

**Magnetic Resonance Augmented Cardiopulmonary Exercise Testing:
Comprehensively Assessing Exercise Intolerance in Children with
Cardiovascular Disease**

Barber et al: MR-CPET in Pediatric Cardiovascular Disease

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Abstract

Background

Conventional cardiopulmonary exercise testing (CPET) can objectively measure exercise intolerance, but cannot provide comprehensive evaluation of physiology. This requires additional assessment of cardiac output (CO) and arterio-venous oxygen content difference (a-vO₂). We developed magnetic resonance (MR) augmented CPET (MR-CPET) 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 (ToF) (n=10) underwent MR-CPET. All exercise was performed on a MR-compatible ergometer and oxygen uptake (VO₂) was continuously acquired using a modified metabolic cart. Simultaneous CO was measured using a real-time MR flow sequence and combined with VO₂ to calculate a-vO₂. Peak VO₂ was significantly lower in the PAH group (12.6±1.31 ml/kg/min, p=0.01) and trended towards lower in the ToF group (13.5±1.29 ml/kg/min, p=0.06) compared to controls (16.7±1.37 ml/kg/min). Although ToF patients had the largest increase in CO, they had lower resting (3±1.2 l/min/m²) and peak (5.3±1.2 l/min/m²) values compared to controls (resting 4.3±1.2 l/min/m², peak 6.6±1.2 l/min/m²) and PAH patients (resting 4.5±1.1 l/min/m², peak 5.9±1.1 l/min/m²). Both the PAH and ToF patients had blunted exercise induced increases in a-vO₂. However, only the PAH patients had significantly reduced peak values (6.9±1.3 mlO₂/100ml) compared to controls (8.4±1.4 mlO₂/100ml, p= 0.005).

Conclusions

MR-CPET is feasible in both healthy children and children with cardiac disease. Using this novel technique we have demonstrated abnormal exercise patterns in VO₂, CO and a-vO₂.

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

Exercise intolerance is a common feature of cardiac disease and measurement of oxygen consumption (VO_2) allows objective evaluation of exercise capacity. Studies have shown that peak VO_2 is highly prognostic¹ and cardiopulmonary exercise testing (CPET) is now routinely performed in these patients².

However, it does not provide a comprehensive assessment of physiology, as this also requires measurement of cardiac output (CO) and tissue oxygen (O_2) extraction. These metrics can be assessed using invasive CPET (I-CPET), in which pulmonary and systemic arterial catheterisation is combined with exercise testing³. Using I-CPET it has been shown that tissue O_2 extraction is reduced in pulmonary hypertension⁴ and this novel finding demonstrates the utility of the technique.

Unfortunately, I-CPET is not practical in many patients groups due to its invasive nature. We have recently demonstrated an alternative non-invasive approach, which combines real-time MR flow assessment with MR compatible respiratory gas analysis⁵. The simultaneous acquisition CO and VO_2 allows subsequent calculation of arterio-venous oxygen content difference ($a-vO_2$)², a recognized measure of O_2 extraction. Thus, MR augmented CPET (MR-CPET) provides a novel non-invasive 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 as invasive CPET is challenging in this population. A secondary aim was to explore differences in VO_2 , CO and $a-vO_2$ 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) were healthy pediatric controls recruited specifically for this study with no suspected or previous past medical history. Group 2 (n=10; 7 female) were children with a diagnosis of stable PAH with no recent changes in medication. Group 3 (n=10; 4 female) children had a primary diagnosis of ToF repaired in infancy with current pulmonary regurgitation.

General exclusion criteria were i) age <7 years, ii) MR incompatible implant, iii) physical or intellectual disability and iv) exercise induced collapse in the preceding 6 months v) previously documented desaturation on exercise, vi) non-trivial tricuspid regurgitation. Specific group 2 exclusion criteria were: i) WHO functional class IV and ii) 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 six-minute walk test following the American Thoracic Society guidelines⁶ by a single operator (NB).

