

Study reveals how sex hormones influence right heart function

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In the largest human study to date on the topic, researchers have uncovered evidence of the possible influence of human sex hormones on the structure and function of the right ventricle (RV) of the heart.

The researchers found that in women receiving [hormone therapy](#), higher [estrogen levels](#) were associated with higher RV ejection fraction and lower RV end-systolic volume — both measures of the RV's blood-pumping efficiency — but not in women who were not on hormone therapy, nor in men. Conversely, higher testosterone levels were associated with greater RV mass and larger volumes in men, but not in women, and DHEA, an androgen which improves survival in animal models of pulmonary hypertension, was associated with greater RV mass and volumes in women, similar to the findings with testosterone in men.

"This study highlights how little is known about the effects of [sex hormones](#) on RV function. It is critical from both research and clinical standpoints to begin to answer these questions," said Steven Kawut, M.D., M.S., senior investigator on the study, associate professor of medicine and epidemiology, and the director of the Pulmonary Vascular Disease Program at the University of Pennsylvania School of Medicine in Philadelphia.

The study was published online ahead of the print edition of the American Thoracic Society's *American Journal of Respiratory and Critical Care Medicine*. The research was funded by the National [Heart, Lung, and Blood Institute](#) (NHLBI) of the National Institutes of Health.

Study participants were part of The MESA-Right Ventricle Study (or MESA-RV), an extension of the Multi-Ethnic Study of Atherosclerosis (MESA), a large, NHLBI-supported cohort focused on finding early signs of heart, lung and blood diseases before symptoms appear. MESA recruited almost 7,000 Caucasian, African-American, Hispanic and Chinese individuals between the ages of 45 and 84 from six U.S. cities. Using blood samples and magnetic resonance imaging (MRI) of the heart, researchers measured sex hormones and RV structure and function in 1957 men and 1738 post-menopausal women. Because the MESA population is ethnically mixed and covers a broad age range of apparently healthy people, the results may be widely applicable to the general U.S. population.

"One of the most interesting things about this research is that we are focusing on individuals without clinical cardiovascular disease so that we may learn about determinants of RV morphology before there is frank RV dysfunction, which is an end-stage complication of many heart and lung diseases," said Dr. Kawut. "When we study people who already have RV failure from long-standing conditions, the horse has already left the barn. We are trying to assess markers that could one day help us identify and intervene in individuals at risk for RV dysfunction before they get really sick."

Because the RV plays a critical role in supplying blood to the lungs and the rest of the body, RV function is closely tied to clinical outcomes in many diseases where both the heart and lungs are involved, such as pulmonary hypertension, COPD and congestive heart failure. However, the RV is more difficult to study and image than the left ventricle and comparatively little is known about its structure and function and how to treat or prevent right heart failure.

"MESA-RV is, to our knowledge, the only published study of the relationship between sex hormones and the RV in humans," said Corey

E. Ventetuolo, M.D., lead author of the study and an instructor of medicine at Columbia University College of Physicians and Surgeons. "Our results have generated some interesting questions about RV response to the hormonal milieu. For example, the finding that higher levels of testosterone (and DHEA) were associated with greater RV mass would first appear to have adverse clinical consequences, since increasing cardiac mass is traditionally thought to be maladaptive. However, another study from MESA-RV has shown that higher levels of physical activity are also linked to greater RV mass, which would suggest an adaptive effect. So, whether the increased RV mass seen with higher hormone levels is helpful or harmful is not yet clear. The sex-specific nature of the associations we found was unexpected and reflect the complexity of the actions of sex hormones."

Sex hormone levels could help explain a key paradox in pulmonary arterial hypertension (PAH), where the RV response is an important determinant of survival. While women are far more likely to develop PAH, they also have better RV function and may have a better survival than men. "It is possible that hormone balance could predispose them to developing PAH, but confer a protective benefit in terms of RV adaptation," explained Dr. Kawut.

"We have shown differences in RV structure that go beyond the sexes and may depend on specific hormone levels," he concluded. "We have future opportunities to pursue these findings. The MESA cohort is currently undergoing repeat MRI, a decade later. These studies could lend important insights into sex hormone-related changes in RV function over time in adults. The ultimate goal would be strategies to treat or prevent RV failure in those at high risk."

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