Sex/Gender Medicine
—— The Biological Basis for Personalized Care in Cardiovascular Medicine ——

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Sex differences in morbidity and mortality associated with cardiovascular disease have been recognized by the medical community for decades. Investigation into the underlying biological basis of these differences was largely neglected by the scientific community until a report released by the Institute of Medicine in the United States in 2001 "Exploring the Biological Contributions to Human Health: Does Sex Matter?" Recommendations from this report included the need for more accurate use of the terms "sex" and "gender", better tools and resources to study the biological basis of sex differences, integration of findings from different levels of biological organization and continued synergy between basic and clinical researchers. Ten years after the Institute's report, this review evaluates some of the sex differences in cardiovascular disease, reviews new approaches to study sex differences and emphasizes areas where further research is required. In the era of personalized medicine, the study of the biological basis of sex differences promises to optimize preventive, diagnostic and therapeutic strategies for cardiovascular disease in men and women, but will require diligence by the scientific and medical communities to remember that sex does matter.

Key Words: Atherosclerosis; Autonomic nervous system; Heart failure; Hypertension

Cardiovascular disease (CVD) is the leading cause of death of both men and women, and worldwide there are clear disparities between men and women in presentation, symptoms, response to therapy and outcomes.[1–7] There is a significant gap in basic and clinical knowledge of specific cellular mechanisms related to CVD in women, thus the biological basis of sex differences in CVD remains a frontier for discovery. The scarcity of information related to sex- specific differences in CVD is partly because women were excluded from research studies and because most basic science inquiries into biological factors contributing to CVD were conducted in male animals.

The importance of defining physiology and medicine in terms of sex was emphasized in a 2001 publication from the Institute of Medicine.[8] One major conclusion from that report was that sex matters in ways that have been unappreciated previously in the development, diagnosis, treatment and prognosis for some diseases.

Since the Institute of Medicine report, many studies have attempted to associate variation in specific genes or gene copy number with cardiovascular risk and drug responsiveness. However, the fundamental genetic difference between individuals in regard to the presence or absence of a Y chromosome, which defines male and female sex, respectively, is often overlooked. This review will examine some of the challenges in investigating the biological basis of sex differences in CVD, with 5 areas of focus: autonomic regulation, hypertension, atherosclerosis, heart failure and cell-based therapies. Here, "sex" is used to define biological attributes such as genetic make up and gonadal type; "gender" will be used to refer to the psychosocial context of how an individual's role in society is perceived by themselves and others, which may or may not reflect genetic sex.

Why Sex Matters

The Y chromosome contains the *Sry* gene, which normally initiates development of the testes.[9–11] This locus is also implicated in development of hypertension by modulation of the synthesis of norepinephrine, the major neurotransmitter of the peripheral sympathetic nervous system.[9]

The X chromosome contains the gene for the androgen receptor. Other genes found on the pseudoautosomal region of the X chromosome include those coding for enzymes affecting oxidative stress, cell survival, apoptosis and fat distribution.[12–14] These findings indicate that the sex chromosomes regulate a wide range of cellular responses that influence the development, progression and outcomes of CVD. Yet investigators often fail to identify the sexual origin of cells studied in culture, which is often the technique of choice to define potential molecular targets and pathways for drug development.[12]

Polymorphisms of genes on the X chromosome are fully expressed in male animals that have only 1 copy of the X,

