Despite the popular concept that heart disease preferentially affects the male population, in every year for the past 16 years, cardiovascular disease has killed more women than men. Unfortunately, a disparity still exists between men and women in the diagnosis and aggressive treatment of heart disease. The perception that women are relatively protected is reflected by the fact that women are much more fearful of dying from some form of cancer than from cardiovascular disease. Understanding any risk factors that predispose or protect the female population from cardiovascular and coronary disease is therefore a compelling goal for the research community.

Left ventricular hypertrophy is a compensatory response of the heart to a variety of stresses, and it is a strong predictor of morbidity and mortality in individuals whether or not they have been diagnosed with cardiovascular disease. Sex differences in the development of this disease over time have been suggested by clinical studies dealing with patients who suffer from aortic stenosis or hypertension. For example, older female patients with aortic stenosis tend to have increased hypertrophy accompanied by greater concentric remodeling and preserved left ventricular function when compared with male patients. Premenopausal women, in fact, exhibit a thinner posterior wall, smaller left ventricular mass, and better load-dependent and load-independent cardiac function than age-matched men under conditions of mild essential hypertension. Population studies have shown an age-dependent increase in left ventricular mass in healthy normotensive women that is not seen in men, as determined by echocardiography. These and many other studies in both humans and animals suggest that estrogens can affect the remodeling of the heart.

Estrogens are potent vasodilators; they act in this capacity by increasing nitric oxide production. However, recent findings indicate that estrogens have direct actions on the myocardium as well. Receptors for estrogens are expressed in cardiomyocytes, although no data exist showing that estrogen has an effect on myocyte hypertrophy in vitro. However, the hormone can inhibit cardiac fibroblast proliferation. In rats, estrogen may influence cardiac gene expression during pressure overload, with female hypertrophic hearts expressing less β-myosin heavy chain mRNA but higher levels of sarcoplasmic reticulum Ca$^{2+}$ ATPase transcripts relative to male hypertrophic hearts.

In the present issue of Circulation, van Eickels et al take a step toward establishing a link between estrogen and a sex-specific response to a cardiovascular insult by determining whether estrogen can directly impact myocardial remodeling in an animal model of pressure overload–induced hypertrophy. One week after ovariectomy, mice were implanted with 17β-estradiol (E2) pellets. Seven days later, an experimental cohort was subjected to transverse aortic constriction (TAC) to induce pressure overload in the heart and a control group was subjected to a sham operation. At both 4 and 8 weeks after constriction, TAC mice treated with E2 showed significantly decreased hypertrophy relative to the placebo-treated, TAC experimental cohort, as determined by ventricular weight to body weight and ventricular weight to tibial length ratios. No effect of E2 was detected in sham-operated animals nor, strikingly, did E2 reduce the cardiac fibrosis evident in the hypertrophied hearts in the TAC mice. Importantly, no differences were seen in the developed pressure gradients or prestenotic pressures between the placebo and E2-treated cohorts.

Because hypertrophy and estrogen can independently affect the activation of mitogen-activated protein kinases (MAPK) in cultured cardiomyocytes, van Eickels et al then went on to examine the status of this family of proteins in the mouse hearts. They found that E2 treatment led to reduced levels of p38 MAPK phosphorylation (and thus potential deactivation) in TAC animals but had no effect on either the amount or phosphorylation status of the c-Jun N-terminal kinase (JNK) or extracellular-signal regulated kinase (ERK1/2) MAPK family members. The importance of the MAPK proteins in mediating the activation and maintenance of cardiac hypertrophy has been demonstrated in a number of animal models, and these pathways may play a central role in the progression to failure in the human heart.

The fact that E2 blocks p38 phosphorylation but has no effect on the other 2 branches of the MAPK pathway is intriguing, because p38 is activated in the failing and not in the compensated human heart. The observation that male hearts transit to failure more quickly than female hearts in pressure-overload rat models may be partially explained if, indeed, p38 plays an active role in the transition to decompensated cardiac failure. Activation of p38 is sufficient to cause hypertrophy, but it is unclear that the E2-mediated block of p38 phosphorylation is the major reason for the reduced hypertrophy observed by van Eickels et al. Calcinurin activation leads to the selective downregulation of...
p38 while stimulating a robust hypertrophic response.14 E2, like calcineurin, stimulates MAPK phosphatase-1 activity in cardiomyocytes; therefore, this represents the most likely mode of the p38 inhibition observed by van Eickels et al, because this phosphatase preferentially inactivates p38.15 Electrically paced heart cells also show reduced p38 activity while undergoing progressive hypertrophy,16 and pharmacological inhibition of p38 does not affect endothelin-1–directed hypertrophy in vitro.17 Conversely, several studies have shown that selective inhibition of p38 can block cardiomyocyte hypertrophy.18

