DOI: 10.1002/pul2.12246

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Muscle strength is reduced in children with pulmonary arterial hypertension

Shari Pepplinkhuizen[1] | **Graziella Eshuis**[1] | **Willemijn M. H. Zijlstra**[1] | **Carola Y. Timmer**[2] | **Mark Jan Ploegstra**[1] | **Otto T. H. M. Lelieveld**[2] | **Ann Marjolein Hepping**[3,4] | **Ernesto A. C. Beenakker**[5] | **Rolf M. F. Berger**[1]

[1]Department of Pediatric Cardiology, Center for Congenital Heart Disease, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

[2]Department of Rehabilitation, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

[3]Department of Orthopedics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

[4]Roessingh Center for Rehabilitation, Enschede, The Netherlands

[5]Department of Neurology, Medical Center Leeuwarden, Groningen, The Netherlands

Correspondence
Graziella Eshuis and Rolf M. F. Berger, Department of Pediatric Cardiology, Center for Congenital Heart Disease, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, PO Box CA 41, 9700 RB Groningen, The Netherlands.
Email: g.eshuis01@umcg.nl and r.m.f.berger@umcg.nl

Funding information
Sebald Fund, Grant/Award Number: 81807

Abstract

Muscle strength is decreased in adults with pulmonary arterial hypertension (PAH). We aim to investigate muscle strength in children with PAH in relation to a cohort of healthy children, and investigate correlations with disease severity markers. This prospective study included children with PAH aged 4–18 years, who visited the Dutch National Referral Center for Pulmonary Hypertension in Childhood between October 2015 and March 2016. Muscle strength was assessed using handgrip strength and maximum voluntary isometric contractility (MVIC) of four peripheral muscles. Dynamic muscle function was evaluated with the Bruininks–Oseretsky test of motor proficiency (BOT-2). These measurements were compared with those in two cohorts of healthy children and correlated with 6-minute walk distance (6MWD), World Health Organization functional class (WHO-FC), N-terminal pro-brain natriuretic peptide (NT-proBNP), and time since diagnosis. Eighteen children with PAH aged 14.0 [interquartile range: 9.9–16.0] years showed reduced muscle strength. Handgrip strength z-score -2.4 ± 1.2, $p < 0.001$, total MVIC z-score -2.9 ± 1.2, $p < 0.001$, and BOT-2 z-score -1.0 ± 0.9, $p < 0.001$. 6MWD ($67 \pm 11\%$ predicted) correlated with most muscle measurements ($r = 0.49–0.71$, $p = 0.001$). Dynamic muscle function (BOT-2) differed between WHO-FC, whereas handgrip strength and MVIC did not. NT-proBNP and time since diagnosis did not show significant correlations with muscle strength measurements. Muscle strength was significantly reduced in children with PAH and correlated with 6MWD, but not with disease severity markers

Abbreviations: 6MWD, six-minute walk distance; BOT-2, Bruininks–Oseretsky test of motor proficiency–2nd edition; HHD, hand-held dynamometer; IQR, interquartile range; MVICs, maximum voluntary isometric contractions; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; RSA, running, speed and agility; SDs, standard deviations; WHO-FC, World Health Organization functional class.

Shari Pepplinkhuizen and Graziella Eshuis shared first authorship.

WHO-FC and NT-pro-BNP. The nature of this reduced muscle strength is yet unclear, but its occurrence in children with seemingly mild or well-controlled PAH supports the concept of PAH being a systemic syndrome involving peripheral skeletal muscles.

KEYWORDS
cardiopulmonary physiology and pathophysiology, muscle, pulmonary arterial hypertension

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, severe, and progressive disease of the small pulmonary arteries.[1] Although the survival of patients with PAH has improved in recent years, the prognosis remains unfavorable.[2,3] Key symptoms in patients with PAH are dyspnea, fatigue, and exercise intolerance, all affecting quality of life.[4,5] The pathogenesis of these symptoms is multifactorial but has been attributed mostly to the cardiopulmonary impact of this disease.[6]

Studies in adult patients with PAH have shown that besides the cardiopulmonary system, also muscles are affected.[7,8] Muscle strength, skeletal muscle mass, and contractility were shown to be reduced.[9] Additionally, alterations on microscopic level were detected: altered skeletal muscle morphology, changes in microcirculation and metabolism.[10-12] These alterations correlated with measurements for exercise capacity including 6-minute walk distance (6MWD) and maximal oxygen uptake (peakVO_2).[7,8] In various diseases, measures for muscle strength, such as handgrip strength, are reported to be predictive of frailty and severity of morbidity.[13]

Whether muscle strength is affected in children with PAH has not been investigated yet. However, muscle strength is reduced in children with chronic diseases, such as mild to moderate kidney disease.[14] We hypothesize that muscle strength in children with PAH is reduced compared with healthy children. In this study, we aim to investigate muscle strength in children with PAH and compare it with a cohort of healthy children. Furthermore, we aim to investigate whether muscle strength in children with PAH correlates with markers of disease severity.

