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Original Article

Feasibility and safety of cardiopulmonary exercise testing in children with pulmonary hypertension

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Abstract *Background:* Cardiopulmonary exercise testing helps prognosticate and guide treatment in adults with pulmonary hypertension. Concerns regarding its feasibility and safety limit its use in children with pulmonary hypertension. We aimed to assess the feasibility and safety of cardiopulmonary exercise testing in a large paediatric pulmonary hypertension cohort. *Methods:* We reviewed all consecutive cardiopulmonary exercise tests performed between March, 2004 and November, 2013. The exclusion criteria were as follows: height <120 cm, World Health Organization class IV, history of exercise-induced syncope, or significant ischaemia/arrhythmias. Significant events recorded were as follows: patient-reported symptoms, arrhythmias, electrocardiogram abnormalities, and abnormal responses of arterial O_2 saturation. *Results:* A total of 98 children underwent 167 cardiopulmonary exercise tests. The median age was 14 years (inter-quartile range 10–15 years). Peak oxygen uptake was 20.4 ± 7.3 ml/kg/minute, corresponding to $51.8 \pm 18.3\%$ of the predicted value. Peak respiratory quotient was 1.08 ± 0.16. All the tests except two were maximal, being terminated prematurely for clinical reasons. Baseline Oxygen saturation was $93.3 \pm 8.8\%$ and was $81.2 \pm 19.5\%$ at peak exercise. A drop in arterial O_2 saturation >20% was observed in 23.5% of the patients. Moreover, five patients (3.0%) experienced dizziness, one requiring termination of cardiopulmonary exercise testing; five children (3.0%) experienced chest pain, with early cardiopulmonary exercise test termination in one patient. No significant arrhythmias or electrocardiogram changes were observed. *Conclusion:* Exercise testing in non-severely symptomatic children with pulmonary hypertension is safe and practical, and can be performed in a large number of children with pulmonary hypertension in a controlled environment with an experienced team. Side-effects were not serious and were resolved promptly with test termination.

Keywords: Pulmonary hypertension; exercise test; CHDs; exercise physiology

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PAEDIATRIC PULMONARY HYPERTENSION IS ASSOCIATED with substantial morbidity and mortality. The measurement of exercise capacity is an accepted means of gauging overall condition throughout the pulmonary hypertension disease course. This is performed by either a 6-minute walking distance test or a standardised cardiopulmonary exercise testing. Both are widely used and are considered valid for determining the severity, prognosis, and management of multiple cardiac and respiratory pathologies.[1–3]

Although the 6-minute walking distance test has some attractive advantages, cardiopulmonary exercise testing is widely considered the gold standard for the objective assessment of exercise capacity and, at the same time, offers information on blood pressure, arterial oxygenation, lung function, ventilation, and

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electrocardiogram changes during exercise. The exclusive prerogatives of cardiopulmonary exercise testing are the measurement of oxygen uptake at peak exercise and at the anaerobic threshold as well as the measurement of ventilatory efficiency. Cardiopulmonary exercise testing further benefits from a higher reproducibility, a more integrated assessment of the patients' physiology, and is more representative of maximal exertion. These additional measures are proven guides to pulmonary hypertension functional capacity and prognosis.[4,5]

In terms of accessibility, there are certain drawbacks to the cardiopulmonary exercise testing. In general, it requires an older patient in order to follow instructions, and also higher degree of motor skills is required to perform the investigation. Furthermore, those with co-morbidities – for example, patients with moderate-to-severe neurodisability – are limited or excluded from the test.

Maximal cardiopulmonary exercise testing is accompanied by certain risk factors.[6,7] Relative contraindications to cardiopulmonary exercise testing include severe pulmonary hypertension, where there is concern that the risks of desaturation, arrhythmia, and syncope can outweigh the benefits of cardiopulmonary exercise test data. Thus far, safety has been robustly demonstrated in selected adult pulmonary hypertension patients, whereas paediatric data remain limited, and pathophysiological differences between these groups void generalisation of outcomes.[8] Current paediatric evidence targeting safety consists of two small retrospective studies, which included 27 and 40 patients, respectively. Neither of the studies differentiated between the different diagnostic groups of pulmonary hypertension.[2,9] This is in part due to the low prevalence of paediatric pulmonary hypertension.

