The Gender/Estrogen Paradox and the Right Ventricle in Pulmonary Vascular Disease

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The Clinical Trials Update highlights new and ongoing research trials that are relevant to the diagnosis and treatment of PAH. In this issue, Corey Ventetuolo, MD, MS, describes a study on the relationships among genetic predictors of sex hormone processing, sex hormones and their metabolites, and RV measures both at baseline and longitudinally in male and female participants from the Multi-Ethnic Study of Atherosclerosis–Right Ventricle Study.

While we have long understood pulmonary arterial hypertension (PAH) to be a female-predominant disease, modern PAH registries suggest this gender bias is increasing.[1] Similar trends have been observed for pulmonary hypertension (PH), and PH providers are now faced with caring for older, postmenopausal patients with complex medical comorbidities and contributors to disease.[1,2] Right ventricular (RV) function ultimately determines outcome for our patients, but the mechanisms and determinants of RV failure are unknown. Surprisingly, despite greater disease prevalence, it appears that women have preserved RV function and survival compared to men with PAH.[3-5] In fact, estrogen therapy has been shown to rescue both pulmonary vasculopathy and RV function in animals.[6] In light of these observations, the study of sex hormone pathways and their associations with RV performance has never seemed so timely.

STUDYING THE RIGHT VENTRICLE IN HEALTH

RV structure and function reflect the afterload imposed by PH and PAH over time, and even small increments or fluctuations in loading may lead to RV sequelae. There is, however, great variability in the clinical trajectory of patients with pulmonary vascular disease. Patients often present late in disease, when RV failure has already occurred, and currently available therapies target only the pulmonary vasculature. The study of RV performance in healthy participants (or those with subclinical disease) may not only generate new hypotheses about the mechanisms of RV failure, but lead to the development of therapeutic approaches for RV dysfunction.

The Multi-Ethnic Study of Atherosclerosis (MESA) is a 10-year, NHLBI-sponsored, multicenter prospective cohort study of 6814 participants 45-84 years old without clinical cardiovascular disease at baseline. Participants were enrolled from 6 geographically diverse field centers around the country. MESA-RV is an ancillary study that has measured RV structure and function in over 4000 MESA participants by cardiac magnetic resonance imaging (MRI), representing the largest and only study of its kind. We have also completed follow-up RV measures (5 years later) in an unselected group of approximately 700 MESA participants, giving us the opportunity to study longitudinal predictors of RV morphology. In addition to the participant diversity inherent in MESA's design, extensive clinical and genetic data are available, representing a unique opportunity to feasibly confirm/refute hypotheses about the impact of gender, sex hormones, and genetic variation in hormonal processing on RV structure and function. Given the increasing prevalence of PAH not only in females but in older individuals, and the high rate of medical comorbidities observed, the MESA cohort offers a unique opportunity to study possible mechanistic pathways in participants with demographics similar to modern PAH registries.[1,7]

GENDER, SEX HORMONES, AND THE RIGHT VENTRICLE

As has been shown for PAH patients, female MESA participants have higher RV ejection fractions (RVEF) than their male counterparts, as well as lesser volumes and end-diastolic mass.[3,8] These morphologic associations with gender may be explained by serum sex hormone levels, and in fact study of baseline levels of estradiol (E2), testosterone, and dehydroepiandrosterone (DHEA) revealed some interesting findings.[9] First, higher levels of E2 were associated with higher RVEF and lower RV end-systolic volume in postmenopausal women using hormone therapy (HT), but not in HT nonusers or men. These associations persisted after adjustment for respective left ventricular (LV) measures, suggesting that exogenous E2 was associated with RV systolic function independent of any effects on the LV. Second, higher testosterone levels were associated with greater RV mass and larger RV volumes in men (but not in women). Third, higher levels of DHEA were associated with greater RV mass and

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larger volumes in women and possibly in men. The associations seen with DHEA and the RV in women were similar to those seen with testosterone in men, suggesting a possible androgenic effect. Our observed small changes in RV function in normals could indeed translate to clinically meaningful effects in individuals at risk for (or after onset of) disease. From these data, we conclude that E2 is associated with better RV performance in women and that androgens (testosterone and DHEA) are associated with greater RV mass and volumes in both genders.

FUTURE DIRECTIONS

We and others have hypothesized that sex hormone-driven angiogenesis may underpin the gender/estrogen paradox in pulmonary vascular disease and RV function. Genetic variation in hormone metabolism and signaling, with resultant effects on downstream angiogenesis, may further modify an individual's risk for disease. While certain polymorphic variants in sex hormone pathways have been associated with PAH, these and other variants have unknown impact on RV function, a key predictor of outcome in pulmonary vascular disease.[10-12]

We plan to investigate the relationships among genetic predictors of sex hormone processing, sex hormones and their metabolites, and RV measures both at baseline and longitudinally in male and female participants from MESA-RV. Our work will be the first to characterize these relationships and the largest genetic study of RV function available. We hope that by studying these pathways in a population-based cohort, we may gain insight into the epidemiologic trends observed in both PH and PAH, and may generate new hypotheses about the complex interplay between gender, sex hormones, and the cardiopulmonary interaction.

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