

Sex Differences in HFpEF: Mechanisms, Manifestations, and Therapeutic Target Identification

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Abstract: Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome that accounts for more than half of heart failure cases and disproportionately affects older women. Biological sex is a key determinant of HFpEF, influencing epidemiology, comorbidity profiles, cardiac structure, clinical outcomes, and therapeutic responses. Women more commonly exhibit concentric left ventricular remodeling and diastolic dysfunction, frequently in association with obesity, hypertension, diabetes, and anemia, whereas men more often present with ischemic heart disease, renal dysfunction, and right ventricular involvement. These sex differences extend to prognosis, quality of life, and responses to therapies such as spironolactone and sacubitril/valsartan. At the mechanistic level, women exhibit greater metabolic dysregulation, heightened inflammatory responses, and more pronounced ventricular–arterial stiffening, whereas men show more prominent ischemic and cardiorenal perturbations. Emerging evidence indicates that these sex-specific features arise from distinct but interconnected pathophysiological pathways, including mitochondrial dysfunction, renin–angiotensin–aldosterone system (RAAS) imbalance, microvascular inflammation, impaired NO–cGMP–PKG signaling, and extracellular matrix remodeling. These pathways are differentially regulated by gonadal hormones, sex chromosome dosage, and X-linked gene escape from inactivation, which together shape cardiac stiffness, fibrosis, oxidative stress, and immune activation. Overall, these findings highlight the complex interplay between hormonal, chromosomal, and molecular mechanisms underlying sex differences in HFpEF. A better understanding of these processes may help explain disease heterogeneity, guide the rational identification of sex-dependent therapeutic targets, and support the development of sex-informed prevention and therapeutic strategies.

Keywords: HFpEF; sex difference; cardiac remodeling

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) is defined by typical heart-failure symptoms in the presence of a left ventricular ejection fraction (LVEF) $\geq 50\%$, together with evidence of diastolic dysfunction or elevated filling pressures, such as abnormal echocardiographic parameters or increased natriuretic peptide levels [1]. Previously described as “diastolic heart failure” or considered a precursor to heart failure with reduced ejection fraction (HFrEF), HFpEF is now recognized as a systemic syndrome. It is characterized by cardiac alterations, including cardiomyocyte hypertrophy, fibrosis, and inflammation, alongside systemic metabolic dysregulation, endothelial dysfunction, and chronic low-grade inflammation [2]. HFpEF now accounts for more than half of all heart-failure cases and continues to increase in prevalence worldwide [3–6]. Importantly, HFpEF confers risks of hospitalization and mortality comparable to those of HFrEF, underscoring its substantial clinical and public health burden [5–7].

Biological sex is an important factor in HFpEF risk. Studies from population cohorts and clinical registries show that women develop HFpEF more often than men, especially in older age groups [3,7–10]. Compared with men, women with HFpEF tend to have a higher burden of comorbidities such as hypertension, obesity, insulin resistance, anemia, and diabetes, whereas men with HFpEF more commonly present with ischemic heart disease, including prior myocardial infarction, as well as chronic kidney or liver disease [11–15]. Notably, women tend to experience more severe symptoms and exercise intolerance despite comparable or less pronounced cardiac



remodeling [16–18]. These sex-specific clinical patterns support the existence of distinct biological mechanisms underlying HFpEF development and progression [3].

This review focuses on the influence of sex on HFpEF pathophysiology, emphasizing insights from animal models, the roles of sex hormones and sex chromosomes, and sex-specific molecular pathways, and their translational implications for therapeutic target discovery.

2. Sex-Specific Epidemiology of HFpEF

HFpEF exhibits a clear sex-specific epidemiological pattern, with a higher prevalence in women than in men across diverse populations. Large registry and cohort studies consistently show that women account for the majority of HFpEF cases, often comprising approximately two-thirds of the affected population [4,19–22].

This sex difference becomes more pronounced with advancing age. HFpEF is relatively uncommon before midlife but increases steeply in older adults, particularly in women. In elderly populations, prevalence in women is nearly double that observed in men, exceeding 8% in those aged ≥ 80 years [3,7,23].

Lifetime risk analyses further highlight distinct sex-related patterns in heart failure phenotypes. While the overall lifetime risk of HFpEF is comparable between men and women, women are more likely to develop HFpEF than HFrEF, whereas men exhibit a more balanced distribution between the two phenotypes [24].

Together, these findings indicate that the burden of heart failure in women is predominantly driven by HFpEF, whereas men exhibit a more heterogeneous distribution of heart failure subtypes.

3. Sex Differences in Clinical Phenotypes of HFpEF

3.1. Pathophysiological Differences

Echocardiographic studies consistently show that women more frequently exhibit concentric left ventricular (LV) remodeling, characterized by smaller LV cavities and thicker ventricular walls compared with men [25–27]. Correspondingly, women demonstrate more pronounced diastolic dysfunction, including impaired LV relaxation, increased diastolic stiffness, and elevated filling pressures at rest [16]. Both end-systolic and end-diastolic LV elastance, as well as arterial stiffness, are higher in women, reflecting a globally stiffer ventricular–arterial system [16].

These sex-specific differences become more evident during physiological stress. In invasive hemodynamic studies combined with exercise echocardiography, women exhibit a reduced diastolic reserve compared with men [16]. Even after adjustment for workload, women show higher pulmonary capillary wedge pressure and greater increases in both systolic and diastolic LV elastance during exercise [28]. In addition, lower systemic and pulmonary compliance and impaired peripheral oxygen kinetics indicate more adverse ventricular–vascular coupling under stress conditions [16].

3.2. Sex-Specific Comorbidity Patterns in HFpEF

Comorbidity patterns in HFpEF display clear sex-specific differences, with additional modulation by age, contributing to distinct clinical phenotypes. Phenotypic analyses from large cohorts suggest that women and men exhibit divergent comorbidity profiles. Women, particularly at younger ages, tend to have milder cardiac remodeling and lower natriuretic peptide levels, whereas older patients—especially men—more often present with chronic kidney disease, pulmonary hypertension, and right ventricular dysfunction, accompanied by more advanced structural remodeling and worse outcomes [29].

