Prognostic Significance of Reduced Blood Pressure Response to Exercise in Pediatric Pulmonary Arterial Hypertension

To the Editor:

Exercise intolerance is a common manifestation of pulmonary arterial hypertension (PAH), and therefore evaluation of exercise capacity has a crucial role in clinical management (1–3). Cardiopulmonary exercise testing (CPET) has been demonstrated to be safe in the pediatric PAH population (4), and the current expert consensus from the European Pediatric Pulmonary Vascular Disease Network suggests CPET for assessment of exercise capacity in those patients (5).

The prognostic value of CPET parameters is now well established in adult PAH (6, 7). In pediatric PAH, it has been shown that CPET parameters correlate with disease severity (8, 9); however, demonstration of prognostic value is lacking. In pediatric PAH, clinical worsening (CW) occurs frequently and is predictive of death or lung transplantation (10). This study aimed to investigate whether CPET parameters predict CW in pediatric PAH.

Materials and Methods

The study was approved by the institutional review board of FuWai Hospital, Beijing, China, and informed consent was obtained from all participants' parents before enrollment. Thirty-seven pediatric patients (<18 years old) diagnosed with group 1 PAH (1) between July 2013 and December 2015 were prospectively enrolled. Patients with World Health Organization functional class IV were excluded. All the patients recruited performed standard incremental CPET on an upright cycle ergometer, as previously described (11).

During follow-up, CW events including death, heart/lung transplantation, hospitalization for PAH deterioration, escalation of PAH targeted therapy, and worsening of World Health Organization functional class were recorded. A patient with at least one CW event was included in the CW group, and the end point was the time from enrollment to the first CW event. The final census date for the study was September 1, 2016.

Cox regression analysis, receiver operative characteristic (ROC) curve, and Kaplan-Meier analysis were used for survival analysis. A *P* value <0.05 was considered significant. Data management

Supported by the Distinguished Young Scholars of National Natural Science Foundation of China (81425002); the Cohort Study of Orphan Diseases, Major Program of the National Natural Science Foundation of China, Precision Medicine, the 13th 5-Year Plan (2016YFC0901500); the Key Program of National Natural Science Foundation of China (81630003); and the British Heart Foundation Senior Basic Science Research Fellowship (FS/13/48/30453). The funding sources had no role in the study design, data selection and analysis, quality assessment, data synthesis and interpretation, or the decision to prepare and submit the manuscript for publication.

Author Contributions: Conception and design: H.-D.Z., Z.-C.L., L.-T.W., and Z.-C.J.; analysis and interpretation: H.-D.Z., Z.-C.L., L.-T.W., A.R., and Z.-C.J.; drafting the manuscript for important intellectual content: H.-D.Z., Z.-C.L., A.R., M.B., and Z.-C.J.; critical revision of the manuscript for intellectual content: H.-D.Z., Z.-C.L., L.-T.W., A.R., T.-Y.L., Y.-Y.H., Y.W., A.L., M.B., and Z.-C.J.; provision of study materials or patients: H.-D.Z., Z.-C.L., L.-T.W., Y.W., and Z.-C.J.; statistical expertise: A.R., A.L., M.B., and Z.-C.J.; collection of data: H.-D.Z., Z.-C.L., L.-T.W., T.-Y.L., Y.-Y.H., and Z.-C.J.; all authors have read the manuscript and approved its final version.

Originally Published in Press as DOI: 10.1164/rccm.201701-0131LE on April 4, 2017

and analyses were performed using SPSS (version 14.0, Chicago, Illinois) and R version 3.3.2 (<https://cran.r-project.org/>).

Results

Of the 37 patients, 18 had idiopathic PAH and 19 had congenital heart disease–associated PAH (10 after correction and 9 with shunts). Patients had a median age of 15.7 years (25th–75th percentiles, 13.0–17.2 yr) at enrollment; 57% of the population was female. At enrollment, 18 (48.6%) patients were incident and 7 (18.9%) were treated with phosphodiesterase type 5 inhibitors, 5 (13.5%) with endothelial receptor antagonist, 4 (10.8%, responders in vasoreactivity testing) with calcium channel blockers, and 3 (8.1%) with combination therapy (endothelial receptor antagonists + phosphodiesterase type 5 inhibitors). Their detailed clinical data and CPET parameters are listed in Table 1. Patients in the CW group had lower peak systolic blood pressure (sBP; *P* = 0.007) and diastolic blood pressure (*P* = 0.019) than those in the non-CW group (Table 1).

The median follow-up time was 15.8 months (25th–75th percentiles, 12.5–26.8 mo), during which CW events occurred in eight (22%) patients, with one death from right heart failure, seven hospitalizations for PAH deterioration, and five escalations of PAH-targeted therapy during hospitalization. The eight patients all had worsening of World Health Organization functional class. No patients were lost to follow-up.

