# CME Newly Appreciated Pathophysiology of Ischemic Heart Disease in Women Mandates Changes in Perioperative Management: A Core Review

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The assumption that males and females are physiologically similar has led to females being clinically evaluated and treated as males. However, there is growing evidence in the literature that, other than the reproductive system, there are other fundamental physiological differences between the two genders. The manifestation of these differences starts soon after puberty and becomes more pronounced with age. The differences in body mass and volume and renal and liver metabolism account for the difference in therapeutic efficacy and side effects of commonly used cardiovascular drugs. Women have smaller coronary arteries, more frequent diastolic dysfunction, present with vague symptoms of coronary artery disease and do worse than men after revascularization procedures. Women also have a shorter cardiac cycle and are more prone to develop arrhythmias and react differently to antiarrhythmic drugs. Most epidemiological trials that have assessed the utility of pharmacological myocardial protection or outcomes after noncardiac surgery have either been performed on men only or women were not identified as a separate group. Recent evidence is suggestive that coronary vasospasm may be the dominant etiology of acute myocardial ischemia in women. This may explain the poor sensitivity and specificity of the routine myocardial perfusion tests. Having considered all this evidence, it has become very essential to view the operative risk stratification as being gender-based. This approach may involve a shift in our present day paradigm of patient management.

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Coronary artery disease (CAD), not cancer, is the leading cause of death in women; 1 in 30 women dies of breast cancer, whereas 1 in 6 women dies of CAD.[1] Dr. Bernadette Healy in 1991 brought attention to this fact by describing the "Yentl Syndrome."[2] She reported that because of the atypical nature of symptoms, there was a tendency not to recognize CAD in women.[2] Yentl, a woman, was the main character in a short story by Isaac Singer, in which she had to dress and act like a man to be able to attend school. This provocative title was a not so subtle reference emphasizing that until quite recently, despite the obvious physiological differences, women had to present themselves as men to receive the same treatment. And, even now if the women do not demonstrate the specific symptoms described in men, they may receive inferior medical care.

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This paper will review the major physiological differences between men and women with CAD and discuss the potential ramifications for preoperative screening for CAD. I will review the differences in the perioperative care of women and men undergoing cardiac and noncardiac surgery, which may be responsible for differences in outcome. Finally, I will review current recommendations, as well as needs for further studies regarding gender-specific perioperative cardiovascular risk stratification.

Women's physiological response to cardiovascular abnormalities is different from men. They have a higher rate of congestive heart failure (CHF), despite normal ejection fraction (EF), than men after myocardial infarction (MI).[3] Women also have a higher prevalence of diastolic heart failure.[4] Women also tend to develop more severe left ventricular (LV) hypertrophy and maintain normal LV systolic function for a longer time when exposed to higher after-load, e.g., hypertension and aortic stenosis.[5,6] The Society of Thoracic Surgery database analysis for the first time revealed that the incidence of postoperative MI, CHF, renal failure, and neurological dysfunction in females after coronary artery bypass surgery was significantly higher than in men.[7–10]

Female gender is also an independent predictor of adverse outcome (short- and long-term) after combined valve and revascularization procedures, and women

**Table 1.** Morbidity Model from Stepwise Logistic Regression Analysis: Comparison of VA and Private Sector Females and Males Undergoing Vascular Surgery

| | | Adjusted odds ratio | | 95% Confidence interval | |
|---|---|---|---|---|---|
| Step | Variable | Females | Males | Females | Males |
| 1. | ASA class | | | | |
| | 4/5 vs 1/2 | 3.21 | 1.34 | 2.24–4.63 | 1.16–1.56 |
| | 3 vs 1/2 | 2.36 | 1.06 | 1.75–3.24 | 0.92–1.12 |
| 2. | Serum albumin | 0.68 | 0.84 | 0.58–0.79 | 0.80–0.90 |
| 3. | Work relative value units | 1.06 | 1.07 | 1.05–1.07 | 1.07–1.08 |
| 4. | Bleeding disorders | 2.03 | 1.40 | 1.57–2.62 | 1.24–1.57 |
| 5. | Ventilator dependent | 2.74 | 2.46 | 1.68–4.52 | 1.86–3.26 |
| 6. | Wound infection | 1.61 | 1.47 | 1.32–1.96 | 1.36–1.58 |
| 7. | Emergency | 1.56 | 1.61 | 1.24–1.96 | 1.46–1.77 |
| 8. | History of COPD | 1.52 | 1.17 | 1.20–1.94 | 1.17–1.36 |
| 9. | Hospital effect (VA vs non) | 0.60 | 0.84 | 0.44–0.81 | 0.78–0.92 |
| 10. | Alkaline phosphatase >125 U/L | 1.28 | Not done | 1.04–1.56 | Not done |
| 11. | >2 alcohol drinks/d | 2.04 | Not done | 1.14–3.55 | Not done |
| 12. | Steroids | 1.44 | 1.18 | 1.06–1.95 | 1.00–1.38 |
| 13. | Blood urea nitrogen >40 mg/dL | 1.37 | 1.15 | 1.04–1.81 | 1.03–1.29 |

Total sample size for women, $n = 3986$; overall morbidity rate = 22.3%.

Total sample size for men, $n = 35{,}051$; overall morbidity rate = 17.96%.

