The role of gender in coronary surgery

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Summary

Gender-based outcome data in coronary artery bypass graft (CABG) surgery has been the focus of extensive research over the last two decades. Increased awareness in gender-specific health and advancements in scientific research have produced evidence that risk profiles vary between genders and alter operative mortality after CABG. Some of these data remain controversial, emphasizing the complexity of gender as an independent variable and questioning processes of care that are intimately associated with outcome. Although patient gender cannot be changed, understanding gender-specific risks and modifying surgical practice may be helpful in improving patient outcomes.

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1. Introduction

Forty years of outcomes research in cardiac surgery have provided abundant data from which to analyze gender-specific issues regarding CABG. Determining why females have a longer life expectancy and present with coronary artery disease (CAD) years after males may explain observed outcome differences. Assessing the role of gender in surgical decision making is fundamental, both for assignment of risk and improving processes of care that alter patient outcomes.

The efficacy of CABG for the treatment of CAD has been demonstrated in multiple prospective, randomized control trials [1,2]. Risk profiles among patients with cardiac disease have been intensely investigated, and gender-specific recommendations including use of internal mammary grafts, management of hyperglycemia, and treatment of anemia have improved hospital practice [1]. Although females comprise less than 30% of patients presenting with symptomatic CAD that undergo CABG, they are at risk for higher mortality and experience less relief of angina following coronary intervention [3,4]. Comparing outcomes data requires understanding specific differences in the clinical characteristics between genders [3].

Risk profiles of males and females who undergo CABG vary [3–7], and a given risk factor can impact surgical outcome in a gender-specific fashion. Although definitive conclusions regarding causation and modifiable predictors have not been completely clarified, a number of evidence-based differences have been described. Female sex is an independent predictor of early morbidity and mortality in the perioperative period, with increased risk for death and postoperative complications 2–3% higher than males [3,4,8,9]. Conversely, female gender may provide a survival benefit after 30 days postoperatively [3,10].

Perioperative variables including use of internal mammary grafts, body surface area, blood transfusion, and referral to intervention influence survival and require consideration. Differentiating these modifiable processes from the inflexible risk factor of gender will have a significant clinical impact. A review of disease physiology, risk factors, and surgical outcomes data emphasizes the role of gender as an independent variable in cardiac surgery.

2. Biology

Biological variations influence the development, progression, and posttreatment outcome associated with CABG. The influence of age on the biology of disease is evidence in life-table statistics; on average females live longer than males (77.79 years vs 72.26 years), and present with symptomatic CAD at a more advanced age [3,11–13]. Moreover, CAD in young females less than 55 years of age carries a poor prognosis; mortality is increased 1.7% after myocardial infarction (MI), 4.3% after percutaneous intervention, and 3.4% after CABG compared to matched males [14,15].
Data from angiography, autopsy specimens, and intravascular ultrasound clearly demonstrate that females have smaller coronary arteries than males, with 10—15% smaller diameter of the mid-left anterior descending (LAD) and left main coronary arteries [16,17]. However, the significance of this variation is unclear; smaller vessel size does not necessarily account for increased mortality in females after coronary angioplasty [18].

CAD and the location of atherosclerotic lesions are also gender specific. While the LAD is most commonly diseased irrespective of gender, males are at increased risk for diffuse three-vessel involvement with extensive collateralization [19]. These variations in CAD location are strongly linked to endogenous steroid hormone exposure, increasing risk for postoperative MI, hospital readmission, and inferior short-term survival [19].

Molecular studies and clinical trials that evaluate steroid hormone intermediates highlight hormonal differences associated with gender-specific CAD formation. Estrogen has long been theorized to restrict atherosclerotic development and delay the presentation of symptomatic CAD in females [20]. Based on temporal changes in exposure, hormone replacement is postulated to be protective, restricting CAD development. This effect was first demonstrated following sex-specific reductions in lipid accumulation, with reduced endothelial cell reactivity compared to matched males [20,21]. In addition, estrogen supplementation modulates coronary vasodilation and prevents atherosclerosis following intimal injury [22]. These mechanisms delay arterial disease formation, reduce vascular smooth muscle proliferation, and improve long-term response to vessel injury [23].

