Sex Hormones Are Associated with Right Ventricular Structure and Function

The MESA-Right Ventricle Study

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Rationale: Sex hormones have effects on the left ventricle, but hormonal influences on the right ventricle (RV) are unknown.

Objectives: We hypothesized that sex hormones would be associated with RV morphology in a large cohort free of cardiovascular disease.

Methods: Sex hormones were measured by immunoassay and RV ejection fraction (RVEF), stroke volume (RVSV), mass, end-diastolic volume, and end-systolic volume (RVESV) were measured by cardiac magnetic resonance imaging in 1,957 men and 1,738 postmenopausal women. The relationship between each hormone and RV parameter was assessed by multivariate linear regression.

Measurements and Main Results: Higher estradiol levels were associated with higher RVEF (β per 1 ln[nmol/L], 0.88; 95% confidence interval [CI], 0.32 to 1.43; $P = 0.002$) and lower RVESV (β per 1 ln[nmol/L], -0.87; 95% CI, -1.67 to -0.08; $P = 0.03$) in women using hormone therapy. In men, higher bioavailable testosterone levels were associated with higher RVSV (β per 1 ln[nmol/L], 1.97; 95% CI, 0.20 to 3.73; $P = 0.03$) and greater RV mass and volumes ($P \leq 0.01$). Higher dehydroepiandrosterone levels were associated with higher RVSV (β per 1 ln[nmol/L], 1.37; 95% CI, 0.15 to 2.59; $P = 0.03$) and greater RV mass (β per 1 ln[nmol/L], 0.25; 95% CI, 0.00 to 0.49; $P = 0.05$) and volumes ($P \leq 0.001$) in women.

Conclusions: Higher estradiol levels were associated with better RV systolic function in women using hormone therapy. Higher levels of androgens were associated with greater RV mass and volumes in both sexes.

Keywords: sex; sex hormones; right ventricle

Sex differences in atherosclerosis and congestive heart failure (CHF) have been well described, with women experiencing a significant lag in the onset of coronary artery disease and lower rates of CHF compared with men (1). Estrogen, testosterone, dehydroepiandrosterone (DHEA), and sex hormone-binding globulin (SHBG) have important, albeit controversial, roles in left ventricular (LV) function and systemic vascular disease,

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Female sex is a risk factor for the development of pulmonary hypertension (PH), yet women appear to have better right ventricular (RV) function and improved survival compared to men with PH. Whereas sex hormones have been well studied in left heart failure, the role of sex hormones in RV function is largely unknown.

What This Study Adds to the Field

We have shown that higher levels of estradiol are associated with better RV systolic function in postmenopausal women using hormone therapy. Higher levels of androgens (both testosterone and dehydroepiandrosterone) are associated with greater RV mass and larger RV volumes in men and postmenopausal women, respectively, in cardiovascular disease-free participants.

whereas the effects of sex hormones on right ventricular (RV) and pulmonary vascular function are unknown.

Estrogen has protective effects on the pulmonary vasculature and improves RV contractility in animals (2–4). Testosterone has been shown to be a pulmonary vasodilator, yet has unclear effects on pulmonary endothelium (5, 6). Treatment with DHEA prevents pulmonary vascular changes and RV hypertrophy, and prolongs survival in animal models of pulmonary hypertension (PH) (7, 8). SHBG is expressed in myocytes of failing human hearts and in murine fetal lung epithelium, but its role in pulmonary vascular function has not been studied (9, 10).

Despite the beneficial effects of estrogen on the pulmonary vasculature, female sex is the best established clinical risk factor for idiopathic pulmonary arterial hypertension (PAH) (11). Yet, women have higher RV ejection fraction (RVEF) and improved survival compared with men with PAH (12–14). In systemic cardiovascular disease, an individual's estrogen:testosterone balance may be more predictive of disease risk than either hormone alone (15, 16). Last, it is unknown how sex hormones affect the interaction of the RV with the pulmonary vasculature, particularly in individuals with no known (or subclinical) PH.

We examined the cross-sectional association of serum estradiol (E2), bioavailable testosterone (bioT), DHEA, SHBG, and the E2:testosterone ratio (E2:T) with RV structure and function assessed by cardiac magnetic resonance imaging (MRI) in a large

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cohort of men and postmenopausal women without clinical cardiovascular disease. We hypothesized that higher E2, DHEA, and E2:T and lower testosterone and SHBG levels would be associated with higher RVEF and RV stroke volume (RVSV) and lower RV mass, RV end-diastolic volume (RVEDV), and RV end-systolic volume (RVESV). Preliminary results from this study have been published in abstract form (17).

