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Acute vasodilator response testing in the adult Fontan circulation using non-invasive 4D Flow MRI: a proof-of-principle study

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Abstract

Background: Pulmonary vasodilator therapy in Fontan patients can improve exercise tolerance. We aimed to assess the potential for *non-invasive* testing of acute vasodilator response using four-dimensional (D) flow MRI during oxygen inhalation. *Materials and Methods:* Six patients with well-functioning Fontan circulations were prospectively recruited and underwent cardiac MRI. Ventricular anatomical imaging and 4D Flow MRI were acquired at baseline and during inhalation of oxygen. Data were compared with six age-matched healthy volunteers with 4D Flow MRI scans acquired at baseline. *Results:* All six patients tolerated the MRI scan well. The dominant ventricle had a left ventricular morphology in all cases. On 4D Flow MRI assessment, two patients (Patients 2 and 6) showed improved cardiac filling with improved preload during oxygen administration, increased mitral inflow, increased maximum E-wave kinetic energy, and decreased systolic peak kinetic energy. Patient 1 showed improved preload only. Patient 5 showed no change, and patient 3 had equivocal results. Patient 4, however, showed a decrease in preload and cardiac filling/function with oxygen. *Discussion:* Using oxygen as a pulmonary vasodilator to assess increased pulmonary venous return as a marker for positive acute vasodilator response would provide pre-treatment assessment in a more physiological state – the awake patient. This proof-of-concept study showed that it is well tolerated and has shown changes in some stable patients with a Fontan circulation.

Single ventricle physiology occurs in approximately 8% of patients with CHDs.[1] Many of these patients are palliated with a Fontan circulation in which blood from the systemic veins is channelled directly into the pulmonary artery, bypassing the right heart. The Fontan circulation relies on a low pulmonary vascular resistance to return adequate blood flow to the heart.[2] Therefore, the pulmonary vascular resistance dictates the preload to the single ventricle and even slight increase in pulmonary vascular resistance can exponentially decrease cardiac output.[3] Increases in pulmonary vascular resistance also correlate with the development of serious complications from this circulation such as pulmonary vascular remodelling and Fontan failure.[4]

Vasodilator medication is an available option for reducing the pulmonary vascular resistance in Fontan patients. The most widely used of these, sildenafil, has been shown to increase exercise tolerance and improve the cardiac output at rest and during exercise.[5] However, its effectiveness differs between patients, with not all benefiting from the therapy.[6] Determining the individual improvement from treatment is currently achieved through trial periods or acute vasodilator response testing, the latter of which often involves general anaesthesia and invasive right heart catheterisation.[7]

Oxygen has pulmonary vasodilatory properties, and its inhalation is used for acute vasodilator testing.[8] Combined with the novel techniques of four-dimensional phase-contrast cardiac magnetic resonance (4D Flow MRI) imaging, this produces the potential for a method of non-invasive acute vasodilator testing with advanced analysis of intracardiac parameters. 4D Flow MRI allows measurement of blood velocity in all directions within a three-dimensional volume and has been shown to improve the accuracy of flow quantification across the atrioventricular valve in Fontan patients.[9] Kinetic energy of blood flow is a novel measurement parameter distinctive to 4D Flow MRI; it represents the work performed by the heart muscle that results in the movement of blood.[10] Previous research has shown diastolic kinetic energy to be reduced in Fontan patients compared to controls,[11] and the sensitivity of kinetic energy testing is capable of identifying subclinical cases of left ventricular dysfunction.[12]

This pilot study aimed to assess the potential for *non-invasive* testing of the acute vasodilator response using 4D Flow MRI during oxygen inhalation.

Methods

Study population and study design

The study group consisted of six patients with a Fontan circulation and six age-matched healthy volunteers. All participants were prospectively recruited and scanned at the University of Oxford. Inclusion criteria for single ventricle patients were adults who had undergone the Fontan surgical palliation, had preserved ventricular function, had minimal or no atrioventricular valve regurgitation, and had no contraindications to MRI in line with recruitment criteria of the FUEL trial.[13] All healthy volunteers had no history or symptoms of cardiovascular dysfunction, did not take any cardiovascular or other relevant medication, and had no contraindications to MRI. The study was approved by the local research ethics committee: South Central-Berkshire (Reference 10/H0505/100) and conducted in line with the Helsinki declaration. All participants gave written informed consent. All Fontan patients and one volunteer participated in two MRI scans within the same study visit. Scan 1 was at normal baseline conditions, and scan 2 was taken during inhalation of oxygen, for non-invasive pulmonary vasodilator response testing. The remaining five volunteers underwent one scan only.