In addition males had 21 more steps/factors in the stepwise logistic regression analysis, which were not assessed in females.

VA = veterans affairs; ASA = American Society of Anesthesiologists; COPD = chronic obstructive pulmonary diseases.

Work relative value units: index of complexity of operation (obtained from Medicare Website).

Preoperative variables: ASA class, hematocrit, serum BUN, alkaline phosphatase, alcohol use, steroid use.

Operative variables: emergency, work relative units.

Postoperative variables: infection, ventilator dependence.

Adapted from:

1. Johnson RG, Wittgen CM, Hutter MM, et al. J Am Coll Surg 2007;204:1137–46

2. Hutter MM, Lancaster RT, Henderson WG, et al. J Am Coll Surg 2007;204:1115–26

have a higher postoperative mortality (7% vs 4%) than men.[11] However, there is evidence that the women may have worse prognosis than men in the immediate postoperative period but may have comparable outcomes in the long term.[12–14] The likelihood of more frequent postoperative complications is not limited to open revascularization procedures. Women also have an increased incidence of morbidity and mortality (bleeding and vascular complications) after percutaneous coronary interventions and angioplasty for myocardial revascularization than age-matched men.[15–17]

The likelihood of women demonstrating worse outcomes than men is not unique to cardiac surgical procedures. Women have a lower relative 5-yr survival than men after elective abdominal aortic aneurysm surgery (88% vs 95%) and demonstrate higher mortality after ruptured abdominal aortic surgery (90.2% vs 75.6%).[18] There is also a higher risk of stroke after carotid endarterectomy (3.3% vs 2.1%) and a lower incidence of graft patency after peripheral vascular surgery (54% vs 74%).[18] The differences in outcome may be due to lack of consideration of unique physiological differences (body size and surface area) in designing therapeutic protocols for women for high-risk noncardiac surgery.[19–22]

Short-term higher mortality and morbidity in women is probably multifactorial. It can be attributed to a more frequent incidence of CAD presenting acutely and with CHF, and a higher prevalence of comorbidities (diabetes, hypertension, valvular heart disease, and old age) at the time of presentation.[11,14,23] But, the inferior cardiovascular morbidity and mortality statistics even after noncardiac surgery[18,24–27] are suggestive of more fundamental anatomical and physiological differences. These factors may significantly affect the outcomes after similar degrees of physiological derangement between genders.

Despite being "well established," the gender-based difference in outcome is not a very well-known fact. And perhaps this apparent ignorance of women as a different patient group is also responsible for lack of development of any gender-based therapeutic protocols. A recent multicenter study comparing the 30-day postoperative morbidity and mortality between Department of Veterans Affairs and private university hospitals after general and vascular surgery did identify women as a separate group in their analysis. But, in the final analysis, they compared men in the Veterans Affairs hospitals with men in the private university hospitals, and a similar comparison between women in the two groups was performed. A morbidity and mortality comparison between men and women in each group or between the two groups was not performed. Also in the final stepwise logistic regression analysis, men were evaluated for more perioperative risk factors than women[28–31] (Tables 1 and 2).

Similarly, major randomized trials assessing the effects of $\beta$-adrenergic blocking drugs, renin-angiotensin enzyme inhibitors, calcium channel blockers, antiarrhythmics, statin drugs, and antiplatelet drugs were

**Table 2.** Mortality Model from Stepwise Logistic Regression Analysis: Comparison of VA and Private Sector Females and Males Undergoing Vascular Surgery

| | | Adjusted odds ratio | | 95% Confidence interval | |
|---|---|---|---|---|---|
| Step | Variable | Females | Males | Females | Males |
| 1. | Ventilator dependent | 3.38 | 1.68 | 1.77–6.46 | 1.20–2.33 |
| 2. | ASA class | | | | |
| | 4/5 vs 1/2 | 16.73 | 3.88 | 3.48–300.46 | 2.34–6.99 |
| | 3 vs 1/2 | 8.38 | 2.01 | 1.80–149.24 | 1.22–3.60 |
| 3. | DNR | 5.53 | 3.20 | 2.50–11.86 | 2.38–4.26 |
| 4. | Emergency | 3.00 | 1.92 | 2.05–4.36 | 1.63–2.26 |
| 5. | Serum albumin | 0.59 | 0.64 | 0.44–0.78 | 0.58–0.71 |
| 6. | Age | 1.03 | 1.04 | 1.02–1.05 | 1.03–1.04 |
| 7. | Weight loss >10% | 2.76 | 1.51 | 1.41–5.12 | 1.71–1.92 |
| 8. | Pneumonia | 2.97 | 1.58 | 1.34–6.52 | 1.13–2.19 |
| 9. | Impaired sensorium | 2.19 | 1.43 | 1.25–3.76 | 1.12–1.81 |
| 10. | Hematocrit >45% | 3.04 | Not done | 1.28–6.52 | Not done |
| 11. | Blood urea nitrogen >40 mg/dL | 2.07 | Not done | 1.29–3.25 | Not done |
| 12. | Work-related value units | 1.03 | 1.04 | 1.01–1.05 | 1.04–1.05 |
| 13. | Coma | 12.61 | 2.72 | 1.78–258.70 | 1.23–6.10 |
| 14. | CVA with neurological deficits | 1.75 | 1.44 | 1.08–2.76 | 1.22–1.70 |
| 15. | Platelets <150,000 $mm^3$ | 1.70 | 1.58 | 1.03–2.72 | 1.32–1.88 |
| 16. | Dyspnea | | | | |
| | On exertion vs none | 1.95 | 1.31 | 1.09–3.39 | 0.99–1.73 |
| | At rest vs none | 1.39 | 1.28 | 0.91–2.09 | 1.10–1.49 |

Total sample size for women, $n = 3986$; overall mortality rate = 22.3%.

