Journal of the Saudi Heart Association (2010) **22**, 47–53

King Saud University

Journal of the Saudi Heart Association

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ORIGINAL ARTICLE

Gender differences in the surgical management and early clinical outcome of coronary artery disease: Single centre experience

Munir Ahmad, Ahmed A. Arifi *, Rawdené van Onselen, Ahmed A. Alkodami, Muayed Zaibag, Abdul Aziz A. Khaldi, Hani K. Najm

King Abdulaziz Cardiac Centre, King Abdul Aziz Medical City, Riyadh, Saudi Arabia

Received 11 December 2009; accepted 2 February 2010
Available online 24 February 2010

KEYWORDS

Gender disparity;
Gender bias;
Coronary artery bypass surgery in females;
Cardiovascular risk factors

Abstract *Objective:* To investigate the gender disparity in the distribution of patient-related risk factors and their effect on the surgical management and clinical outcome of coronary artery disease in Saudi population.

Materials and methods: We carried out a retrospective analysis of prospectively collected data of 971 patients undergoing isolated coronary artery bypass grafting (CABG) at our institution between January 2005 and December 2008. Seven hundred and eighty seven patients (81%) were males and 184 patients (19%) were females. We analyzed gender-based difference in clinical presentation and patient-related pre-operative risk factors and studied their impact on surgical management and clinical outcome.

Results: The mean age was 59.5 years in males and 63.4 years in females ($p = <0.0001$). Associated co-morbidities were higher in females. Prevalence of diabetes mellitus was 61.2% in males and 78.8% in females (p-value $= <0.0001$); hypertension 61.9% in males and 79.9% in females (p-value <0.0001); hyperlipidemia 66.7% in males and 77.7% in females (p-value 0.0035); morbid obesity 24.7% in males and 45.1% in females (p-value <0.0001); and Hypothyroidism 2.5% in males and 13.6% in females (p-value <0.0001). Smoking was the only risk factor with higher prevalence in males compared to females (44.2% v/s 2.2%; p-value <0.0001). The mean logistic euroSCORE was 3.94 in males and 5.51 in females ($p < 0.0003$). On-pump and off-pump CABG was

* Corresponding author. Address: King Abdul Aziz Cardiac Centre, Mail Code: 1404, P.O. Box 22490, Riyadh 11426, Saudi Arabia.
E-mail address: arifiahmed@hotmail.com (A.A. Arifi).

doi:10.1016/j.jsha.2010.02.004

Production and hosting by Elsevier

carried out in equal numbers in two groups. Females required urgent surgery and less than 3 grafts more frequently while males underwent elective surgery and more than 3 grafts in greater numbers. No significant difference was present between the two gender groups in aortic occlusion times and bypass times. Univariant analysis revealed females gender as an independent risk factor for higher in-hospital mortality (1.1% versus 4.9% $p = 0.0026$) and higher incidence of post-operative complications like surgical wound infection, need for prolonged ventilation, low cardiac output state and multi-organ failure (p-values 0.01 or less).

Conclusion: Female gender is an independent predictor of adverse outcome after isolated CABG due to significantly higher co-morbidities and acute presentation and independent of their peri-operative management. Therefore, major socioeconomic education and preventive measures are needed to reduce the burden of major co-morbidities in females and to seek early cardiac advice and care.

1. Introduction

Despite world wide advances in medical field, disparities in health care delivery systems still exist and may be based on factors like patient's age, gender, ethnicity and socio-economical status (Alexander et al., 2007; Lantz et al., 1998; Alter et al., 1999; Fascella et al., 2000). Gender disparity in the management of coronary artery disease has remained a subject of controversy for over twenty years in medical literature (Tobin et al., 1987; Steingart et al., 1991; Bearden et al., 1994; Kostis et al., 1994; Mark et al., 1994; Lincoff et al., 1993; Roeters van Lennep et al., 2000; Miller et al., 2001). Many aspects of this issue yet remain unanswered. Under-treatment and worst outcome of female patients suffering from acute and chronic coronary artery disease (CAD) has been highlighted by various studies (Crilly et al., 2008; Daly et al., 2006; Raine et al., 2002; Hussain et al., 1998; Hachamovitch et al., 1995; Ayanian and Epstein, 1991) and is probably multi-factorial (Ghali et al., 2002). The problem exists to a variable extent in different ethnic and geographical populations and thus the difference noted in the management and outcome of CAD in female gender must be caused by variable interplay of ethnic, social, genetic and pathological factors affecting female CAD patients in these populations.