In women with HFpEF, comorbidities more often reflect a cardiometabolic profile and a higher prevalence of hypertension (Figure 1). Hypertension is a major contributor to HFpEF [30] and is more prevalent in women across most age groups, becoming particularly prominent after 75 years of age [24]. In postmenopausal women, it remains a dominant HFpEF risk factor across multiple racial and ethnic groups, including White, African American, and Hispanic women [31]. Obesity is also more prevalent in female HFpEF patients [19]. Notably, body mass index correlates with plasma B-type natriuretic peptide (BNP) levels, a relationship not observed in men [20]. In addition, epicardial fat accumulation is associated with worse outcomes and shows a stronger adverse effect in women [32–34]. Diabetes further contributes to this cardiometabolic phenotype, conferring a disproportionately higher risk of HFpEF [35], and more pronounced left ventricular remodeling in women compared with men [36,37].

In contrast, men with HFpEF more frequently exhibit a cardiorenal and ischemic comorbidity profile. Chronic kidney disease and liver dysfunction are more prevalent in male HFpEF patients [19,20], who also show higher rates of ischemic heart disease, prior percutaneous coronary intervention, or coronary artery bypass graft surgery [19,20,38,39]

(Figure 1). Furthermore, men are also more prone to a right heart phenotype, characterized by pulmonary vascular disease, elevated diastolic pressure gradients, impaired right ventricular function, and increased cardiac mortality [21].

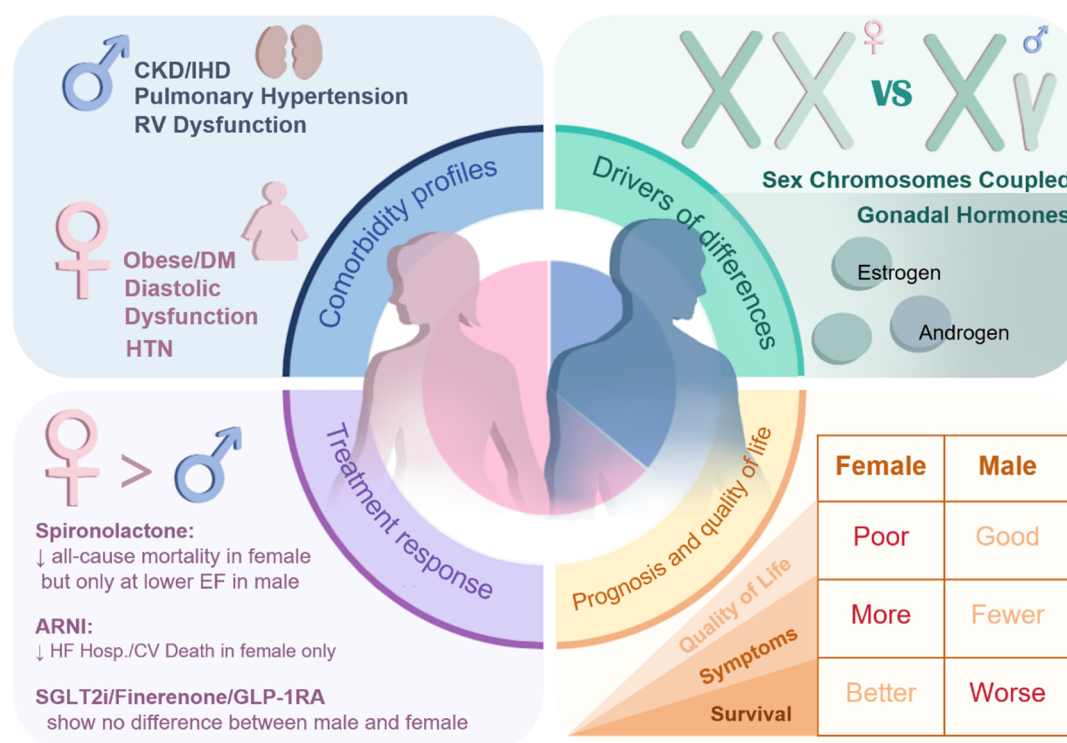


Figure 1. Sex differences in HFpEF. HFpEF exhibits marked sex differences in comorbidity profiles, treatment responses, clinical presentation, and prognosis. Women more commonly present with obesity, diabetes mellitus (DM), and hypertension (HTN), accompanied predominantly by left ventricular diastolic dysfunction, whereas men more frequently have chronic kidney disease (CKD) and ischemic heart disease (IHD) and are more prone to pulmonary hypertension and right ventricular (RV) dysfunction. Some therapies show potential sex-specific effects, with women appearing to derive greater benefit from spironolactone and sacubitril/valsartan, while SGLT2 inhibitors demonstrate consistent benefits across sexes; emerging therapies such as finerenone and GLP-1 receptor agonists also show clinical benefit, although sex-specific effects remain under investigation. Women tend to have worse symptoms but better survival, whereas men show the opposite pattern.

3.3. Sex-Specific Responses to HFpEF Therapies

Evidence from large clinical trials indicates that women and men with HFpEF can respond differently to pharmacological therapies. The TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) was overall neutral and did not meet its primary endpoint. However, subgroup and exploratory analyses have suggested potential sex-specific differences in treatment response. Spline analyses from sex-specific and phenomapping analyses suggested that women derived benefit from spironolactone across a wide range of LVEF, whereas men showed benefit mainly at lower EF values [29]. Furthermore, additional subgroup analysis indicated that spironolactone was associated with reduced all-cause mortality in women, but not in men [40,41]. Similarly, the PARAGON-HF trial (Prospective Comparison of ARNI with ARB Global Outcomes in HFpEF) demonstrated a significant interaction between sex and treatment, with women appearing to derive greater benefit from sacubitril/valsartan, whereas no clear benefit was observed in men [42,43].

In contrast, large-scale trials of sodium–glucose cotransporter 2 inhibitors, including EMPEROR-Preserved [44] and DELIVER [45], demonstrated consistent benefits in both women and men, without significant sex–treatment interactions. Emerging therapies such as finerenone [46] and glucagon-like peptide-1 receptor [47] agonists have also demonstrated clinical benefit in HFpEF, although data on sex-specific differences remain limited.