MR-CPET

Magnetic resonance augmented CPET was performed on a 1.5 Tesla MR scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany) using two six-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 MRI 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 UNFOLDed-SENSE spiral PCMR sequence^{5,7}. Parameters 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 (VENC)=250 cm/s, R=6, temporal resolution=35 ms. The UNFOLDed-SENSE reconstruction was performed 'online' using a GPU-equipped external computer (Tesla C2070, Nvidia, Santa Clara, CA, USA) that was networked to the native scanner reconstruction system⁸.

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: field of view=320 mm, matrix=128x128, voxel size 2.5x2.5x8, TR/TE= 2.4/1.17ms, flip angle=47°, R=8, temporal resolution=36ms.

Respiratory gas analysis - Breath-by-breath gas exchange was analysed using a commercial CPET system (Ultima, MedGraphics, St. Paul, USA) equipped with an electro-galvanic oxygen sensor, a non-dispersive infrared carbon dioxide sensor and a calibrated differential pressure flow sensor. As the analyser 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 wave-guide (Figure 1) and attached to the patient via a pneumotach and facemask (Hans Rudolph, Kansas City, USA). The primary modifications to the umbilicus were increased length (470 cm compared to the standard 234 cm) and removal of ferromagnetic parts (see data supplement for full description of modifications). This customised umbilicus was

extensively tested by the manufacturer and met all of the normal quality control standards (data supplement). Gas and flow calibrations were performed before each patient was tested. All measures were taken at body temperature ambient pressure.

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 Watts/minute for the first five minutes and subsequently 3 Watts/minute 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 in order to maintain a high heart rate and prolong the exercise state. During this period, ventricular volumes (peak exercise) were assessed again (acquisition approximately 30 seconds).

Image analysis

All images were processed using in-house plug-ins for the open-source software OsiriX (OsiriX Foundation, Geneva, Switzerland)⁹. Flow data was processed as previously described⁸. All magnitude images (up to 25000 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 VO_2 data were further analysed using Matlab (Matlab 2012). The flow curves were automatically split into separate heart beats as previously described⁵ (data supplement) and the stroke volume (SV) was calculated by integration. The heart rate (HR) and SV data were combined to calculate CO (HR x SV). Arterio-venous oxygen content gradient ($a-vO_2$) was then calculated as VO_2/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 stroke volume (SV) was the difference between these two values and ejection fraction (EF) was SV/EDV . As subjects with tricuspid regurgitation were excluded, it was possible to assess pulmonary regurgitation fraction (PRF) indirectly as: $[(RVSV-LVSV)/RVSV] \times 100$.

Septal curvature was measured from the short axis images at the mid-papillary level¹¹. 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 five-point Likert scale: (i) degree of concern prior to the test (1=very intense concern, 3=moderate, 5=no concern), (ii) comfort during the test (1=very poor, 3=moderate, 5=very good), and (iii) degree of perceived helplessness (1=very intense helplessness, 3=moderate, 5=no helplessness). Responses ≥ 3 were considered clinically acceptable.

Statistical Analysis

All statistical analysis was performed using StataSE 13.0 (StataCorp, College Station, USA). Data were examined for normality using the Shapiro-Wilk normality test and non-normally distributed data was transformed using a log transform to ensure normal distribution prior to analysis. Descriptive statistics were expressed as mean (\pm standard deviation) or geometric mean (\pm geometric standard deviation) where data was log transformed for skewness. Between group differences were assessed using one-way analysis of variance (ANOVA) with post-hoc Bonferroni corrected pairwise comparisons. Differences in absolute metrics with exercise in different groups were assessed using repeated measures ANOVA 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 intraclass correlation coefficients. Likert scale data was compared using the Kruskal Wallis test and gender distribution compared using Fisher's 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 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 37.2 ± 12.1 mmHg 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, Sildenafil: 8/10, Tadalafil: 2/10, Amlodipine: 6/10, Ambrisentan: 1/10 and inhaled Iloprost: 2/10. In the repaired ToF patients, 9/10 were functional class 1 and 1/10 functional class II. The median age of primary surgery was 0.78 years (range 0.4-1.7 years) and 7/10 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 six-minute walk test distances between the control (444 ± 1.1 m), PAH (429 ± 1.2) or ToF groups (449 ± 1.1).

