Genes and hormones: sex differences in myocardial hypertrophy

Ute Seeland · Vera Regitz-Zagrosek

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Abstract Female hearts develop a more favorable physiological form of myocardial remodeling when subjected to pressure or volume overload than male hearts involving the synergistic activity of several cellular-based protective pathways induced by estrogen signaling via estrogen receptors (ERs), influencing mitochondrial function, and myocardial energy metabolism. In contrast, testosterone induces matrix remodeling and growth factor signaling via androgen receptors (AR) and contributes to eccentric remodeling. This review focuses on sex differences in ventricular morphology and function and in myocardial-signaling pathways in myocardial hypertrophy (MH) to understand protective mechanisms or alternatively suppressed or avoided maladaptive-signaling pathways in the female sex.

Keywords Myocardial hypertrophy · Sex differences · Estrogen · Testosterone · Sex hormone receptor

Gene und Hormone – Geschlechterunterschiede bei der Myokardhypertrophie

List of abbreviations

AS	Aortic stenosis
AR	Androgen receptor
AVR	Aortic valve replacement
E2	17 β -estradiol
ECM	Extracellular matrix
ER	Estrogen receptor
HF	Heart failure
LVH	Left ventricular hypertrophy
MH	Myocardial hypertrophy
MMP	Matrix metalloproteinases
NO	Nitric oxide
PO	Pressure overload
PPAR	Peroxisome proliferator-activated receptor
PGC-1	PPAR- γ coactivator 1
TAC	Transverse aortic constriction
TGF	Transforming growth factor

Introduction

Average life expectancy is better in women than in men and in most of female animal models compared with the males. Evidently, in the female aging heart apoptosis and fibrosis as well as hypertrophy are less pronounced than in the aging male heart. These functional and survival advantages for women could be based on different gene products of sexual chromosomes as well as different morphological and metabolic effects of sex hormones and their receptors. Animal models for physiological and pathological myocardial hypertrophy (MH) and heart failure (HF) [1], in combination with cell-specific and/or cell-inducible genetic deletion

Dr.med. U. Seeland (✉)
Institut für Geschlechterforschung in der Medizin,
Universitätsmedizin Berlin Charité, Campus Mitte,
Luisenstraße 65, 10117 Berlin, Germany
e-mail: ute.seeland@charite.de

Prof. Dr. V. Regitz-Zagrosek
Institut für Geschlechterforschung in der Medizin und Center
for Cardiovascular Research—CCR, Universitätsmedizin Berlin
Charité, Campus Mitte, Hessische Str. 3–4, 10115 Berlin,
Germany

or over-expression of hormone receptors, have been used to analyze hormone-related and chromosome-based sex differences. It has yet to be determined whether the mechanisms observed in animal models can be applied to the human heart or not.

Physiological myocardial hypertrophy

Physical exercises as well as pregnancy are two major conditions associated with physiological concentric MH due to adaptation to pressure or volume overload or hormonal effects. Even so these conditions differ in a number of changes in gene expression, they also have great similarities [2]. Both are characterized by MH with normal or enhanced cardiac function. There is no evidence of interstitial fibrosis and apoptosis. Expression of fetal genes such as major histocompatibility complex heavy-chain, atrial natriuretic peptide precursor, phospholamban, and sarcoplasmic reticulum ATPase are not increased. Mechanical and hormonal effects induce myocardial adaptation, e.g., myocyte hypertrophy without major influence on myocyte gene expression patterns. Reversibility of myocardial adaptation is very common. However, providing pathological stimuli, transition to pathological MH may occur in these conditions as well. In particular, the pregnant heart is prone to greater damage when exposed to ischemic injury than the normal heart [3].