Together, these findings suggest that while some therapies may exhibit sex-specific effects, others provide comparable benefit across sexes (Figure 1). These heterogeneous responses may be partly explained by underlying biological differences. Sex-related variation in aldosterone signaling and myocardial fibrosis may contribute to the greater benefit of mineralocorticoid receptor antagonists observed in women, while differences in natriuretic peptide signaling and ventricular–vascular coupling may influence responses to sacubitril/valsartan [48,49]. In

addition, women with HFpEF tend to exhibit more concentric remodeling, smaller left ventricular volumes, and higher LVEF than men, such that a similar LVEF may reflect more advanced functional impairment and greater responsiveness to therapies that promote reverse remodeling. Differences in pharmacokinetics and pharmacodynamics may further contribute to variability in treatment response [50].

3.4. Sex Differences in Prognosis and Quality of Life

Sex differences in HFpEF extend beyond pathophysiology and treatment response to include prognosis and quality of life. Women with HFpEF exhibit more congestion-related symptoms and generally report poorer quality of life than men [12,14,51]. Large trials involving over 8000 HFpEF patients from CHARM-Preserve, I-PRESERVE, and TOPCAT-Americas have shown that women experience orthopnea and paroxysmal nocturnal dyspnea more frequently than men [14]. Contemporary studies show that, even after accounting for age and other clinical factors, women score lower on the Kansas City Cardiomyopathy Questionnaire (KCCQ), with median differences exceeding 10 points [14]. In addition, women report higher levels of anxiety and depression [52,53].

Despite reporting lower quality of life, women with HFpEF generally have similar or slightly better long-term survival than men (Figure 1), and their risk of sudden cardiac death is roughly half that of male patients [14]. The I-PRESERVE trial, which included 2500 female HFpEF patients, further confirmed this finding. Even after adjusting for age and other baseline characteristics, women had a 20% lower risk of cardiovascular and non-cardiovascular death or hospitalization compared with men [11]. However, in a recent Chinese cohort of 51,711 patients followed for one year, women had higher adjusted risks of heart failure hospitalization, cardiovascular death, and all-cause hospitalization or death. These associations were consistent across different levels of LVEF [54].

4. Genetic and Hormonal Determinants of Sex Differences in HFpEF

To understand sex differences in HFpEF, it is useful to refer to the conceptual framework proposed by Arnold [55]. According to this framework, sex differences are primarily driven by gonadal hormones and direct effects of sex chromosome genes (Figure 1). Gonadal hormones influence tissue and organ function throughout development and adulthood, while sex chromosome genes can affect phenotype independently of hormones.

4.1. Mouse Models to Dissect Hormonal and Chromosomal Effects

Owing to the natural coupling of chromosomal and gonadal sex, traditional animal models cannot distinguish hormonal from chromosomal effects, so two genetic mouse models—the Four Core Genotypes (FCG) model and the XY* model—were created to overcome this limitation [56] (Figure 1).

The FCG model separates gonadal sex from sex chromosome complement by manipulating the Sry gene, enabling the independent assessment of hormonal and chromosomal influences. Proteomic analyses identified proteins regulated by hormones, sex chromosomes, or both [57].

The XY* model further isolates sex chromosome effects by varying X chromosome number independently of gonadal sex, demonstrating that X chromosome dosage influences susceptibility to cardiac injury [58].

These studies demonstrate that the FCG and XY* mouse models are valuable tools for dissecting the separate and combined effects of sex hormones and sex chromosomes on cardiac structure, function, and molecular pathways. By systematically comparing cardiac phenotypes, molecular pathway activity, and response to interventions between groups with distinct gonadal status and sex chromosome dosage, these models enable researchers to pinpoint critical sex-biased mechanisms, validate their causal roles in HFpEF, and define them as actionable, sex-dependent therapeutic targets for precision drug development.

4.2. Sex Chromosome-Mediated Regulation of Cardiac Function

Growing evidence shows that sex chromosomes exert direct effects on the heart that are independent of gonadal hormones. Studies of cardiac gene expression show clear differences between males and females even before sex hormones rise and before sexual maturation. These differences also appear later in aged females with declining reproductive function, as shown in mouse studies [59]. Proteomic studies also show sex differences which do not depend on gonadal hormones. Analyses of embryonic mouse hearts at E9.5 (embryonic day 9.5, before gonad formation) show that many cardiac proteins already exhibit sex differences. These protein differences are mainly established through post-transcriptional mechanisms [57].

X chromosome inactivation (XCI) ensures dosage compensation in females, but a subset of genes escapes XCI and remains transcriptionally active, contributing to sex-specific gene expression patterns and cardiovascular phenotypes [60–63].

Research directly addressing HFpEF remains limited, but emerging disease models provide complementary evidence for the role of sex chromosomes beyond specific epigenetic mechanisms. In a recent report using a two-hit HFpEF model (high-fat diet combined with L-NAME), experiments with FCG mice and ovariectomized females showed that both sex hormones and sex chromosomes influence HFpEF development. Estradiol had protective effects, whereas a second X chromosome appeared to exacerbate HFpEF features. Mechanistic studies using RNA sequencing are ongoing [64].

4.3. Estrogen and Estrogen Receptor–Related Phenotypic Modulation in HFpEF

Estrogen, particularly 17 β -estradiol (E2), declines markedly after menopause and is closely associated with sex-specific phenotypic features of HFpEF [39,65,66]. Estrogen deficiency has been linked to increased vascular and myocardial stiffness—key pathophysiological features of HFpEF—in women, particularly in older women, and to a diminished cardiac ability to adapt to abnormal hemodynamic load [39,66]. Evidence further shows that estrogen plays an important role in diastolic function by shortening the isovolumic relaxation time (IVRT) and increasing the E/A ratio, thereby improving left ventricular relaxation and early diastolic filling [67]. These alterations provide a potential explanation for the higher prevalence and symptom burden of HFpEF observed in postmenopausal women. Clinical data show that estrogen deficiency is linked to greater left ventricular hypertrophy.