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 VO_2 data was collected in all subjects allowing calculation of $a-vO_2$ 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 ($RER = VCO_2/VO_2$) ≥ 1.1 . Healthy children achieved approximately 72% predicted heart rate, which was significantly higher than the PAH (62%, $p < 0.001$) and ToF groups (56%, $p < 0.001$). There were trends towards longer exercise duration and greater Watts achieved in the control group compared to the PAH and ToF groups

(table 2).

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 VO_2 between the groups (figure 5, table 3). At peak exercise VO_2 increased $4.1\pm 1.3x$ in controls, which was significantly greater than the increase in ToF ($3.2\pm 1.2x$, $p=0.04$) and PAH ($2.9\pm 1.3x$, $p=0.01$) patients. These differences resulted in peak VO_2 being lower in the PAH group (12.6 ± 1.31 ml/kg/min, $p=0.01$) and trending towards lower in the ToF group (13.5 ± 1.29 ml/kg/min, $p=0.06$) compared to controls (16.7 ± 1.37 ml/kg/min).

Resting CO was significantly ($p<0.001$) lower in ToF patients compared to controls and PAH patients (figure 5, table 3). In PAH patients augmentation of CO was non-significantly lower ($1.3\pm 1.3x$) than in controls ($1.6\pm 1.3x$, $p=0.174$) and peak CO only trended ($p=0.1$) towards being lower (table 3). Augmentation of CO was greater in ToF patients ($1.8\pm 1.3x$) than controls, but did not reach significance ($p=0.217$). Due to the lower baseline CO, peak CO was still significantly lower in ToF patients (5.3 ± 1.2 vs. 6.6 ± 1.2 , $p=0.003$).

The ToF group had significantly higher $a\text{-vO}_2$ (4.7 ± 1.2 mlO₂/100ml) at rest compared to the PAH (3.0 ± 0.34 mlO₂/100ml, $p=0.001$) and control groups (3.1 ± 0.76 mlO₂/100ml, $p=0.003$). There was no significant difference in $a\text{-vO}_2$ augmentation between controls ($2.7\pm 0.5x$) and PAH patients ($2.3\pm 0.6x$, $p=0.18$). Nevertheless, peak $a\text{-vO}_2$ was lower in the PAH patients (6.9 ± 1.3 mlO₂/100ml vs. 8.4 ± 1.4

mI_O2/100ml, p=0.005). Conversely, a-vO₂ augmentation was significantly lower in ToF patients (1.9±0.3x, p=0.001) compared to controls. However, due to 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 to controls (p<0.03). In all groups, RVEDV and RVESV decreased significantly by a similar amount with exercise (table 4). RVEF 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 LVEF (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 only increased significantly during exercise in the ToF group (p=0.035). In all groups, LVEF was significantly higher at peak exercise (table 4).

Other metrics – Rest and Exercise

Non-trivial PR was only present in the ToF group and at peak exercise PRF 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 PA pressure (mPAP) of 30±0.4mmHg at rest, rising to 55±0.53mmHg at peak exercise.

Intra and Inter-observer reliability

There was good intraobserver reliability in real time CO data (ICC 0.995, 95% CI 0.98–0.999 $p < 0.001$). There was also good interobserver reliability (ICC 0.996, 95% CI 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 i) MR-CPET was safe in healthy children and those with right heart disease, ii) peak VO_2 was reduced in pediatric PAH and ToF patients and iii) PAH and ToF patients had different peak values and patterns of augmentation of CO and a- VO_2 compared to controls.