METHODS

Design, setting, and patients

This study is an exploratory, prospective, and observational study to measure muscle strength in children with PAH and to compare these measurements with those of a cohort of healthy children. In the Netherlands, all children diagnosed with PAH are followed at the Dutch National Referral Center for Pulmonary Hypertension in Childhood.[15] Patients aged 4–18 years were consecutively screened for eligibility between October 2015 and March 2016. PAH was confirmed by cardiac catheterization (defined according to contemporary recommendations including mean pulmonary artery pressure ≥25 mmHg, mean pulmonary capillary wedge pressure ≤15 mmHg, and indexed pulmonary vascular resistance ≥3 Wood units.m^2). Exclusion criteria comprised: mental or physical limitations that prohibit the execution of the functional tests (i.e., age <4 years, mental retardation, severe autism, or Down syndrome), interfering secondary diseases including muscular dystrophic disease and spondyloepimetafysal dysplasia. The Medical Ethical Review Board of the University Medical Center of Groningen approved the Dutch National Registry for Pulmonary Hypertension in Childhood (approval number M11.097816) and all children and/or their guardians provided written informed consent.

Patient and disease characteristics were collected including age, sex, age at diagnosis, body mass index, PAH etiology, time since diagnosis, and measures of disease severity: 6MWD, World Health Organization functional class (WHO-FC), and serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP). Patients were classified into PAH subgroups according to the updated Clinical Classification for Pulmonary Hypertension (2013).[16] Physical functional parameters (i.e., 6MWD and WHO-FC) were collected at the time of muscle strength tests or within 3 months before or after the test. The 6 min walk test was conducted as previously described[16] and walking distance was expressed as meters, and the percentage of predicted.[17]

Muscle strength measurements

To obtain a comprehensive image of muscle strength and function, we selected three tests that are widely accepted

as representative measurements of general muscle strength: handgrip strength, maximal voluntary isometric contraction,[18] and dynamic muscle function.[19,20] Handgrip strength and maximal voluntary isometric contraction of the upper and lower extremities were tested using previously validated instruments (Jamar Dynamometer and Hand-Held Dynamometer Citec; type CT 3001; CIT Techniques).[1,21,22] Dynamic muscle function, as a reflection of daily activity, was tested using the Bruininks–Oseretsky test of motor proficiency edition 2 (BOT-2)[19] All tests were performed in the same room, under the same circumstances by two experienced physiotherapists.

Handgrip strength was measured according to the guidelines of the American Society of Hand Therapists: in a sitting position with shoulders adducted and neutrally rotated, the elbow 90° flexed, and the forearm and wrist in a neutral position. Patients were allowed three attempts per hand, the highest of three was used for the analyses. In the healthy cohort, two attempts per hand were allowed, also the highest was used for the analyses. To overcome the effect of hand dominance, the mean handgrip (highest value of the left hand plus the highest value of the right hand, divided by two) was used for the analyses. Results were compared with measurements in a cohort of healthy children, previously described by Hepping et al.[23]

Maximal voluntary isometric contractions (MVIC) were measured bilaterally of the arm and hip flexors, and the arm and knee extensors. The "break" technique was used: the participant kept a certain position, the examiner gradually overcame the muscle force and stopped when the extremity gave away. Out of three attempts per muscle group, the highest was reported and averaged for the left and right sides to prevent the influence of left-to-right differences. Results were compared with measurements in a cohort of healthy children, previously described by Beenakker et al.[18]

Dynamic muscle function was measured by the BOT-2, consisting of a standard summary score (Strength and Agility) and two subtests scale scores "Running, speed, and agility" and "Strength." The summary score was a calculated score based on both subtests. The subtest Running, speed, and Agility included: shuttle run, stepping sideways, one-legged hop stationary and sideways, and two-legged side hop. The Strength subtest included: standing long jump, push-ups, and sit-ups in 30 s, wall sit, and V-up in maximal 60 s. There was a 30 s resting interval between all exercises to prevent fatigue. Exercises were verbally and visually explained and participants were verbally encouraged. Another trial was allowed in case of unreliable results. All measurements were compared with references separated for age and sex as provided in the *BOT-2* manual.

Statistical analyses

Patient characteristics and disease severity markers were described as mean with standard deviation or median with interquartile ranges (IQR) as appropriate. All variables were checked for normality using histograms, PP- and QQ-plots, and the Shapiro–Wilk test. Ordinal data were presented as percentages. A p-value <0.05 was considered statistically significant. Patients' muscle strength was compared with the cohorts of healthy children by calculating z-scores based on the mean and standard deviation of the healthy populations,[18,23] taking age and sex into account. One-sample t-test was used to compare z-scores to the reference z-score $= 0$. The software RefCurv was used to construct reference curves of the muscle strength measures.

Differences between WHO-FC were analyzed using one-way ANOVA for normally distributed variables and Kruskal–Wallis for skewed variables. Correlations between muscle strength measurements and 6MWD and NT-proBNP were analyzed using the Pearson's correlation coefficient for continuous, normally distributed variables, and the Spearman's rank correlation for skewed distributions or ordinal variables.

RESULTS

A total of 18 patients (67% female) were included (Table 1). One patient did not perform handgrip strength measurements and 1 patient did not perform the BOT-2 test. PAH diagnoses included: 14 (78%) patients with heritable or idiopathic PAH, 3 (17%) patients with PAH associated with congenital heart disease, and 1 (5%) patient with PAH associated with connective tissue disease.

