IMPRS Award Finalist

Myocardial Perfusion Reserve in Children with Friedreich Ataxia

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Abstract

Children with Friedreich's Ataxia (FA) are at risk of perioperative morbidity and mortality from severe unpredictable heart failure. There is currently no clear way of identifying patients at highest risk. We used myocardial perfusion reserve (MPR), an MRI technique used to assess the maximal myocardial blood flow above baseline, to help determine potential surgical risk in FA subjects. In total, seven children with genetically confirmed FA, ages 8 to 17 years, underwent MPR stress testing using regadenoson. Six of the seven demonstrated impaired endocardial perfusion during coronary hyperemia. The same six were also found to have evidence of ongoing myocardial damage as illustrated by cardiac troponin I leak (range 0.04 – 0.17 ng/mL, normal <0.03 ng/mL). None of the patients had a reduced ejection fraction (range 59 – 74%) or elevated insulin level (range 2.46 – 14.23 mCU/mL). This retrospective study shows that children with FA develop MPR defects early in the disease process. It also suggests MPR may be a sensitive tool to evaluate underlying cardiac compromise and could be of use in directing surgical management decisions in children with FA.

Introduction

Friedreich's Ataxia (FA) is an autosomal recessive disease affecting approximately 1:50,000 individuals, mostly Caucasian. Nearly all cases are caused by an expanded trinucleotide repeat (GAA) resulting in gene silencing and quantitative deficiency of the protein frataxin [1]. Frataxin is integral in the assembly of iron-sulfur clusters required for numerous mitochondrial matrix cofactors involved in oxidative phosphorylation [2]. It is the most common hereditary ataxia, but the heart is also severely affected and most patients with FA succumb to hypertrophic cardiomyopathy (HCM) during the third to fifth decade of life [3,4]. FA is also commonly associated with scoliosis. Surgical correction of this scoliosis has a heightened risk of unpredictable severe heart failure and death [5,6].

MPR is an MRI technique used to show the maximal possible increase in myocardial blood flow in response to exercise or pharmacologic stimuli. It is commonly used in the diagnosis and management of patients with known or suspected coronary heart disease [7]. MPR defects have recently been shown in adults with FA and correlated with increased left ventricular mass and signs of metabolic syndrome [8]. To date no one has used it in FA patients less than 18 years of age, nor has regadenoson been reported in this patient population. We used MPR in children with FA as part of a pre-surgical risk assessment and found that it was well tolerated by the patients. We found that children with FA had perfusion reserve defects early in life, and this data was useful to guide risk assessment for possible scoliosis surgery.

Methods

Study Population:

Patients under the age of 18 with genetically confirmed FA were evaluated as part of a pre-surgical risk assessment. Their records were retrospectively reviewed. All assessments were conducted at Riley Hospital for Children in Indianapolis, Indiana, USA. No patients had abnormal renal function (calculated glomerular filtration rate ≤30 mL/min/m^2) or contraindication to MRI. All patients had baseline demographic and clinical characteristics recorded. Prior to pharmacologic stress testing, all patients had baseline electrocardiogram and echocardiography studies. Serum labs collected prior to cardiac MRI included cardiac troponin I (cTnI), insulin, fasting blood glucose, and fasting lipid profile.

Echocardiography:

All patients underwent standard echocardiography using state-of-the-art machines as recommended by the American Society of Echocardiography [9]. M-mode images of the left ventricle (LV) were taken in the parasternal long axis and short-axis distal to the mitral valve leaflet tips after alignment of the cursor perpendicular to the LV wall. Measurements for the left ventricular posterior wall and interventricular septum were performed from the parasternal long-axis acoustic window with z-scores reported from the Pediatric Heart Network Database [10]. Interpretation of all echocardiograms was independently performed by pediatric cardiologists.

Relative wall thickness (RWT) was defined as two times the posterior wall thickness divided by the left ventricular end-diastolic internal diameter [11]. Left ventricular mass was indexed by dividing the body weight by the patient's height raised to the 2.7 power [12]. Thresholds for left ventricular mass index (LVMI) and RWT in children were consistent with 95% confidence intervals published by de Simeone et al. The limit for LVMI was set at 44 g/$m^{2.7}$ in males and 40g/$m^{2.7}$ in females. The limit for RWT was set at 0.39 for both sexes [12,13]. Eccentric hypertrophy was defined as normal RWT with increased LVMI while concentric remodeling was defined as increased RWT with normal LVMI, and concentric hypertrophy was defined as increased RWT with increased LVMI [14].

