Research Article

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Clinical and genetic associations with prostacyclin response in pulmonary arterial hypertension

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Abstract

Parenteral prostacyclin therapy is the most efficacious pharmacologic treatment for pulmonary arterial hypertension (PAH), but clinical response is variable. We sought to identify clinical, hemodynamic, and genetic associations with response to prostacyclin therapy. We performed a retrospective analysis of patients within a de-identified electronic health record and associated DNA biobank. Patients with PAH and a right heart catheterization (RHC) in the six months before initiation of a parenteral prostacyclin were included. Responders were defined a priori by attainment of World Health Organization (WHO) functional class (FC) 2 or better at the time of repeat RHC within two years. We performed exploratory analyses to identify genomic associations with prostacyclin response. Of 129 patients identified, 54 met our criteria for "responders." These patients were younger, more likely to be male, and were less likely to have connective tissue disease-related PAH. At follow-up, responders had improved hemodynamics, 6-min walk distance, and long-term survival. Baseline PA oxygen saturation (hazard ratio [HR] 0.568 [0.34–0.95]) and follow-up FC (HR = 2.57 [1.22–5.43]) were associated with survival. Prostacyclin responders were enriched in alleles related to cell development and circulatory system development and pathways related to aldosterone metabolism, cAMP signaling, and vascular smooth muscle contraction ($P < 0.001$). Age at treatment initiation, WHO FC at short-term follow-up, and PA O_2% are associated with survival in patients with PAH exposed to parenteral prostacyclins. Exploratory genetic analysis yielded associations in biologically relevant pathways in the pathogenesis of PAH.

Keywords

pulmonary artery catheterization, hemodynamics, personalized medicine

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Pulmonary arterial hypertension (PAH) is a highly morbid disease characterized by progressive pulmonary vascular obliteration and remodeling that leads to progressive right heart failure and death.[1] Survival has improved in the modern treatment era, with multiple drugs targeting three pathways now approved for treatment of PAH, but the most efficacious treatments remain the parenteral prostacyclin analogues epoprostenol and treprostinil.[2–4] Despite decades

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of experience with these drugs, relatively little is known about predicting which patients will derive the most benefit. Heterogeneity of response is seen clinically, with some patients living well beyond what would be expected by current risk prediction models, while others rapidly deteriorate despite appropriate treatment.[5]

It would be of value to know which of these patients are likely to respond to prostacyclin therapy, prolonging their survival and improving their functional status, and which patients are less likely to respond, and might therefore benefit from different therapy or early referral for lung transplant evaluation.

Tailoring treatment to patients' clinical and molecular characteristics, or "precision medicine," has garnered significant attention in recent years.[6–11] This concept has precedent in PAH, as the subset of vasodilator responsive patients that have long-term response to calcium channel blockers have been recognized for decades.[12–15] With this concept in mind, we sought to better characterize prostacyclin responders and non-responders. We hypothesized that favorable changes in hemodynamics after initiation of prostacyclin therapy would be associated with improved survival and sought to explore genetic associations with response to therapy.

Methods

Study population

The Vanderbilt Institutional Review Board (no. 140544) approved this study. Patients were identified from Vanderbilt's de-identified electronic health record database, which is linked to a prospective DNA biorepository (BioVU).[16,17] We have previously developed an algorithm for identifying PAH patients using the right heart catheterization (RHC) reports within this database.[18] Patients with RHC hemodynamic variables consistent with PAH (mean pulmonary arterial pressure ≥ 25 mmHg, pulmonary capillary wedge pressure ≤ 15 mmHg, pulmonary vascular resistance ≥ 3 WU) were electronically screened for any mention of epoprostenol or treprostinil within the chart. Those patients with a RHC meeting diagnostic criteria for PAH and any mention of epoprostenol or treprostinil within the medical record were manually reviewed to confirm PAH diagnosis and subtype, date of initiation of parenteral prostacyclin, concomitant PAH therapy, WHO functional class (FC), and 6-min walk distance (6MWD) when available (Suppl. Fig. 1). We restricted our cohort to individuals with a RHC in the six months preceding initial parenteral prostacyclin exposure. Demographic data were extracted from the clinic visit closest to the date of the RHC.