Markers with potential prognostic value (*P* < 0.1 in univariate Cox regression analysis) were included in the multivariate model (Figure 1A). After adjustment, peak sBP was identified as an independent prognostic factor for CW (hazard ratio, 0.807; 95% confidence interval, 0.665–0.980; Figure 1A). The optimum cutoff value for predicting CW derived from a ROC curve was 119 mm Hg (*c*-statistic = 0.77; *P* = 0.021; sensitivity, 75%; specificity, 76%). In Kaplan-Meier analysis, patients with peak sBP of 119 mm Hg or higher had worse survival.

Subgroup analysis was performed in patients without shunts (idiopathic PAH plus congenital heart disease–associated PAH after correction). Peak sBP was the only multivariate predictor (hazard ratio, 0.717; 95% confidence interval, 0.554–0.927; Figure 1B). The optimum value (119 mm Hg) derived from ROC curve (*c*-statistic = 0.82; *P* = 0.009; sensitivity, 75%; specificity, 80%) was the same as in the overall population. Kaplan-Meier analysis showed that patients with peak sBP of 119 mm Hg or higher had worse survival in this population.

During CPET, there were no significant adverse events, such as cardiac arrest, ventricular tachycardia, supraventricular tachycardia, syncope, chest pain, or dizziness. The reasons for stopping exercise were leg fatigue (65%), shortness of breath (22%), and general fatigue (8%). Mild ST-segment changes (1–3 mm) were detected in eight patients (22%), and moderate changes (>3 mm) in three patients (8%).

Discussion

CPET is a safe and informative tool to assess and monitor exercise tolerance in pediatric PAH (5). In the present study, we investigated for the first time the prognostic value of CPET in pediatric PAH, demonstrating that peak sBP during CPET predicts CW, and for each further 5 mm Hg reduction in peak sBP the risk of CW is increased by 20% (Figure 1A).

It has been identified that patients with peak sBP of 120 mm Hg or higher had worse survival in an adult population (6). This finding is replicated using our dataset and the adult cutoff value 120 mm Hg

Table 1. Baseline Characteristics and Exercise Parameters of Non-Clinical Worsening Versus Clinical Worsening in the Overall Population with Pulmonary Arterial Hypertension

	Overall (n = 37)	Non-CW (n = 29)	CW (n = 8)	P Value*
Age, yr	15.7 (13.0–17.2)	15.7 (13.1–17.2)	14.5 (10.9–16.9)	0.335
Female, n (%)	21 (56.8)	16 (55.2)	5 (62.5)	0.711
Birth weight, kg	3.0 (2.9–3.5)	3.1 (2.9–3.5)	3.0 (2.8–3.3)	0.493
BMI, kg/m ²	18 (17–20)	18 (17–21)	18 (16–19)	0.293
BSA, m ²	1.45 (1.34–1.59)	1.47 (1.34–1.63)	1.42 (1.34–1.52)	0.438
WHO-FC, III/I-II	7/30	6/23	1/7	0.601
NT-proBNP, pg/ml	239 (78–833)	231 (75–939)	609 (178–1,429)	0.170
Pericardial effusion, n (%)	1 (2.7)	0 (0)	1 (12.5)	0.054
Family history of PAH, n (%)	0 (0)	0 (0)	0 (0)	—
Comorbidities, n (%)	1 (2.7) [†]	1 (3.4) [†]	0 (0)	0.594
Time from initial symptoms to enrollment, yr	2.6 (0.9–8.0)	3.4 (0.9–11.1)	1.4 (0.5–2.9)	0.135
Hemodynamics				
mRAP, mm Hg	8 (5–12)	8 (5–11)	9 (6–13)	0.786
mPAP, mm Hg	74 ± 22	73 ± 22	76 ± 22	0.743
PAWP, mm Hg	11 (9–12)	11 (9–12)	11 (9–12)	0.526
PVR, Wood Units	15.2 ± 8.0	14.3 ± 7.1	18.6 ± 9.8	0.170
PVRI, Wood Units × m ²	22.6 ± 11.7	21.3 ± 10.5	27.4 ± 15.1	0.194
CO, L/min	4.3 (3.7–5.5)	4.3 (3.9–6.2)	3.9 (3.5–4.6)	0.128
CI, L/min/m ²	2.9 (2.4–3.7)	2.9 (2.6–4.0)	2.9 (2.1–3.5)	0.354
CPET parameters				
RER at peak exercise	1.15 ± 0.09	1.16 ± 0.08	1.11 ± 0.09	0.125
Peak workload, Watt	73 (58–100)	74 (61–104)	65 (40–76)	0.137
Exercise time, min	7.7 ± 1.3	7.7 ± 1.3	7.5 ± 1.0	0.741
Resting HR, bpm	88 ± 13	89 ± 14.0	84 ± 10	0.211
Peak HR, bpm	156 ± 19	156 ± 17	160 ± 19	0.479
Resting sBP, mm Hg	102 ± 17	104 ± 17	96 ± 15	0.275
Peak sBP, mm Hg	130 ± 21	134 ± 21	116 ± 12	0.007
Resting SpO ₂ , %	97 (96–98)	97 (95–98)	98 (97–98)	0.502
Peak SpO ₂ , %	93 (85–95)	90 (84–95)	94 (90–97)	0.266
Peak V _E , L/min	36 (29–45)	39 (29–45)	32 (26–34)	0.251
Peak V _{O₂} , ml/kg/min	16.9 (13.5–19.8)	17.2 (14.5–20.7)	15.6 (12.3–19.8)	0.299
AT, ml/kg/min	12.8 ± 3.0	12.9 ± 3.1	12.6 ± 2.9	0.698
V _E /V _{CO₂} slope	36 (31–45)	36 (31–44)	37 (33–47)	0.236
Estimated peak CO, L/min	5.4 (4.2–6.5)	5.7 (4.3–6.8)	4.8 (3.5–5.4)	0.083