E2 treatment also led to increased production of atrial natriuretic factor (ANF) in the ventricles of TAC animals. Several studies indicate that ANF may reduce the hypertrophic response of the heart. The ANF locus was defined genetically as contributing to reducing hypertrophy in rats,19 and in vitro experiments showed that an ANF receptor antagonist could potentiate a hypertrophic response in cultured primary cardiomyocytes.20

Although the results of the study by van Eickels et al9 are exciting, much work remains to be done so that these new data can be reconciled with results obtained in both animal models and in clinical trials. For example, male rats develop an early transition to heart failure relative to female rats whether the failure is caused by chronic hypertension12 or by pressure overload.13 The sex gap in failure is thought to be due to the greater hypertrophic reserve of the female heart. The greater innate hypertrophic response of females versus males is probably due, at least in part, to the preferential preservation of cardiomyocytes in female versus male hearts, because cardiomyocyte volumes in compensated male hearts with left ventricular hypertrophy tend to be larger than those found in female hearts. A recent study implicating estrogen in the activation of the anti-apoptotic protein AKT in the heart adds mechanistic weight to these observations.21

Interestingly, van Eickels et al9 found no differences in the amount of cardiac fibrosis present in the estrogen-treated versus nontreated hearts, suggesting that myocyte loss was similar in both populations. It may be productive in future experiments to measure load-independent functional parameters in the model, as well as regional wall stress, to determine if there is, in fact, a preferential conservation of cardiomyocytes in female versus male hearts, because cardiomyocyte volumes in compensated male hearts with left ventricular hypertrophy tend to be larger than those found in female hearts. A recent study implicating estrogen in the activation of the anti-apoptotic protein AKT in the heart adds mechanistic weight to these observations.21

Loss of function studies in both humans22 and mice23 show that estrogen can be a determinant in mediating overall risk to cardiovascular disease. However, surprisingly little is known about how hormone replacement therapy affects left ventricular mass or cardiac remodeling. For example, one study that followed normotensive postmenopausal women on hormone replacement therapy for >10 years found significant reductions in septal and posterior wall thickness relative to controls.24 Observations such as this indicate that estrogen may prevent cardiac hypertrophy and that lack of estrogen plays a role in the development of left ventricular hypertrophy late in life. However, in all of these studies, the reduction of hypertrophy cannot be attributed to the effects of estrogen on the myocardium alone because of the potent vasodilator properties of the hormone (a phenomenon that was not observed in the mouse study).

Extension of the present study’s conclusions to a human therapeutic modality remains problematic. A large number of retrospective and cross-sectional studies showed that postmenopausal women on estrogen replacement therapy were at reduced risk for coronary heart disease relative to the untreated female population. However, the one randomized, prospective, controlled clinical trial that has been published to date (the Heart and Estrogen-progestin Replacement Study; HERS) showed that estrogen replacement had no effect on attenuating risk.25 Although HERS can be criticized on the basis of the selection of its patient population, which consisted of older women with established cardiovascular disease, the negative findings highlight the need for more studies of the basic mechanisms that are involved.

A number of important clinical trials that will further test the clinical efficacy of estrogen-based replacement therapies are ongoing. These include the Women’s Estrogen/Progesterin and Lipid Lowering Hormone Atherosclerosis Regression Trial (WELL-HART), Estrogen and Graft Atherosclerosis Trial (EAGER), and the Women’s Angiographic Vitamin and Estrogen Trial (WAVE). Hopefully, these clinical data will provide evidence for a target patient population whose risk and/or morbidity can be decreased. Although many of these data will perhaps be more relevant to coronary artery disease, the molecular mechanism(s) of the estrogen-mediated antihypertrophic effects clearly need to be determined.

In the future, the use of the mouse models can be extended so that their value is fully realized. These experiments can thus be done in the different knockout models that are relevant, such as the estrogen receptor-α and estrogen receptor-β mice. The different strains of mice that are available may also prove useful, because it would not be surprising if the effects of hormone replacement therapy on TAC-induced hypertrophy differed radically between the different lines. Considering the rapid progress being made in assigning genetic loci to different physiological traits in the murine system using in silico techniques,26 the relevant modifying loci could be identified relatively rapidly, opening up new targets for therapeutic treatment.

References


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