

Sex Differences in Animal Models for Cardiovascular Diseases and the Role of Estrogen

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Abstract Clinical findings show sex differences in the manifestation of a number of cardiovascular diseases (CVD). However, the underlying molecular mechanisms are incompletely understood. Multiple animal models suggest sex differences in the manifestation of CVD, and provide strong experimental evidence that different major pathways are regulated in a sex-specific manner. In most animal studies females display a lower mortality, less severe hypertrophy, and better preserved cardiac function compared with male counterparts. The data support the hypothesis that female sex and/or the sex hormone estrogen (17 β -estradiol; E2) may contribute to the sexual dimorphism in the heart and to a better outcome of cardiac diseases in

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females. To improve our understanding of the sex-based molecular and cellular mechanisms of CVD and to develop new therapeutic strategies, the use of appropriate animal models is essential. This review highlights recent findings from animal models relevant for studying the mechanisms of sexual dimorphisms in the healthy and diseased heart, focusing on physiological hypertrophy (exercise), pathological hypertrophy (volume and pressure overload induced hypertrophy), and heart failure (myocardial infarction). Furthermore, the potential effects of E2 in these models will be discussed.

Keywords Animal model • Estrogen • Estrogen receptor • Heart disease • Myocardial hypertrophy • Sex differences

Abbreviations

CVD	Cardiovascular disease
MH	Myocardial hypertrophy
I/R	Ischemia/reperfusion
E2	Estrogen (17 β -estradiol)
ER	Estrogen receptor

1 Introduction

Recent epidemiological and clinical data emphasized that sex differences play a major role in the manifestation and outcome of cardiovascular disease (CVD) [for review see Oertelt-Prigione and Regitz-Zagrosek (2012)]. In response to sustained pressure overload, women develop a more concentric hypertrophy with a better preserved left ventricular function than men. In contrast, men tend to develop more eccentric hypertrophy and left ventricular dilatation (Fig. 1) (Carroll et al. 1992; Petrov et al. 2010). Understanding of the mechanisms underlying these sex-based differences in pressure overload is important to develop new approaches for prevention, diagnosis, and treatment. For these purposes, animal models can greatly improve our understanding of the cause and progression of CVD and provide a useful tool to elucidate the mechanisms of sexual dimorphisms in the healthy and diseased heart. Various studies in which animals were subjected to exercise or surgical procedures, treated with drugs or genetically modified, support the existence of sex differences in the cardiovascular system as observed in clinical studies, and showed that females fare better than males (Leinwand 2003; Luczak and Leinwand 2009). Additionally, these animal studies corroborate the hypothesis that the sex hormone estrogen (17 β -estradiol; E2) and its respective receptors [estrogen receptors (ER)] protect females and mediate the sex-related differences in the cardiovascular responses to different

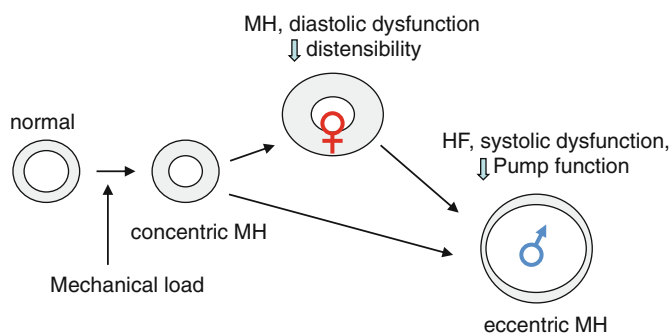


Fig. 1 Schematic illustration of sex differences in the manifestation of heart failure (HF): In response to hypertrophic stimuli, such as pressure overload, hypertension or aortic stenosis, women have a more concentric form of myocardial hypertrophy and better-preserved myocardial function, whereas men exhibit a larger myocyte volume and develop an eccentric form of hypertrophy with a loss of systolic function

physiological and pathological stimuli (Du 2004; Leinwand 2003; Mendelsohn and Karas 2005). In spite of these experimental findings, the molecular mechanisms underlying the sexual dimorphism are very complex and still not clearly elucidated. Learning from the beneficial effects in females could help to build strong foundations for the development of novel sex-sensitive strategies for drug therapies.

E2 mediates its effects predominantly via ER alpha (ER α) and beta (ER β), which are members of the nuclear receptor superfamily (Mendelsohn and Karas 2005). The ER act as ligand-induced transcription factors and regulate the expression of E2-target genes (genomic effects) (Mendelsohn 2002). They also exert rapid nongenomic effects by interacting with cytosolic proteins and signal transduction pathways (Mendelsohn 2002; Simoncini et al. 2006). The ER are expressed in human and rodent (Fig. 2) hearts in both sexes (Grohe et al. 1997; Nordmeyer et al. 2004), and regulate upon E2 activation the expression of relevant E2-target genes, including connexin 43 (Cx43), alpha-myosin heavy chain (α -MHC), matrix metalloproteinases (MMP), and atrial natriuretic peptide (ANP), which in turn play a role in the pathogenesis of myocardial hypertrophy (Babiker et al. 2004; Grohe et al. 1997; Mahmoodzadeh et al. 2010). They have also been associated with the prevention of apoptosis, regulation of cell–cell interaction, and with the regulation of activity of calcium (Ca²⁺) channels (Groten et al. 2005; Johnson et al. 1997; Jovanovic et al. 2000; Patten et al. 2004).

Sex differences in cardiac physiology and pathology are multifactorial, and may arise from genetic differences (e.g., differences in X- and Y-chromosome, epigenetic), the action of other sex steroid hormones (e.g., effects of testosterone), or a combination of these factors. The present review focuses on our current understanding of the impact of E2 and its receptors on sex differences in normal cardiac physiology and pathophysiology obtained from animal models.