Sex-specific ventricular morphology and function

Sex steroid hormones such as 17 β -estradiol (E2) and testosterone affect cardiac growth. The effects are mainly mediated by their nuclear receptors—ER α , ER β , and androgen receptors (AR), shown in rodent as well as human hearts. These receptors are functionally active not only in myocytes, but also in fibroblasts, vascular endothelial cells, and smooth muscle cells of rodents and humans [4–6]. ER α and β are expressed in human hearts and regulated in pathological conditions [7, 8]. ERs act as transcription factors in a ligand-dependent manner and bind as hetero- or homodimers to hormone-responsive DNA elements initiating the transcription of hormone-sensitive genes. The activity of ERs is modulated by alternative intracellular-signaling pathways downstream of peptide growth factors and neurotransmitters. Recent research suggests a role for ER in epigenetic DNA modifications. ER can act together with histone acetylases to modify gene expression. ERs may also be active in immature mice before gonadal production of sex hormones as well as in ovariectomized adult mice. This sex hormone ligand-independent activation of ERs is consistent with the fact that ER-mediated effects are not limited to premeno-

pausal women, but may play a role in aging women and in men [9]. Furthermore, white fat synthesizes estrogens and plays a role in local and systematic signaling in men.

Changes in left-ventricular mass in response to age and hypertrophic stimuli are different in women and men. The decline in myocyte number and increase in myocyte size is more pronounced in men [10]. In general, normal female hearts are smaller and stiffer than male hearts [11]. This may favor a greater tendency in women to develop diastolic instead of or prior to systolic dysfunction and HF with preserved ejection fraction (HF-PEF). Major risk factors for HF-PEF include aging, hypertension, obesity, diabetes, and ischemia. Ischemia may play a greater role in men, hypertension and diabetes in women.

Under pressure overload (PO), women are more prone to develop concentric MH with thickening of the left ventricle wall due to addition of sarcomeres in parallel and an increase in myocyte cell width. Men tend to develop eccentric hypertrophy with thinner ventricular walls and larger cavities due to the addition of sarcomeres in series increasing myocyte cell length. Sex differences in cardiac pathology following PO are observed in particular in elderly patients with aortic stenosis (AS). Women develop a more concentric form of hypertrophy with smaller ventricular diameters and less ventricular dilatation with better systolic ventricular function than men [12]. Left ventricular mass as well as ventricular and arterial stiffness increase with age in both sexes, but the increase is more striking in women, especially in the postmenopausal years. For review see Scantlebury and Borlaug [13].

A number of molecular mechanisms can contribute to the gender differences in MH. Effects of estrogen provide benefit to premenopausal women, and the loss of its protective mechanisms may render the heart of postmenopausal women more vulnerable. The underlying molecular mechanisms include E2 effects, e.g., on collagen synthesis and degradation, inhibition of the activated renin-angiotensin system following pathological conditions as well as gender differences in myocardial calcium handling and in the nitric oxide (NO) system. According to Kim et al. [14], E2 also directly protects cardiomyocytes. It inhibits hypoxia/reoxygenation (H/R)-induced apoptosis of cultured rat cardiomyocytes via estrogen receptor (ER) signaling. E2-activated phosphoinositol-3 kinase (PI3K) was found to inhibit mitochondrial-reactive oxygen species (ROS) formation, leading to modification of downstream p38 signaling and cardiomyocyte survival. The rapid nongenomic effects and the long-term effects of estrogens on vasculature are described elsewhere [15].

Cardiac hypertrophy in response to PO due to hypertension or AS is not only characterized by increased cardiomyocyte diameter, but also by increased interstitial fibrosis. Estrogen and testosterone modulate extracellular matrix

(ECM) turnover, which contributes to the structural and functional integrity of the heart. Estrogen regulates collagen synthesis differently in male and female cardiac fibroblasts [16]. Estrogen also modulates matrix metalloproteinase-2 (MMP-2) via MAPK pathway [17]. In addition, testosterone effects are involved in synthesis of collagen proteins as well as in increased expression and activity of collagen degrading enzymes such as matrix metalloproteinases (MMPs) and contributes to cavity dilatation and rupture after myocardial infarction [18]. Among the various known MMPs, MMP-2 (gelatinase A) plays a dominant role in cardiac remodeling. An increase in MMP-2 expression and activity occurs in PO-, myocardial infarction-, in MH- and HF- conditions and is associated with adverse cardiac remodeling [19]. These findings correspond to the fact that extracellular fibrosis is more evident in the aging male human heart compared with female hearts of older age. Furthermore, in surgical biopsies of patients with aortic valve replacement (AVR) gene expression of collagen type I and III and MMP-2 was significantly higher in male than in female patients [20]. Dysregulation of ECM turnover appears to be another potential molecular mechanism to explain sex differences in left ventricular adaptation and remodeling.

