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RESEARCH LETTER

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Sex differences in right ventricular function between Groups 1 and 3 pulmonary hypertension

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Abstract

Group 3 pulmonary hypertension (PH) patients have disproportionate right ventricular dysfunction (RVD) compared to pulmonary arterial hypertension. We evaluated how sex and PH etiology modulated RVD. Strain echocardiography showed no intrasex differences between PH types. Heightened RVD in Group 3 PH may be due to a greater male proportion.

KEYWORDS
echocardiography, right ventricle function and dysfunction, sex differences

1 | INTRODUCTION

Pulmonary hypertension (PH) due to chronic lung disease (Group 3 PH) is the second most common cause of PH,[1] and Group 3 PH patients have the worst survival rates of all the PH etiologies.[2] An important prognostic factor in Group 3 PH is the presence of right ventricular dysfunction (RVD), as RVD results in heightened rates of heart failure hospitalization and death.[3] Interestingly, Group 3 PH patients have more pronounced RVD despite having less severe PH when compared to pulmonary arterial hypertension (PAH) patients.[4] Currently, the mechanisms underlying the disproportionate RVD in Group 3 PH patients are unknown. A deeper understanding of this observation is important because this patient population currently has limited treatment options.

One potential explanation for heightened RVD in Group 3 PH may be biological sex as Group 3 PH does not have as strong of a female predominance as PAH.[4] Multiple studies reveal females have superior RV function as compared to males,[5,6] but the potential synergetic effects of PH etiology and biological sex on RV function in PH patients are unexplored. To address this important unknown, here, we used strain echocardiography to assess the effect of sex and PH etiology on RV function. We used strain echocardiography as it has the strongest correlation with cardiac magnetic resonance derived RV function, the gold standard noninvasive modality to evaluate cardiac volumes.[7]

Abbreviations: mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RV, right ventricle/ventricular; RV GLS, right ventricular global longitudinal strain; RVD, right ventricular dysfunction.

2 | METHODS

Group 1 PAH and Group 3 PH patients were identified from the Minnesota PH Repository and were defined according to the World Health Organization criteria. We used pulmonary function tests, high-resolution computed tomography, and sleep studies to define Group 3 PH. RV global longitudinal strain (GLS) and RV free wall strain were determined using TOMTEC software (TOMTEC Corporation) by FK without any knowledge of invasive hemodynamic measures. We evaluated the relationship between RV GLS and RV free wall strain and pulmonary vascular resistance (PVR) based on sex and PH etiology. PVR was defined as (mean pulmonary artery pressure-pulmonary capillary wedge pressure)/cardiac output. Statistical analysis was performed on GraphPad Prism version 10.0.2. Unpaired *t* test compared means of two groups. If the data were not normally distributed as determined by the Shapiro–Wilk test, Mann–Whitney *U* test was completed. Linear regression assessed differences in slopes and *y*-intercepts of the best-fit lines of RV strain versus PVR. Data are presented as mean ± standard deviation.

3 | RESULTS

We identified 217 PAH (60 males and 157 females) and 233 Group 3 PH patients (105 males and 128 females) for our analysis (Supporting Information: Table 1). We obtained RV echocardiographic strain data from 117 PAH (30 males and 87 females) and 103 Group 3 PH patients (47 males and 56 females; Supporting Information: Table 2). Five Group 3 patients with RV strain data had incomplete or absent hemodynamic data. The median acquisition time difference between the echocardiogram and right heart catheterizations was 14.5 days (range 0–279 days) for those with RV strain data (Supporting Information: Table 2). Group 3 PH patients were older than PAH patients in both male (Group 3: 67 ± 11 vs. Group 1: 53 ± 13 years, $p < 0.0001$) and female sexes (Group 3: 64 ± 11 vs. Group 1: 54 ± 18 years, $p < 0.0001$; Supporting Information: Table 1). Male Group 3 PH patients had lower mean pulmonary arterial pressure (mPAP) than PAH males (Group 3: 40 ± 10 vs. Group 1: 47 ± 16 mmHg, $p = 0.007$; Supporting Information: Table 1). Female Group 3 PH patients had lower PVR than female PAH patients with no difference in mPAP (Group 3: 7.2 ± 3.8 vs. Group 1: 9.5 ± 5.9 WU, $p = 0.004$). In summary, Group 3 patients had either similar or less severe pulmonary vascular disease compared to PAH patients of the same sex.

Consistent with previous results,[5] males had worse RV function as quantified by RV GLS and RV free wall strain than females in both PH types (Figure 1a–d). Importantly, the superior RV function in females held true at all levels of PVR so this was not due to differences in afterload (Figure 1a–d). Next, we evaluated how PH etiology modulated RV function in both sexes. Surprisingly, RV function was similar in PAH and Group 3 females (Figure 1e,f) and males (Figure 1g,h). Because there were differences in pulmonary vascular disease severity between these PH types, we plotted the relationship between RV function and afterload to provide a surrogate measure for RV-pulmonary artery coupling. The RV's response to increased load was not statistically different in PAH and Group 3 PH males and females, respectively (Figure 1e–h). As there was a wide range of time difference between the acquisition of the echocardiography and invasive hemodynamic studies, we subsequently restricted the analysis to those patients who had echocardiograms and right heart catheterizations within a 90-day time period (25 PAH males, 71 PAH females, 41 Group 3 males, and 46 Group 3 females). Similarly, there was no difference in RV response to PVR between PAH and Group 3 PH in the intrasex comparisons (Supporting Information: Supplemental Figure).

