Sex and Hemodynamics in Pulmonary Arterial Hypertension

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ABSTRACT

Introduction: Female sex is a risk factor for pulmonary arterial hypertension (PAH), yet women have better survival than men. We sought to determine if sex was associated with baseline hemodynamics in subjects with PAH, and whether age modified these relationships.

Material and Methods: We conducted a pooled analysis from 11 randomized trials submitted to the U.S. Food and Drug Administration. The study sample included 1211 subjects with idiopathic PAH, 25% of whom were men, and 489 subjects with connective tissue disease (CTD)-associated PAH, 13% of whom were men.

Results: After multivariable adjustment, right atrial pressure was 1.36 mm Hg higher (95% CI 0.44 – 2.27, P=0.004), cardiac index was -0.14 L/min/m² lower (95% CI -0.23 – 0.04, P=0.01), and pulmonary vascular resistance was 1.23 Wood units higher (95% CI 0.18 – 2.27, P=0.02) in men compared to women. Younger men had 5.43 mm Hg (95% CI 2.20 – 8.66, P=0.001) higher mean pulmonary artery pressures than younger women, but these relationships were attenuated after age 45. In the subgroup of CTD-associated PAH, men may have had higher RAP.

Discussion: These findings provide further evidence of sex-related differences in pulmonary vascular disease and implicate age as a possible modifier of sexual dimorphism in PAH.

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Key Words: sex, hemodynamics, pulmonary hypertension
INTRODUCTION

Female sex is the best established risk factor for pulmonary arterial hypertension (PAH) [1, 2]. Despite having greater disease burden, it appears that women have better right ventricular (RV) function and increased survival compared to men with PAH [3-6]. Hemodynamics, particularly indices of RV response to increased afterload such as right atrial pressure (RAP) and cardiac output (CO), are well-described predictors of outcome in PAH, but whether hemodynamic measures vary by sex, possibly contributing to sex-related differences in outcome, has not been clearly established [7-10].

Numerous basic science and clinical observations have implicated estrogen in PAH disease pathogenesis [11-15]. Yet, estrogen therapy has been shown to rescue both pulmonary vasculopathy and RV function in animal models of pulmonary hypertension [16, 17]. This paradoxical effect of estrogen is as yet unexplained. Why women with PAH appear to fare better than men with disease (and the role that other sex hormones may play in this process) is also poorly understood.

Recent observational data indicate that age may be an important modifier of disease risk and outcomes in pulmonary vascular disease [7, 18]. In systemic cardiovascular disease, male and female risk profiles converge following the menopausal transition, and much debate has surrounded hormone therapy and the impact of sex hormones on vascular homeostasis as individuals age [19-21]. We have shown that sex hormones are associated with RV size and function in health, and that women with PAH have greater responses to endothelin receptor antagonists than men with PAH, but the association of sex with hemodynamic burden in well-phenotyped patients is unknown [22, 23].
We sought to determine whether sexual dimorphism in PAH could in-part be explained by differences in baseline hemodynamics, and whether age modified this relationship. We hypothesized that younger men would have higher mean RAP, mean pulmonary artery pressures (mPAP), and pulmonary vascular resistance (PVR), and lower CO at baseline compared to young women with PAH, and that these differences would attenuate with age.

Methods

Study Population

De-identified individual patient data from 12 placebo-controlled randomized trials of targeted PAH therapies was acquired from the United States Food and Drug Administration (FDA). The trials, ARIES-1 & -2, Bosentan-351, BREATHE-1, AIR, AIR II, SUPER, PHIRST, STRIDE-1, -2, and -4, and the Phase III subcutaneous treprostinil trial, compared seven active therapies to placebo (ambrisentan, bosentan, iloprost, sildenafil, tadalafil, sitaxsentan, and subcutaneous treprostinil, respectively). Details of these trials are provided elsewhere; all had similar inclusion criteria and data collection processes [24-33]. We included subjects with a diagnosis of idiopathic or CTD-associated PAH and excluded subjects with missing baseline data and those from the PHIRST trial, since some subjects in this trial had been treated with background bosentan therapy [34]. As idiopathic and CTD-associated PAH patients are known to have different hemodynamic profiles, we chose to analyze these two groups separately [35].

Variables

The dependent variables were baseline hemodynamic values from the trials as reported to the FDA. Individuals with missing RAP, mPAP, pulmonary capillary wedge pressure (PCWP),
or CO were excluded from analyses. The independent variable was sex. Covariates (and effect modifiers) included age, race, height, weight, and study.