Total sample size for men, $n = 35{,}051$; overall mortality rate = 3.53%.

In addition males had 10 more steps/factors in the stepwise logistic regression analysis, which were not assessed in females.

VA = veterans affairs; ASA = American Society of Anesthesiologists; DNR = do not resuscitate; CVA = cerebrovascular accident; work relative value units: measure of the complexity of the case.

Preoperative variables: ASA class, DNR status, weight loss >10%, hematocrit, platelet count <150,000 $cm^3$, serum albumin, serum BUN, alkaline phosphatase, alcohol use, steroid use, impaired sensorium, neurological deficits, dyspnea, ventilator dependent.

Operative variables: emergency, work relative units.

Postoperative variables: infection, ventilator dependence.

Adapted from:

1. Johnson RG, Wittgen CM, Hutter MM, et al. J Am Coll Surg 2007;204:1137–46.

2. Hutter MM, Lancaster RT, Henderson WG, et al. J Am Coll Surg 2007;204:1115–26

performed in males only, or females were not identified as a separate group[32–47] (Table 3). Even the trials that have actually demonstrated gender-based differences in the metabolism of drugs have not been translated into a change in the management protocols. Hence, despite this overwhelming evidence in the literature of the inequality between genders, the legacy of the Yentl Syndrome lives on.

### Gender-Based Differences in the Incidence/Presentation and Diagnosis of CAD

It is generally believed that women are somehow protected against CAD by sex hormones but only during their fertile age, and this protection precipitously fades after menopause. The incidence of CAD increases in both men and women as they age, but that the acceleration or step-up in incidence occurs 10 yr earlier in men than in women.[1] In men, the rate of the first major cardiovascular event is 7/1000 between ages 35–44 yr and increases to 68/100 between ages 85–94 yr. However, it has been demonstrated that CAD-related mortality in women has always been higher than that due to malignancies (38% in CAD vs 22% malignancies).[48] In Europe, 55% of the women die of CAD annually when compared with 43% of men. Almost a quarter-million women die from CAD every year and "almost every minute, a woman in the United States dies of cardiovascular disease."[49] Another alarming statistic is the progressive increase in the incidence of CAD in older women as opposed to men in whom this incidence is decreasing, especially in younger men, yet CAD is considered a man's disease.[50]

Women differ in their clinical manifestation of ischemic heart disease and 43% of women do not demonstrate chest pain as a presenting symptom of angina.[51] Traditional diagnostic tests for CAD have different sensitivity and specificity between genders and the seminal Coronary Artery Surgery Study revealed that women were 4.5 times more likely to manifest a false-positive exercise test response even in the presence of normal coronary angiography.[52] This finding was recently reconfirmed in the Women's Ischemia Syndrome Evaluation study, which showed that almost 60% of women investigated for chest pain have no flow-limiting lesions in their coronary arteries, despite evidence of persistent chest pain.[53] This reinforces the observation that because of atypical symptoms the women experiencing actual ischemia are not selected for intervention. It is speculated that microvascular coronary involvement is the likely source of misdiagnosis and mistreatment.[54]

**Table 3.** Major Randomized Trials Comparing the Effects of Different Drugs on Genders

| | Clinical trial | Year | No. of patients | Gender M/F | Outcome |
|---|---|---|---|---|---|
| 1. | Mangano, et al.[42] Studies involved | 1996 | 200 | 200/0 | No gender-based analysis |
| 2. | Wallace, et al.[47] assessment of | 1998 | 200 | 200/0 | No gender-based analysis |
| 3. | Poldermans, et al.[44] beta adrenergic | 1999 | 112 | 112/0 | No gender-based analysis |
| 4. | Raby, et al.[45] blocking drugs | 1999 | 201 | 201/0 | No gender-based analysis |
| 5. | Boersma, et al.[33] | 2001 | 1097 | 1097/0 | No gender-based analysis |
| 6. | Luzier, et al.[40] (Pharmacokinetic & Pharmacodynamic differences in metoprolol) | 1999 | 20 | 10/10 | Clearance M > F, greater drug exposure in females |
| 7. | Gottlieb, et al.[36] (Cooperative Cardiovascular Database) pts with myocardial infarction | 1998 | 201,752 | 109,193/92,559 | No gender-based analysis |
| 8. | Stone, et al.[46] | 1988 | 128 | Not specified | No gender-based analysis |
| 9. | Lindenauer, et al.[39] (Premier Prospective Database for Quality and Use of Healthcare) | 2005 | 663,635 | 304,795/358,824 | Final analysis did not look at women as a separate group with risk score |
| 10. | Kodaka, et al.[37] (Propofol dosing study) | 2006 | 50 | 25/25 | Women required higher dose. Clearance M > F |
| 11. | Eidelman, et al.[35] (Aspirin for primary prevention)literature research | 2003 | 55580 | 44,114/11,466 | No gender specific analysis |
| 12. | Dahlof, et al.[34] (Amlodipine/Perindopril vs Atenolol/Diuretic) | 2005 | 19,257 | 14.472/4785 | Amlodipine was superior in females for hypertension. Higher mortality for females with atenolol therapy |
| 13. | Makkar, et al.[41] (Utility of antiarrhythmic drugs) meta-analysis | 1993 | 332 | 100/232 | Women have more likelihood of Torsade de point after antiarrhythmic drugs |
| 14. | Mehilli, et al.[43] (Sex and effect of abciximab) retrospective analysis | 2007 | 2022 | 1524/498 | Female experience major bleeding 3.6% vs 0.75% |
| 15. | Krecic-Shepard, et al.[38] (Clearance of Verapamil in men vs women) | 2000 | 84 | 42/42 | 1.8 times increase drug concentration in females |
| 16. | Alexander, et al.[32] (Women on GPIIb/IIIa inhibitors | 2006 | 39,730 | 20,449 Males | Women have higher incidence of bleeding secondary to decreased clearance of drugs |