Sex-specific myocardial-signaling pathways and myocardial metabolism

Both ER α and ER β are upregulated in human MH. The increase in ER α is similar in both sexes. The induction of ER β is stronger in female than in male hearts and shows a close correlation with ejection fraction (EF) of the left ventricle [7]. Evidence for a dominant and cardioprotective role of ER β in the cardiac response to PO has been reported in animal experiments. Angiotensin infusion in female mice resulted in marked hypertrophy of the left ventricle, exacerbated by the loss of ovarian steroid hormones after ovariectomy. Pedram et al. [21] determined the cellular effects of E2 in female mice with marked hypertrophy due to AngII infusion. Hypertrophy was 51 % reduced by the administration of E2. AngII induced a switch of myosin heavy-chain production from alpha to beta, but this was inhibited by E2 via ER β . AngII-induced ERK activation and calcineurin activity were inhibited by E2 through the beta-receptor. E2 substantially prevented ventricular interstitial cardiac fibrosis as induced by AngII. Taking into account all these aspects, E2 mitigates AngII signaling that produces cardiac hypertrophy and fibrosis in female mice. These results underline the important role of E2 regarding cardiomyocyte protection. Studies with ER β (-/-) knockout mice confirm these data. Female ER knockout mice lacking ER β responded to transverse aortic constriction (TAC) with a significantly greater increase in HW/BW ratio compared with

female wild-type (WT) littermates [22]. Echocardiographic measurements of these ER β (-/-) mice by Fliegner et al. [23] revealed the supposed concentric form of hypertrophy in females, while males developed eccentric hypertrophy 9 weeks after TAC surgery. The lack of ER β augmented the TAC-induced increase in cardiomyocyte diameter in both sexes. Cardiac fibrosis was more pronounced in male WT/TAC than in female mice. This difference was abolished in ER β (-/-) mice. The number of apoptotic nuclei increased in both sexes of ER β (-/-)/TAC mice, most prominent in males. The data show that both—female sex and ER β —attenuate the development of fibrosis and apoptosis, thus slowing the progression to HF in this animal model [23].

To gain better understanding of E2-induced ER α action in the human heart, Mahmoodzadeh et al. [24] identified and functionally analyzed E2-induced interaction partners with ER α in the human heart. The authors identified atrial natriuretic peptide precursor A (NPPA), a well-known cardiac hypertrophy marker, as an ER α interaction partner. The LXXLL motif within NPPA is necessary for its E2-induced interaction with ER α , its action as a corepressor of ER α and its translocation into the nucleus of human and rat cardiomyocytes. Experiments in a human left ventricular cardiomyocyte cell line showed that NPPA interacts with E2/ER α , suppressing the transcriptional activity of ER α on E2-target genes such as NPPA, connexin43, α actinin-2, nuclear factor of activated T-cells, and collagens I and III. These findings may be crucial in physiological and pathological cardiac processes, thereby representing a potential therapeutic target [24].

Expression of the ER α gene in patients with AS is regulated in a disease-dependent manner. In various cell lines and tissues as well as in the human heart, the ER α mRNA is transcribed from multiple promoters. One of them binds NF- κ B which inhibits transcription. The NF- κ B pathway takes part in a negative regulatory mechanism for the expression of ER α in human heart. Inflammatory stimuli suppress hER α expression via activation and subsequently bind NF- κ B to the ER α promoter. In contrast, E2 induced the transcriptional activity of the hER α promoter in human myocardium. This may lead to an interplay between estrogen effects and the pro-hypertrophic and inflammatory responses to NF- κ B [8]. Testosterone contributes to the inflammatory mechanisms in MH via activation of NF- κ B and its dependent target genes [25, 26].