Muscle strength

All muscle strength measurements showed significantly lower results (below the 50th percentile) compared with the healthy cohorts (Figures 1 and 2). Most patients were right-hand dominant (89%), this was similar to the prevalence in the healthy cohorts.[23] Mean handgrip strength in patients with PAH was 16 ± 9 kg, significantly lower compared with healthy controls (z-score -2.4 ± 1.2, $p < 0.001$), Figure 3. All MVICs of the upper

TABLE 1 Patient characteristics.

	$n = 18$	
Age, years	14.0	[9.9–16.0]
Female sex, *n*	12	67%
Age at diagnosis, years	6.2	[2.0–12.2]
Time since diagnosis, months	50	[6–124]
Body height, cm	154	[134–165]
Body weight, kg	41.7	±16.8
Body mass index, kg/m^2	18.2	±3.4
Vasodilator therapy		
Mono (B)	4	22%
Dual (B + S)	12	67%
Triple (B + S + E)	2	11%
Disease severity markers		
WHO functional class		
I	4	22%
II	10	56%
III	4	22%
IV	0	
NT-proBNP, ng/L	131	[49–247]
6-MWD, m	430	±82
% predicted[a]	67	±11

Note: Patient characteristics of 18 patients with PAH.

Abbreviations: B, bosentan; Cm, centimeters; E, continuous intravenous epoprostenol; IQR, interquartile range; Kg, kilograms; M, meters; Ng/L, nanograms per Liter; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; S, Sildenafil.

[a]Percentage predicted based on Geiger et al.[17] Mean ± SD when normally distributed, median [IQR] when skewed. Counts with percentages.

and lower body muscles were decreased compared with healthy controls (total muscle strength *z*-score −2.9 ± 1.2, $p < 0.001$), and this was most pronounced in the lower extremities (Table 2). Dynamic muscle function (BOT-2) showed significantly lower results on the summary score and both subtests compared with reference values (Table 2).

Correlations with disease severity markers

6MWD (in meters) correlated significantly with handgrip strength ($r = 0.53$; $p = 0.03$) and with MVICs of the upper and lower body muscles (Table 3). Additionally, 6MWD correlated significantly with the BOT-2 standard summary score ($r = 0.52$; $p = 0.03$) and the subtest, Running, Speed, and Agility ($r = 0.65$; $p = 0.005$). The summary score of the BOT-2 differed significantly between WHO-FC ($p = 0.02$), while both BOT-subtests showed differences that did not reach statistical significance (Running, Speed, and Agility $p = 0.054$, Strength $p = 0.082$), Figure 4. Handgrip strength and MVIC did not differ significantly between WHO-FC. No correlations between NT-proBNP levels and muscle strength measurements could be demonstrated (Table 3). In this small sample size, we could not identify correlations between muscle strength measures and time since diagnosis (Supporting Information: Table 1). Neither did we find a relation with treatment intensity, defined as the number of pulmonary vasodilators used.

DISCUSSION

This is the first study to show that isometric muscle strength and dynamic muscle function (BOT-2) are significantly reduced in children with PAH compared with healthy controls. Remarkably, reduced muscle strength occurred in children in all classes of WHO-FC, not just in the compromised classes (WHO-FC III). Furthermore, muscle strength measures in almost all measured muscle groups correlated with reduced functional capacity expressed as 6MWD ($r = 0.49–0.71$).

The pathophysiological origin of decreased muscle strength in patients with PAH is unclear. Whether decreased muscle strength is primarily related to systemic pathobiology of the disease PAH or secondary to muscle underuse due to cardiorespiratory limitations has still to be unraveled. Our study showed that decreased muscle strength is correlated with reduced functional capacity, for example, 6MWD (mean 67 ± 11% of predicted). Exercise intolerance and inactivity have been associated with limited muscle oxygenation in patients with PAH.[24,25] This limitation in muscle oxygenation might lead to skeletal muscle dysfunction and possibly impaired muscle growth and underuse.[9] In addition to exercise intolerance, Zijlstra et al. reported that children with PAH show reduced physical activity levels compared with healthy controls.[25] Until recently, exercise training was generally believed to be unsafe in patients with PAH and was discouraged due to the risk of syncope and cardiac events.[26] In children with PAH, the combination of anxiety and concerns of patients, parents, or relatives, and healthcare professionals often leads to protection and restricted physical activity.[26] Currently, the assumption of exercise training being harmful in patients with PAH is gradually rejected. The most recent guidelines for pulmonary hypertension recommend moderate aerobic activity, but avoidance of strenuous and isometric exertion.[1] Furthermore, the implementation of rehabilitation