METHODS

Study Sample

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter prospective cohort study to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease in white, African-American, Hispanic, and Chinese subjects (18). In 2000–2002, MESA recruited 6,814 subjects aged 45–84 years from six U.S. communities: Forsyth County, North Carolina; Northern Manhattan and the Bronx, New York; Baltimore City and Baltimore County, Maryland; St. Paul, Minnesota; Chicago, Illinois; and Los Angeles, California. Exclusion criteria included clinical cardiovascular disease, weight greater than 300 lb, pregnancy, or impediment to long-term participation. The presence of clinical cardiovascular disease was determined at participant screening by questionnaire. Participants were excluded if they answered “yes” to having been diagnosed by a physician with heart attack, stroke, transient ischemic attack, heart failure, angina, current atrial fibrillation, and/or to having undergone any prior cardiovascular procedure. The protocols of MESA and studies described herein were approved by the institutional review boards of all collaborating institutions and the National Heart, Lung, and Blood Institute. The MESA-Right Ventricle Study measured RV morphology in participants eligible for MRI (without metal implants, device or fragment). We included all subjects from MESA-RV with interpretable cardiac MRIs and available sex hormone levels.

Cardiac Magnetic Resonance Imaging Measures

The cardiac MRI protocol has been described elsewhere (19). All imaging was performed on 1.5-T magnets with a four-element phased-array surface coil positioned anteriorly and posteriorly and electrocardiographic gating. Imaging consisted of fast gradient echo cine images with temporal resolution not greater than 50 milliseconds.

Methods for interpretation of LV and RV parameters have been previously reported (19, 20). Briefly, RV image analysis was performed by two independent analysts on Windows workstations using QMASS software (v4.2; Medis, The Netherlands). The endocardial and epicardial borders of the RV were traced manually on short-axis cine images at the end-diastolic and end-systolic phases. Papillary muscles and trabeculae were included in the RV volumes and excluded from RV mass (21). RVEDV and RVESV were calculated using Simpson's rule by summation of areas on each slice multiplied by the sum of slice thickness and image gap. RV mass was determined at the end-diastolic phase as the difference between end-diastolic epicardial and endocardial volumes multiplied by the specific gravity of the heart (1.05 g/cm^3) (19). RVSV was calculated by subtracting RVESV from RVEDV. RVEF was calculated by dividing RVSV by RVEDV. The intrareader intraclass correlation coefficient (ICC) from random, blinded rereads of 229 scans for RV mass was 0.94 and for 230 scans was 0.99, 0.95, and 0.89 for RVEDV, RVESV, and RVEF, respectively. The intrareader ICC was 0.96 for RVSV. The interreader ICC from random, blinded rereads of 240 scans for RV mass, RVEDV, RVESV, and RVEF was 0.89, 0.96, 0.94, and 0.80, respectively. The interreader ICC for RVSV was 0.93.

Serum Sex Hormones

Fasting morning blood samples were drawn and stored using standardized procedures (22). Serum hormone concentrations (nmol/L) were measured in the Steroid Hormone Laboratory at the University of Massachusetts Medical Center (Worcester, MA). E2 was measured via an ultrasensitive radioimmunoassay kit (Diagnostic System Laboratories, Webster, TX). Total testosterone (total T) and DHEA were measured directly with radioimmunoassay kits and SHBG was measured

by chemiluminescence enzyme immunometric assay using Immulite kits (Diagnostic Products Corporation, Los Angeles, CA). BioT was calculated from total T and SHBG, using the method described by Södergård (23). Assay quality control has been described elsewhere (24). The intraassay coefficients of variation for E2, total T, DHEA, and SHBG were 10.5, 12.3, 11.2, and 9.0%, respectively.

Other Covariates

Race/ethnicity was self-reported during the baseline examination according to year 2000 U.S. Census criteria as race (white, African-American, etc.) and ethnicity (Hispanic or non-Hispanic). Standard questionnaires were used to ascertain smoking status and level of education. Medication use, including current postmenopausal hormone therapy (HT), testosterone therapy, and DHEA supplement use, was ascertained by medication inventory (25). Self-report was used to determine pre-, peri-, or postmenopausal status. Intentional exercise (MET-min/wk) was assessed by survey. Height was measured to the nearest 0.1 cm with the participant in stocking feet and weight was measured to the nearest pound with the participant in light clothing, using a balanced scale. Resting blood pressure was measured with a Dinamap Monitor PRO 100 (Critikon, Tampa, FL) automated oscillometric device. Hypertension was defined as systolic blood pressure equal to or greater than 140 mm Hg, diastolic blood pressure equal to or greater than 90 mm Hg, or current use of antihypertension medication. Fasting blood samples were drawn and sent to a central laboratory for measurement of glucose and lipids. Presence of diabetes mellitus was based on self-reported physician diagnosis or a fasting glucose value equal to or greater than 126 mg/dl, the latter measured by rate reflectance spectrophotometry (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY). Fasting glucose of 100–125 mg/dl was considered impaired fasting glucose. Spirometry, urine cotinine, and computed tomographic (CT) lung density (percentage of emphysema-like lung) measures were available for 2,406 participants (26, 27).