Outcomes

Vital status was confirmed via the Social Security Death Index and manual chart review. Patients were censored at time of death from any cause, date of lung transplant, or date of last Social Security Death Index search (9 January 2017). Responders were defined by attainment of WHO FC 2 or better at the time of repeat RHC within two years of initiation of parenteral prostacyclin, as supported by recent guidelines.[19] Non-responders were defined by WHO FC > 2 at repeat RHC, or death within two years of drug initiation if there was no repeat RHC. It is standard of care at our institution that all patients on prostacyclin therapy undergo repeat RHC approximately one year after initiating therapy. We included only patients with a repeat RHC as responders to test our hypothesis that changes in hemodynamics would be associated with survival.

Genetics data and analysis

Genotyping was performed on the Illumina MEGA^{EX} chip. Only patients of European ancestry were included in genetic analyses, due to limited sample size from other ancestries. Single nucleotide variants (SNVs) with minor allele frequency $<5\%$ were excluded. In total, 630,804 polymorphic SNVs were included in the analysis. A total of 11,397 SNVs with nominal significance ($P < 0.01$) were identified using Fisher's exact test in which prostacyclin responders were compared to non-responders. A list of closest genes associated with the significant SNVs was compiled by ANNOVAR. Pathway analysis was performed on the genes represented by these SNVs using the WEB-based Gene Set Analysis Toolkit (WebGestalt).[20,21] Gene ontology (GO) analysis was performed to determine the presence of significant GO groups (defined as a false discovery rate-$< 5\%$ for this exploratory analysis). To assess if significant SNVs identified in our genome-wide association study corresponded to genetically predicted expression of genes in specific tissues, we carried out an analysis using the Genotype-Tissue Expression (GTEx) project database. See online supplement for full details.

Statistical analysis

Data are expressed as mean $\pm$ standard deviation (SD) or median $\pm$ interquartile range (IQR) for continuous variables, and absolute value and percentage for categorical variables, unless stated otherwise. Differences between two groups were assessed by using the Mann–Whitney U test or Chi-square test, as appropriate. For regression analyses, missing data were excluded. Kaplan–Meier curves with log rank tests were performed for survival analysis. A Cox proportional hazards model was used to identify variables associated with survival based on demographic and hemodynamic values at the baseline RHC ($n = 71$ patients with complete data). Variables in the multivariable models were selected based on published literature and clinical knowledge. In patients with a repeat RHC ≥ 6 months and ≤ 2 years after therapy, a Cox proportional hazards model was used to identify variables associated

with survival at the follow-up RHC (n = 65 patients with complete data). Hazard ratios (HR) are reported comparing the value corresponding to the 25th percentile of the population to the 75th percentile for continuous variables. Multiple logistic regression was used to identify variables associated with survival at five years after initiation of prostacyclin therapy (n = 71 with complete data). Results are reported as odds ratios with 95% confidence intervals (CIs) and *P* values. Statistical analysis was performed using R statistical software (version 3.4.3, R Foundation for Statistical Computing, Vienna, Austria).[22]

Results

Demographics and clinical characteristics

In total, 129 patients were identified with a RHC diagnostic of PAH within six months before starting prostacyclin therapy and either a repeat RHC or death within two years of starting therapy (Table 1). The cohort had advanced disease, with 98% in WHO FC $\geq$ 3, a mean 6MWD of 215 $\pm$ 132 m, and hemodynamics indicative of decompensated right heart failure. Less than half of the cohort was on PAH-directed therapy at the time of prostacyclin initiation, partially due to the fact this cohort begins in 1998, and additional PAH-specific therapy was not available until 2001. The median date of drug initiation was 9 June 2004 (IQR 5/29/2001–4/30/2007). The median duration of follow-up was 4.56 years (IQR = 1.52–7.92 years). The cohort is mostly female (85.3%) and white (91%), with a mean age of 47.4 $\pm$ 12.9 years at the time of parenteral prostacyclin initiation. Idiopathic or heritable PAH was the most common etiology of PAH (50%), followed by PAH associated with connective tissue disease (34%).

We analyzed time to death in patients that had died at the time of study completion. Thirty-four patients (26%) died within two years, but some patients had excellent response to therapy, including nine patients (7%) surviving > 10 years (Fig. 1).