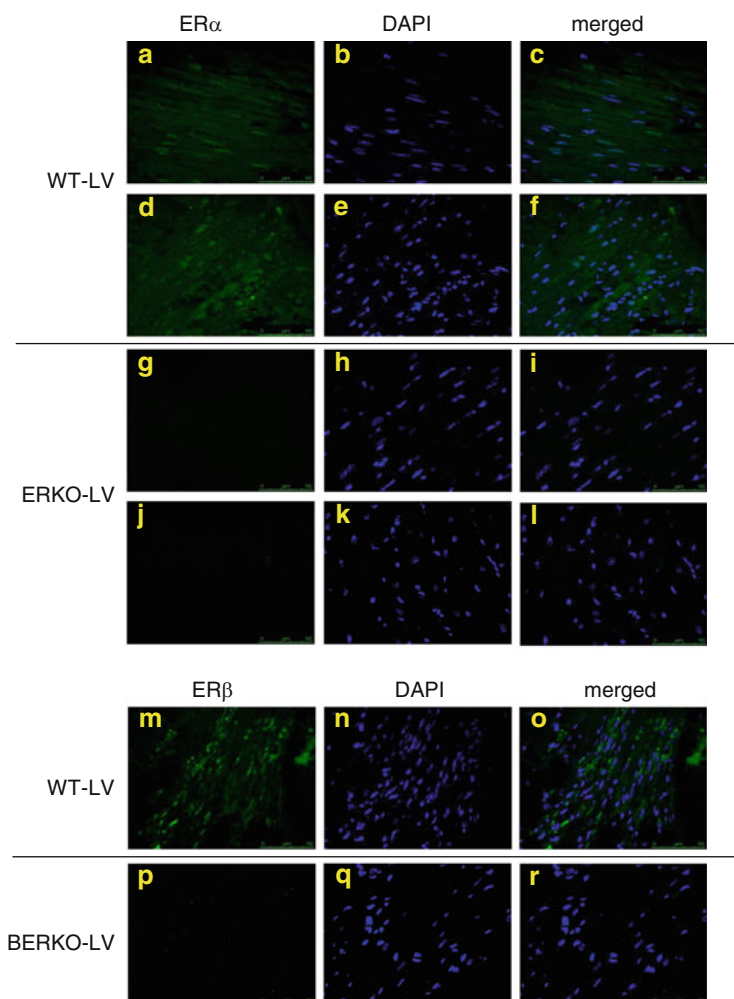


Fig. 2 Representative immunofluorescence (IF) images for localization of ER α and ER β in LV of WT and estrogen receptor knockout mice. (a–l) Detection of ER α in 3 μ m paraffin sections of LV from WT and ERKO mice by IF staining and confocal laser-scanning microscopy. IF using two different antibodies against ER α [(a): MC-20 (Santa Cruz) and (d): G-20 (Santa Cruz)] showed that ER α (green signal) is localized in the nuclei of cardiomyocytes and fibroblasts, as well as in the sarcoplasmic reticulum and cytoplasm of cardiomyocytes of WT mice. (b) and (e) show nuclear staining with DAPI. (c) and (f) are merged images. (g–l): as expected, the same antibodies against ER α showed no signals in the LV section of ER α -deletion mice (ERKO), supporting the specificity of signals for ER α in WT mice. (m–r): Detection of ER β in 3 μ m paraffin sections of LV from WT and BERKO mice by IF staining and confocal laser-scanning microscopy. (m–o) show the same section of LV of WT stained for ER β [SP5198P (Acris), green signal]; (m); DAPI (blue) (n); and merged images from ER β and DAPI (c). ER β is mainly localized in the cytoplasm, nuclei and mitochondria of cardiomyocytes. (p–r) show the same section of LV of a BERKO mouse stained for ER β [SP5198P (Acris), green signal]. As expected, the signal for ER β is lacking in the LV section of BERKO mice (p), indicating the specificity of the signal for ER β antibody in the LV of WT mice, DAPI [(q), blue]; and (r) merged images from ER β and DAPI

2 Sex Differences in Animal Models of Myocardial Hypertrophy

2.1 Sex Differences in Models of Physiological Myocardial Hypertrophy: Exercise

Development of physiological myocardial hypertrophy (MH) is characterized by an increase in cardiac mass and cardiomyocyte dimension. In contrast to the pathological growth of the heart, physiological MH shows preserved or enhanced cardiac function, normal cardiac structure and is reversible (Bernardo et al. 2010). Exercise, pregnancy, and postnatal growth promote the physiological growth of the heart (Hill and Olson 2008). In this review we focus on sex differences in exercise-induced physiological MH, because understanding of the involved cardioprotective signaling pathways and genes is of great importance to treat or prevent heart failure (HF). So far, sex differences in the development of physiological MH induced by exercise have been examined very rarely. But nevertheless in these few studies sex differences have been observed (Table 1). Exercise, independent of voluntary or forced character, induces a sexually dimorphic hypertrophy response of the heart. For example in rats, females subjected to chronic swimming exhibited a marked increase in absolute heart mass associated with increased contractile performance compared with their male counterparts (Mole 1978; Schaible and Scheuer 1979, 1981). In contrast, chronic treadmill running did not increase heart mass in both female and male rats. However, male hearts could show improved performance of the left ventricle (Schaible et al. 1981).

In mouse models, either subjected to voluntary or forced exercise, females exhibited a higher increase in cardiac hypertrophic response compared with male mice (De Bono et al. 2006; Foryst-Ludwig et al. 2011; Konhilas et al. 2004). Additionally, female mice run more on a voluntary wheel than male mice in an age- and strain-independent manner, suggesting that sexual dimorphic cardiac responses are mainly mediated by differences in running distance (De Bono et al. 2006; Konhilas et al. 2004). When the increase in cardiac mass was normalized to running distance, female mice still have an augmented hypertrophic response compared to males, indicating a true sexual dimorphic cardiac response (Konhilas et al. 2004). Whether this differential response to exercise between males and females in response to exercise is due to sex hormones or to genetic properties of the myocardium is still unclear.

2.2 Sex Differences in Models of Pathological Myocardial Hypertrophy: Pressure Overload

Sex differences in the manifestations or significance in MH have been described in human beings. So far, only a few studies focused on sex differences in cardiac hypertrophy in rodents exclusively (Table 1).

Table 1 Sex differences in animal models of physiological and pathological hypertrophy

Physiological/ pathological	Model	Species	Phenotype with sex differences	Pathways involved	Reference(s)
Physiological	Swimming	Rat	Significantly increase in cardiac mass only in females	n.d.	Schaible and Scheuer (1979) and Schaible and Scheuer (1981)
Physiological	Treadmill	Rat	Better contractile function in male hearts	n.d.	Schaible and Scheuer (1981)
Physiological	VCR	Mouse	Significantly higher increase in cardiac mass in females	CaMK, phosphorylation of GSK-3 β	Konhilas et al. (2004)
Physiological	VCR	Mouse	Significantly higher increase in cardiac mass in females	n.d.	De Bono et al. (2006)
Physiological	Treadmill	Mouse	Significantly higher increase in cardiac mass in females	Akt pathway	Foryst-Ludwig et al. (2011)
Pathological	I/R	Rat	Postischemic recovery of LV function significantly better, and infarct size significantly smaller in female	Akt- and PKC ϵ pathway	Bae and Zhang (2005)
Pathological	I/R	Mouse	Improved myocardial function in female hearts	PI3K/Akt and pro-apoptotic signaling	Wang et al. (2009)
Pathological	I/R + Isoproterenol (Iso-), or Ca ²⁺ -treatment	Mouse	Higher postischemic contractile function and lesser ATP-depletion in female	NO/eNOS signaling	Cross et al. (2002)
Pathological	LAD occlusion/reperfusion	Rabbit	Significantly less infarct size in female hearts as compared to males	eNOS signaling	Wang et al. (2006a)
Pathological	I/R + Iso-treatment	Mouse	Increased S-nitrosylation of the L-type Ca ²⁺ channels, reduced Ca ²⁺ entry and reduced heart injury in female hearts	eNOS signaling	Sun et al. (2006)
Pathological	I/R	Rat	Significantly improved postischemic myocardial function in females compared with males	p38-MAPK and pro-inflammatory cytokine	Wang et al. (2005)
Pathological	LAD occlusion	Mouse	Reduced activities of MMP-2 and 9; less accumulation of inflammatory cells, and lower risk of rupture in female hearts	n.d.	Cavasin et al. (2004) and Fang et al. (2007)

