Aging Modifies the Cardiac Response to Estrogen
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In this issue of Hypertension, Jazbutyte et al1 introduce the novel idea that aging impairs the ability of the heart to respond to estrogen replacement. Using young (3-month-old) and senescent (24-month-old) spontaneously hypertensive rats (SHRs), they compared the effect of estrogen on cardiac hypertrophy and gene expression in rats given ovariectomy with and without estrogen replacement. They hypothesized that estrogen replacement would differentially alter the cardiac hypertrophic response to ovariectomy. After sham or ovariectomy surgery with and without estrogen replacement, the young and senescent rats were followed for 6 weeks. Blood pressure was elevated in all of the groups and was not affected by estrogen supplementation. Estrogen attenuated the increase in relative heart weight in the ovariectomized young group but not in the senescent group. Cardiac estrogen receptor α levels were lower in the senescent rats (both intact and ovariectomy groups) compared with the corresponding young groups, and estrogen replacement increased receptor levels. In addition, α myosin heavy chain levels decreased and β myosin heavy chain levels increased in all 3 of the senescent groups. In rodents, α myosin heavy chain is the predominant isoform, and a shift in isoforms is a marker of cardiac hypertrophy.2 Estrogen attenuated the decrease in α myosin heavy chain in young ovariectomized rats but not senescent rats. Together, these data implicate an age-related loss in cardiac estrogen sensitivity with the development of cardiac hypertrophy. That the same levels of estrogen can have differential effects on the left ventricle depending on the age that replacement is initiated offers a whole new way of thinking about estrogen and its potential effects.

Several important questions are raised by the article. First, how well does this study compare with hormone replacement clinical trials? As discussed by the authors, the senescent rats given estrogen stopped cycling ~12 months before this study was conducted. It would be interesting to determine whether estrogen supplementation at the time when cycling first ends, which would more closely mimic menopausal hormone replacement therapy in humans, would also alter the cardiac hypertrophic response. This study measures the acute 6-week response of estrogen given at a time when the rats are young or already senescent. As the authors correctly point out, the next step from here would be to evaluate the response of ovariectomy with and without estrogen supplementation on middle-aged rats.

Along these same lines, what effect does estrogen alone, versus estrogen and progesterone, have on cardiovascular profiles? The combination of conjugated equine estrogen plus low-dose medroxyprogesterone acetate has historically been the most frequently used form of estrogen supplementation.3 Reuben et al3 demonstrated recently that estrogen plus progestins, but not estrogen alone, potentiated the interleukin 6–mediated increase in plasma C-reactive protein levels. This suggests that progestin effects on inflammation may be a primary mechanism for the observed adverse cardiovascular events. The final report on whether estrogen treatment provides an overall benefit to postmenopausal women has certainly not been made. In the heart, estrogen potentially exerts beneficial effects by attenuating the age-related stimulation of the renin–angiotensin–aldosterone system, in part through downregulation of the angiotensin type 1 receptor.4 Although cardiac hypertrophy results from a multitude of stimuli, upregulation of the renin–angiotensin–aldosterone system is one very well-described mechanism.5

If traditional hormone replacement therapies are not effective, will alternatives treatments induce beneficial effects in older cardiac tissue? Selective estrogen receptor modulators (SERMs) are nonhormone estrogen receptor ligands that have both estrogenic and antiestrogenic actions. The dual action of SERMs is a result of their ability to activate both estrogen receptor subtypes (α and β) and their interactions with various coregulators. SERMs may offer cardiovascular benefits with less risk than exogenous estrogen treatment. The cardioprotective effects of the SERM raloxifene are currently being evaluated in postmenopausal women in the Raloxifene Use for the Heart (RUTH) clinical trial.6 Information from clinical trials and animal studies, such as that of Jazbutyte et al,1 will provide valuable information for refining the biological activity of SERMs to maximize cardioprotection in older postmenopausal women.

A fourth question raised by this study is how does chronic hypertension affect the aging response to estrogen? Interestingly, the increase in relative heart weight in the young ovariectomized group could be reversed with estrogen supplementation, whereas the senescent ovariectomized group showed no decrease with estrogen. The senescent sham relative heart weight was also significantly elevated compared with the young sham group, indicating that hypertrophy occurred in senescent rats in the absence of ovariectomy. The lack of an additional increase in cardiac mass with ovariectomy suggests that a maximum hypertrophic threshold has been attained with aging alone and that...
additional stimuli will not be additive. Alternatively, this may suggest that the 2 methods of inducing cardiac hypertrophy, by aging or ovariectomy, share a common loss of estrogen mechanism. Because SHRs are already hypertensive by 2 months of age, the hypertrophy observed in the senescent SHRs is, by the very definition of senescence, a chronic stimulation. Although the data indicate that hypertrophy in senescent SHR is irreversible and cannot be influenced by estrogen supplementation, additional studies using normotensive rats at 24 months of age are needed to confirm that desensitization has not occurred because of a prolonged rise in blood pressure.

Lastly, what additional mechanisms (other than the direct estrogen effect) might explain the irreversibility of chronic hypertrophy? Because male animal models and humans also show increased left ventricular mass with age, estrogen is likely not the only player. The other mechanisms mentioned by the authors include altered cardiac atrial natriuretic peptide expression and mitogen-activated protein kinase activation. An additional factor is changes in extracellular matrix. Extracellular matrix remodeling occurs during and in response to the development of cardiac hypertrophy. Indeed, extracellular matrix remodeling is a major cause in the transition from compensatory hypertrophy to heart failure. Based on the hemodynamic measurements, none of the groups showed indications of left ventricular dysfunction or failure, which tells us that the hypertrophy is still compensatory. In a study by Xu et al., middle-aged Sprague–Dawley rats showed increased left ventricular/body weight ratios 1 month after ovariectomy, which was associated with increased β myosin heavy chain levels and an increased collagen I/collagen III ratio, all of which were attenuated by estrogen replacement. This illustrates that the fibrotic response during acute pressure overload is responsive to estrogen. Estrogen also influences levels of matrix metalloproteinases, the family of zinc-dependent enzymes that proteolyze the extracellular matrix. Collagen and matrix metalloproteinase levels were not evaluated in this study, so effects on fibrosis and extracellular remodeling cannot be commented on.

Regardless of these questions raised, the study by Jazbutyte et al. has laid a strong foundation for future studies in this arena.

Dissecting out the effects of age alone versus age superimposed on chronic pressure overload (with and without the estrogen component) will provide insight into hypertension-induced hypertrophy and its transition to heart failure. Hypertension is a major cause of congestive heart failure, and elucidating these pathways is highly clinically relevant. This study should serve to stimulate future experiments that further refine the model established here.

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References
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