Sex-based differences in veterans with pulmonary hypertension: Results from the veterans affairs-clinical assessment reporting and tracking database

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

Citation
Ventetuolo, C. E., E. Hess, E. D. Austin, A. E. Barón, J. R. Klinger, T. Lahm, T. M. Maddox, et al. 2017. "Sex-based differences in veterans with pulmonary hypertension: Results from the veterans affairs-clinical assessment reporting and tracking database." PLoS ONE 12 (11): e0187734. doi:10.1371/journal.pone.0187734. http://dx.doi.org/10.1371/journal.pone.0187734.

Published Version
doi:10.1371/journal.pone.0187734

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:34493200

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
Sex-based differences in veterans with pulmonary hypertension: Results from the veterans affairs-clinical assessment reporting and tracking database

Corey E. Ventetuolo¹,², Edward Hess³, Eric D. Austin¹, Anna E. Barón³, James R. Klinger¹, Tim Lahm⁵,⁶, Thomas M. Maddox³, Mary E. Plomondon⁹, Lauren Thompson⁷, Roham T. Zamanian⁸, Gaurav Choudhary¹,⁹, Bradley A. Maron¹⁰,¹¹

¹ Department of Medicine, Alpert Medical School of Brown University, Providence, Rhode Island, United States of America, ² Department of Health Services, Policy and Practice, Brown University School of Public Health, Providence, Rhode Island, United States of America, ³ Veterans Affairs Eastern Colorado Health Care System, Denver, Colorado, United States of America, ⁴ Division of Pediatric Pulmonary, Allergy, and Immunology, Vanderbilt University, Nashville, Tennessee, United States of America, ⁵ Division of Pulmonary, Critical Care, Occupational and Sleep Medicine, Indiana University School of Medicine, Indianapolis, Indiana, United States of America, ⁶ Richard L. Roudebush Veterans Affairs Medical Center, Indianapolis, Indiana, United States of America, ⁷ University of Colorado School of Medicine, Aurora, Colorado, United States of America, ⁸ Vera Moulton Wall Center for Pulmonary Vascular Disease, Stanford University School of Medicine, Stanford, California, United States of America, ⁹ Providence Veterans Affairs Medical Center, Providence, Rhode Island, United States of America, ¹⁰ Boston Veterans Affairs Healthcare System, Boston, Massachusetts, United States of America, ¹¹ Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts, United States of America

* corey_ventetuolo@brown.edu

Abstract

Women have an increased risk of pulmonary hypertension (PH) but better survival compared to men. Few studies have explored sex-based differences in population-based cohorts with PH. We sought to determine whether sex was associated with hemodynamics and survival in US veterans with PH (mean pulmonary artery pressure [mPAP] ≥ 25 mm Hg) from the Veterans Affairs Clinical Assessment, Reporting, and Tracking database. The relationship between sex and hemodynamics was assessed with multivariable linear mixed modeling. Cox proportional hazards models were used to compare survival by sex for those with PH and precapillary PH (mPAP ≥ 25 mm Hg, pulmonary artery wedge pressure [PAWP] ≤ 15 mm Hg and pulmonary vascular resistance [PVR] > 3 Wood units) respectively. The study population included 15,464 veterans with PH, 516 (3%) of whom were women; 1,942 patients (13%) had precapillary PH, of whom 120 (6%) were women. Among those with PH, women had higher PVR and pulmonary artery pulse pressure, and lower right atrial pressure and PAWP (all p < 0.001) compared with men. There were no significant differences in hemodynamics according to sex in veterans with precapillary PH. Women with PH had 18% greater survival compared to men with PH (adjusted HR 0.82, 95% CI 0.69–0.97, p = 0.020). Similarly, women with precapillary PH were 29% more likely to survive as compared to men with PH (adjusted HR 0.71, 95% CI 0.52–0.98, p = 0.040). In
conclusion, female veterans with PH have better survival than males despite higher pulmonary afterload.

**Introduction**

Pulmonary hypertension (PH) refers to an elevation in pulmonary artery pressures (PAP) due to various etiologies. Precapillary PH is characterized by an increase in pulmonary vascular resistance (PVR) which may be idiopathic, heritable, or associated with systemic diseases (all referred to as World Health Organization [WHO] Group 1 pulmonary arterial hypertension [PAH]) [1]. As many as 80% of prevalent WHO Group 1 patients are women [2]. Precapillary PH also occurs in chronic lung disease and sleep disordered breathing (WHO Group 3 PH), chronic thromboembolic disease (WHO Group 4 PH), or combined with post-capillary PH in left heart disease (WHO Group 2 PH) [3]. PH is a frequent complication of highly prevalent cardiopulmonary diseases and is associated with increased morbidity and mortality when present [4–9]. In the last two decades, disease burden for all types of PH has increased, particularly among women [4]. Despite greater disease prevalence, it appears that women with PH have improved survival compared to men with PH [5, 10–13], but sex-based differences in outcomes have not been well-characterized outside of WHO Group 1 PAH.

Hemodynamics are required for the diagnosis and treatment of PH (i.e., to detect increased PVR and distinguish pre- from post-capillary PH) and are established predictors of survival [14–17]. We have previously shown that in patient-level data from clinical trials men with PAH had more severe hemodynamic abnormalities as compared to women with PAH [18]. Similarly, in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) men with PAH had more hemodynamic derangement than women with PAH [14]. Age appeared to modify the associations between sex and hemodynamics in our prior study and sex and survival in REVEAL, with some discrepancies observed between the two studies [14,18]. Since both were limited to patients with WHO Group 1 PAH, it is unknown whether these observations extend to other quite common forms of PH. Large epidemiologic cohorts with hemodynamic assessments in which to replicate these observations in a “real world” unselected population of men and women with all forms of PH have to this point been lacking.