**Statistical Analysis**

Continuous variables were expressed as means and standard deviations. Categorical variables were expressed as percentages. Independent sample \( t \) tests were used to compare continuous variables and chi-square was used to compare categorical variables in men and women. Multivariable linear regression was used to assess the relationship between sex and baseline hemodynamics. Results were expressed as adjusted effect estimates and least-square means. We assessed for a sex by age interaction, and stratified results by age group when the interaction was significant (\( P<0.05 \)). Age groups (< 45, 45 – 54, 55 – 64, and ≥ 65) were chosen \textit{a priori} to correlate with typical changes in the hormonal milieu with age (e.g., menopause) [36, 37]. Main results were adjusted for age (if no sex by age interaction), race/ethnicity, height, weight, and study. Models for cardiac index (CI) and pulmonary vascular resistance index (PVRI) were adjusted for age (if no sex by age interaction), race/ethnicity, and study. Statistical significance was defined as \( P<0.05 \). Analyses were performed using SAS version 9.2.

**RESULTS**

A total of 2581 subjects were enrolled in 12 randomized controlled trials which were submitted for FDA approval (Figure 1). Of these, we excluded 406 (16%) from the PHIRST trial, 364 with non-idiopathic, non-CTD-associated PAH (17%), and 111 with missing data (5%). The final study sample consisted of 1211 subjects with idiopathic PAH, 303 (25%) of whom were men, and 489 subjects with CTD-associated PAH, 61 (13%) of whom were men.

Characteristics of the study sample with idiopathic PAH are shown in Table 1. Men were
older, taller and heavier, and had greater six-minute walk distances (6MWD) than women. In our study sample, more men than women were from AIR and ARIES-2 (12.2% of the men versus 6.3% of the women and 12.2% of the men versus 8.5% of the women, respectively), whereas more women than men were from ARIES-1 (10.5% versus 5%, respectively). Comparing unadjusted hemodynamic values, men had higher CO and lower PVR than women, however women had higher CI (P = 0.01). There was no difference in PVRI between men and women.

Adjusted associations between sex and baseline hemodynamics for those with idiopathic PAH are shown in Table 2. Adjustment for height and weight in the multivariate models made it unnecessary to index the parameters to body surface area, as the former also accounts for differences in body size. After adjustment for age, race, height, weight, and study, men had 1.36 mm Hg higher RAP (95% confidence interval [CI] 0.44 – 2.27 mm Hg, P=0.004) compared to women. There was a significant interaction between sex and age for mPAP (P<0.05). Young men (age < 45 years) had higher mPAP compared to young women (5.43 mm Hg difference, 95% confidence interval [CI] 2.20 – 8.66 mm Hg, P=0.001) after adjustment for race, height, weight, and study. After age 45 however, there were no significant differences in mPAP between men and women. There were no significant interactions between sex and age for the remainder of the hemodynamic measures (all P for interaction > 0.05). Men had higher PVR (1.23 Wood units, 95% CI 0.18 – 2.27 Wood units, P=0.02) on average compared to women. Men also tended to have lower CO than women (with adjustment for body size), but this association did not reach statistical significance (-0.21 L/min difference, 95% CI -0.43 – 0.01, P=0.06). The results for CI and PVRI without adjustment for height and weight were similar. Men had lower CI as compared to women, with a mean difference of -0.14 L/min/m² (95% CI -0.23 – 0.04 L/min/m², P=0.01). There was a sex by age interaction for PVRI (P < 0.05) such that young men
(age < 45 years) had higher PVRI compared to young women (3.16 Wood units•m² difference, 95% CI 0.77 – 5.55 Wood units•m², P=0.01) without associations in the older ages. Figure 2 depicts estimated baseline mPAP, CO, and PVR by multivariable linear regression, by sex and age group (age < 45, 45 – 54, 55 – 64, and ≥ 65). In both men and women with idiopathic PAH, hemodynamic burden, particularly mPAP and PVR, tended to decrease with age.

We examined the smaller group of patients with CTD-associated PAH. Baseline characteristics for 61 men and 428 women are presented in Table E1. The CTD-associated PAH group was similar to the cohort with idiopathic PAH, except those with CTD used less warfarin and tended to have lower mPAP and PVR, as has been previously described [38]. While limited by smaller sample size, male sex seemed to be associated with higher RAP in CTD-associated PAH (1.60 mm Hg difference, 95% CI -0.04 – 3.25, P=0.06). There were no significant associations between sex and the remainder of the hemodynamic indices (Table E2). There were no obvious trends in baseline hemodynamic values across age, although the small number of patients (particularly men) in each age group limited the precision of these estimates (Figure E1).

