narrow the well described gender differences after on-pump surgery. In another large retrospective study, Puskas et al. evaluated 11,413 patients (females: n=3248), comparing OPCAB to CABG and found that women were older and had higher predicted risk than males. Among women undergoing CABG they confirmed an increased OR for death, stroke, MI and for major cardiac adverse events (MACE). Among women, OPCAB was associated with a significant risk reduction for death, stroke and MACE. Moreover, they demonstrated that women treated with OPCAB had outcomes statistically similar to men regardless of operative strategy. The authors concluded that OPCAB is associated with fewer major adverse cardiac events, narrow gender differences and even benefits women disproportionately [15]. In contrast to these data, our results suggest that gender differences remain present after off-pump procedures. On the other hand, the univariate analysis of our composite endpoint components showed that the statistical significance was mainly driven by the longer stay at the ICU (>2 days). When excluding this factor, and as all other components failed to reach statistical significance, they might be partially comparable to their findings [15].

In conclusion, despite modern OPCAB gender differences in regard to outcomes and remain present and cannot be fully compensated by this minimally-invasive approach. Without a doubt OPCAB seems to benefit women compared to conventional on-pump CABG. However, it remains unclear to what extent off-pump procedures narrow these gender differences. Additional studies are needed to address this question, particularly since women have always been under-represented in the current data. Finally, the suggestion that genetic factors might contribute to worse outcomes in females has to be recognized and elucidated in future studies.

References

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The results of Emmert et al. [1] clearly demonstrate the effect of gender on postoperative mortality and morbidity. Their analysis of 983 patients revealed the risk of mortality in females to be 1.8 times that of males. Furthermore women had a longer ICU stay, a higher stroke rate and were found to be more likely to develop postoperative complications compared to the European system for cardiac operative risk evaluation (EuroSCORE) [2]. Despite performing revascularization using an off-pump technique the groups results for mortality were significantly greater than the 1% increase calculated by the EuroSCORE. Other investigators have also found similar differences. Vaccarino et al. [3] reported in-hospital mortality rates in women younger than 50 years old three times higher than that of men. Although alluded to in the article the pathophysiology behind increased mortality in women remains unclear. Women tend to be older at the time of surgery with a greater number of co-morbidities. They have smaller coronary arteries thereby making the task of performing anastomoses more challenging. Fewer arterial grafts are performed in women, and smaller chamber volume as well as cardiac mass and circulating volume may reduce functional reserve to a greater extent compared to men.

We performed coronary revascularization on a male patient who had undergone bilateral orchidectomy during childhood for undescended testes. The patient had feminine features of peripheral obesity, lack of facial hair and gynaecomastia. He was also non-compliant with his testosterone replacement therapy. During the procedure it was noted that his coronary arteries were of a smaller diameter and fragile in nature when compared to an equivalent male patient. The hypothesis was then postulated: should this patient score an additional point on the EuroSCORE? Clearly this is a rare occurrence, but should the patient be scored as a woman?

References
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