Veterans are characterized by a particularly high prevalence of PH, and the presence of PH is a strong predictor of increased mortality in this population [8]. We therefore sought to determine whether sex is associated with hemodynamics and survival in a cohort of US veterans who underwent right heart catheterization (RHC) in whom outcomes were tracked as part of a national clinical quality initiative, the Veterans Affairs (VA) Clinical Assessment, Reporting, and Tracking (CART) program [19]. We hypothesized that in PH and precapillary PH, women would have less severe hemodynamic impairment as compared to men. Second, we hypothesized that women would have more favorable survival as compared to men with PH and precapillary PH respectively. Finally, we explored whether survival differences (if present) could be explained by hemodynamic differences and whether age modified any of the observed relationships.

**Funding:** The work was supported by the following: CEV: (NIH) Institutional Development Award (IDeA) from the National Institute of General Medical Sciences P20GM103652, American Heart Association (11FTF740032); TL: Department of Veterans Affairs (VA Merit 1101BX002042-01A2), Catherine and Lowe Berger and Pauline L. Ford Chair at Indiana University; GC: National Institutes of Health, 1R01HL128661; B.A.M.: National Institutes of Health 1K08HL11207-01A1, American Heart Association (AHA 15GRNT25080016), Pulmonary Hypertension Association, Cardiovascular Medical Research and Education Fund (CMREF), and Klarman Foundation at Brigham and Women’s Hospital. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** C.E.V. has served as a consultant for Bayer Pharmaceuticals, Actelion, United Therapeutics, and Acceleron Pharma. Her institution has received grant funding from Actelion. T.L. received funding for investigator-initiated research from Gilead and remuneration for investigator-initiated research from Eli Lilly & Co and serves on the speaker bureau for Bayer. R.T.Z. has consulted for Selten, Actelion, and Bayer Pharmaceuticals, owns stocks in Stelten and Genentech Pharmaceuticals, and has received research funding from Gilead, Selten, and United Therapeutics. G.C. has an investigator-initiated grant from Novartis. B.A.M. reports research funding from Gilead and consulting for Hovione. This does not alter our adherence to PLOS ONE policies on sharing data and materials. There are no patents, products in development or marketed products to declare.
Methods

Study population

We evaluated all veterans with procedural data recorded in CART who underwent RHC as an outpatient or inpatient in the VA system between October 1, 2007 and September 30, 2013. In patients undergoing multiple RHCs, the first RHC was used to characterize hemodynamics and values from this index procedure were included in the analysis. Further details about the 76 participating centers and RHC volume by center have previously been published [8,19]. Catheterization reports generated by the CART system pass rigorous quality control [20], in concordance with the definitions and standards of the American College of Cardiology’s National Cardiovascular Data Registry [21].

The source population included all subjects with RHC data available including values for mean pulmonary artery pressure (mPAP), pulmonary artery wedge pressure (PAWP), cardiac output (CO) measured by either assumed Fick and/or thermodilution methods, and height and weight for calculation of body surface area. Variables were assessed for physiologic plausibility and validated by two cardiologists with expertise in hemodynamic analysis and were assigned a corrected value based on ancillary data (i.e., values that could be confirmed in the medical record or could be calculated from other variables), or a value of missing where correct value(s) could not be identified, as previously described [8]. PVR was calculated as (mPAP—PAWP)/CO and pulmonary artery pulse pressure (PAPP), a marker of RV loading that predicts poor outcomes in various forms of PH [22,23], was calculated as systolic PAP—diastolic PAP.

The final study population included those with PH (defined as a mPAP ≥ 25 mm Hg) and those with precapillary PH (defined as a mPAP ≥ 25 mm Hg, a PAWP ≤ 15 mm Hg, and a PVR > 3 Wood units) [24] stratified by sex.

Covariates

Clinical characteristics representing a comprehensive group of risk factors for the development of PH [24–26] were captured via CART or from VA administrative data [8, 27–29]. Covariates included age, sex, race (black, white, or other which included American Indian, Alaskan Native, Asian, Native Hawaiian, or other Pacific Islander), body mass index (BMI) (categorized as underweight, overweight, obese, and severely obese), history of systemic hypertension, left heart failure (i.e., heart failure due to left ventricular systolic or diastolic dysfunction), congestive heart failure (i.e., heart failure that may include RV or biventricular dysfunction), diabetes mellitus, coronary artery disease (CAD) (considered present if history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or presence of any obstructive disease on cardiac catheterization was present), chronic obstructive pulmonary disease (COPD), human immunodeficiency virus (HIV), liver cirrhosis (viral and non-viral hepatitis), chronic kidney disease (including patients receiving renal replacement therapy), connective tissue disease, atrial fibrillation or flutter, interstitial lung disease, obstructive sleep apnea (OSA) and/or sleep disordered breathing, pulmonary embolism, any valvular disease (regurgitation or stenosis), and tobacco use. Depression and posttraumatic stress disorder (PTSD) were also included as their prevalence varies by sex and they are associated with cardiovascular outcomes and survival in US veterans and other populations [27, 28].

Outcomes

Our primary outcome of interest was survival. A minimum of one year of follow-up survival data was available for all subjects. CART data was combined with longitudinal records.
captured in the VA electronic health record including survival and also linked to claims data outside of the VA system. The Colorado Multiple Institutional Review Board approved this study.

## Statistical analysis

Continuous data were summarized as median (interquartile range [IQR]) and categorical data was summarized as percentages (frequency) with Kruskal-Wallis or Chi-Square tests for continuous or categorical comparisons respectively. The relationship between sex and hemodynamic outcomes in the two cohorts with PH and precapillary PH was assessed with multivariable linear mixed modeling and expressed as least square means. Cox proportional hazards models were used to examine the relationship between sex and survival in the PH and precapillary PH cohorts. Kaplan Meier plots were constructed stratified by sex for both groups.

All linear mixed models included a random intercept for hospital site and were adjusted for multiple covariates of interest (detailed above) including: age, sex, race, BMI, history of systemic hypertension, left heart failure and/or congestive heart failure, diabetes mellitus, CAD, COPD, HIV, liver disease, chronic kidney disease/dialysis, connective tissue disease, atrial fibrillation or flutter, interstitial lung disease, OSA and/or sleep disordered breathing, pulmonary embolism, any valvular regurgitation or stenosis, tobacco use, cancer, depression, PTSD, and inpatient status. Chronic kidney disease/dialysis was included in the final Cox models as it had the greatest impact (changing the parameter estimate for sex by > 15%, whereas all others had a much smaller impact, with a change of typically a few percent in all cases).