Hence, women seem to differ from men in the etiology, clinical presentation, diagnosis and, above all, the incidence and nature of cardiovascular complications. Despite these obvious differences, there is surprising paucity of literature addressing the potential causes and management strategies tailored specifically for women. The clinical importance of women as a separate group with its own unique physiological response to CAD was further elaborated when the American Heart Association released evidence-based guidelines for the prevention of cardiovascular disease in women. Also, a risk assessment system for women was described based on data specific for women (Tables 4 and 5).[55]

With this background, it is reasonable to state that the assumption of "physiological equality" between the genders is erroneous and at least subject to question.

## Pathophysiologic Differences

The cyclical hormonal changes that females undergo during their lives (menstrual cycle/pregnancy/ menopause) may be responsible for the varied cardiovascular physiological responses. Endogenous steroid hormones may have an important role in cardiovascular protection and their absence increases the risk for CAD in older women. It had been believed that the beneficial effects of estrogen were possibly due to its favorable effects on serum cholesterol.[56,57] Only in the 1990s it was realized that estrogen receptors were involved in modulating normal endothelial function and also in prevention of atherosclerosis.[58,59]

### Sex Steroid Hormonal Effects

Estradiol levels are higher in prepubertal girls than boys, and thereafter at puberty the cyclic variation of estrogen and progesterone starts in women and continues for almost four decades.[60] The plasma estrogen levels remain at the premenopausal levels in the perimenopausal period but decline precipitously and to only one-tenth the level during menopause.[60] Other than modulating menstrual cycle, estrogen has antiatherosclerotic effects, reduces cellular hypertrophy, and also has antioxidant and antiinflammatory properties.[61] Estrogen can cause vasodilatation through an increase in nitric oxide (NO) levels and induction of

**Table 4.** Guidelines for Prevention of Cardiovascular Disease in Women (American Heart Association): Clinical Recommendation

| | |
|---|---|
| Life Style Interventions | |
| Cigarette smoking, physical activity , rehabilitation, dietary intake, weight maintenance/reduction, omega-3 fatty acids, depression | |
| Major risk factors | Interventions |
| Blood pressure control | Optimal level <120/80 mm Hg<br>Control through lifestyle and pharmacotherapy<br>Pharmacotherapy for BP ≥140/90 mm Hg<br>Recommended drugs: thiazide diuretics. β Adrenergic blocking drugs and ACE inhibitors |
| Lipids and lipoprotein levels | Optimal levels<br>LDL-C <100 mg/dL<br>HDL-C >50 mg/mL<br>Triglycerides < 150 mg/mL<br>Non-HDL-C < 130 mg/dL<br>Pharmacotherapy<br>LDL-C reduction to <70 mg/dL required for high risk women with ischemic heart disease<br>Niacin or fibrate therapy when HDL-C is low or non-HDL-C is elevated in high risk women<br>For intermediate and low risk women- based on relative risk reduction |
| Diabetes mellitus | Lifestyle and pharmacotherapy as indicated in women with diabetes to achieve a $HbA_{1C}$ <7% |
| Aspirin | 75–325 mg/d for high risk women. Clopidogrel if aspirin is contraindicated |
| β Adrenergic blocking drugs | Should be indefinitely used in ALL women after MI, acute coronary syndrome, or LV dysfunction with or without CHF symptoms unless contraindicated |
| ACE inhibitors | Should be used in women unless contraindicated:<br>After MI<br>With clinical evidence of CHF<br>LVEF ≤40%<br>Diabetes mellitus |
| Aldosterone blockade | Should be used:<br>After an MI (without history of renal dysfunction or hypokalemia when already receiving other drugs and have an LVEF ≤40% |

BP = blood pressure; ACE inhibitor: angiotensin converting enzyme inhibitor; LDL = low-density lipoprotein; HDL = high-density lipoprotein; MI = myocardial infarction; LV = left ventricle; CHF = congestive heart failure; LVEF = left ventricular ejection fraction.

Adapted from Mosca L, Banka CL, Benjamin EJ, et al. J Am Coll Cardiol 2007;49:1230–59. Used with permission from Elsevier.