Pathological	I/R	Rat, dog	Significantly smaller infarct size, increased activation of sarcKATP- and mitoKATP-channels in female hearts	n.d.	Johnson et al. (2006) and Lee et al. (2000)
Pathological	PO (TAC)	Mouse	Less LVH in females	n.d.	Skavdahl et al. (2005)
Pathological	PO (TAC)	Mouse	Gene cluster response-sex-specific manner to PO	n.d.	Weinberg et al. (2003)
Pathological	PO (TAC)	Mouse	LVH greater in WT males, BERKO mice no SD in LVH, BERKO females highest levels of fibrosis, sex- and genotype-specific gene expression	n.d.	Fliegner et al. (2010)
Pathological	PO (TAC)	Rat	Early transition to HF with cavity dilatation, loss of concentric remodeling elevated wall, and diastolic dysfunction in males	n.d.	Douglas et al. (1998)
Pathological	PO (TAC)	Rat	Males develop diastolic dysfunction, elevated wall stress, and depressed contractile reserve. Females have elevated systolic pressure, no progress into HF	n.d.	Weinberg et al. (1999)
Pathological	PO (SHR)	Rat	Female SHR had normal heart dimensions and function; male SHR LV dysfunction and heart failure	n.d.	Pfeffer et al. (1982)
Pathological	VO (AV Shunt)	Rat	Pro-apoptotic key players such as BAX, caspases 3 and 9 were increased in males and decreased in females	Apoptotic signaling pathway	Dent et al. (2010)
Pathological	VO (AV Fistula)	Rat	Reduced heart failure in females, preserved LV function and chamber size of female hearts	n.d.	Brower et al. (2003) and Gardner et al. (2002)
Pathological	VO (DOCA)	Mouse	Male developed LVH, females maintained their initial physiological adaptive cardiac phenotype	Calcineurin-dependent pathway	Karatas et al. (2008)
Pathological	VO (DOCA)	Mouse	WT males showed a greater degree of LVH than WT females, this effect was diminished in BERKO mice	P38-ERK1/2 pathway	Gurgen et al. (2011)

n.d. not determined

In rodents, the Transverse Aortic Constriction (TAC) has been validated as a reproducible model to study the cardiac response to pressure overload (PO). The TAC model is characterized by a first phase of compensated hypertrophy followed by a transition to HF and mimics human pressure overload-induced heart failure in a number of aspects.

Skavdahl et al. reported that male mice exhibit a significantly higher increase in heart weight-to-body weight ratio than females after TAC. The authors did not specify the form of hypertrophy, i.e., concentric or eccentric (Skavdahl et al. 2005). Other investigators could show in a chronic model of PO that the development of left ventricular hypertrophy (LVH) in WT mice is more pronounced in males than in females. This effect was associated with a greater myocyte hypertrophy and more fibrosis in males (Fliegner et al. 2010; Witt et al. 2008).

PO-induced hypertrophy in male and female Wistar rats led to the observation that males develop a dilated heart accompanied with diastolic dysfunction and elevated wall stress 20 weeks after TAC. In contrast, females develop elevated systolic pressure but they do not progress into HF (Douglas et al. 1998). In a more detailed study with isolated hearts from rats 6 weeks after banding, sex-specific differences in LV contractile reserve and in the genomic response to PO were examined (Weinberg et al. 1999). Higher pressures (contractile force) were observed in females than in males. Despite a similar degree of LVH and systolic wall stress, female hearts had a preserved contractile reserve, whereas male hearts had depressed contractile reserve. The mRNA levels of β -myosin heavy chain (β -MHC) and of the atrial natriuretic factor (ANF) in the ventricular myocardium was greater in male than in female hearts, while the expression of sarcoplasmic reticulum calcium ATPase2A (SERCA2a) was reduced in males and not changed in females (Weinberg et al. 1999).

In spontaneously hypertensive rats (SHR), another model of pressure overload cardiomyopathy, Pfeffer et al. (1982) reported differences in geometric remodeling and an earlier onset of impaired systolic pump performance in male versus female animals. Female SHR (aged 6–18 months) had normal heart dimensions and function whereas male SHR had LV dysfunction and HF by 12 months. When compared with male SHR, female SHR had greater ejection fraction (EF) and cardiac index and smaller end-diastolic and -systolic volumes, despite similar systolic blood pressure values.

A number of animal studies support the anti-hypertrophic effect of estrogens in the myocardium. Long-term E2 treatment of ovariectomized mice after TAC limited the increase in LV mass, ANP, and β -MHC gene expression, while preserving LV chamber size and function (Patten et al. 2008). A different study described similar effects (van Eickels et al. 2001). E2 treatment of ovariectomized female mice caused a reduction of 31 and 26% in PO-induced LVH compared to vehicle-treated animals at 4 and 8 weeks. E2-supplemented animals showed a more pronounced ventricular expression of ANF compared to the vehicle-treated animals. In line with this study, Babiker et al. (2004) demonstrated that E2 exerts profound anti-hypertrophic effects

on ventricular myocytes by transactivation of the ANF gene, and concluded that this mechanism might be responsible for reduction of LVH in female hearts. Another model of PO, the abdominal aortic constriction, performed in ovariectomized female rats exerts also the protective effects of E2 on the development of LVH (Cui et al. 2011). Pathological alterations observed in ovariectomized rats, such as a significant increase of LVH, myocyte diameter and HW/BW ratio, and a decrease of fractional shortening (FS) and EF were largely reversed by administration with E2.

