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ORIGINAL PAPER

Pediatric heterozygous familial hypercholesterolemia patients have locally increased aortic pulse wave velocity and wall thickness at the aortic root

Andrew Tran[1] · Barbara Burkhardt[2] · Animesh Tandon[3] · Sarah Blumenschein[3] · Arna van Engelen[4] · Marina Cecelja[5] · Song Zhang[6] · Sergio Uribe[7,8,9] · Joaquin Mura[9,10] · Gerald Greil[3,4] · Tarique Hussain[3,4]

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Abstract

Familial hypercholesterolemia (FH) is an autosomal dominant disorder that affects 1 in 250 people. Aortic stiffness, measured by pulse wave velocity (PWV), is an independent predictor for cardiovascular events. Young FH patients are a unique group with early vessel wall disease that may serve to elucidate the determinants of aortic stiffness. We hypothesized that young FH patients would have early changes in aortic stiffness compared to healthy, age- and sex-matched reference values. Thirty-three FH patients (≥ 7 years age; mean age 14.6 ± 3.3 years; 26/33 on statin therapy) underwent cardiac MRI. PWV was determined using propagation of flow waveform from aortic arch phase contrast images. Distensibility and aortic wall thickness (AWT) were measured at the ascending, proximal descending, and diaphragmatic aorta. Ventricular volumes and left ventricular (LV) myocardial mass were measured from 2D cine images. These parameters were compared to age- and sex-matched reference values. FH patients had significantly higher PWV (4.5 ± 0.8 vs. 3.5 ± 0.3 m/s; $p < 0.001$), aortic distensibility, and ascending aortic wall thickness (1.37 ± 0.18 vs. 1.30 ± 0.02 mm; $p < 0.05$) compared to reference. There was no difference in aortic area or descending aortic wall thickness between groups. Young FH patients had aortic changes with increased aortic pulse wave velocity in the setting of increased aortic distensibility, accompanied by increased thickness of the ascending aortic wall. Presence of these early findings in young patients despite the majority being on statin therapy support enhanced screening and aggressive treatment of familial hypercholesterolemia to prevent potential future cardiovascular events.

Keywords Familial hypercholesterolemia · Pediatrics · Magnetic resonance imaging (MRI) · Atherosclerosis · Prevention

✉ Andrew Tran
andrewtranmd@outlook.com

1 Heart Institute, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 2003, Cincinnati, OH 45229, USA

2 University Children's Hospital Zurich, Zurich, Switzerland

3 Division of Pediatric Cardiology, University of Texas Southwestern Medical Center, Dallas, TX, USA

4 Division of Imaging Sciences and Biomedical Engineering, King's College London, London, UK

5 Department of Clinical Pharmacology, King's College London British Heart Foundation Centre, School of Cardiovascular Medicine and Sciences, St Thomas' Hospital, London, UK

6 Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, TX, USA

7 Radiology Department, School of Medicine, Pontificia Universidad Catolica de Chile, Santiago, Chile

8 Biomedical Imaging Center, School of Medicine, Pontificia Universidad Catolica de Chile, Santiago, Chile

9 Millennium Nucleus for Cardiovascular Magnetic Resonance, Ministry of Economy, Development, and Tourism, Santiago, Chile

10 Mechanical Engineering Department, Technical University Federico Santa Maria, Santiago, Chile

Introduction

One in 250 people are heterozygous for familial hypercholesterolemia (FH) [1]. Individuals with FH have cholesterol levels that are two to three times higher than normal putting them at increased risk for atherosclerosis, myocardial infarction, and other cardiovascular events [2–4]. Despite the relatively common prevalence of FH, many people remain undiagnosed for years, and screening practices are variable [5, 6]. Even when treated with statins and other lipid lowering therapies, patients with FH still have increased risk for cardiovascular events compared to the normal population [7, 8].

Various markers of cardiovascular health exist that can help to stratify patient risk [9, 10]. Aortic stiffness in particular has been found to be an independent predictor of all-cause and cardiovascular mortality [11]. To estimate aortic stiffness, aortic pulse wave velocity (PWV) and compliance can be determined noninvasively by applanation tonometry, Doppler ultrasound, or cardiac magnetic resonance imaging (MRI). Pulse wave velocity determination by applanation tonometry and Doppler ultrasound is relatively inexpensive and easy to obtain but can be inaccurate [12]. Cardiac MRI offers advantages in accuracy and the ability to assess local pulse wave velocity and aortic wall thickness in evaluating presence of atherosclerosis.

