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Review

Targeted basic research to highlight the role of estrogen and estrogen receptors in the cardiovascular system

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ABSTRACT

Epidemiological, clinical and animal studies revealed that sex differences exist in the manifestation and outcome of cardiovascular disease (CVD). The underlying molecular mechanisms implicated in these sex differences are not fully understood. The reasons for sex differences in CVD are definitely multifactorial, but major evidence points to the contribution of sex steroid hormone, 17β-estradiol (E2), and its receptors, estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ). In this review, we summarize past and present studies that implicate E2 and ER as important determinants of sexual dimorphism in the physiology and pathophysiology of the heart. In particular, we give an overview of studies aimed to reveal the role of E2 and ER in the physiology of the observed sex differences in CVD using ER knockout mice. Finally, we discuss recent findings from novel transgenic mouse models, which have provided new information on the sexual dimorphic roles of ER specifically in cardiomyocytes under pathological conditions.

Contents

1. Sexual dimorphism in the cardiovascular system

For both men and women, cardiovascular disease (CVD) is the leading cause of death and disability. In CVD, sex differences in the epidemiology, clinical manifestation, pathophysiology, treatment and outcomes are well documented. Women develop CVD, such as myocardial infarction (MI), on average 10 years later than men [1]. Women with a non-ischemic etiology of heart failure show higher ejection fraction and better survival than non-ischemic men [2]. The remodeling process of male and female hearts also appears to be different. In aortic stenosis (AS), women develop a more concentric form of myocardial hypertrophy with smaller ventricular diameters and less dilatation than men [3–8]. Further, female patients with AS [6,8], coronary artery disease (CAD) [9], and atherosclerosis [10] exhibit less cardiac fibrosis with smaller activation of pro-fibrotic genes and repression of inflammatory markers compared with men [7,11].

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Table 1
Sex differences in animal models in cardiovascular disease.

Injury Model	Species	Phenotype	Reference(s)
I/R	Rat	Females showed significant better post-ischemic recovery of LV function and smaller infarct size compared to male rats	[20]
I/R	Mouse	Female hearts demonstrated improved myocardial function compared to males	[21]
I/R	Rat	Females showed significant better preserved post-ischemic myocardial function, LV end-diastolic pressure, and +/−dP/dt compared with males	[22]
I/R	Rat, dog	Female hearts exhibited significant smaller infarct size, increased activation of sarcKATP- and mitoKATP-channel subunits than male hearts	[23,24]
I/R and Isoproterenol treatment	Mouse	Female hearts exhibited significantly higher S-nitrosothiol (SNO) content, increased S-nitrosylation of the L-type Ca^{2+} channels, reduced Ca^{2+} entry and sarcoplasmic reticulum loading, and reduced heart injury compared with male hearts	[25]
LAD occlusion/reperfusion	Rabbit	Female hearts showed significant smaller infarct size compared to males	[26]
LAD occlusion	Mouse	Female hearts showed reduced matrix metalloproteinase 2 and 9 activity, less inflammation in infarct area, and lower risk of rupture compared with male mice	[12,13]
PO induced hypertrophy by TAC	Mouse	Significant less LVH development in females compared with male mice	[16]
PO induced hypertrophy by TAC	Mouse	Gene cluster response in a sex-specific manner to PO	[27]
PO induced hypertrophy by TAC	Mouse	Male mice displayed greater LVH development than females. Global gene expression patterns were sex-specific	[17]
PO induced hypertrophy by TAC	Rat	Male rats showed an early transition to heart failure, in comparison to females, with onset of cavity dilatation, and diastolic dysfunction. Left ventricular systolic pressures were higher in female compared with male rats. Gene cluster response was in a sex-specific manner to PO	[28,29]
SHR	Rat	Male SHR rats showed LV dysfunction and heart failure signs in comparison to females	[30]
DOCA-salt	Mouse	Females maintained initial physiological adaptive cardiac phenotype. In comparison to female mice, males developed LVH	[19]
DOCA-salt	Mouse	Female mice showed significant less LVH development than males	[31]

I/R: Ischemia reperfusion; LAD: left anterior descending; TAC: transverse aortic constriction; PO: pressure overload; SHR: spontaneously hypertensive rats; DOCA: deoxycorticosterone acetate; LV: left ventricle; LVH: left ventricular hypertrophy.

In line with clinical data, sex differences have also been found in an increasing body of studies using animal models of human CVD. In mouse models of MI, male mice show maladaptive remodeling with more prominent dilatation, significant cardiomyocyte hypertrophy and significant impaired left ventricular (LV) function compared to females [12–14]. In response to volume overload, female rat hearts develop a concentric form of myocardial hypertrophy, sufficient to maintain a stable compensated state, thus preventing the development of ventricular dilation and heart failure in comparison to males [15]. Pressure overload-induced myocardial hypertrophy, after transverse aortic constriction (TAC), was significantly more pronounced in male than in female mice, associated with greater myocyte hypertrophy, more fibrosis and pro-fibrotic gene expression [16–18]. In a deoxycorticosterone acetate (DOCA)-salt model, independent of blood pressure, an increase in pro-inflammatory and pro-fibrotic markers has been reported only in hearts from male mice [19]. Table 1 summarizes the data from studies using different animal models assessing sex differences in CVD.

2. Contribution of sex hormone 17β-estradiol (E2) to the sexual dimorphism in cardiovascular disease

The reasons for observed sex differences in CVD are multifactorial, and may arise from genetic differences, e.g. X- and Y-chromosome and/or epigenetic factors. However, an accumulating number of studies in humans and animal models suggest that the sex hormone estrogen, in particular 17β-estradiol (E2), also plays an important role in observed sex differences in CVD.

Findings from clinical studies suggest that premenopausal women are relatively protected from the incidence of CVD and resultant morbidity and mortality compared to age-matched men. The occurrence of CVD was found to increase after menopause [32–34]. This led to the generally accepted conclusion that the sex hormone E2 protects against CVD in women. Additionally, it has been shown that the E2-level also plays a role in CVD in men. Men with abnormal low (<12.90 pg/mL) and high (≥37.40 pg/mL) E2-levels have been found to show the highest death rates from congestive heart failure [35]. Taken together, these data point out that E2 modulates CVD development and outcome in both sexes, and should be considered in the prognosis and treatment of CVD.

Similar to humans, animal studies led to the assumption that E2 plays a protective role in the diseased heart. E2-supplemented ovariectomized mice showed less increase in LV mass, preserved LV chamber size and function after TAC [36,37]. In a chronic volume overload model, significant increase of myocardial hypertrophy and cardiomyocyte diameter, as well as decrease of fractional shortening and ejection fraction in ovariectomized rats were largely reversed by administration of E2 [38]. In line with these studies, E2-treatment led to improved myocardial recovery, impairment of MI size and cardiomyocyte apoptosis in ovariectomized animal models after MI or ischemia/reperfusion (I/R) [39–44]. Studies using male rodents also showed an E2-mediated cardioprotective effect. Administration of E2 attenuated volume overload-induced cardiac remodeling and function in male rats [45] and decelerated heart failure progression after MI in male mice [46].