A recent American Heart Association scientific statement found that only 65% of academic institutions perform cardiopulmonary exercise testing in paediatric pulmonary hypertension patients.[7] The paucity of evidence in its favour creates a paradox whereby clinicians are reluctant to properly evaluate its feasibility and safety through further use, stifling the development of further evidence.[2,9–11] These issues among others have led to preference for the 6-minute walking distance test over cardiopulmonary exercise testing, despite the more limited data gained from the test.

Given the above factors, we undertook a retrospective analysis of all consecutive cardiopulmonary exercise tests performed in children with pulmonary hypertension at our centre. The purpose of our study was to assess the feasibility and safety profile of cardiopulmonary exercise testing in a large cohort of patients with pulmonary hypertension and to understand whether specific features – including pulmonary hypertension diagnostic groups – are associated with an increased risk of events during cardiopulmonary exercise testing. This might, therefore, facilitate a greater uptake of this useful test in other institutions.

Materials and methods

The present study was a single-centre retrospective study including all eligible consecutive children with pulmonary hypertension who underwent a cardiopulmonary exercise testing between March, 2004 and November, 2013.

Exclusion criteria

Local exclusion criteria for cardiopulmonary exercise testing included height <120 cm. Exclusions due to resting symptoms were also made based on clinical judgement. Broadly, but not exclusively, this applied to patients in World Health Organization functional class IV and to patients with a history of syncope or significant ischaemia/arrhythmias during exercise. Furthermore, children with physical disability such as neurodisability or who were unable to follow commands for cardiopulmonary exercise testing were excluded.

Classification

All the patients underwent an extensive workup to identify the diagnostic pulmonary hypertension group and to assess the extent of pulmonary hypertension. Pulmonary hypertension was defined via catheterisation studies whenever possible; two patients had a diagnosis of pulmonary hypertension based on high-velocity measures from tricuspid regurgitation jets.

Demographic data – including age, gender, and body surface area – cause of pulmonary hypertension, World Health Organization functional class, and the patients medical therapies were abstracted from patient charts and records.

Participants were grouped according to Dana point pulmonary hypertension classification,[12] which included Dana Point group 1.1 idiopathic (36 patients, 59 tests), Dana point group 1.4.4 CHDs (45 patients, 76 tests), Dana point group 2 pulmonary hypertension due to left heart disease (three patients, six tests), and Dana Point group 3 pulmonary hypertension due to lung disease (10 patients, 19 tests). Patients who fell outside these groups and who were not in sufficient number to justify their own group were categorised as "Other" (four patients, seven tests). The "Other" group was composed of two children

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from group 1.4.1 connective tissue disease and two children from group 4 chronic thromboembolic pulmonary hypertension patients. The CHDs group included both univentricular (five patients) and biventricular defects (40 patients). The latter included atrial septal defects, ventricular septal defects, patent ductus arteriosus, other defects, such as an aorto-pulmonary window, or a state bridging more than one of these categories termed 'multiple defects'.

Exercise tests

All the cardiopulmonary exercise tests were performed using an electronically braked ergometer cycle. Oxygen uptake, carbon dioxide elimination, and minute ventilation were measured using a computerised breath-by-breath analyzer (Medgraphics, St. Paul, Minnesota, United States of America). Patients performed a symptom-limited maximal exercise test using a continuous incremental bicycle protocol with a work rate increment between 5 and 15 W/minute, with the aim of completing the test within 10–12 minutes of exercise. A 12-lead electrocardiogram and transcutaneous oxygen saturation were also monitored throughout the study, and cuff blood pressure was determined manually every 2 minutes. The test was considered as maximal when the patient reported exhaustion, which was confirmed by an experienced physiologist attending the test, or when a respiratory exchange ratio $\geqslant 1.09$ was reached. Patients continued load-less, slow (20 revolutions/minute) cycling in the 1st minute of recovery in order to minimise the risk of post-exercise hypotension. The technical details relating to peak oxygen uptake measurement and other exercise variables are previously published.[13,14] Ventilatory efficiency was measured as the slope of minute ventilation/CO_2 elimination (VE/VCO_2 slope) for the whole duration of exercise. Resting heart rate and arterial O_2 saturation were measured after at least 2 minutes of complete rest in a seated position. Peak heart rate was defined as the maximal heart rate achieved during exercise. The lowest value of arterial O_2 saturation was also recorded. Significant and adverse events were recorded, as were any reasons for investigation termination.