**DISCUSSION**

We have shown that men have higher RAP and PVR compared to women with idiopathic PAH and may have lower CO and CI after adjustment for covariates. Age appears to modify the relationship between sex and mPAP and PVRI. Younger men with PAH had higher mPAP and PVRI than women, but these differences were attenuated at age 45 and older. Both men and women with idiopathic PAH tended to have lower mPAP and PVR in older age as compared to younger age. In the smaller cohort of patients with CTD-associated PAH, men appeared to have higher RAP than women. Taken together, these observations suggest that men with PAH
enrolled in clinical trials have worse hemodynamics than women in these trials and that age may modify sex differences in pulmonary vascular disease. While the effect sizes are modest, the differences in baseline hemodynamic profiles between the sexes (higher RAP, mPAP, PVR/PVRI and lower CO/CI in men as compared to women) may translate to significant differences in the risk of death [4-6]. For example, the differences in RAP and CO between men and women found in this study could be associated with 5-8% increases in mortality risk [4].

A recent registry of PAH patients also showed that men had higher RAP and mPAP at diagnosis, and that men had worse survival especially in older age [5, 7]. Male sex has been associated with mortality in European registries as well [4, 6]. It is biologically plausible that sex and sex hormones influence not only the development of pulmonary vascular disease but disease severity (i.e., hemodynamic impairment) and outcomes [15]. In fact, in animal models of pulmonary hypertension, females have less vascular remodeling and hemodynamic compromise than males and aged females develop less severe pulmonary vascular changes than male and younger animals, respectively [39-41]. As in our study, greater hemodynamic burden has been observed in younger patients (age < 50 years) as compared to older patients in the United Kingdom and Ireland, although similar hemodynamics were noted in men and women in this cohort [42].

We considered age as a continuous measure (unless there was significant effect modification) in multivariable modeling, which is a different methodological approach than used in prior studies. In the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL), Benza et al. identified age > 60 in males as a significant predictor which was then validated as part of a risk stratification equation [5]. Based on this work, Shapiro et al. stratified the REVEAL cohort by age at enrollment (≤ 60 vs. > 60
years), and then confirmed poorer 2-year survival among older men in the registry and worse hemodynamics among men in general [7]. In that study, survival curves started to diverge at age 50, while we demonstrated an attenuation of sex differences in mPAP after age 45 and less hemodynamic burden in aged men and women overall. Of course, it is difficult to compare our results to those from REVEAL and other registries, given the inherent differences between the populations sampled (i.e., registry participants with Group 1 PAH from various etiologies versus idiopathic patients from pooled clinical trials).

While there has been much focus on the role of estrogen in explaining sex differences in PAH, androgens (namely, testosterone) may also be important. Higher levels of testosterone may be more detrimental to males as compared to females, and testosterone is associated with maladaptive RV hypertrophy and fibrosis in murines and greater RV mass and volumes in an epidemiologic cohort [22, 39, 40, 43, 44]. While androgen replacement in testosterone deficient men has been studied in heart failure, a recently terminated trial of testosterone administration in aged men demonstrated an increased risk of cardiovascular events, highlighting the uncertainties that remain [45-47]. Therefore, sex differences in hemodynamics in pulmonary vascular disease may not be explained by estrogen signaling alone.

The associations seen here pertain not only to disease burden in the pulmonary vascular bed (i.e., mPAP, PVR/PVRI), but to RV function specifically (i.e., RAP and CO/CI). Hemodynamic and morphologic parameters of RV function are important predictors of survival in PAH, and women tend to have more favorable RV indices than men [3, 8-10]. In health, men have accelerated cardiomyocyte loss with aging, lower RV ejection fraction, and larger age-related decrements in RV mass as compared to women, although age-related changes in RV function have not been studied in a large-scale manner in PAH [22, 48-50].
Age and the menopausal transition have long been implicated as potential risk modifiers in systemic cardiovascular disease [19, 51, 52]. Estrogen has variable effects on the vasculature dependent on age, which may explain why the risk/benefit of hormone therapy in post-menopausal women varies depending upon the age of the population studied (the so-called “timing hypothesis”) [20, 53]. Differences in tissue-specific estrogen receptor expression, estrogen-mediated genetic modifications, and estrogen metabolism have all been proposed as possible mechanisms to explain the time-dependent vascular effects of estrogen [17, 54-58]. While we do not have specific data on menopausal status of the study subjects, our results suggest that young women tend to have higher mPAP and PVR as compared to older women but less hemodynamic impairment as compared to young men. Yuan and colleagues have recently demonstrated an endogenous estrogen deficiency following monocrotaline injury, leading to alterations in estrogen receptor signaling and metabolism and a pro-proliferative, anti-apoptotic state that is rescued by exogenous estradiol [17]. These findings have interesting implications when considered in the context of female menopause and waning estrogen levels, and given our previous work demonstrated that hormone therapy use is associated with improved RV ejection fraction in healthy post-menopausal women [22]. In PAH, it is unknown whether the hormonal milieu before mid-life increases risk of disease, or perhaps favorably impacts RV adaptation and/or response to PAH therapy. Prior work using a subset of this same data source showed that women were more responsive to endothelin receptor antagonists than were men, although age did not modify the strength of this relationship [23].