In contrast, estrogen or hormone therapy can reduce vascular resistance, systolic blood pressure, left ventricular mass index, and relative wall thickness in postmenopausal women [68]. However, large clinical trials of hormone therapy in older postmenopausal women have not demonstrated cardiovascular benefit, suggesting that timing and aging may limit efficacy (“critical window” hypothesis) [69–71]. However, as these studies were not specifically designed to address HFpEF, the relevance of estrogen signaling to HFpEF therapy remains unclear and warrants further investigation in studies specifically designed for HFpEF.

Estrogen exerts its effects through nuclear receptors estrogen receptor alpha (ER α), estrogen receptor beta (ER β), and the membrane-bound G-protein-coupled estrogen receptor (GPER/GPR30), which are expressed in multiple cardiac cell types and regulate myocardial remodeling, stiffness, and diastolic function [72–76]. Experimental studies suggest that ER α is associated with preservation of right ventricular structure and function, a key determinant of outcomes in HFpEF [77–79], whereas ER β and GPER signaling are linked to attenuation of hypertrophy, fibrosis, and diastolic dysfunction [72,80–94]. Together, estrogen receptor–mediated signaling contributes to sex-specific differences in cardiac structure, function, and clinical presentation in HFpEF.

4.4. Androgens and HFpEF-Related Cardiac Phenotypes

Testosterone is the predominant circulating androgen in men and is present at much lower levels in women [95,96]. Its cardiovascular effects are mainly mediated by the androgen receptor (AR), which is expressed in cardiomyocytes, vascular smooth muscle cells, and endothelial cells [97].

Circulating testosterone declines with age and is associated with increased cardiometabolic risk [97–107]. In men with HFpEF, low testosterone relates to worse clinical status and cardiac dysfunction. In a study of 120 male HFpEF patients, those with low testosterone had more severe symptoms (higher New York Heart Association [NYHA] functional class), higher BNP levels, poorer metabolic and inflammatory profiles, and impaired endothelial function [108]. A pilot study found that about 37% of male HFpEF patients had testosterone deficiency [109].

Mechanistic studies have shown that testosterone can induce vasodilation [110] and that long-term testosterone deficiency leads to diastolic dysfunction and impaired myocardial calcium handling [111]. Given the importance of endothelial function, myocardial relaxation, and calcium handling in HFpEF, testosterone deficiency may represent an underrecognized contributor to HFpEF progression.

5. Key Molecular Pathways Underlying Sex Differences in HFpEF

5.1. Sex-Specific Regulation of Mitochondrial Function in HFpEF

Increasing evidence indicates that mitochondria play a critical role in cardiac function and HFpEF pathophysiology [112,113]. Mitochondrial dysfunction impairs ATP production, disrupts substrate metabolism, increases reactive oxygen species (ROS), and perturbs calcium homeostasis. These alterations compromise cardiomyocyte relaxation and contractile reserve, promote oxidative damage, and exacerbate diastolic dysfunction and ventricular stiffness [114].

Our laboratory previously investigated sex-dependent mitochondrial regulation in HFpEF using the HMDP mouse panel and “two-hit” HFpEF models [115]. Female mice developed more pronounced diastolic dysfunction than males, accompanied by lower cardiac mitochondrial DNA (mtDNA) content, which negatively correlated

with diastolic indices [115]. Gonadectomy and hormone replacement experiments demonstrated that sex hormones modulate mtDNA levels and mitochondrial function, with corresponding effects on diastolic performance (Figure 2): removal of endogenous hormones decreased mtDNA and worsened relaxation in males, whereas ovariectomy in females had the opposite effect [115]. These findings indicate that estrogen and androgens regulate mitochondrial abundance and function, influencing HFpEF susceptibility.

Acs16 was further identified as a female-biased cardiac gene whose expression correlated with diastolic function [115]. Genetic variation controlling Acs16 expression associated with HFpEF-relevant traits, highlighting a potential mechanistic link between sex, mitochondrial regulation, and myocardial relaxation.

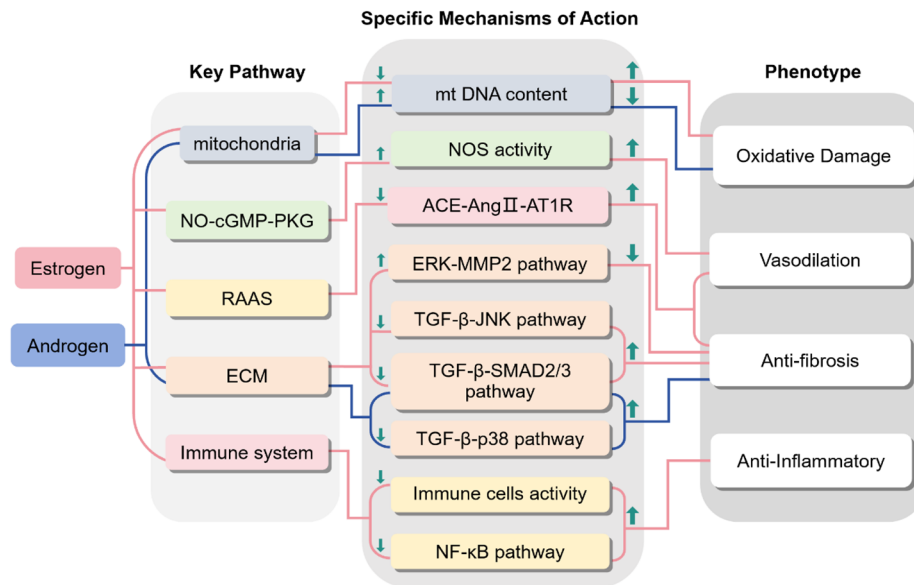


Figure 2. Sex hormone-dependent regulatory networks in HFpEF. Estrogen and androgen signaling modulate multiple key regulatory systems, including mitochondrial function, the NO-cGMP-PKG pathway, RAAS, ECM remodeling, and immune responses. These upstream regulatory networks converge on specific molecular mechanisms, such as mtDNA content, NOS activity, ACE-Ang II-AT1R signaling, ERK-MMP2 activation, TGF- β -dependent JNK, SMAD2/3, and p38 MAPK pathways, as well as NF- κ B-mediated inflammatory signaling. Through coordinated regulation of these mechanisms, sex hormones influence key cardiovascular phenotypes in HFpEF, including oxidative damage, vasodilation, myocardial fibrosis, and inflammation. Arrows indicate the direction of regulation, with red and blue lines representing estrogen- and androgen-associated effects, respectively.