Statistical analysis

Data distribution was tested using the Kolmogorov–Smirnov test. Normally distributed data are reported as mean ± standard deviation. Non-normally distributed data are reported as median (inter-quartile range). Categorical variables are reported as a number and percentage. Comparison of the rates of cardiopulmonary exercise test-related side-effects across different pulmonary hypertension diagnostic groups was performed using the χ^2-test. Subsequently, a pairwise comparison between each of the five different diagnostic groups within each type of side-effect was performed using the χ^2 test with Bonferroni correction to account for multiple comparisons. In brief, a family-wise significant threshold of 0.05 was chosen, and as 10 comparisons were made the new threshold was reduced to 0.05/10, or 0.005. Data were analysed using Graph Pad Prism Version 5. A two-tailed probability value $\leqslant 0.05$ was used as the criterion for statistical significance.

Results

A total of 167 cardiopulmonary exercise tests were performed in 98 patients (48.8% males). Of these, 69 were repeat investigations, with an average of 1.70 cardiopulmonary exercise tests/patient (range 1–7 cardiopulmonary exercise tests). In 96 patients (98.0%), pulmonary hypertension was confirmed via catheter studies. Of the remaining two patients, one had Eisenmenger syndrome and was diagnosed on the basis of an unrestrictive right-to-left cardiac shunt. The remaining patient had transthoracic echocardiography showing right ventricular dilatation and estimated right ventricular systolic pressure of 45 mmHg in the context of substantial interstitial lung disease. During the same time periods, 350 children taller than 120 cm were seen by the national pulmonary hypertension team (average age 10.8 ± 3.7 years), with 4.7% being in NYHA class 4.

The median age at cardiopulmonary exercise testing was 14 years (inter-quartile range 10–15 years). Demographic and cardiopulmonary exercise test data are outlined in Table 1, whereas the medications taken at the time of exercise for all 167 cardiopulmonary exercise tests are provided in Table 2.

Peak oxygen uptake for all pulmonary hypertension patients was 20.4 ± 7.3 ml/kg/min, which corresponded to 51.8 ± 18.3% of the predicted value. Peak respiratory quotient was 1.08 ± 0.16. Resting heart rate was 93.7 ± 16.1 bpm, and peak heart rate was 154.7 ± 23.3 bpm, which corresponded to 84 ± 13% of the predicted peak heart rate. Mean systolic blood pressure at rest averaged 103.8 ± 16.1 mmHg. Peak exercise systolic blood pressure was 120 ± 30.7 mmHg, and peak ventilatory equivalent for carbon dioxide was 43.0 ± 8.03.

Safety of cardiopulmonary exercise testing

Of 167 cardiopulmonary exercise test studies, two were terminated before peak exercise. This was due to symptoms of chest pain in one child and dizziness in another.

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Table 1. Cardiopulmonary exercise test (CPET) demographics and test results categorised according to PH class and presented as mean ± SD, unless otherwise stated.

Variable	All Tests (167)
Age (years)	14.0 (10–15.0)
Height (cm)	151 ± 16.1
Weight (kg)	45.3 ± 16.4
Idiopathic PH	59
PH associated with CHD	76
PH due to left heart disease	6
PH due to lung disease/hypoxaemia	19
Other forms of PH	7
WHO functional class	2.25 ± 0.8
6MWD	381.7 ± 106.9
CPET variable	Values (n = 167)
Rest HR (beats/minute)	93.7 ± 16.1
Peak HR (beats/minute)	154.7 ± 23.3
Percentage of predicted peak HR (%)	84.0 ± 12.6
Rest SaO_2 (%)	93.3 ± 8.8
Peak SaO_2 (%)	81.2 ± 19.5
Absolute SaO_2 change (%)	12.1 ± 14.3
Resting systolic BP (mmHg)	103.8 ± 16.1
Peak systolic BP (mmHg)	120 ± 30.7
Peak respiratory quotient	1.08 ± 0.16
Peak VO_2 (ml/kg/minute)	20.4 ± 7.28
Peak VO_2 (% of predicted)	51.8 ± 18.3
Peak VE/VCO_2 slope	43.0 ± 8.03
Peak workload (Watts)	69.5 ± 37.85

BP = blood pressure; WHO = World Health Organization; HR = heart rate; PH = pulmonary hypertension; SaO_2 = arterial oxygen saturation; VO_2 = oxygen uptake; VE/VCO_2 = ventilatory equivalent for carbon dioxide.

