Magnetic Resonance Imaging

Magnetic Resonance–Augmented Cardiopulmonary Exercise Testing

Comprehensively Assessing Exercise Intolerance in Children With Cardiovascular Disease

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Background—Conventional cardiopulmonary exercise testing can objectively measure exercise intolerance but cannot provide comprehensive evaluation of physiology. This requires additional assessment of cardiac output and arteriovenous oxygen content difference. We developed magnetic resonance (MR)–augmented cardiopulmonary exercise testing to achieve this goal and assessed children with right heart disease.

Methods and Results—Healthy controls (n=10) and children with pulmonary arterial hypertension (PAH; n=10) and repaired tetralogy of Fallot (n=10) underwent MR-augmented cardiopulmonary exercise testing. All exercises were performed on an MR-compatible ergometer, and oxygen uptake was continuously acquired using a modified metabolic cart. Simultaneous cardiac output was measured using a real-time MR flow sequence and combined with oxygen uptake to calculate arteriovenous oxygen content difference. Peak oxygen uptake was significantly lower in the PAH group (12.6±1.31 mL/kg per minute; P=0.01) and trended toward lower in the tetralogy of Fallot group (13.5±1.29 mL/kg per minute; P=0.06) compared with controls (16.7±1.37 mL/kg per minute). Although tetralogy of Fallot patients had the largest increase in cardiac output, they had lower resting (3±1.2 L/min per m²) and peak (5.3±1.2 L/min per m²) values compared with controls (resting 4.3±1.2 L/min per m² and peak 6.6±1.2 L/min per m²) and PAH patients (resting 4.5±1.1 L/min per m² and peak 5.9±1.1 L/min per m²). Both the PAH and tetralogy of Fallot patients had blunted exercise–induced increases in arteriovenous oxygen content difference. However, only the PAH patients had significantly reduced peak values (6.4±1.3 mL/O2/100 mL) compared with controls (8.4±1.4 mL/O2/100 mL; P=0.005).

Conclusions—MR-augmented cardiopulmonary exercise testing is feasible in both healthy children and children with cardiac disease. Using this novel technique, we have demonstrated abnormal exercise patterns in oxygen uptake, cardiac output, and arteriovenous oxygen content difference. (Circ Cardiovasc Imaging. 2016;9:e005282. DOI: 10.1161/CIRCIMAGING.116.005282.)

Key Words: cardiovascular magnetic resonance imaging ■ exercise physiology ■ pediatric ■ pulmonary hypertension ■ tetralogy of Fallot

Exercise intolerance is a common feature of cardiac disease, and measurement of oxygen consumption (VO₂) allows objective evaluation of exercise capacity. Studies have shown that peak VO₂ is highly prognostic, and cardiopulmonary exercise testing (CPET) is now routinely performed on these patients. However, it does not provide a comprehensive assessment of physiology because this also requires measurement of cardiac output (CO) and tissue oxygen (O₂) extraction. These metrics can be assessed using invasive CPET (I-CPET), in which pulmonary and systemic arterial catheterization is combined with exercise testing. Using I-CPET, it has been shown that tissue O₂ extraction is reduced in pulmonary hypertension, and this novel finding demonstrates the utility of the technique. Unfortunately, I-CPET is not practical in many patient groups because of its invasive nature. We have recently demonstrated an alternative noninvasive approach, which combines real-time magnetic resonance (MR) flow
assessments with MR compatible respiratory gas analysis.\textsuperscript{5} The simultaneous acquisition of CO and VO\textsubscript{2} allows subsequent calculation of arteriovenous oxygen content difference (a-vO\textsubscript{2})\textsuperscript{,2} a recognized measure of O\textsubscript{2} extraction. Thus, MR-augmented CPET (MR-CPET) provides a novel noninvasive method of comprehensively assessing exercise intolerance.

The primary aim of this proof-of-concept study was to demonstrate the feasibility of MR-CPET in a pediatric population. In children, MR-CPET is particularly appealing because I-CPET is challenging in this population. A secondary aim was to explore the differences in VO\textsubscript{2}, CO, and a-vO\textsubscript{2} during exercise in children with right heart disease.

**Methods**

**Study Population**

Thirty children divided into 3 groups were recruited into the study between February 2015 and February 2016. Group 1 (n=10; 6 female) was healthy pediatric controls recruited specifically for this study with no suspected or past medical history. Group 2 (n=10; 7 female) was children with a diagnosis of stable pulmonary arterial hypertension (PAH) with no recent changes in medication. Group 3 (n=10; 4 female) was children who had a primary diagnosis of tetralogy of Fallot (ToF) repaired in infancy with current pulmonary hypertension (PAH) with no recent changes in medication.

General exclusion criteria were (1) age <7 years, (2) MR-incompatible implant, (3) physical or intellectual disability, (4) exercise-induced collapse in the preceding 6 months, (5) previously documented desaturation on exercise, and (6) nontrivial tricuspid regurgitation. Specific group 2 exclusion criteria were (1) World Health Organization functional class IV and (2) continuous intravenous therapy. The study was undertaken with National Research Ethics Committee approval (National Health Service Health Research Organization functional class IV and (2) continuous intravenous therapy. The study was undertaken with National Research Ethics Committee approval (National Health Service Health Research Authority; UKCRN ID 17282), and full written consent was obtained for all subjects.

