Sex Differences in Congenital Heart Disease
Should a Woman Be More Like a Man?

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Sex differences in the clinical presentation, diagnosis, and treatment outcomes of cardiac disease have long been recognized. Since the mid-1980s, the total number of deaths from cardiovascular disease has been higher for women than for men. A greater proportion of women (52%) than men (42%) with myocardial infarction die of sudden cardiac death before reaching the hospital, perhaps in part because women tend to have nonspecific prodromal symptoms rather than chest pain and these symptoms are not recognized as being cardiac in origin.1 Even after acute myocardial infarction, chest pain and these symptoms are not recognized as being.

Women with stable angina have higher in-hospital mortality rates2 and worse outcomes after coronary interventions, both percutaneous and surgical. Following percutaneous coronary interventions women have higher rates of short- and long-term mortality, cardiac events, and the need for emergency coronary artery bypass grafting. This may relate to the comparatively smaller coronary artery size of women,7 although this is unproven.8 Higher mortality and complication rates of coronary artery bypass grafting also occur, with women obtaining less functional relief, more frequent hospital readmissions, and lower functional gains than their male counterparts.9 Whether some of these sex disparities relate to an autoimmune precursor for atherosclerotic disease remains speculative. Sex-specific differences in C-reactive protein, as an inflammatory marker, are consistent with the 10-fold increased frequency of inflammatory-mediated autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and thyroiditis in women compared with men.4,10 Recent studies report atherosclerotic plaque in both the carotid and coronary arteries to be significantly increased in women with systemic lupus erythematosus.

Sex differences may also extend to cardiac electrophysiology. Women have higher resting heart rates and longer corrected QT intervals compared with men.11 Variations in arrhythmia frequency in relation to the menstrual cycle have also been observed. Sudden cardiac death with coronary artery disease has a male-to-female ratio of 1.4:1.12

Now, in the current issue of Circulation, the article by Verheugt et al13 from the CONgenital CORvitia (CONCOR) Dutch national registry reports sex differences in outcomes of congenital heart disease. This database comprises over 7000 adult patients with congenital heart disease with a median age of 35 years; half of them are women. No sex differences in mortality were found but 4 specific cardiac outcomes appeared to be different in men and women.

Pulmonary Hypertension
Pulmonary arterial hypertension was defined as a systolic pulmonary pressure above 40 mm Hg. Women had a 35%-higher risk of pulmonary hypertension with an odds ratio of 1.33, an observation which has been noted previously. Atrial and ventricular septal defects were the 2 most frequent defects in this whole series and these defects were associated with pulmonary hypertension more commonly than any other lesion.

The association of pulmonary hypertension with female sex is intriguing. Idiopathic pulmonary arterial hypertension is also much more common in women with a ratio of approximately 2.5:1, and although various genetic mutations and polymorphisms have been found to be associated with idiopathic pulmonary arterial hypertension, none appear to be sex-linked. In the study by Verheugt et al,13 no sex difference was found in patients with irreversible pulmonary vascular disease but perhaps secundum atrial septal defect (ASD) deserves special examination. In our adult congenital heart disease clinic at Mayo Clinic, comprising over 4000 patients, the frequency of isolated secundum ASD with Eisenmenger syndrome in women exceeds that in males by 28:1. Some authors have even speculated that the ASD in this situation is really an “innocent bystander” and that the underlying pathology is really that of idiopathic pulmonary arterial hypertension. Nonetheless the female vulnerability to the development of pulmonary hypertension in this setting is striking, perhaps suggesting that a “two-hit hypothesis” is necessary (ie, a genetic susceptibility exists) and then the trigger of a secundum ASD initiates the vascular injury in the lungs which, in turn, leads to endothelial and vascular smooth muscle dysfunction and subsequent pulmonary vascular remodeling. The explanation that hormonal differences and pregnancy account for these sex disparities appears somewhat simplistic.
Aortic Outcomes

Aortic outcomes in this study included dissection, aortic surgery, and aneurysm formation, the latter defined as dilatation of the ascending aorta $>3.7$ cm. Here, women fared better, with a $33\%$-lower risk of aortic outcomes (odds ratio 0.67), largely because of lower rates of aortic surgery. This is not surprising because bicuspid aortic valve, aortic stenosis, and coarctation of the aorta, conditions all associated with an aortopathy, are more common in men. In addition, the female aorta is smaller, so women might not be expected to reach the critical surgical threshold as early as men.