Cardiac Magnetic Resonance Imaging and Myocardial Perfusion Reserve:

All patients were imaged using a Siemens 1.5T Avanto scanner (Siemens Inc., Erlangen, Germany) at rest and during pharmacologic stress in accordance with ACC/AHA recommendations [15]. Patients were asked to abstain from caffeine for 24 hours prior to the procedure. A standard twelve-lead electrocardiogram was obtained prior to imaging, and continuous cardiac telemetry and pulse oximetry were monitored throughout the procedure. Three short axis and one four-chamber image were captured immediately following rapid intravenous administration of 0.075 mMol/kg gadolinium-based contrast reagent. To induce hyperemia, regadenoson at a dose of 10 mCg/kg capped at the adult dose of 0.4 mg was given over ten seconds followed by saline flush one minute prior to contrast. This dose is consistent with prior publications in pediatrics and pharmacokinetic modeling [16-18]. Resting images were completed prior to stress testing in case of intolerance to regadenoson and premature discontinuation of the exam. Blood pressure and heart rate were measured at baseline and every minute for 15 minutes after administration of the vasodilator regadenoson. Aminophylline was available in case of severe dyspnea or chest pain.

Clinical Lab values:

All clinical laboratory tests, including cardiac troponin I (cTnI), insulin levels, and lipid panels, were conducted at Riley Hospital for Children clinical laboratories.

Results

Baseline Characteristics and Demographic Data:

In this retrospective study, seven children 8 to 17 years of age underwent MPR scans (Table 1). Five of the seven were male and all were Caucasian. All had genetically confirmed GAA triplet expansions of the FRDA allele although one subject did not provide the medical records for this analysis. Their Body Mass Indexes (BMIs) ranged from 12.8 to 18.1 kg/m^2. Two of the seven were taking angiotensin-receptor blockers and one was taking a β-blocker, and one was taking a non-dihydropyridine calcium channel blocker. Trinucleotide repeat lengths on both alleles are included where available.

Table 1 Baseline Characteristics

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6	Patient #7
Age (yrs)	17	9	13	14	14	10	8
Race	White	White	White	White	White	White	White
Sex	F	M	M	F	M	M	M
Height (cm)	166	134.5	163	152	178	139	132
Weight (kg)	48	27	48	37	53	25	27
BMI (kg/m^2)	17.3	18.1	18.1	15.8	16.6	12.8	15.3
Cardiac Meds	Losartan	None	Atenolol	Losartan	None	None	Verapamil
GAA1/GAA2	486/953	900/1300	850/1200	800/1000	650/940	NA	1100/1300

Table 2 Echocardiography*

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6	Patient #7
Diastole							
RV	1.74 (-0.72)	1.61 (-0.50)	1.92 (-0.32)	1.38 (-01.50)	1.96 (-0.39)	1.57 (-0.60)	1.50 (-0.79)
IVS	1.26 (2.68)	1.38 (3.92)	1.16 (2.26)	1.30 (3.09)	0.99 (1.30)	1.72 (4.94)	1.44 (4.13)
LV	3.73 (-1.75)	2.93 (-3.25)	4.01 (-1.07)	3.13 (-3.20)	3.86 (-1.78)	3.03 (-2.92)	2.93 (-3.23)
LVPW	1.43 (4.05)	1.64 (5.74)	1.09 (2.62)	1.27 (3.76)	1.11 (2.46)	0.77 (1.76)	1.35 (4.73)
Systole							
IVS	1.75	1.90	1.36	1.63	1.33	1.83	1.76
LV	2.01	1.43	2.22	1.74	2.31	2.09	1.66
LVPW	2.16	2.14	1.31	1.62	1.82	1.32	1.54
LAD	3.00 (1.42)	2.45 (0.74)	3.04 (1.49)	2.64 (0.79)	NA	NA	2.32 (0.37)
Ao	2.19 (0.87)	1.90 (1.91)	1.77 (-0.07)	1.70 (-0.09)	2.33 (0.19)	1.83 (-0.01)	1.60 (0.23)
SF (%)	46.3	51.1	44.6	44.4	40	31.1	43.2
EF (%)	78	84	76	77	71	60	76
RWT	0.77	1.12	0.54	0.81	0.58	0.51	0.92