**Six-Minute Walk Test**

All participants completed a 6-minute walk test following the American Thoracic Society guidelines\textsuperscript{6} by a single operator (N.J. Barber).

**MR-Augmented Cardiopulmonary Exercise Testing**

MR-CPET was performed on a 1.5-Tesla MR scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany) using two 6-element body matrix coils. The scanning room was temperature controlled, and full pediatric resuscitation facilities and resuscitation team were available. ECG was continuously monitored using the Siemens magnetic resonance imaging vectorcardiogram (Siemens Medical Solutions, Erlangen, Germany).

**MR Techniques**

Cardiac output was assessed by measuring aortic flow at the level of the sino-tubular junction. Flow measurements were continuously acquired during exercise using a previously validated real-time unaliasing by Fourier-encoding the overlaps using the temporal dimension and sensitivity encoding spiral phase-contrast magnetic resonance sequence.\textsuperscript{3,5} Parameters used were as follows: field of view =450 mm, matrix=160×160, voxel size =2.8×2.8×7 mm, TR/TE=5.8/1.4 ms, flip angle=20°, velocity encoding =250 cm/s, R=6, and temporal resolution =35 ms. The unaliasing by Fourier-encoding the overlaps using the temporal dimension and sensitivity encoding reconstruction was performed online using a graphics processing unit-equipped external computer (Tesla C2070; Nvidia, Santa Clara, CA) that was networked to the native scanner reconstruction system.\textsuperscript{4}

Ventricular volumes and septal curvature were assessed on a short-axis stack using a previously validated real-time radial k-t SENSE steady-state free precession sequence. The parameters used were as follows: field of view =320 mm, matrix=128×128, voxel size 2.5×2.5×8, TR/TE=2.4/1.17 ms, flip angle =47°, R=8, and temporal resolution =36 ms.

**Respiratory Gas Analysis**

Breath-by-breath gas exchange was analyzed using a commercial CPET system (Ultima, MedGraphics, St Paul) equipped with an electro-galvanic oxygen sensor, a nondispersive infrared carbon dioxide sensor, and a calibrated differential pressure flow sensor. Because the analyzer was not MR compatible, it was placed in the control room, and a modified MR-compatible set of sampling tubes (umbilicus) were passed through the waveguide (Figure 1) and attached to the patient via a pneumotach and facemask (Hans Rudolph, Kansas City). The primary modifications to the umbilicus were increased length (470 cm compared with the standard 234 cm) and removal of ferromagnetic parts (see Data Supplement for full description of modifications). This customized umbilicus was extensively tested by the manufacturer and met all of the normal quality control standards (Data Supplement). Gas

**Figure 1.** Magnetic resonance (MR)–augmented cardiopulmonary exercise testing (MR-CPET) set-up. This image demonstrates a volunteer using the MR-compatible ergometer while inside the bore of the scanner. An optical interface cable (orange) passes from the control room through the waveguide to control the ergometer. The modified MR-compatible umbilicus (white) also passes from the metabolic cart through the waveguide and connects to the patient via a pneumotach and facemask.
Exercise Protocol
Exercise was performed on a supine MR-compatible ergometer (MR Cardiac Ergometer Up/Down; Lode, Groningen, The Netherlands) as shown in Figure 1. This ergometer uses an up-down pedaling motion, with the thighs relatively immobilized with straps. All participants underwent a standardized preparation protocol involving a verbal explanation, demonstration video, and practice exercise prior to going into the scanner. Before starting the exercise protocol, resting ventricular volumes were assessed. The exercise protocol consisted of a 1-minute rest period followed by 2 minutes of unloaded exercise (Figure 2) and then a stepped workload protocol (increase of 2 W/min for the first 5 minutes and subsequently 3 W/min until exhaustion). Ergometry was undertaken in hyperbolic mode, and participants were encouraged to maintain revolutions per minute between 40 and 70 to ensure workload was independent of cadence. During the exercise protocol, CO and VO2 were continuously measured. At the point of exhaustion, resistance was reduced to zero, and the subject was asked to exercise as hard as possible to maintain a high heart rate and prolong the exercise state. During this period, ventricular volumes (peak exercise) were assessed again (acquisition =30 s).

Image Analysis
All images were processed using in-house plug-ins for the open-source software OsirIX (OsirIX Foundation, Geneva, Switzerland).8 Flow data were processed as previously described.1 All magnitude images (≤25,000 frames) were segmented using a registration-based segmentation algorithm10 with manual operator correction (see Data Supplement for full description of flow analysis). The resultant raw flow curves and VO2 data were further analyzed using Matlab (Matlab 2012). The flow curves were automatically split into separate heartbeat cycles as previously described (Data Supplement), and the stroke volume (SV) was calculated by integration. The heart rate and SV data were combined to calculate CO (heart rate×SV). a-VO2 was then calculated as VO2/CO.