Statistical Analysis

Continuous variables were expressed as means and standard deviations. Categorical variables were expressed as percentages. Sex hormones were logarithmically transformed, except in the case of E2:T.

Multivariate linear regression was used to assess the relationship of each hormone with each RV parameter. Initial models included age, race/ethnicity, height, weight, waist circumference, and current hormone supplementation. Adjustment for height and weight avoided the assumptions made in indexing the RV measures to certain parameters of body size (e.g., body surface area), while accounting for differences in body size between participants. Models were further adjusted for smoking, diabetes mellitus, impaired glucose tolerance, hypertension and use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high-density lipoprotein levels, statin use, intentional exercise, education level, and respective LV parameters (e.g., the model for RVEF was adjusted for LV ejection fraction, the model for RV mass for LV mass, and so forth). Adjustment for LV parameters was performed to account for the contribution of LV abnormalities to RV changes (e.g., increased LV mass causing pulmonary venous hypertension leading to increased RV mass), to account for body size differences, and to examine RV-specific associations. RVSV was not adjusted for LV stroke volume, considering the significant interdependence of these measures.

We performed adjustments for lung function in the subgroup with available lung function measures ($n = 2,406$). Statistical significance was defined as $P < 0.05$. As each hormone analysis was considered an independent hypothesis, there was no correction made for multiple comparisons (28). Analyses were performed with STATA 10.0 (Stata-Corp, College Station, TX).

RESULTS

MESA enrolled 6,814 participants of whom 5,098 had cardiac MRIs and 5,004 had interpretable scans (Figure 1). Of these, 4,634 were selected for RV interpretation, and 4,204 had RV measures completed. We excluded women missing HT data ($n = 221$), those who reported pre- ($n = 146$), unknown ($n = 60$), or

Figure 1. Study sample. DHEA = dehydroepiandrosterone; LV = left ventricle; MESA = Multi-Ethnic Study of Atherosclerosis; MRI = magnetic resonance imaging; RV = right ventricle.

missing ($n = 1$) menopausal status, and participants with missing data for covariates ($n = 81$). The final study sample of 3,695 participants included 1,957 men and 1,738 postmenopausal women, of whom 61 were missing E2 levels, 66 were missing bioT levels, 61 were missing DHEA levels, and 60 were missing SHBG levels.

Participant characteristics are shown in Table 1 and Table E1 in the online supplement. One-third of women reported current HT use. Women tended to have higher RVEF (72.6 ± 6.0 vs. $68.2 \pm 6.2\%$) and lower RVSV (77.5 ± 16.3 vs. 95.9 ± 20.7 ml), RV mass (18.9 ± 3.6 vs. 23.1 ± 4.4 g), RVEDV (107.2 ± 22.5 vs. 140.9 ± 29.7 ml), and RVESV (29.7 ± 10.0 vs. 45.1 ± 14.1 ml) than men.

Estradiol

Among women, there were significant or borderline significant interactions between E2 and HT for several RV measures (RVEF, $P = 0.02$; RV mass, $P = 0.09$; RVESV, $P = 0.10$); the E2 analyses were therefore stratified by HT use. Higher levels of E2 were associated with higher RVEF in women using HT (Figure 2 and Table 2). This association persisted in the fully adjusted model and after adjustment for LVEF, suggesting that exogenous E2 was associated with RV systolic function independent of any effects on the LV. There was a 2% difference in RVEF across quintiles of E2 levels (data not shown). There was no association between E2 and RVEF in HT nonusers or in men (Table 2).

Similarly, a higher E2 level was associated with lower RVESV in HT users, corresponding to a 6% difference across quintiles of E2 levels (data not shown), but not in HT nonusers or in men. This association persisted after adjustment for LVEF (Table 2). In the subset of women with available data ($n = 1,072$), adjustment for lung function variables did not affect the results (Table E2).

Bioavailable Testosterone

Higher levels of bioT were associated with larger RVSV, greater RV mass, and larger RVEDV and RVESV in men but not in women (Table 3). There was a 4% difference in RVSV, a 3% difference in RV mass, and a 1 and 3% difference in RVEDV and RVESV, respectively, across quintiles of bioT levels (data not shown). These associations persisted after adjustment for respective LV measures (Table 3) and after adjustment for lung function ($n = 1,303$) (Table E3). Similar associations were seen

between total T and RVSV, RV mass, and RV volumes, and results were unchanged when participants taking testosterone supplementation ($n = 27$) were excluded from analysis (data not shown).