Finally, exploratory analyses were conducted to determine whether 1) age modified the sex-hemodynamic and sex-survival relationships and 2) whether a significant proportion of the relationship between sex and survival was mediated (explained by) by the hemodynamic variables. We assessed for a sex by age interaction and included an interaction term (sex*age) in the multivariable models when there was evidence of effect modification (p < 0.05) to determine whether there was a change in effect estimates. Age was assessed as both a categorical variable (age < 55, [55–65], and ≥ 65) and a continuous variable.

Modeling for the mediator analysis required that 1) multivariate linear mixed models confirmed that sex was an independent predictor of hemodynamics and 2) Cox proportional hazards modeling demonstrated sex was a significant predictor of survival after adjustment for multiple covariates. A test statistic for mediation was then created using the product method [30,31], such that “a” was the coefficient of sex in a multivariate mixed model with the hemodynamic mediator of interest as the outcome and “b” was the coefficient of the hemodynamic mediator in the adjusted Cox model for survival:

\[
Z_{\text{statistic}} = \frac{\text{numerator}}{\text{denominator}},
\]
where
\[
\text{Numerator} = \left( a \div \text{standard error of } a \right) \times \left( b \div \text{standard error of } b \right)
\]
\[
\text{Denominator} = \sqrt{\left[ a^2 \div (\text{standard error of } b)^2 + b^2 \div (\text{standard error of } b)^2 + 1 \right]}
\]

The Z statistic was then compared to the percentiles of a standard normal distribution, and mediation was considered significant if \( p < 0.05 \).

Each hemodynamic variable was treated as a separate hypothesis, and therefore modeled independently in all models. Data preparation and analyses were conducted using SAS version 9.4 (SAS Institute, Cary North Carolina) and R version 3.3.1. Statistical significance was defined as \( p < 0.05 \).

**Results**

We identified 28,775 index RHC records available for analysis in which subjects had mPAP \( \geq 25 \) mm Hg. Of these, \( N = 15,464 \) (54%) had CO recorded (by Fick, thermodilution, or both). The final dataset included 22 subjects (0.1%) who were assigned a corrected hemodynamic measurement based on ancillary data (i.e., values that could be confirmed in the medical record or could be calculated from other variables). The final study population included 15,464 subjects with PH, 516 (3%) of whom were women. There were 1,942 (13%) subjects with precapillary PH, 120 (6%) of whom were women.

Characteristics of the two study cohorts are presented in Tables 1 and 2, respectively, by sex. Among those with PH, women tended to be younger, black, more severely obese (BMI \( \geq 33.5 \) kg/m\(^2\)) and were less likely to have systemic hypertension as compared to men (Table 1). While these differences were highly statistically significant due to the large sample size, the relative proportions were similar. As expected, men were much more likely to have a diagnosis of left heart failure, CAD, atrial fibrillation and chronic kidney disease while women were much more likely to have a diagnosis of depression. There were similar rates of pulmonary comorbidities and PTSD, while men were more likely to have been inpatients during cardiac catheterization and have cancer. In those with precapillary PH, these observations were similar (Table 2). Women with precapillary PH were more likely to have a history of connective tissue disease than men with precapillary PH (13.3% vs. 4.4%, \( p < 0.001 \)).

Unadjusted median (IQR) hemodynamic values by sex are presented in Table 3 for the cohorts. There were moderate elevations in pulmonary pressures across all groups. Women with PH had higher PVR and PAPP and lower PAWP and right atrial pressure (RAP) \( (p < 0.001 \) for all) compared to men (Table 4). For example, women with PH tended to have approximately a 1 mm Hg lower RAP (-0.9 mm difference, 95% confidence interval [CI] -1.4 to -0.4 mm Hg, \( p < 0.001 \)) and a 2 mm Hg higher PAPP (1.9 mm Hg difference, 95% CI 0.9 to 2.8, \( p < 0.001 \)) as compared to men with PH controlling for demographics, body size, medical comorbidities, inpatient status, and site. In the cohort with precapillary PH, there were no significant differences in hemodynamics although effect estimates and trends were similar (higher PVR and PAPP, lower PAWP and RAP in women compared to men) in this smaller sample. Despite higher levels of pulmonary afterload (PVR and PAPP) in women with precapillary PH, there were no differences in RV diastolic pressures between men and women (\( p = 0.78 \)) with precapillary PH.

Women with PH had 18% increased survival compared to men with PH (hazard ratio [HR] 0.82, 95% CI 0.69–0.97, \( p = 0.020 \)) after adjustment for multiple clinical variables and potential confounders. Similarly, in the precapillary PH subgroup women had a 29% reduction in the
risk of death as compared to men although precision was decreased for this comparison due to a smaller sample size (HR 0.71, 95% CI 0.52–0.98, p = 0.040). Figs 1 and 2 demonstrate the Kaplan-Meier survival curves for PH and precapillary PH respectively for up to 1750 days after RHC.

