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EDITORIAL COMMENT

Heart Failure With Preserved Ejection Fraction in Women

New Clues to Causes and Treatment*

Matthias Barton, MD,[a,b] Matthias R. Meyer, MD[a,c]

Coronary artery disease, myocardial infarction, and heart failure affect men and women differently, with women being largely protected before menopause (1). Estrogens exert multiple protective effects in the cardiovascular system; these include antioxidant effects, anti-inflammatory effects, and inhibition of cell proliferation, atherogenesis, and thrombosis (1). In the cardiovascular system, estrogens exert both chronic (genomic) and rapid (nongenomic) effects through activation of target proteins, the estrogen receptors (2). The classic estrogen receptors, ERα and ERβ, are nuclear transcription factors that regulate gene expression (2). In addition, membrane subpopulations of these receptors mediate rapid signaling events following estrogen stimulation (2). Estrogen can also mediate its effects through the G protein–coupled estrogen receptor (GPER), a membrane G protein-coupled receptor (GPCR) localized in the endoplasmic reticulum that mediates both the rapid and chronic effects meditated by estrogens (1).

Cyclic guanosine monophosphate (cGMP) is an important intracellular messenger that contributes to coronary vasodilation, inhibition of cardiomyocyte proliferation, and inflammation, thus counteracting the development of cardiac hypertrophy and fibrosis (3). Soluble guanylate cyclase (sGC) is the primary receptor for nitric oxide (NO) in mammalian NO signaling, which leads to formation of cGMP as a second messenger (3). In macrovascular and microvascular coronary endothelium, activation of membrane ERα and GPER induces the L-arginine/NOS3/NO/cGMP pathway (1,2). In addition to direct stimulation of cGMP formation through NO, estrogen may also prolong the half-life of cGMP by inhibiting phosphodiesterase 5 (PDE5), an enzyme responsible for the hydrolytic inactivation of cGMP (4). In endothelial cells, PDE5 is localized to caveolae, where it breaks down cGMP but at the same time also stimulates NOS3 and NO bioactivity, thereby simultaneously contributing to both inactivation and synthesis of cGMP (3).

Heart failure is a clinical syndrome with a high prevalence and high mortality (5). Heart failure with preserved ejection fraction (HFpEF) results from abnormal left ventricular diastolic function caused by multiple factors causing coronary microvascular dysfunction and subsequent development of cardiomyocyte hypertrophy and myocardial fibrosis; predisposing factors include arterial hypertension, diabetes, obesity, and aging (5). HFpEF is now the most common form of heart failure and a condition predominantly of post-menopausal women (5). It is largely absent in pre-menopausal women but its prevalence rises after menopause, which indicates a protective role of endogenous estrogen (5).

Drugs that stimulate cGMP production by directly activating sGC, as well as PDE5 inhibitors (6) that interfere with the breakdown of cGMP, are being

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From the [a]University of Zürich, Zürich, Switzerland; [b]Andreas Grüntzig Foundation, Zürich, Switzerland; and the [c]Division of Cardiology, Triemli City Hospital, Zürich, Switzerland. This work was supported by the Swiss National Science Foundation (Nr. 108 258 and 102 544 to Dr. Barton and Nr. 135 874 and 141 501 to Dr. Meyer). Dr. Barton has served on the Diabetic CKD Advisory Board and the Steering Committee of the SONAR trial conducted by AbbVie, Inc; and has been a consultant for AbbVie Inc.
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explored as new approaches for the treatment of HFpEF. Using an experimental model of heart failure, Sasaki et al. (4) previously reported that surgical menopause in female mice abrogates the beneficial effects of endogenous estrogens on the efficacy of a PDE5 inhibitor, sildenafil. The estrogen-dependent NO-cGMP–mediated effect that protected against left ventricular remodeling was dependent on Gq-coupled receptor activation and the presence of functional cGMP-dependent protein kinase Iα (PKGIα) (7). Whether this protective effect involved genomic or nongenomic effects and which estrogen receptor(s) were involved remained unknown.