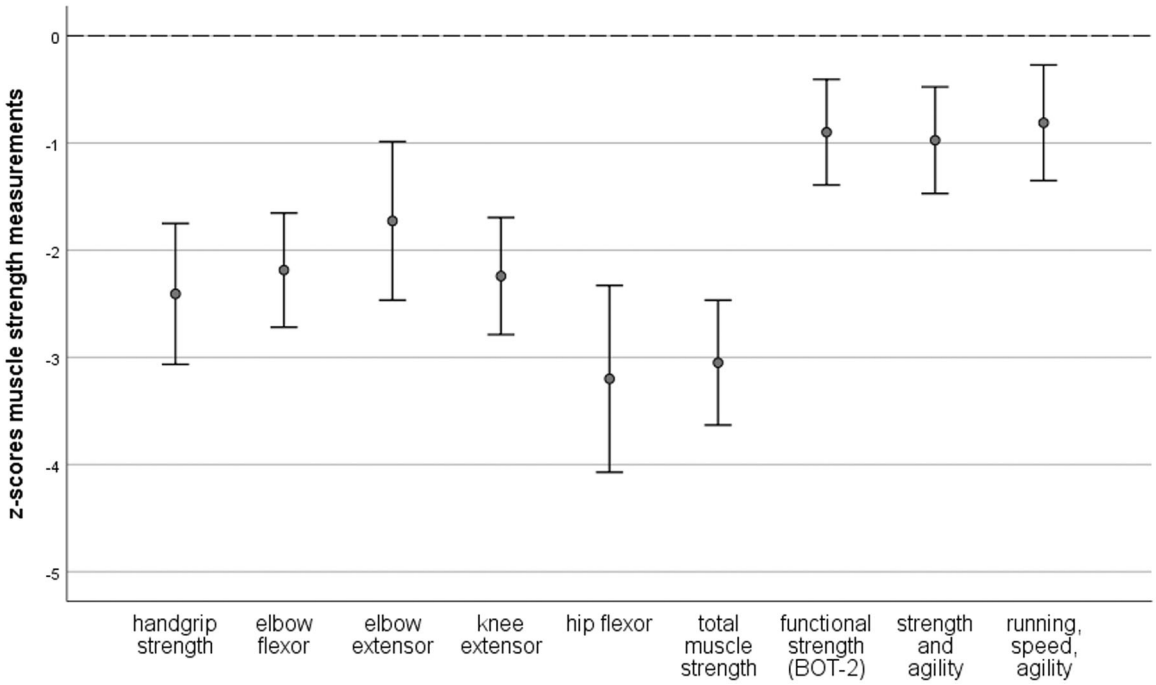

FIGURE 1 z-score and 95% CI overview of all muscle strength measures, based on the populations Hepping et al.,[23] Beenakker et al.,[18] and the reference values from the BOT-2 manual. BOT-2, Bruininks–Oseretsky test of motor proficiency–2nd edition.

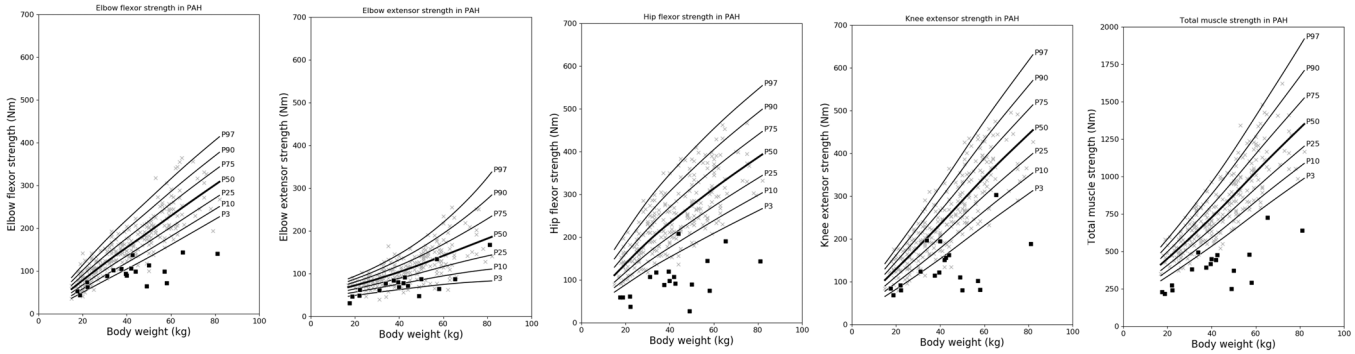

FIGURE 2 Percentiles curves of maximal voluntary isometric contraction versus body weight based on healthy children from the Northern Netherlands: Beenakker et al.[18] Gray: healthy children. Black squares: children with PAH. Be aware of the scale shift of the *Y*-axis for total muscle strength. PAH, pulmonary arterial hypertension.

programs by centers experienced in both PAH patient care and rehabilitation is being recommended in the most recent pulmonary hypertension guidelines.[1] It remains to be investigated whether such rehabilitation programs will improve muscle function in PAH. However, our results confirm the importance of monitoring physical activity as suggested by Zijlstra et al.[25] In this study, young children with a relatively good clinical condition (mainly WHO-FC I and II) supported by relatively low median NT-pro-BNP values of 131 [IQR: 49–247] nanogram per liter,[26] showed decreased muscle strength and reduced 6MWD. This may imply that the decrease in muscle strength and exercise intolerance is not solely secondary due to compromised cardiac performance. This could explain the lack of correlation of isolated muscle strength with WHO-FC, whereas the BOT-2 test, a composite reflecting motor skills, may correspond more with daily activity and thus WHO-FC.