*All lengths measured in cm with z-scores in parentheses where available. RV: Right Ventricle; IVS: Interventricular Septum; LV: Left Ventricle; LVPW: Left Ventricular Posterior Wall; LAD: Left Anterior Descending coronary artery; Ao: Ascending Aorta; EF: Ejection Fraction; SF: Shortening Fraction; RWT: Relative Wall Thickness;

Echocardiography:

All patients had evidence of myocardial thickening on echocardiography (Table 2). Six of the seven patients had left ventricular posterior wall thickness more than two standard deviations greater than the mean when adjusted to body surface area for age, sex, race, and ethnicity. Similarly, all but one had an interventricular septum diameter greater than two standard deviations from the adjusted mean. Shortening fraction (SF) ranged from 31.1 to 51.1% and ejection fraction (EF) ranged from 60 to 84%. All patients had hypertrophic left ventricles as determined by RWT on echocardiography, ranging from 0.51 to 1.12.

Table 3 Cardiac MRI*

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6	Patient #7
Basal anteroseptum	NA	1.40	NA	1.24	1.20	1.40	1.37
Mid anteroseptum	1.36	1.40	1.09	1.51	0.80	1.60	1.32
Mid inferoseptum	1.31	1.40	1.30	1.73	1.10	1.30	0.85
Mid inferior wall	1.06	NA	1.08	NA	0.60	NA	NA
Mid inferolateral wall	NA	1.40	NA	NA	0.80	0.70	NA
Mid posterior wall	1.20	NA	0.96	NA	NA	NA	NA
Basal inferolateral wall	NA	1.30	NA	NA	1.10	0.60	NA
Basal posterior wall	NA	NA	NA	1.47	NA	NA	1.05
LVEDD at the base	3.97	2.9	4.60	3.04	NA	NA	3.96
RWT	0.60	0.89	0.42	0.97	0.43	0.45	0.53
LV mass	150.0	107.3	103.9	131.6	126.0	73.0	89.04
LVMI	38.2	62.7	28.0	42.2	26.6	30.0	42.1
LVEDV	80.0	59.7	95.4	53.0	110.0	70.0	59.5
LVEDVI	20.4	34.9	25.7	17.0	23.2	28.8	28.1
LVESV	21.0	22.9	34.4	21.6	39.0	29.0	16.9
LVESVI	5.3	13.4	9.3	6.9	8.2	11.9	8.0
LVEF (%)	74.0	61.7	64.0	59.3	64.0	59.0	71.5
LV Hypertrophy	CR	CH	CR	CH	CR	CR	CR

*All lengths reported in cm and volumes reported in mL. LV: Left ventricle; EDD: End-diastolic diameter; RWT: Relative wall thickness; MI: Mass index; EDV(I): End-diastolic volume (index); ESV(I): End-systolic volume (index); EF: Ejection fraction; CR: Concentric remodeling; CH: Concentric hypertrophy

Cardiac Magnetic Resonance Imaging:

All patients had measurable LV hypertrophy by RWT, ranging from 0.42 to 0.97 (Table 3). Two of seven also had severe LV hypertrophy by LVMI, and the range was 26.6 to 62.7 g/m$^{2.7}$. Thus, two of the seven met the previously defined criteria for concentric hypertrophy (CH) while the remainder were characterized as having concentric remodeling

(CR). No patient had a reduced left ventricular EF with values ranging from 59-74%. The remaining results are displayed in Table 3.

Figure 1 shows representative results from the MPR imaging in all seven subjects. Six of the seven children sampled were found to have a myocardial perfusion reserve defect. The only child who did not was Patient #3. The arrows in Figure 1 illustrate the region of hypoenhancement within the left ventricular endocardium following administration of the vasodilator regadenoson. Most commonly seen was a ring of hypoperfusion in the subendocardial region showing as a darkened area on contrast enhancement although some subjects, such as Patient #4, has more localized hypoperfusion involving the papillary muscles. A resting perfusion image from Patient #4 is included for reference.