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In this issue of *JACC: Basic to Translational Science*, Fukuma et al. (7) present experimental evidence to suggest that partial protection that results from PDE5 inhibition in a model of pressure overload–induced left ventricular remodeling and heart failure requires non-nuclear estrogen receptor signaling that is linked to the activity of PKGIα. The investigators also show that estrogen-dependent cardiac protection can be achieved with the PDE5 inhibitor sildenafil but not with the direct sGC stimulator riociguat, which provides important insights to the mechanisms involved. The investigators also show that short-term stimulation of cardiomyocyte NOS activity by estrogen was completely abrogated in female animals that lacked non-nuclear ERα signaling. The findings are remarkable and provide new hints as to why heart failure pathophysiology and therapy may be different between men and women (5). Importantly, these data confirm that hormone treatment with estrogen (17β-estradiol, the biologically most important endogenous estrogen in pre-menopausal women) has remarkable beneficial effects on the failing female heart, and that estrogen treatment alone prevents many of the contractile and structural abnormalities (8). The investigators report that estrogen largely normalized many of the measured parameters, whereas adding sildenafil to hormone therapy further improved systolic and diastolic function and reduced heart weight, cardiomyocyte hypertrophy, and myocardial fibrosis, which suggests additional therapeutic potential (7). Importantly, all these beneficial effects, as well as myocardial PKGIα activation, were absent in animals that lacked non-nuclear ERα signaling. Similar additive effects were seen with regard to the regulation of genes implicated in the pathogenesis of heart failure.

The results presented by Fukuma et al. (7), which might help to explain, in part, the previous failure of PDE5 inhibition in estrogen-deficient post-menopausal women with heart failure (6), are unexpected and novel, and require us to rethink how sex hormones are integrated into the regulation of cardiovascular function and disease at the level of the endothelium and myocardium. They also may provide clues regarding the future development of sex-specific therapies for diseases such as heart failure, and HFpEF in particular, also specifically targeting women (5,9). Fukuma et al. (7) found that the interaction between estrogen and PDE5 was also present in male mice, albeit to a lesser extent, which suggests that the potentiation of PDE5 effects by estrogen might be independent of sex. Acute (non-nuclear) relaxation of human coronary arteries by estrogen has been previously demonstrated, with effects more pronounced in women than those in men (1).

A question that is still unresolved is how precisely non-nuclear ERα-dependent signaling contributes to the observed effects that partially protect from heart failure. Non-nuclear estrogen signaling via membrane ERα and GPER has been implicated in rapid responses to steroid hormones, particularly through activation of NOS3 and subsequent formation of cGMP (1,2). However, rapid signaling cascades can induce downstream targets that are involved in chronic (genomic) responses and thereby regulate cell proliferation, inflammation, and fibrosis (1), thus inhibiting pathways that contribute to the development of HFpEF. Although inhibition of myocardial fibrosis has also been reported in models deficient of nuclear ERβ, the experimental models of myocardial injury used must be clearly distinguished. Finally, the understanding of estrogen receptor signaling has been complicated by the fact that nuclear estrogen receptors ERα and ERβ can form heterodimers or homodimers, and that cross-talk between ERα and GPER may determine whether a receptor is active or not (1). Finally, constitutive, that is, ligand-independent activity in the absence of hormone stimulation, has been demonstrated for both ERα and GPER. Whether and how interaction(s) among membrane ERα, ERβ, or GPER (1) contributed to the results reported by Fukuma et al. (7) remains to be shown.