Application of oxygen vasodilation

Traditionally, nitric oxide has been used but increasingly oxygen inhalation is also used for acute vasodilator testing.[8] Importantly, the physiology of inhaled pulmonary vasodilator differs from oral systemic vasodilators,[14] but in the acute, short-term test setting, inhaled vasodilators are preferred as they have a faster onset of vasodilation.

Following a baseline scan, each Fontan patient and one of the volunteers underwent oxygen inhalation at 15 L/min through a non-rebreath mask. Patients were monitored until they reached a steady state, around 5 minutes, before the second scan was performed. It was assumed that at this stage, maximum oxygen saturation had been achieved. Oxygen administration was continued for the duration of the second MRI scan.

Cardiovascular image acquisition

The MRI protocol was the same as published previously by Stoll et al.[15] In brief, participants were scanned on a 3 T system (Trio, Siemens Healthcare Erlangen, Germany) and images were ECG-gated. Cine images were acquired using retrospectively gated balanced steady-state free precession (bSSFP) cine sequences with single breath-hold per acquired slice: slice thickness 8 mm with contiguous slice position, echo time 1.5 milliseconds (ms), repetition time 3 ms and flip angle 50 degrees. 4D Flow MRI data covered the entire heart, planned in the sagittal orientation, and were obtained during free breathing, with respiratory navigator gating using a prototype three-dimensional time-resolved phase-contrast MRI sequence. Retrospective gating was employed, and 30 cardiac phases were reconstructed to represent one full cardiac cycle. 4D Flow MRI parameters were as follows: spatial resolution 3 mm^3; echo time 2.75 ms; repetition time 4.3 ms; temporal resolution 52 ms; flip angle 7 degrees; velocity encoding range ± 100 cm/s.

Table 1. Description of all MRI flow parameters measured in this study

Net forward flow volume	The forward flow through the valve minus any regurgitant flow
Systolic peak KE	The maximum KE of the LV during systole
E-wave peak KE	The maximum KE of the LV during early diastolic filling
A-wave peak KE	The maximum KE of the LV during late diastolic filling

All KE parameters in this study are indexed to end-diastolic volume or stroke volume, and all were measured in μJ/ml; KE = kinetic energy.

4 D Flow MRI image analysis

The evaluation of net forward flow volume through the mitral valve was completed with valve tracking using the commercially available CAAS MR Solutions 5.1 (Pie Medical Imaging, Maastricht, The Netherlands). The mitral valve was identified in the two-chamber and four-chamber cine images and tracked throughout the cardiac cycle. The mitral valve flow was delineated in the resulting 2D flow plane throughout the cardiac cycle. All images were corrected for aliasing at the mitral inflow. A significant change in mitral inflow (improved or worsened) was defined as at least a 5% change in forward flow (increase or decrease respectively) in keeping with a recent systematic review.[16]

Ventricular function, 4D Flow MRI analysis, and kinetic energy quantification were performed using the research MASS software (MASS; Version 2019EXP, Leiden University, The Netherlands). The endocardial border of the left ventricle in healthy volunteers and the single ventricle in Fontan patients was manually traced in the short-axis cine stack throughout the entire cardiac cycle. Papillary muscles were disregarded. The hypoplastic right ventricle was included in the atrioventricular septal defect case. End-diastolic volume, stroke volume, and ejection fraction were calculated. A decrease in ejection fraction was defined as at least 10% reduction as this was considered clinically significant.