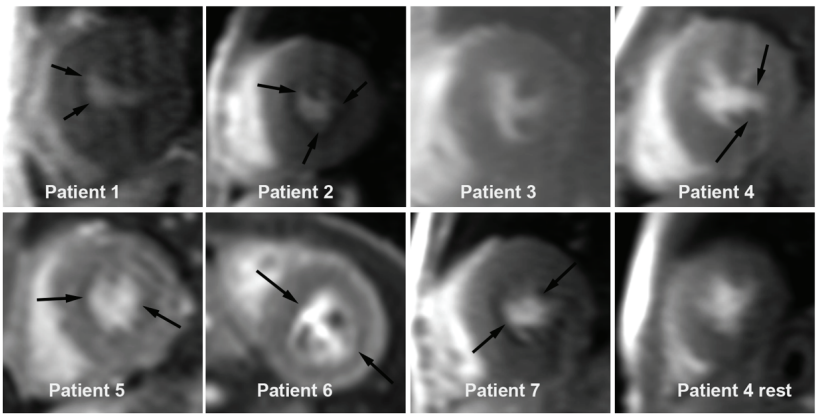

Figure 1. Myocardial Perfusion Reserve study on seven patients with Friedreich Ataxia. Left ventricle shown in cross-section after regadenoson infusion with gadolinium enhancement. Black arrows denote areas of hypoperfusion with regadenoson stress. Patient 4 rest demonstrates left ventricle prior to regadenoson stress.

Figure 2 illustrates the cardiovascular stress response of each child to the vasodilator regadenoson. Heart rates increased in all ranging from 15 to 82% above baseline. Conversely, systolic blood pressure fell from baseline in all subjects by 10 to 41%, and diastolic blood pressures fell from baseline 24 to 54%. Interestingly, the only patient who saw a larger percentage decrease from baseline in systolic blood pressure than diastolic blood pressure was Patient #3, the one without a detectable MPR defect. All patients tolerated the procedure with most reporting only mild to moderate shortness of breath and chest discomfort. Aminophylline was never needed.

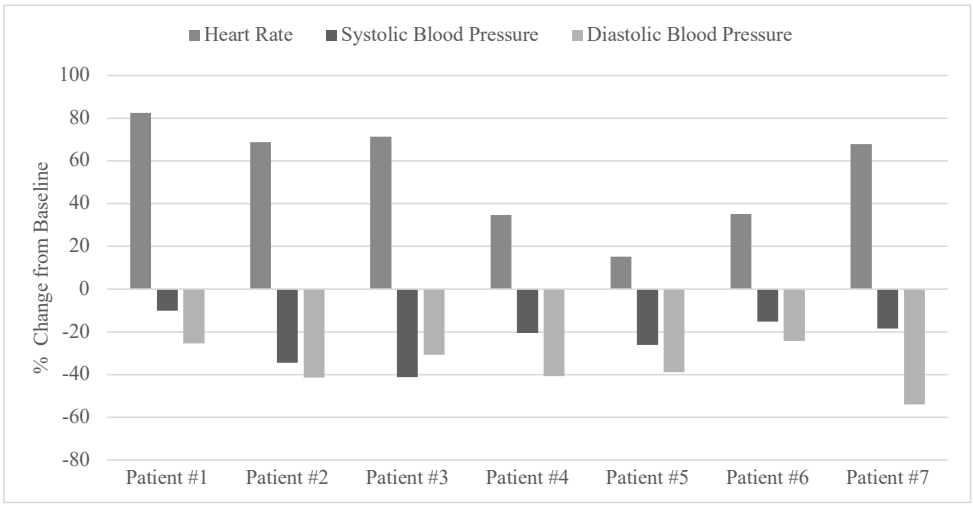

Figure 2. Cardiovascular Stress Response. Heart rate, systolic blood pressure, and diastolic blood pressure were measured in all seven subjects during administration of the vasodilator regadenoson. The percentage of change from baseline was plotted for all three parameters on the Y-axis.