Adult studies have suggested that PAH might be a systemic syndrome.[8] Respiratory muscle strength and function are decreased in PAH patients.[7,27] Mitochondria were reported to have a different structure and decreased density compared with those in healthy controls.[28] Also, there is a strong relationship between mitochondrial metabolism and angiogenesis.[28] It is not clear whether such mitochondrial alterations are a secondary

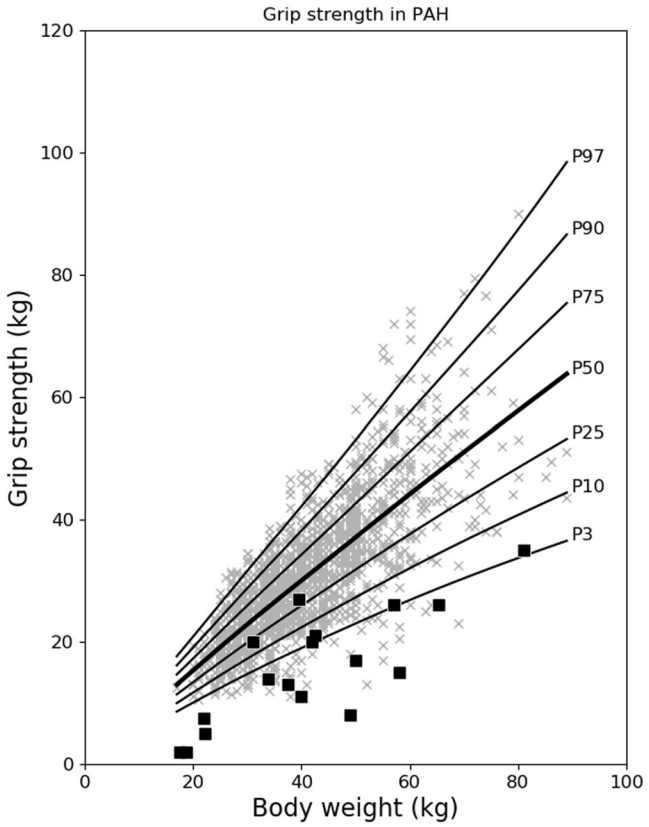

FIGURE 3 Percentile curves of grip strength versus body weight based on healthy children from the Northern Netherlands: Hepping et al.[23] Gray: healthy children, black squares: children with PAH. PAH, pulmonary arterial hypertension.

phenomenon associated with decreased perfusion and oxygenation, and loss of microcirculation, or a primary phenomenon, intrinsically associated with PAH.[11,12,23] In patients with PAH, microRNA-126, an endothelial-specific regulator of angiogenesis, is downregulated. This could hypothetically lead to loss of muscular microcirculation, which may correlate with early reduced muscle strength and possibly, secondary exercise intolerance.[12] Alterations in the microcirculation were associated with decreased oxygenation but not with cardiac output.[11,23] This implies that altered microcirculation in the peripheral muscles of PAH patients might affect exercise capacity independent of cardiopulmonary function.[12] Both the loss of microcirculation and alterations of mitochondrial metabolism resulting in impaired skeletal and respiratory muscle function may be, at least partly independent from cardiovascular performance, supporting the concept of PAH being a systemic syndrome involving peripheral skeletal muscles.

In summary, the underlying pathology of decreased muscle strength in PAH remains insufficiently known. A decreased cardiopulmonary function, the systemic effects of PAH, independent of cardiorespiratory function, and muscle underuse may all contribute to decreased muscle strength. Therefore, further research is needed. Specifically, studies including cardiac performance, monitoring physical activity and muscle strength, microcirculation and oxygenation, and muscular metabolic activity, both at rest and during exercise will be helpful. Also, the effects of training programs or metabolic supplements might identify therapeutic interventions that improve skeletal muscle function and thereby may improve quality of life.

This study is exploratory and is limited by its small sample size precluding definitive conclusions on correlations of specific muscle group strengths with exercise tolerance or disease severity and precluding the use of multivariate analysis. In this study, the time points of muscle strength measurements were not aligned with cardiac catheterization or cardiac function measurements by cardiac magnetic resonance imaging or cardiopulmonary exercise tests, precluding analyses of its association with muscle strength. Instead, we used 6MWD, a submaximal exercise assessment, as a relevant outcome parameter in PAH. Also, measurements of muscle mass or lean body mass were not performed in this study. Nevertheless, this study is the first to evaluate muscle strength in pediatric PAH in relation to healthy controls[18,23] and showed that isometric muscle strength and dynamic muscle function were significantly reduced in children with PAH compared with healthy children. Reduced muscle strength correlated with a prominent clinical manifestation of PAH, namely reduced exercise tolerance, measured as 6MWD, which is regarded as an important contributor to quality of life. Given the improved prognosis of children with PAH, addressing quality of life is of great importance in the management of pediatric PAH. A better understanding of the etiology of reduced muscle strength in patients with PAH will help us to design interventions such as physical activity programs, aimed at improving the quality of life and perhaps even prognosis in these patients. Skeletal muscle dysfunction was present not only in patients with long-standing PAH or advanced clinical (WHO-FC) or biochemical (NT-pro-BNP) compromise but also in children with a seemingly satisfactory clinical condition. These observations are in line with the concept of a systemic syndrome in PAH involving peripheral skeletal muscles. Deconditioning due to chronic inactivity, however, may also cause skeletal muscular alterations. More research is needed to clarify the exact underlying mechanisms and to investigate the possible prognostic value of muscle strength and whether muscle strength may represent a therapeutic target in pediatric PAH.