Misalignment was assessed visually, and if necessary, motion correction was performed using the automated image-based 3D rigid registration toolbox.[17] Kinetic energy was computed following the previously published method.[18] Kinetic energy for each voxel within the left ventricle was computed as ½ mv^2, with (m) as the mass representing the voxel volume multiplied by the density of blood (1.025 g/mL) and (v) as the three-directional velocity from 4D Flow MRI. For each acquired time phase, volumetric kinetic energy was then computed by integrating (by cumulative sum) the computed kinetic energy over the segmented 3D left ventricular volume. Peak systolic kinetic energy, peak E-wave kinetic energy, and peak A-wave kinetic energy were assessed normalised to end-diastolic volume and stroke volume (Table 1). Improved diastolic inflow was defined as an at least 10% increase in maximum E-wave kinetic energy. Improvement in systolic peak kinetic energy was defined as an at least 10% decrease. 10% change was chosen in line with the 10% change in ejection fraction above which was deemed to be clinically significant. This change is also likely larger than can be explained by re-scan variability.[15,19]

Energy loss was calculated using Circle CVI42, v 5.13 (Circle Cardiovascular Imaging Inc., Calgary, Canada) at the inferior caval vein to conduit junction. 4D Flow MRI magnitude data were used to create an isosurface area of the vessel. Two planes were placed (one in the inferior caval vein after the hepatic veins entered, one in

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Table 2. Demographic characteristics of the six Fontan patients

Subject	Age at time of MRI (y)	Gender	BSA (m2)	Ventricular morphology	Diagnosis	Type of Fontan	Size of extracardiac TCPC (mm)
1	20	M	1.82	Left	Tricuspid atresia	Extracardiac TCPC	22
2	19	M	1.65	Left	Pulmonary atresia	Extracardiac TCPC	19
3	20	M	1.99	Left	Tricuspid atresia, VSD	Extracardiac TCPC	22
4	27	M	2.06	Left	Pulmonary atresia	Extracardiac TCPC	17
5	31	M	1.49	Left	Pulmonary atresia	Right atrium to PA Fontan	n/a
6	21	M	2.15	Left	Complete unbalanced AVSD	Extracardiac TCPC	16

the proximal conduit) to define the junction for energy loss calculation. Maximum energy loss across this vessel segment was reported. Analysis was not possible in one patient due to artefact from percutaneous fenestration closure device.

Statistical analysis

Data analysis was performed using SPSS Statistics version 26.0 (International Business Machines, Armonk, USA). Normality was tested by the Shapiro–Wilk test. Continuous non-normal data are presented as median and interquartile range. MRI measures at baseline and during oxygen inhalation were compared using the paired Wilcoxon signed-rank test for non-parametric scale data.

Results

Demographic characteristics

Characteristics of the Fontan patients are shown in Table 2. The underlying pathology leading to a Fontan circulation was as follows: two patients with tricuspid atresia, with or without an associated ventricular septal defect; three patients with pulmonary atresia, and one patient with a complete unbalanced atrioventricular septal defect. All Fontan patients were male, and the median age was 20.5 years with ages ranging between 19 and 31 years of age. Median heart rate was 75 [19] bpm. Patients and volunteers were similar in median age (20.5 [8] versus 20.5 [17] years, $p = 0.82$), heart rate (75 [19] versus 62 [17] beats per minute, $p = 0.24$), and body surface area (1.91 [0.5] versus 1.83 [0.3] m^2, $p = 0.49$).

Five patients had an extracardiac conduit, and one patient (patient 5) had an atrial-pulmonary Fontan circulation. The individual diameter of the extracardiac conduit is described in Table 2. No patient had a patent fenestration or any stents inserted. Oxygen saturation at baseline was >95% in all participants and increased to 100% during oxygen administration.

Flow-related response to oxygen therapy

The change in 4D Flow MRI parameters after non-invasive vasodilator response testing (scan 2 during oxygen inhalation) in comparison to baseline (scan 1) is shown in Table 3. Comparing all patients together, no significant difference was seen between the mitral valve net forward flow volume in scan 2 (73 [53] ml, $p = 0.94$) to scan 1 (73 [42] ml) (Fig 1).

Systolic peak kinetic energy was significantly lower in scan 2 (15.5 [2.8] μJ/ml) compared to scan 1 (19.8 [5.1] μJ/ml, $p = 0.046$) when indexed to both end-diastolic volume and stroke volume. However, there was no significant difference in average systolic kinetic energy between the scans (10.7 [3] μJ/ml in scan 1 versus 8.7 [1]0.4 μJ/ml in scan 2, $p = 0.1$). There was also no significant difference in the E-wave peak kinetic energy between scan 1 (12.3 [5.2] μJ/ml) and scan 2 (13.4 [6.5] μJ/ml, $p = 0.4$) when analysed within the whole cohort.