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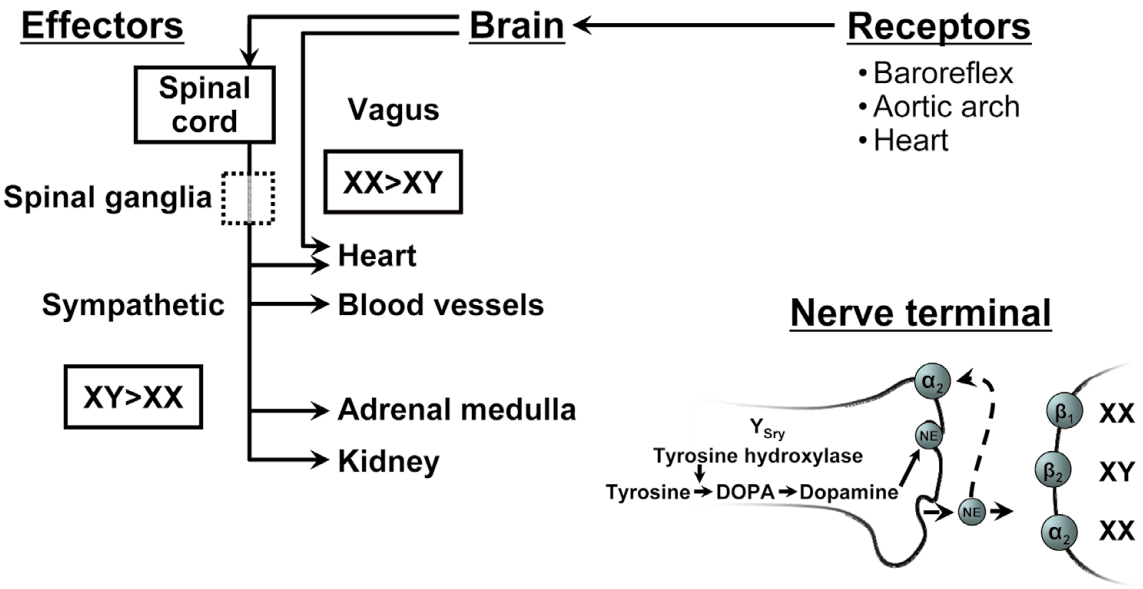

Figure. Schematic of autonomic reflexes influencing cardiovascular control. Every cell has a sex defined by the presence of XX or XY chromosomes. Transcription of genes on these chromosomes will affect the function of each component of the autonomic arch, including sensitivity of receptors, and neuronal transmission in the brain, spinal cord and effector organs. In addition, sex hormones (estrogen and testosterone) will regulate the expression of receptors for neurotransmitters, neuronal conductivity and functions of effector organs themselves, such as the content and release of vasoactive factors from the vascular endothelium, contractile elements and their calcium sensitivity in vascular and cardiac muscle, production of adrenergic transmitter and components of the renin–angiotensin system. The effect of genetic polymorphisms in adrenergic receptors on cardiovascular risk differentially segregate with genetic sex. α_2, adrenergic receptor subtype; $\beta_{1,2}$, adrenergic receptor subtypes; DOPA, dihydroxyphenylalanine; NE, norepinephrine; Y_{Sry}, gene locus on the Y chromosome.

but because of random inactivation of 1 of the 2 X chromosomes in females, gene polymorphisms would present with an allelic mosaic phenotype in females.[15,16] However, the sex difference in the number of X chromosomes does not usually lead to sex differences in the expression or effect of X genes. In general, sex differences in the expression of X genes are approximately the same as for autosomal genes.[17] In addition to allelic mosaicism, other factors leading to sex differences in the effects of X genes include escape from X inactivation and parental imprinting of X loci, because females, but not males, receive a paternal imprint.[18]

Sex differences in physiology are influenced not only by the genetic sex of the animal (cell), but also by the hormonal environment created by production of sex steroid hormones. In a microarray analysis of over 23,574 transcripts in adult mice, sexual dimorphism in the expression of genes varied by tissue and ranged from approximately 14% in the brain to 72% in the liver,[19] thus emphasizing the need to account for both sex and hormonal environment in studies of gene expression. However, it is difficult to separate the influences of hormones from those of genetic sex in such studies, as well as accounting for the influence of hormones on critical periods in development and structural organization of tissues, which may be permanent. An experimental model called the "four core genotypes" has been developed in mice in order to gain a better understanding of interactions between the sex chromosomes and sex hormones.[11] In this approach, *Sry* is deleted from the Y chromosome so that the Y chromosome no longer determines the gonadal sex of the mouse. When *Sry* is absent, animals with ovaries are produced with either XX or XY sex chromosome complement. When a *Sry* transgene is inserted onto an autosome, that chromosome determines gonadal sex. The sex-determining autosome is inherited independently of the Y chromosome, so animals with testes are produced with either an XX or XY sex chromosome complement. Comparing XX vs XY mice of the same gonadal type enables evaluation of the effect of XX vs XY on the trait of interest. A preliminary finding emerging from this model is that XX animals have more body fat than XY animals, independent of the type of gonads, which suggests that inherent sex differences in X gene expression can, under some conditions, affect adiposity (abstract, Chen X, et al, 2009 meeting of the Organization for the Study of Sex Differences). This observation has implications for understanding risk factors for diabetes. The "four core genotypes" model is beginning to be used to investigate biological mechanisms associated with hypertension, and although a somewhat complicated model, it should prove useful for defining the interaction of sex chromosomes and hormones.