Dehydroepiandrosterone

In women, higher levels of DHEA were associated with decreased RVEF, greater RV mass, and larger volumes (Table 4). There was a 3% difference in RVEF, a 1% difference in RV mass, and 3 and 6% differences in RVEDV and RVESV, respectively, across quintiles of DHEA (data not shown). There appeared to be similar associations between DHEA and RVEF, RV mass, and RVESV in men, although these were not statistically significant. Similar associations were seen in the subset of participants with available measures of lung function (Table E4). Results were unchanged when participants taking DHEA supplementation ($n = 36$) were excluded and, among women, effect estimates were unchanged when adjusted for HT (data not shown).

Sex Hormone-binding Globulin

Among women and possibly men, higher levels of SHBG were associated with higher RVSV in limited models, but these associations were attenuated and not statistically significant when fully adjusted for all covariates (Table 5). Similarly, among men there was an association between higher SHBG levels and greater RV mass ($P = 0.05$) that did not persist in multivariate analysis. Results were unchanged when adjusted for HT (in women) and testosterone supplementation (in men). In the smaller subgroup of participants with lung function measures, there were no significant associations seen in men or women but effect estimates were unchanged after adjustment for these measures (Table E5).

Estradiol:Testosterone Ratio

There was a suggestion of an association between higher E2:T and lower RV volumes in men only (Table E6). For example, a 1-unit increase in E2:T was associated with an 18.98-ml decrement in RVESV after multivariate adjustment (95% CI, -37.19 to -0.77 ml; $P = 0.04$), although this association was attenuated after adjustment for LVEF (-15.08 ; 95% CI, -31.22 to 1.07 ml; $P = 0.07$). Similar associations were seen in the models for RVEDV, although not significant, among men with available lung function measures (Table E7).

TABLE 1. PARTICIPANT CHARACTERISTICS

	Sex	
	Men	Women
Number of participants	1,957	1,738
Demographics		
Age, yr	61.5 ± 10.1	64.0 ± 9.1
Race/ethnicity, %		
White	38.6	40.2
African-American	25.2	26.2
Hispanic	23.5	21.1
Chinese	12.8	12.4
Education, %		
<High school	15.5	18.9
High school	15.7	22.0
<College (>high school)	26.0	30.3
≥College	42.8	28.8
Anthropometrics		
Height, cm	173.4 ± 7.7	159.7 ± 7.1
Weight, kg	83.0 ± 14.8	71.8 ± 15.3
Body mass index, kg/m ²	27.5 ± 4.1	28.1 ± 5.5
Waist circumference, cm	98.2 ± 11.4	96.1 ± 14.5
Comorbid factors		
Hypertension, %	40.9	49.8
Systolic blood pressure, mm Hg	125.1 ± 18.9	128.3 ± 23.1
Diastolic blood pressure, mm Hg	74.9 ± 9.3	69.3 ± 10.4
Diabetes mellitus, %		
Normal	71.6	76.6
Impaired fasting glucose	15.7	12.0
Untreated diabetes	2.9	2.2
Treated diabetes	9.8	9.2
Total cholesterol, mg/dl	188.1 ± 33.8	202.1 ± 35.2
High-density lipoprotein, mg/dl	45.0 ± 11.5	57.1 ± 15.6
Statin use, %	13.8	17.6
Smoking status		
Never-smoker, %	42.6	60.8
Former smoker, %	43.4	28.7
Current smoker, %	14.1	10.6
Pack-years, among ever-smokers	15.4 ± 26.7	13.1 ± 21.9
Serum sex hormone levels		
Estradiol, nmol/L	0.1 ± 0.0	0.1 ± 0.2
Hormone therapy users		0.3 ± 0.2
Hormone therapy nonusers		0.1 ± 0.1
Bioavailable testosterone, nmol/L	5.5 ± 2.1	0.3 ± 0.3
DHEA, nmol/L	14.2 ± 7.3	11.6 ± 6.4
Sex hormone-binding globulin, nmol/L	43.9 ± 18.7	77.6 ± 55.2
Estradiol:testosterone ratio	0.01 ± 0.03	0.23 ± 0.63
Hormone therapy user		0.50 ± 1.01
Hormone therapy nonuser		0.10 ± 0.16
Hormone supplementation		
Hormone therapy, %	0.0	33.1
Testosterone compounds, %	0.7	0.0
DHEA supplement, %	0.01	0.01
RV measures		
RVEF, %	68.2 ± 6.2	72.6 ± 6.0
RVSF, ml	95.9 ± 20.7	77.5 ± 16.3
RV mass, g	23.1 ± 4.4	18.9 ± 3.6
RVEDV, ml	140.9 ± 29.7	107.2 ± 22.5
RVESV, ml	45.1 ± 14.1	29.7 ± 10.0

Definition of abbreviations: DHEA = dehydroepiandrosterone; RV = right ventricle; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVSF = right ventricular stroke volume.