Individual patient differences in flow

There were mixed individual responses to oxygen administration (Fig 2). Three patients had improved net forward flow through the mitral valve (patients 1, 2, and 6), by 40, 9, and 52%, respectively, and higher E-wave peak kinetic energy, by 31, 13, and 75%, respectively. Patients 2, 3, 4, and 6 exhibited a decrease in the systolic peak kinetic energy from scan 1 to scan 2 by 11, 17, 39, and 40%, respectively.

In comparison, the healthy volunteer who underwent assessment during oxygen inhalation had a stable net forward flow through the mitral valve (baseline 76 mls and on oxygen 75 mls). E-wave peak kinetic energy decreased by 37%. Systolic peak kinetic energy decreased by 44%. Heart rate also decreased.

Individual energy loss across the extracardiac conduit from inferior caval vein to conduit is detailed for each patient in Table 4. Patient 1 had a percutaneously closed fenestration. The occluder device caused artefact and did not allow for energy loss quantification at the anastomosis from inferior caval vein to conduit.

Table 4 summarises changes for each patient individually and the additional healthy volunteer. On combined 4D Flow MRI assessment patients 2 and 6 showed improved preload with increased mitral inflow and maximum E-wave kinetic energy as well as systolic peak kinetic energy decrease. Patient 1 showed improved preload only. Patient 5 showed no change, and patient 3 had equivocal results. Patient 4, however, showed a decrease in preload and cardiac filling/function during oxygen administration (Table 4). Patients 2 and 6 had higher kinetic energy loss at the inferior caval vein to conduit junction. Patients 4 and 5 were older than the other patients. Furthermore, patient 5 was the only patient with an atrio-pulmonary Fontan connection. No other clear demographic differences were found between those that benefitted from oxygen inhalation compared to those that did not.

Discussion

This study has demonstrated that in two out of six patients, oxygen administration (and presumed pulmonary vasodilation) in Fontan patients leads to a decrease in the systolic peak kinetic energy of the

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Table 3. Comparison of 4D Flow MRI parameters in Fontan patients before and after oxygen therapy

Parameter	Healthy volunteers	Healthy volunteers	Baseline Fontan	During oxygen therapy	p-value baseline versus oxygen	Baseline Fontan	During oxygen therapy	p-value baseline versus oxygen
HR (bpm)	62 [17]		75 [19]	67.7 [13.9]	0.28			
EDV (mls)	146 [35]		188 [93]	196 [125]	0.12			
SV (mls)	95 [12]		96 [34]	91 [46]	0.60			
Kinetic energy (μJ/ml)	Normalised to EDV	Normalised to SV	Normalised to EDV			Normalised to SV		
Systolic average KE	10.3 [5.4]	60.0 [7.5]	10.7 [3]	8.7 [1.4]	0.12	25.2 [6.7]	21.6 [6.3]	0.12
Systolic peak KE	21.6 [13.7]	34.0 [20.6]	19.8 [5.1]	15.5 [2.8]	**0.046**	47.1 [12.9]	38.2 [11.4]	**0.028**
Diastolic average KE	7.8 [3.2]	11.5 [4.5]	6.7 [2.2]	6.5 [2.8]	0.92	16.4 [7.4]	16.4 [9.8]	0.92
Diastolic minimum KE	0.9 [0.6]	1.5 [1.0]	2.5 [1]	2 [1]	0.25	6.3 [2.7]	4.9 [2.7]	0.25
E-wave peak KE	26.9 [15.9]	40.4 [26.6]	12.3 [5.2]	13.4 [6.5]	0.35	29.4 [18.2]	34.0 [21.4]	0.25
A-wave peak KE	6.0 [1.7]	9.3 [2.4]	10.2 [4.9]	9.5 [4]	0.6	24 [11.9]	23.8 [13.8]	0.92
E-wave basal peak KE	18.0 [9.9]	26.5 [18.4]	7.2 [2.8]	7.7 [2.7]	0.46	17 [6.1]	18.7 [6]	0.6
A-wave basal peak KE	4.5 [2.4]	6.4 [2.8]	5.3 [3]	4.7 [1.6]	0.25	12 [5.2]	11.3 [2.9]	0.35

Data are presented as median and interquartile range [IQR].
Bold text = significant p-values. KE = kinetic energy; HR = heart rate; EDV = end-diastolic volume; SV = stroke volume.