For ventricular volumetric assessment, end systolic and diastolic frames were identified by visual assessment. Manual segmentation allowed measurement of right ventricular (RV) and left ventricular (LV) end diastolic volume (EDV) and end systolic volume (ESV). The SV was the difference between these 2 values, and ejection fraction was SV/EDV. Because subjects with tricuspid regurgitation were excluded, it was possible to assess pulmonary regurgitation fraction indirectly as [(RVSV−LVSV)/RVSV]×100.

Septal curvature was measured from the short-axis images at the mid-papillary level.11 Raw curvature was taken as the inverse of the radius of the circle that was circumscribed by 3 points placed in the septum and propagated to all frames. The raw curvature was normalized using the lateral wall curvature, and the minimum septal curvature ratio was taken as the lowest or most negative value.

MR-CPET Experience Questionnaire
Participants were asked to rate their experience of MR-CPET on a 5-point Likert scale: (1) degree of concern prior to the test (1, very intense concern; 3, moderate; and 5, no concern), (2) comfort during the test (1, very poor; 3, moderate; and 5, very good), and (3) degree of perceived helplessness (1, very intense helplessness; 3, moderate; and 5, no helplessness). Responses ≥3 were considered clinically acceptable.

Statistical Analysis
All statistical analysis was performed using StataSE 13.0 (StataCorp, College Station). Data were examined for normality using the Shapiro–Wilk normality test, and non-normally distributed data were transformed using a log transform to ensure normal distribution prior to analysis. Descriptive statistics were expressed as mean (±standard deviation) or geometric mean (geometric standard deviation) where data were log-transformed for skewness. Between group differences were assessed using 1-way analysis of variance with post hoc Bonferroni corrected pairwise comparisons. Differences in metrics with exercise in different groups were assessed using repeated measures analysis of variance, with main effects of disease type and exercise and an interaction term representing disease multiplied by exercise. Greenhouse–Geisser epsilon for all the repeated measures models was calculated to assess sphericity, and in all cases, it equaled 1. Post hoc pairwise comparisons were performed for simple main effects with Bonferroni correction, and these are the P values reported in the results when comparing groups. Inter- and intra-observer variability was tested using intra-class correlation coefficients. Likert scale data were compared using the Kruskal–Wallis test, and sex distribution compared using Fisher exact test. A P value <0.05 was considered statistically significant.

Results
Demographics
The mean age of the overall study population was 12.45±2.58 years, with ToF patients being slightly older (P=0.03) than those in the PAH group (Table 1). There were no significant group differences in height, weight, or body surface area (Table 1).

All PAH patients had idiopathic disease, with 6/10 patients in functional class I and 4/10 patients in class II. Eight subjects had undergone right heart catheterization in the 2 years preceding the study (median time, 9.1 months; range, 6.4–17.9 months). The average mean pulmonary arterial pressure was

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>PAH</th>
<th>ToF</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female</td>
<td>4:6</td>
<td>3:7</td>
<td>6:4</td>
<td>0.53</td>
</tr>
<tr>
<td>Age, y</td>
<td>13±3</td>
<td>11±2.2</td>
<td>14±1.8</td>
<td>0.033</td>
</tr>
<tr>
<td>Height, cm*†</td>
<td>154±1.1</td>
<td>147±1.1</td>
<td>159±1.1</td>
<td>0.066</td>
</tr>
<tr>
<td>Weight, kg*</td>
<td>47±1.5</td>
<td>41±1.3</td>
<td>50±1.4</td>
<td>0.432</td>
</tr>
<tr>
<td>Body surface area, m2†</td>
<td>1.50±0.38</td>
<td>1.3±0.17</td>
<td>1.5±0.29</td>
<td>0.145</td>
</tr>
</tbody>
</table>

PAH indicates pulmonary arterial hypertension; and ToF, tetralogy of Fallot. *Log transformed (geometric mean). †W-test applied.
37.2±12.1 mm Hg, and pulmonary vascular resistance index was 9.6±5.0 WU m². All patients were treated with either targeted mono or dual therapy: Bosentan, 9/10 patients; Sildenafil, 8/10 patients; Tadalafil, 2/10 patients; Amlodipine, 6/10 patients; Ambrisentan, 1/10 patients; and inhaled Iloprost, 2/10 patients. In the repaired ToF patients, 9/10 patients were in functional class 1 and 1/10 patient in functional class II. The median age of primary surgery was 0.78 years (range 0.4–1.7 years), and 7/10 patients had transannular patch placement during their primary repair. Secondary surgical or catheter right ventricular outflow tract interventions had not been performed in any patients.

There were no significant \((P=0.71)\) differences in mean 6-minute walk test distances between the control (444±1.1 m), PAH (429±1.2 m), or ToF groups (449±1.1 m).

**Feasibility and Acceptability**

All recruited subjects successfully mastered the exercise technique and safely completed the MR-CPET protocol with no premature suspension of exercise. Cardiac output and VO₂ data were collected in all subjects, allowing calculation of a-\(\text{vO}_2\) in all cases. A representative example of the image data is shown in Figure 3 and the processed data in Figure 4.

