

A Fresh Look at Estrogen and Heart Disease

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For years, estrogen has had a bad rap when it comes to cardiovascular disease. However, the latest research suggests that it might be time to rethink how we approach the hormone's role in the heart. At the Houston Methodist Center for Bioenergetics, scientists are exploring alternatives to traditional estrogen replacement therapy. One of the most promising approaches is using selective estrogen receptor agonists for more tightly targeted therapy, hopefully without the side effects of estrogen replacement.

Throughout the 1990s, estrogen replacement therapy was the go-to treatment for any number of maladies for women during and after menopause. However, after the Women's Health Initiative Trials were cancelled in the early 2000s due to an unexpected increase in heart problems and cancer in post-menopausal participants taking estrogen replacements, estrogen experienced a dramatic fall from grace. Now 15 years removed from those trials, researchers are beginning to reassess the conflicting evidence linking estrogen to heart disease.

Reanalysis of the trials indicates that the case against estrogen isn't so cut and dried. "When they went back and did some reanalysis of the Women's Health Initiative Trials, they realized that they were giving estrogen to older women who already had progressive heart disease," says Anisha Gupte, Ph.D., from the Center for Bioenergetics. "At that point, estrogen wasn't going to reverse the damage. However, if it was given at an earlier point to women who had just started menopause or were in the transition state, estrogen actually protected them from cardiovascular events. So that's why replacement—just giving back estrogen—might not be the solution. We have to look beyond that."

Gupte is one of the scientists "looking beyond." She recently teamed up with colleague Shumin Li, Ph.D., to coauthor a [review of estrogen's role in cardiac metabolism and diastolic function](#) in the *Methodist DeBakey Cardiovascular Journal*. In the review, they explore the evidence that loss of estrogen

negatively impacts the heart through fibrosis, stiffening, and remodeling; changes in calcium uptake; oxidative stress; and mitochondrial damage. Collectively, this puts women who have lost ovary function at a higher risk of diastolic heart failure and left ventricular hypertrophy. Interestingly, studies in mice and rats (and some in women) indicate that various estrogen therapies early in menopause can mitigate or even reverse those changes before the irreparable damage occurs.

Indeed, data collected at the Center for Bioenergetics supports these findings. Gupte and her team have engineered a novel mouse model that combines the major comorbidities for diastolic heart disease: loss of estrogen, obesity, and hypertension. The first step is removing the ovaries, cutting off the supply of estrogen. Few women would be surprised to learn

THE SECOND HIT

Cardiologists have long agreed that healthy lifestyles are key to healthy hearts. Diastolic dysfunction in women is no different. Although loss of estrogen makes older women more vulnerable to heart disease, it doesn't make disease inevitable. It's usually a comorbidity that adds the extra stress that tips patients over the edge; it's called a "second hit." The most common second hits are obesity and hypertension, which can—to some extent—be regulated by diet and exercise.

So, can women ward off heart disease simply by adopting healthier lifestyle habits?

"Yes and no," says Gupte. "There are women who have been exercising their entire lives and then go into menopause and realize that they're not able to perform the same exercise at the same level as before. They don't have that estrogen anymore, so they're more tired and start gaining weight even while exercising and eating the same. In those cases, yes, giving back the estrogen is going to help them a lot."

But it's a combination of the first and second hit. Loss of estrogen has this huge metabolic impact that we think we'll be able to fix with the agonist treatment. But you can't eat McDonald's every day and take a pill—that's not going to get you anywhere. There are no shortcuts here."

that these “menopausal” mice gain weight much faster than their control counterparts. Add in drugs to induce hypertension, and the mice begin to develop heart disease.

So, with the combination of estrogen loss, weight gain, and high blood pressure, why is Gupte so sure estrogen is the key? The difference comes down to sex. Given the same diet and cocktail of hypertensive drugs, female and male mice have different cardiovascular responses. Ovariectomized female mice develop diastolic dysfunction, while males experience contractile problems. “That gender difference got us excited,” Gupte says. “It’s the exact same dosage of drugs, but you see such different disease forms in males versus females.” (Obesity and/or hypertension are characterized as the “second hit”—the final straw that pushes estrogen-deprived women into heart disease.)