Variations in the autosomal genes encoding estrogen receptors also affect the development of CVD in men and women.[20–24] Therefore, it is important to better understand the biological basis of hormone-mediated effects in both sexes. The usual approach to investigating sex/gender-based differences in CVD in animals is to study animals with functional gonads, comparing responses with animals that have been either gonadectomized or gonadectomized and treated with various combinations of sex hormones. Likewise, in humans the usual approach is to define differences in a parameter between age-matched males and females, or between males and females of defined hormonal status. Most of the studies discussed in the following sections have taken these approaches.

Autonomic Function

A gene on the Y chromosome is implicated in the synthesis of adrenergic neurotransmitter that may affect development of hypertension and orthostatic hypotension. Indeed, hypertension develops at earlier ages in men than women,[25,26] and alternatively, women are more likely to suffer from orthostatic hypotension than men.[27] Potential sites at which autonomic regulation may differ in males and females are: (1) afferent receptor sensitivity, (2) central reflex and efferent neuronal signaling (production and release of neurotransmitters) and (3) post-synaptic effector organs, (receptors and effector functions, ie, secretion, contractility; **Figure**).[28]

Sex Differences in the Afferent Receptor Sensitivity

Analysis of baroreflex sensitivity provides information on the integrated reflexes of the sympathetic and vagal nerves in controlling heart rate and blood pressure. Typical experimental manipulations used to study baroreflex sensitivity include intravenous injection of a bolus of an alpha-adrenergic agonist, most often phenylephrine, which induces a 20–30 mmHg increase in systolic pressure or by monitoring changes in heart rate and blood pressure during an upright table tilt test, during lower body negative pressure or during and following a Valsalva maneuver. There is generally a linear relationship between the increase in systolic pressure and the decrease in heart rate. The slope of this relationship is used to quantify the sensitivity of the arterial baroreflex. Using this parameter, sex differences in baroreflex function are inconsistent with reports of an attenuated sensitivity in young women,[29,30] no sex differences during orthostatic challenges,[31,32] or a greater sensitivity in women when compared with men.[33] Reasons for these discrepancies are unclear, but may reflect differences in the type of test used or the hormonal status of participants.[32,34,35] More studies with adequate sample size and with attention to hormonal status are needed to clarify the factors contributing to differences in baroreflex control in orthostatic tolerance in young adults.

Sex Differences in the Central Regulation of the Autonomic Nervous System

Cardiovascular autonomic function is regulated through multiple central nuclei, many of which express estrogen receptors.[36–40] The brain is a sexually dimorphic organ;[18] however, studies that take an integrative approach to simultaneously evaluating hormonal status, central hormone receptor expression and autonomic function in males and females are lacking.

Sex Differences in Efferent Neuronal Activity

In humans, sympathetic drive to the periphery is measured directly by monitoring sympathetic nerve activity to skeletal muscles by microneurography. Using this technique, sympathetic nerve activity is lower in young women than age-matched men.[33,41,42] Muscle sympathetic nerve activity increases with age in both men and women, but the magnitude of the increase is greater in women than men, and the increase is closely related to increases in blood pressure, particularly in women over the age of 40 years.[43] Whether this phenomenon relates to the decline in estrogen status, changes in central modulation of baroreflex function or a direct inhibitory influence of estrogen on neuronal activity as contributing factors to development of hypertension remains to be determined.