All subjects exercised to exhaustion, achieving a peak respiratory exchange ratio \((\approx V\text{CO}_2/V\text{O}_2) \geq 1.1\). Healthy children achieved \(\approx 72\%\) predicted heart rate, which was significantly higher than that in the PAH (62%; \(P<0.001\)) and ToF groups (56%; \(P<0.001\)). There were trends toward longer exercise duration and greater Watts achieved in the control group compared with the PAH and ToF groups (Table 2).

**Figure 3.** Examples of magnetic resonance (MR) flow images subsets at rest and exercise throughout the cardiac cycle.

**Figure 4.** Representative oxygen uptake (VO₂), cardiac output (CO), and arteriovenous oxygen content gradient (a-\(\text{vO}_2\)) curves for a high-performing individual volunteer from the control group (red line) and individual volunteers from the pulmonary arterial hypertension (pale blue line) and tetralogy of Fallot groups (purple line). Combined VO₂, CO, and a-\(\text{vO}_2\) curves for all subjects are provided in the Data Supplement.
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There were no recorded complications (including documented arrhythmia) associated with exercise. All subjects reported clinically acceptable levels of satisfaction, comfort, worry, and helplessness (Table 2). There were no significant differences in these measures between groups (P > 0.3).

MR-CPET Metrics: Rest and Exercise

At rest, there was no significant difference in VO₂ between the groups (Figure 5 and Table 3). At peak exercise, VO₂ increased 4.1±1.3× in controls, which was significantly greater than the increase in TOF (3.2±1.2×; P = 0.04) and PAH (2.9±1.3×; P = 0.01) patients. These differences resulted in peak VO₂ being lower in the PAH group (12.6±1.3 mL/kg per minute; P = 0.01) and trending toward lower in the TOF group (13.5±1.29 mL/kg per minute; P = 0.06) compared with controls (16.7±1.3 mL/kg per minute).

Resting CO was significantly (P < 0.001) lower in TOF patients compared with that in controls and PAH patients (Figure 5 and Table 3). In PAH patients, augmentation of CO was nonsignificantly lower (1.3±1.3×) than in controls (1.6±1.3×; P = 0.174), and peak CO only trended (P = 0.1) toward being lower (Table 3). Augmentation of CO was greater in TOF patients (1.8±1.3×) than in controls, but did not reach significance (P = 0.217). Because of the lower baseline CO, peak CO was still significantly lower in TOF patients (5.3±1.2 versus 6.6±1.2; P = 0.003).

The TOF group had significantly higher a-vO₂ (4.7±1.2 mL/O₂/100 mL) at rest compared with the PAH (3.0±0.34 mL/O₂/100 mL; P = 0.001) and control groups (3.1±0.76 mL/O₂/100 mL; P = 0.003). There was no significant difference in a-vO₂ augmentation between controls (2.7±0.5×) and PAH patients (2.3±0.6×; P = 0.18). Nevertheless, peak a-vO₂ was lower in the PAH patients (6.9±1.3 mL/O₂/100 mL versus 8.4±1.4 mL/O₂/100 mL; P = 0.005). Conversely, a-vO₂ augmentation was significantly lower in TOF patients (1.9±0.3×; P = 0.001) compared with controls. However, because of the higher baseline value, there was no significant difference (P = 0.57) in peak a-vO₂ (Table 3).

Ventricular Volumes: Rest and Exercise

Resting RVEDV, RVESV, and RVSV were higher in the TOF group compared with the controls (P < 0.03). In all groups, RVEDV and RVESV decreased significantly by a similar amount with exercise (Table 4). RV ejection fraction increased during exercise in all groups (Table 4) but only reached significance in the PAH group (P = 0.01).

At rest, there were no group differences in LVEDV, LVESV, LVSV, and LV ejection fraction (Table 4). At peak exercise, LVEDV fell significantly in controls (P = 0.004) and PAH patients (P = 0.006) but not in TOF patients. LVESV also fell at peak exercise but only reached significance in the control (P = 0.002) and PAH groups (P = 0.013). LVSV increased significantly only during exercise in the TOF group (P = 0.035). In all groups, LV ejection fraction was significantly higher at peak exercise (Table 4).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>PAH</th>
<th>ToF</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Six-min walk test distance, m*</td>
<td>452±1.1</td>
<td>432±1.2</td>
<td>449±1.1</td>
<td>0.718</td>
</tr>
<tr>
<td>MR-CPET duration, min†</td>
<td>8.9±3</td>
<td>7.3±1.6</td>
<td>7±2.2</td>
<td>0.078</td>
</tr>
<tr>
<td>Peak work, W*†</td>
<td>12.0±2</td>
<td>8.7±1.5</td>
<td>7.7±1.9</td>
<td>0.145</td>
</tr>
<tr>
<td>Peak work, METS*</td>
<td>4.8±1.4</td>
<td>3.6±1.3</td>
<td>3.8±1.3</td>
<td>0.079</td>
</tr>
<tr>
<td>Percent predicted HR</td>
<td>72±8.2</td>
<td>62±9.6</td>
<td>56±8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RER†</td>
<td>1.7±0.43</td>
<td>1.5±0.28</td>
<td>1.4±0.15</td>
<td>0.011</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>4.4±0.7</td>
<td>4.3±0.48</td>
<td>4.6±0.52</td>
<td>0.45</td>
</tr>
<tr>
<td>Comfort*</td>
<td>3.5±1.3</td>
<td>3.5±1.3</td>
<td>3.8±1.2</td>
<td>0.82</td>
</tr>
<tr>
<td>Helplessness*</td>
<td>3.7±1.4</td>
<td>4±1.2</td>
<td>4.4±1.2</td>
<td>0.35</td>
</tr>
</tbody>
</table>