MR CPET findings

In this study, we recruited relatively well patients in whom there was no significant difference in 6MWT distance compared to controls. Nevertheless, PAH patients had reduced peak VO_2 and ToF patients had a trend towards 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 weren't apparent with VO_2 alone. For example, PAH patients had a slightly blunted CO response to exercise and a trend towards lower peak CO. On the other hand, 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 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 non-representative sampling.

Still there are some CMR studies that suggests CO is lower in pediatric ToF patients when compared to normal children (assessed in a separate study but by the same group)^{14,15}. 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 due to a fall in PR¹⁶. However, peak CO is still lower in ToF patients (due to the lower baseline value) and this might have important consequences for exercise tolerance.

Our MR-CPET data also allows evaluation of differences in tissue oxygen extraction (as assessed by $a-vO_2$). 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-CPET⁴, but the exact cause is unclear. Biopsy studies have demonstrated skeletal muscle abnormalities in animal and human models of PAH including reduced capillary density¹⁷, changes in ratio of muscle fiber type¹⁸ and alterations in mitochondrial function¹⁹. 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 $a-vO_2$ in ToF patients could simply due to mathematical coupling between a CO and VO_2 , although it may have physiological relevance. The ToF patients also had a significantly blunted increase in $a-vO_2$, although they reached a

similar peak to controls. Further work is required to understand if and how these abnormalities impact on exercise tolerance.

We believe that these results demonstrate that MR-CPET allows incremental improvement in understanding of exercise dysfunction. Specifically, it provides insights not available if CO and VO₂ are measured alone. Similar data is also available using invasive 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 biomarker²⁰. Unfortunately, invasive CPET is difficult to perform in children, as 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 mPAP in children with PAH²¹. Our results suggest that mPAP increases significantly during exercise in this group. This is consistent with invasive studies in adults²⁰, but has not been shown in children due to 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 as conventional CPET has been shown to be safe in these patient groups^{13,22} and we only chose to study functional class 1

and 2 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 study⁵ in which ECGs were non-interpretable. We believe that superior quality of the ECG signal in children was due to 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 to monitoring electrical activity is developed.

Technical considerations

Although real-time techniques are invaluable when performing exercise CMR, there are concerns over reduced image quality and robustness. Real-time MR techniques have been extensively tested against conventional gated MR with good agreement²³. In addition, a recent study has demonstrated good agreement between SV assessed using real-time MR volumes and the direct Fick method during exercise²⁴. Thus, we believe 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 gating²⁴ and improved automated segmentation¹⁰ may also improve measurement fidelity.

A further complication in this study was the need to continuously measure flow in order to guarantee acquisition of data at peak exercise. The resultant data consisted of up to 25,000 frames of flow images, representing a massive reconstruction and post-processing problem. We used an online GPU reconstruction system⁸ to ensure that data was 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 post-processing 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 approximately 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 as 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 $\dot{V}O_2$, CO and a- $\dot{V}O_2$ 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 compatible²⁵. Importantly even though these modifications resulted in increased dead space, there was no significant measurement difference compared to an unmodified system. Another possible solution is to adapt the fully MR-compatible gas analysis systems for monitoring of 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 RERs, the exercise performed was sub-maximal. 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 cycling partially explaining the significantly lower power output achieved in this study compared to conventional CPET. In addition, peak VO_2 and SV augmentation are consistently found to be lower at peak supine exercise compared to upright exercise in both adults and children^{26,27,8,28}. Thus, our form of supine exercise cannot be directly compared to 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 believe 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 is known that these patient groups do exhibit abnormalities in lung function²⁹ and therefore, it would be important to evaluate this in future studies.

The ergometer used in this study is also heavy and may in the case of obese adults and adolescents exceed the recommended weight limit of the MRI table. Thankfully, a wide range of alternative commercial ergometers with more acceptable dimensions are available³⁰⁻³² and could be used for MR-CPET.

Conclusions

This proof of concept study demonstrates the innovative use of an integrated MR-CPET approach both in healthy children and 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.