Table 2. Medications used at the time of exercise testing.

PH-related medication	Number of patients (%)
Prostanoid	27 (16.26)
Endothelin-1 antagonist	91 (54.5)
Phosphodiesterase-V inhibitor	90 (53.9)
Calcium channel antagonist	34 (20.4)
Anticoagulant	87 (52.1)
Digoxin	7 (4.19)
Diuretic	31 (18.56)
Oxygen	26 (15.7)
No medication	21 (12.6)

Overall, dizziness was the most frequently reported symptom, predominantly developing after cardiopulmonary exercise test. The incidence of adverse events is demonstrated in Table 3.

In addition, five patients experienced chest pain during the test, which was associated with drops in arterial O_2 saturation >5% in three (60%). Of the five patients who experienced dizziness, two (40%) had concurrent arterial O_2 saturation drops >5%; 34.1% of the patients did not demonstrate any symptoms or adverse effects. Mean arterial O_2 saturation was 93.3 ± 8.8% at rest and was 81.2 ± 19.5% at peak exercise. A drop in arterial O_2 saturation >10% occurred in 68 patients (40.9%), and a drop >20% occurred in 39 patients (23.5%).

Association between diagnostic group and side-effects during cardiopulmonary exercise testing

The frequency of some side-effects observed during exercise varied depending on the pulmonary hypertension diagnostic group (Table 3). Ventricular ectopics were significantly more common in children with pulmonary hypertension due to lung disease/hypoxaemia than in children with idiopathic pulmonary hypertension ($p < 0.05$) or in children with pulmonary hypertension associated with CHDs ($p < 0.001$). A drop in arterial O_2 saturation (>5%) was more common in children with pulmonary hypertension due to lung disease/hypoxaemia compared with children with idiopathic pulmonary hypertension ($p < 0.05$), and it was more common in those with CHD than in those with left heart disease ($p < 0.05$) or lung disease ($p < 0.01$). There was no significant difference between groups with regard to dizziness and chest pain. Overall, no specific diagnostic group had a greater risk of side-effects than any other; however, the response of arterial O_2 saturation to exercise was different across diagnostic groups. Table 4 demonstrates the numbers of patients experiencing changes in saturations according to pulmonary hypertension categories. Table 5 shows the results of peak exercise systolic blood pressure and ventilatory efficiency of children who experienced cyanosis during exercise compared with those who remained acyanotic, and again of those who experienced dizziness and those who did not. Children who developed cyanosis had similar peak systolic blood pressure (125 ± 28 versus 114 ± 32 mmHg, $p = 0.477$) but higher ventilatory equivalent for carbon dioxide (49.9 ± 9.8 versus, 41.8 ± 9.7, $p < 0.0001$). Patients who experienced dizziness ($n = 5$) had similar peak systolic blood pressure (115.0 ± 18 versus, 120 ± 30 mmHg, $p = 0.448$) and ventilatory equivalent for carbon dioxide (42.4 ± 10.3 versus 46.0 ± 10.6, $p = 0.442$).

Discussion

The use of cardiopulmonary exercise testing in the context of paediatric pulmonary hypertension is controversial due concerns regarding feasibility and safety. Feasibility is affected by patient size, but can also be affected by children being developmentally unable to reliably exercise or unwilling to undergo placement of the monitoring required for the test. Safety is also a concern as noted in a recent statement regarding paediatric exercise testing from the American

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Table 3. Frequency of complications observed in different PH diagnostic groups with p-values representing the χ^2-test results.