Decreased concentrations of androgens upregulate inflammatory cells and influence lipoprotein processing, extracellular signaling, and fibrinolysis; mechanisms that precipitate CAD formation in males [24]. Older males with low bioavailable testosterone are at increased risk for CAD, suggesting that testosterone influences atheroma formation and that supplementation may be protective [25].

However, exogenous supplementation in postmenopausal females has not proved to be clinically useful. Prospective studies including the Heart and Estrogen/Progestin Replacement Studies (HERS) and Women’s Health Initiative have not demonstrated cardioprotective benefits of supplementation, and thrombotic complications associated with conjugated estrogens have been intensely scrutinized [26,27]. Current data are not definitive to explain the divergence between clinical trials and well-established animal models that show a benefit from exogenous estrogen [25].

On the other hand, esterified estrogens, associated with reduced thrombotic risk, might prove beneficial in improving survival via reductions in serum cholesterol and CAD [28].

In summary, endogenous hormones play a complex role in the processing of inflammatory mediators and CAD formation that is gender specific. The role of estrogen supplementation in postmenopausal females continues to remain controversial, and future research directed at gender-specific hormone therapy to reduce atherosclerosis is currently underway.

3. Risk factors

Gender-specific risk factors that influence the presentation and severity of CAD are well defined [1,3,12,14,15,29,30] (Table 1). Explanations for these observations are varied; however, the risk factors themselves may be more important than gender when assessing their impact on outcome data [31—33].

Female gender is an independent predictor of morbidity and mortality after cardiac surgery, and is included on most risk stratification scores [3,4,9,34,35]. Surgical outcome is associated with parameters specific to female gender, namely smaller coronary artery size, fewer bypass grafts, and underutilization of the internal mammary [3,32]. Females more often present with a reduced preoperative hematocrit, lower New York Heart Association (NYHA) functional classification, and increased need for urgent surgical intervention [8]. After adjustment for older age at presentation, diabetes, and the presence of valvular disease, female gender is still an independent predictor of increased mortality after cardiac surgery (3.81% vs 2.43% for males) [34].

Inferior survival and increased morbidity is likely due to patient age and need for urgent revascularization. Females present for CABG in a delayed fashion compared to males—on average 3.1 years later [34]. Advanced age is associated with diabetes, hypercholesterolemia, hypertension, and cerebrovascular disease, each of which may accelerate CAD formation [10,12,14,34—38]. In addition, urgent revascularization increases perioperative mortality several-fold and correlates with fewer placed arterial grafts [34]. The need for urgent revascularization is also linked to the development of CAD at an advanced age in association with significant co-morbidities that influence the severity of symptoms at presentation.

Females are less likely to be smokers, have a prior MI, coronary interventions, or abnormal renal function [39]. Those who exhibit hemodynamic instability during hospitalization are at risk for reduced short-term survival after CABG. Long-term outcome is reduced in the presence of intrinsic lung disease, diabetes, prior heart failure, peripheral vascular disease (PVD), and left main disease [35]. Males more likely present with class 3 or 4 angina, hypertension, and symptomatic PVD [34], and are less likely to have poorly controlled diabetes [3,4,39].

Body surface area (BSA) is an additional risk factor in CABG; a BSA of less than 1.6 m² [2] is associated with a fivefold increased mortality compared with BSA greater than 1.8 m² [2].

<table>
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<th>Table 1. Common risk factors per gender.</th>
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<td><strong>Female preoperative risk factors</strong></td>
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<td>Older age at presentation</td>
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<td>Angina Class 3 or 4</td>
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<td>Urgent surgical interventions</td>
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<td>Preoperative IABP usage</td>
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2.0 m², independent of gender [16]. Females, on average, present with smaller BSA than males which correlates with smaller coronary diameter and reduced graft patency [16]. Insufficient coronary diameter is independently associated with increased risk for postoperative heart failure (3.4—10.5 times increased risk) [4, 16, 40]. On the contrary, larger BSA is associated with decreased hospital mortality [41] and reduced risk for intra-operative hemodilution and blood transfusions which are additional predictors of mortality [42]. Other studies have not demonstrated BSA to be associated with poor outcome, but have shown that smaller BSA increases the risk for low-output cardiac syndrome [42]. Regardless, BSA clearly plays an important role in the use of cardiopulmonary bypass and associated hemodilution.