One-hundred and one patients (78%) survived to have a repeat RHC (median time to repeat RHC = 1.04 years, IQR = 0.95–1.31 years). Of these, 54 patients (53%) met our criteria for response by attaining WHO FC $\leq$ 2 (Table 2). Twenty-eight patients (22%) died or progressed to lung transplant before repeat RHC. Responders tended to be younger (42.2 $\pm$ 12.3 vs. 51.1 $\pm$ 12.0 years, $P < 0.001$) and were less likely to have connective tissue disease-associated PAH (20% vs. 44%, $P = 0.04$). Baseline WHO FC and hemodynamics were similar between the two groups, except responders had higher PVR (17.3 $\pm$ 12.7 vs. 13.3 $\pm$ 5.6 WU, $P = 0.025$) (Table 1). Baseline PAH-directed therapy was also similar between the two groups, with the exception of less frequent endothelin receptor antagonist (ERA) use in responders (15% vs. 32%, $P = 0.023$). The median date of drug initiation was similar in responders and non-responders (20 July 2004 vs. 15 March 2004, $P = 0.745$).

Outcomes

Responders vs. non-responders. Patients who achieved FC $\leq$ 2 at the time of repeat RHC had significantly improved survival compared to those who did not ($P < 0.0001$) (Fig. 2). At follow-up, the responders also had significantly longer 6WMD (421 $\pm$ 92 m vs. 319 $\pm$ 105 m, $P < 0.001$) and more favorable hemodynamics, with lower mean right atrial (RA) pressure (6.2 $\pm$ 4.3 mmHg vs. 9.1 $\pm$ 6.0 mmHg, $P = 0.015$) and higher pulmonary artery oxygen saturation (PA O_2%) (67.7 $\pm$ 7.6% vs. 63.3 $\pm$ 8.0%, $P = 0.023$) (Table 2). Other hemodynamics were similar.

Survival. The variables most significantly associated with survival at the RHC before prostacyclin initiation were older age (HR = 3.03 [1.63–5.65]) and higher PA O_2% (HR = 0.568 [0.34–0.95]) (Fig. 3). Gender, race, idiopathic or heritable PAH vs. associated PAH, heart rate, cardiac index (CI), and RA pressure were not associated with survival in multivariable analysis.

Among patients with follow-up RHC data, higher WHO FC at follow-up (HR = 2.57 [1.22–5.43]) and older age at drug initiation (HR = 2.04 [1.01–4.10]) were associated with worsened survival (Fig. 4). When these were included in multivariable analysis, no hemodynamic values were significantly associated with survival. However, when only hemodynamic variables were considered in the multivariable analysis, higher PA O_2% (HR = 0.54 [0.32–0.91]) was associated with survival.

The effects of age, gender, etiology of PAH, mean RA pressure, CI, PA O_2%, and heart rate on survival at five years were analyzed in all patients in a logistic regression model. For this population, the C-statistic was 0.787 and R^2 of 0.304. The corrected C-statistic was 0.646 (Suppl. Table 1).

Genetic analysis. Among the 32 patients with European ancestry and available MEGA^{EX} chip genotyping, 16 met criteria for responders and 16 were non-responders. After annotating SNVs to the nearest gene, 1275 genes had different frequencies of common allelic variants between the groups at a level of $P < 0.01$. GO analysis revealed significant enrichment in genes related to cell development, cell adhesion, circulatory system development, and proteoglycan metabolic process (Table 3). Significant pathways included glutamatergic synapse, aldosterone synthesis and secretion, calcium signaling, insulin secretion, cAMP signaling, and vascular smooth muscle contraction (Table 4).

We assessed whether the SNVs identified had functional relevance to the pulmonary vascular system. GTEx annotation of nominally significant SNVs by genome-wide association study identified enriched expression of genes in

Table 1. Baseline characteristics of the cohort.