Definition of abbreviations: AT = anaerobic threshold; BMI = body mass index; bpm = beats per minute; BSA = body surface area; CO = cardiac output; CI = cardiac index; CPET = cardiopulmonary exercise testing; CW = clinical worsening; HR = heart rate; mPAP = mean pulmonary artery pressure; mRAP = mean atrial artery pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; peak V_{O₂} = peak oxygen uptake; PVR = pulmonary vascular resistance; PVRI = PVR index; RER = respiratory exchange ratio; sBP = systolic blood pressure; SpO₂ = oxygen saturation as measured by pulse oximetry; V_E/V_{CO₂} slope = the slope of ventilatory equivalent for carbon dioxide; WHO-FC = World Health Organization functional class.

Values are expressed as n (%), ratio, mean ± standard deviation, or median (25th–75th percentiles).

*Comparison between patients in non-CW and CW groups; Student's *t* test or Mann-Whitney *U* test for continuous data, and chi-square test for categorical data.

[†]One patient had obesity.

(log rank *P* = 0.004 in Kaplan-Meier analysis). We suggest peak sBP of 120 mm Hg can be used as a predictor both in pediatric and adult PAH.

The predictive value of peak sBP during CPET may be because of its relationship to right ventricular function. Cardiac output (CO) during exercise can be noninvasively estimated from CPET parameters, and we investigated its correlation with peak sBP. Peak sBP had strong positive correlations with peak CO (*r* = 0.749; *P* < 0.001) and the increase of CO from baseline to peak exercise (*r* = 0.733; *P* < 0.001), which indicated lower peak sBP was associated with worse right ventricle function.

In the present study, some patients were receiving PAH-targeted therapies before admission to our center, including endothelial receptor antagonists, phosphodiesterase type 5 inhibitors, or both. Because of their limited availability and cost, no patients received prostanoid therapy.

This study is limited by small sample size. PAH is rare in children, and because of subject age and the need for parental consent, the sample size is smaller than in adult studies. To counter this, we combined idiopathic PAH and congenital heart disease-associated PAH analyses; however, this may have increased heterogeneity. The size and the heterogeneity may explain why no other CPET-derived parameters emerged as independent predictors of outcome. Because of safety issues, this study did not examine the invasive hemodynamic parameters during exercise. The age of patients enrolled (9–18 years) may also be a potential bias, and the cutoff value of peak sBP for predicting outcomes may not be valid for younger children.

Conclusions

Pediatric patients with PAH incapable of achieving a significant increase in peak sBP during CPET are more likely to have CW

Figure 1. Forest plots of univariate and multivariate Cox regression survival analysis in (A) the overall population (n = 37) and in (B) patients without shunts (n = 28). CI = confidence interval; CO = cardiac output; CW = clinical worsening; peak VO₂ = peak oxygen consumption; peak sBP = systolic blood pressure at peak exercise; peak dBP = diastolic blood pressure at peak exercise; VE/VO₂ = ventilation per unit increase in carbon dioxide production; non-CW = non-clinical worsening.

events. A peak sBP of less than 119 mm Hg could be used to identify patients at higher risk for worse outcomes in pediatric PAH. Further multicenter studies may help in risk stratification and define treatment goals related to CPET. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Rare Genetic Variants in *PARN* Are Associated with Pulmonary Fibrosis in Families

To the Editor:

Rare genetic variation in genes related to telomere biology has been implicated in 10–20% of familial interstitial pneumonia (FIP), the inherited form of idiopathic interstitial pneumonia (1). Recently, heterozygous rare variants (RVs) in the gene encoding polyadenylation-specific RNase deadenylation nuclease (*PARN*) were reported in six

Supported by National Institutes of Health, NHLBI grants K08HL130595 (J.A.K.), P01HL92870 (T.S.B.), R01HL085317 (T.S.B.), and HL0097163 (D.A.S.); Vanderbilt University Clinical and Translational Science award UL1 RR024975 (J.D.C.); Department of Veterans Affairs (T.S.B. and D.A.S.); Francis Family Foundation (J.A.K.); and the Pulmonary Fibrosis Foundation (J.A.K.).