HR indicates heart rate; MR-CPET, magnetic resonance–augmented cardiopulmonary exercise testing; PAH, pulmonary arterial hypertension; RER, respiratory exchange ratio; and ToF, tetralogy of Fallot.

*Log transformed (geometric mean).
†W test applied.

Figure 5. Changes in mean magnetic resonance–augmented cardiopulmonary exercise testing (MR-CPET) metrics between rest and peak exercise, in the control (continuous line), pulmonary arterial hypertension (PAH; dashed line), and tetralogy of Fallot (ToF; dotted line). Error bars represent SEM. There was no significant difference in resting oxygen uptake (VO₂) but a lower peak VO₂ in the PAH group than in the control group (P = 0.01). Note higher resting arteriovenous oxygen content gradient (a-vO₂) in the ToF group with no significant difference at peak exercise and lower a-vO₂ at peak exercise in the PAH group than in the control group (P = 0.005). CO indicates cardiac output.
Other Metrics: Rest and Exercise
Nontrivial pulmonary regurgitation was only present in the ToF group, and at peak exercise, pulmonary regurgitation fraction fell significantly in this group \((P<0.001)\). Abnormal septal curvature was only present at rest (Table 3) in the PAH group, with significant worsening during exercise \((P<0.001)\). This corresponds to an estimated mean pulmonary artery pressure of 30±0.4 mmHg at rest, rising to 55±0.53 mmHg at peak exercise.

Intraobserver and Interobserver Reliability
There was good intraobserver reliability in real-time CO data (intraclass correlation coefficient 0.995, 95% confidence interval 0.98–0.999; \(P<0.001\)). There was also good interobserver reliability (intraclass correlation coefficient 0.996, 95% confidence interval 0.983–0.999; \(P<0.001\)).

Discussion
This proof-of-concept study demonstrates the feasibility of MR-CPET in children with cardiovascular disease. The main findings of our study were the following: (1) MR-CPET was safe in healthy children and those with right heart disease, (2) peak VO\(_2\) was reduced in pediatric PAH and ToF patients, and (3) PAH and ToF patients had different peak values and patterns of augmentation of CO and a-vO\(_2\) compared with the controls.

Table 3. MR-CPET-Derived Measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Rest</th>
<th>PAH Rest</th>
<th>ToF Rest</th>
<th>Disease Effect</th>
<th>Time Effect</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>83±17</td>
<td>149±18*</td>
<td>82±9.3</td>
<td>74±12</td>
<td>116±17*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SV, ml/m(^2)</td>
<td>49±11</td>
<td>46±8.2</td>
<td>49±5.9</td>
<td>41±8.4</td>
<td>46±5.4</td>
<td>0.43</td>
</tr>
<tr>
<td>CO, l/m/min†</td>
<td>4.3±1.2</td>
<td>6.6±1.2*</td>
<td>4.5±1.1</td>
<td>3±1.2</td>
<td>5.3±1.2*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VO(_2), ml/kg/min†</td>
<td>4.06±1.35</td>
<td>16.7±1.37*</td>
<td>12.6±1.13*</td>
<td>4.24±1.17</td>
<td>13.5±1.29*</td>
<td>0.51</td>
</tr>
<tr>
<td>a-vO(_2), mlO(_2)/100 mL blood</td>
<td>3.1±0.76</td>
<td>8.4±1.4*</td>
<td>3±0.34</td>
<td>6.9±1.3*</td>
<td>8.7±1.5*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

a-vO\(_2\) indicates arteriovenous oxygen content gradient; CO, cardiac output; HR, heart rate; MR-CPET, magnetic resonance–augmented cardiopulmonary exercise testing; PAH, pulmonary arterial hypertension; SV, stroke volume; ToF, tetralogy of Fallot; and VO\(_2\), oxygen uptake.

*Significant difference rest to peak.
†Log transformed (geometric mean).

MR-CPET Findings
In this study, we recruited relatively well patients in whom there was no significant difference in six minute walk test distance compared with controls. Nevertheless, PAH patients had reduced peak VO\(_2\), and ToF patients had a trend toward lower peak VO\(_2\). This is in keeping with previous studies in relatively well patients\(^{12,13}\) and demonstrates the sensitivity of conventional CPET for assessing mild exercise intolerance. Using MR-CPET, we were also able to demonstrate significant differences between the groups that were not apparent with VO\(_2\) alone. For example, PAH patients had a slightly blunted CO response to exercise and a trend toward lower peak CO. On the contrary, ToF patients had reduced resting and peak CO, despite a slightly amplified CO response to exercise. The findings in the PAH patients are unsurprising, but the findings in ToF patients are unexpected and warrant further study.