Clinical Perspective

This study demonstrates the feasibility and safety of an innovative combined magnetic resonance augmented cardiopulmonary exercise test (MR-CPET) in non-invasively assessing exercise physiology in children with cardiovascular disease. Reduced exercise capacity is a common feature of cardiovascular disease and is recognised 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 to healthy controls. Importantly, it provides significantly more information than magnetic resonance assessment of the cardiovascular system alone. We believe that MR-CPET 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.

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Figure Legends

Figure 1. 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 wave-guide to control the ergometer. The modified MR-compatible umbilicus (white) also passes from the metabolic cart through the wave-guide and connects to the patient via a pneumotach and facemask.

Figure 2. Schematic representation of the MR-CPET protocol.

Figure 3. Examples of MR flow images subsets at rest and exercise throughout the cardiac cycle.

Figure 4. Representative oxygen uptake (VO_2) cardiac output (CO) and arterio-venous 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 VO_2 , CO and a- vO_2 curves for all subjects are provided in the supplemental data section.

Figure 5. Changes in mean MR-CPET metrics between rest and peak exercise, in the control (continuous line) PAH (dashed line) and ToF (dotted line). Error bars represent SEM. There was no significant difference in resting oxygen uptake (VO_2) but a lower peak VO_2 in the PAH group than the control group ($p=0.01$). Note higher resting arterio-venous oxygen content gradient (a- vO_2) in the ToF group with no significant difference at peak exercise and lower a- vO_2 at peak exercise in the PAH group than the control group ($p= 0.005$).

Disclaimer: The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed.

Table 1. Demographics.

Variable	Control	PAH	ToF	p-value
Male:Female	4:6	3:7	6:4	0.53
Age, years	13±3	11±2.2	14±1.8	0.033
Height, cm*†	154±1.1	147±1.1	159±1.1	0.066
Weight, kg*	47±1.5	41±1.3	50±1.4	0.432
Body Surface Area m ² †	1.5±0.38	1.3±0.17	1.5±0.29	0.145

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

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Table 2. Exercise capacity and acceptability data.

Variable	Control	PAH	ToF	p-value
Six minute walk test distance, m*	452±1.1	432±1.2	449±1.1	0.718
MR-CPET Exercise duration, min†	8.9±3	7.3±1.6	7±2.2	0.078
Peak Work, Watts*†	12.0±2	8.7±1.5	7.7±1.9	0.145
Peak Work, METS*	4.8±1.4	3.6 ± 1.3	3.8 ± 1.3	0.079
Percept Predicted HR	72±8.2	62±9.6	56±8.1	<0.001
RER†	1.7±0.43	1.5±0.28	1.4± 0.15	0.011
Satisfaction	4.4±0.7	4.3±0.48	4.6±0.52	0.45
Comfort*	3.5±1.3	3.5±1.3	3.8±1.2	0.82
Helplessness*	3.7±1.4	4±1.2	4.4±1.2	0.35

RER, respiratory exchange ratio; HR, heart rate; *Log transformed (geometric mean).† W test applied.

Table 3. MR-CPET derived measures.

Variable	Control		PAH		ToF		p-value		
	Rest	Peak	Rest	Peak	Rest	Peak	Disease effect	Time effect	Disease-time interaction
HR, bpm	83±17	149±18†	82±9.3	131±20†	74±12	116±17†	<0.001	<0.001	<0.001
SV, ml/m ²	49±11	46±8.2	49±5.9	46±6.3	41±8.4	46±5.4	0.43	0.75	<0.001
CO, l/m ² /min*	4.3±1.2	6.6±1.2†	4.5±1.1	5.9±1.1†	3±1.2	5.3±1.2†	<0.001	<0.001	0.0016
VO ₂ , ml/kg/min*	4.06±1.35	16.7±1.37†	4.32±1.18	12.6±1.31†	4.24±1.17	13.5± 1.29†	0.51	<0.001	0.011
a-vO ₂ , mlO ₂ /100ml blood	3.1±0.76	8.4±1.4†	3±0.34	6.9±1.3 †	4.7±1.2	8.7±1.5†	<0.001	<0.001	0.013

HR, heart rate, beats per minute; SV, stroke volume; CO, cardiac output; VO₂, oxygen uptake; a-vO₂, arterio-venous oxygen content gradient. *Log transformed (geometric mean). †significant difference rest to peak.