Most of the studies on gender disparity have so far been done on North American and European patients. There are very few studies that has addressed the issue of gender differences in the management of CAD and outcome of invasive procedures in the Middle East and Golf region populations. Our study is aimed at addressing some of these issues in Saudi Arabian CAD population. We wished to investigate whether any gender disparity existed in the prevalence of risk factors and clinical presentation of CAD patients in our population undergoing coronary artery bypass grafting (CABG). We have also noted that there is a gender difference in the clinical outcome after CABG surgery and we have made an endeavor to find out whether this difference in outcome is the result of gender bias in the surgical management of CAD or is caused by difference in prevalence of pre-operative risk factors between the two gender groups.

2. Materials and methods

2.1. Patient selection

Study population consisted of a consecutive series of 971 patients, who underwent primary isolated coronary artery bypass grafting at King Abdulaziz Cardiac Centre in Riyadh, Saudi Arabia between January 2005 and December 2008. All patients had been investigated for the presence of significant coronary artery disease requiring coronary artery bypass grafting and full pre-operative risk stratification based on euroSCORE was carried out. Patients undergoing concomitant valve or other major surgery and re-do surgery were excluded. All the data related to patients' pre-operative clinical status, peri-operative events and post-operative hospital course was extracted prospectively by qualified data managers and was retrospectively analyzed for the impact of gender on clinical course of this group of patients undergoing isolated coronary artery bypass grafting.

2.2. Demographic and clinical data

Seven hundred and eighty seven (81%) patients undergoing isolated CABG were males and 184 (19%) were females. Pre-operative risk factors leading to causation and determining the severity of CAD including prevalence of diabetes mellitus, hypertension, hypercholesterolemia, morbid obesity and smoking habit were recorded. Co-morbidities which are well known to affect the outcome of CABG were also recorded and included hypothyroidism, chronic renal failure, chronic obstructive airway disease, cerebro-vascular accidents, peripheral vascular disease, pre-operative critical state, unstable angina, recent myocardial infarction, pre-operative ejection fraction and urgency of surgery. Additive and logistic euroSCORE was tabulated for pre-operative risk stratification.

2.3. Procedural and outcome data

Intra-operative figures were analyzed to find out if any gender bias existed in the choice of revascularization method, number of grafts performed, the choice of conduits or myocardial protection methods. The clinical outcome of surgical intervention was measured by the differences in operative mortality and morbidity parameters such as incidence of wound infection, low cardiac output state, prolonged ventilation and multi-organ dysfunction.

2.4. Statistical analysis

Fisher's exact test was employed to evaluate the relation of male or female gender to individual patient variables, procedural variables and outcome data. Two-tailed t-test was used to analyze the differences in continuous variables like age,

euroSCORE and length of post-operative stay. A two-tailed *p*-value of 0.05 or less was considered statistically significant. All analysis were performed with GraphPad statistical package (GraphPad Software Inc., CA, USA).

3. Results

3.1. Patient data

There were 787 males and 184 females who underwent isolated primary CABG during three year period. The mean age of males was 59.5 years and of females was 63.4 years ($p < 0.0001$). The pre-operative patient characteristics between males and females are compared in Table 1. The female population had a significantly worst risk factor profile than males and had an increased incidence of diabetes (78.8% vs. 61.2% $p < 0.0001$); hypertension (79.9% vs. 61.9% $p < 0.0001$); hypercholesterolemia (77.7% vs. 66.7% $p = 0.0035$); morbid obesity (45.1% vs. 24.7% $p < 0.0001$) and hypothyroidism (13.6% vs. 2.5% $p < 0.0001$). Prevalence of smoking was, however, higher in males compared to females in our population (44.2% vs. 2.2% $p < 0.0001$). There was no significant difference in the prevalence of chronic renal or pulmonary disease, pre-operative critical state, peripheral vascular disease and recent myocardial infarction. Females had a significantly higher incidence of critical carotid artery disease compared to males (8.1% vs. 3.8%; $p = 0.018$) but there was no difference in the incidence of cerebro-vascular accidents prior to admission. Left ventricular ejection fraction was comparable between males and females and there was non-significant difference in the prevalence of left main coronary artery disease (16% vs. 17.4%; $p = 0.660$). There was a trend towards increased number of coronary vessel involvement in males compared to females but the figures did not reach statistical significance. Females presented more commonly with unstable angina ($p = 0.049$) and required more urgent surgery than males ($p = 0.017$). Mean logistic euroSCORE representing pre-operative risk profiling was also significantly higher in females compared to males (5.51 vs. 3.94, respectively, $p < 0.0003$).