The preponderance of bicuspid aortic valve disease in men, however, is also intriguing, and because it often occurs in multiple members of the same family, a genetic cause is likely. Both coarctation and bicuspid aortic valve occur more frequently in men, with a prevalence of approximately 4:1. A high prevalence of these same lesions is found in Turner syndrome, a sex aneuploidy syndrome caused by the complete absence of a sex chromosome or the presence of a structurally abnormal one. Structural cardiac anomalies are most prevalent in those women with pure 45X monosomy than in those with an isochromosome Xq karyotype and when Turner patients are compared with the general population, aortic valve disease occurs 146 times more commonly.

Thus, because aortic disease is dominantly a “male domain” and the absence of a normal second X chromosome is associated with aortopathy, one might speculate that a genetic factor that modulates the development of the aorta and aortic valve might be located on the X chromosome. X-linked genes that might be implicated in cardiovascular development include the genes encoding for vascular endothelial growth factor D and the angiotensin type-2 receptor, both of which have roles in fetal development.

Infective Endocarditis

Women were noted to have a $47\%$-lower risk of endocarditis. Whether this relates to the sex distribution of vulnerable lesions (most commonly ventricular septal defect, bicuspid aortic valve, aortic stenosis and tetralogy of Fallot) is uncertain. Another possible explanation might be better oral hygiene in women. It is noteworthy, however, that if more than 1 diagnosis occurred in a patient, a hierarchical scheme was applied so that the patient was categorized with the diagnosis expected to have the most serious sequel in the future. This may explain why 10 patients with secundum ASD reportedly had endocarditis, presumably affecting a cardiac valve, because patients with isolated secundum ASD do not develop endocarditis.

Implantable Cardioverter-Defibrillator Use

Women had a $55\%$-lower risk of receiving an implantable cardioverter-defibrillator (ICD) compared with men (odds ratio 0.45), although they had the same frequency of ventricular arrhythmias. This is a phenomenon well recognized with acquired cardiac disease, wherein the ratio of ICD use may be up to 6-times higher in men. Medicare data from 1991 to 2005 confirmed that men were 3.2-times more likely to receive an ICD for primary prevention of sudden cardiac death than women and 2.4-times more likely for the secondary prevention cohort. This occurred despite the fact that the survival benefit for ICD is the same in men and women, and the sex differences persisted even adjusted for age and comorbidities.

If these devices are safe and efficacious in women, why are they implanted at such a comparatively low rate remains unclear. Does this reflect the overall underutilization of medication and cardiac procedures in women compared with men? If so, why is the implantation rate of pacemakers in men and women the same? Are women erroneously perceived to be at lower risk of sudden cardiac death, or do they decline treatment? Is the reason for low ICD implantation in women that they are older and sicker with more comorbidities? These speculations, however, would appear not to apply to the younger population of patients with congenital heart disease.

It is fascinating that in both acquired and congenital heart disease, these sex disparities exist for ICD implantation. This should form the basis of investigational studies to determine the cause of this disparity. Are we missing the opportunity to save lives, or is there something fundamentally different about women and their risk of preventable arrhythmic cardiac death? Primary prevention trials show survival benefit of ICD therapy only in patients with significant left ventricular dysfunction. Women with heart failure are more likely than men to have normal systolic function, but this alone should not account for the magnitude of difference. Whether more men in the study by Verheugt et al exhibited systemic ventricular dysfunction than women remains unexplored. Indications for ICD implantation for the adult congenital heart disease population remain ill defined, and, although it is tempting to extrapolate indications from acquired heart disease, no such data currently exist. Risk stratification remains imprecise, and, in contrast to acquired cardiac disease, which mainly affects the left ventricle, it is more common to receive an ICD for ventricular arrhythmias associated with right ventricular dysfunction, for example after repair of tetralogy of Fallot with pulmonary regurgitation.

Conclusions

Thus, sex differences in outcomes for patients with adult congenital heart disease are apparent from this study. Whether this relates to inherent biological differences, the smaller size of women, or intrinsic genetic differences remains uncertain. Observational studies such as this one are vulnerable to recognized and unrecognized biases that may lead to erroneous conclusions. Nonetheless, it is plausible that genetic polymorphisms have different expressions in men and women, just as specific genotypes confer susceptibility to myocardial infarction in women but not in men. This may relate not simply to the presence or absence of the genetic variant but to the influence of sex or sex hormones on the expression of various genes and their potential to modify cellular function. Understanding the different genetic susceptibility and pathophysiology of these defects in the future might enable us to prevent the development of such lesions and complications such as pulmonary hypertension and permit the development of sex-specific treatment modalities to improve the outcomes for the more than 1 million adults in the United States with congenital heart disease.
Disclosures

None.

References


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