Spectral analysis of heart rate variability by calculating the time series of R-R intervals from electrocardiograms is another technique used to evaluate cardiac sympatho-vagal balance. Using this non-invasive technique, women are found to have a preponderance of vagal over sympathetic tone to the heart; the opposite is found for men.[28] Metaiodobenzylguanidine imaging of the heart has confirmed this conclusion, as sympathetic tone was found to be greater in men than women and found to increase in both sexes with age, with the rate of increase being influenced by menopause in women.[44] Collectively, although these studies identify differences in sympathetic tone between the sexes, causality of genetics, age, hormonal status and biological mechanisms of neuronal function remain to be elucidated as pertaining to the development of treatment of hypertension and orthostatic hypotension.

Sex Differences in the Regulation of Neurotransmitter Synthesis, Release and Uptake

Tyrosine hydroxylase, an enzyme involved in synthesis of norepinephrine, may be regulated by *Sry* transcription factor on the Y chromosome.[9] Expression of tyrosine hydroxylase in the central nervous system may also be regulated through estrogen receptor activation.[45,46] Alternatively, disposition of norepinephrine may be modulated by estrogen through competitive binding with catecholestrogens for cathecol-*O*-methyl transferase, or modulation of presynaptic α_2 adrenergic receptors.[47–49] Much remains to be learned about sex differences in adrenergic release and uptake.

The cardiopressor response to acute stress (cold pressor test, mental stress and isometric exercise) is attenuated in young women compared with men and postmenopausal women.[50–52] Estrogen may influence the stress response by altering β-adrenergic receptor expression and sensitivity.[26] However, the components of the stress response that show sexual dimorphisms require further investigation. Understanding the mechanisms of sex differences in autonomic function and all components of the autonomic arch has implications in understanding sex differences in the etiology of essential hypertension, heart palpitations, thermoregulatory vasomotion and orthostatic hypotension.

Hypertension

Sex differences in hypertension have been known for over 100 years.[53] The severity and etiologies of hypertension in men and women differ as might be expected, given the linkage of specific functions to the Y chromosome and modulation of adrenergic neurotransmission by sex hormones. Analysis of approximately 60,000 genotypes in white Americans also identified sex differences in the genetic polymorphisms in hypertensive individuals, with polymorphism in β_1- and α_2-adrenergic receptors associated with hypertension in women, whereas haplotypes of β_2-adrenergic receptors and angiotensinogen were associated with hypertension in men.[54] There are 2 primary causes of hypertension that occur only in women: pre-eclampsia and hypertension associated with the use of contraceptive pills. Research is needed to better understand how sex hormones modulate blood pressure in order to identify women at risk for these conditions. In addition, studies of gene–sex interaction for other racial/ethnic groups may help to define optimal therapeutic approaches for individuals with essential hypertension.

In addition to sex differences in autonomic function, 2

Table 1. Drugs With Sex/Gender Therapeutic Responses

Drug	Sex/gender differences
Angiotensin-converting enzyme inhibitors	More side-effects in women Less effective in women
Aspirin	More effective in primary prevention of myocardial infarction in men More effective in primary prevention of stroke in women
Digitalis	More reported deaths in women than men
β-blockers	More tachycardia in women; or not as effective in women as in men

Adapted from *Nat Rev Drug Discov* 2006.[126]

other regulatory systems are implicated in hypertension: the vascular endothelium and the renin-angiotensin system (RAS). Endothelial dysfunction is assessed by a shift in the ratio of production/release of endothelium-derived vasodilator to vasoconstrictor substances. Sex hormones modulate the production endothelium-derived factors in both men and women, with the balance of vasodilatory factors being observed under estrogen-replete conditions.[55–64] However, the extent to which these responses undergo organizational imprinting or whether there are some endothelial responses that are programmed by the X and Y chromosome independent of the presence of gonads remains to be determined.

Sex hormones also regulate components of the RAS, including angiotensin-converting enzyme and angiotensin receptors.[65–67] As mentioned earlier, the interaction of sex chromosomes and hormonal environment as related to development of hypertension are being investigated using the "four core genotypes" approach using different experimental models of hypertension (one kidney wrap, salt sensitive and spontaneously hypertensive rats).[11,25] These novel approaches provide models to dissect genetic compared from hormonal factors in the development of hypertension and perhaps to the discovery of therapeutic targets for improved prevention and treatment of hypertension in humans.