After confirming that sex was significantly associated with both hemodynamics and survival in the PH cohort, we sought to determine if hemodynamics explained a significant proportion of the sex-survival relationship in those with PH. None of the hemodynamic parameters met the threshold for mediation (data not shown; p > 0.05 for all). In our

| Variable | All | Women | Men | P value |
|----------|-----|-------|-----|---------|
| Number   | 15464 | 516  | 14948 |         |
| Age, years | 65.2 (60.4,73.3) | 59.3 (53.3,66.9) | 65.3 (60.6,73.5) | <0.001 |
| Race, % (n) | White | 73.3 (11333) | 60.7 (313) | 73.7 (11020) | <0.001 |
| | Black | 19.6 (3038) | 31.6 (163) | 19.2 (2875) |        |
| | Other | 7.1 (1093) | 7.8 (40) | 7.0 (1053) |        |
| Body mass index, % (n) | Normal (18.5–25 kg/m²) | 17.6 (2725) | 17.4 (90) | 17.6 (2635) | <0.001 |
| | Underweight (<18.5 kg/m²) | 0.9 (133) | 2.1 (11) | 0.8 (122) |        |
| | Overweight (25–30 kg/m²) | 29.5 (4561) | 23.6 (122) | 29.7 (4439) |        |
| | Obese (30–35 kg/m²) | 24.7 (3814) | 23.8 (123) | 24.7 (3691) |        |
| | Severely obese (≥35 kg/m²) | 27.4 (4231) | 32.9 (170) | 27.2 (4061) |        |
| Systemic hypertension, % (n) | 89.9 (13901) | 82.9 (428) | 90.1 (13473) | <0.001 |
| Diabetes mellitus, % (n) | 52.6 (8131) | 44.8 (231) | 52.8 (7900) | <0.001 |
| Tobacco use, % (n) | 59.3 (9171) | 47.9 (247) | 59.7 (8924) | <0.001 |

Cardiac conditions

| Condition | All | Women | Men | P value |
|-----------|-----|-------|-----|---------|
| Congestive heart failure, % (n) | 69.4 (10728) | 56.2 (290) | 69.8 (10438) | <0.001 |
| Left heart failure, % (n) | 15.2 (2347) | 9.1 (47) | 15.4 (2300) | <0.001 |
| Coronary artery disease, % (n) | 57.9 (8957) | 30.4 (157) | 58.9 (8800) | <0.001 |
| Valvular disease, % (n) | 39.4 (6066) | 37.6 (194) | 39.4 (5892) | 0.432 |
| Atrial fibrillation or flutter, % (n) | 33.3 (5145) | 19.6 (101) | 33.7 (5044) | <0.001 |

Pulmonary conditions

| Condition | All | Women | Men | P value |
|-----------|-----|-------|-----|---------|
| COPD, % (n) | 38.0 (5882) | 32.9 (170) | 38.2 (5712) | 0.017 |
| Obstructive sleep apnea, % (n) | 13.3 (2062) | 12.4 (64) | 13.4 (1998) | 0.571 |
| Pulmonary embolism, % (n) | 3.9 (602) | 5.4 (28) | 3.8 (574) | 0.086 |

Systemic conditions

| Condition | All | Women | Men | P value |
|-----------|-----|-------|-----|---------|
| Chronic kidney disease, % (n) | 35.2 (5442) | 18.2 (94) | 35.8 (5348) | <0.001 |
| HIV infection, % (n) | 0.5 (79) | 0.2 (1) | 0.5 (78) | 0.476 |
| Liver cirrhosis, % (n) | 7.4 (1139) | 5.8 (30) | 7.4 (1109) | 0.198 |
| Connective tissue disease, % (n) | 3.0 (465) | 10.3 (53) | 2.8 (412) | <0.001 |
| Sickle cell anemia, % (n) | 0.0 (6) | 0.2 (1) | 0.0 (5) | 0.495 |
| Posttraumatic stress disorder, % (n) | 13.5 (2082) | 13.2 (68) | 13.5 (2014) | 0.899 |
| Depression, % (n) | 27.9 (4311) | 44.2 (228) | 27.3 (4083) | <0.001 |
| Inpatient status, % (n) | 52.1 (8063) | 43.4 (224) | 52.4 (7839) | <0.001 |
| Active cancer, % (n) | 16.2 (2504) | 11.4 (59) | 16.4 (2445) | 0.003 |

*Defined as a mean pulmonary artery pressure ≥ 25 mm Hg. Data are shown as % (n) or median (interquartile range). COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus

https://doi.org/10.1371/journal.pone.0187734.t001
exploratory analyses age did not modify the associations seen between sex and hemodynamics or sex and survival (data not shown).

**Discussion**

In a large cohort of US veterans with PH women have different hemodynamic profiles and improved survival compared to men. Hemodynamics in women were characterized by a more compensatory RV response (lower RAP) despite increased afterload (higher PVR, higher PAPP) as compared to men; assessment for age-related interactions did not influence these
results. Sex-based hemodynamic and survival differences persisted after adjustment for multiple comorbid conditions and potential confounders. In veterans with precapillary PH, survival differences persisted and hemodynamic patterns were similar, although not statistically significant. The difference in survival between women and men with PH was not mediated by the

Table 3. Unadjusted hemodynamic variables for pulmonary hypertension cohort and precapillary pulmonary hypertension subgroup, by sex.

| Variable      | Pulmonary hypertension* | Precapillary pulmonary hypertension† |
|---------------|-------------------------|-------------------------------------|
|               | N missing               | All       | Women     | Men       | P value | N missing | All       | Women     | Men       | P value  |
| RAP, mm Hg    |                         | 143 (120) | 12.0 (8.0,15.0) | 10.0 (7.0,14.0) | <0.001 | 10 (8.0,10.0) | 8.0 (5.0,10.0) | 8.0 (5.0,10.0) | 0.908 |
| mPAP, mm Hg   |                         | 0 (34.0) | 34.0 (29.0,41.0) | 33.0 (28.8,40.0) | 0.731 | 0 (32.0,40.0) | 32.0 (28.0,41.0) | 32.0 (28.0,40.0) | 0.907 |
| PAWP, mm Hg   |                         | 0 (21.0) | 21.0 (16.0,26.0) | 19.0 (14.0,25.0) | <0.001 | 0 (12.0,9.0) | 12.0 (9.0,14.0) | 12.0 (9.0,14.0) | 0.555 |
| CI, L/min/m²  |                         | 0 (2.3)  | 2.3 (1.9,2.8) | 4.0 (3.0,5.0) | 0.856 | 0 (2.2,3.0) | 2.2 (1.9,2.6) | 2.2 (1.9,2.6) | 0.008 |
| PVR, Wood units |                 | 46 (2.5) | 2.5 (1.7,3.8) | 3.1 (2.0,4.6) | 0.448 | 0 (4.6) | 4.9 (3.8,7.0) | 4.5 (3.6,6.5) | 0.189 |
| PAPP, mm Hg   |                         | 34 (28.0) | 28.0 (21.0,35.0) | 27.0 (22.0,35.8) | 0.448 | 8 (31.0) | 31.0 (24.0,40.0) | 31.0 (24.0,40.0) | 0.575 |

* Defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg;
† Defined as a mPAP ≥ 25 mm Hg, a pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg, and a pulmonary vascular resistance (PVR) > 3 Wood units; RAP = right atrial pressure; CI = cardiac index; PAPP = pulmonary artery pulse pressure.

https://doi.org/10.1371/journal.pone.0187734.t003

Table 4. Associations between sex and hemodynamics in pulmonary hypertension * cohort and precapillary pulmonary hypertension subgroup after multivariable adjustment‡.

| Variable      | Pulmonary hypertension* | Precapillary pulmonary hypertension† |
|---------------|-------------------------|-------------------------------------|
|               | Women       | Men       | Difference, women vs. men | P value | Women       | Men       | Difference, women vs. men | P value |
| RAP, mm Hg    | 12.3 (11.6,12.9) | 13.2 (12.7,13.7) | -0.9 (-1.4,-0.4) | <0.001 | 8.1 (7.0,9.2) | 8.2 (7.4,9.0) | -0.2 (-1.0,0.7) | 0.710 |
| mPAP, mm Hg   | 36.3 (35.4,37.3) | 36.0 (35.3,36.7) | 0.4 (-0.4,1.1) | 0.352 | 35.9 (33.7,38.0) | 36.7 (35.1,38.3) | -0.8 (-2.5,0.8) | 0.318 |
| PAWP, mm Hg   | 19.1 (18.3,20.0) | 20.6 (20.0,21.3) | -1.5 (-2.1,-0.9) | <0.0001 | 10.8 (10.1,11.6) | 10.5 (9.9,11.1) | 0.3 (-0.3,0.9) | 0.278 |
| CI, L/min/m²  | 2.6 (2.5,2.7) | 2.6 (2.5,2.6) | 0.0 (0.0,0.1) | 0.132 | 2.5 (2.3,2.6) | 2.4 (2.3,2.5) | 0.1 (0.0,0.2) | 0.154 |
| PVR, Wood units | 4.2 (4.0,4.5) | 3.4 (3.2,3.6) | 0.8 (0.6,1.0) | <0.0001 | 6.1 (5.4,6.8) | 5.8 (5.3,6.3) | 0.3 (-0.3,0.8) | 0.283 |
| PAPP, mm Hg   | 32.0 (30.7,33.2) | 30.1 (29.2,31.0) | 1.9 (0.9,2.8) | 0.0001 | 37.2 (34.1,40.3) | 36.7 (34.5,39.0) | 0.5 (-1.9,2.9) | 0.700 |

Data are presented as least square means estimates (95% confidence interval).
* Defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg;
† Defined as a mPAP ≥ 25 mm Hg, a pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg, and a pulmonary vascular resistance (PVR) > 3 Wood units; RAP = right atrial pressure; CI = cardiac index; PAPP = pulmonary artery pulse pressure.
‡ Models included a random intercept for hospital site and were adjusted for age, sex, race, body mass index, systemic hypertension, left heart failure and/or congestive heart failure, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, human immunodeficiency virus infection, liver disease, chronic kidney disease, connective tissue disease, atrial fibrillation or flutter, interstitial lung disease, obstructive sleep apnea and/or sleep disordered breathing, pulmonary embolism, any valvular disease, tobacco use, cancer, depression, posttraumatic stress disorder, and inpatient status.

https://doi.org/10.1371/journal.pone.0187734.t004
hemodynamic differences observed by sex. These results suggest distinct sex-based phenotypes in an unselected, population-based cohort of veterans with elevated pulmonary pressures.

Female sex is a well-known risk factor for WHO Group 1 PAH, but recent epidemiologic data suggests that men with PAH have poorer survival than women with PAH [4, 11, 12]. Hormonal regulation of cardiopulmonary function, sex-based differences in response to PAH therapy [32, 33], or differences in RV adaptation have been proposed as possible explanations for these observations. RV function has been identified as a major determinant of outcome in PAH, but also in PH due to left heart disease [5–7]. Heart failure with preserved ejection fraction (HFpEF) is more common in women [34, 35], yet women are less likely to develop RV dysfunction than men with HFpEF [13]. In idiopathic PAH, women have greater improvements in RV function with PAH therapy despite similar reductions in PVR as compared to men, and sex-based differences in the RV response explain a significant portion of the survival benefit seen in women as compared to men [36]. Women demonstrated lower RAP as compared to men in our study. Elevated RAP occurs in RV failure and has been consistently
associated with poor survival in pulmonary vascular disease [15,16]. The associations demonstrated here are akin to earlier observations from "pure" WHO Group 1 PAH patients as well as patients with HFpEF and presumed pulmonary venous (or postcapillary) PH, suggesting persistent sex-based phenotypes across all types of pulmonary vascular disease.

The principal determinant of RV afterload is classically thought of as PVR, but more recently stiffening of large pulmonary arteries has also been shown to be important. Our findings that survival in women with PH was increased compared to men with PH despite higher PVR and higher PAPP (a measurement of RV loading) suggests that sex-specific RV adaptation patterns may exist and account for differences in survival. These data provide a clinical correlate to converging lines of experimental data showing a favorable effect by estrogen on pulmonary artery-RV coupling in PH in vivo [37–39]. In the systemic circulation, female sex and sex hormones have been proposed to contribute to vascular-ventricular coupling as well [40,41]. Assessment of RV function was limited to central hemodynamic measurements in our...
study and hemodynamic differences did not mediate the survival differences observed, perhaps due to sample or effect size limitations; more robust measures of RV morphology (e.g., echocardiography or cardiac magnetic resonance imaging) may have improved sensitivity to detect such relationships.