Data are shown as mean ± standard deviation or as a percentage.

DISCUSSION

Serum sex hormones were associated with RV structure and function in an ethnically and racially diverse cohort without clinical cardiovascular disease. Higher levels of E2 were associated with higher RVEF and lower RVESV in postmenopausal women using HT (but not in HT nonusers or men), and higher testosterone levels were associated with greater RV mass and

larger RV volumes in men (but not in women). Contrary to our hypothesis, higher levels of DHEA were associated with greater RV mass and larger volumes in women and possibly in men. These associations were similar to those seen with testosterone in men, suggesting an androgenic effect. Higher levels of SHBG may have been associated with higher RVSF among women and possibly men in limited models only. With E2, bioT, and DHEA, most of the results remained significant after adjustment for the respective LV measures, implying RV-specific or RV-disproportionate associations, as well as after adjustment for measures of lung function (in a smaller subset), implying unique associations between sex hormones and the RV independent of pulmonary effects. To our knowledge, this is the only study of sex hormones and RV structure and function assessed by cardiac MRI.

Although some of the effect sizes seem small, they are comparable to those seen in the LV related to active smoking and diabetes mellitus (29). In severe PAH, intravenous epoprostenol improves RVEF by only 4% while leading to significant improvements in exercise capacity, functional status, and survival (30, 31). In the normal RV (with a lower “signal:noise ratio” compared with that seen in disease), similar or smaller differences may have important physiological effects.

We have shown that higher E2 levels in HT users were associated with higher RVEF and lower RVESV. In men, higher E2:T was possibly associated with lower RV volumes. High estrogen/low testosterone states have been associated with a lower risk of cardiovascular disease in aging men (15, 16). Estrogen has been associated with elevated markers of angiogenesis and heart neovascularization, and human ventricular myocardium contains functional estrogen receptors (ERs) (32, 33). Cardiac neovascularization promotes collateral blood flow, which may promote beneficial remodeling and improve RV systolic function (34). There are several possible explanations as to why these associations (in women) were demonstrated only in HT users. A 1-ln increment in E2 in HT users may have different biological implications than a 1-ln increment in non-users, either because of greater E2 levels (as seen here) or variance in HT users, altered or unmeasured metabolites, or protein–receptor interactions. HT up-regulates ER tissue expression and may lead to altered E2 sensitivity among HT users (35). The appearance of this association in HT users only may be explained by unmeasured differences between users and non-users, although they had similar baseline characteristics (36).

We have shown that bioT levels were associated with greater RV mass and larger RV volumes, independent of these LV measures. Testosterone increases the myocardial inflammatory response, promotes cardiac remodeling, and increases LV mass in animals (37, 38). On the other hand, epidemiologic studies suggest testosterone deficiency is associated with worse cardiovascular outcomes among men, and there is some evidence that testosterone supplementation improves functional capacity in androgen-deficient men with CHF (39, 40). The association between androgens (both bioT and DHEA) and greater RV mass and volumes here may not be detrimental per se, as has been proposed with exercise-induced increases in LV mass in trained athletes and in RV mass in MESA participants (41). In fact, higher levels of both bioT (in men) and DHEA (in women) were associated with higher RVSF. Ultimately, maintaining androgen balance may be most important for cardiopulmonary health.

The associations of DHEA with greater RV mass and volumes contradict extensive animal and preclinical data demonstrating that DHEA prevents or reverses PH and improves vascular remodeling (7, 8, 42). Similarly, previous epidemiologic studies have shown lower levels of DHEA associated with increased cardiovascular risk (43). It has been proposed that DHEA may have important intracellular signaling effects independent of

Figure 2. Natural log-transformed estradiol [ln(E2)] parameter estimates with 95% confidence intervals for right ventricular ejection fraction (RVEF) stratified by hormone therapy use in limited and adjusted regression models (women only). *Adjusted for age, race/ethnicity, height, weight, waist circumference. **Adjusted for age, race/ethnicity, height, weight, waist circumference, smoking (status and pack-years), diabetes mellitus, impaired glucose intolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, and level of education. HT = hormone therapy; LV = left ventricle.

hormonal or steroid action (42). DHEA stimulates both nitric oxide and endothelin-1, two important but antagonistic mediators in PH (44). As such, DHEA may have more complex effects on the pulmonary vasculature and RV than previously appreciated. As our findings relate to RV morphology, it is possible that DHEA has pleiotropic effects on the pulmonary vasculature and the RV. It has been shown that extremes (low or high levels) and variability in serum DHEA predict mortality in older adults more so than a single measurement (45). Thus, it is possible that baseline measurement may not accurately capture DHEA trajectory and therefore disease risk. The sulfate ester of DHEA (DHEA-S), known to have higher and more stable serum levels than DHEA, was not measured in this study and may have been more informative.