TABLE 2 Muscle strength measurements in PAH.

Grip strength	***n* = 17**				***p* Value**[a]
Hands	Absolute		*z*-scores		
Left, kg	14.9	±9.4	−2.3	±1.4	**<0.001**
Right, kg	15.8	±9.1	−2.4	±1.1	**<0.001**
Maximum voluntary isometric contraction (MVIC)	*n* = 18				*p* Value[a]
Upper extremity	Absolute		*z*-scores		
Elbow flexor, Nm	94	±29	−2.2	±1.0	**<0.001**
Elbow extensor, Nm	74	[58–88]	−1.7	±1.3	**<0.001**
Lower extremity	Absolute		*z*-scores		
Hip flexor, Nm	101	±48	−2.7	[−3.3 to −2.5]	**<0.001**
Knee extensor, Nm	118	[83–169]	−2.2	±1.0	**<0.001**
Dynamic muscle function (BOT-2)	*n* = 17				*p* Value[b]
Strength and agility	Absolute		*z*-scores		
Standard summary score	40	±9	−1.0	±0.9	**<0.001**
Subtest scale score running, speed, and agility	11	±5	0.8	±1.0	**0.004**
Subtest scale score strength	10	±5	−0.9	±0.9	**0.001**

Note: Muscle strength in patients with PAH. Mean ± SD when normally distributed, median [IQR] when skewed. Bold values indicate significant differences between patients with PAH and z-score of zero.

Abbreviations: BOT-2, Bruininks–Oseretsky test of motor proficiency–2nd edition; IQR, interquartile range; Kg, kilograms; Nm, nanometer; PAH, pulmonary arterial hypertension.

[a]Differences between these *z*-scores of the healthy population[21,22] and the *z*-scores of the patient population by Student *t*-test.

[b]Differences between BOT-scores and *z*-score = 0 by one-sample *t*-test.

TABLE 3 Univariate correlations between muscle strength and disease severity markers.

Determinants	**Univariate correlation coefficient (*r*) 6MWD**	***p* Value**	**Univariate correlation coefficient (*r*) log NT-proBNP**	***p* Value**
Handgrip strength	0.53	**0.03**[a]	−0.22	0.40[a]
Elbow flexor	0.71	**0.001**[a]	−0.19	0.45[a]
Elbow extensor	0.70	**0.001**[b]	−0.27	0.29[b]
Hip flexor	0.39	0.11[a]	−0.08	0.75[a]
Knee extensor	0.49	**0.04**[b]	−0.07	0.80[b]
Standard score BOT-2	0.52	**0.03**[a]	−0.22	0.39[a]
Scale score running, speed, and agility	0.65	**0.01**[a]	−0.25	0.33[a]
Scale score strength	0.21	0.42[a]	−0.11	0.68[a]

Note: The univariate correlation coefficient between disease severity markers (6MWD [m]) and log (NT-proBNP [ng/L]) and muscle strength measures. Univariate correlation coefficient (*r*) based on Pearson's correlation (a) or Spearman's rank test (b) depending on the distribution of the determinant. Bold values indicate significant correlations between muscle strength and 6MWD.

Abbreviations: BOT-2, Bruininks–Oseretsky test of motor proficiency–2nd edition; NT-proBNP, N-terminal pro-brain natriuretic peptide; 6MWD, 6-minute walk distance.