While our observations are certainly not generalizable to WHO Group 1 PAH, our findings may be more representative of a “real world” population of patients with PH. In fact, subgroups of classically idiopathic PAH, pre- and post-capillary PH patients may have similar genetic features and hemodynamic derangements that contribute to poor outcomes in all groups [3, 42]. These clinical phenotypes may represent a spectrum of pulmonary vascular abnormalities with shared pathobiologic mechanisms. As in right heart failure, women with left heart failure have a better prognosis, but this is not explained by the etiology of heart failure or degree of left ventricular dysfunction [43–46] (interestingly PAWP was lower in women than in men in our study). It is plausible that sex-based prevalence and outcome differences in left heart failure are driven by differences in pulmonary hemodynamics and the right heart and that sex and/or sex hormones may play an important role in PH regardless of how it is classified clinically.

We failed to detect any significant interactions between sex and age for the outcomes of hemodynamics or survival, which may be due to the low number of younger age subjects (particularly women) in this population. We have previously shown that in clinical trial participants with WHO Group 1 PAH, men had greater hemodynamic burden (including higher RAP, as seen here, but also higher mPAP and PVR) as compared to women, but some of these differences were attenuated after age 45 [18]. In REVEAL, men with PAH had higher RAP and mPAP at diagnosis (as well as worse survival especially in those older than 60 years of age) as compared to women with PAH [12–14]. These observations have not been consistent across all WHO Group 1 PAH registries [47,48], however, and it is therefore not surprising that our results from an unselected veteran population would be somewhat inconsistent with prior reports. Given the average age of the study subjects, it is likely that almost all women included were post-menopausal. Although we do not have confirmation of menopausal status, the inclusion of pre-menopausal women in the study sample were this data available may have provided additional insights.

There was a greater proportion of black women compared to men in both the PH and the precapillary PH groups. Observational studies have shown a more exaggerated female predominance among blacks as compared to whites with WHO Group 1 PAH [2,16]. Outcomes in both right and left heart failure may be poorer in blacks, there are baseline differences in RV structure in function that vary by race/ethnicity in health, and we have shown a strong relationship between echocardiographic PH and heart failure admissions among black participants from the Jackson Heart Study [9, 49–51]. It is somewhat surprising then that women had improved survival compared to men given the baseline differences in race, although the models for both hemodynamics and survival accounted for race in the PH and precapillary PH groups.

Study limitations include those inherent to a retrospective cross-sectional study with data derived from electronic records. Still, excellent quality control is maintained in the CART database [20] and we undertook additional steps to ensure physiologic plausibility of all hemodynamic values assessed. There was a very small amount of missing data and at least one year of follow-up was required with confirmed survival status in the VA electronic health record and via outside claims data. Our study population was middle-aged US veterans with multiple medical comorbidities, roughly 50% of whom were inpatient during their right heart catheterizations, making “pure” WHO Group classification difficult and increasing the likelihood of confounding by indication and selection bias. Detailed data on medication use, including use
of targeted PAH therapies, was not available. We adjusted for many factors and comorbid conditions that varied by sex as well as inpatient status with persistence of our findings, but residual confounding could certainly still exist and explain our findings.

The cohorts were predominantly male (reflecting the population of all US veterans) and the subset with precapillary PH was modest (n = 1930, with n = 120 women), limiting our power to detect hemodynamic differences in this group. The hemodynamic differences observed between men and women were small, raising the question of clinical relevance. We do not have repeated hemodynamic measures over time or additional measures of RV function (e.g., echocardiography or magnetic resonance imaging), both of which would potentially lend greater insight to our cross-sectional observations. CART does represent to our knowledge the largest available database of hemodynamics worldwide with extensive complementary information available on patient demographics, anthropometrics, and all comorbid conditions relevant to the pulmonary circulation, however, and the sample size still dwarfs those available in WHO Group 1 PAH (a rarer condition with much smaller cohorts of hemodynamic information available).

In summary, our data demonstrate clinical, hemodynamic, and outcome differences by sex among a general population of US veterans with elevated pulmonary pressures. Women have improved survival compared to men with PH and precapillary PH despite higher PVR and PAPP, which is perhaps explained by better RV adaptation. This work should generate additional hypotheses about unique sex-based phenotypes in all forms of pulmonary vascular disease.

Disclaimer
The views expressed are those of the authors alone and do not represent the views of the Veterans Affairs or other Federal government agencies.

Author Contributions
Conceptualization: Corey E. Ventetuolo, Eric D. Austin, Tim Lahm, Gaurav Choudhary, Bradley A. Maron.

Data curation: Edward Hess, Anna E. Barón, Mary E. Plomondon, Gaurav Choudhary, Bradley A. Maron.

Formal analysis: Edward Hess, Anna E. Barón, Mary E. Plomondon.

Investigation: Corey E. Ventetuolo, Roham T. Zamanian.

Methodology: Corey E. Ventetuolo, Tim Lahm, Thomas M. Maddox, Bradley A. Maron.

Writing – original draft: Corey E. Ventetuolo, Bradley A. Maron.

Writing – review & editing: Corey E. Ventetuolo, Eric D. Austin, Anna E. Barón, James R. Klinger, Tim Lahm, Thomas M. Maddox, Mary E. Plomondon, Lauren Thompson, Roham T. Zamanian, Gaurav Choudhary, Bradley A. Maron.

References
1. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013; 62:029.
2. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, et al. Pulmonary arterial hypertension: Baseline characteristics from the REVEAL registry. Chest. 2010; 137:376–387. https://doi.org/10.1378/chest.09-1140 PMID: 19937821
3. Opitz CF, Hoepner MM, Gibbs JS, Kaemmerer H, Pepke-Zaba J, Coghlan JG, et al. Pre-Capillary, combined, and post-capillary pulmonary hypertension: a pathophysiologic continuum. J Am Coll Cardiol. 2016; 68:368–78. https://doi.org/10.1016/j.jacc.2016.05.047 PMID: 27443433

4. Hyduk A, Croft J, Ayala C, Zheng K, Zheng Z and Mensah G. Pulmonary hypertension surveillance—United States, 1980–2002. MMWR Survell Summ. 2005; 54:1–28.

