CONTEMPORARY REVIEW

Sex-dependent pathophysiological mechanisms in hypertrophic cardiomyopathy: Implications for rhythm disorders

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Differences in cardiac physiology are seen between men and women in terms of health and disease. Sex differences start to develop at puberty and are maintained during aging. The prevalence of almost all cardiovascular diseases is found to be higher in men than in women, and disease progression tends to be more rapid in male than in female patients. In cohorts of patients with hypertrophic cardiomyopathy (HCM), the most common autosomal inherited cardiac disease, men are over-represented, suggesting increased penetrance of HCM-causing mutations in male patients. Cardiac remodeling in patients with HCM is higher in men than in women, the same is seen in HCM animal models. Patients with HCM are at increased risk of sudden cardiac death (SCD) and developing rhythm disorders. There seems to be no sex effect on the risk of SCD or arrhythmias in patients with HCM; however, animal studies suggest that certain mutations predispose men to SCD.

KEYWORDS Hypertrophic cardiomyopathy; Arrhythmias; Pathophysiology; Atrial fibrillation; Sex; Sudden cardiac death

ABBREVIATIONS **AF** = atrial fibrillation; **ASA** = alcohol septal ablation; **cTnT-R92Q** = cardiac Troponin T missense R92Q mutation; **cTnT-trunc** = truncated cardiac troponin T; **HCM** = hypertrophic cardiomyopathy; **HET** = heterozygous point mutation on exon 6; **HOCM** = hypertrophic obstructive cardiomyopathy; **IVS** = interventricular septum; **LTCCs** = L-type Ca^{2+} channels; **LV** = left ventricle/ventricular; **MyBP-C** = myosin binding protein C; **MyHC** = myosin heavy chain; **NCX** = Na^{+}/Ca^{2+} exchanger; **PKA** = protein kinase A; **SCD** = sudden cardiac death; **SSM** = surgical septal myectomy; **TG** = transgenic; **WT** = wild type

(Heart Rhythm 2015;12:433–439)

Introduction

The incidence of most cardiovascular diseases differs greatly between men and women. The prevalence of coronary heart disease and heart failure is markedly lower in women than in men, especially at a younger age.[1] Sex differences in cardiac rhythm disorders are also seen, with some forms being more prevalent in men (eg, atrial fibrillation [AF][2]) and others in women (eg, atrioventricular nodal reentrant tachycardia[3]). A plethora of factors are thought to contribute to these differences, including effects of sex hormones and different risk factor profiles. Intriguingly, sex differences are found even in autosomal dominant inherited cardiomyopathies. Men and women carrying the same disease-causing mutation can still have different disease penetrance and prognosis. The most common inherited cardiomyopathy is hypertrophic cardiomyopathy (HCM).

Although sex differences are studied, diagnosis of cardiac disease is mostly based on symptoms found in men. Most therapies for cardiac disease are based on research in male patients and control groups, while pathophysiology of cardiac disease has distinct sex differences. Surprisingly, women are still underrepresented in clinical trials. The American Heart Association reported that of all patients with heart failure in 2010, 47% were women[4]; however, large clinical trials showed that the percentages of male patients enrolled ranged from 70% to 83%.[5–7] This phenomenon is not a relic of the past, as the 3 largest clinical trials of 2013 studying cardiac disease used patient cohorts consisting of 77%–83% male patients.[8–10] Women show differences in symptoms and cellular pathomechanisms compared with men and therefore may react differently on treatment. Sex differences in disease onset and progression emphasize the need to study pathophysiological mechanisms in both men and women.

Sex differences in HCM disease presentation and HCM-related arrhythmias are the subject of this review. As sex is a

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purely biological description of being male or female, it is used in this review rather than the more culturally loaded term "gender."

Physiology of the heart

Sex difference in healthy hearts

Sex differences not only manifest themselves in cardiac disease but are already present in healthy hearts. However, differences between men and women do not arise until puberty. The number and size of cardiomyocytes are initially equal in boys and girls,[11] which is reflected in almost equal heart weights in prepubescent children of either sex.[12] Because cardiomyocytes become postmitotic after birth, the growth of the heart after this period is the result of the growth of individual heart muscle cells.

During puberty, changes between male and female hearts become apparent. The ability to predict left ventricular (LV) weight on the basis of age alone decreases; however, growth remains proportional to body size.[13,14] The rate of growth of heart weight remains constant in young women but is significantly higher in young men.[12] As a consequence, the absolute cardiac mass after puberty is 15%–30% higher in men than in women.[14] Further differences between male and female hearts arise during adulthood.