Although the effects were modest, there was a suggestion that higher levels of SHBG were associated with higher RVSV. In left heart failure, higher levels of SHBG are associated with poor outcomes and we have found associations with subclinical atherosclerosis (46, 47). Whether SHBG has unique effects on the pulmonary vasculature and the RV is unknown.

Our study has several limitations. Because this is a cross-sectional observational study, no conclusions can be drawn about causality. However, the MESA cohort offers a unique opportunity to generate hypotheses about hormonal influences on the RV, given (1) it is population based, (2) it includes female and minority participants, and (3) to our knowledge, it is the largest study of RV structure and function assessed by cardiac MRI to date. Cardiac MRI is considered the “gold standard” for assess-

TABLE 2. ASSOCIATIONS BETWEEN ESTRADIOL AND RIGHT VENTRICULAR MEASURES IN LIMITED AND ADJUSTED MODELS AMONG MEN AND WOMEN, BASED ON HORMONE THERAPY USE

	Men (n = 1,927)		Women: HT Users (n = 567)		Women: HT Nonusers (n = 1,140)	
	β (95% CI)*	P Value	β (95% CI)	P Value	β (95% CI)	P Value
RVEF, %						
Limited†	-0.23 (-0.97 to 0.50)	0.54	1.07 (0.49 to 1.65)	< 0.001	0.15 (-0.39 to 0.69)	0.58
Adjusted‡	-0.26 (-1.00 to 0.48)	0.49	0.91 (0.32 to 1.50)	0.003	0.13 (-0.41 to 0.67)	0.65
Adjusted + LVEF	-0.35 (-1.02 to 0.32)	0.30	0.88 (0.32 to 1.43)	0.002	0.05 (-0.46 to 0.55)	0.86
RVSV, ml						
Limited	-1.72 (-3.92 to 0.47)	0.12	1.04 (-0.29 to 2.37)	0.13	-0.31 (-1.53 to 0.91)	0.61
Adjusted	-1.25 (-3.43 to 0.93)	0.26	0.57 (-0.76 to 1.90)	0.40	-0.29 (-1.50 to 0.93)	0.40
RV mass, g						
Limited	-0.16 (-0.60 to 0.29)	0.49	0.08 (-0.20 to 0.37)	0.57	-0.25 (-0.51 to 0.01)	0.06
Adjusted	-0.08 (-0.53 to 0.37)	0.72	0.02 (-0.27 to 0.30)	0.90	-0.24 (-0.50 to 0.02)	0.07
Adjusted + LV mass	-0.02 (-0.44 to 0.39)	0.91	0.11 (-0.16 to 0.38)	0.42	-0.20 (-0.44 to 0.05)	0.12
RVEDV, ml						
Limited	-2.21 (-5.20 to 0.76)	0.15	-0.08 (-1.83 to 1.67)	0.93	-0.71 (-2.31 to 0.89)	0.38
Adjusted	-1.47 (-4.44 to 1.50)	0.33	-0.50 (-2.26 to 1.25)	0.57	-0.64 (-2.24 to 0.96)	0.43
Adjusted + LVEDV	1.17 (-1.03 to 3.38)	0.30	0.17 (-1.13 to 1.47)	0.80	0.57 (-0.62 to 1.76)	0.35
RVESV, ml						
Limited	-0.49 (-1.99 to 1.01)	0.52	-1.12 (-1.99 to -0.26)	0.01	-0.40 (-1.19 to 0.39)	0.32
Adjusted	-0.22 (-1.73 to 1.29)	0.77	-1.07 (-1.94 to -0.21)	0.02	-0.36 (-1.15 to 0.44)	0.38
Adjusted + LVESV	0.50 (-0.84 to 1.83)	0.47	-0.87 (-1.67 to -0.08)	0.03	0.02 (-0.71 to 0.75)	0.95

Definition of abbreviations: CI = confidence interval; HT = hormone therapy; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; RV = right ventricle; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVSV = right ventricular stroke volume.

* Per ln(nmol/L) increase in estradiol.

† Adjusted for age, race/ethnicity, height, weight, waist circumference.

‡ Adjusted for age, race/ethnicity, height, weight, waist circumference, smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, and level of education.