	PAH patients treated with parenteral prostacyclin (n = 129)	Patients achieving WHO FC 2 or better at repeat RHC (n = 54)	Patients with WHO FC > 2 or deceased (n = 75)	*P* value responders vs. non-responders
Age (years)	47.4 ± 12.9	42.2 ± 12.3	51.1 ± 12.0	<0.001
Gender (female)	85.30	42 (78)	68 (91)	0.042
Ethnicity				0.371
Asian	1 (1)	1 (2)	0	
Black	9 (7)	3 (6)	6 (8)	
Hispanic	2 (2)	0	2 (3)	
White	117 (91)	50 (93)	67 (89)	
Etiology				0.04
Heritable	10 (8)	8 (15)	2 (3)	
Idiopathic	54 (42)	24 (44)	30 (40)	
Congenital heart disease	6 (5)	4 (7)	2 (3)	
HIV	4 (3)	2 (4)	2 (3)	
Connective tissue disease	44 (34)	11 (20)	33 (44)	
Portopulmonary	8 (6)	4 (7)	4 (5)	
Anorexigen/ stimulant	3 (2)	1 (2)	2 (3)	
6MWD (m)	215 ± 132	276 ± 123	174 ± 123	0.002
WHO FC before prostanoid therapy				0.579
2	2 (2)	1 (2)	1 (1)	
3	67 (52)	29 (54)	38 (51)	
4	59 (46)	24 (44)	35 (47)	
Heart rate	81 ± 13	79.4 ± 12.6	82.25 ± 13.5	0.293
RAP (mmHg)	12.9 ± 5.9	12.3 ± 6.5	13.4 ± 5.4	0.216
mPAP (mmHg)	58.4 ± 12.9	60.1 ± 14.7	57.1 ± 11.2	0.264
PVR (WU)	15.0 ± 9.5	17.3 ± 12.7	13.3 ± 5.6	0.025
Cardiac index (L/min/m^2)	1.95 ± 0.6	1.82 ± 0.5	2.0 ± 0.6	0.059
Pulmonary artery oxygen saturation	56.2 ± 9.5	55.9 ± 10.0	56.4 ± 9.2	0.948
Stroke volume index (mL/m^2)	24.8 ± 9.1	23.7 ± 8.2	25.6 ± 9.6	0.435
Treatment before prostanoid Therapy				
PDE5 inhibitors	19 (15)	7 (13)	12 (16)	0.609
ERA	32 (25)	8 (15)	24 (32)	0.023
Inhaled/Oral prostacyclin analog	9 (7)	3 (6)	6 (8)	0.577
Calcium channel blocker	29 (23)	10 (19)	19 (26)	0.339
Warfarin	42 (33)	19 (35)	23 (31)	0.625

Values are presented as mean ± SD or n (%).

PAH, pulmonary arterial hypertension; HIV, human immunodeficiency virus; WHO, World Health Organization; PDE5, phosphodiesterase type 5; ERA, endothelin receptor antagonist; 6MWD, 6-min walk distance; RAP, right atrial pressure; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance.

multiple tissues including the heart and lung ($P = 2 \times 10^{-6}$ and $P = 6 \times 10^{-4}$, respectively (Suppl. Fig. 1).

Discussion

In this study, we identified clinical, hemodynamic, and genetic associations with long-term survival in PAH patients treated with parenteral prostacyclins. This is a highly morbid population, reflected by 26% of patients dying within two years, but some had remarkable improvement with treatment, and survival upwards of 15 years (Figs. 1 and 2). We found that older patients and those with connective tissue disease-associated PAH were less likely to achieve FC 2 at short-term follow-up. We also found that age, PA O_2%, and FC at follow-up were associated with survival (Fig. 3 and 4). Exploratory genetic comparison between responders and non-responders revealed statistically significant differences in several GO groups and pathways, and GTEx analysis revealed enriched genetically predicted expression in multiple tissues, including heart and lung.

We chose attainment of FC 2 at follow-up as the definition of response because it would represent meaningful

clinical improvement for 98% of our cohort based on their FC before treatment, whereas achievement of FC 1 may be an unrealistic threshold for patients with severe disease at baseline. The use of FC as the sole criteria has limitations, such as relatively poor inter-observer reliability, but has the advantage of being universally available for our cohort, whereas other markers of response, such as 6MWD and brain natriuretic peptide were frequently not available.[23] Notably, all FC assessments were made by the same two providers throughout the study period.

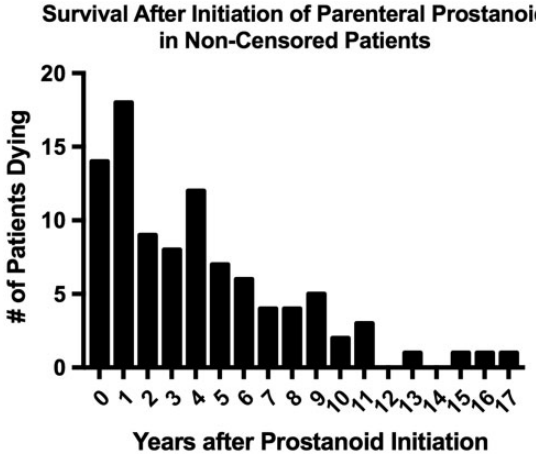

Fig. 1. Histogram displaying survival (in years) of non-censored patients after initiation of parenteral prostanoids.