Adverse Event	All tests (n = 167)	Idiopathic PH (n = 59)	PH associated with CHD (n = 76)	PH due to left heart disease (n = 6)	PH due to lung disease/hypoxaemia (n = 19)	Other (n = 7)	p-value
Dizziness (n (%))	5 (3.0)	2 (3.4)	1 (1.3)	1 (16.7)	1 (5.3)	0 (0)	<0.0001
Chest pain (n (%))	5 (3.0)	1 (1.7)	4 (5.3)	0 (0)	0 (0)	0 (0)	0.634
SaO_2 drop ⩾5% (n (%))	94 (56.6)	23 (39.0)	48 (63.2)	1 (16.7)	18 (89.5)	4 (71.4)	0.0004
Ventricular ectopic beats (n (%))	21 (12.6)	8 (13.6)	4 (5.3)	1 (16.7)	8 (42.1)	0 (0)	0.0003
ST depression (n (%))	8 (4.8)	2 (3.3)	6 (7.9)	0 (0)	0 (0)	0 (0)	0.502
T wave changes (n (%))	5 (3.0)	3 (5.1)	1 (1.3)	0 (0)	1 (5.3)	0 (0)	0.0003
Other events (n (%))	12 (7.2)	2 (3.4)	6 (8.0)	2 (33.3)	0 (0)	2 (28.6)	0.016
No events (n (%))	57 (34.1)	24 (40.6)	26 (34.2)	3 (50)	3 (15.8)	1 (14.3)	0.407

CHD = congenital heart disease; PH = pulmonary hypertension; SaO_2 = arterial oxygen saturation.
The other group is composed of two children with connective tissue disease and two children with chronic thromboembolic PH.

Table 4. Extent and frequencies of SaO_2 changes from rest to peak exercise for patients with measurable peak exercise SaO_2 values (n = 166) with p-values representing the χ^2-test results.

SaO_2 change (%)	All (n = 166)	Idiopathic PH (n = 59)	PH associated with CHD (n = 76)	PH due to left heart disease (n = 6)	PH due to lung disease/ hypoxaemia (n = 19)	Other (n = 6)	p-value
⩽5%	72 (43.4%)	36 (61.0%)	28 (36.8%)	5 (83.3%)	1 (5.2%)	2 (33.3%)	0.0004
5.1–10%	26 (15.7%)	11 (18.6%)	9 (11.8%)	0 (0%)	3 (15.8%)	3 (50%)	0.0035
10.1–15%	13 (7.8%)	1 (1.7%)	6 (7.8%)	0 (0%)	5 (26.3%)	1 (16.7%)	0.1796
15.1–20%	16 (9.6%)	6 (10.2%)	6 (7.8%)	1 (16.6%)	3 (15.8%)	0 (0%)	0.9967
>20%	39 (23.5%)	5 (8.5%)	27 (35.5%)	0 (0%)	7 (36.8%)	0 (0%)	0.0002

PH = pulmonary hypertension; SaO_2 = arterial oxygen saturation.
The other group is composed of two children with connective tissue disease and two children with chronic thromboembolic PH.
NB: for one patient, pulse oximetry data were unavailable, and thus has not been included in this table.

Table 5. Cardiopulmonary exercise test (CPET) test results categorised according to reported adverse complications and presented as mean ± SD unless otherwise stated with p-values representing the χ^2-test results.

CPET Variable	Cyanosis (n = 87)	Acyanotic (n = 80)	p-value	Dizziness (n = 5)	No dizziness (n = 162)	p-value
Peak Systolic BP (mmHg)	125 ± 28	114 ± 32	0.477	115 ± 18	120 ± 30	0.448
Peak VE/VCO_2 slope	49.9 ± 9.8	41.8 ± 9.7	<0.0001	42.4 ± 10.3	46.0 ± 10.6	0.442

BP = blood pressure; VE/VCO_2 = ventilatory equivalent for carbon dioxide.

Heart Association, which showed that only about 65% of academic paediatric cardiology programmes routinely test children with pulmonary hypertension.

The 6-minute walking test and cardiopulmonary exercise test have all been used to assess exercise ability in children with pulmonary hypertension. Although the 6-minute working test is more versatile, does not require extensive monitoring apparatus, and can be used in younger children, exercise testing can only be performed in children who are taller than 120 cm and are developmentally able to cycle at a constant rate. On the other hand, cardiopulmonary exercise testing has several well-known advantages including the reproducibility and ability to perform a more integrated assessment of the patients' physiology. Data on cardiopulmonary exercise testing in children with pulmonary hypertension show that only about 67% of children older than 7 years of age are able to exercise reliably.[15] In the time period covered by our study, only 98 of the 350 children >120 cm where tested with cardiopulmonary exercise test, and 4.7% of them were not tested because of very severe clinical condition (NYHA class 4); however, our data, which covered an early phase where referral for cardiopulmonary exercise test was also limited by practice rather by patient eligibility or suitability, suggest that the test is under-utilised in our patient cohort.