Sex-based variability among obesity, type 2 diabetes and hypertension warrants further investigation. Obesity presents a major and sex/gender-specific health problem because of its dramatic increase in young women, with visceral obesity being closely related to the risk and development of hypertension by affecting neurohormonal activation, intra-abdominal pressure, and renal glomerular.[68] The pathophysiology of the metabolic syndrome shows sex/gender differences, and hence differences in the relative risk for heart failure and cardiovascular events.[69–72]

The incidence of isolated systolic hypertension and higher pulse pressure with increased left ventricular mass is greater in elderly women than in elderly men. Processes regulating apoptosis mediated by estrogen receptors and processes associated with genes of the X chromosome contribute to these differences, but more work is needed to determine similarities and differences in the molecular pathways regulating hypertrophy and fibrosis of cardiac tissue and vascular smooth muscle.[73,74]

Implications for Therapies

The first therapeutic trial in hypertensive subjects was conducted exclusively in men, all selected from the United States veteran population after the second World War.[75] Representation of women in cardiovascular treatment trials has increased because of a small number of large-scale single sex trials.[76] Other therapeutic trials with the major entry criterion of elevated diastolic blood pressure have included both men and women. The first meta-analysis of various therapeutic trials of hypertension showed a diastolic blood pressure reduction of 5.7 mmHg, which was associated with an approximately 40% reduction of strokes and an 8% reduction of coronary heart disease in men and women.[75] There is growing interest in the development of uni- and multi-therapeutic approaches for regulation of systolic and/or diastolic pressure. However, much remains to be learned about the selection of antihypertensive drugs in the context of sex/gender-specific dose responses (**Table 1**).[77]

Atherosclerosis

Atherosclerosis begins in childhood and is the precursor of systemic CVD, which includes coronary artery disease (CAD), cerebrovascular disease and peripheral arterial disease. Because women have been excluded from many research studies, much remains to be learned about sex differences in the causes and effects of atherosclerosis. In this section, consideration is given to sex-based differences in risk stratification, initiation, progression and treatment of atherosclerosis.

Sex Differences in Risk Factor Profiles

The Framingham risk score is used to estimate the 10-year absolute risk of developing CAD.[78] It is calculated by summing the point scores given to age, blood pressure, cholesterol values, diabetes, and smoking status (or by adding risk equivalents).[2] This score discriminates short-term risk well for men and women, but does not identify subjects with low short-term but high lifetime risk for CAD.[79] This difference is likely because of changes in risk factor status over time (**Table 2**).[78]

Therefore, it is imperative to develop more sensitive markers of cardiovascular risk in women. Some proposed soluble biomarkers being considered for risk stratification include C-reactive protein, other so-called inflammatory cytokines, B-type natriuretic factor, tissue factor, uric acid and cell-derived microvesicles (microparticles). Even though many studies investigating the role of biomarkers in cardiovascular risk stratification have included women, only a few have sufficient statistical power for sex-specific analysis or have evaluated correlations of a marker with disease progress in a single sex.[80–89] Normative ranges for various biomarkers by sex and decade of life need to be developed.

Sex Differences in Markers of Subclinical Atherosclerosis

Coronary artery calcification (CAC), which is a direct marker of subclinical atherosclerosis, shows sex-specific differences.[79,90,91] In a study of asymptomatic individuals referred for CV risk evaluation by CAC, there was a higher mortality risk for women compared with men, even though

Table 2. Comparison of Gender Differences in Traditional Cardiac Risk Factors

Risk factor	Men	Women
Age threshold for higher risk of CAD	≥45 years	≥55 years
Family history of premature CAD	<55 years	<65 years
Smoking	Women lag the declining rates of smoking as seen in men and there is increased prevalence of smoking in young women	
HDL-cholesterol	<40 mg/dl is lower for men	<50 mg/dl is lower for women. Decreases after menopause.
Total cholesterol	Higher for men	Higher for postmenopausal women*
Hypertension		Higher for postmenopausal women*
Physical inactivity		Higher for postmenopausal women*
Obesity		Higher for postmenopausal women*
Diabetes mellitus		Higher for postmenopausal women*

*Note the clustering of multiple risk factors in women after menopause.
CAD, coronary artery disease; HDL, high-density lipoprotein.
Adapted from *J Am Coll Cardiol* 2006.[2]

women had lower overall calcium scores than men.[79,90] In addition, women had 3–5-fold higher risk of death than men with the same coronary calcification scores, a relationship that persisted even after adjustment for traditional cardiovascular risk factors. A meta- and pooled analysis of the literature found that women with 3 or more conventional cardiovascular risk factors had an 11% higher mortality risk with increasing CAC scores compared with men with the same scores. These data are similar to studies noting that women with obstructive CAD have worse outcomes compared with men.[91] The biological basis of these differences remains to be elucidated.