5. Meyer P, Filippatos GS, Ahmed MI, Iskandrian AE, Bittner V, Perry GJ, et al. Effects of right ventricular ejection fraction on outcomes in chronic systolic heart failure. Circulation. 2010; 121:252–8. https://doi.org/10.1161/CIRCULATIONAHA.109.887570 PMID: 20048206

6. Mohammed SF, Hussain I, Abou Ezzeddine OF, Takahama H, Kwon SH, Forfia P, et al. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. Circulation. 2014; 130:2310–20. https://doi.org/10.1161/CIRCULATIONAHA.113.008461 PMID: 25391518

7. Morrison DA, Adcock K, Collins CM, Goldman S, Caldwell JH and Schwarz MI. Right ventricular dysfunction and the exercise limitation of chronic obstructive pulmonary disease. J Am Coll Cardiol. 1987; 9:1219–29. PMID: 3584714

8. Maron BA, Hess E, Maddox TM, Opotowsky AR, Tedford RJ, Lahm T, et al. Association of borderline pulmonary hypertension with mortality and hospitalization in a large patient cohort: insights from the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. Circulation. 2016; 133:1240–8. https://doi.org/10.1161/CIRCULATIONAHA.115.020207 PMID: 26873944

9. Choudhary G, Jankowich M and Wu WC. Elevated pulmonary artery systolic pressure predicts heart failure admissions in African Americans: Jackson Heart Study. Circ Heart Fail. 2014; 7:558–64. https://doi.org/10.1016/j.chjf.2014.04.007 PMID: 24902739

10. Kawut SM, Al-Naamani N, Agerstrand C, Berman Rosenzweig E, Rowan C, Barst RJ, et al. Determinants of right ventricular ejection fraction in pulmonary arterial hypertension. Chest. 2009; 135:752–759. https://doi.org/10.1378/chest.08-1758 PMID: 18849396

11. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation. 2010; 122:156–163. https://doi.org/10.1161/CIRCULATIONAHA.110.991181 PMID: 20585011

12. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation. 2010; 122:164–172. https://doi.org/10.1161/CIRCULATIONAHA.109.911181 PMID: 20585012

13. Melovansky V, Hwang SJ, Lin G, Redfield MM and Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J. 2014; 35:3452–62. https://doi.org/10.1093/eurheartj/ehu193 PMID: 24875795

14. Shapiro S, Traiger GL, Turner M, McGoon MD, Wason P and Barst RJ. Sex differences in the diagnosis, treatment, and outcome of patients with pulmonary arterial hypertension enrolled in the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (CHEST). 2012; 141:363–373. https://doi.org/10.1378/chest.10-3114 PMID: 21757572

15. McLaughlin VV, Shillington A and Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation. 2002; 106:1477–1482. PMID: 12234951

16. D’Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991; 115:343–9. PMID: 18630263

17. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Hervé P, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: Prognostic factors and survival. J Am Coll Cardiol. 2002; 40:780–788. PMID: 12204511

18. Ventetuolo CE, Praestgaard A, Palevsky HJ, Klinger JR, Halpem SD and Kawut SM. Sex and haemodynamics in pulmonary arterial hypertension. Eur Respir J. 2014; 43:523–30. https://doi.org/10.1183/09031936.00027613 PMID: 23949961

19. Maddox TM, Plomondon ME, Petrich M, Tsai TT, Gethoffer H, Noonan G, et al. A national clinical quality program for Veterans Affairs catheterization laboratories (from the Veterans Affairs clinical assessment, reporting, and tracking program). Am J Cardiol. 2014; 114:1750–7. https://doi.org/10.1016/j.amjcard.2014.08.045 PMID: 25439452

20. Byrd JB, Vigen R, Plomondon ME, Rumsfeld JS, Box TL, Fihn SD, et al. Data quality of an electronic health record tool to support VA cardiac catheterization laboratory quality improvement: the VA Clinical Assessment, Reporting, and Tracking System for Cath Labs (CART) program. Am J Heart. 2013; 165:434–40. https://doi.org/10.1016/j.ajh.2012.12.009 PMID: 23453115
Sex differences in veterans with PH

21. Brindis RG, Fitzgerald S, Anderson HV, Shaw RE, Weintraub WS and Williams JF. The American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR): building a national clinical data repository. J Am Coll Cardiol. 2001; 37:2240–5. PMID: 11419906

22. Blyth KG, Syed R, Chalmers J, Foster JE, Saba T, Naeije R, et al. Pulmonary arterial pressure and mortality in pulmonary arterial hypertension. Resp Med. 2007; 101:2495–501.

23. Castelain V, Herve P, Lecarpentier Y, Duroux P, Simonneau G and Chemla D. Pulmonary artery pulse pressure and wave reflection in chronic pulmonary thromboembolism and primary pulmonary hypertension. J Am Coll Cardiol. 2001; 37:1085–92. PMID: 11263613

24. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol. 2013; 62:D42–50. https://doi.org/10.1016/j.jacc.2013.10.032 PMID: 24355641

25. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension. Circulation. 2009; 119:2250–2294. https://doi.org/10.1161/CIRCULATIONAHA.109.192230 PMID: 19332472

26. Galié N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2015; 46:903–975. https://doi.org/10.1183/13993003.01032-2015 PMID: 26318161

27. Davis MB, Maddox TM, Langner P, Plomondon ME, Rumsfeld JS and Duvernoy CS. Characteristics and outcomes of women veterans undergoing cardiac catheterization in the Veterans Affairs Healthcare System: insights from the VA CART Program. Circ Cardiovasc Qual Outcomes. 2015; 8:S39–47. https://doi.org/10.1161/CIRCOUTCOMES.114.001613 PMID: 25714820