Our study provides the largest available body of evidence, suggesting that cardiopulmonary exercise testing is safe in selected children with pulmonary hypertension in the context of a trained and experienced team. At the same time, the size of the data set presented has sufficient power to recognise the

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heterogeneity present within individual pulmonary hypertension subtypes.

We documented that side-effects during cardiopulmonary exercise testing are relatively frequent, but they are minor and self-resolving and very rarely require the premature termination of the test. Importantly, there were no severe side-effects such as syncope, no evidence of clinical deterioration, or need for hospital admission, and most importantly no fatality was associated with testing. Arterial desaturation during exercise was common in this cohort, although it was infrequently associated with symptoms. A drop in arterial O_2 saturation >5% from the baseline value was observed in over half of the study cohort; however, a significant drop in arterial O_2 saturation – >20% from the baseline value – occurred in 23.5% of the patients.

The use of cardiopulmonary exercise test in this population also offers the theoretical advantage that patients could receive a more individualised exercise prescription once the results are available – for example, in our centre, we follow the recommendations of Takken et al,[16] using both the data from cardiopulmonary exercise testing, along with clinical status to delineate the patient's exercise limitations, and our recommendations for exercise intake.

The findings of this study are in agreement with those of two smaller previous studies.[2,9] In particular, we observed a not dissimilar rate of arterial desaturation to that recorded previously by Smith – that is, 56.6% in our study compared with 39%.[9] Nevertheless, we observed a higher incidence of chest pain and dizziness, whereas these symptoms were not reported by Smith or Yetman.[2] It is possible that this relates to the extent of the effort put in during cardiopulmonary exercise testing.

We also recognised that certain types of side-effects occurred more commonly in certain diagnostic subgroups. Ventricular ectopic beats were more common in patients with pulmonary hypertension secondary to lung disease/hypoxaemia than in those with pulmonary hypertension associated with CHDs or idiopathic pulmonary hypertension. We have no clear explanation for this observation.

As previously documented, children with pulmonary hypertension had reduced values of peak oxygen uptake and increased ventilator respiratory rate when compared with normal individuals, with the source of limitation being multifactorial, including both impaired stroke volume response to exercise and ventilation/perfusion mismatch.[2,9]

Limitations

The present study has certain limitations. First, this was a retrospective study and it shares the limitations of such a study, as such numerical data on management decisions based on cardiopulmonary exercise testing are not possible. Moreover, these data do not permit us to delineate its prognostic significance. If outcome data were available, this may have been inferred by the ventilatory equivalent for carbon dioxide. Second, some specific patient subgroups had to be excluded from this study, and this included younger children who did not reach the 120-cm cut-off criterion and those with more advanced disease and symptoms at rest, therefore deemed clinically unsuitable for cardiopulmonary exercise testing. Furthermore, those with certain medical diagnoses such as neurodisability were also excluded as they could not exercise under instruction. A further limitation is that patients in good clinical condition and with little symptoms might have not been referred for cardiopulmonary exercise testing. That stated, we have used a non-selective approach to inclusion in this study in order to minimise the bias with clearly defined referral criteria. The effectiveness of this is re-inforced by the demographic parameters of our own study not differing greatly from other epidemiological studies on paediatric pulmonary hypertension at our institution.[17]

Finally, our cohort consisted largely of children with idiopathic and CHDs associated pulmonary hypertension. This meant that the number of patients included in other diagnostic groups was relatively small, and therefore had lower statistical power. Future works with greater sample sizes may address this issue.

Clinical perspective

We have demonstrated the feasibility and safety of cardiopulmonary exercise testing throughout the most common subgroups of paediatric pulmonary hypertension. This study advocates a more liberal use of cardiopulmonary exercise testing in the paediatric pulmonary hypertension population, particularly to completely harness its utility as a tool to guide and monitor treatment, as has been achieved in the adult pulmonary hypertension population. Perhaps, more pertinently, where in adults it has demonstrated prognostic capability, an interesting question remains to be answered in children.

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Conflicts of Interest

None.

Ethical Standards

The local institutional review board reviewed the application and waived the need for consent.

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