3.2. Operative data

Operative data of two gender groups is compared in Table 2. Conventional CABG and off-pump surgery (OPCAB) were employed with equal frequency in both groups. More males required 4–6 grafts ($p = 0.003$) and more females required 1–2 grafts ($p = 0.015$). Internal thoracic artery was used in 100% males and 98.3% females ($p = 0.373$) and radial artery was used in 32.6% males and 20.5% females ($p = 0.076$). Average aortic cross clamp time was 61.0 min vs. 59.9 min ($p = 0.979$) and average cardio-pulmonary bypass time was 85.8 min vs.

Table 1 Patient characteristics.

Variable ($n = 787$)	Males	Females	*p*-Value ($n = 185$)
Mean age (years)	59.5	63.4	<0.0001
Diabetes mellitus (%)	61.2	78.8	<0.0001
Hypertension (%)	61.9	79.9	<0.0001
Hypercholesterolemia (%)	66.7	77.7	0.0035
Morbid obesity (%)	24.7	45.1	<0.0001
Smoking (%)	44.2	2.2	<0.0001
Hypothyroidism (%)	2.5	13.6	<0.0001
Past cerebro-vascular accident (%)	5.3	5.4	ns
Peripheral vascular disease (%)	5.1	2.2	0.113
>75% Carotid stenosis (%)	3.8	8.1	0.018
Chronic renal failure (%)	2.3	3.2	0.431
Chronic pulmonary disease (%)	0.8	0.5	0.623
Pre-operative critical state (%)	12.8	13.0	0.903
Unstable angina (%)	11.7	17.4	0.049
Recent myocardial infarction (%) (within 3 weeks)	29.9	31.5	0.660
Pre-operative ejection fraction			
Mean (%)	48.8	49.4	ns
Median (%)	52.0	52.0	ns
Extent of coronary artery disease			
1-Vessel disease (%)	1.8	2.7	0.381
2-Vessel disease (%)	11.6	14.7	0.259
3-Vessel disease (%)	85.3	79.3	0.056
>50% Left main disease (%)	16.0	17.4	0.660
Urgency of surgery			
Elective (%)	31.0	21.2	0.009
Urgent (%)	67.0	76.1	0.017
Emergent (%)	1.7	2.7	0.223
Mean euroSCORE			
Additive	3.5	4.85	<0.0001
Logistic	3.94	5.51	<0.0003

Table 2 Intra-operative variables.

Intra-operative variables	Males (n = 787)	Females (n = 184)	p-Value
Choice of operation			
Conventional CABG (%)	93.0	93.5	ns
OPCAB (%)	6.7	6.5	ns
Number of grafts			
1–2 Grafts (%)	11.8	19.0	0.015
3 Grafts (%)	35.8	40.8	0.234
4–6 Grafts (%)	52.3	40.2	0.003
Mean grafts/patient	3.47	3.2	
Choice of conduit			
Left internal mammary (%)	100.0	98.3	0.373
Right internal mammary (%)	0.3	0.5	0.094
Left radial artery (%)	32.6	20.5	0.076
Endarterectomy (%)	1.5	1.6	ns
Cardiopulmonary bypass time (min)	85.8	85.7	0.979
Aortic cross clamp time (min)	61.0	59.9	0.655
Re-operation (%) (bleeding/temponade)	3.6	2.7	0.821

Table 3 Patients' outcome data.

Post-operative variables	Males (n = 787)	Females (n = 185)	p-Value
Low cardiac output state (%)	1.5	8.2	< 0.0001
Prolonged (> 24 h) ventilation (%)	6.4	14.1	0.001
Multi-organ dysfunction (%)	0.8	2.7	0.040
Cerebro-vascular accident (%)	2.2	2.7	0.59
Renal dysfunction (%)	6.2	4.3	0.39
Post-op IABP insertion (%)	0.1	0.5	0.34
In-hospital mortality			
Within 30 days (%)	0.9	2.7	
After 30 days (%)	0.3	2.2	
Total (%)	1.1	4.9	0.0026
Wound infection			
Deep sternal (%)	1.4	4.3	0.0161
Superficial sternal (%)	4.3	7.6	0.0864
Leg wound (%)	5.6	14.7	0.0001
Urinary tract infection (%)	2.3	10.3	< 0.0001
Mean post-operative stay (h)	218.9	325.8	< 0.0001

85.7 min (p = 0.655), respectively. Incidence of early re-operation for post-operative bleeding and cardiac temponade was comparable between the two genders.