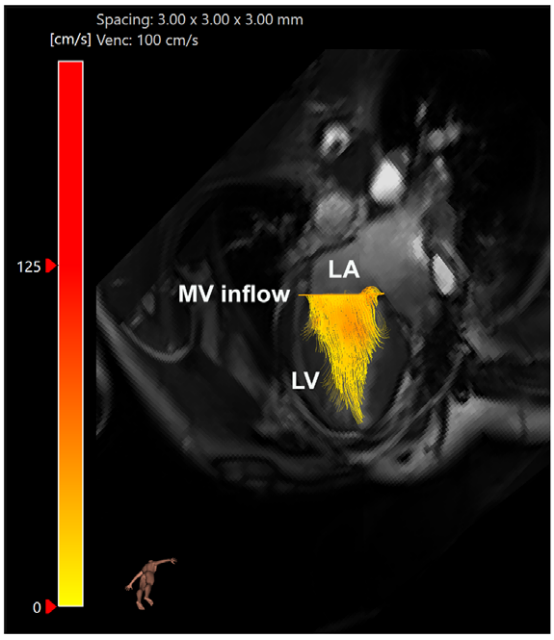

Figure 1. 4D flow MRI mitral inflow during max E-wave inflow in a patient with tricuspid atresia and Fontan circulation. LV = left ventricle; LA = left atrium; MV = mitral valve.

left ventricle and in three out of six patients to improved diastolic inflow with an increase in E-wave peak kinetic energy and an increase in the mitral net forward flow volume. The other three patients showed no change or decreased ventricular flow.

Systolic kinetic energy

Previous studies have demonstrated that peak systolic kinetic energy values are higher in Fontan patients than in healthy volunteers,[20–22] especially in those with impaired ejection fraction.[22] This is also reflected in research into other conditions of cardiac dysfunction including Tetralogy of Fallot, myocardial infarction, and heart failure.[23–25] Furthermore, dobutamine stress MRI has shown to increase systolic kinetic energy in the Fontan circulation, and a larger kinetic energy increase was associated with markers of reduced exercise tolerance.[21] It has been suggested that increased systolic peak kinetic energy indicates a lower efficiency in the cardiac circulation, as there is a higher workload required to pump a lower volume of blood.[20] This higher systolic kinetic energy in the ventricle may also be a marker for ventricular dysfunction.[11] Therefore, the reduction in systolic kinetic energy with oxygen therapy seen in patient 2-6 can be interpreted as a subtle improvement in ventricular efficiency.

Diastolic kinetic energy

E-wave kinetic energy is reduced in the Fontan circulation.[11,22] Previous research has also highlighted that patients have a lower E-wave peak kinetic energy after myocardial infarction.[24] This decreased early diastolic kinetic energy has been shown to correlate with increased energy loss within the cardiac cycle and to represent below optimal ventricular filling[26] due to reduced passive inflow by impaired ventricular relaxation. An improvement in E-wave peak kinetic energy is therefore suggestive of improved diastolic function.

Response of the Fontan circulation to oxygen administration

From the kinetic energy time curves of patients between scan 1 and scan 2, and the changes in flow parameters, it is reasonable to conclude that three patients exhibited beneficial effects from pulmonary vasodilation. These three patients (1, 2, and 6) all showed improved diastolic inflow. Two of these patients had the complete improvement pattern of a lower systolic peak kinetic energy and a higher E-wave peak kinetic energy returning these patients towards kinetic energy values from healthy individuals. In a study of Fontan patients by Sjöberg et al.,[11] the post-intervention kinetic energy curves after beneficial cardiac intervention appear to show this same pattern, a lowering of the peak systolic kinetic energy and an increase in the peak early diastolic kinetic energy. This further alludes to the possibility that this pattern contributes to