Table 4. Conventional MR derived measures.

Variable	Control		PAH		ToF		p-value		
	Rest	Peak	Rest	Peak	Rest	Peak	Disease effect	Time effect	Disease-time interaction
RV EDV, ml/m ²	77±16	68±13†	83±9.2	71±9.1†	95±16	86±14†	<0.001	<0.001	0.6
RV ESV, ml/m ² *	29±1.3	20±1.6†	34±1.3	28±1.3†	39±1.3	30±1.5†	0.041	<0.001	0.44
RV SV, ml/m ²	47±11	45±9.5	48±6.7	46±6.9	55±7.8	54±7.1	0.045	0.095	0.9
RV EF, %	62±5	67±12	58±7.8	66±9.8†	58±6	63±8.6	0.59	<0.001	0.67
LV EDV, ml/m ²	67±13	59±9.6†	68±7.4	61±8.1†	63±5.2	64±6.2	0.87	<0.001	0.011
LV ESV, ml/m ² *	18±1.3	11±2†	20±1.2	14±1.4†	19±1.3	17±1.3	0.18	<0.001	0.14
LV SV, ml/m ²	48±9.9	47±7.2	48±6.7	47±7	43±6.1	46±5.5	0.55	0.59	0.024
LV EF, %	72±5.5	80±11†	70±4.4	77±7.3†	68±7.1	73±5.9	0.17	<0.001	0.54
PRF, %	0.48±1.0	0.29±0.89	1.11±1.47	0.14±0.43	30.24±8.03	16.3±5.79†	<0.001	<0.001	<0.001
Septal curvature ratio*	0.84±0.05	0.82±0.08	0.15±0.42	-0.44±0.53	0.85±0.13	0.86±0.071	<0.001	<0.001	<0.001

RV, right ventricle; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; PRF, pulmonary regurgitant fraction; mPA, estimated mean pulmonary arterial pressure. *Log transformed (geometric mean). †significant difference rest to peak.



MRI:

Continuous Real Time CO measurement

Real Time CO

Resting Real Time
Short Axis Stack

Peak Real Time
Short Axis Stack

Gas Analyzer:



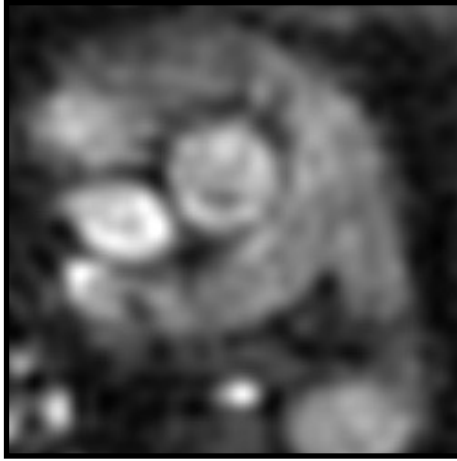
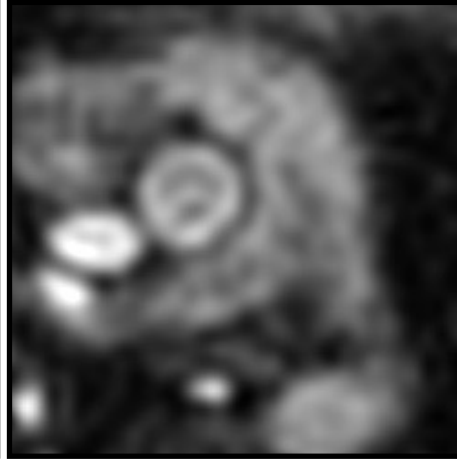