Building on those findings, Gupte is exploring a new approach for estrogen treatment. Instead of replacement with synthetic or equine estrogens, Gupte is looking at ways to target estrogen receptors (ER) with specific agonists. There are three main types of ER in the body: ER α , ER β , and G protein-coupled ER (GPR30). To Gupte, “the beauty of” these receptors is that their distributions vary across different tissues, which opens up a variety of options for personalized medicine. For instance, the heart’s primary ER is ER α , which makes it an appealing metabolic target. However, ER α is also found in reproductive organs, which makes it a less-specific (and higher-risk) choice. A less risky option is GPR30, which is common in the heart but not reproductive tissues and has similar, if less potent, metabolic effects. Indeed, Gupte reports that preliminary data in mice show “a nice protection from diastolic heart failure with GPR30 agonists.” ER β is more predominant in vessels than the heart. The uneven distribution of ERs means scientists have options. “We can target receptors differently in different tissues using specific drugs that activate one ER and not the other. That would potentially lead to more targeted effects of estrogen without its detrimental side effects,” Gupte says.

Another benefit of using ER agonists is that there are already drugs on the market—both GPR30 and ER β agonists—that could be repurposed to prevent estrogen loss-induced cardiovascular disease. So far, these drugs have been used to treat the more obvious symptoms of menopause such as hot flashes. Of course, these drugs would have to pass clinical trials before being approved for cardiovascular therapies, but Gupte points out that their existence on the market could speed up the usually long process of drug approval. “The good part is that a lot of these drugs have already gone through the rigorous safety requirement for other diseases. We’re looking at using the same drugs for a different reason, which could actually speed up the transition a little bit. We might be able to get something into the clinic in the next five to seven years,” Gupte says.

Li and Gupte agree that early treatment is likely critical to success, whether using low-dose estrogen replacement or ER agonists. “Estrogen affects all these pathways involving inflammation, fibrosis, and energy depletion. So when you have heart failure, you’re already at the end of this path. You’re probably not going to be able to wipe out all that fibrosis. It’s like cement blocks in between your cells—it’s hard to remove,” Gupte explains. “We know that these changes are happening during the transition to menopause. I think that prevention would be more workable than trying to reverse dysfunction at the end.”

Of course, early treatment depends on early detection. Not all women are going to develop diastolic dysfunction, which largely depends on that “second hit” from comorbidities like obesity and hypertension. Thus, another puzzle piece is developing better methods for identifying early signs of heart strain, particularly the diastolic problems that affect women. Li is on the front lines of this challenge, having recently mastered a new speckle-tracking echocardiography technique to detect left ventricular strain in mice. “I think modern echocardiography techniques like speckle-tracking and Doppler T-pulse can be used to look for diastolic dysfunction in menopausal women earlier than with traditional echocardiographs,” Li says.

Gupte suggests a three-pronged approach to characterizing early diastolic changes in women throughout menopause. First, monitor estrogen levels. Second, check markers of diastolic dysfunction using the aforementioned imaging techniques or testing for elevated brain natriuretic peptide (BNP). Third, use PET imaging to identify metabolic changes in a stressed heart. (Female mice ramp up fatty acid metabolism during diastolic dysfunction, whereas male mice shift toward glucose for fuel in systolic dysfunction.)

Ultimately, the goal is personalized medicine: different combinations of treatments at different points in diastolic dysfunction. Depending on a patient’s clinical profile, physicians could choose from a menu of ER agonists, estrogen replacement therapies, and medications to target the individual’s specific needs. It’s an exciting prospect, but will require cross-disciplinary cooperation and a new way of looking at estrogen and the heart.

“I think the best thing would be to have endocrinologists and cardiologists working together on this; it needs to be routine,” Gupte says. “Because of the Women’s Health Initiative trials, estrogen became a scary thing, so let’s look at it from a fresh perspective. It’s not about estrogen making a miracle at 65 years of age, it’s about keeping the estrogen in the woman in the perimenopausal phase and afterwards.”

Conflict of Interest Disclosure:

Laura Gerik is assistant managing editor at the *Methodist DeBakey Cardiovascular Journal*.