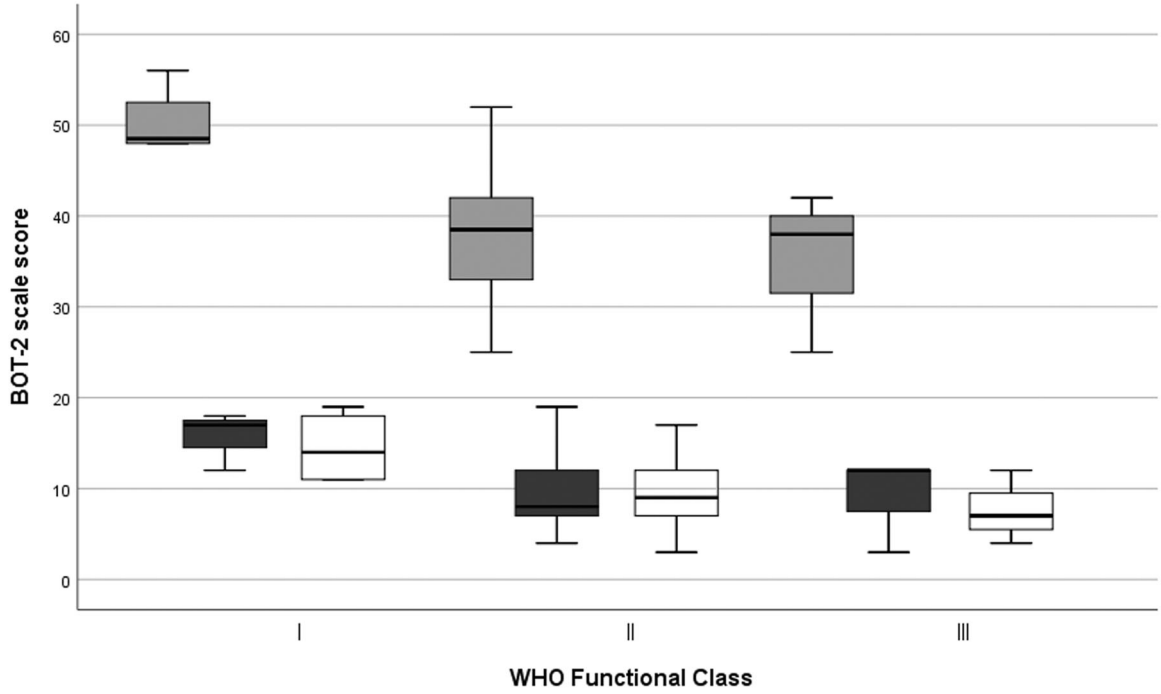

FIGURE 4 Shows the dynamic muscle strength (BOT-2) in relation to the WHO-FC. Light gray boxplot: Strength and agility standard score. Dark gray boxplot: Running, speed, and agility scale score. White boxplot: Strength scale score. BOT-2, Bruininks–Oseretsky test of motor proficiency–2nd edition; WHO-FC, World Health Organization functional class.

AUTHOR CONTRIBUTIONS

Conception or design of the work: Graziella Eshuis, Willemijn M. H. Zijlstra, Shari Pepplinkhuizen, Ann Marjolein Hepping, Ernesto A. C. Beenakker, and Rolf M. F. Berger. *Data collection*: Shari Pepplinkhuizen, Carola Y. Timmer, Otto T. H. M. Lelieveld, Ann Marjolein Hepping, and Ernesto A. C. Beenakker. *Data analysis and interpretation*: Graziella Eshuis and Mark Jan Ploegstra. *Drafting the article*: Shari Pepplinkhuizen and Graziella Eshuis. *Critical revision of the article*: Shari Pepplinkhuizen, Graziella Eshuis, Willemijn M. H. Zijlstra, Carola Y. Timmer, Mark Jan Ploegstra, Otto T. H. M. Lelieveld, Ann Marjolein Hepping, Ernesto A. C. Beenakker, and Rolf M. F. Berger. *Final approval of the version to be published*: Shari Pepplinkhuizen, Graziella Eshuis, Willemijn M. H. Zijlstra, Carola Y. Timmer, Mark Jan Ploegstra, Otto T. H. M. Lelieveld, Ann Marjolein Hepping, Ernesto A. C. Beenakker, and Rolf M. F. Berger. Guarantor: Rolf M. F. Berger.

ACKNOWLEDGMENTS

The authors would like to thank all colleagues from the pediatric cardiology department and exercise laboratory of the University Medical Center Groningen. This study was supported by the Sebald fund [grant number 81807].

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The institutional medical ethical board approved the Dutch national registry for pulmonary hypertension in childhood (approval number M11.097816) and all children and/or their guardians provided written informed consent.

ORCID

Graziella Eshuis https://orcid.org/0000-0001-6469-1566
Ernesto A. C. Beenakker https://orcid.org/0000-0001-7786-0285

REFERENCES

1. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlse J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O,

Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S, ESC/ERS Scientific Document Group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). Eur Heart J. 2022;43:3618–3731.