The study by Fukuma et al. (7) has some limitations and some questions remain. First, surgical menopause was induced in young animals that had reached sexual maturity only a few weeks before surgery. Thus, this model does not reflect the course of menopause in adult women with constant exposure to estrogen over several decades. Second, the investigators used a prevention protocol, i.e. hormone treatment, PDE5 inhibition or guanylate cyclase stimulation therapy was initiated *before* the experimental induction of heart failure. This approach differs from patients in whom treatment is initiated once heart failure was

established and diagnosed after the patient complained of symptoms. Heart failure therapy is aimed at preventing progression, achieving stabilization, or even inducing regression of the functional and structural abnormalities. Thus, future studies might want to investigate whether the effects observed by Fukuma et al. (7) are also present in a regression model of experimental heart failure, that is, in which treatment is initiated only after the disease has been fully established. This would more closely mimic the clinical situation in patients with heart failure. Finally, the question of whether estrogen also modulates the activity of phosphodiesterase isoforms other than PDE5 is of interest.

HFpEF is characterized by microvascular dysfunction, cardiomyocyte hypertrophy, fibrosis, and diastolic dysfunction, which are abnormalities all present in the model used by Fukuma et al. (7). In their study, estrogen treatment alone was sufficient to completely restore diastolic function and to prevent cardiac fibrosis, and there was no additive effect and/or interaction with PDE5 inhibition. In contrast, systolic function was only improved, in part, by estrogen treatment alone but completely restored after PDE5 inhibitors had been added. What do these findings tell us? Because HFpEF primarily affects post-menopausal women (5), the findings by Fukuma et al. (7) support the notion that estrogen deficiency is one of the main contributors underlying HFpEF development in the post-menopausal state (5). In contrast, the mechanisms that underlie systolic heart failure (heart failure with reduced ejection fraction [HFrEF]) only partially involve estrogen signaling, but instead pathomechanisms that include an accelerated breakdown of cGMP. Fukuma et al. (7) also showed that direct stimulation of guanylate cyclase is an effective treatment for treating both diastolic and systolic heart failure that involved upregulation of PKGIα, an effect that did not require concomitant estrogen therapy. Moreover, because of the high prevalence of HFpEF among post-menopausal women, who are also at an increased risk of developing salt-sensitive resistant hypertension, obesity, and diabetes—all risk factors that predispose to HFpEF—future clinical studies should take into account the potential modulatory effects of estrogens on PDE5 activity and PDE5 inhibitor function.

It is possible that the efficacy of PDE5 inhibitors is greater in women than that in men, either in pre- or in post-menopausal women who receive estrogen therapy. Certain forms of hormone therapy, such as horse-urine derived equine steroid hormone mixtures (so-called “conjugated equine estrogens”) in combination with synthetic progestins in the Women’s Health Initiative (WHI) and the HERS (Heart and eStrogen/progestin Replacement Study) have been associated with an increased risk for thrombosis and pulmonary embolism (1). Thus, the use of bioidentical hormones such as 17β-estradiol could be explored instead (1). The data by Fukuma et al. (7) also indicate that estrogen therapy has no effect on the efficacy of the direct sGC stimulator riociguat. Whether this also applies to post-menopausal patients with HFpEF needs to be addressed in future clinical studies.

In the recent subanalysis of the PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction) trial, which studied patients with HFpEF treated with the angiotensin receptor antagonist valsartan, reported that combining valsartan with the neutral endopeptidase/neprilysin inhibitor sacubitril reduced hospitalizations and death due to heart failure in women but not in men (9). The investigators concluded that the study did not provide a definite mechanistic basis for this finding. While neprilysin inhibitors are known to degrade vasoactive peptides (e.g., endothelin-1), enkephalins, and adrenomedullin, they also—just like PDE5 inhibitors—increase the bioavailability of cGMP (10), a mechanism that in part could have contributed to the recent findings reported by McMurray et al. (9). While in the PARAGON-HF trial postmenopausal women diagnosed with HFpEF with obesity and low BNP levels were not eligible to be included in the study (11), they could still benefit from therapies that increase cGMP (11).

ADDRESS FOR CORRESPONDENCE: Dr. Matthias Barton, University of Zürich, Y44 G22, Winterthurerstrasse 190, 8057 Zürich, Switzerland. E-mail: barton@access.uzh.ch.

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