There was no difference in RV GLS ($p = 0.86$) or RV free wall strain ($p = 0.51$) between pre- (less than 55 years of age) and post-menopausal (55 years of age or older) PAH women. As premenopausal Group 3 females had significantly reduced PVR (4.6 ± 1.4 vs. 7.8 ± 3.4 WU, $p = 0.001$) compared to post-menopausal Group 3 females, we normalized RV function to afterload and found no difference (RV GLS vs. PVR: $p = 0.46$ for slopes, $p = 0.68$ for *y*-intercepts; RV free wall strain vs. PVR: $p = 0.55$ for slopes, $p = 0.51$ for *y*-intercepts) between pre- and post-menopausal Group 3 females. Moreover, the relationship between RV GLS ($p = 0.39$ for slopes, $p = 0.59$ for *y*-intercepts) or RV free wall strain ($p = 0.47$ for slopes, $p = 0.24$ for *y*-intercepts) to PVR was similar between premenopausal Groups 1 and 3 females. Finally, there was no change in RV response to afterload (RV GLS vs. PVR: $p = 0.35$ for slopes, $p = 0.68$ for *y*-intercepts; RV free wall strain vs. PVR: $p = 0.47$ for slopes, $p = 0.47$ for *y*-intercepts) between post-menopausal Groups 1 and 3 females.

4 | DISCUSSION

In conclusion, strain echocardiography confirmed sex differences in RV function in both PAH and Group 3 patients. Unexpectedly, when making intrasex comparisons between PH etiologies, RV strain rates and the RV's response to afterload were not statistically different. This

