CHEST

Original Research

PULMONARY VASCULAR DISEASE

The Right Ventricle Explains Sex Differences in Survival in Idiopathic Pulmonary Arterial Hypertension

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Background: **Male sex is an independent predictor of worse survival in pulmonary arterial hypertension (PAH). This finding might be explained by more severe pulmonary vascular disease, worse right ventricular (RV) function, or different response to therapy. The aim of this study was to investigate the underlying cause of sex differences in survival in patients treated for PAH.**

Methods: **This was a retrospective cohort study of 101 patients with PAH (82 idiopathic, 15 heritable, four anorexigen associated) who were diagnosed at VU University Medical Centre between February 1999 and January 2011 and underwent right-sided heart catheterization and cardiac MRI to assess RV function. Change in pulmonary vascular resistance (PVR) was taken as a measure of treatment response in the pulmonary vasculature, whereas change in RV ejection fraction (RVEF) was used to assess RV response to therapy.**

Results: **PVR and RVEF were comparable between men and women at baseline; however, male patients had a worse transplant-free survival compared with female patients (*P* = .002). Although male and female patients showed a similar reduction in PVR after 1 year, RVEF improved in female patients, whereas it deteriorated in male patients. In a mediator analysis, after correcting for confounders, 39.0% of the difference in transplant-free survival between men and women was mediated through changes in RVEF after initiating PAH medical therapies.**

Conclusions: **This study suggests that differences in RVEF response with initiation of medical therapy in idiopathic PAH explain a significant portion of the worse survival seen in men.**

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Abbreviations: 6MWD = 6-min walk distance; CMR = cardiac MRI; CO = cardiac output; GFR = glomerular filtration rate; IPAH = idiopathic pulmonary arterial hypertension; IQR = interquartile range; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RHC = right-sided heart catheterization; RV = right ventricular; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVSV = right ventricular stroke volume; VUMC = VU University Medical Centre; WHO = World Health Organization

Pulmonary arterial hypertension (PAH) is a rare disease characterized by obstructive lesions of the small pulmonary vessels, leading to increased pulmonary artery pressure (PAP), right-sided heart failure, and death within several years.[1,2] Despite the advent of improved therapies, outcome remains poor.[3,4] Prognosis correlates with severity of right ventricular (RV) structure and function.[2,5] More recently, male sex was identified as an independent predictor of mortality.[6-10] Men treated with endothelin receptor antagonists had less 6-min walk distance (6MWD) improvement.[11] The cause of these sex differences is unknown; however, a distinct vascular and/or RV response to medical therapies is one possibility. Considering the need for improved treatments and "personalized therapy,"

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a better understanding of these sex differences would be important. The aim of our study was to investigate the role of the pulmonary vasculature and the right ventricle in explaining sex differences in the survival

of treated idiopathic pulmonary arterial hypertension (IPAH).

Materials and Methods

Study Design and Patients

All patients with IPAH, anorexigen-associated PAH, and heritable PAH treated at the VU University Medical Centre (VUMC) between February 1999 and January 2011 were eligible. Diagnosis was according to the guidelines and included right-sided heart catheterization (RHC). Medical treatment comprised prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors either alone or in various combinations. Patients with a positive vasodilator challenge were treated with calcium antagonists.[1] This was a retrospective cohort study of patients enrolled in an ongoing prospective study to assess the clinical value of cardiac MRI (CMR) in PAH. All patients who had RHC and CMR performed prior to initiation of medical therapy (101 out of 186 patients evaluated during this period) were included.

Right-Sided Heart Catheterization

Hemodynamic assessment was performed with a 7F balloon-tipped flow-directed Swan-Ganz catheter (131HF7; Baxter). Baseline and follow-up RHC measurements of PAP, right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) were obtained. Pulmonary vascular resistance (PVR) was calculated as ($80 \times$ [meanPAP − PCWP]/CO). Vasoreactivity testing was with inhaled nitric oxide (20 parts per million). Acute vasoreactivity was defined as a mean PAP reduction ≥ 10 mm Hg to reach an absolute value ≤ 40 mm Hg with increased or unchanged CO.

Cardiac MRI

CMR was performed on a Siemens Avanto 1.5 T and 1.5 T Sonata scanner (Siemens AG), equipped with a six-element phased-array coil. ECG-gated cine imaging was performed using a balanced steady, free precession pulse sequence, during repeated breath-holds. Short-axis slices were obtained, with slice thickness 5 mm and interslice gap 5 mm, fully covering both ventricles from base to apex. Temporal slice resolution was between 35 and 45 milliseconds, voxel size was $1.8 \times 1.3 \times 5.0$ mm^3, flip angle was 60°, receiver bandwidth was 930 Hz/pixel, repetition time/echo time was 3.2/1.6 milliseconds, and matrix was 256×156.

End-diastolic and end-systolic endocardial and epicardial contours were delineated manually by an observer blinded to other clinical information and processed using MASS software (Department of Radiology, Leiden University Medical Center) to obtain RV end-diastolic and RV end-systolic volumes (RVEDV and RVESV, respectively) and RV mass. Papillary muscles and trabeculae were excluded from the cavity and included in RV mass. RV stroke volume (RVSV) and ejection fraction (RVEF) were calculated: RVSV = RVEDV − RVESV and RVEF = RVSV/RVEDV.[12] RV mass/RVEDV was used as a measure of relative RV wall thickness.[13,14]

Data Analysis

Measurements are reported as mean ± SD and median (interquartile range [IQR]) where appropriate. Continuous variables were compared using Student *t* tests or Mann-Whitney *U*, where not normally distributed. Categorical variables were compared using Pearson χ^2 tests and Fisher exact tests, as needed.

Follow-up was until September 2011. Transplant-free sex survival differences were confirmed using Kaplan-Meier curves and log-rank test. Confounders were accounted for by Cox regression. Variables leading to a $\geq 10\%$ change in the coefficient for sex were included in the final survival prediction model. Variables screened for confounding included age, height, weight, World Health Organization (WHO) functional class, number of comorbidities (1, 2, and ≥ 3), RVEF, RV wall thickness, glomerular filtration rate ([GFR] Cockroft), PVR, and type of medical therapy used (prostacyclin yes/no, endothelin receptor antagonist yes/no, and phosphodiesterase type 5 inhibitor yes/no).

Sex differences in secondary treatment outcomes (N-terminal pro-brain natriuretic peptide [Nt-proBNP] level, 6MWD, and renal function), RHC hemodynamics, and CMR were confirmed using linear regression with the follow-up measurement as the dependent variable and the baseline measurement and sex as independent variables. WHO class change differences were confirmed by ordinal regression. Multiple imputation was used for missing follow-up MRI scan variables. We multiply imputed 100 datasets. Linear regression models were estimated in each dataset and regression coefficients and SEs pooled, and the *P* value of each coefficient in the model was determined. To correct for confounders, a similar approach was used as discussed previously for the survival analysis.

An exploratory mediator analysis was done to confirm that transplant-free sex survival differences were mediated through differences in RVEF change. Analysis was done according to Baron and Kenny[15] and consists of three steps. In step 1, sex was confirmed as an independent predictor of transplant-free survival by Cox regression. Step 2 was to confirm that sex was an independent predictor of the proposed mediator by linear regression. Step 3 uses a Cox regression model for transplant-free survival including sex and the potential mediator as independent variables, and its purpose is to confirm the proposed mediator is a significant predictor of survival, while controlling for sex. RVEF and PVR changes were both examined as potential mediators. This was done by adding follow-up measurements of, respectively, RVEF and PVR to a Cox regression equation containing sex and the baseline value. A $>10\%$ change in the coefficient of sex after adding the follow-up value of the proposed mediator was accepted as evidence of significant mediation. The magnitude of the indirect (mediated) effect was calculated according to the following formula:

$$\text{Indirect effect} = 1 - (c'/c)$$

In the formula, c is the coefficient for sex in the Cox regression formula predicting survival, corrected for baseline RVEF; c′ is the

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