**Table 5.** Classification of Cardiovascular Risk in Women (American Heart Association)

| Risk status | Criteria |
|---|---|
| High risk | Established coronary artery disease<br>Cerebrovascular disease<br>Peripheral arterial disease<br>Abdominal aortic aneurysm<br>End-stage or chronic renal disease<br>Diabetes mellitus<br>10-year Framingham global risk >20% |
| At risk | ≥Major risk factors for CVD including<br>Cigarette smoking<br>Poor diet<br>Physical inactivity<br>Obesity<br>Family history of premature CVD<br>Hypertension<br>Dyslipidemia<br>Evidence of subclinical vascular disease (coronary calcification)<br>Metabolic syndrome<br>Poor exercise capacity on treadmill/ abnormal heart rate recovery after stopping exercise |
| Optimal risk | Framingham global risk <10% and a healthy lifestyle with no risk factors |

CVD = cardiovascular disease.

Source: Mosca L, Banka CL, Benjamin EJ, et al. J Am Coll Cardiol 2007;49:1230–59. Used with permission from Elsevier.

the NO synthetase gene.[62] Vasodilatation and cyclical arterial blood pressure changes can even be appreciated during the normal menstrual cycle with variations in hormonal levels.[63,64] This leads to lower systolic blood pressure in premenopausal women when compared with age-matched men. Conversely, a lack of the cyclic vasodilatory effect of estrogen during menopause causes a progressive increase in the incidence of hypertension and increased pulse pressure during menopause.

The role of estrogen in modulating vascular wall elasticity, vasodilatation, and in determining the stability of atherosclerotic plaques in the coronary arteries may explain the differences in pathophysiology of CAD between men and women.[65] There is growing evidence that estrogen receptors can mediate cell transduction pathways at the cell membrane level. In the myocardium, these signal cascades control rapid vasodilatation, inhibition of response to cell injury, and control of the size of cellular injury after MI and attenuation of myocardial hypertrophy.[66–70]

Menopause is also associated with a change in serum lipid profiles, with a rapid decrease in high-density lipoprotein (HDL) levels accompanied by an increase in low-density lipoproteins and triglyceride

levels.[71,72] It has been shown that hormonal replacement therapy decreases low-density lipoprotein level and increases HDL levels but also increases triglyceride levels. However, the potential benefits of hormonal therapy in optimizing serum lipid profile may be offset by an increased incidence of thromboembolism with the replacement therapy apart from other complications such as an increased risk of breast and uterine cancer.[72]

In women, the presence of sex hormones leads to attenuated sympathoadrenal activation. Also the sympathoadrenal inhibition is augmented because the pathways regulating the sympathetic nervous system appear to be less sensitive to excitatory stimuli and more sensitive to inhibitory stimuli when compared with men.[64,73–75] This protective mechanism is believed to be eliminated with the onset of menopause. However, postmenopausal hormone replacement therapy has not been shown to decrease the incidence of these complications.[76–78]

With the recent awareness of the Takotsubo syndrome, it is evident that females can develop acute left heart failure with emotional or physical stress in the absence of any occlusive CAD.[79,80] This syndrome is predominantly observed in postmenopausal women and the probability of developing this syndrome is increased with a history of diabetes mellitus, hypertension, hyperlipidemia, smoking, and obesity.[81] Postmenopausal women presenting with this syndrome have been shown to have higher levels of catecholamine levels in almost 70% of the cases, indicating that it is adrenergic-mediated effect under stress.[81] The global issue of hormones and vascular relaxation, coronary atherosclerosis and restenosis, and modulation of catecholamine response deserves further study.

Women also have a higher incidence of undiagnosed diabetes mellitus.[82] Diabetes itself increases the risk of CAD to 3%–7% in women when compared with 2%–3% increase in men over and above the other risk factors. The presence of metabolic syndrome in women almost doubles the incidence of CAD.[40] The term "metabolic syndrome" is used to define a specific body habitus (abdominal adiposity) along with the presence of two to three risk factors, such as high blood pressure, an increased blood glucose/insulin resistance, and an increase in triglyceride/high-density lipoprotein ratio. This syndrome is associated with a higher incidence of CAD.[50] It is more prevalent in women, as almost 45% of the female population meets the criteria of the metabolic syndrome.[83,84] The balance of endothelial damage and repair is disrupted in the metabolic syndrome, enhancing arterial atherosclerosis.[85,86] It has been shown that the restoration of endothelial function leads to a seven-fold decrease in cardiovascular events in metabolic syndrome.[87]

The role of hormone therapy for postmenopausal women has been controversial. It has recently been suggested that hormone replacement therapy may be beneficial if initiated between the ages of 50 and 59-yr-of-age or within 10 yr of menopause than after 10 yr of menopause.[88–91] This suggests that estrogen may be protective before atherosclerosis sets in the vessels and it may not be beneficial after that.