3.3. Outcome data

Analysis of post-operative data revealed higher in-hospital mortality in females (4.9%) compared to males (1.1%); p-value < 0.0026. This was well reflected by the difference in their pre-operative euroSCORE. In line with higher incidence of diabetes mellitus, all infections were more frequent in females compared to males. Incidence of deep sternal infections was 4.3% vs. 1.4% (p = 0.016); graft-site infection was 14.7% vs. 5.6% (p = 0.0001) and urinary tract infection was 10.3% vs. 2.3% (p < 0.0001), respectively. Low cardiac output state, need for prolonged (> 24 h) mechanical ventilation and multi-organ dysfunction were also more common in female population (see Table 3). Accordingly, post-operative length of hospital stay was significantly higher in female patients (p < 0.0001). The incidence of peri-operative myocardial infarction, cerebro-vascular accident, post-operative renal dysfunction and atrial fibrillation was not statistically different.

4. Discussion

Coronary artery disease affects women in post-menopausal age with the same frequency as men and in western world; it has now surpassed cancers of all types as the leading cause of mortality in females (Crouse and Kramer, 1996). It is known that when female patients present with chest pain, they are more likely to have other problems than coronary artery disease compared to males with chest pain (Crouse and Kramer, 1996; Miller et al., 2001). This notion may probably been the cause of gender disparities noted in the management of female CAD population not only at primary healthcare level (Crilly et al., 2008; Bosner et al., 2009) but also at the level of diagnostic work up and choice of revascularization procedure. Under-referral of female patients for exercise test and coronary angiography has not only been shown when they present with chest pain (Daly et al., 2006; D'Hoore et al., 1994; Petticrew et al., 1993) but also when they have proven coronary artery disease presenting in the form of acute myocardial infarction (Ayanian and Epstein, 1991; Nguyen et al., 2008; Dellborg and Swedberg, 1993; Alpert and Dalen, 1993). This pattern is, however, not universal and there are other reports denying the presence of such a bias (Ghali et al., 2002; Miller et al., 2001; Wong et al., 2001; Travin et al., 1997; Hochman et al., 1997; Ramsey et al., 1997; Amanullah et al., 1996; Krumholz et al., 1992). The variability in the results of these studies could be explained by differences in the practice patterns of different centres and could also be influenced by regional, cultural and socio-economical factors affecting the healthcare dynamics of female patients (Ghali et al., 2002). Since the interplay of above factors is unique in each society, the results from any given study can not to universally applied. There is thus need to study the local factors affecting any population before healthcare practices and policies may be modified.

Whether this gender disparity is the result of true gender bias or it results from difference in the extent or severity of coronary artery disease is a subject of on-going debate (Roeters van Lennep et al., 2000; Ghali et al., 2002; Nguyen et al., 2008; Ramsey et al., 1997). It has also been recognized that female CAD patients present with different set of symptoms and their symptoms do not have same relationship to the extent and severity of coronary artery disease as their male counterparts. Females may present more frequently with congestive heart failure or unstable angina compare to men who present more frequently with myocardial infarction or cardiac death (Travin et al., 1997). Females tend to present later in age by about 10 years (Crouse and Kramer, 1996), and are likely to have less severe coronary artery disease with worse symptoms (Hochman et al., 1997; Bell et al., 1995). The Euro Heart Survey enrolled 3779 patients assessed by a cardiologist to have stable angina and followed for 1 year, have demonstrated that women were less likely to receive anti-platelet and statin therapies, were less likely to undergo exercise ECG and angiogra-

phy, and those with confirmed coronary disease were less likely to be re-vascularized and were twice likely to suffer death or nonfatal myocardial infarction than their male counterparts (Daly et al., 2006). When female patients have more extensive ischemia demonstrated on myocardial perfusion scan, they have been shown to be at higher risk for major cardiac death and myocardial infarction than are men with similar findings. Under-referral of this subset of high risk female patients for cardiac catheterization compared to their increased risk has been demonstrated over a follow up period of 1 year by Hachamovitch et al. (1995).

It has also been shown in various studies that female CAD patients have an adverse risk factor profile for the prevalence of diabetes mellitus, hypertension and hypercholesterolemia (Hussain et al., 1998; Ghali et al., 2002; Hochman et al., 1997; Bell et al., 1995). We have clearly demonstrated the same finding in our current study and shown that all risk factors thought to contribute to the progression of atherosclerotic coronary artery disease are significantly higher in prevalence in our female patients undergoing coronary artery surgery, with the exception of smoking which is more prevalent in males. Whether similar gender discrepancy in risk factor profile exists in our coronary artery disease population in large and in our Saudi general population need to be investigated.