The observed sex differences in animal models support the idea that sex hormones and their sex steroid hormone receptors regulate these cardiovascular responses. Several studies tried to verify the roles of ER α and ER β in mediating the beneficial effects of E2 using mice with genetic deletion of ER α (ERKO) or ER β (BERKO). Babiker et al. reported in ovariectomized ERKO mice a significantly reduced ventricular weight comparable to wild type (WT) littermates after addition of E2 (Babiker et al. 2006). This effect was not observed in BERKO mice. Moreover, in BERKO mice, there was a nonsignificant tendency toward hypertrophy when E2 was present, and a tendency toward decreased hypertrophy in the absence of E2. This study supports the hypothesis that E2 has direct, modulating effects on cardiac myocytes and the heart. Similar results were also obtained by the Skavdahl group (2005). ERKO females developed HW/BW nearly identical to that seen in WT littermate females in response to TAC, indicating that ER α is not essential for the attenuation of hypertrophy observed in WT females. In contrast, BERKO females responded to TAC with a significantly greater increase in HW/BW than WT littermate females. These data suggest an important role for ER β in attenuating the hypertrophic response to PO in females. Another study also supported the involvement of ER β in the development of cardiac hypertrophy and specified the role of ER β (Fliegner et al. 2010). The investigators demonstrated that LVH in WT mice is more pronounced in males than in females. This is associated with greater myocyte hypertrophy and more fibrosis in males. The lack of ER β was leading to an increase of cardiomyocyte hypertrophy and it diminished the observed sex differences in WT mice. It could be assumed that endogenous ER β acts differently in male and female hearts: while ER β promotes fibrosis in males, it inhibits fibrosis in female hearts. ER β limits cardiomyocyte hypertrophy and inhibits apoptosis in both sexes, but with a greater anti-apoptotic effect in male hearts that develop more apoptosis per se. Thus, under PO the loss of ER β is detrimental for both males and females. These findings indicate that ER β mediates anti-hypertrophic effects of endogenous E2 in chronic PO. Another study reported demonstrated also that E2 exerts its positive effects via ER β (Pedram et al. 2008). E2 replacement in female animals inhibited interstitial fibrosis, which was mediated by ER β .

Taken together, these investigations illustrate the importance of ER β for the cardiovascular system, in particular for cardiac dimension and its function. ER β seems to inhibit the development of fibrosis and cardiac growth in both sexes by still unknown mechanism.

2.3 Sex Differences in Models of Pathological Myocardial Hypertrophy: Volume Overload and Mineralcorticoide Excess

Volume overload (VO) leads to eccentric hypertrophy and eventually to HF. There are various models described to achieve VO-induced hypertrophy in an animal model. The most common model is the arteriovenous (AV) *Shunt model*, but also the infrarenal aortoclaval fistula model.

Investigations in rats support the evidence of sex differences during VO. It could be demonstrated that female rats adapt more favorably to VO induced by an infrarenal aortoclaval fistula than male rats do (Gardner et al. 2002). Female hearts developed a concentric hypertrophy with no impairment of the function. This was accompanied by minimal ventricular dilation and no changes in myocardial compliance after 8 weeks of volume-induced dilation. Mortality rate was also higher in males than in females (25 versus 3%), despite a similar degree of VO. The main sex difference in this study was rather the degree of dilation than the degree of hypertrophy. Female hearts develop an appropriate concentric hypertrophy sufficient to maintain a stable compensated state, thus preventing the development of ventricular dilation and HF. In another study, ovariectomy of females abolished these effects and E2 treatment restored the sex-associated patterns of remodeling in this model (Brower et al. 2003).

Furthermore, sex differences in cardiac dysfunction, remodeling, and apoptotic signaling in HF due to VO were identified (Dent et al. 2010). After 4 weeks of AV shunt in rats, both sexes develop cardiac hypertrophy, whereas HF was detected only in males after 16 weeks of AV shunt. Apoptotic key players, such as BAX, caspases 3 and 9 were increased in males and decreased in females at that time point. Phospho Bad was increased and phospho-BCL2 protein was decreased in males. In contrast, females showed an increase only in phospho-BCL2. Ovariectomy abolished this effect and it could be restored by the treatment with E2.

The deoxycorticosterone acetate (DOCA) salt model in rodents serves as a model of secondary hypertension induced by mineralocorticoid excess and volume overload and shows sex differences in blood pressure development. However, independent of blood pressure, a sex-specific dimorphism in cardiac adaptation in response to DOCA-salt was demonstrated in mice (Karatas et al. 2008). Development of LVH in male mice was linked to calcineurin-dependent pathway activation, which increased pro-inflammatory and pro-fibrotic responses. In contrast, female DOCA mice maintained their initial physiological adaptive cardiac phenotype despite mineralocorticoid and salt challenge. In order to investigate the role of ER β , a follow-up study from the same group was performed (Gurgen et al. 2011). Sex differences, which were observed already earlier in WT mice, were verified also in this study. Furthermore, it could be shown that BERKO mice show another phenotype than WT mice under VO conditions. BERKO females developed the highest HW/TL ratios, exceeding those observed in WT males. Left ventricular wall and septum thicknesses were increased in all of the DOCA animals except for

BERKO females. BERKO female mice instead developed increased left ventricular diameters. In comparison to all other investigated groups, the hypertrophic response in female BERKO mice was accompanied by the highest degree of collagen deposition. Thus, the absence of ER β in normotensive DOCA-salt mice leads to maladaptive dilative cardiac fibrosis in female mice, implicating a regulatory role of ER β -related signaling pathways in blood pressure-independent cardiac remodeling processes.

2.4 Sex Differences in Models of Myocardial Injury

Similar to humans (Mehilli et al. 2005), significant sex differences were also found in some animal models of myocardial injury (Table 1). In a model of coronary ligation, female rats showed a concentric form of MH with less cavity dilation and no measurable scar thinning after myocardial infarction (MI), in comparison to male counterparts (Jain et al. 2002). Mice demonstrate a similar sex-dependent response to coronary ligation, such that male mice are more likely to die acutely from cardiac rupture after MI, have significantly worse LV function, greater chamber dilatation and more pronounced cardiomyocyte hypertrophy compared with females (Cavasin et al. 2004; Fang et al. 2007). In a rabbit ischemia/reperfusion (I/R) model, infarct size and apoptotic cell death were significantly attenuated in female rabbits (43.7% and 0.51) compared with males (56.4% and 4.29) (Bouma et al. 2010).

In an in vitro rat model of I/R, Bae and Zhang (2005) observed significantly better postischemic recovery of LV function and smaller infarct size in female (37.1%) than in male (48.3%) hearts. In a similar model, other studies confirmed that isolated perfused female rat hearts have a better recovery and smaller infarct size than male hearts (Brown et al. 2005; Johnson et al. 2006). Mice subjected to I/R demonstrated similar responses, such that female hearts showed improved recovery of contractility (+dP/dt) and compliance (−dP/dt) and less necrosis in comparison with male hearts (Gabel et al. 2005; Wang et al. 2006c).