### LV Hypertrophy and Diastolic Dysfunction

There are very few cardiovascular differences between the genders until the onset of puberty.[92] However, shortly after, LV mass increases more rapidly in men and is 15%–30% larger than in women during early adulthood[93–98] (Table 6). As opposed to younger men, younger women have a more favorable remodeling of the LV in response to increased after-load with less LV dilation,[5,99,100] predisposing them to more severe diastolic dysfunction in later life.[101,102] The higher incidence of diastolic dysfunction may be multifactorial, and in addition to the preserved systolic function a combination of hypertension, stiffer aorta and higher total peripheral resistance may also be responsible for increased incidence of diastolic heart failure.[5,62,74,75,103,104] Women in general have smaller heart size, smaller end diastolic and end systolic volume, but increased peak and end systolic pressure. Stroke volume is smaller in women, but the cardiac output is normal due to a higher baseline heart rate in women. Initially, women have higher systolic and arterial elastance; later the elastance decreases in arteries and women develop lower diastolic compliance leading to greater loading sensitivity in women despite normal EF.[61]

Estrogen favorably affects the collagen synthesis and, through its effects on the rennin-angiotensin system, NO, and calcium handling may be beneficial in preserving diastolic distensiblity in this age group.[62] It has been shown that ER-$\alpha$ (estrogen receptor-$\alpha$) and ER-$\beta$ (estrogen receptor-$\beta$) are upregulated by pressure overload. We need further studies to assess the sex-specific prohypertrophic or antihypertrophic remodeling pathways for deriving future therapies and interventions.

### Coronary Artery Physiology

Women have smaller coronary arteries and lesser collateral circulation than men, thus leading to increased incidence of ischemia during increased myocardial work.[105,106] Coronary vessel diameter is independent of body surface area and the smaller coronary diameter cannot be attributed to the smaller body surface area in females.[106] Women's hearts, when transplanted into other females, show little coronary artery changes over time, but when transplanted into men, show progressive coronary enlargement independent of body size and LV hypertrophy.[53,107,108] The donor hearts in these studies were from premenopausal women and were transplanted into men and postmenopausal women (both groups with very low estrogen levels). In addition, immunosuppression suppresses estrogen levels.[107] The exact mechanism of this phenomena is unknown but appears to be multifactorial.[107] Sex hormones,

**Table 6.** Physiological Differences Between Genders

| | |
|---|---|
| *Body composition* | |
| More muscle mass | Consequence of effects of gonadal hormones on skeletal muscles |
| More bone mass | |
| Lower body fat percentage | |
| *Pulmonary physiology* | |
| Males have | Limited exercise capacity in females with aging |
| Larger lungs | |
| Wider airways | |
| Greater lung diffusion capacity | |
| *Neurocognitive function* | |
| Males have | Differences result from fetal exposure to steroid hormones and receptors for steroid hormones in multiple parts of brain |
| Lesser stress glucocorticoid response | |
| Different pain threshold and cognitive style | |
| Different level sex steroid receptors in the autonomic control regions | |
| *Cardiovascular physiology* | |
| Males have | 1. Differences in HR and QT interval manifest after adolescence. |
| Greater LV mass and size | |
| Same EF as females—hence females have a smaller stroke volume | 2. BP lower in than men in premenopausal women. |
| Women have | 3. BP rises to levels equalants of men in postmenopausal women. |
| Lower resting BP | |
| Higher heart rate | 4. Increased PP, reduced LV volume, and stiffness |
| Reduced tolerance to orthostatic stress | |
| Impaired venous return | |
| Prolonged Q-T interval | |
| *Renal physiology* | |
| Men have | Lack of correction of reduced GFR and creatinine clearance during drug dosing can lead to toxic drug levels |
| 15% more creatinine clearance | |
| 25% more GFR | |

LV = left ventricle; BP = blood pressure; HR = heart rate; EF = ejection fraction; PP = pulse pressure.

Source:

1. Leinwand LA. J Clin Invest 2003;302–7
2. Blair ML. Adv Physiol Educ 2007;31:23–5

such as estrogen, take part in arterial remodeling and modulating the vasodilatory effects by increasing the NO levels. Also, estrogen causes favorable vascular effects by affecting the vascular collagen synthesis and degradation, inhibiting smooth muscle cell growth, the rennin-angiotensin system, and the aldosterone hormone.[62,64]

### Electrophysiology

A finding of particular interest for perioperative management is the observation that baseline heart rate is 4–5 beats higher in women.[73] It has been shown to be related to sinus node automaticity. Women have more baroreflex sensitivity; hence, rapid alterations of arterial blood pressure can be controlled better, but with less heart rate response to these blood pressure changes.[109] After puberty, the rate-corrected QT interval is prolonged in women along with a shortened sinus node recovery time. The implications of a prolonged QTc are considered further in this article.[41,110] The length of the cardiac cycle is longer in men when compared with that in women in whom it varies with the stage of menstrual cycle and is prolonged during menstruation[111] (Table 6). Women also develop more pathological tachycardia and atrioventricular nodal reenterant tachycardias than men.[109] Men are more than 1.5 times likely to have atrial fibrillation than females in all age groups.[112,113] But, since there are twice as many >75-yr-old women than men, the absolute number of women with atrial fibrillation is more than men.[109]

The above discussion clearly illustrates that the physiological milieu in women is significantly different than men resulting in differing incidences, presentations, and outcomes of cardiovascular disease.