This study has limitations. First, the pooled data analyzed here are subject to limitations of the clinical trials. Measurement error in hemodynamics (if non-differential with respect to sex and age) would bias toward the null, so that the true associations of sex and age with
hemodynamics may be stronger than we have shown. There were some differences in the
inclusion criteria (i.e., upper- and lower- limits for 6MWD) and PAH severity (e.g., functional
class) across trials [24-34]. Neither distance walked nor functional class would impact the
exposure variable (sex) and so are unlikely to confound the exposure-outcome (sex-
hemodynamic) relationship in the pooled analysis, however. It is possible that sex differences
and the hemodynamic trends across age groups observed were subject to survivor or lead time
bias, i.e. that young patients with the greatest hemodynamic impairment succumb early and are
therefore not recruited into clinical trials, leaving only the older patients with less hemodynamic
derangement. This could be especially true for men, given sex has been associated with a
diagnostic delay in other chronic pulmonary diseases, although sex and timing of diagnosis do
not appear to be related in PAH [59, 60]. Our results may be subject to selection bias introduced
by the enrollment of certain subjects in clinical trials (i.e., younger patients) over others (i.e.,
older patients with advanced PAH), although there were reasonable numbers of patients in the ≥
65 age group (Figure 2 and E1). Registry data suggest that younger age is associated with a delay
in PAH diagnosis, but how this may impact subjects enrolled into clinical trials is not known[60].
Finally, the relatively small numbers of CTD-associated patients, particularly men, limits our
ability to draw firm conclusions about the relationships between sex, age, and hemodynamics in
CTD-associated PAH, and it is important to note that age has previously been shown to amplify
the risk of PAH and to worsen disease severity in systemic sclerosis [61, 62].

In conclusion, we have shown that men with idiopathic PAH have higher RAP, higher
mPAP, and PVR compared to women, and lower CO/CI. Future work exploring sexual
dimorphism in PAH should consider the impact of age on the sex hormone-pulmonary vascular
relationship, and define the impact of androgens in men with PAH.
ACKNOWLEDGEMENTS

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References


**Figure Legends**

**Figure 1: Study sample**

RCT=randomized controlled trial; PHIRST=Pulmonary Arterial Hypertension and Response to Tadalafil trial; CTD=connective tissue disease; PAH=pulmonary arterial hypertension

**Figure 1.**

- 2581 subjects, 12 pooled RCTs
  - 406 subjects in PHIRST
  - 2175 subjects, 11 pooled RCTs
    - 364 subjects with non-idiopathic, non-CTD PAH
    - 111 subjects with missing data
  - 1700 subjects
    - 1211 subjects with idiopathic PAH
      - 303 men, 908 women
      - 489 subjects with CTD PAH
        - 61 men, 428 women
Figure 2: Least square means of baseline hemodynamics by sex and age with adjustment for race, height, weight, and study in subjects with idiopathic pulmonary arterial hypertension. Marker=point estimate; whiskers=95% confidence interval

RAP=right atrial pressure; MPAP=mean pulmonary artery pressure; CO=cardiac output; PCWP=pulmonary capillary wedge pressure; PVR=pulmonary vascular resistance