All these data provide evidence that female hearts are more resistant to I/R-induced injury and myocardial infarction suggesting that E2 contributes to myocardial salvage after injury in females and to the mechanistic differences between males and females. The cardioprotective effect of E2 in females is supported by the findings that hearts from ovariectomized rodent females exhibits a greater infarct size, reduced functional recovery and myocardial viability in reperfusion, which were reversed by E2 administration (Kolodgie et al. 1997; Liu et al. 2004; Nikolic et al. 2007). Further, a growing body of evidence supports that E2 and/or its receptors are involved in improved myocardial recovery and impairment of myocardial infarct size and cardiomyocyte apoptosis after I/R in different animal models (Booth et al. 2003, 2007; Lee et al. 2004; Nikolic et al. 2007; Patten et al. 2004). For example, experimental administration of E2 reduces the infarct size in rabbit, mice, and rat models (Booth et al. 2003; Hale et al. 1996;

Patten et al. 2004). Administration of the ER antagonist, ICI182 780, dramatically blocked this effect indicating that the E2-induced reduction of infarct size is ER-mediated (Booth et al. 2003; Dubey et al. 2001).

Several studies attempted to determine the role of ER α or ER β in mediating the beneficial actions of E2 using ERKO or BERKO mice. Under hypercontractile conditions, female BERKO mice exhibit a significantly greater degree of I/R injury than ERKO or WT female mice (Gabel et al. 2005). Babiker et al. (2007) showed that E2 treatment resulted in smaller infarct size in ovariectomized female ERKO mice than in ovariectomized BERKO mice. Pelzer et al. (2005b) showed that deletion of ER β in ovariectomized female mice subjected to chronic MI increases mortality and aggravates clinical and biochemical markers of HF. These observations support the relevant role for ER β in mediating an attenuated response in females to MH and HF. In contrast to these studies, other studies reported that the cardioprotective effect of E2 is ER α -mediated. Wang et al. (2006b) showed that female ERKO mice subjected to I/R had a similar recovery of \pm dP/dt to WT and ERKO males, which was worse than that observed in WT females. In a similar study, it has been demonstrated that the deletion of ER α is associated with more severe cardiac damage following ischemia–reperfusion injury (Zhai et al. 2000). Although these studies utilizing ERKO and/or BERKO mice failed to provide a clear consensus regarding which ER mediates the protection against cardiac injury, nevertheless they suggest that both ER may be involved in cardioprotective function of E2.

To investigate, whether ER α and/or ER β mediates the beneficial effects of E2, pharmacological studies were also performed using application of ER α - and ER β -selective agonists (Table 2). Administration of an ER β agonist, DPN (2,3-bis(4-hydroxyphenyl)-propionitrile), in ovariectomized female mice restored cardioprotection abolished by ovariectomy and resulted in increased functional recovery in postischemic isolated hearts following trauma-hemorrhage (T-H) or isolated perfused hearts (Nikolic et al. 2007; Yu et al. 2006). In a rat model of T-H, Hsieh et al. (2006) reported that E2 as well as DPN, but not PPT [4,4',4''-(4-propyl-(1H)-pyrazole-1,3,5-triyl) trisphenol; ER α agonist] treatment attenuated the decrease in cardiac mitochondrial ATP and abrogated the T-H-induced lipid accumulation in cardiomyocytes. By contrast to these data reporting the role of ER β in cardioprotection, there are other studies, which support the cardioprotection effects mediated by activation of ER α . In an in vivo rabbit model of I/R injury, acute treatment with E2 and PPT, but not DPN, resulted in significant reduction of infarct size (Booth et al. 2005). A similar in vivo study with ovariectomized female rats (Jeanes et al. 2008), as well as an in vitro study on isolated perfused ovariectomized female rat hearts (Novotny et al. 2009) showed that acute administration of ER α -agonist significantly reduced the infarct size, neutrophil infiltration, oxidant stress, and necrosis following I/R. In contrast to these studies showing the protective effects by either ER α or ER β , Vornehm et al. (2009) demonstrated that an acute postischemic treatment with ER α -agonist (PPT) or ER β agonist (DPN) improves myocardial recovery, indicating both ER α and ER β are involved in mediating E2-induced rapid cardioprotection following I/R.

Table 2 Cardioprotective effects of ER activation on heart disease

Model	Conditions/treatment	Observed effects	Conclusion from authors	References
Rabbit	Intact, OVX rabbits/LAD occlusion + PPT, DPN, E2, or vehicle	Acute treatment with E2 and PPT, but not DPN significantly decreased infarct size	ER α , but not ER β , mediates cardioprotective effects of E2	Booth et al. (2005)
Rabbit	OVX rabbits/LAD occlusion + E2, 17 α -estradiol or vehicle	E2 led to significantly smaller infarct, rel. normal sarcomere structure and minimal swelling	E2-mediated cardioprotection is mediated by ER	Booth et al. (2003)
Rat	OVX rats/IR + ER α -agonist ERA-45, ER β antagonist or vehicle	E2 and ERA-45 significantly reduced neutrophil infiltration, oxidant stress and necrosis	ER α mediates the cardioprotective properties of E2	Jeanes et al. (2008)
Mouse	OVX-mice/IR + DPN or vehicle	DPN treatment resulted in better cardiac functional recovery	Chronic treatment of ER β agonist may confer cardioprotective effects	Nikolic et al. (2007)
Rat	Male rats/T-H + PPT, DPN or vehicle	Only DPN prevented T-H mediated decrease in cardiac output, stroke volume and \pm dP/dt _{max}	Salutary effects of E2 on cardiac function are mediated via ER β	Yu et al. (2006)
Rat	OVX-Female SHR or sham + E2, ER α agonist 16 α -LE2 or ER antagonists	16 α -LE2 or E2 attenuated LVH and increased cardiac output, LV stroke volume and contractility	Activation of ER α affects MH and contractility in OVX SHR	Pelzer et al. (2005a)
Rat	OVX young versus aged female rats/IR + PPT or vehicle	PPT treatment led to reduced infarct size, higher activation of mitochondrial PKC ϵ and pAkt	Acute administration of ER α mediates cardiac protection	Novotny et al. (2009)
Rat	Male rats/T-H + PPT, DPN, E2 or vehicle	Only E2 and DPN normalized cardiac function and mitochondrial gene expression after T-H	ER β mediates the salutary effects of E2 on cardiac function following T-H	Hsieh et al. (2006)
Rat	Isolated male rat hearts/IR + PPT or DPN	PPT and DPN significantly increased myocardial functional recovery following I/R	Both ER α and ER β mediate E2-induced rapid cardioprotection following I/R	Vornheim et al. (2009)