Age at drug initiation was most strongly associated with survival, a trend seen in contemporary studies in the modern treatment era. Age did not have a significant association with survival in previous PAH cohorts, such as the NIH or French Registries, but in a recent study from the French Registry age at diagnosis was highly significant.[24–26] The REVEAL registry associated poor survival with men aged > 60 years; previous experience at our institution has also suggested that age is an important factor in patients treated with epoprostenol.[27,28] This may be reflective of older patients having more advanced disease at the time of treatment initiation, but may also be due to the fact that PAH treatment is more efficacious now than 20 years ago and older patients may have worse survival due to co-morbidities rather than PAH alone.

When we examined factors associated with survival after initiation of treatment, WHO FC was most significant, which has been seen consistently in PAH studies, although age at drug initiation remained significant as well.[24]

We also found that higher PA O_2% was associated with survival, both before and after initiation of treatment, when

Table 2. Characteristics of parenteral prostacyclin responders and non-responders at follow-up.

	Patients achieving WHO FC 2 or better at repeat RHC (n = 54)	Patients with WHO FC > 2 or deceased (n = 75)	*P* value
6MWD (m) at repeat RHC	421 ± 92	319 ± 105	<0.001
WHO FC at repeat RHC			
1	12 (22)	0	
2	42 (78)	0	
3	0	44 (59)	
4	0	3 (4)	
Dead (no repeat RHC)	0	28 (37)	
Heart rate	79.4 ± 12.6	82.3 ± 13.5	0.29
RAP (mmHg)	6.2 ± 4.3	9.1 ± 6.0	0.015
mPAP (mmHg)	47.7 ± 13.4	48.5 ± 11.3	0.62
PVR (WU)	9.02 ± 5.5	9.18 ± 4.1	0.45
Cardiac index (L/min/m^2)	2.6 ± 0.6	2.5 ± 0.8	0.072
Pulmonary artery oxygen saturation	67.7 ± 7.6	63.3 ± 8.0	0.023
Stroke volume index (mL/m^2)	32.1 ± 9.9	28.9 ± 10.2	0.088
Additional treatment after prostanoid therapy			
PDE5 inhibitors	9 (17)	12 (26)	0.27
ERA	6 (11)	7 (15)	0.57
Inhaled/Oral prostacyclin analog	0	0	1
Warfarin	42 (78)	34 (72)	0.53

Values are presented as mean ± SD or n (%). Hemodynamic variables and medications are from follow-up RHC.
WHO, World Health Organization; FC, functional class; RHC, right heart catheterization; HIV, human immunodeficiency virus; PDE5, phosphodiesterase type 5; ERA, endothelin receptor antagonist; 6MWD, 6-min walk distance; RAP, right atrial pressure; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance.

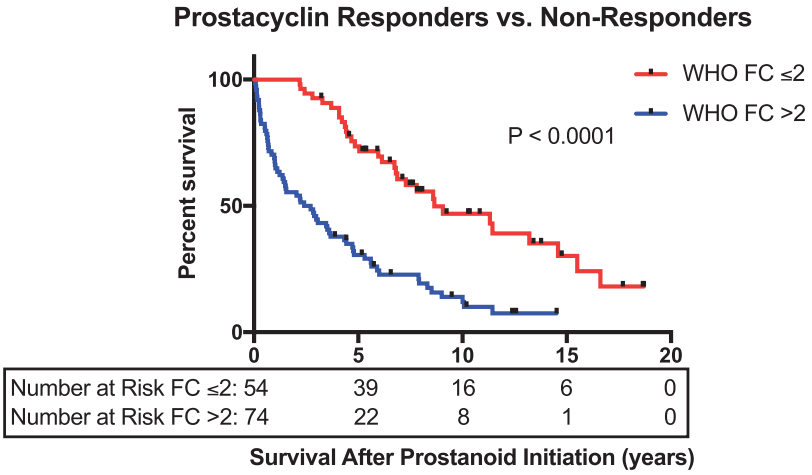

Fig. 2. Unadjusted survival between parenteral prostacyclin responders and non-responders ($P < 0.0001$ by log-rank test).