In evaluating gender-specific risk factors, it is important to emphasize that females possess unique physiology and are not simply ‘smaller males.’ Risk profiles between males and females are vastly different, and extrapolating data from a gender-based comparison may not truly be representative of the actual patient population [37]. Future research directed at risk factor modification and its impact on CABG outcomes will be important for improvements in both short and long-term survival.

4. Outcomes

Following CABG, female patients have considerably higher operative mortality compared to males; in some studies up to twofold greater (Table 2) [3, 4, 9, 15, 16]. Postoperative complications vary; females are more likely to have postoperative Q-wave MIs, prolonged need for pressors, and increased ventilatory requirements [15, 37, 43]. Females are also at increased risk for deep sternal wound infection, postoperative sepsis/endocarditis, and respiratory failure [10]. The risk of cerebrovascular accidents following cardiac surgery is not gender-specific within 24 h postoperatively, and predictors of increased risk for stroke including advanced age, MI, smoking, PVD, postoperative sepsis, and respiratory failure are gender independent [44]. However, after 24 h and until discharge females are more likely to suffer from stroke, usually in the context of poorly controlled diabetes [44].

Five-year survival following CABG is inferior in females, likely due to systemic diseases including renal failure, diabetes, and diffuse atherosclerosis [45]. However, after adjustment of these risk factors, gender is not necessarily associated with reduced 5-year survival [10, 46, 47]. The largest gender-based study of CABG patients to date, including 344,913 patients from the Society of Thoracic Surgery (STS) database, demonstrated a significant increase in operative mortality in females (4.5% vs 2.6% for males) [5]. When patients were classified according to low-, medium-, or high-risk subsets, females had higher mortality rates in the low- and medium-risk groups. However, gender was not independently associated with mortality in the high-risk subset. High-risk females were older, diabetic, obese, and required dialysis. They were also more likely to present in cardiogenic shock after MI and require emergent intervention [5]. Beyond the range of medium- to high-risk, gender appears to play less of a role in cardiac surgical outcome, emphasizing the importance of the risk factors themselves.

5. Referral bias

In examining processes of care that influence outcomes, referral bias and delayed surgical intervention are significant. Studies suggest that females are subject to increased referral delay for surgery compared to males [9]; this is perhaps related to a more frequent presentation with atypical symptoms of MI and resultant delays in hospital admission [9]. ‘Referral bias’ is associated with increased morbidity, particularly following emergent procedures. A review of 2297 patients undergoing CABG demonstrated that females presented with more advanced NYHA functional class and older age compared to males. Females were referred for CABG later in the course of their disease, which correlated with increased risk for perioperative death [48]. Another retrospective review of 2473 patients demonstrated that females who were hospitalized for CAD underwent fewer diagnostic and therapeutic procedures than males, including coronary revascularization and CABG [49]. Additional studies have found gender to be an independent risk factor for referral bias to CABG, but not cardiac catheterization [50].

Improved awareness of heart disease in females has risen as media coverage and public education have increased. Inherent risk factors associated with female gender, including the development of late onset CAD, have been postulated as a cause of delayed presentation for CABG and reduced postoperative survival [8, 36]. As previously stated, women typically are older and more frequently require urgent intervention, have smaller BSA, and are at increased risk for gender-specific co-morbidities associated with perioperative mortality after CABG. A delay in presentation is more likely due to these risk factors, rather than ‘referral bias’, which is ultimately associated with increased risk for perioperative death [36, 43]. For example, in a review series of 1743 patients by Aldea, females were more likely to present with acute or unstable coronary disease, although revascularization was performed with equal frequency irrespective of gender [36]. Additional studies support this hypothesis [4, 46]. At present, however, no definitive conclusions can be made based on the current literature.
6. Long-term outcome

Postoperative recovery following CABG varies by gender, particularly following the 30-day perioperative period. Readmission rates are significantly higher in females than males (20.5% vs 11%), commonly due to recurrent angina and CHF (15.2% vs 8.5% respectively) [9,15], despite the fact that females generally have superior left ventricular function prior to CABG [51]. Associated risk factors for recurrent angina include fewer bypass grafts and decreased use of the IMA [1,3,8,9]. The incidence of sternal wound infection, renal dysfunction, and CHF leading to readmission is also higher in females [9,45]. Volume shifts and transient ischemia in the setting of left ventricular hypertrophy or diastolic dysfunction may also play a role [51].