Figure 2.
Table 1. Baseline characteristics of the study sample with idiopathic pulmonary arterial hypertension, by sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>303</td>
<td>908</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>50.5 ± 15.2</td>
<td>46.6 ± 14.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>Caucasian</td>
<td>265 (87.5)</td>
<td>726 (80.0)</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>9 (3.0)</td>
<td>41 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4 (1.3)</td>
<td>19 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>24 (7.9)</td>
<td>114 (12.6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.3)</td>
<td>8 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>173.9 ± 8.3</td>
<td>160.7 ± 7.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.6 ± 17.0</td>
<td>72.1 ± 17.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.9 ± 4.7</td>
<td>27.9 ± 6.6</td>
<td>0.18</td>
</tr>
<tr>
<td>Warfarin use, n (%)</td>
<td>167 (66.0)</td>
<td>496 (61.5)</td>
<td>0.19</td>
</tr>
<tr>
<td>Study, n (%)</td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>AIR</td>
<td>37 (12.2)</td>
<td>57 (6.3)</td>
<td></td>
</tr>
<tr>
<td>AIR-II</td>
<td>9 (3.0)</td>
<td>22 (2.4)</td>
<td></td>
</tr>
<tr>
<td>ARIES-1</td>
<td>15 (5.0)</td>
<td>95 (10.5)</td>
<td></td>
</tr>
<tr>
<td>ARIES-2</td>
<td>37 (12.2)</td>
<td>77 (8.5)</td>
<td></td>
</tr>
<tr>
<td>Bosentan 351</td>
<td>4 (1.3)</td>
<td>22 (2.4)</td>
<td></td>
</tr>
<tr>
<td>BREATHE-1</td>
<td>31 (10.2)</td>
<td>107 (11.8)</td>
<td></td>
</tr>
<tr>
<td>STRIDE-1</td>
<td>25 (8.3)</td>
<td>68 (7.5)</td>
<td></td>
</tr>
<tr>
<td>STRIDE-2</td>
<td>37 (12.2)</td>
<td>91 (10.0)</td>
<td></td>
</tr>
<tr>
<td>STRIDE-4</td>
<td>11 (3.6)</td>
<td>52 (5.7)</td>
<td></td>
</tr>
<tr>
<td>SUPER</td>
<td>41 (13.5)</td>
<td>118 (13.0)</td>
<td></td>
</tr>
<tr>
<td>Treprostinil</td>
<td>56 (18.5)</td>
<td>199 (21.9)</td>
<td></td>
</tr>
<tr>
<td>NYHA functional class, n (%)</td>
<td></td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>I</td>
<td>11 (3.6)</td>
<td>26 (2.9)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>110 (36.4)</td>
<td>372 (41.2)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>160 (53.0)</td>
<td>464 (51.4)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>21 (7.0)</td>
<td>40 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Baseline 6MWD, m</td>
<td>362.6 ± 91.4</td>
<td>344.5 ± 83.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Baseline hemodynamics

|                                |               |              |           |
|                                | Men           | Women        |           |
| Right atrial pressure, mm Hg   | 9.6 ± 5.8     | 9.1 ± 5.6    | 0.12      |
| Mean pulmonary artery pressure, mm Hg | 54.4 ± 15.5   | 55.2 ± 14.5  | 0.15      |
| Cardiac output, L/min          | 4.3 ± 1.3     | 4.1 ± 1.4    | 0.02      |
| Cardiac index, L/min/m²        | 2.2 ± 0.6     | 2.3 ± 0.8    | 0.01      |
| Pulmonary capillary wedge pressure, mm Hg | 9.3 ± 3.6     | 9.1 ± 3.5    | 0.41      |
| Pulmonary vascular resistance, Wood units | 12.0 ± 6.2   | 13.1 ± 6.9   | 0.004     |
| Pulmonary vascular resistance index, Wood units•m² | 23.2 ± 11.4 | 22.9 ± 11.6 | 0.90      |

Data are shown as mean ± standard deviation or percentage. BMI=body mass index; AIR=Aerosolized Iloprost Randomized; ARIES=Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter Efficacy Studies; BREATHE=Bosentan: Randomized Trial of Endothelin receptor Antagonist Therapy;
STRIDE=Sitaxsentan To Relieve Impaired Exercise; SUPER=Sildenafil Use in Pulmonary Hypertension; NYHA=New York Heart Association; 6MWD=six-minute walk distance.
Table 2. Associations between sex and baseline hemodynamics in subjects with idiopathic pulmonary arterial hypertension, stratified by age group for mean pulmonary artery pressure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age</th>
<th>Difference between men and women</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td></td>
<td>1.36</td>
<td>0.44 – 2.27</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>&lt; 45</td>
<td>5.43</td>
<td>2.20 – 8.66</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>45-54</td>
<td>1.37</td>
<td>-2.64 – 5.37</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>-1.45</td>
<td>-5.70 – 2.81</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>3.06</td>
<td>-1.31 – 7.43</td>
<td>0.17</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td></td>
<td>-0.21</td>
<td>-0.43 – 0.01</td>
<td>0.06</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td></td>
<td>0.19</td>
<td>-0.38 – 0.77</td>
<td>0.51</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, Wood units</td>
<td></td>
<td>1.23</td>
<td>0.18 – 2.27</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Adjusted for age (if no sex*age interaction), race, height, weight, study