Key experimental findings contributing to our understanding of pathological and physiological heart growth focus on signaling pathways influenced by sex hormones (Fig. 1) [27]. Because of crosstalk and integration of various pathways, signaling cascades involved in cardiac hypertrophy are complex. Since Akt signaling is known to have a greater activity in the female than in the male human heart, the stimulation of this pathway may contribute to sex dif-

Fig. 1 Signaling cascades involved in estrogen-mediated cardiac hypertrophic responses. Estrogen receptors (ER α and ER β) are up-regulated in human myocardial hypertrophy. The induction of ER β is stronger in female than in male hearts. Estrogen acts via PI3K to induce physiological hypertrophy and attenuates pathological signaling cascades. Akt signaling is more active in female hearts. Nuclear ERs alter gene expression to regulate cardiac hypertrophic responses. *Ang II*

ferences in the development of hypertrophy. Camper-Kirby et al. [28] found higher levels of nuclear-localized Akt, a protein kinase that regulates a broad range of physiological responses including metabolism, gene transcription, and cell survival, in young women relative to comparably aged men or postmenopausal women. Cytosolic localization of phospho-forkhead, a downstream nuclear target of Akt, is also increased in female relative to male mice, suggesting a potential mechanism for cardioprotective nuclear signaling resulting from Akt activation. The activation of Akt in a sex-dependent manner may help explain differences observed in cardiovascular disease risk between the sexes and supports the potential beneficial effects of estrogenic stimulation. Increased activation of the phosphoinositide 3-kinase (PI3K) pathway has been described in mice with swim training. This training had a favorable effect on cardiac function and fibrosis in this PO model [29]. Thus, Akt signaling is more active in female hearts and a putative protective mechanism contributing to physiological MH.

angiotensin II, *ANP* atrial natriuretic peptide, *BNP* B-type natriuretic peptide, *CN* calcineurin, *ER* estrogen receptor, *ERK* extracellular regulated kinase, *ET-1* endothelin-1, *GPCR* G protein-coupled receptor, *IGF1* insulin-like growth factor 1, *IRS1* insulin receptor substrate 1, *PI3K* phosphoinositide 3-kinase, *PKC* protein kinase C, *Ub* ubiquitin. (Adapted from [27])

Myocardial function is dependent on substrate utilization and metabolism. Key enzymes in glucose and fatty acid metabolism are regulated by sex hormones [30]. Beneficial effects of estrogens on the lipid profile such as increasing HDL- and decreasing LDL cholesterol play a part in contributing to the lower incidence of cardiovascular disease in premenopausal women. Free fatty acids (FFA) are liberated from triglyceride-rich lipoproteins by lipoprotein lipase (LPL) and are considered to be a principal energy source for the heart. Peroxisome proliferator-activated receptors (PPAR- α , PPAR- γ , and others), a family of nuclear receptors, modulate transcription of key genes in mitochondrial metabolism and control the balance of glucose and fatty acid utilization in the myocardium. The PPAR- γ coactivator 1 (PGC-1), which is a central activator of mitochondrial biogenesis and function as well as fatty acid oxidation is regulated by estrogens [30]. PGC-1 gene expression is lower in males compared with females in TAC mice. PPAR- α is a key regulator of FFA catabolism [31]. Gene deletion of

PPAR- α in animal models with simultaneous modulation of fatty acid utilization (PPAR- α transgenic mice overexpressing LPL in skeletal and cardiac muscle) led to sex-specific phenotypes with HF-related death in male animals and survival in females. Changes in plasma glucose, FFA, lactate, and triglycerides did not clearly account for sex-specific differences in mortality; however, the authors indicated a critical role for PPAR- α in myocardial pump function during fasting [1, 32].