Differences in Initial Plaque Morphology

As atherosclerotic plaque develops, arteries tend to remodel by enlarging outward, thus maintaining lumen diameter.[92] This phenomenon is termed "diffuse atherosclerosis" rather than "focal atherosclerosis", which limits or obstructs the lumen. There is more diffuse atherosclerosis and less luminal stenosis in women compared with men. Women also have a higher prevalence of microvascular dysfunction,[2,93] and inflammatory pathways have been proposed as contributing to these differences,[94,95] many of which may be associated with enzymes coded on the X chromosome. However, more work is needed to identify how these pathways relate to microvascular dysfunction.

Progression to Thrombus Formation: The Final Common Pathway

Most acute coronary syndromes are caused by thrombus formed on top of plaque. As discussed, the patho-anatomic characteristics of plaque relative to calcification and extension of lipid accumulation may differ between men and women. In men, 80% of coronary thrombi result from plaque rupture,[96,97] whereas in women, 40% of coronary thrombi occur on plaque with superficial erosion.[96,97] Several mechanisms, some of which have already been considered, may contribute to sex differences in plaque erosion, including differences in the regulation of apoptosis, enzymes that degrade matrix proteins, and secretion of inflammatory cytokines from leukocytes that have infiltrated the plaque.[98–100] Although some proteins involved with coagulation are regulated by sex hormones,[101,102] specific studies to evaluate the biological basis for differences in coagulation and thrombotic risk between males and females remain to be performed.

Effects of Sex Hormones

As mentioned throughout this review, sex hormones have biological effects in both males and females, but the type and magnitude of the response is influenced by genetic sex and the presence of functional gonads. Cardiovascular effects of both estrogen and testosterone have been reviewed in detail by others.[70,103–105] In general, estrogen treatment of ovariectomized female animals and women reduces atherosclerotic disease, but efficacy of treatment of women who undergo a natural menopause may be affected by the time at which treatment begins, the formulation, dose and mode of delivery of the treatment.[106–113]

Existing data do not support that androgen therapy is associated with increased cardiovascular risk in either of the sexes, but some studies suggest a beneficial effect on vasomotor function.[114] In addition, androgen therapy may improve cardiac ischemic indices and enhance coronary blood flow and endothelial function, but have no beneficial effect on peripheral arterial disease.[103] Testosterone activates both androgen and estrogen receptors (by aromatase conversion to estradiol) in cardiovascular tissues. The relative importance and the specific genes regulated by these receptors and the regulation of the expression of the sex steroid receptors themselves require further study before hormone-receptor modulators can be developed and recommended for prevention of atherosclerosis.

Sex Differences in Response to Treatment for Prevention of Atherosclerosis

Aspirin, considered an important drug from primary prevention of coronary heart disease, shows sex-specific differences in efficacy. It has been shown that low-dose aspirin did not prevent first heart attack in women, but did so in men, whereas it prevented first stroke in women, but not in men.[115] These differences may reflect sex-specific differences in metabolic pathways and utilization of arachidonic acid, as described in experimental animals, but not confirmed in human studies.[115–122]

Statins are another major class of drugs prescribed to slow progression of atherosclerosis and prevent myocardial infarction.[123] Most studies evaluating the efficacy of these drugs have not been powered to specifically compare efficacy between women and men. However, in a large observational study in Japan, serum low-density lipoprotein-choresterol (LDL-C) was related to increased risk for adverse cardiovascular events in both men and women, and

the percent decline in LDL-C in response to low-dose simvastatin was the same in both sexes.[124] In another study, even though statins were effective in reducing all-cause and cardiovascular mortality in both sexes, there was better risk reduction in men than women.[125] In spite of these data, studies are needed to evaluate the effects of statins on specific molecular pathways associated with atherosclerosis and plaque formation in males and females and the influence of sex hormones on these pathways.