Table 3 Sex differences in numerous transgenic mouse models for cardiovascular disease

Transgenic model	Males	Females	References
PLB-KO	DCM at 6 months	Normal EF	Cross et al. (2003)
PLB-OE	Hypertrophy, death at 15 months	No hypertrophy	Dash et al. (2003)
TNF α -OE	HF; increased mortality	Hypertrophy	Kadokami et al. (2000)
PPAR α -KO	100 % die early	25 % die early	Djouadi et al. (1998)
HDAC5-OE	100 % die within 7–10 days; mitochondrial dysfunction	Survive during 30 days	Czubryt et al. (2003)
FKBP12-KO	Hypertrophy	No hypertrophy	Xin et al. (2002)

In summary, neither studies using ER deletion mouse models nor studies with ER-agonists did provide a clear answer which ER mediates the effects of E2 in cardiac injury. This discrepancy may be due to the use of different species, different models of injury, different end-points, and different dose and timing of the addition of agonists (Murphy and Steenbergen 2007). However, these studies suggest that the short-term activation of ER α (acute treatment) and long-term activation of ER β (chronic treatment) are involved in mediating the cardioprotective effects of E2, particularly in females.

3 Sex Differences in Transgenic Mouse Models of Heart Disease

Sex differences in the onset and progression of MH and HF have also been reported in several transgenic mouse models, where the expression of a gene is knocked out or overexpressed (Table 3). Data suggest that male mice are more sensitive than their female counterparts to genetic interventions leading to pathological hypertrophy and HF (Du 2004). Disruption of FKBP12.6 gene, a sarcoplasmic reticulum (SR) protein, which regulates ryanodine Ca²⁺ release channels in cardiomyocytes, results in cardiac hypertrophy in male mice but not in females (Xin et al. 2002). However, female FKBP12.6 knockout mice treated with tamoxifen, an ER antagonist, develop cardiac hypertrophy to a similar level as observed in male mice (Xin et al. 2002). These findings suggest that E2/ER play a protective role in the hypertrophic response of cardiomyocytes to FKBP12.6 deletion. Phospholamban (PLB) is also a SR protein which modifies the activity of the cardiac SR Ca²⁺-ATPase (SERCA2a) by reducing the affinity for Ca²⁺. Cross et al. (2003) showed that ablation of PLB exacerbates ischemic injury to a lesser extent in female than male mice. Interestingly, male mice with fourfold overexpression of PLB exhibit ventricular hypertrophy and mortality at 15 months, whereas females do not show these phenotypes at this age (Dash et al. 2003).

Genetic modulation of central molecules in energy metabolism leads also to sex-specific cardiac phenotypes. Peroxisome proliferator-activated receptor α (PPAR α) is a nuclear receptor implicated in the control of cellular lipid utilization. Disruption of PPAR α gene (PPAR α -KO) caused massive cardiac lipid accumulation and death in 100% of male, but only in 25% of female PPAR α -KO mice. Interestingly, the metabolic phenotype of male PPAR α -KO mice was rescued by a pretreatment with E2 (Djouadi et al. 1998). Male doxycycline-regulated transgenic mice that overexpressed a histone deacetylase 5 mutant (HDAC5S/A) specifically in the heart showed also severe cardiac phenotypes (Czubryt et al. 2003). Transgene expression resulted in sudden death in male mice accompanied by loss and morphological changes of cardiac mitochondria and downregulation of mitochondrial key enzymes, such as PGC1 α and MEF2A.

Sex differences have also been documented in transgenic mice with cardiac-specific overexpression of tumor necrosis factor- α (TNF- α), a pro-inflammatory cytokine. In this mouse model (TNF1.6), males exhibit HF and increased mortality compared to females (Janczewski et al. 2003; Kadokami et al. 2000). These differences appear to be attributable to the sex-related expression of TNF α within the myocardium. As hearts from E2-deficient rats subjected to I/R have a marked increase in TNF α levels and an E2 replacement reduced TNF levels in LV myocardium and decreased its release after I/R, which was accompanied by improved functional recovery and a decrease in markers of tissue injury and apoptosis (Xu et al. 2006). Furthermore, E2 replacement was associated with increased expression of TNF α -receptor 1. These observations suggest that E2 may have cardioprotective effects, in part, by inhibiting the expression of cardiac TNF α and modulating TNF α receptors expression (Xu et al. 2006).

4 Potential Molecular Mechanisms Involved in the Sex-Based Differences in the Physiology and Pathophysiology of Myocardium: The Role of E2/ER

During recent years, a large number of studies have been performed to assess the molecular and cellular mechanisms associated with sex differences in cardiac physiology and pathology. Different mechanisms and distinct pathways for these sex differences have been proposed. This review focuses on recent findings from animal models relevant for studying the major molecular mechanisms of sexual dimorphisms in the healthy and diseased heart, and highlights the relevant signaling pathways by which E2 and ER affect the cardiac response to mechanical loads.