## Preoperative Risk Stratification

Women not only differ in the etiology, pathogenesis, and presenting symptoms of CAD, the accuracy of routine diagnostic tests for cardiovascular risk stratification is also radically different in women. Preoperative risk stratification has to be based on the epidemiological evidence of the existence of gender as a separate risk factor. For an appropriate risk stratification, it is important to identify women with intermediate or high risk factors with appropriate diagnostic criteria and then follow-up with a gender-based preventive approach.[114]

Chest pain is generally not the typical presenting symptom of angina in women.[115] The majority of the women have vague symptoms during angina, such as fatigue, dyspnea, and lack of energy.[51] Older women present more commonly as acute coronary syndrome or severe LV failure after physical or mental stress. Since myocardial ischemia is common in the absence of coronary artery narrowing in women, anginal attacks can be confused with depression and mental

stress, which is three times more common in women than in men, frequently leading to misdiagnosis and eventually mistreatment.[72,116] Almost 50% of women have normal coronary arteries, despite an abnormal myocardial stress test when compared with 17% of men.[117]

The routine tests for assessment of CAD and risk stratification are geared to diagnose stenotic lesions in the coronary arteries of more than >60% severity. The positive-predictive value of the exercise stress test is lower for women due to earlier fatigue and an impaired ability to reach target heart rate.[118,119] In addition, these tests may also have decreased diagnostic accuracy in women because their ischemia is often caused by coronary vasospasm versus flow-limiting coronary artery stenosis.[52,53,73,117,120–122] Hence, an apparently negative stress test in the presence of specific risk factors is of little value in the assessment of prognosis. In premenopausal women, endogenous estrogen may have a digoxin-like effect during the stress test leading to ST segment changes, resulting in false positive results.[65] The QRS duration on the 12-lead electrocardiogram has been found to be a strong predictor of cardiovascular outcome in women. A wider QRS complex in women with chest pain and preserved systolic function is associated with adverse cardiovascular events independent of CAD severity.[123,124]

Since the relationship between endothelial dysfunction and CAD has been established, this vascular endothelium dysfunction, e.g., lack of response to vasodilator therapy, may also be used as a prognostic index.[122] Furthermore, if the endothelial dysfunction is a prognostic indicator in women, it should be the target for the therapeutic interventions and reversibility should signify improved cardiovascular performance.[53] This hypothesis was tested in a study of 400 postmenopausal women with hypertension during the assessment of the response of their brachial artery to chemically mediated vasodilatation.[87] The women were followed-up in the ambulatory setting for an average of 6–7 mo and the cardiovascular event rate was seven-fold higher in women in whom the flow-mediated vasodilatation did not improve in the brachial artery by 10%.[87] The optimum investigation for the assessment of cardiac performance in women includes ventricular function assessment, regional flow assessment, assessing vessel wall abnormalities, and identifying markers of inflammation (C-reactive protein, amyloid A).[53,65]

It may be more prudent to use a gender-based preoperative risk stratification approach. Indirect evidence suggests that traditional tests for risk stratification have lower sensitivity and specificity in women than men.[65] Thus, it may be more appropriate to develop a prognosis-based approach and identify the culprit patient as opposed to the culprit stenosis.[125] It may be important to manage the women with the specific risk factors with a gender-based protocol.

Preoperative clinics may risk-stratify female patients based on the "Aloha approach."[126] According to this protocol, female patients should be identified as high risk if they are >55 yr of age and have history of smoking, hypertension, HDL <40 mg/dL, and a strong family history of CAD. Diabetes mellitus, established atherosclerotic disease, or renal insufficiency should be considered CAD equivalents and women with these comorbidities should be managed appropriately. The exact definition of gender-based appropriate management of these high-risk patients is not well defined. The change in management may involve preoperative risk stratification for women based on the presence or absence of specific risk factors rather than the traditional risk stratification. Because of the vague presentation of CAD, it may be important to have a detailed questionnaire designed specifically for women. Functional capacity in women should be assessed more carefully and objectively because women are more likely to have a sedentary life style. Traditional tests of myocardial function and perfusion should be analyzed in the presence or absence of the already described risk factors. In addition, the failure of the female patients to achieve the predicted heart rate due to either physical exhaustion or inability to increase their heart rate further decreases the utility of these investigations. The presence of a normal EF should not be considered absolute evidence of the normalcy of myocardial function, especially in women, who have a more frequent incidence of diastolic dysfunction. New risk assessment paradigms, such as inflammatory markers and coronary flow reserve (ratio of myocardial blood flow during hyperemia to myocardial blood flow at rest) for myocardial ischemia, may be the future strategies for risk stratification.

### Differences in pharmacokinetic and pharmacodynamics

Women have been known to respond differently to multiple drugs.[127–135] For the purposes of this article, I have limited the discussion to a few of the drugs that are routinely used intraoperatively. It is becoming obvious that alteration of dosages to women simply based on their body surface area may not be entirely correct, because it seems that a host of other physiological factors determine the differences in response to these drugs, e.g., antiarrhythmics, and calcium channel blockers which have a different response pattern in females.