Heart Failure

Heart failure is the final pathway of many forms of CVD and there are some sex differences in the prevalence and type of heart failure. Diastolic heart failure is common in elderly females who are usually obese, have type 2 diabetes and are hypertensive. The prevalence of diastolic dysfunction increases significantly with age in women, whereas the prevalence does not show an age-dependent increase in men.[73,74] Mortality with diastolic heart failure may be as high as that among patients with systolic heart failure, but has only recently been considered a condition to be specifically diagnosed and treated.[74,77]

Risk factors for heart failure also show sex/gender disparity. For example, ischemic heart disease is the most common cause of heart failure in men of all ages and in elderly women. However, heart failure in younger women is often from non-ischemic heart disease, such as valvular heart disease and hypertension. Women also are more likely to develop heart failure after myocardial infarction and coronary artery bypass grafting.[77]

Sex/gender differences in the molecular mechanisms affecting the development of heart failure include pathways that affect fibrosis of cardiac tissue and apoptosis with ventricular hypertrophy, apoptosis and fibrosis being less prominent in women.[73,74] As indicated in previous sections, some genes involved in the regulation of cell growth and apoptosis are located on the X chromosome. In addition, estrogen through estrogen receptor activation might modulate hypertrophic signaling in females, as estrogen treatment reduced myocardial hypertrophy in female ovariectomized mice with aortic stenosis.[126]

Data from the Framingham study demonstrate that there is a sex disparity in the 5-year survival following a diagnosis of heart failure: 38% for women compared with 25% for men.[127] These findings point to the need to understand the biological basis of these sex differences to improve preventive and treatment strategies for both men and women.

Cell-Based Therapies

Defining the sex of cells used for stem cell and other cell-based therapies may be important because of sex differences in cell-specific proliferative capacity and production of inflammatory cytokines and angiogenic factors.[128–130] In addition, the sex of the recipient of cell-based therapy may also affect outcomes. For example, when male and female mice with severe diet-induced atherosclerotic plaque were given bone marrow cells from either male or female donors, vascular and endothelial progenitor cells increased to a greater extent in female compared with male recipients. In spite of this increase in circulating progenitor cells, only female donor cells administered to male recipients reduced the plaque burden. Male donor cells did not reduce plaque burden in either males or females.[131,132] These results suggest that in females the mechanism of plaque development and regression involves cells other than endothelial progenitor cells. Therefore, as methods are developed to expand non-autologous cells for therapies, the ability of these cells to expand in culture, the formula of the media, including perhaps the presence or absence of sex hormones, and the sexes of both donor cells and recipients should be considered in order to maximize outcomes. However, preclinically, cell-based therapies often are tested only in male animals and the hormonal status and sex of the donor cells are not reported.[133] Therefore, the implications of results from such studies may be limited.

Conclusions and Future Directions

There are clear sexual dimorphisms in the presentation, progression, response to treatment and outcomes for CVD. However, much remains to be learned regarding the biological basis of these differences. Basic scientists need to determine whether or not the sex of cells in culture affect the regulation of particular intracellular pathways implicated in disease etiology or for potential therapeutic targets. More information is needed regarding imprinting of sex-specific responses and how fetal imprinting relates to development of cardiovascular risk in adults. New animal models need to be developed to better define interactions of hormonal modulation of sex-linked responses affecting cardiovascular risk. Genetic association studies also need to determine if the expression of a particular polymorphism shows dichotomy by sex.[54,134] Phenotypic and molecular mechanisms should be explored in both male and female genetically manipulated animals. Care should be taken by authors and journal editors to assure that the sex, age and hormonal status of cells, animals, and humans are reported in scientific and clinical papers. The Organization for the Study of Sex Differences (www.ossdweb.org) is an interdisciplinary society of investigators interested in unraveling the biological basis of sex differences. Collaborative efforts between scientists and clinicians interested in understanding the biological basis of sex differences will result in novel individualized approaches to improve care and health for men and women.

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