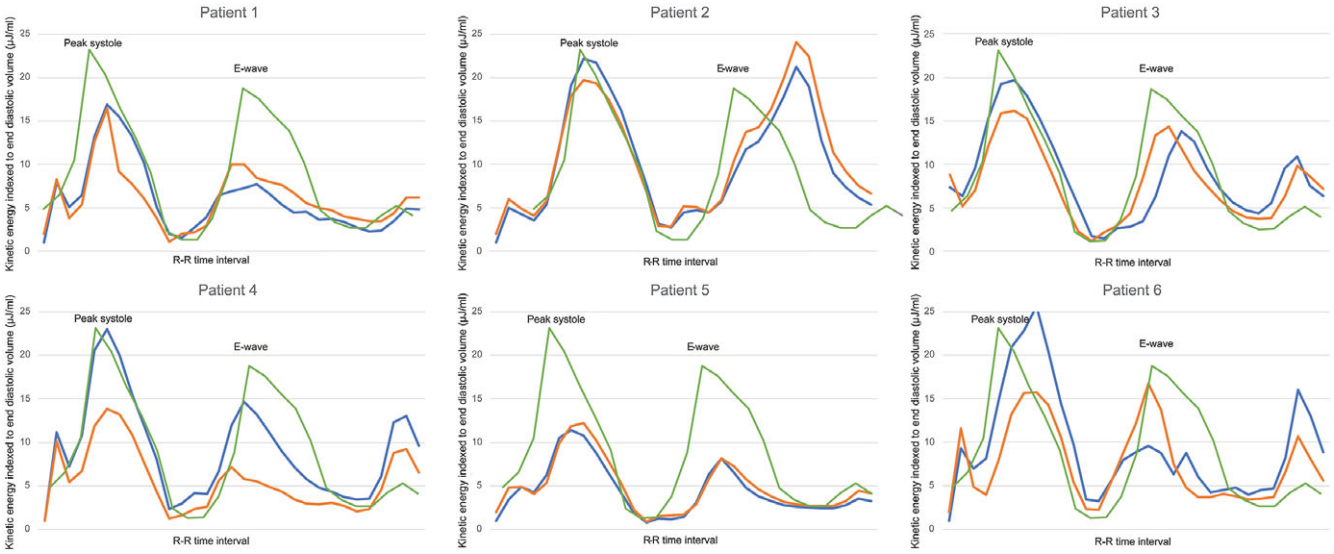

Figure 2. Patients 1, 2, and 6 show improved kinetic energy profile with improved diastolic E-wave kinetic energy, Patient 4 shows worsened kinetic energy profile; Blue = baseline; Orange = on oxygen therapy; green = average kinetic energy profile of 6 age-matched healthy volunteers.

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Table 4. Patient 1–6 changes with oxygen administration

Patient	Age	Baseline ejection fraction	Ejection fraction change with O_2	Stroke volume change with O_2	Mitral inflow change with O_2	End-diastolic volume change with O_2	Maximum E-wave KE change with O_2	Maximum systolic KE change with O_2	Heart rate change with O_2	Energy loss in mW
1	20	52	No change	↑	↑	No change	↑	No change	No change	–
2	19	53	No change	↑	↑	↑	↑	↓	No change	0.10
3	20	53	No change	↓	↓	↓	No change	↓	↓	0.02
4	27	61	↓	↓	↓	No change	↓	↓	No change	0.06
5 (AP)	31	49	No change	No change	No change	No change	No change	No change	No change	0.00
6	21	43	No change	↑	↑	↑	↑	↓	No change	0.17
HV	21	62	No change	No change	No change	No change	↓	↓	↓	n/a

KE = kinetic energy; AP = atrio-pulmonary Fontan; O_2 = oxygen; mW = milli Watts.

advantageous cardiac filling in the Fontan circulation. One possible explanation for this pattern is that an increase in venous return into the left atrium, caused by the pulmonary vasodilation, leads to greater filling during early diastole which leads to a more efficient cardiac cycle.[27] Another explanation could come from findings that Zajac et al. documented in patients with dilated cardiomyopathy[28]: Decreased early diastolic filling and increased late diastolic filling can impact the ventricular flow pattern away from efficient systolic ejection.[28] Interestingly, patients 2 and 6 also showed slightly higher energy loss at the inferior caval vein to conduit junction. This might be another indicator of positive response to vasodilation.