5.2. Sex-Specific Regulation of the Renin-Angiotensin-Aldosterone System (RAAS)

Persistent activation of the RAAS is a key mechanism underlying left ventricular hypertrophy (LVH) and left ventricular diastolic dysfunction [116,117]. Beyond increasing blood pressure and afterload, RAAS promotes myocardial fibrosis and inflammation, exacerbating ventricular stiffness.

RAAS effects depend on the balance between two opposing axes: a deleterious “classical axis” centered on angiotensin-converting enzyme (ACE)-angiotensin II (Ang II)-angiotensin II type 1 receptor (AT1R) and a protective “counter-regulatory axis” centered on angiotensin-converting enzyme 2 (ACE2)-angiotensin-(1-7) [Ang-(1-7)]-Mas receptor (MasR) [117,118] (Figure 3).

Sex hormones modulate RAAS activity (Figures 2 and 3). Estrogen deficiency enhances vascular and myocardial responses to Ang II, increasing AT1R expression, whereas estrogen replacement reverses this effect [119]. Consequently, premenopausal women exhibit a blunted ACE-Ang II-AT1R response, partially limiting RAAS-mediated cardiac injury. Beyond hormones, sex chromosomes may also contribute. ACE2, which encoded on the X chromosome and potentially escaping X inactivation [120,121], converts Ang II to Ang-(1-7), a peptide that counteracts the harmful effects of the classical RAAS axis. Higher ACE2 expression in females may further contribute to sex differences in RAAS activity [122-124].

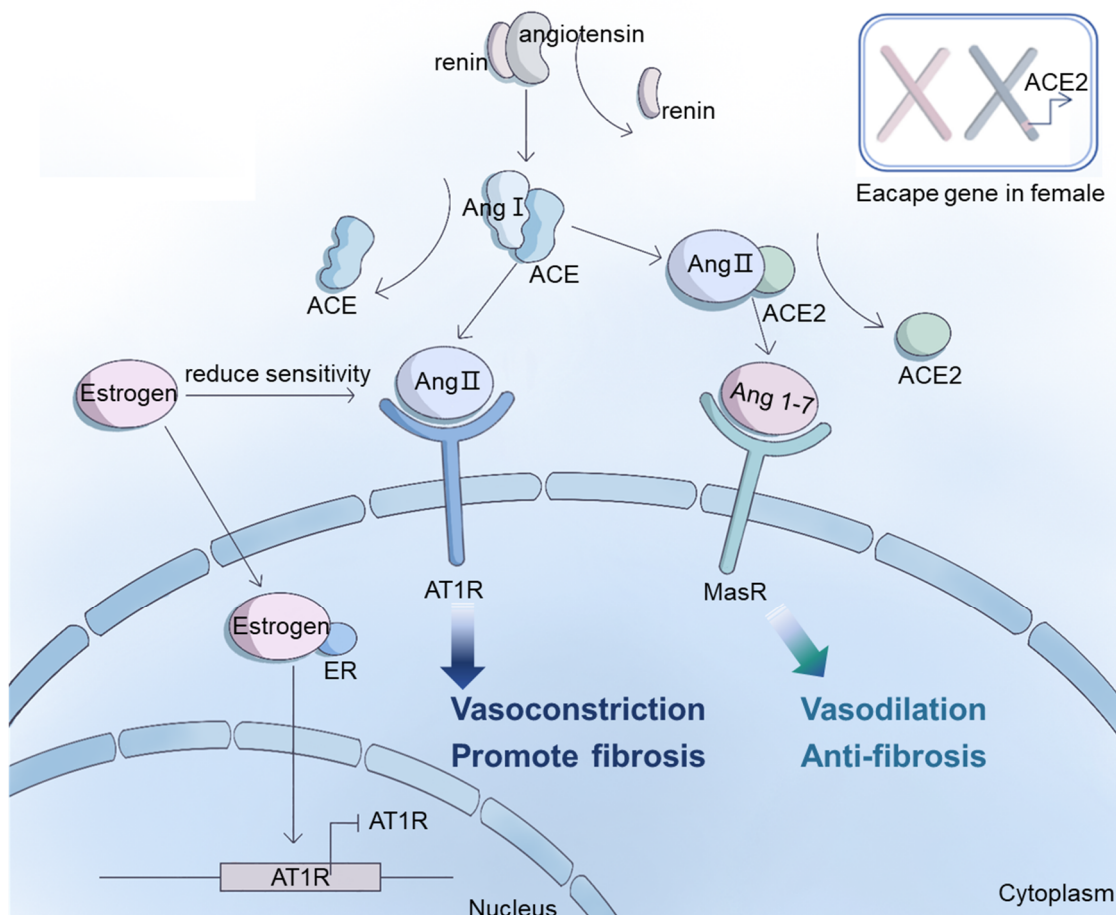


Figure 3. Sex hormone and sex chromosome modulation of RAAS signaling in the heart. Activation of the classical Ang II–AT1R axis promotes myocardial fibrosis, with associated pathological hypertrophy, leading to increased myocardial stiffness and impaired diastolic function. Estrogen signaling through estrogen receptor α ($ER\alpha$) attenuates this pathway by reducing AT1R expression and receptor sensitivity. In contrast, the ACE2–Ang-(1–7)–MasR axis represents a protective arm of the RAAS and exerts antifibrotic and antihypertrophic effects, thereby preserving ventricular compliance and diastolic function. In females, partial escape of the ACE2 gene from X-chromosome inactivation may contribute to higher ACE2 expression and enhanced protective RAAS signaling.