2. van Loon RLE, Roofthooft MTR, Delhaas T, van Osch-Gevers M, ten Harkel ADJ, Strengers JLM, Backx A, Hillege HL, Berger RMF. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol. 2010;106:117–24.
3. McLaughlin VV, Presberg KW, Doyle RL, Abman SH, McCrory DC, Fortin T, Ahearn G. Prognosis of pulmonary arterial hypertension*. Chest. 2004;126:78S–92S.
4. Halank M, Einsle F, Lehman S, Bremer H, Ewert R, Wilkens H, Meyer FJ, Grünig E, Seyfarth HJ, Kolditz M, Wieder G, Höffken G, Köllner V. Exercise capacity affects quality of life in patients with pulmonary hypertension. Lung. 2013;191:337–43.
5. Mullen MP, Andrus J, Labella MH, Forbes PW, Rao S, McSweeney JE, Kulik TJ, DeMaso DR. Quality of life and parental adjustment in pediatric pulmonary hypertension. Chest. 2014;145:237–44.
6. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation. 2001;104:429–35.
7. Bauer R, Dehnert C, Schoene P, Filusch A, Bärtsch P, Borst MM, Katus HA, Joachim Meyer F. Skeletal muscle dysfunction in patients with idiopathic pulmonary arterial hypertension. Respir Med. 2007;101:2366–69.
8. Mainguy V, Maltais F, Saey D, Gagnon P, Martel S, Simon M, Provencher S. Peripheral muscle dysfunction in idiopathic pulmonary arterial hypertension. Thorax. 2010;65:113–117.
9. Marra AM, Arcopinto M, Bossone E, Ehlken N, Cittadini A, Grünig E. Pulmonary arterial hypertension-related myopathy: an overview of current data and future perspectives. Nutr Metab Cardiovasc Dis. 2015;25:131–139.
10. Batt J, Ahmed SS, Correa J, Bain A, Granton J. Skeletal muscle dysfunction in idiopathic pulmonary arterial hypertension. Am J Respir Cell Mol Biol. 2014;50:74–86.
11. Dimopoulos S, Tzanis G, Manetos C, Tasoulis A, Mpouchla A, Tseliou E, Vasileiadis I, Diakos N, Terrovitis J, Nanas S. Peripheral muscle microcirculatory alterations in patients with pulmonary arterial hypertension: a pilot study. Respir Care. 2013;58:2134–41.
12. Potus F, Malenfant S, Graydon C, Mainguy V, Tremblay È, Breuils-Bonnet S, Ribeiro F, Porlier A, Maltais F, Bonnet S, Provencher S. Impaired angiogenesis and peripheral muscle microcirculation loss contribute to exercise intolerance in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2014;190:318–28.
13. Bohannon RW. Grip strength: an indispensable biomarker for older adults. Clin Interv Aging. 2019;14:1681–91.
14. Hogan J, Schneider MF, Pai R, Denburg MR, Kogon A, Brooks ER, Kaskel FJ, Reidy KJ, Saland JM, Warady BA, Furth SL, Patzer RE, Greenbaum LA. Grip strength in children with chronic kidney disease. Pediatr Nephrol. 2020;35:891–899.
15. van Loon RLE, Roofthooft MTR, van Osch-Gevers M, Delhaas T, Strengers JLM, Blom NA, Backx A, Berger RMF. Clinical characterization of pediatric pulmonary hypertension: complex presentation and diagnosis. J Pediatr. 2009;155:176–182.
16. Douwes JM, Hegeman AK, van der Krieke MB, Roofthooft MTR, Hillege HL, Berger RMF. Six-minute walking distance and decrease in oxygen saturation during the six-minute walk test in pediatric pulmonary arterial hypertension. Int J Cardiol. 2016;202:34–9.
17. Geiger R, Strasak A, Treml B, Gasser K, Kleinsasser A, Fischer V, Geiger H, Loeckinger A, Stein JI. Six-minute walk test in children and adolescents. J Pediatr. 2007;150:395–399.
18. Beenakker EAC, van der Hoeven JH, Fock JM, Maurits NM. Reference values of maximum isometric muscle force obtained in 270 children aged 4-16 years by hand-held dynamometry. Neuromuscular Disord. 2001;11:441–6.
19. Brown T. Structural validity of the Bruininks-Oseretsky test of motor proficiency—second edition brief form (BOT-2-BF). Res Dev Disabil. 2019;85:92–103.
20. Bohannon RW. Considerations and practical options for measuring muscle strength: a narrative review. BioMed Res Int. 2019;2019:1–10.
21. Hamilton GF, McDonald C, Chenier TC. Measurement of grip strength: validity and reliability of the sphygmomanometer and Jamar grip dynamometer. J Orthopaedic Sports Physical Therapy. 1992;16(5):215–9. https://doi.org/10.2519/jospt.1992.16.5.215
22. Stark T, Walker B, Phillips JK, Fejer R, Beck R. Hand-held dynamometry correlation with the gold standard isokinetic dynamometry: a systematic review. PM&R. 2011;3:472–9.
23. Hepping AM, Ploegmakers JJW, Geertzen JHB, Bulstra SK, Stevens M. The influence of hand preference on grip strength in children and adolescents; a cross-sectional study of 2284 children and adolescents. PLoS One. 2015;10:e0143476.
24. Malenfant S, Potus F, Mainguy V, Leblanc E, Malenfant M, Ribeiro F, Saey D, Maltais F, Bonnet S, Provencher S. Impaired skeletal muscle oxygenation and exercise tolerance in pulmonary hypertension. Med Sci Sport Exercise. 2015;47:2273–82.
25. Zijlstra WMH, Ploegstra MJ, Vissia-Kazemier T, Roofthooft MTR, Sarvaas GM, Bartelds B, Rackowitz A, van den Heuvel F, Hillege HL, Plasqui G, Berger RMF. Physical activity in pediatric pulmonary arterial hypertension measured by accelerometry. A candidate clinical endpoint. Am J Respir Crit Care Med. 2017;196:220–227.
26. Ploegstra MJ, Douwes JM, Roofthooft MTR, Zijlstra WMH, Hillege HL, Berger RMF. Identification of treatment goals in paediatric pulmonary arterial hypertension. Eur Respir J. 2014;44:1616–26.
27. Meyer FJ, Lossnitzer D, Kristen AV, Schoene AM, Kübler W, Katus HA, Borst MM. Respiratory muscle dysfunction in idiopathic pulmonary arterial hypertension. Eur Respir J. 2005;25:125–30.
28. Malenfant S, Potus F, Fournier F, Breuils-Bonnet S, Pflieger A, Bourassa S, Tremblay È, Nehmé B, Droit A, Bonnet S,

Provencher S. Skeletal muscle proteomic signature and metabolic impairment in pulmonary hypertension. J Mol Med. 2015;93:573–84.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pepplinkhuizen S, Eshuis G, Zijlstra WMH, Timmer CY, Ploegstra MJ, Lelieveld OTHM, Hepping AM, Beenakker EAC, Berger RF. Muscle strength is reduced in children with pulmonary arterial hypertension. Pulm Circ. 2023;13:e12246. https://doi.org/10.1002/pul2.12246