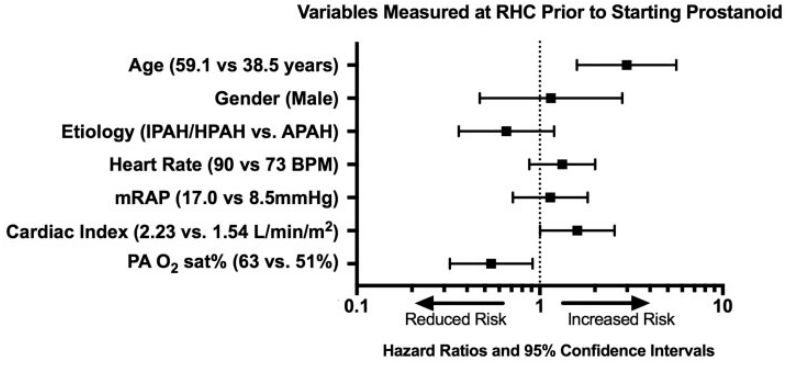

Fig. 3. Forest plot of HRs and 95% CIs of variables included in the Cox proportional hazards model from the RHC before starting parenteral prostacyclin. RHC, right heart catheterization; IPAH, idiopathic pulmonary arterial hypertension; HPAH, heritable PAH; APAH, associated PAH; BPM, beats per minute; mRAP, mean right atrial pressure; PA O_2 sat %, pulmonary artery oxygen % saturation.

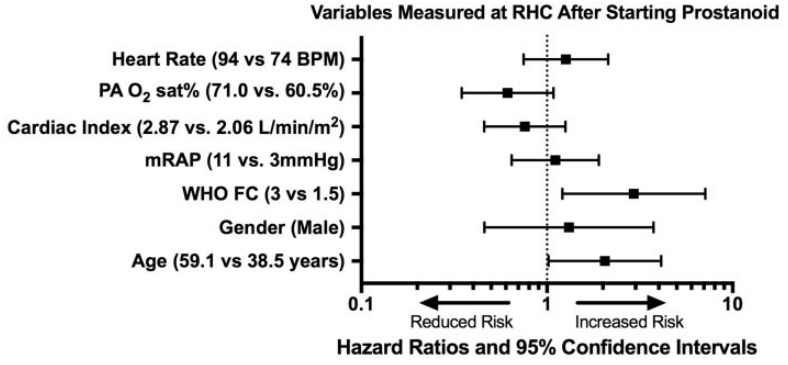

Fig. 4. Forest plot of HRs and 95% CIs of variables included in the Cox proportional hazards model from the RHC after starting parenteral prostacyclin. See Fig. 3 for acronym definitions. WHO FC, World Health Organization functional class.

WHO FC was excluded from multivariable analysis. We interpret this to signify that WHO FC, a comprehensive assessment of clinical status, is the best measurement of response to therapy, and PA O_2% is likely collinear with FC as a marker of right heart failure. Other studies have shown various markers of RV failure, such as CI, stroke volume index, RA pressure, and brain natriuretic peptide to be associated with survival in PAH, but most have not reported mixed venous or PA O_2% in their analyses or incorporated it in into predictive models.[3,24–27,29]

Table 3. Significant GO groups identified in 1275 genes significantly different ($P < 0.01$) between responders and non-responders.

GO group (SNV $P < 0.01$)	Genes in GO group (n)	Observed variant genes in GO group (n)	Expected variant genes in GO group (n)	*P* value	False discovery rate
Generation of neurons	1319	112	63.5	1.67×10^{-9}	8.94×10^{-6}
Cell development	1857	144	89.4	2.89×10^{-9}	8.94×10^{-6}
Cell adhesion	1667	123	80.3	7.83×10^{-7}	5.58×10^{-4}
Circulatory system development	920	75	44.3	4.84×10^{-6}	2.18×10^{-3}
Proteoglycan metabolic process	85	15	4.1	1.17×10^{-5}	4.35×10^{-3}

Table 4. Significant KEGG pathways identified in 1275 genes significantly different ($P < 0.01$) between responders and non-responders.