5.3. Sexual Dimorphism in Immune Regulation and Inflammation

In HFpEF, chronic low-grade systemic inflammation and coronary microvascular endothelial inflammation link comorbidities to left ventricular diastolic dysfunction [125]. An illustrative example of how heightened immune responses interact with HFpEF susceptibility comes from autoimmune diseases: these conditions are more prevalent in women and are associated with diastolic dysfunction and an increased risk of HFpEF, as exemplified by impaired left ventricular diastolic function in patients with rheumatoid arthritis [126].

Inflammatory and immune responses display marked sexual dimorphism. Women generally exhibit greater immune responsiveness, characterized by more active transcription of immune-related genes, higher cytokine production, and stronger $CD4^+/CD8^+$ T-cell activation [127,128]. This enhanced responsiveness aids pathogen clearance but could predispose to excessive inflammation. In women, estrogen plays a key modulatory role in maintaining immune balance. Specifically, estrogen regulates the activity of T lymphocytes, B cells, and monocyte–macrophage populations through $ER\alpha$, and suppresses nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B)–dependent transcription of pro-inflammatory genes, lowering the expression of cytokines such as tumor necrosis factor alpha (TNF- α) and interleukin-6 (IL-6) [129,130] (Figures 2 and 4).

Sex differences in inflammation are also evident at the cardiac tissue level. Transcriptomic analyses show sex-dimorphic gene expression, with female hearts expressing higher levels of genes enriched in inflammatory pathways, including KLF4 and NF- κ B [131].

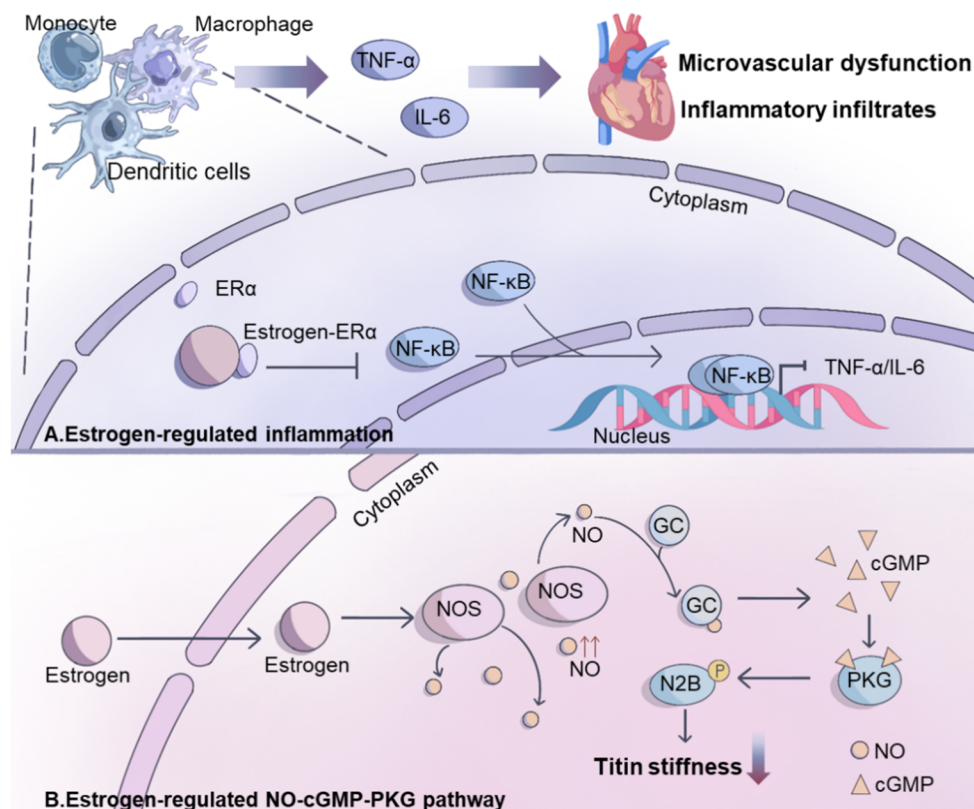


Figure 4. Estrogen modulation of inflammation and the NO–cGMP–PKG–Titin axis in HFpEF. **(A)** Estrogen-regulated inflammation. In HFpEF, activated immune cells release pro-inflammatory cytokines, including TNF- α and IL-6, which contribute to cardiovascular dysfunction, endothelial activation, and inflammatory cell infiltration. Estrogen signaling through ER α inhibits NF- κ B–dependent transcription of pro-inflammatory genes, thereby reducing the levels of these cytokines. **(B)** Estrogen-regulated NO–cGMP–PKG pathway. Estrogen enhances the NO–cGMP–PKG signaling pathway by increasing NOS expression and NO bioavailability. This leads to sGC activation and elevated cGMP levels in cardiomyocytes. Increased cGMP activates PKG, which phosphorylates the N2B region of titin, reduces titin-based passive stiffness, and supports myocardial compliance. Collectively, these effects preserve diastolic function and limit pathological remodeling.

5.4. Estrogen Modulation of the NO–cGMP–PKG Pathway in HFpEF

Within cardiomyocytes, the nitric oxide (NO)–cyclic guanosine monophosphate (cGMP)–protein kinase G (PKG) axis is central to maintaining diastolic function and limiting pathological remodeling (Figure 2). NO, mainly produced by endothelial (eNOS) and neuronal (nNOS) nitric oxide synthases, activates soluble guanylyl cyclase (sGC) to increase cGMP, which in turn activates PKG. PKG phosphorylates titin, reducing cardiomyocyte stiffness and improving diastolic compliance. In HFpEF patients, attenuated NO–cGMP–PKG signaling leads to titin hypophosphorylation, increased passive tension, and diastolic dysfunction [132–136].

Experimental studies indicate that estrogen enhances this axis. Estrogen upregulates eNOS and nNOS expression in cardiomyocytes, promoting NO production and maintaining endothelial function [137–140] (Figures 2 and 4). Through ER β signaling, estrogen increases eNOS activity in female cardiac myocytes [84]. In addition, Chen et al. have shown higher nNOS expression in female cardiac myocytes [141,142]. Overall, these findings highlight a key role of estrogen in modulating the NO–cGMP–PKG pathway in HFpEF, linking hormonal status to diastolic function and myocardial stiffness.

5.5. Sex Hormone Regulation of Extracellular Matrix Remodeling in HFpEF

Diastolic function is shaped not only by cardiomyocyte properties but also by the extracellular matrix (ECM), composed mainly of type I and III collagens, elastic fibers, and proteoglycans. Alterations in collagen content, isoform ratio, cross-linking, or ECM turnover affect ventricular stiffness and compliance [143,144].

Sex hormones regulate ECM remodeling through distinct pathways in cardiac fibroblasts (Figures 2 and 5). Estrogen signals through nuclear receptors ER α and ER β as well as the membrane receptor GPER. Activation of ER β inhibits transforming growth factor beta 1 (TGF- β 1)-induced SMAD2/3 activation and nuclear translocation,

blocks c-Jun N-terminal kinase (JNK) signaling, prevents fibroblast-to-myofibroblast differentiation, and reduces collagen, vimentin, and fibronectin synthesis [80]. GPER activation suppresses fibroblast proliferation by downregulating cyclins and CDK1 [145]. Androgen–AR signaling also participates in this regulation. Androgens act through AR to inhibit TGF- β 1/Ang II-induced fibroblast proliferation, myofibroblast differentiation, and collagen synthesis [146,147]. These effects involve reduced p38 mitogen-activated protein kinase (MAPK) and SMAD2/3 activation [146,147]. AR knockout mice show more severe fibrosis under Ang II stimulation, with increased type I/III collagen, TGF- β 1, and SMAD2 activity, highlighting the protective role of androgen–AR signaling [148].

Beyond increased collagen synthesis, impaired ECM degradation also contributes to sex-related fibrosis. ECM turnover is regulated by the balance between matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) [143,144,149]. Tissue inhibitor of metalloproteinases 1 (TIMP1) is an X-linked gene [97,150,151], and elevated TIMP1 inhibits matrix metalloproteinase 2/9 (MMP2/9)-mediated ECM degradation [152,153]. TIMP1 expression is higher in female hearts than in age-matched males in both mice and humans. In human myocardium, this difference is most pronounced in women aged 50–65 years, while younger women (<40 years) show a smaller increase [154,155]. In addition, physiological concentrations of E2 (10^{-8} M) reduce MMP2 expression in cardiac fibroblasts from adult rats and in HT1080 cells via ER α - and MAPK/extracellular signal-regulated kinase (ERK1/2)-dependent phosphorylation of Elk-1 and subsequent repression of the MMP2 promoter [156] (Figure 5).

In summary, sex hormones and X-linked genes act through distinct signaling mechanisms to regulate the development and progression of myocardial fibrosis in HFpEF.

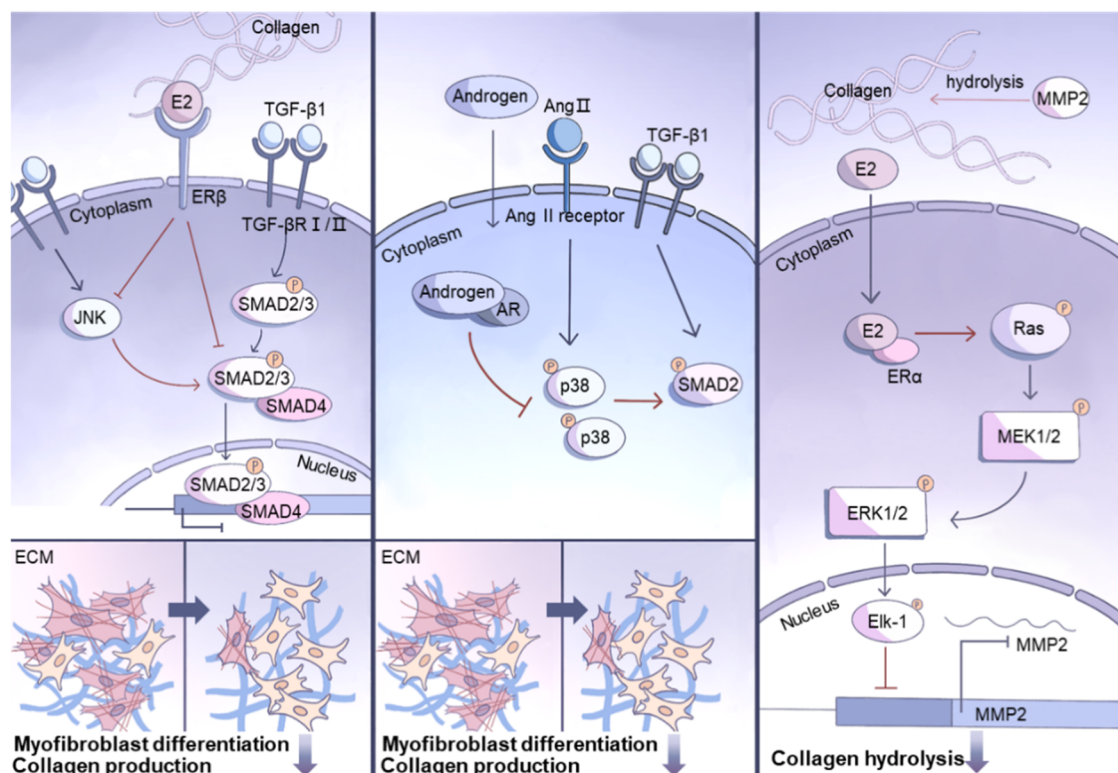


Figure 5. Sex-specific regulation of cardiac ECM remodeling and fibrosis in HFpEF. TGF- β signaling is a central driver of cardiac ECM remodeling and fibrosis in HFpEF. Activation of TGF- β receptors induces SMAD2/3-dependent and stress-activated signaling pathways, promoting myofibroblast differentiation and collagen synthesis. Estradiol signaling through ER β attenuates TGF- β -dependent profibrotic signaling by modulating SMAD2/3 pathways, thereby limiting collagen production. Similarly, testosterone signaling via the AR suppresses TGF- β /Ang II-induced collagen synthesis through differential regulation of SMAD and MAPK signaling. In parallel, estradiol signaling through ER α influences ECM turnover by regulating MMP2 expression, thereby modulating collagen degradation and overall matrix remodeling. Collectively, sex hormones shape TGF- β -driven ECM remodeling and fibrosis, contributing to sex-specific myocardial stiffness and diastolic dysfunction in HFpEF. TGF- β RII, transforming growth factor- β type II receptor; TGF- β RI, transforming growth factor- β type I receptor.

6. Translational Implications for Therapeutic Target Discovery

The sex-specific pathophysiological mechanisms and preclinical models described in this review provide a robust framework for rational drug discovery in HFpEF. By integrating sex as a fundamental biological variable, researchers can prioritize high-value targets and design more effective clinical trials.

The distinct sex-related pathophysiological patterns observed in HFpEF provide a rational basis for precision therapeutic target discovery. In women, the prominent features of metabolic dysfunction, microvascular inflammation, ventricular-arterial stiffening, and myocardial fibrosis collectively highlight several actionable targets: mitochondrial energy metabolism, NO–cGMP–PKG signaling, inflammatory microvascular injury, and extracellular matrix remodeling. These pathways are not only more severely dysregulated in female patients but also underpin the observed sex-specific therapeutic advantages of spironolactone and sacubitril/valsartan.

In men, the predominant ischemic cardiopathy, cardiorenal involvement, and right ventricular dysfunction shift therapeutic priorities toward cardiorenal protection, anti-ischemic signaling, and right ventricular functional preservation. Although SGLT2 inhibitors and finerenone exhibit consistent cardioprotection across sexes, male patients may derive additional benefit from combined anti-ischemic strategies. Sex differences in pharmacokinetics and pharmacodynamics further warrant sex-stratified dose optimization during early drug development to maximize efficacy and safety.

7. Conclusions

HFpEF is highly prevalent in women and is associated with worse clinical outcomes and reduced quality of life. Women with HFpEF often present with distinct cardiac phenotypes, including concentric left ventricular remodeling, smaller ventricular cavities, pronounced diastolic dysfunction, and common comorbidities such as hypertension, obesity, and diabetes. Systemic factors—such as heightened inflammation, endothelial dysfunction, and metabolic disturbances—further contribute to disease progression.

Accumulating evidence suggests that these sex-specific patterns arise not only from traditional risk factors but also from the interplay of gonadal hormones, sex chromosomes, and downstream molecular pathways. Sex hormones—particularly estradiol and testosterone—their receptors, and X- or Y-linked genes modulate key mechanisms, including mitochondrial function, RAAS signaling, immune activation, nitric oxide–cGMP–PKG signaling, and extracellular matrix remodeling. Studies using genetic mouse models, such as the FCG and XY* models, demonstrate that hormonal and chromosomal factors can act independently or synergistically to shape cardiac responses to stress. These insights help explain the higher HFpEF burden in women and the potential for sex-specific therapeutic responses.

To advance HFpEF research and drug discovery, sex must be considered a fundamental biological variable at every stage of the translational pipeline. Preclinical studies should move beyond the exclusive use of young male animals and incorporate the sex-specific models described herein to identify and validate sex-dependent therapeutic targets. Clinically, many previous heart failure trials underrepresented women or lacked pre-specified sex-stratified analyses, leading to missed opportunities for effective therapies. Future clinical trials should ensure adequate female representation, incorporate pre-specified sex-based subgroup analyses, and evaluate sex-specific dosing regimens to develop truly personalized, sex-informed therapies for HFpEF.

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List of Abbreviations

Abbreviation	Full Term
HFpEF	heart failure with preserved ejection fraction
LVEF	left ventricular ejection fraction
HFrfEF	heart failure with reduced ejection fraction
RAAS	renin–angiotensin–aldosterone system
LV	left ventricular

BNP	B-type natriuretic peptide
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
PARAGON-HF	Prospective Comparison of ARNI with ARB Global Outcomes in HFpEF
ARNI	angiotensin receptor–neprilysin inhibitors
KCCQ	Kansas City Cardiomyopathy Questionnaire
DM	diabetes mellitus
HTN	hypertension
CKD	chronic kidney disease
IHD	ischemic heart disease
RV	right ventricular
CV	cardiovascular
FCG	four core genotypes
Xic	X-inactivation center
XIST	X-inactive specific transcript
PRC2	polycomb repressive complex 2
H3K27	histone H3 lysine 27
XCI	X chromosome inactivation
E2	17 β -estradiol
IVRT	isovolumic relaxation time
ER α /ER β	estrogen receptor alpha / beta
GPER/GPR30	G-protein-coupled estrogen receptor
AR	androgen receptor
NYHA	New York Heart Association
ROS	reactive oxygen species
mtDNA	mitochondrial DNA
LVH	left ventricular hypertrophy
ACE	angiotensin-converting enzyme
ACE2	angiotensin-converting enzyme 2
Ang II	angiotensin II
AT1R	angiotensin II type 1 receptor
MasR	Mas receptor
TNF- α	tumor necrosis factor alpha
IL-6	interleukin-6
NF- κ B	nuclear factor kappa-light-chain-enhancer of activated B cells
NO	nitric oxide
eNOS	endothelial nitric oxide synthase
nNOS	neuronal nitric oxide synthase
sGC	soluble guanylyl cyclase
cGMP	cyclic guanosine monophosphate
PKG	protein kinase G
ECM	extracellular matrix
TGF- β	transforming growth factor beta
MMPs	matrix metalloproteinases
MMP2	matrix metalloproteinase 2
MMP9	matrix metalloproteinase 9
TIMPs	tissue inhibitors of metalloproteinases
TIMP1	tissue inhibitor of metalloproteinases 1
TGF- β RII	transforming growth factor- β type II receptor
TGF- β RI	transforming growth factor- β type I receptor
JNK	c-Jun N-terminal kinase
MAPK	mitogen-activated protein kinase
ERK	extracellular signal-regulated kinase

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