Females also have a higher incidence of small-vessel disease and may obtain less relief following percutaneous intervention or CABG leading to hospital readmission [9,15]. Graft occlusion and progression of CAD likely contribute to the risk for postoperative angina. When admitted for recurrent angina, females are less likely to undergo repeat attempts at revascularization compared to males (0.6% vs 4.1%) [3], and less often undergo CABG for recurrent disease after percutaneous intervention [52,53].

Current fast track recovery protocols have been created to standardize postoperative care and hospital stay to improve short- and long-term outcome. A review of 517 consecutive ‘fast track’ patients demonstrated that only 30% of females were discharged by postoperative day 5 following on-pump CABG, compared to 44% of males [39]. Older age at presentation, increased incidence of MI, obesity, diabetes, hypertension, and PVD were all associated with increased length of stay. Continued research seeks to evaluate whether female gender is independently associated with slower recovery and increased risk for readmission, and to determine if modification of risk factors and awareness of these trends may improve long-term outcomes.

7. CABG/valve surgery

Combined CABG/valve surgery is associated with higher mortality than CABG alone (increased risk of 4–10%). Increased mortality after combined surgery is gender specific and associated with the presence of diabetes, CHF, hypertension, unstable angina, atrial fibrillation, and urgent procedures. In this setting, females are at increased risk for both mortality and postoperative stroke [54,55].

Males and females present with equal risk for aortic and mixed valvular disease. However, mitral disease is more common in females and usually occurs in the context of previous rheumatic fever (35.7% vs 16.3% in males) [56]. Males tend to present with myxomatous mitral valve disease for which repair rather than replacement is performed. Increased rates of valve replacement in females are associated with perioperative left ventricular dysfunction, arrhythmias, and bleeding [57]. Furthermore, the presence of postoperative mitral regurgitation in the setting of ischemic heart disease is more common in women; this increases the risk for postoperative complications and need for readmission, as well as reducing 5-year survival [58].

Following mitral valve surgery, females have higher in-hospital mortality, associated with advanced age, emergent procedures, and endocarditis [55]. Improvements in operative technique, cardiac protection, and valve technology have decreased mortality for males following CABG/valve surgery (from 6.9% to 0.9% from 1990 to 2000); however, females have shown no significant reduction in mortality under similar conditions [59].

Although risk factor profiles and outcome data favor males in the short-term, females have superior long-term survival after isolated valve and combined CABG/valve surgery. This is true even in the context of associated co-morbidities that preclude favorable short-term survival [59]. Causation for this gender disparity is unknown.

8. Off-pump surgery

Off-pump coronary artery bypass (opCAB) surgery has emerged over the last decade with theorized improvements on adverse effects associated with extracorporeal circuits, including precipitation of platelet dysfunction, coagulopathy, hemodilution, and hypothermia [60,61]. Extracorporeal circulation activates host-defense mechanisms and promotes a systemic inflammatory response [60,61]. Advancements in cardiac stabilizers and improvements in opCAB techniques have led to increased use in the United States; currently 20% of CABG surgeries performed are off-pump [5]. As a result, decreased risk for cerebrovascular accidents, bleeding, and renal failure have been observed [62].

Without the associated morbidity of cardiopulmonary bypass, improvements in opCAB seem to favor female gender with decreased rates of infection, acute respiratory distress syndrome, shock, renal failure, and stroke [63]. OpCAB is associated with decreased transfusion requirements and shorter length of stay [62], with 42–73% decreased mortality compared to on-pump surgery [60,63]. Despite differences in gender-specific risk factors which favor short-term survival in males, opCAB surgery has been associated with reduced operative mortality in females from 4.07% to 1.52% vs 1.8% to 1.3% in males [62].