A number of pathways that are involved in MH and are modulated by sex or sex hormones include the insulin-like growth factor/PI3K-axis that may lead to sex-dependent stimulation of nitric oxide synthases (NOSs). Changes in the constitutive endothelial NOS expression and activity are a function of estrogen and hypertrophic status. Stimulation of NOS leads to an increase in NO production under various circumstances depending upon the isoforms and has recently been linked with sex-specific phenotypes. Estrogens are necessary for the highest NOS activity, while PO per se increased total NOS activity in the left ventricle. Estrogen deficiency primarily affects endothelial NOS activity through a mechanism involving caveolin-1 [33].

Sex-specific genomic response and the E2/ER β axis

Weinberg et al. [34] characterized responses of male and female mouse left ventricles (LV) to PO (TAC) at the genomic level by high-density microarray analysis. Interestingly, a greater number of genes were regulated in response to acute overload than in response to chronic overload, and sex modified these responses.

Two studies were published recently dealing with sex-specific effects and the genomic response on cardiac hypertrophy. Gene expression was regulated in a sex-specific manner 2 weeks after PO in WT mice, despite the fact that sex differences in cardiac morphology and function did not occur at this early time point [35]. Female hearts responded to PO with a better adaptation in cardiac energy metabolism. Genes encoding for mitochondrial function and fatty acid oxidation were less downregulated in female hearts, while a relative upregulation of matrix remodeling- and ribosomal genes was identified in males. These processes have been observed in the early stage of hypertrophy and may represent the molecular basis for the sex-specific functional changes that were found at later stages of PO and left ventricular hypertrophy (LVH). Fliegner et al. [23] analyzed LV samples of male and female WT and ER β ($-/-$) knockout mice 9 weeks after TAC by microarray and real-time RT-PCR. Gene expression profiling revealed that WT male hearts had a stronger induction of ECM-related genes due to increased MAPK signaling and pathways related to the regulation of

the cytoskeleton and a stronger repression of mitochondrial genes than WT female hearts. These pathways, if activated, lead to the induction of fibroblast growth factors and the renin-angiotensin system. Categories and pathways with a significant enrichment of genes and a potential relevance for the development of hypertrophy are shown in Table 1.

In mice with MH upon TAC, a number of genes related to energy metabolism and mitochondrial function are more downregulated in males compared with females. ER β ($-/-$) mice exhibited a different global gene expression pattern, which was affected by the genotype and the hypertrophic response. Female ER β ($-/-$) mice showed a relatively stronger expression of genes involved in ubiquitin-mediated proteolysis, Wnt and p53 signaling (Table 1). Male ER β ($-/-$) mice were characterized by relatively stronger expression of genes that play a role in the regulation of programmed cell death, cell proliferation, and in transforming growth factor (TGF) signaling (Table 1).

To determine the role of the E2/ER β axis in the genomic response to PO-induced hypertrophy, Kararigas et al. [36] used the microarray dataset of female WT and female ER β ($-/-$) mice after TAC. Data analysis was done for differences in the expression of individual probe sets between female TAC and sham mice followed by comparison of these differences between the two genotypes, WT and ER β ($-/-$). This approach revealed that the two genotypes have distinct transcriptional profiles. Considerably, more genes were modulated in response to PO induced by TAC in ER β ($-/-$) mice than in WT mice. The majority of the identified candidates in female ER β ($-/-$) mice were induced, e.g., genes related to inflammatory- and oxidative stress-induced pathways, while those in female WT mice were repressed. The data show that the presence of ER β is essential for the strict control of the induction of numerous genes in PO and suggest a repressive role of gene expression for ER β . The absence of ER β leads to a dramatic number of modulated probe sets in response to PO. These data may offer the molecular explanation for the cardioprotective role of ER β , while ER β acquires the role of a gatekeeper of the genomic response of the heart to PO-induced hypertrophy.

Clinical implications

The most frequent precursor and facilitator of HF in women is MH due to hypertension or other nonischemic origins; whereas in men, an ischemic etiology predominates [37]. Increased left ventricular mass is an important cardiovascular risk factor for morbidity and has a greater impact on survival in women than in men [38]. The adaptations in men and women are different as described above. Understanding these differences could result in novel therapies that would be beneficial for both sexes.