Myocardial Injury and Metabolic Dysfunction:

All patients with a MPR defect also had evidence of ongoing myocardial injury as measured by cardiac troponin I (cTnI) leak greater than or equal to 0.03 ng/mL (Table 4). Similarly, the only patient without an MPR defect did not have evidence of myocardial injury as measured by cTnI. None of the patients sampled were found to have an elevated insulin level, elevated triglycerides, elevated BMI, or elevated blood pressure although four were on antihypertensive cardiac medications at baseline. Two patients had an elevated fasting blood glucose, and two patients had a low HDL.

Table 4 Heart Damage and Metabolic Dysfunction

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6	Patient #7
cTnI (ng/mL)	0.05	0.12	0.02	0.17	0.04	0.05	0.12
Insulin (mCU/mL)	5.06	3.35	14.23	6.25	7.13	NA	2.46
FBG (mg/dL)	77	84	89	84	104	115	85
HDL mg/dL)	44	46	42	44	41	55	52
LDL (mg/dL)	68	113	42	127	55	78	92
TG (mg/dL)	78	101	101	81	50	49	54
BP (mmHg)	108/71	119/58	107/62	107/59	126/77	105/62	103/65

cTnI: Cardiac Troponin I (normal <0.03ng/mL). FBG: Fasting Blood Glucose. HDL: High-Density Lipoprotein. LDL: Low-Density Lipoprotein. TG: Triglycerides. BP: Blood Pressure.

Discussion

To our knowledge, this retrospective study is the first to demonstrate the presence of MPR defects in children with FA. MPR stress testing as part of a comprehensive pre-surgical risk assessment found six of seven children had impaired myocardial perfusion after administration of the vasodilator regadenoson. These results suggest individuals with FA develop impaired myocardial blood flow as children. They also provide evidence for why these children may be at heightened risk of perioperative complications with stressful surgeries.

Approximately 70% of children with Friedreich's Ataxia (FA) develop scoliosis [5,6]. Many require surgery to maintain mobility and functional status. Surgery in children with FA, is associated with an increased risk of perioperative cardiovascular complications [5,6].Currently, left

ventricular ejection fraction (LVEF) is the most cited pre-operative assessment of cardiovascular risk [19]. However, reductions in LVEF typically occur very late in FA making it a poor marker of cardiac disease status in these patients [20].

We did not find concurrent presentation of MPR defects with elevation of LVMI or metabolic dysfunction in children. This correlation was previously described in adults with FA by Raman et al [8]. This suggests that MPR defects appear earlier in the FA disease process than either LV mass hypertrophy or metabolic dysfunction. These results also suggest the microvascular changes exposed by stress testing precede the development of cardiac hypertrophy and metabolic derangements. This has recently been discussed by Koeppen et al [21].

We did find evidence of myocardial damage in these children as illustrated by cTnI leak. This also indicates that chronic myocardial injury begins early in the disease. Cardiac troponin I leak correlated with the presence or absence of MPR defects in all patients although the sample size is too small to be statistically significant. Thus, in this small retrospective study, myocardial damage appears in concert with MPR defects and predates both severe LV mass hypertrophy and the development of metabolic dysfunction.

The remainder of the pre-surgical assessment was consistent with what has previously been described in children with FA. This includes preserved EF on both echocardiography and cMRI. All patients were found to have thickening of the left ventricular wall as measured by RWT consistent with either concentric remodeling or concentric hypertrophy.

We used regadenoson (Lexiscan®) to dilate the coronary vasculature and maximize coronary blood flow. To our knowledge, this is the first time regadenoson has been used in children with FA. Our experience was positive in that all patients achieved maximal increase in coronary blood flow, and the procedure was tolerated without significant complications.

Conclusion

This small retrospective study shows that MPR defects in FA begin earlier in life than previously suspected. Based on these findings, cMRI with MPR appears to be a sensitive indicator of underlying cardiac compromise and could help direct surgical management of children with FA. Strengths of this approach are that it is non-invasive, the FA subjects tolerated the vasodilator, regadenoson, very well, and informative data was obtained. Weakness of this study are that the subject numbers are small, there is no randomization, and the study is retrospective. However, these data support the rationale of a larger prospective trial to determine if MPR defects precede LV mass hypertrophy or metabolic dysfunction in children with FA.

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