However, gender-specific outcomes in opCAB vary. In a recent analysis of 2123 patients who underwent isolated opCAB, females received fewer distal anastomoses and suffered higher in-hospital mortality compared to males (2.0% vs 0.8%). Despite these outcomes, multivariate analysis failed to independently associate female gender with significant morbidity or mortality. These data raise some concerns about the surgical equivalency and risk associated with fewer bypass conduits performed in opCAB [64].

Most recently, a prospective evaluation of 1104 opCAB patients with 1-year outcome data was compared to a matched cohort of 1099 on-pump patients, and demonstrated that opCAB was associated with inferior outcomes and graft patency than on-pump procedures [65]. Patients treated by opCAB had fewer grafts placed with an overall graft patency that was significantly lower than the on-pump cohort. Thirty-day survival was not significant between groups [65]. Although these conclusions question the future of opCAB, this study cohort was almost entirely composed of males (99%) with significant multi-vessel disease, making...
gender-specific conclusions impossible [65]. Further studies with gender-specific opCAB outcome data may confirm an important use for this minimally invasive technique.

9. Discussion

Modifying gender-specific practices in cardiac surgery to improve morbidity and mortality remains a significant challenge. Clearly, outcomes are multifactorial and influenced by gender, genetics, and environment, and affected by invasive procedures, inflammatory mediators, and catabolic changes. Specific recommendations for females undergoing CABG have been carefully reviewed in recent STS guidelines (Table 3). Moving forward with the data reviewed may include further gender-specific recommendations to improve results.

The impact of BSA on hemodilution, cardiopulmonary bypass, and transfusion requirements must be considered when operating on smaller patients. Strict guidelines for blood transfusion should be maintained during cardiopulmonary bypass, with clear communication between surgeon, perfusionist, and anesthesia teams. In this regard, opCAB has significant potential with reduced hemodilution and lower transfusion requirements.

The presence of diffuse atherosclerotic changes, particularly in diabetic patients, is more commonly encountered at surgery since the advent of drug eluting stents. Patients referred for CABG often have poor targets and advanced disease. Consideration for arterial grafts is critical, especially in younger patients, and should translate into improved patency and decreased rates of recurrent angina [66].

Adequate replacement of thyroid hormone is important. Data from multiple studies have demonstrated that thyroid hormone improves hemodynamic performance and decreases risk for arrhythmias. Cardiopulmonary bypass results in a euthyroid sick syndrome characterized by decreased total and free T3 levels. Interestingly, reduced thyroid levels are not alleviated by opCAB [67]. The influence of additional factors, including urgency of operation, poor left ventricular function, and diabetes, also plays a role in the stress response and should be considered.

In the current health care environment, frequent readmission and increased hospital length of stay are gaining increased attention. Techniques to reduce length of stay may include stabilizing some patients and performing delayed CABG electively. Detailed patient education at the time of discharge and supportive home resources are important in preventing readmission. Specifically for women, readmission for CHF, despite the lower incidence of decreased ejection fraction compared to males, may be secondary to diastolic dysfunction. This diagnosis requires careful medical management prior to discharge.

Finally, improving readmission rates for anginal symptoms and small-vessel disease with graft occlusion or disease progression is necessary. Aside from arterial grafting, the issue of differential response to aspirin has been demonstrated in primary prevention trials and may impact graft patency. Administration of aspirin and clopidogrel, particularly in patients presenting with acute coronary syndrome, may prevent graft thrombosis [68]. The presence of aspirin resistance and risk for thrombosis also need to be addressed, particularly with the recent debate on endothelial cell disruption associated with endoscopic vein harvest [69].

10. Conclusion

The role of gender is cardiothoracic surgery is a complex issue that influences presentation, biology, risk factors, postoperative complications, and ultimately survival. Recognition of gender-specific risk profiles is essential to understand their impact on survival. Awareness of health care practices that contribute to gender-based differences help minimize modifiable causes of outcome disparities.

New procedures continue to evolve, including minimally invasive and percutaneous therapies, which expand on available therapeutic modalities. An understanding of the risk profiles and processes of care associated with gender, in addition to gender itself, is important for optimal management of both male and female cardiac patients.

References