Table 4. Conventional MR-Derived Measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Rest</th>
<th>PAH Rest</th>
<th>ToF Rest</th>
<th>Disease Effect</th>
<th>Time Effect</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEDV, mL/m(^2)</td>
<td>77±16</td>
<td>68±13*</td>
<td>83±9.2</td>
<td>71±9.1*</td>
<td>95±16</td>
<td>86±14*</td>
</tr>
<tr>
<td>RVESV, mL/m(^2)†</td>
<td>29±1.3</td>
<td>20±1.6*</td>
<td>34±1.3</td>
<td>28±1.3*</td>
<td>39±1.3</td>
<td>30±1.5*</td>
</tr>
<tr>
<td>RVSV, mL/m(^2)</td>
<td>47±11</td>
<td>45±9.5</td>
<td>48±6.7</td>
<td>46±6.9</td>
<td>55±7.8</td>
<td>54±7.1</td>
</tr>
<tr>
<td>RVEF, %</td>
<td>62±5</td>
<td>67±12</td>
<td>58±7.8</td>
<td>66±9.8*</td>
<td>58±6</td>
<td>63±8.6</td>
</tr>
<tr>
<td>LVEDV, mL/m(^2)</td>
<td>67±13</td>
<td>59±9.6*</td>
<td>68±7.4</td>
<td>61±8.1*</td>
<td>63±5.2</td>
<td>64±6.2</td>
</tr>
<tr>
<td>LVESV, mL/m(^2)†</td>
<td>18±1.3</td>
<td>11±2*</td>
<td>20±1.2</td>
<td>14±1.4*</td>
<td>19±1.3</td>
<td>17±1.3</td>
</tr>
<tr>
<td>LVSV, mL/m(^2)</td>
<td>48±9.9</td>
<td>47±7.2</td>
<td>48±6.7</td>
<td>47±7</td>
<td>43±6.1</td>
<td>46±5.5</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>72±5.5</td>
<td>80±11*</td>
<td>70±4.4</td>
<td>77±3.3*</td>
<td>68±7.1</td>
<td>73±5.9</td>
</tr>
<tr>
<td>PRF, %</td>
<td>0.48±1.0</td>
<td>0.29±0.89</td>
<td>1.11±1.47</td>
<td>0.14±0.43</td>
<td>30.24±8.03</td>
<td>16.3±5.79*</td>
</tr>
<tr>
<td>Septal curvature ratio†</td>
<td>0.84±0.05</td>
<td>0.82±0.08</td>
<td>0.15±0.42</td>
<td>0.44±0.53</td>
<td>0.85±0.13</td>
<td>0.86±0.071</td>
</tr>
</tbody>
</table>

EDV indicates end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LV, left ventricle; mPA, estimated mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PRF, pulmonary regurgitant fraction; RV, right ventricle; SV, stroke volume; and ToF, tetralogy of Fallot.

*Significant difference rest to peak.
†Log transformed (geometric mean).
further explanation. It is conventionally believed that resting CO is preserved in ToF patients until late in the disease. Thus, our findings may simply be an artifact of nonrepresentative sampling. Still, there are some cardiovascular magnetic resonance studies that suggest that CO is lower in pediatric ToF patients when compared with normal children (assessed in a separate study but by the same group). These studies would seem to strengthen the validity of our resting findings, but larger studies are still required for further corroboration. The slightly better augmentation of CO in ToF patients is the result of increased effective RVSV because of a fall in pulmonary regurgitation. However, peak CO is still lower in ToF patients (because of the lower baseline value), and this might have important consequences for exercise tolerance.

Our MR-CPET data also allow evaluation of differences in tissue oxygen extraction (as assessed by a-vO2). Our results demonstrate a blunted response to exercise in PAH patients, which resulted in lower peak tissue oxygen extraction. Similar findings have been demonstrated in adults with PAH using I-CPET, but the exact cause is unclear. Biopsy studies have demonstrated skeletal muscle abnormalities in animal and human models of PAH, including reduced capillary density, changes in ratio of muscle fiber type, and alterations in mitochondrial function. Such changes could be the cause of reduced peak tissue oxygen extraction in these patients. Tissue oxygen extraction could also be affected by the vasodilator therapy, which was universal in our population. Possible mechanisms for this are intramuscular shunting and direct effects on muscle/mitochondrial physiology. Therefore, it would be useful to evaluate tissue oxygen extraction on a vasodilator naïve population in a future study.

Children with repaired ToF also had abnormal patterns of tissue oxygen extraction. The higher resting a-vO2 in ToF patients could simply be because of mathematical coupling between a CO and VO2, although it may have physiological relevance. The ToF patients also had a significantly blunted increase in a-vO2, although they reached a similar peak as that of the controls. Further work is required to understand if and how these abnormalities affect exercise tolerance.