Table 1 Regulated pathways in WT and ER β (-/-)/TAC mice. (Copyright American Physiological Society, with permission, [23])

Gene ontology category or KEGG pathway		Count (%)	P value
<i>Subset a: relative higher expression in WT females</i>			
BP	Electron transport	12 (3.3)	0.055635
	Oxidative phosphorylation	4 (1.1)	0.087204
CC	Mitochondrial part	14 (3.9)	0.004262
MP	Electron carrier activity	8 (2.2)	0.031429
KEGG	Oxidative phosphorylation	9 (2.5)	0.001461
<i>Subset b: relative higher expression in WT males</i>			
BP	Regulation of cell proliferation	24 (4.4)	0.000021
	Biopolymer metabolic process	140 (25.4)	0.000424
	Muscle fiber development	7 (1.3)	0.005933
CC	Intracellular part	255 (46.5)	<0.000001
	Cytoskeletal part	20 (3.6)	0.085629
MP	Cytoskeletal protein binding	17 (3.1)	0.0207
	Growth factor binding	5 (0.9)	0.035409
KEGG	MAPK-signaling pathway	14 (2.5)	0.020864
	Regulation of actin cytoskeleton	11 (2.0)	0.059141
<i>Subset c: relative higher expression in ERβ (-/-) females</i>			
BP	Biopolymer metabolic process	160 (32.1)	<0.000001
	Cell cycle process	25 (5.0)	0.001884
	Regulation of programmed cell death	19 (3.8)	0.010344
CC	Intracellular part	259 (52.1)	<0.000001
	Ubiquitin ligase complex	5 (1.0)	0.020774
MP	Ubiquitin protein ligase activity	16 (3.2)	<0.000001
KEGG	Ubiquitin-mediated proteolysis	17 (3.4)	<0.000001
	Wnt-signaling pathway	11 (2.2)	0.003519
	p53-signaling pathway	5 (1.0)	0.082801
<i>Subset d: relative higher expression in ERβ (-/-) males</i>			
BP	Biopolymer metabolic process	102 (27.7)	0.000064
	Regulation of cell proliferation	16 (4.4)	0.000719
	Regulation of programmed cell death	16 (4.4)	0.006024
CC	Intracellular part	190 (51.6)	<0.000001
MP	Cytoskeletal protein binding	11 (3.0)	0.084934
KEGG	Dentatorubropallidolusian	3 (0.8)	0.027815
	Chronic myeloid leukemia	5 (1.4)	0.044170

BP biological process, CC cellular compartment, MP molecular process, KEGG kyoto encyclopedia genes and genomes, WT wild type

Sex differences are well described in MH due to AS. Women with AS develop greater wall thickness and more concentric LV hypertrophy and have LVs with smaller diameters; whereas, men more commonly demonstrate eccentric remodeling. Estrogen may limit the development of MH [39]. At present, there is no therapeutic exploitation of this potential approach, since estrogens have major side effects in men and have been shown to lead to an increase in cardiovascular risk and breast cancer in women [40]. However, novel therapeutic approaches with specific modulators of sex-specific signaling such as selective estrogen receptor modulators (SERM), ER α - or ER β -specific agonists, or other substances that interfere with sex-specific pathways

could be used to specifically target the beneficial mechanisms [41].

Studies focusing on clinical response to the reduction of the transvalvular gradient after transcatheter aortic valve implantation (TAVI) found that regression of hypertrophy occurred in men and women, but female sex was an independent predictor of early improvement of the ejection fraction (EF) after AVR [42]. C-reactive protein and interleukin-6 were elevated at baseline more in men than in women, decreased after TAVI, and normalized at 3 months only in women. Peri-interventional complications and 3-months mortality were not different in this prospectively analyzed cohort of TAVI patients. Stangl et al. [42] conclude

that women and men benefit from TAVI with sex differences involving the recovery response of the left ventricle after TAVI. Whether the less invasive approach of TAVI compared with conventional surgery is particularly beneficial for women or not has to be discussed with the help of future studies.

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