28. Bradley SM, Stanislawska MA, Bekelman DB, Monteleth LL, Cohen BE, Schilling JH, et al Invasive coronary procedure use and outcomes among veterans with posttraumatic stress disorder: insights from the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. Am Heart J. 2014; 168:381–390.e6. https://doi.org/10.1016/j.ahj.2014.05.015 PMID: 25173551

29. Bradley SM, Maddox TM, Stanislawska MA, O’Donnell CI, Grunwald GK, Tsai TT, et al. Normal coronary rates for elective angiography in the Veterans Affairs Healthcare System: insights from the VA CART program (Veterans Affairs Clinical Assessment Reporting and Tracking). J Am Coll Cardiol. 2014; 63:417–26. https://doi.org/10.1016/j.jacc.2013.09.055 PMID: 24184244

30. Iacobucci D. Mediation analysis and categorical variables: the final frontier. J Consum Psychol. 2012; 22:582–594.

31. VanderWeele TJ. Causal mediation analysis with survival data. Epidemiology. 2011; 22:582–5. https://doi.org/10.1097/EDE.0b013e31821db37e PMID: 21642779

32. Mathai SC, Hassoun PM, Puhua MA, Zhou Y and Wise RA. Gender differences in response to tadalafil in pulmonary arterial hyperten ion. Chest. 2015; 145:1230–6. https://doi.org/10.1378/chest.13-1291 PMID: 24306900

33. Lahm T, Frump AL, Albrecht ME, Fisher AJ, Cook TG, Jones TJ, et al. 17beta-Estradiol mediates superior adaptation of right ventricular function to acute strenuous exercise in female rats with severe pulmonary hypertension. Am J Physiol Lung Mol Cell Physiol. 2016; 311:L375–88.

34. Liu A, Tian L, Golob M, Eickhoff JC, Boston M and Chesler NC. 17beta-estradiol attenuates conduit pulmonary artery mechanical property changes with pulmonary arterial hypertension. Hypertension. 2015; 66:1082–8. https://doi.org/10.1161/HYPERTENSIONAHA.115.05843 PMID: 26418020

35. Frump AL, Goss KN, Vayl A, Albrecht M, Fisher A, Tursunova R, et al. Estradiol improves right ventricular function in rats with severe angioproliferative pulmonary hypertension: effects of endogenous and exogenous sex hormones. Am J Physiol Lung Cell Mol Physiol. 2015; 308:L873–90. https://doi.org/10.1152/ajplung.00006.2015 PMID: 25713318

36. Jacobs W, van de Veerdonk MC, Trip P, de Man F, Heymans MW, Marcus JT, et al. The right ventricle explains sex differences in survival in idiopathic pulmonary arterial hypertension. Chest. 2014; 145:1230–6. https://doi.org/10.1378/chest.13-1291 PMID: 24306900

37. Lane AD, Yan H, Ranadive SM, Kappus RM, Sun P, Cook MD, et al. Sex differences in ventricular-vascular coupling following endurance training. Eur J Appl Physiol. 2014; 114:2597–606. https://doi.org/10.1007/s00421-014-2981-z PMID: 25142819
41. Najjar SS, Schulman SP, Gerstenblith G, Fleg JL, Kass DA, O’Connor F, et al. Age and gender affect ventricular-vascular coupling during aerobic exercise. J Am Coll Cardiol. 2004; 44:611–7. https://doi.org/10.1016/j.jacc.2004.04.041 PMID: 15358029

42. Assad TR, Hennes AR, Larkin EK, Glazer AM, Xu M, Wells QS, et al. Clinical and biological insights into combined post- and pre-capillary pulmonary hypertension. J Am Coll Cardiol. 2016; 68:2525–2536. https://doi.org/10.1016/j.jacc.2016.09.942 PMID: 27931609

43. Frazier CG, Alexander KP, Newby LK, Anderson S, Iverson E, Packer M, et al. Associations of gender and etiology with outcomes in heart failure with systolic dysfunction: a pooled analysis of 5 randomized control trials. J Am Coll Cardiol. 2007; 49:1450–8. https://doi.org/10.1016/j.jacc.2006.11.041 PMID: 17397674

44. Ho KK, Anderson KM, Kannel WB, Grossman W and Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation. 1993; 88:107–15. PMID: 8319323

45. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-term trends in the incidence of and survival with heart failure. New Engl J Med. 2002; 347:1397–402. https://doi.org/10.1056/NEJMoao20265 PMID: 12409541

46. O’Meara E, Clayton T, McIntegart MB, McMurray JJ, Pina IL, Granger CB, et al. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Circulation. 2007; 115:3111–20. https://doi.org/10.1161/CIRCULATIONAHA.106.673442 PMID: 17562950

47. Ling Y, Johnson MK, Kiely DG, Condille R, Elliott CA, Gibbs JS, et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. Am J Respir Crit Care Med. 2012; 186:790–6. https://doi.org/10.1164/rcrm.201203-0383OC PMID: 22798326

48. Zhang R, Dai LZ, Xie WP, Yu ZX, Wu BX, Pan L, et al. Survival of Chinese patients with pulmonary arterial hypertension in the modern treatment era. Chest. 2011; 140:301–9. https://doi.org/10.1378/chest.10-2227 PMID: 21330386

49. Davis KK, Lillientfeld DE and Doyle RL. Increased mortality in African Americans with idiopathic pulmonary arterial hypertension. J Natl Med Assoc. 2008; 100:69–72. PMID: 18277811

50. Kawut SM, Lima JAC, Barr RG, Chahal H, Jain A, Tandri H, et al. Sex and race differences in right ventricular structure and function: the Multi-Ethnic Study of Atherosclerosis-Right Ventricle Study. Circulation. 2011; 123:2542–2551. https://doi.org/10.1161/CIRCULATIONAHA.110.985515 PMID: 21646505

51. Dries DL, Strong MH, Cooper RS and Drazner MH. Efficacy of angiotensin-converting enzyme inhibition in reducing progression from asymptomatic left ventricular dysfunction to symptomatic heart failure in black and white patients. J Am Coll Cardiol. 2002; 40:311–317. PMID: 12106937