We think that these results demonstrate that MR-CPET allows incremental improvement in the understanding of exercise dysfunction. Specifically, it provides insights not available if CO and VO2 are measured alone. Similar data are also available using I-CPET, which has the added benefit of providing simultaneous assessment of pulmonary artery pressure. This is pertinent in PAH patients because exercise-induced increase in pulmonary artery pressure may be a useful clinical biomarker. Unfortunately, I-CPET is difficult to perform in children because general anesthesia is usually required to perform cardiac catheterization. Consequently, MR-CPET may be useful as a substitute in the pediatric population, as well as in other groups.

One finding that has not been previously described is worsening septal curvature in PAH during exercise. It has been shown that septal curvature (measured using MR) correlates strongly with resting mean pulmonary artery pressure in children with PAH. Our results suggest that mean pulmonary artery pressure increases significantly during exercise in this group. This is consistent with invasive studies in adults, but has not been shown in children because of the difficulties in performing exercise catheterization in this age group. The ability to non-invasively assess pulmonary hemodynamics during exercise has several clinical uses. These include unmasking borderline PAH patients, assessing exercise-induced pulmonary hypertension, and investigating the causes of unexplained exercise intolerance.

Feasibility and Safety
In this study, all exams were completed safely, with no arrhythmia or exercise-induced complications. This is unsurprising because conventional CPET has been shown to be safe in these patient groups, and we only chose to study functional class I and II children. However, full 12-lead ECG monitoring is not readily available in MR, and this does prevent the use of MR-CPET in patients with significant risk of ischemia or arrhythmia. It was possible to obtain a continuous single-lead ECG during exercise in children unlike our previous adult study, in which ECGs were noninterpretable. We think that superior quality of the ECG signal in children was because of less movement during exercise and, consequently, less motion artifacts. Of course, for MR-CPET to become a useful clinical tool, it is vital that a universal and robust solution for monitoring electric activity is developed.

Technical Considerations
Although real-time techniques are invaluable when performing exercise cardiovascular magnetic resonance there are concerns over reduced image quality and robustness. Real-time MR techniques have been extensively tested against conventional gated MR with good agreement. In addition, a recent study has demonstrated good agreement between SV assessed using real-time MR volumes and the direct Fick method during exercise. Thus, we think that real-time MR is a valid method of evaluating physiology during exercise. Furthermore, recent innovations in real-time MR post-processing, such as pseudo-cardiac and respiratory gating and improved automated segmentation, may also improve measurement fidelity.

A further complication in this study was the need to continuously measure flow to guarantee acquisition of data at peak exercise. The resultant data consisted of ≤25,000 frames of flow images, representing a massive reconstruction and postprocessing problem. We used an online graphics processing unit reconstruction system to ensure that data were available in a clinically meaningful time. Currently, there are no commercial software solutions that can handle this amount of data, and consequently, we had to use an in-house postprocessing tool. Even using this optimized system, data analysis was time-consuming and could take several hours with operator adjustments. One method of reducing total processing time is to only segment the data at rest and around the point of exhaustion. This takes 30 minutes, and the reduced time makes MR-CPET more feasible in the clinical environment. Reducing the amount of image segmentation might also enable data to be more easily processed on commercial software. This is vital because the inability to process data using validated and quality-controlled software is a major limitation of this technique and an impediment to dissemination. One disadvantage of only processing a portion of the data is...
that the shape of the full VO$_2$, CO, and a-vO$_2$ curves may be clinically important. We have not explored the shape of these curves in the current study, but this is an important area for future research.

We used a standard clinical CPET system that was made MR compatible by a simple and inexpensive modification to the umbilicus. Other studies have made similar modifications (with removal of ferromagnetic parts) to commercially available gas analysis systems to make them MR compatible.\(^\text{23}\) Importantly, even though these modifications resulted in increased dead space, there was no significant measurement difference compared with an unmodified system. Another possible solution is to adapt the fully MR-compatible gas analysis systems for monitoring patients under general anesthesia. These systems are not validated for exercise, but do suggest a future direction for development.

**Limitations**

The main limitation of this study is that although the subjects exercised until exhaustion with satisfactory respiratory exchange ratios, the exercise performed was submaximal. Performing normal rotary exercise in the confined space of a MR scanner is difficult. Therefore, we used an up-down ergometer that requires a swimming-like, rather than cycle-like, motion. Unfortunately, this type of motion uses fewer muscle groups than used during cycling, partially explaining the significantly lower power output achieved in this study compared with that in conventional CPET. In addition, peak VO$_2$ and SV augmentation are consistently found to be lower at peak supine exercise compared with those at upright exercise in both adults and children.\(^\text{23-28}\) Thus, our form of supine exercise cannot be directly compared with that of conventional CPET, and this must be taken into consideration when interpreting the results. Nevertheless, we have previously demonstrated a good correlation between peak VO$_2$ obtained during MR-CPET and conventional CPET. Consequently, we that that peak VO$_2$ measured during MR-CPET is still a good marker of exercise capacity.