The aging process of the heart has notable dissimilarities between sexes. There are conflicting reports on the changes in LV weight between men and women during aging. In a small necropsy-based study, the average number of ventricular cardiomyocytes in men and women younger than 45 years was determined to be approximately 8 billion ($(5.9 \pm 1.4) \times 10^9$ and $(2.1 \pm 0.4) \times 10^9$ in the LV and the right ventricle, respectively), which in women did not change appreciably until death.[15] In men, the number of cardiomyocytes decreased by 64 million myocytes/y till the age of 45,[15] which was partly compensated by cardiomyocyte hypertrophy. This cell death is likely due to increased cardiomyocyte apoptosis, which is higher in men than in women.[16] Some studies suggest a reduction in ventricular weight during aging only in men,[14,15] although a large recent study in the Framingham study population showed loss of ventricular weight in both sexes.[17]

Sex-specific changes in cardiac function are observed during aging. It seems that systolic function (if expressed as the related term *ejection fraction* or *fractional shortening*) either does not change[18] or actually increases[17,19] with age in both sexes. This increase in fractional shortening is more pronounced in women.[19] However, this is at least in part explained by a reduction in LV volumes (both diastolic and systolic), which results in a lower stroke volume and cardiac output in older men and women.[17]

Diastolic function decreases with age,[18] leading to filling impairments. In both sexes, there is a progressive slowing of cardiac relaxation with age.[14] In general, deterioration of diastolic function with age is more pronounced in women than in men.[20,21] This difference is mainly attributed to the exacerbated diastolic stiffness of the LV observed in aging women.[21] This would also contribute to the reduced diastolic long-axis and radial velocities observed in older women compared with older men and younger women.[22] The decrease in diastolic function with age has been suggested to make women more susceptible to developing heart failure with preserved ejection fraction.[23]

Sex differences in healthy hearts are not only confined to cardiac morphology but also seen in the pacemaker and conduction system. Differences in heart rates between men and women mirror the changes seen in heart size. No differences in heart rates between female and male fetuses are seen in utero.[24] From puberty to menopause, women have higher heart rates than do men,[24] and this difference decreases after menopause.[25] Again, sex differences in electrocardiograms arise only after puberty. For example, the QT interval, which represents ventricular depolarization and repolarization, of adolescent boys shortens to the duration measured in adult men, while this interval does not change in women.[24] Thus, adult men have shorter QT intervals than do women.[26] This is likely caused by testosterone that is thought to shorten ventricular repolarization, as the QT interval was longer in castrated men than in control subjects.[27]

Calcium and cardiomyocyte contractility

Both diastolic and systolic function of the heart are the macroscopic effects of the behavior of individual cardiomyocytes. Cardiac contraction is initiated by Ca^{2+}-induced Ca^{2+} release, which follows membrane depolarization. In short, depolarization leads to Ca^{2+} influx through L-type Ca^{2+} channels (LTCCs). This small and localized Ca^{2+} influx leads to activation of ryanodine receptors on the sarcoplasmic reticulum, resulting in a large Ca^{2+} release into the cytosol and allowing cardiac contraction to occur. After contraction, the cytosolic Ca^{2+} concentration is lowered by active sarcoplasmic reticulum Ca^{2+}-ATPase and by Na^+/Ca^{2+} exchanger (NCX) in the sarcolemma.

An important modulator of Ca^{2+} homeostasis and thus contraction is protein kinase A (PKA). Noradrenaline released as a result of sympathetic stimulation binds to β_1-adrenergic receptors on cardiomyocytes, leading (indirectly) to PKA activation. PKA phosphorylates proteins involved in excitation-contraction coupling, such as LTCCs, ryanodine receptors, and phospholamban, which together lead to a positive inotropic and lusitropic response.[28]

Both male and female sex hormones have modulatory effects on Ca^{2+} handling. Estrogen seems to attenuate Ca^{2+} transients in rats, as ovariectomy increases Ca^{2+} transients, which could be normalized by estrogen replacement.[29] This effect was ascribed to estrogen-reducing PKA activity rather than a direct effect on Ca^{2+}-handling proteins.[29,30] Chu et al[31] found that estrogen deprivation in rats does affect protein levels of Ca^{2+}-handling proteins, as levels of NCX were decreased and LTCCs levels were increased in ovariectomized rats. This resulted in a higher diastolic Ca^{2+} concentration because of the decreased NCX protein levels, and again, these changes were normalized by estrogen replacement.[31] In contrast, testosterone increased expression