KEGG pathway (SNV $P < 0.01$)	Genes in KEGG pathway (n)	Observed variant genes in KEGG pathway (n)	Expected variant genes in KEGG pathway (n)	*P* value	False discovery rate
Glutamatergic synapse	114	19	5.54	1.96×10^{-6}	5.94×10^{-4}
Aldosterone synthesis and secretion	82	14	3.98	3.38×10^{-5}	3.4×10^{-3}
Calcium signaling	182	20	8.84	4.96×10^{-4}	0.019
Insulin secretion	85	12	4.13	7.58×10^{-4}	0.021
cAMP signaling	200	20	9.71	1.62×10^{-3}	0.031
Vascular smooth muscle contraction	121	14	5.88	2.09×10^{-3}	0.036

Four previous studies have specifically examined prognostic features associated with parenteral prostacyclin treatment.[3,28–30] In comparing our results to these studies, it becomes clear that PAH etiology, baseline WHO FC, and improvement in FC after treatment are the most consistent predictors of survival in patients treated with parenteral prostacyclins, followed by objective measures of right heart failure. In all of these studies, patients with less severe disease at baseline had improved long-term outcomes; this suggests that earlier treatment initiation may be more likely to be efficacious.[3,28–30] Our study adds to this literature by having the longest follow-up period to date, which may partially explain why we found age to be predictive of survival, whereas other studies with shorter follow-up did not. The finding that previous ERA use was more common in non-responders is interesting and hypothesis generating, but was not controlled for in multivariate analysis and must be interpreted as such. It has previously been established that combination bosentan and parenteral epoprostenol is not superior to parenteral therapy alone.[31]

The availability of genotyping data from a subset of this cohort allowed us to perform an exploratory genetic analysis. In doing so, we found significant enrichment in genes related to aldosterone synthesis and secretion, insulin secretion, cAMP signaling, and vascular smooth muscle contraction. The role of aldosterone in PAH has been studied by several groups, with mounting evidence that it contributes to PAH pathobiology.[32–34] Multicenter trials of spironolactone in PAH are currently recruiting patients (Clinicaltrials.gov; NCT02253394, NCT01712620). Prostacyclin causes vasodilation via cAMP as a second messenger; which raises hypotheses for a potential mechanism for the observed heterogeneity of response to treatment.[35,36] Our group also has a longstanding interest in the role of insulin resistance and diabetes in PAH patients and have found these to be prevalent and associated with worse prognosis.[37–39] These data suggest genetic differences in biologically relevant pathways may play a role in PAH prognosis and response to treatment, and merits further study in larger groups of patients with available genetic data as a pathway to precision medicine in PAH.

Limitations

This is a single-center observational study from a large regional referral center for PAH. This study encompasses >18 years of experience with PAH patients, which spans several eras of PAH treatment and the introduction of many new therapies. The present study does not account for inherit immortal time bias caused by the changes in management of PAH that occurred over the study period. The median date of prostacyclin initiation in our study (2004) was after the availability of oral agents and was similar between groups, but the characteristics of patients treated with parenteral prostacyclins may have changed over the study period. Further, some groups of patients are not

well represented in our cohort, e.g. sickle cell disease, and thus our data cannot be extrapolated to all subtypes of PAH.

This cohort also consists primarily of idiopathic, heritable, and connective tissue disease-related PAH, which limits extrapolation of these findings to other subtypes of PAH. Also, modern prognostication of PAH often involves multifaceted assessment of right ventricular function via echocardiography or cardiac magnetic resonance imaging, which were not available for our analysis.

Lastly, our exploratory genetic analysis is limited by the small number of patients with available genotyping data and applies only to patients of European ancestry. While biologically plausible, these findings will need replication in larger, more diverse cohorts.

Conclusions

PAH patients treated with parenteral prostacyclins display a wide range of response to treatment and long-term survival. In general, responders were younger, more likely to have IPAH/HPAH than associated PAH, and more likely to be male. Age at treatment initiation, WHO FC at short-term follow up, and PA O_2% are associated with survival in this population. Exploratory genetic comparison between these groups yielded associations in biologically relevant pathways in the pathogenesis of PAH.

An earlier version of these findings was published in abstract form and presented at the ATS International Conference in Washington, DC on 24 May 2017.

Conflict of interest

SJH reports no conflicts of interest. ARH has served as a consultant to Actelion, Bayer, GSK, Accleron, United Therapeutics, and Pfizer. She has received research/grant support from the NIH and Cardiovascular Medical Research and Education Fund. ELB has served as a consultant for Hovione Pharmaceuticals.

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