TABLE 3. ASSOCIATIONS BETWEEN BIOAVAILABLE TESTOSTERONE AND RIGHT VENTRICULAR MEASURES IN LIMITED AND ADJUSTED MODELS, BY SEX

	Men (n = 1,925)		Women (n = 1,696)	
	β (95% CI)*	P Value	β (95% CI)	P Value
RVEF, %				
Limited [†]	−0.37 (−0.97 to 0.23)	0.23	−0.15 (−0.51 to 0.20)	0.40
Adjusted [‡]	−0.36 (−0.95 to 0.24)	0.25	−0.01 (−0.38 to 0.36)	0.97
Adjusted + LVEF	−0.40 (−0.94 to 0.14)	0.15	0.02 (−0.33 to 0.37)	0.92
RVSF, ml				
Limited	1.42 (−0.37 to 3.21)	0.12	−0.66 (−1.47 to 0.14)	0.11
Adjusted	1.97 (0.20 to 3.73)	0.03	−0.04 (−0.88 to 0.79)	0.92
RV mass, g				
Limited	0.40 (0.03 to 0.76)	0.03	−0.03 (−0.20 to 0.15)	0.77
Adjusted	0.49 (0.13 to 0.85)	0.01	0.08 (−0.10 to 0.26)	0.38
Adjusted + LV mass	0.44 (0.10 to 0.77)	0.01	0.04 (−0.13 to 0.21)	0.66
RVEDV, ml				
Limited	2.90 (0.47 to 5.33)	0.02	−0.70 (−1.75 to 0.36)	0.20
Adjusted	3.71 (1.31 to 6.11)	0.001	−0.05 (−1.15 to 1.06)	0.93
Adjusted + LVEDV	2.43 (0.64 to 4.21)	0.01	0.13 (−0.69 to 0.94)	0.78
RVESV, ml				
Limited	1.48 (0.26 to 2.70)	0.02	−0.03 (−0.55 to 0.49)	0.91
Adjusted	1.74 (0.53 to 2.96)	0.01	−0.01 (−0.55 to 0.54)	0.98
Adjusted + LVESV	1.63 (0.55 to 2.71)	0.001	−0.01 (−0.51 to 0.49)	0.96

Definition of abbreviations: CI = confidence interval; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; RV = right ventricle; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVSF = right ventricular stroke volume.

* Per ln(nmol/L) increase in bioavailable testosterone.

[†] Adjusted for age, race/ethnicity, height, weight, waist circumference, and testosterone supplementation (in men).

[‡] Adjusted for age, race/ethnicity, height, weight, waist circumference, testosterone supplementation (in men), smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, and level of education.

ment of the RV, and RV measures have been found to be highly accurate and reproducible in normal individuals (and in those with heart failure) (48). We included postmenopausal women; the results may not apply to younger, premenopausal women.

Measurement of hormones was performed only at baseline, although single measurements of sex hormones are reliable and reproducible over several years in postmenopausal women (49). Although hemodynamic data would have allowed for hypothesis

TABLE 4. ASSOCIATIONS BETWEEN DEHYDROEPIANDROSTERONE AND RIGHT VENTRICULAR MEASURES IN LIMITED AND ADJUSTED MODELS, BY SEX

	Men (n = 1,927)		Women (n = 1,696)	
	β (95% CI)*	P Value	β (95% CI)	P Value
RVEF, %				
Limited [†]	−0.19 (−0.83 to 0.44)	0.55	−0.54 (−1.07 to −0.01)	0.05
Adjusted [‡]	−0.19 (−0.82 to 0.45)	0.56	−0.54 (−1.08 to 0.00)	0.05
Adjusted + LVEF	−0.24 (−0.82 to 0.33)	0.40	−0.44 (−0.94 to 0.07)	0.09
RVSF, ml				
Limited	0.16 (−1.73 to 2.05)	0.87	0.77 (−0.42 to 1.97)	0.21
Adjusted	0.55 (−1.32 to 2.42)	0.56	1.37 (0.15 to 2.59)	0.03
RV mass, g				
Limited	0.08 (−0.30 to 0.47)	0.67	0.21 (−0.04 to 0.47)	0.10
Adjusted	0.13 (−0.25 to 0.52)	0.51	0.36 (0.10 to 0.62)	0.01
Adjusted + LV mass	0.19 (−0.17 to 0.55)	0.31	0.25 (0.00 to 0.49)	0.05
RVEDV, ml				
Limited	0.87 (−1.69 to 3.43)	0.51	2.00 (0.43 to 3.57)	0.01
Adjusted	1.39 (−1.16 to 3.94)	0.29	2.80 (1.20 to 4.40)	0.001
Adjusted + LVEDV	1.30 (−0.59 to 3.19)	0.18	2.28 (1.09 to 3.46)	<0.001
RVESV, ml				
Limited	0.71 (−0.57 to 2.00)	0.28	1.23 (0.45 to 2.01)	0.001
Adjusted	0.84 (−0.45 to 2.13)	0.20	1.43 (0.63 to 2.22)	<0.001
Adjusted + LVESV	0.92 (−0.23 to 2.10)	0.12	1.28 (0.55 to 2.00)	0.001

Definition of abbreviations: CI = confidence interval; DHEA = dehydroepiandrosterone; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; RV = right ventricle; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVSF = right ventricular stroke volume.