The pre-operative additive and logistic euroSCORE of our female patient population was significantly higher than males. This complies well with findings from many other studies. This reflected into a significant difference in the in-hospital mortality between the two genders following coronary artery bypass grafting although there was no difference in the operative technique as evident from comparable intra-operative variables. The mortality figures in the two genders, however, were within the predicted figures based on pre-operative euroSCORE. A more accurate prediction of operative mortality was given by euroSCORE in the female cohort while the mortality figure in males was significantly lower than that predicted by the risk scoring system.

There is growing evidence in literature that female patients do worst as a result of all cardiovascular interventions compared to their male counterparts especially so after coronary artery bypass grafting (Hussain et al., 1998; Bell, 1996; El-Menyar and Al Suwaidi, 2009; Bennet and Redberg, 2004). This might have resulted in proportionately fewer female patients being referred for coronary artery bypass surgery and more for per-cutaneous angioplasty than males (Roeters van Lennep et al., 2000; Nguyen et al., 2008; Bell et al., 1995). Total number of revascularization procedures, however, have been shown to be proportionately equal following coronary angiography (Bell et al., 1995) and apparent bias in referral to one or the other revascularization modality has been explained by differences in the extent and severity of coronary artery disease between two genders (Roeters van Lennep et al., 2000; Ghali et al., 2002; Nguyen et al., 2008; Ramsey et al., 1997).

The increased post-operative morbidity in females after coronary artery bypass grafting in our patients is also more likely to be due to increased prevalence of risk factors and co-morbidities as the peri-operative management was not different. A significantly increased prevalence of diabetes mellitus, obesity and hypothyroidism compounded by restrictive physical activity noted in most of our elderly female patients would thus account for increased incidence of infective and respiratory complications. More advanced atherosclerotic vascular disease and microvascular arteriopathy due to increased incidence of diabetes, hypertension and hypercholesterolemia explains increased incidence of end-organ dysfunction after coronary artery surgery in females.

5. Conclusions

We have studied 971 patients (787 males, 184 females) undergoing isolated primary coronary artery bypass grafting over a period of three years (January 2005 to December 2008) and demonstrated that female gender is an independent and strong predictor of adverse outcome after bypass surgery compared to males due to significantly higher co-morbidities and more acute presentation; and independent of their peri-operative management. The female coronary artery disease patients should therefore be recognized as a higher risk subset of patients. We have also demonstrated that if proper pre-operative risk stratification is carried out, coronary artery bypass surgery in female patients will still yield internationally comparable results. Since other studies have shown that female patients with significant ischemia are at a greater risk of major adverse cardiac events, the benefits of coronary artery surgery will greatly surpass the involved risk and in appropriate patients, this modality of treatment should not be denied. Better primary and secondary risk factor control and optimal peri-operative management is likely to improve results of coronary artery surgery in this high risk population of patients.

5.1. Limitations of study

Our study is a retrospective analysis of prospectively collected data and has the limitations associated with all non-randomized uncontrolled studies. The conclusions drawn from the study are therefore bound by above limitations. We have, however, mainly focused upon demonstrating the differences exhibited by female patients undergoing coronary artery bypass grafting and for this purpose our male population undergoing similar treatment in same hospital setting could be considered as close a control as possible. Thus using the gender comparison, we have been able to demonstrate very clearly that our female population presents for coronary artery surgery with a clearly increased risk factor profile and thus represents a higher risk patient population.

Our study is a single centre study which reflects the practices of a tertiary care hospital. Because we generally tend to get referrals from many peripheral centre, our patient cohort is likely to comprise of selected high risk patients. These might not entirely represent patient populations in other centres and generalization of results needs to be done cautiously.

Since the data presented here only pertains to a subset of patients who underwent coronary artery bypass grafting, our patient population represents one extreme of a larger population of patients with coronary artery disease. The inferences may thus be applied to other subsets of patients with CAD keeping this limitation in mind.

Since our study is limited to patients who had already been worked up and accepted for coronary artery bypass surgery, no inference from this study can be made about the presence or absence of any bias at the level of referral, choice and timing of diagnostic procedures.

5.2. Future prospective

Future research is needed to address the increased prevalence of cardiovascular risk factors like diabetes mellitus, hypertension, obesity and hypercholesterolemia in Saudi female population. This difference seems very significant and certainly predisposes our female population to significantly increased risks and complications related to CAD. Various factors may play a causative role and may include genetic predisposition or social and cultural factors like restricted lifestyle, reduced physical activity and limited access to health education or primary healthcare for diagnosis and timely management of cardiovascular risk factors. Research into these issues may guide to modulate healthcare programmes and policies and help in the better future management of high risk female population with coronary artery disease.

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