Additionally, it is important to note that three out of six patients (3, 4, and 5) did not respond to the pulmonary vasodilation in the pattern which we have defined as beneficial for Fontan patients.

Patient 5 showed no change. This patient had an atrio-pulmonary Fontan circulation with a severely dilated right atrium, where positive vasodilatory effects might be minimal.

Patient 3 had equivocal results. This was expected, as research suggests that not all Fontan patients improve from pulmonary vasodilator therapy[29] and some patients are "non"-responders, and patient 3 might be one of them. Interestingly, energy loss across the inferior caval vein to conduit was smaller compared to the other patients, suggesting that one reason for non-respondence might be already favourable haemodynamics in the Fontan circulation.

Patient 4, however, showed a similar response to the healthy volunteer. In healthy volunteers, oxygen inhalation increases pulmonary blood flow but also shows negative effects such as increased systemic vascular resistance; it reduces heart rate with a largely stable cardiac output.[30–33] The marked decrease in systolic kinetic energy as well as peak E-wave kinetic energy in the healthy volunteer might be a response to increased systemic vascular resistance. Interestingly, while patient 4 was older with a smaller extracardiac conduit than some of the other patients, he still had a normal ejection fraction. Furthermore, the timing of peak E-wave kinetic energy was earlier and more aligned with the healthy volunteers than in the other patients. Delay in diastolic peak kinetic energy is often observed in the Fontan circulation.[20] These findings suggest that patient 4 might have more favourable intracardiac haemodynamics at baseline and therefore displays a similar response to oxygen administration as seen in healthy volunteers. Further research is necessary to delineate, whether a similar (negative) response would also be seen with medical vasodilators.

These results suggest that "non"-responders might have a number of underlying reasons such as unfavourable anatomy (atrio-pulmonary Fontan circulation) or favourable haemodynamics at baseline (Fontan circulation and/or intracardiac haemodynamic). This may in part explain the modest results of the randomised FUEL trial which overall showed some mild benefit in exercise performance but no statistically significant difference in the primary endpoint of improved maximal oxygen consumption during cardiopulmonary exercise testing.[34] An overall small but not statistically significant improvement in maximal oxygen consumption during cardiopulmonary exercise testing is also reported by a recent meta-analysis.[35] This suggests that careful patient selection might be important to show a statistically significant improvement in exercise tolerance in a more specifically defined patient cohort.

Study limitations

This pilot study lacks invasive measurement; therefore, the exact cardiac loading conditions are not fully known. Other parameters such as ventricular energy loss might be even more reproducible than kinetic energy[19] but analysis software for these is not widely available, and the common denominator of the majority of 4D Flow MRI publications is kinetic energy, as this is a key component of cardiac work.[36] Furthermore, kinetic energy and energy loss correlate well in healthy volunteers and Fontan patients.[19,21] The inflow improvement seen in patient 6 is quite large, and some degree of measurement error cannot be excluded. However, the increase in inflow is in keeping with the other results of this patient and the 4D Flow MRI sequence used in this publication has been extensively evaluated for reproducibility.[15]

Long-term functional and symptomatic improvement in patients was outside the scope of this pilot study, and the correlation of oxygen-induced vasodilation with vasodilator medication response requires demonstration in future studies. However, this pilot study provides important proof-of-concept data for a larger follow-on study.

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Conclusions

This study showed the potential of non-invasive acute vasodilator response testing in Fontan patients using oxygen administration and 4D Flow MRI imaging. Vasodilator testing led to positive haemodynamic responses in some patients, with increased mitral forward flow, decreased systolic peak kinetic energy, and increased E-wave peak kinetic energy, leading to a pattern of more efficient cardiac filling.

The differing response to oxygen in Fontan patients may suggest that 4D Flow MRI can help to identify those expected to respond to vasodilator therapy and would benefit from a trial of pulmonary vasodilator medication in Fontan patients. However, the correlation of the oxygen response with the response to vasodilator medication requires confirmation in further studies.

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Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation in the United Kingdom and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the research ethics committee: South Central-Berkshire.

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