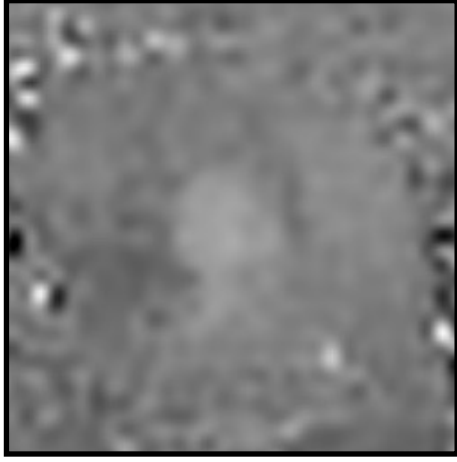
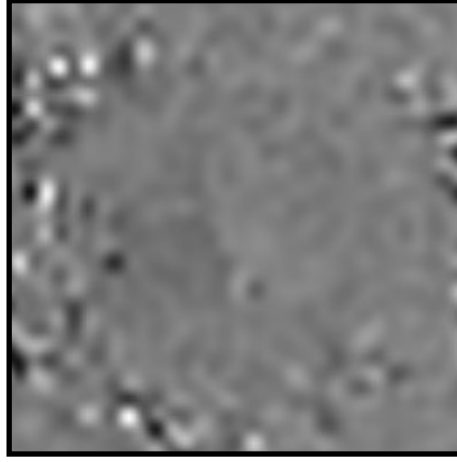
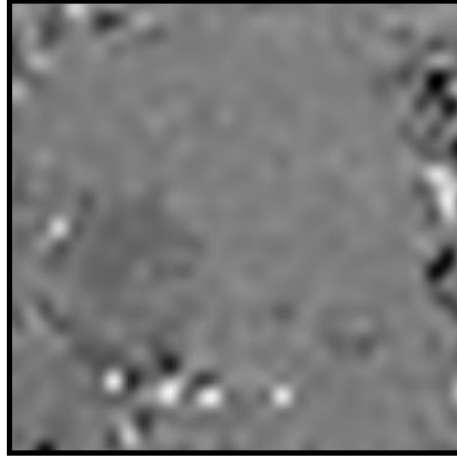
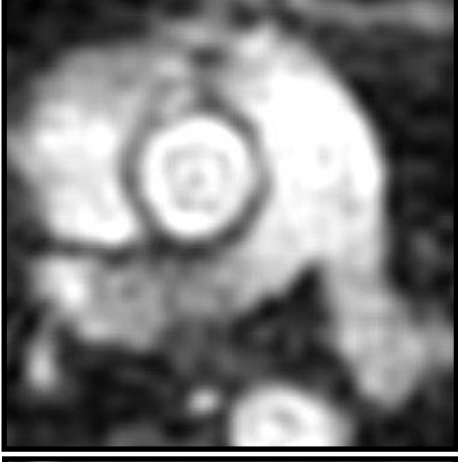

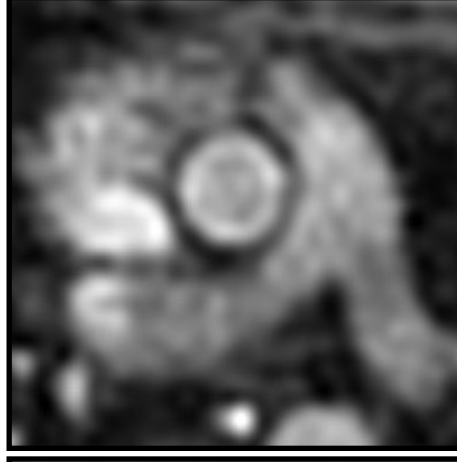

Continuous Breath by Breath CPET

Ergometer:

1min rest

Start. 2min unloaded exercise. 2W/min 5min then 3W/min to peak

Unload. Recovery. End

		Peak Systole	End Systole	Early Diastole	Late Diastole
Rest	Magnitude				
	Phase				
Exercise	Magnitude				
	Phase	