Estrogens and Myocardial Chymase
New Insights Into Pathological Hypertrophy and Remodeling

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Cardiovascular disease in women is increasing, and presently it kills more North American women than men, underscores the need for research aimed to understand the interactions between sex, aging, and cardiovascular health.

In this issue of Hypertension, in an experimental model of pressure overload induced heart disease in ovariectomized rats (as an equivalent to postmenopausal women), Li et al found left ventricular hypertrophy (LVH), normal systolic function, and increased myocardial collagen. Their model is rather similar to heart failure with preserved ejection fraction (HFpEF), commonly because of diastolic dysfunction induced by hypertensive heart disease. In response to pressure overload, they observed that ovariectomy induced higher levels of LVH.

Prevalence of HFpEF is 1.5% to 4.8%, it is increasing and women seem to outnumber men by a 2:1 ratio. In the recent trial of preserved cardiac function heart failure (HF) with the aldosterone antagonist spironolactone (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist [TOPCAT]), mean age was 68.6 years, 91% had hypertension, and 52% of the patients were women. In the TOPCAT trial body mass index was 32 kg/m² while comorbidities were common. Patients with HF with reduced ejection fraction and HFpEF each make up approximately half of the overall HF burden. Mortality in patients with HFpEF was close to that in patients with HF with reduced ejection fraction.

Patients with HFpEF have increased intracardiac filling pressure and natriuretic peptide as well as reduced exercise capacity. Key pathophysiological features of HFpEF are increased LVH and impaired diastolic function. Diastolic function was not assessed in Li’s study, but it was most probably abnormal. Diastolic dysfunction induces elevated LV end-diastolic pressure leading to pulmonary congestion and HF symptoms because the LV, left atrium, and the pulmonary veins form 1 chamber while the mitral valve opens. Among patients with HFpEF, LVH, high LV filling pressure, and pulmonary artery pressure are predictive of HF hospitalization, cardiovascular death, or aborted cardiac arrest independent of clinical and laboratory predictors.

The major issue in the development and progression of HFpEF is concentric LVH, which is the result of accelerated growth of both the myocyte and the extracellular matrix compartments. The stimulus for LVH is prolonged pressure overload because of hypertension, aortic stenosis, or age dependent arterial stiffening. Increased myocardial fibrillar collagen accumulation and fibroblast/myofibroblast proliferation within the extracellular matrix in the context of HFpEF are common features. Although concentric LV remodeling is common, it is by no means universal and many patients exhibit normal LV geometry or an eccentric pattern, which means different pathophysiological relevant subphenotypes within this syndrome.

In HFpEF, it has been proposed, a systemic proinflammatory state is induced by comorbidities such as obesity or diabetes mellitus as the origin of microvascular endothelial cell inflammation and subsequent concentric cardiac remodeling and dysfunction, with interactions of the endothelium with cardiac fibroblasts and cardiomyocytes and with cardiac neurohormonal status. Myocardial damage, by different noxious causes, triggers an inflammatory reaction driving postinjury repair mechanisms and chronic remodeling processes that are detrimental to cardiac function. Li et al observed here high mast cell density and degranulation in response to transverse aortic constriction only in ovariectomized rats.

Cardiomyocytes have recently emerged as important players in coordinating this inflammatory response. Injured cardiomyocytes release damage-associated molecular pattern molecules (such as high-mobility group box 1, DNA fragments, heat shock proteins, and matricellular proteins), which instruct surrounding healthy cardiomyocytes to produce inflammatory mediators such as interleukin-1β, interleukin-6, macrophage chemoattractant protein, and tumor necrosis factor α that activate signaling networks within surviving cardiomyocytes and trigger leukocyte activation and recruitment.

In response to hypertension, women seem to have more concentric LV remodeling and less ventricular dilatation. In addition, ventricular and arterial stiffness increases with age in both sexes, but the increase is more dramatic in women. LV function changes across the lifespan, and systolic and diastolic function and functional reserve become more compromised in women compared with men in the postmenopausal years, despite similar function in women during youth.

Additionally, clinical and basic science have implicated activation of the renin–angiotensin–aldosterone system, linked to the loss of ovarian estrogens, in the pathogenesis of postmenopausal diastolic dysfunction. As a consequence of increased tissue angiotensin II and low estrogen, a maladaptive nitric oxide synthase
system produces reactive oxidative species that may contribute to female sex-specific hypertensive heart disease. Recent insights from models that mimic the cardiac phenotype of an estrogen-insufficient/deficient woman (eg, premature ovarian failure or postmenopausal), including the ovariectomized congenic mRen2. Lewis female rat, as well as the current model, provide evidence that estrogen modulates the tissue renin–angiotensin–aldosterone system and nitric oxide synthase system and related intracellular signaling pathways, in part via the membrane G protein–coupled receptor 30 also called G protein–coupled estrogen receptor 1, which might also be related to the pro remodeling Rho A/Rho kinase signaling pathway.

In this article, myocardial chymase, which is able to hydrolyze angiotensin I to form angiotensin II, was increased after transverse aortic constriction. However, plasma chymase levels were increased by transverse aortic constriction only in ovariectomized rats.

Little or no progress has been made in identifying evidence-based, effective treatments, and no medical therapy to date does improve survival in patients with HFrEF, including β-blockers, renin–angiotensin system antagonists, aldosterone antagonists, and phosphodiesterase-5 inhibitors. Thus, treatment of HFrEF remains largely empirical, and almost no acknowledged standards exist. Current guidelines emphasize volume control and antihypertensive therapy. At this point, it is important to consider 2 aspects. First, the degree of contribution of different pathophysiologic mechanisms and phenotypes (Figure) to clinical symptoms and outcome varies among patients. Besides, the stage of structural heart disease and the grade of diastolic dysfunction should be considered when designing specific interventions.

In this well conducted preventive study by Li et al in ovariectomized rats under aortic constriction, estrogen replacement reduced LVH and collagen volume fraction, it markedly attenuated constriction-increased myocardial chymase, mast cell density/degranulation, plasma chymase, and myocardial active transforming growth factor-I. In addition, by inhibiting chymase with chymostatin or by using the mast cell stabilizer nedocromil, similar findings were observed. These observations underscore the role of the estrogen–chymase–angiotensin II–pathological LVH path and add new insights into the mechanisms, prevention, and possibly treatment of HFrEF (and possibly of other myocardial diseases), particularly in postmenopausal women.

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None.

**References**

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