Another possible cause of these findings is abnormal pulmonary reserve, which was not formally tested in this study. It must be taken into consideration when interpreting the results. Therefore, we were able to show significant differences in the exercise responses in our patient groups. The technique is potentially of wider utility in cardiovascular disease, particularly when symptoms are induced or exacerbated by exercise.

**Conclusions**

This proof-of-concept study demonstrates the innovative use of an integrated MR-CPET approach both in healthy children and in children with cardiac disease. Using this novel non-invasive methodology, we were able to show significant differences in the exercise responses in our patient groups. The technique is potentially of wider utility in cardiovascular disease, particularly when symptoms are induced or exacerbated by exercise.

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**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

This study demonstrates the feasibility and safety of an innovative combined magnetic resonance–augmented cardiopulmonary exercise test in noninvasively assessing exercise physiology in children with cardiovascular disease. Reduced exercise capacity is a common feature of cardiovascular disease and is recognized to be prognostic in several conditions. This novel technique was able to demonstrate distinct patterns of oxygen consumption, cardiac output, and arteriovenous oxygen concentration gradient in patients with pulmonary hypertension and tetralogy of Fallot compared with healthy controls. Importantly, it provides significantly more information than magnetic resonance assessment of the cardiovascular system alone. We think that magnetic resonance–augmented cardiopulmonary exercise test provides a more comprehensive assessment of abnormal physiology during exercise and will enable better understanding of exercise dysfunction. In the future, this might allow better identification and management of exercise intolerance with the development of patient-specific treatments.
Magnetic Resonance–Augmented Cardiopulmonary Exercise Testing: Comprehensively Assessing Exercise Intolerance in Children With Cardiovascular Disease
Nathaniel J. Barber, Emmanuel O. Ako, Gregorz T. Kowalik, Mun H. Cheang, Bejal Pandya, Jennifer A. Steeden, Shahin Moledina and Vivek Muthurangu

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SUPPLEMENTAL MATERIAL

Supplemental methods.

Flow analysis.

Using the magnitude data set a large region of interest was drawn around the aorta ensuring that the vessel was within it throughout exercise (Figure A).

Figure A. Large region of interest drawn around the aorta.

This ROI was used to generate a ‘rough’ flow curve as seen in Figure B. Peak detection was then performed on this flow curve and the data divided into approximate heartbeats (Figure B).

Figure B. ‘Rough’ flow curve.

Peak detection was then performed on this flow curve and the data divided into approximate heartbeats (Figure B). Each frames was then placed into 1 of 12 bins depending on its position in the approximate heartbeat. The resulted in each bin
containing frames at a similar approximate position in the cardiac cycle but at different respiratory and exercise motion positions (Figure C).

**Figure C. Example systolic and diastolic bin.**

![Systolic Bin vs Diastolic Bin](image)
Segmentation was then carried out independently for each bin using an optical flow registration based segmentation algorithm that was developed for assessment of real-time flow\(^1\). Segmentation was initiated by manually segmenting the aorta on one reference frame. This was then propagated to the remaining frames in the bin. The resultant regions of interests were then visually inspected and corrected where necessary. Finally, phase and magnitude data sets were recombined and flow calculated.

Further processing of flow data was then undertaken in Matlab (Matlab 2012). The start of ejection in each cardiac cycle determined using the intersection of the tangent of the steepest part of the upstroke with the time axis (Figure D). This allowed calculation of the length of each individual r–r interval.

**Figure D. Identification of r-r interval and calculation of stroke volume.**

![Flow curve](image)

The stroke volume in each heartbeat was then calculated by integrating the flow curve across each r–r interval. This allowed creation of HR and SV curves and calculation of the CO curve (HR x SV).
Supplemental Figure 1. Gas exchange system validation data.

**GESV Target Values (VO₂, VC₀₂, RQ, VE) for Gas Exchange System (Field Use Only)**

1. Enter the Dry Gas Concentrations, the current Relative Humidity, Temperature and Barometric Pressure — in the blue bordered boxes of the ‘TEST DATA’ Section.
2. Do not enter data into the yellow boxes on this form — the yellow boxes will be populated automatically from data you enter into the blue boxes.
3. Enter the Respiratory Rates into the appropriate blue boxes as well as your measured values for the VO₂ - STPD, VCO₂ - STPD, VE - STPD or V - BTPS.

### Supplemental Figure 1.

| Gas exchange system validation data for the modified umbilical provided by the manufacturer. All measured gas variables (VO₂, VC₀₂) RER and volume measures at both standard pressure dry (STPD) conditions and body temperature and pressure saturated (BTPS) fell with in the same acceptable ranges as the standard length commercial umbilical. |
Supplemental figure 2. Standard length (a) and modified umbilical (b) and magnification demonstrating diameter of sampling tubes.

Although the modified umbilical was significantly longer, (470 cm v. 234 cm standard length) the dead space was still small due to the narrow gage of the sampling tubes.
Supplemental figure 3. Combined VO₂, CO and a-VO₂ curves
Supplemental figure 3. VO₂, a-vO₂ and CO curves for all subjects; controls (light blue) PAH (dark blue) and TOF (red).

Supplemental References: