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,”

For editorial comment see page 1184

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 $(80 \times [\text{mean PAP} - \text{PCWP}]/\text{CO})$. 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 $1.8 \times 1.3 \times 5.0$ mm³, 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: $\text{RVSV} = \text{RVEDV} - \text{RVESV}$ and $\text{RVEF} = \text{RVSV}/\text{RVEDV}$.¹² RV mass/RVEDV was used as a measure of relative RV wall thickness.^{13,14}

Data Analysis

Measurements are reported as mean $\pm$ 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] Cockcroft), 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 Kenny¹⁵ 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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coefficient for sex in the Cox regression formula predicting survival corrected for RVEF baseline value and RVEF change by adding the follow-up RVEF value to the equation. In addition, a mediator analysis corrected for all potential confounders mentioned earlier was performed.¹⁶

Analyses were performed using SPSS statistics 19.0 software (IBM). This study was approved by the VUMC research and ethics review boards, and informed consent was obtained (approval number, 2012288).

RESULTS

Patient Characteristics and Treatments

One hundred eighty-six patients (155 IPAH, 25 heritable PAH, and six anorexigen-associated PAH) were treated at the VUMC between February 1999 and January 2011. Eight-five patients were excluded. Reasons for exclusion were no MRI because of logistical reasons ($n = 44$), first-line treatment elsewhere ($n = 25$), contraindications for MRI ($n = 11$), and no PAH medication initiated ($n = 5$). Apart from age, e-Table 1 indicates similar characteristics compared with those included for further analysis ($n = 101$). The 6MWD tended to be greater in those included; however, the % predicted distance was similar.

The remaining 101 patients all had CMR and RHC at baseline before starting PAH-specific medical therapies (Table 1). In these patients, men had larger RVEDV and RVESV but had similar invasively measured hemodynamics and similar RVSV and RVEF compared with women. Median (IQR) time between baseline CMR and RHC was 0.2 (0.0-1.95) months.

e-Table 2 depicts prescribed medications between baseline and follow-up assessment. Follow-up CMR and RHC were performed after 1.1 (0.9-1.7) and 1.1 (0.9-2.2) years, respectively. Time on PAH-specific medication was 5.4 (2.1-7.7) years. Time to addition of other PAH-specific therapy was 5.0 (2.3-6.0) months for those patients who had PAH-specific drugs added before follow-up measurements.

Survival and Secondary Treatment Outcomes

In the 101 patients included, median (IQR) follow-up time was 5.7 (2.5-8.1) years, and there were 26 deaths and five lung transplants. In men, cumulative transplant-free survival was 84% at 1 year and 57% at 5 years. In women, survival was 100% at 1 year and 85% at 5 years (log-rank $P = .002$; hazard ratio, 3.04; 95% CI, 1.45-6.41) (Fig 1). The association between sex and survival after adjustment for confounders in multivariate analysis remained (hazard ratio, 7.21; 95% CI, 4.18-12.43; $P < .001$). The confounders retained in the final model were height, GFR, and WHO functional class. Male patients had higher NT-proBNP level, lower 6MWD, and more severe functional class at follow-up in basic (Table 2) and covariate-adjusted (Table 3) models.

Table 1—Baseline Patient Characteristics and RHC and CMR Measurements in Male and Female Patients With Pulmonary Arterial Hypertension

Characteristic	Male (n = 26)	Female (n = 75)	P Value
Age, y	50 ± 19	47 ± 15	.31
Idiopathic PAH	23 (88)	59 (79)	.55
Heritable PAH	3 (12)	12 (16)	.75
Anorexigen PAH	0 (0)	4 (5)	.57
BMI, kg/m ²	27 ± 3	26 ± 6	.34
WHO FC			.09
Class I	1 (4)	0 (0)	
Class II	7 (27)	12 (16)	
Class III	13 (50)	40 (53)	
Class IV	5 (19)	23 (31)	
Comorbidities			.82
0	9 (35)	25 (33)	
1	6 (23)	26 (35)	
2	8 (31)	12 (16)	
≥ 3	3 (12)	12 (16)	
6MWD, m	388 ± 189	353 ± 150	.40
6MWD, % predicted	62 ± 27	61 ± 23	.82
Creatinine, mmol/L	110 ± 27	94 ± 17	.001
GFR, mL/min	88 ± 31	75 ± 19	.01
NT-proBNP, ng/L ^a	1,414 ± 1,668	1,887 ± 1,913	.34
RHC			
RAP, mm Hg	10 ± 6	9 ± 5	.11
mPAP, mm Hg	53 ± 15	57 ± 13	.29
PCWP, mm Hg	8 ± 4	8 ± 5	.65
CO, L/min	4.73 ± 1.63	4.55 ± 1.63	.61
PVR, dyn × s × cm ⁵	903 ± 545	963 ± 473	.61
Acute vasoreactivity ^b	3/23 (13%)	7/66 (11%)	.71
CMR			
RVEDV, mL	177 ± 68	137 ± 41	.001
RVEDV index, mL/m ²	89 ± 36	76 ± 21	.03
RVESV, mL	124 ± 54	93 ± 35	.001
RVESV index, mL/m ²	62 ± 28	52 ± 19	.04
RVEF, %	31 ± 13	33 ± 11	.44
RVSV, mL	53 ± 30	44 ± 19	.38
RVSV index, mL/m ²	27 ± 17	25 ± 10	.38
RV mass, g	104 ± 41	81 ± 28	.009
RV mass/RVEDV, g/mL	0.64 ± 0.31	0.62 ± 0.23	.75

Data are presented as No. (%) or mean ± SD unless otherwise noted. CMR volumes are also provided indexed for body surface area. RV mass/RVEDV is a measure of relative RV wall thickness. 6MWD = 6-min walk distance; CMR = cardiac MRI; CO = cardiac output; GFR = glomerular filtration rate; mPAP = mean pulmonary artery pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; 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. WHO FC = World Health Organization functional class.

^aNT-proBNP was measured in a subgroup of men ($n = 20$) and women ($n = 52$).

^bAcute vasoreactivity was measured in a subgroup of women ($n = 66$) and men ($n = 23$).

RHC Hemodynamics and CMR

RHC showed no significant differences in treatment response associated with sex (Tables 2, 3). Median PVR changes (IQR) were −78 (−523 to +10)

FIGURE 1. Transplant-free survival in male (solid line) and female (dashed line) patients with pulmonary arterial hypertension starting first-line pulmonary arterial hypertension-specific therapies ($P = .002$).

$\text{dyn} \times \text{s} \times \text{cm}^5$ in men and -165 (-436 to $+92$) $\text{dyn} \times \text{s} \times \text{cm}^5$ in women.

Eighty patients had baseline and follow-up CMR performed. Reasons for not performing follow-up measurements in men were as follows: patient deceased ($n = 3$), patient follow-up < 1 year ($n = 3$), patient too disabled to undergo CMR ($n = 3$), and unknown ($n = 1$). In women, these were patient refusal ($n = 4$), patient follow-up < 1 year ($n = 3$), patient too disabled ($n = 2$), psychiatric disorder ($n = 1$), and technical CMR problem ($n = 1$). Corrections for missing follow-up measurements were made by multiple imputation.

After the baseline assessment, RVEF decreased in men (median, [IQR]) -1.0% (-11.9% to $+6.9\%$) and increased in women $+3.6\%$ (-3.0% to $+13.0\%$).

Tables 2 and 3 depict results of univariate and multivariate analysis of sex difference in CMR changes. Calculated RVEF change corrected for confounders was $-1.8\% \pm 6.5\%$ in men and $+5.3\% \pm 5.4\%$ in women ($P < .001$).

Mediator Analysis

Step 1 and step 2 of the mediator analysis were reported in the Materials and Methods section. In step 1, sex was confirmed as an independent predictor of survival. In step 2, sex was confirmed as an independent predictor of RVEF change. Results of step 3 are reported in Table 4, which shows the results of Cox regression for transplant-free survival with sex and the baseline value of the potential mediator. The B coefficient of sex changed substantially after RVEF follow-up measurements were added to the equation and significance of sex as predictor of transplant-free survival was lost, thus showing evidence that the impact of sex on survival was mediated through RVEF at follow-up. There is no evidence for mediation through PVR changes, as the B coefficient for sex remains similar in the Cox regression formula with sex and baseline PVR compared with the formula with sex, baseline PVR, and follow-up PVR. The amount of change in B for sex after adding follow-up values of RVEF or PVR to the Cox regression equation gives a sense of how much of the variance in outcome associated with sex is explained by changes of each hemodynamic parameter. In the basic model, 42.8% of the effect of sex on survival was mediated through RVEF. After adjustment for confounders, this was 39.0%.

Table 2—Results of Linear Regression of Sex Differences in RHC, MRI, and Other Secondary Treatment Outcome Parameters Corrected for the Baseline Value

Parameter	Difference for Men vs Women in Follow-up Measure After Adjustment for Baseline	95% CI	P Value
NT-proBNP, ng/L	+1,385	+482 to +2,288	$< .01$
6MWD, m	-71	-123 to -19	$< .01$
Creatinine, mmol/L	+17	+6 to +29	$< .01$
GFR, mL/min	-5	-11 to +1	.12
WHO FC	+1.4	+0.4 to +2.3	$< .01$
Heart rate, beats/min	+3	-7 to +13	.56
RAP, mm Hg	+2	-1 to +6	.17
mPAP, mm Hg	+1	-7 to +9	.81
CO, L/min	+0.2	-1 to +1	.78
Stroke volume, mL	-4	-19 to +11	.59
PVR, $\text{dyn} \times \text{s} \times \text{cm}^5$	-60	-301 to +182	.63
RVEF, %	-8.1	-14 to -2	$< .01$
RVEDV, mL	+11.9	-5 to +29	.18
RVESV, mL	+13.8	-2 to +30	.09
RVSV, mL	-5.5	-14 to +3	.19
RV mass, g	+2.9	-12 to +18	.70
RV mass/RVEDV, g/mL	+0.04	-0.09 to +0.16	.57

See Table 1 legend for expansion of abbreviations.

Table 3—Results of Multivariate Analysis^a of Sex-Specific RHC, MRI, and Other Treatment Outcome Parameter Changes Compared With Baseline

Parameter	Difference for Men vs Women in Follow-up Measure After Adjustment for Baseline and Confounders	95% CI	P Value
NT-proBNP, ng/L	+1,385	+482 to +2,288	< .01
6MWD, m	−70	−127 to −12	.02
Creatinine, mmol/L	+14	+3 to +25	.01
GFR, mL/min	−6	−13 to 0	.05
WHO FC	+1.9	+0.9 to +3.0	< .001
Heart rate, beats/min	+5	−7 to +17	.42
RAP, mm Hg	+2	−1 to +6	.25
mean PAP, mm Hg	+2	−8 to +11	.73
CO, L/min	+0.0	−1 to +1	.99
Stroke volume, mL	−7	−24 to +11	.45
PVR, dyn × s × cm ⁵	−35	−337 to +267	.82
RVEF, %	−7.2	−13 to −1	.02
RVEDV, mL	−0.4	−19 to +18	.97
RVESV, mL	+5.2	−13 to +23	.58
RVSV, mL	−9.5	−19 to 0	.04
RV mass, g	+3.8	−13 to +21	.67
RV mass/RVEDV, g/mL	+0.09	−0.05 to +0.24	.22

^aMultivariate analysis results corrected for potential confounding by age, weight, height, number of comorbidities, baseline RVEF, GFR, PVR, WHO FC, and type of PAH-specific medical therapy initiated. See Table 1 legend for expansion of abbreviations.

DISCUSSION

Our data confirmed previous findings of worse outcome in men.⁶ This survival difference was not associated with either baseline characteristics or differences in responsiveness of the pulmonary vascular bed to therapy but rather with differences in RVEF after starting medical therapies. Brain natriuretic peptide changes are correlated with RV strain and RVEF measured by CMR, and the brain natriuretic peptide differences found in our study further support our CMR findings.^{17–19} In an earlier study, RVEF change difference between survivors and nonsurvivors in PAH was 8%, further illustrating that the difference found in our study is clinically meaningful.²⁰

Sex differences have been well documented in diseases of the left ventricle. In the Framingham study, worse survival was observed in male patients with heart failure.²¹ Systolic heart failure is predominantly found in men, whereas women present with heart failure with preserved ejection fraction.²² In analogy, female pressure-loaded hearts showed more preserved ejection fractions in aortic stenosis.²³ In a study of patients with hypertension, left ventricular mass variance explained by arterial BP was much higher in women. This could be interpreted as further evidence of better cardiac adaptation in women.²⁴

Little is known about sex differences in disease of the right ventricle. Healthy women have lower RV mass, smaller RV volumes, and higher RVEF than men.²⁵ Ventetuolo et al²⁶ showed an association between higher estradiol levels and improved RVEF in women and an association between increased androgen levels

and increased RV mass and RV volumes. In a rodent model, testosterone and estradiol both caused pulmonary vasodilation.²⁷ In male mice, testosterone affected RV hypertrophic stress response after pulmonary artery banding through increased myocyte size and increased fibrosis. Testosterone deprivation through castration improved survival in these mice.²⁸ In addition, estrogen and estrogen receptor agonist therapy restored RV structure and function in a rodent model of monocrotaline-induced PH.²⁹

Our study found no differences in pulmonary vascular responses to PAH-specific medications. Hitherto, no other studies in humans reported on sex differences in pulmonary vascular response, to our knowledge. We found no sex differences in CO, and this further points out the problems with only looking at resting CO, rather than at RV structure and RV systolic function (RVEF). During disease progression, resting CO can be maintained through an increased heart rate. In addition, stroke volume can be relatively preserved through the Starling mechanism. However, in progressive RV dilation, RVEF will decrease and RVEF may be a more sensitive parameter for disease progression.² It cannot be ruled out that CO differences do occur with exercise.

Our study has some limitations. Not all patients evaluated at our center were included. Although those included appeared similar to those excluded, selection bias could still be possible. We attempted to account for a variety of confounders; however, we cannot exclude residual or unmeasured confounding. There were some missing data; we used multiple imputation

Table 4—Results from Cox Regression for Transplant-Free Survival With, Respectively, Sex and the Baseline Measurement and Subsequently Sex, the Baseline Measurement, and the Follow-up Measurement for, Respectively, RVEF and PVR

Variable	B	Exp (B)	95% CI of Exp (B)	P Value
A				
Sex (male vs female)	1.029	2.80	1.33-5.91	.007
Baseline RVEF	−0.05	0.95	0.92-0.99	.007
Sex	0.589	1.80	0.81-4.01	.15
Baseline RVEF	−0.01	0.99	0.95-1.04	.81
Follow-up RVEF	−0.07	0.94	0.89-0.98	.006
B				
Sex	1.397	4.04	2.50-6.54	.004
Baseline RVEF	−0.05	0.95	0.93-0.97	.009
Sex	0.852	2.34	0.93-5.92	.07
Baseline RVEF	−0.01	0.99	0.95-1.04	.76
Follow-up RVEF	−0.07	0.94	0.89-0.98	.006
A				
Sex	1.11	3.04	2.08-4.45	.003
Baseline PVR	0.00	1.00	1.00-1.00	.95
Sex	1.20	3.31	1.53-7.16	.002
Baseline PVR	0.00	1.00	1.00-1.00	.53
Follow-up PVR	0.00	1.00	1.00-1.00	.12
B				
Sex	1.51	4.52	1.83-11.18	.001
Baseline PVR	0.00	1.00	1.00-1.00	.84
Sex	1.476	4.38	1.77-10.84	.001
Baseline PVR	0.00	1.00	1.00-1.00	.48
Follow-up PVR	0.00	1.00	1.00-1.00	.19

Crude analysis (A) and analysis including corrections for confounders (B) are reported. Exp = exponent. See Table 1 legend for expansion of other abbreviations.

to allow inclusion of all subjects in the study sample in all analyses. Finally, this is an observational study, preventing us from confirming causality; however, the use of sex as our exposure and prospective reassessments of RV function support causal inferences. We only studied the idiopathic, heritable, and anorexigen-associated forms of PAH, so these findings may not be generalizable to other forms of PAH. However, sex differences in survival are also reported in connective tissue disease-associated PAH,³⁰ although in associated PAH the survival difference was limited to elderly patients.⁹ Since RVEF could explain 40% of the observed survival difference, other factors must contribute. However, these factors cannot be identified through our study, as the small patient number prohibits further exploratory analysis.

In conclusion, our study suggests a sex difference in cardiac adaptation to treatment with long-term improvements in RVEF in women but not in men. Mediator analysis suggests this different cardiac adaptation may cause decreased survival in men. To further improve treatments, the pathophysiology of sex differences in cardiac response to medical therapies should further be elucidated. Evidence for differences in cardiac responses in associated forms of PAH should

be studied. Furthermore, the role of sex hormones, and the potential of substances targeting sex-specific pathways, such as estrogen receptor agonists, should be further evaluated.²⁹

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Dr Jacobs: contributed to conceptual design of the study, data analysis planning, data acquisition, interpretation of results, and writing of the manuscript.

Dr van de Veerdonk: contributed to conceptual design of the study, data acquisition, interpretation of results, and writing of the manuscript.

Dr Trip: contributed to conceptual design of the study, data acquisition, interpretation of results, and writing of the manuscript.

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Dr Bogaard: contributed to data acquisition, interpretation of the results, and writing of the manuscript.

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Additional information: The e-Tables can be found in the "Supplemental Materials" area of the online article.

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