* Per ln(nmol/L) increase in DHEA.

[†] Adjusted for age, race/ethnicity, height, weight, waist circumference, and DHEA supplementation.

[‡] Adjusted for age, race/ethnicity, height, weight, waist circumference, DHEA supplementation, smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, and level of education.

TABLE 5. ASSOCIATIONS BETWEEN SEX HORMONE-BINDING GLOBULIN AND RIGHT VENTRICULAR MEASURES IN LIMITED AND ADJUSTED MODELS, BY SEX

	Men (<i>n</i> = 1,928)		Women (<i>n</i> = 1,707)	
	β (95% CI)*	<i>P</i> Value	β (95% CI)	<i>P</i> Value
RVEF, %				
Limited [†]	0.08 (−0.69 to 0.85)	0.85	0.38 (−0.12 to 0.87)	0.14
Adjusted [‡]	0.12 (−0.68 to 0.91)	0.78	0.20 (−0.34 to 0.75)	0.47
Adjusted + LVEF	0.03 (−0.68 to 0.74)	0.93	0.09 (−0.42 to 0.60)	0.73
RVSF, ml				
Limited	1.96 (−0.34 to 4.25)	0.09	1.16 (0.05 to 2.27)	0.04
Adjusted	0.64 (−1.69 to 2.97)	0.59	0.08 (−1.15 to 1.31)	0.90
RV mass, g				
Limited	0.46 (−0.01 to 0.93)	0.05	0.09 (−0.14 to 0.33)	0.44
Adjusted	0.17 (−0.31 to 0.65)	0.48	−0.09 (−0.35 to 0.17)	0.51
Adjusted + LV mass	0.16 (−0.28 to 0.61)	0.47	−0.03 (−0.28 to 0.21)	0.78
RVEDV, ml				
Limited	2.90 (−0.20 to 6.01)	0.07	1.03 (−0.43 to 2.50)	0.17
Adjusted	0.78 (−2.40 to 3.95)	0.63	−0.18 (−1.80 to 1.44)	0.83
Adjusted + LVEDV	−0.13 (−2.47 to 2.22)	0.92	−0.42 (−1.62 to 0.77)	0.49
RVESV, ml				
Limited	0.95 (−0.61 to 2.51)	0.23	−0.13 (−0.85 to 0.60)	0.73
Adjusted	0.14 (−1.47 to 1.75)	0.86	−0.26 (−1.07 to 0.54)	0.52
Adjusted + LVESV	−0.07 (−1.49 to 1.36)	0.93	−0.09 (−0.82 to 0.65)	0.82

Definition of abbreviations: CI = confidence interval; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; RV = right ventricle; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVSF = right ventricular stroke volume.

* Per ln(nmol/L) increase in sex hormone-binding globulin.

[†] Adjusted for age, race/ethnicity, height, weight, and waist circumference.

[‡] Adjusted for age, race/ethnicity, height, weight, waist circumference, smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, and level of education.

generation about the associations between sex hormones and pulmonary vascular function specifically, these measurements were not available, nor would they have been feasible in a cohort of this size.

We included women taking HT given (1) the potential for selection bias if excluded, as it has been well documented that women taking HT are fundamentally different (e.g., lower cardiovascular risk, higher socioeconomic status) than those who are not (36), (2) E2 levels regardless of source (i.e., endogenous or exogenous) may directly affect RV structure and function, and (3) available data on HT use and related covariates allowed for adjustment for potential unmeasured confounders. A small number of individuals were receiving either testosterone or DHEA supplementation; analyses excluding such individuals provided identical results. The relationship of E2 with RV measures depended on HT use, justifying this approach and indicating an important interaction for further study. Unmeasured or residual confounding of our results is still possible.

We have shown that serum E2 in the setting of HT is associated with better RV systolic function in postmenopausal women and that higher levels of androgens (bioT and DHEA) are associated with larger RVs in men and postmenopausal women without cardiovascular disease. The estrogen:testosterone balance may be particularly informative in men and further study is needed to define the role of SHBG in pulmonary vascular and RV function. The associations seen for E2 and DHEA, in particular, contradict what is known about pulmonary vascular disease, suggesting that certain hormones may have pleiotropic actions for the RV and the pulmonary vasculature.

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