4.1 *Molecular Mechanisms Involved in Physiological Hypertrophy*

To identify the mechanisms underlying the sexual dimorphic cardiac response to exercise, Konhilas et al. (2004) examined multiple signaling pathways involved in the development of cardiac hypertrophy in a voluntary exercise mouse model. In trained hearts from females, Ca^{2+} /calmodulin-dependent protein kinase (CaMK) was found to be significantly higher compared with males. Furthermore, females showed a persistent phosphorylation of glycogen synthase kinase 3 β (GSK-3 β) indicating an inactivation of this anti-hypertrophic factor and stimulation of heart growth (Antos et al. 2002; Haq et al. 2000). Sex differences in the phosphorylation of GSK-3 β in trained female hearts could be due to E2 signaling through ER as suggested by studies in the nervous system (Garcia-Segura et al. 2006; Mende et al. 1983; Mendez et al. 2003, 2006). In neuronal cells, E2-induced association of ER α with the insulin-like growth factor-1 receptor (IGF-1R) leads to activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway resulting in phosphorylation and therefore inactivation of GSK-3 β (Varea et al. 2010). Data from Foryst-Ludwig et al. (2011) showing increased phosphorylation of Akt only in female hearts and higher increase of LVM compared to males in a forced exercise model emphasize the sex-specific activation of this pathway in physiological myocardial hypertrophy. Studies with transgenic mouse models demonstrated the critical role of the IGF-1R-PI3K-Akt pathway in the physiological cardiac growth (Bernardo et al. 2010). Mice with a cardiac myocyte-specific deletion of the IGF-1R gene attenuated the hypertrophic cardiac response to swim exercise compared to intact mice (Kim et al. 2008). In contrast, transgenic mice overexpressing the IGF-1R in cardiac myocytes displayed cardiac hypertrophy due to increased cardiomyocyte size without necrosis or fibrosis and elevated activation of PI3K and Akt pathway (McMullen et al. 2004). Further studies with mice expressing a cardiac-specific dominant negative form of the catalytic p110 α subunit or gene deletion of the regulatory subunit p85 of PI3K, demonstrated that PI3K is also critical for exercise-induced physiological myocardial hypertrophy (Luo et al. 2005; McMullen et al. 2007). Akt, existing in three isoforms (Akt1, Akt2, and Akt3), is a well-known target of PI3K and is also majorly involved in cardiac growth as indicated by studies with Akt transgenic mice (Bernardo et al. 2010). Akt1 gene knockout mice subjected to swim training showed no induction of cardiac hypertrophy, suggesting that Akt1 is required for physiological heart growth (DeBosch et al. 2006). Taken together, it can be assumed that the E2/ER modulation of the IGF-1R-PI3K-Akt signaling pathway in the female heart may be one possible mechanism underlying the sexual dimorphic cardiac response to exercise.

Furthermore, Foryst-Ludwig et al. showed that the hypertrophic response in female mice was associated with increased expression of genes involved in fatty acid uptake and oxidation compared with male mice. They suggest that sex differences in exercise-induced myocardial hypertrophy are also associated with changes in cardiac substrate availability and utilization between males and females (Foryst-Ludwig et al. 2011).

4.2 *Molecular Mechanisms Involved in Pathophysiology of MH and HF*

The PI3K pathway and its downstream target, Akt, is also one of the best characterized signaling pathways involved in sex-related differences in the development of pathological cardiac hypertrophy. This pathway is involved in a number of physiological responses, including cell survival, gene expression and metabolism (Camper-Kirby et al. 2001). Bae and Zhang showed that there are significant increases in phospho-AKT (p-AKT) and phospho-protein kinase C ϵ (p-PKC ϵ) levels during reperfusion in female but not in male hearts (Bae and Zhang 2005). They suggested that the increase in p-AKT and p-PKC ϵ levels is likely to play an important role in protecting female hearts and to contribute to the sex-related differences in cardiac susceptibility to I/R injury. As inhibition of PI3K/Akt pathway or PKC before ischemia significantly reduced postischemic recovery and increased infarct size in female rat hearts. In agreement with this study, Bell et al. (2008) also showed that female hearts have increased Akt expression/activity. As a cardioprotective mechanism, Camper-Kirby et al. showed that the localization of phospho-Akt⁴⁷³ in myocardial nuclei and Akt kinase activity in nuclear extracts are elevated in female mice hearts versus males (Camper-Kirby et al. 2001). The activation of AKT in a sex-dependent manner may help to explain different susceptibility to cardiovascular disease and support the beneficial role of E2. Another evidence for the beneficial role of E2 in promoting Akt signaling has been shown in cultured rat cardiomyocytes (Camper-Kirby et al. 2001). E2 enhances the accumulation of phospho-Akt⁴⁷³ in the nucleus of cultured rat cardiomyocytes, which in turn increases the phosphorylation of forkhead, a pro-apoptotic transcription factor and thus its enhanced translocation from the nucleus to the cytoplasm. Patten et al. (2004) also demonstrated that E2 increases the activation of Akt and reduces the apoptosis in murine cardiomyocytes both in vivo and in vitro. These findings illustrate the importance of the PI3K/Akt signaling pathway in the pro-survival effects of E2 during pathophysiology of the heart, which may partially account for observed sex differences in the myocardial responses to injury. These effects of E2 might be mediated by ER interacting directly with the PI3K. Wang et al. (2009) showed that ER β , probably through binding to PI3K, increased the PI3K/Akt activation, subsequently decreased caspase-3 and -8, and increased Bcl-2 expression in female hearts. On the other hand, Simoncini et al. (2000) showed that the ligand-activated ER α binds to the p85 α regulatory subunit of PI3K in endothelial cells through a nongenomic mechanism by which E2 rapidly activates the ER α -associated PI3K/AKT pathway and endothelial nitric oxide synthase (eNOS).

It has been reported that eNOS plays an important role in the sex-specific cardioprotection. The expression of eNOS is higher in female than in male rodent hearts, and NOS inhibitor (L-NAME) abolishes sex differences in cardiac susceptibility to I/R (Cross et al. 2002; Wang et al. 2006a). One mechanism for the cardioprotective effect in female hearts could be due to the known inhibitory effect of eNOS on Ca²⁺ channel activity and thus reduction of cytosolic Ca²⁺ overload (Cross et al. 2002),

one of the main causes of I/R injury. NOS enhances the S-nitrosylation of the L-type Ca^{2+} channel resulting in a decreased activity of the channel. Sun et al. (2006) showed that the S-nitrosylation of the L-type Ca^{2+} channel is increased in female WT hearts following I/R, which led to the reduced Ca^{2+} entry and sarcoplasmic reticulum loading, and thus into the reduced heart injury. Several studies showed that E2 stimulates the expression of eNOS in cardiomyocytes in vivo and in vitro. E2 increases the expression/production of eNOS/NO during I/R resulting in reduction of infarct size and myocardial injury (Node et al. 1997), suggesting that females may be protected at least partly via a NOS-mediated mechanism. In this regard, it has been shown that ovariectomy decreases eNOS level and increases the expression of L-Type Ca^{2+} channel in rat hearts, while a treatment with E2 reversed this effect (Chu et al. 2006; Nuedling et al. 1999). Similarly, E2 treatment of guinea pig cardiac myocytes reduces the Ca^{2+} current and intracellular Ca^{2+} concentration (Jiang et al. 1992). This effect of E2 is apparently mediated by ER, since cardiomyocytes from ER α -deleted mice (ERKO) showed an increased expression and activity of L-type Ca^{2+} Channel (Johnson et al. 1997). Moreover, Lin et al. (2009) showed that chronic E2 treatment and activation of ER β by DPN treatment lead to increased NOS/NO signaling and cardioprotection against ischemia/reperfusion injury. All these findings suggest that E2/ER may also exert its beneficial effects by acting on Ca^{2+} channel activity in a NOS-dependent manner, thus providing protection against I/R injury.