Author Contributions: J.A.K. designed the study, performed experiments, collected data, analyzed data, interpreted data, and wrote and revised the manuscript; S.R. performed experiments and analyzed and interpreted data; C.M. collected and analyzed data; K.K.B. collected data, analyzed data, interpreted data, and revised the manuscript; D.A.S. collected data, analyzed data, interpreted data, and revised the manuscript; M.I.S. collected data and revised the manuscript; J.E.L. designed the study, collected data, analyzed data, interpreted data, and revised the manuscript; J.A.P. designed the study, collected data, analyzed data, interpreted data, and revised the manuscript; T.S.B. designed the study, collected data, analyzed data, interpreted data, and wrote and revised the manuscript; and J.D.C. designed the study, performed experiments, analyzed and interpreted data, and wrote and revised the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.201703-0635LE on April 17, 2017

unrelated families with pulmonary fibrosis (2), consistent with reports of biallelic *PARN* RVs in children with dyskeratosis congenita (3–5). Subsequently, heterozygous *PARN* RVs were identified in five patients with sporadic idiopathic pulmonary fibrosis (IPF) among 262 patients who underwent whole-exome sequencing (6).

We queried whole-exome sequencing data from genomic DNA obtained from 188 unrelated FIP kindreds (7) for RVs in *PARN*, identified variants with a minor allele frequency <0.001 among Caucasian patients in the Exome Aggregation Consortium database, and confirmed these RVs by Sanger sequencing. Using this approach, we found 13 unique *PARN* RVs in 12/188 (6.4%) unrelated families (Figure 1); seven families (3.7%) had variants predicted to be protein-altering (frameshift, nonsense, splicing, missense; Table 1). In five of these families (2.6% of the cohort), *PARN* RVs identified as likely to be damaging fully cosegregated with disease in individual family members. These *PARN* RVs included one nonsense, one frameshift, one splicing, and two missense variants. The two missense variants, Asn7His and Lys56Asn, are conserved and predicted to affect protein function. For the c.620+5G>A splicing variant, we generated immortalized lymphocytes and performed complementary DNA sequencing; this confirmed that this variant results in alternative splicing, which is likely to affect *PARN* structure and function.

Surprisingly, in three families, intronic *PARN* variants that did not appear to affect mRNA splicing cosegregated with disease. Complementary DNA sequencing demonstrated that c.178–3C>T does not affect splicing, indicating this is likely benign. Another intronic variant, c.703–11_703–10delAT, is located in an intron near a splice site but is not predicted to alter the canonical splice site or create a cryptic splice site. A third intronic *PARN* variant c.1006–11G>A cosegregated with disease in one family but is not predicted to alter splicing. In this family, however, affected subjects share a novel cosegregating RV in the gene telomerase reverse transcriptase (Thr839Lys). Although available evidence suggests these intronic RVs are benign, their cosegregation with disease and association with otherwise unexplained short telomeres in affected individuals raises the possibility that these intronic variants have effects on *PARN* expression or other regulatory mechanisms.

In the remaining four families, *PARN* RVs did not fully segregate with disease. In two of these families, there was a family history of IPF through both parental lineages, making it possible that affected individuals inherited a different genetic risk factor through each parental line. In one family, an intronic *PARN* RV that could affect splicing (c.245+75_245+77delCCC) was identified in a patient with IPF, whereas the other affected individuals shared a frameshift variant (Phe418PhefsX6). In a different family, an affected individual with short peripheral blood mononuclear cell telomeres carried a missense RV (Ser498Asn) that is predicted to be deleterious (PolyPhen2 0.996) (8), but the RV was not identified in the other family member with disease.

We measured peripheral blood mononuclear cell telomere length in all affected individuals from these families from whom sufficient DNA was available and found that all had telomere shortening adjusted for age (Table 1). Thirteen of the 18 subjects tested (72%) had telomere length below the 10th percentile, whereas the others ranged from the 12th to the 22nd percentile. All these families were of Caucasian ancestry, and 62% of affected subjects were men. The median age at diagnosis was 60 years (range, 42–82 years), slightly younger than the median age of onset in our entire cohort of patients with FIP (66 years) (7). Forty-three percent of affected subjects had a history of cigarette smoking. Baseline FVC was 68.5% ($\pm 17.7\%$, SD) predicted,