Gender-related and hormonal effects on drug distribution and effects have been known for the last 70 yr. However, these discrete differences have not been translated into gender-based therapeutic regimens.[136] Different hormonal levels in premenopausal stages affect protein binding, body weight, and fat distribution, leading to a different volume of distribution and relatively decreased glomerular filtration rate. These

**Table 7.** Selected Studies Evaluating the Difference in Metabolism of Drugs Commonly Used in Anesthetic Practice

| *Clearance* | | Mean clearance mL/kg/min | | |
|---|---|---|---|---|
| Drug | Patients | Males | Females | |
| Lidocaine | 9 males, 9 females | 55.2 | 42.2 | Wing, et al.[133] |
| Midazolam | 10 males, 10 females | 20.4 | 15.2 | Thummel, et al.[132] |
| Midazolam | 9 males, 11 females | 8.8 | 19.7 | Greenblatt, et al.[129] |
| Verapamil | 6 males, 6 females | 15.8 | 27.5 | Sasaki, et al.[130] |
| Verapamil | 6 males, 6 females | 9 | 8.8 | Schwartz, et al.[131] |
| Methadone | 11 males, 9 females | 0.03 | 0.021 | De Vos, et al.[128] |
| *Distribution* | | | | |
| 1. Diazepam | Less metabolism than men | Xu, et al.[134] | | |
| 2. Vecuronium | | Xu, et al.[135] | | |
| 3. Rocuronium | | Shwartz[137] | | |
| *Metabolism* | | | | |
| 1. Clonazepam | Less metabolism than men | Boudikova, et al.[127] | | |
| 2. Levo DOPA | | Shwartz[137] | | |
| 3. Caffeine | | | | |
| 4. Meteoprolol | | | | |
| 5. Propranolol | | | | |
| 6. Codeine | | | | |
| 7. Alfentanil | More than men | | | |

factors affect drug pharmacokinetics and pharmacodynamics.[137] In postmenopausal women, there is larger volume of distribution of lipophilic drugs and their decreased excretion secondary to decrease in renal function. There are also discrete differences in hepatic enzyme activity as well as differences in body fat distribution, plasma volume, protein levels, and gastric emptying time.[138,139]

Several studies have reported increased serum levels and a more pronounced effect of cardioselective and nonselective β-adrenergic blocking drugs in women.[140–142] Women have decreased ability to increase their heart rate, have a prolonged QTc interval, and they are more likely to develop ventricular arrhythmias.[111,143,144] Women with a prolonged QTc interval at baseline are more susceptible to develop torsede de pointe with antiarrhythmic drugs, which prolong QTc interval, such as sotalol, quinidine, amiodarone, ibutalide, and certain antimicrobial, antihistamine, and psychiatric drugs.[41,145] It is important to keep these physiological characteristics in mind when designing β-adrenergic blocking drug administration protocols, e.g., shorter-acting and smaller dosage.

Gender differences in metabolism and distribution have also been seen for digoxin,[146] verapamil,[38] and aspirin.[147,148] Digitalis has been associated with a higher mortality rate in women due to fatal arrhythmias[146] and long-term aspirin use is helpful for stroke prevention but has no preventive effect against cardiovascular thromboembolic events in women.[148] Women's response to thrombolytic therapy has also been associated with more bleeding complications. Even in patients presenting with acute coronary syndrome, the beneficial effect of abciximab is less in women for percutaneous coronary intervention.[43] Sexual dimorphism also has an effect on metabolism of angiotensin converting enzyme inhibitors, these drugs being less effective in treating hypertension in older females than in age-matched males.[149]

Drugs that are commonly used in anesthetic practice, e.g., benzodiazepines[111] and methadone,[128] have been shown to have gender-related metabolism (Table 7). Higher levels of methadone lead to prolonged analgesic and sedative effects because of decreased clearance in women, and postmenopausal women also have a decreased ability to metabolize alfentinal[150] and prednisone.[151] Gender differences have been seen in drugs used specifically in anesthetic management. Women are 30%–40% less sensitive than men to propofol for a similar degree of sedation, and hence require higher dosing for the same effect.[37,152] Women require 30%–40% less opioid analgesia and k receptor agonists than men for the same degree of pain control.[153–155] On the other hand, women are more prone to develop respiratory depression than men, despite smaller dose requirements for pain control.[153]

**Anesthetic Implications**

Over the years, patient management protocols have been integrated into routine clinical practice that are based on epidemiological studies in which either the gender was never considered as a variable, or research was conducted in males only [32–42,44–47,143] (Table 3). This is despite an accumulating body of evidence to suggest that women have different etiologies, presenting features, response to therapeutics, and outcome.

Women were assumed to be less susceptible to develop CAD due to the protection offered by the sex hormones. This hypothesis was tested by extensive clinical use of replacement hormonal therapy. However, hormonal therapy, which was considered the "gold standard" for prevention of cardiovascular disease in

postmenopausal women, is no longer universally recommended for the that purpose.[156] Women have been treated differently only as far as adjusting drug dosages based on body weight and surface area. Despite evidence to suggest a different pathophysiology and clinical presentation of CAD in women, we continued to rely on perioperative risk stratification strategies geared to identify men at risk. It is being realized now that the differences between men and women go beyond the obvious differences in reproductive physiology.

It is perhaps a completely different milieu of anatomy and physiology (smaller heart size, narrower coronary arteries, increased heart rate, longer cardiac cycle, different autonomic reflexes, different renninangiotensin and aldosterone system, reduced glomerular filtration rate, and volume of distribution of drugs) that may be responsible for the differences in outcome. These differences in outcome have been described primarily after cardiac surgical interventions, and after high-risk noncardiac vascular surgical procedures. No gender-based perioperative protocols have been studied, and we may need to conduct such studies to revise our perioperative management protocols using a gender-based paradigm.

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