Sex differences have also been observed in activation of the mitogen-activated protein kinase signaling pathway in pathological hypertrophy. Females are relatively protected against cardiac injury, also possibly due to a less activation of the p38 MAPK signaling pathway (Wang et al. 2005). Because it has been reported that E2 decreases the activation of p38 MAPK (Angele et al. 2003; Wang et al. 2006c), which is ER α -mediated (Wang et al. 2006b), therefore the sex-specific regulation of p38 MAPK might be, in part, responsible for the sexually dimorphic response following cardiac injury.

It has been reported that the activation of p38 and ERK signaling was sex-specifically regulated in DOCA-induced hypertrophy (Gurgen et al. 2011). Male animals showed only minimal p38 MAPK phosphorylation, whereas WT females had strikingly high levels of phosphorylated p38 MAPK. In contrast to all of the groups of male mice with moderate amounts of phosphorylated ERK1/2, WT females showed increased and female DOCA WT mice had very high levels of phosphorylated ERK1/2. Both p38 and ERK1/2 phosphorylation was greatly reduced in female BERKO mice. These findings show explicitly the sex dimorphism in the p38 and ERK1/2 signaling pathway and the involvement of ER β .

In a model of VO-induced hypertrophy, the arteriovenous (AV) fistula or shunt model could show not only a sex-specific remodeling, with a greater degree of cardiac hypertrophy and larger increase in cardiac output in male than in female animals, but also a sex-specific signaling in the β -adrenoceptor system (b-AR) (Dent et al. 2011). Increases in plasma levels of the catecholamines norepinephrine and epinephrine due to AV shunt were also higher in males than in females. There was no difference in the b1-AR affinity between the sexes observed. But AV shunt induced an increase in b1-AR density higher in female rats than that in males. While

these data demonstrate sex-associated differences in various components of the β -AR system in cardiac hypertrophy due to AV shunt, only higher levels of plasma catecholamines may account for the greater increase in cardiac output and higher degree of cardiac hypertrophy in males.

Not only during VO-induced hypertrophy, also in PO-induced hypertrophy, it was demonstrated that p38 and ERK signaling plays an important role in the development of LVH and being sex-specifically regulated (Cui et al. 2011). The ERK1/2 signaling pathway and also caveolin-3 are important key players in the pathogenesis of hypertension-induced cardiac hypertrophy and it could be shown that E2 attenuates the development of cardiac hypertrophy. In female ovariectomized rats after induction of PO, pathological alterations of cardiac function and dimension were observed. These effects were accompanied with the enhanced expression of ERK1/2 and decreased expression of caveolin-3 in the left ventricle. E2 treatment reversed these alterations. The treatment with E2 restored the levels of caveolin-3 expression and of ERK phosphorylation in these pressure-overloaded rats (Cui et al. 2011). These data indicate that the protective effect of E2 against cardiac hypertrophy induced by PO is mediated by upregulation of caveolin-3 expression and downregulation of ERK1/2 phosphorylation.

Sex differences have been also observed in the cardiac inflammatory response to acute myocardial injury. Female's protection against cardiac injury could be possibly due to a decreased inflammatory cytokine production, e.g., decreased myocardial TNF- α , IL-1, and IL-6 expression (Fang et al. 2007; Wang et al. 2005; Xu et al. 2006). Xu et al. (2006) demonstrated that an increase of TNF- α production after I/R correlated with declined circulating E2 levels in E2-deficient female rats, while E2 replacement reduced TNF- α production and release in LV myocardium after I/R. These data suggest that the sex differences in myocardial inflammation during acute cardiac injury are partly mediated by E2 through regulation of TNF- α levels in the ischemic heart.

Sex differences in cardiac remodeling have also been documented in rodent (Cavasin et al. 2004; Fang et al. 2007). Female hearts show a better cardiac outcome during the development of HF due to a lower rate of cardiac remodeling and thus reduced risk of rupture compared to male hearts. The reduced activities of matrix metalloproteinase-2 and -9 (MMP-2 and MMP-9) may represent the molecular mechanism underlying the lower risk of rupture in female hearts (Cavasin et al. 2004; Fang et al. 2007). Additionally, Cavasin et al. (2004) suggested that the mechanisms underlying these differences may be related in part to relative concentrations of collagen type I/III, since E2 treatment prevents increase of collagen type I/III ratio in old female rats (Xu et al. 2003). The effect of E2 in this study is in agreement with the findings from other studies which showed that E2 reduces the expression of collagen I, III and MMP-2 in female rat cardiac fibroblasts (Mahmoodzadeh et al. 2010; Petrov et al. 2010).

It has also been observed that the cardioprotection associated with female sex was accompanied by a greater protein expression of the sarcolemmal and mitochondrial ATP-sensitive potassium (KATP) channels; their blockade during the ischemia increased the degree of injury in the female heart (Johnson et al. 2006;

Lee et al. 2000; Ranki et al. 2001). Thereby, the female sex hormone E2 seems to play an important role. Ranki et al. showed that E2 treatment increases sarcolemmal KATP channel expression and protects cardiac cells from hypoxia re-oxygenation; and that KATP channel antagonist abolished the protection afforded by E2 (Ranki et al. 2002). These data indicate that sarcolemmal and mitochondrial KATP channels may be involved in mechanisms that underlie sex differences in the susceptibility of the heart to I/R injury, which is partly regulated by E2.

5 Conclusions and Clinical Implications

Multiple epidemiological and clinical studies indicate that the predictors and progression to heart diseases are often sex-sensitive. Experimental animal studies have also shown that males and females often differ in their biological responses to cardiac mechanical loads and pharmacological interventions. Although, there are obvious sex differences in the cardiovascular physiology and pathology, most studies fail to include both sexes, and only a limited number of animal researches include female subjects or differentiate between sexes in the data analysis. These might be the reason that nowadays our understanding of molecular and cell-based mechanisms underlying sex-based differences in cardiovascular system is incomplete. Therefore, we do need to take into account sex differences in designing our investigations, and they should also be considered by the selection of optimum diagnostic and therapeutic procedures in clinical practice.

Take Home Messages

- Research on female and male animals is important to understand the mechanisms underlying sex-based differences in the development of cardiac diseases.
- Animal studies allow identifying factors/pathways that confer female's cardioprotection in physiological and pathological hypertrophy, which could help to find appropriate therapeutic targets to inhibit pathological pathways and activate physiological regulators in both sexes.
- Learning from the beneficial effects in females could help to build strong foundations for novel sex-sensitive strategies for drug therapies.
- Female hormone E2 must interfere with a large number of pathways, such as PI3K/AKT, p38MAPK, NO, sarcolemmal and mitochondrial channels and Ca^{2+} -signaling. Identification of these protective pathways could also offer novel therapeutic aspects.

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