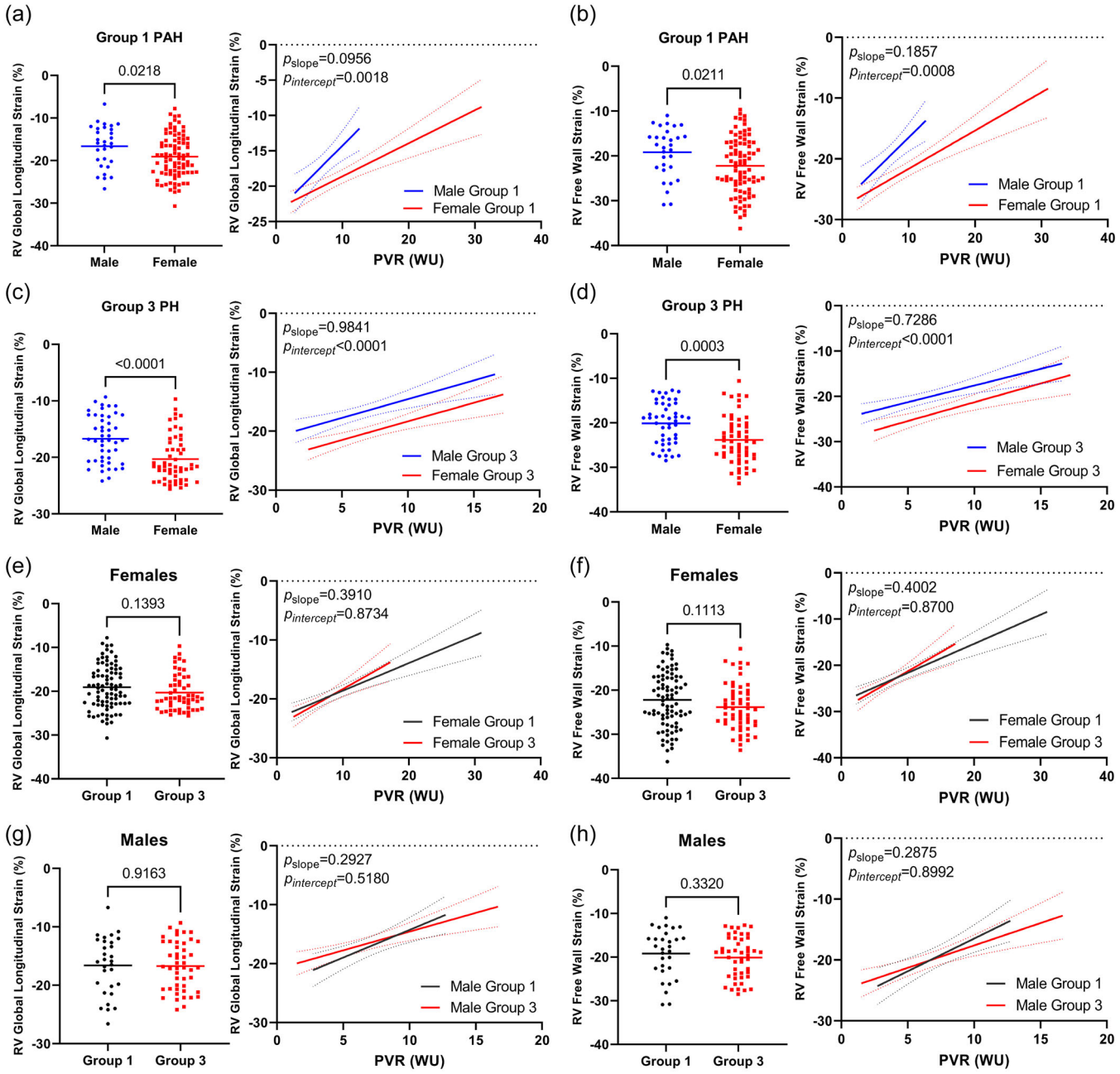

FIGURE 1 Strain echocardiography reveals sex differences in RV function, but PH etiology does not significantly modulate RV function in males and females, respectively. PAH females had significant differences in RV GLS (95% confidence interval [CI] of the difference: −3.55 to −2.7%) (a) and RV free wall strain (95% CI of the difference: −5.9% to −0.5%) (b) overall and at every PVR when compared to males. Female Group 3 PH patients had less RV impairment overall (95% CI of the difference for RV GLS: −5.5% to −2.0%, 95% CI of the difference for RV free wall strain: −6.2% to −1.9%) and at every PVR load as compared to males (c and d). There were no differences in RV GLS (95% CI of the difference: −2.8% to 0.4%) (e) or RV free wall strain (95% CI of the difference: −3.9% to 0.4%) (f) in total or when afterload was accounted for between Groups 1 and 3 females. There was no difference in total RV GLS (95% CI of the difference: −2.5% to 2.0%) (g) or RV free wall strain (95% CI of the difference: −3.6% to 1.3%) (h) or RV strain normalized to afterload between Groups 1 and 3 males. GLS, global longitudinal strain; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RV, right ventricular.

unanticipated observation requires further investigation. Because both males and females with Group 3 PH were older than PAH patients, we expected this age discrepancy would result in divergent levels of sex hormones. In particular, Group 3 females would be predicted to have less estrogen, which is a known RV-protective molecule.[8] Interestingly, our demonstration of a comparable RV phenotype in females regardless of age is similar to results from van Wezenbeek et al.[9] as they showed older PAH (≥55) females have similar RV ejection fraction as

young PAH females (≤45 years) using cardiac MRI. These results do not dispute the estrogen hypothesis, as there may be protective effects of estrogen over a long duration for which we cannot account for in this study design. In addition, other sex hormones likely play important roles in the distinctions in RV function. Certainly, higher testosterone is associated with impaired RV function in both preclinical pulmonary artery banding[5] and in PAH patients,[9] and thus testosterone is likely an important contributor to sex differences in RV function. When comparing PH etiologies, there was a nonsignificant (potentially due to small sample size) trend that Group 3 males could better maintain RV function as load increases than PAH males (Figure 1g–h). Perhaps the older Group 3 males had lower testosterone levels, which could explain this observation. However, larger studies are needed to evaluate this hypothesis. Finally, because there were no significant intrasex disparities in RV function when PH etiologies were compared, we propose the heightened RVD in Group 3 PH as compared to PAH is due to a greater proportion of males in Group 3 PH.[4]

Our study has important limitations. First, this study was conducted at a single-center referral center, and thus these patients may not be representative of the overall PAH and Group 3 PH patient populations. Additionally, we may not have had a large enough sample size to detect a difference between PAH and Group 3 PH in the intrasex comparisons. Second, we were unable to determine RV strain for all patients due to the quality of the echocardiographic images, which may have introduced bias. Third, differences in treatments, comorbidities, and RV afterload between the PAH and Group 3 cohorts could have led to no intrasex differences. Finally, we did not assess menopausal status and used age greater than or equal to 55 years as a surrogate. Future studies with larger multicenter cohorts are needed to assess potential interactions between PH type and sex.

KEYWORDS

echocardiography, right ventricle function and dysfunction, sex differences

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design of the work. Felipe Kazmirczak, Thenappan Thenappan, Kurt W. Prins, and Sasha Z. Prisco completed the data acquisition and analysis. Sasha Z. Prisco and Kurt W. Prins drafted the manuscript. All authors revised the manuscript and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Thenappan Thenappan served on an advisory board for Actelion, United Therapeutics, Altavant Sciences, Acceleron, and Aria CV. Thenappan Thenappan receives research funding for clinical trials from United Therapeutics, Aria CV, GossimerBio, and Acceleron. Kurt W. Prins served on an advisory board for Edwards and received grant funding from United Therapeutics. The other authors have declared that no conflict of interest exists.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ETHICS STATEMENT

The authors identified PAH and Group 3 PH patients from the University of Minnesota Pulmonary Hypertension Program. This study was approved by the University of Minnesota Institutional Review Board and the participants gave written informed consent to participate in the Minnesota Pulmonary Hypertension Repository, a prospective registry initiated in 2014.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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