Several adult studies examined aortic atherosclerosis by MRI in FH patients. Caballero et al. found higher aortic wall volume and aortic atherosclerotic plaques in FH patients compared to controls, with aortic MRI detecting plaques in 94% of patients compared to 14% by carotid ultrasound [13]. Similarly, Schmitz et al. found larger aortic vessel wall area and vessel wall thickness in FH patients compared to control patients [7]. Contrasting this, Soljanlahti et al. found no differences in aortic wall volume, pulse wave velocity, or compliance between FH patients and control patients [14]. The Soljanlahti et al. study consisted primarily of adult patients with 9 pediatric patients included. Otherwise, there is little pediatric data on aortic stiffness or plaque burden assessed by MRI in FH patients.

The purpose of this study was to evaluate aortic stiffness, plaque burden, and subtle alteration in cardiac function or chamber size by cardiac MRI in asymptomatic FH pediatric patients compared to normal values from healthy children. We hypothesized that FH patients would have early aortic changes compared to healthy children.

Materials and methods

Subjects

Patients diagnosed with heterozygous familial hypercholesterolemia aged 7 years or greater were prospectively recruited from the preventive cardiology clinic at the Children's Medical Center of Dallas over a 1-year study period (2016–2017). These patients were phenotypically diagnosed with heterozygous FH if they had untreated fasting LDL-C levels > 160 mg/dL or total cholesterol levels > 230 mg/dL and family history of premature atherosclerotic cardiovascular disease (< 55 years in males, < 60 years in females) or severely elevated cholesterol levels. FH patients with known premature atherosclerotic cardiovascular disease were excluded from the study along with those who were unable to tolerate undergoing a cardiac MRI, e.g. due to extreme claustrophobia, or who had other contraindications to MRI.

This was a cross-sectional study with reference control data with subjects compared to age- and sex-matched reference data [15–18]. Patients underwent cardiac MRI evaluating aortic pulse wave velocity, aortic distensibility, aortic cross-sectional area, aortic wall thickness, and ventricular dimensions. Reference values from Voges et al. were used for aortic pulse wave velocity, aortic distensibility, and aortic cross-sectional area [18]. A gender-specific equation from Mensel et al. was used to determine reference values for aortic wall thickness [16]. Ventricular dimension reference values were calculated using a gender-specific equation from Buechel et al. [15] for pediatric subjects, whereas reference values from Kawel-Boehm et al. [17] were used for adult subjects. Each subject was matched to the expected imaging parameter value by age and sex per the references noted above. The expected values for all subjects were then averaged by parameter to determine the reference means which were then compared to the parameter means of the actual subjects. Height, weight, and blood pressure for patients were obtained on the day of the MRI. Lipid levels for patients were obtained from the patient's most recent clinic visit. The primary outcome measure for the patients was aortic pulse wave velocity. The secondary outcome measures were aortic distensibility, aortic area, aortic wall thickness, and ventricular volumes. Data was organized using a research electronic data capture (REDCap) database [19]. The study was approved by the University Texas Southwestern Medical Center Institutional Review Board (IRB number: STU 032,016–089) with informed consent and/or assent obtained from all individual participants included in the study.

Lab results

Fasting lipid levels were obtained from patients as part of the usual Preventive Cardiology clinic visit protocol, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation [20]. A cholesterol-year score was calculated as described by Hoeg et al. to provide a measure of lifetime cholesterol burden [21]. A pretreatment cholesterol-year value was calculated by multiplying the total cholesterol measurement (in mg/dL) at diagnosis with the age at diagnosis. A posttreatment cholesterol-year value was calculated by multiplying the most recent total cholesterol value to the number of years on treatment. The pretreatment and posttreatment values were summed up forming the total cholesterol-years score.

Cardiac MRI

Cardiac MRI was performed on a 1.5 T Philips Ingenia (Amsterdam, Netherlands) using a 32-channel torso phased-array digital receiver coil. PWV was determined using phase-contrast flow obtained at the ascending and proximal descending aorta. Automated 3D-centerline tracking (Fig. 1) was performed to determine aortic length to calculate the PWV as previously described [22]. For all patients high-temporal resolution 2D through-plane velocity-encoded phase-contrast (PC-MRI) in the ascending (ASC), descending (DESC) and diaphragmatic (DIAPH) aorta were obtained. This sequence was performed free-breathing with signal averaging to compensate for respiratory motion. Imaging parameters included: echo time 2.9 ms, repetition time 5 ms, slice thickness 8 mm, acquired resolution 2 × 2 mm, 2 to 3 signal averages, 125 cardiac phases, temporal resolution 5.1 to 6.9 ms, and acquisition duration 2–3 min. The transit time describing the delay between the arrival of the pulse wave at two locations was subsequently computed using the foot-to-foot method [23]. The foot of each curve was determined based on the intersection of a fit against the average maximum gradient during systole and a horizontal projection through

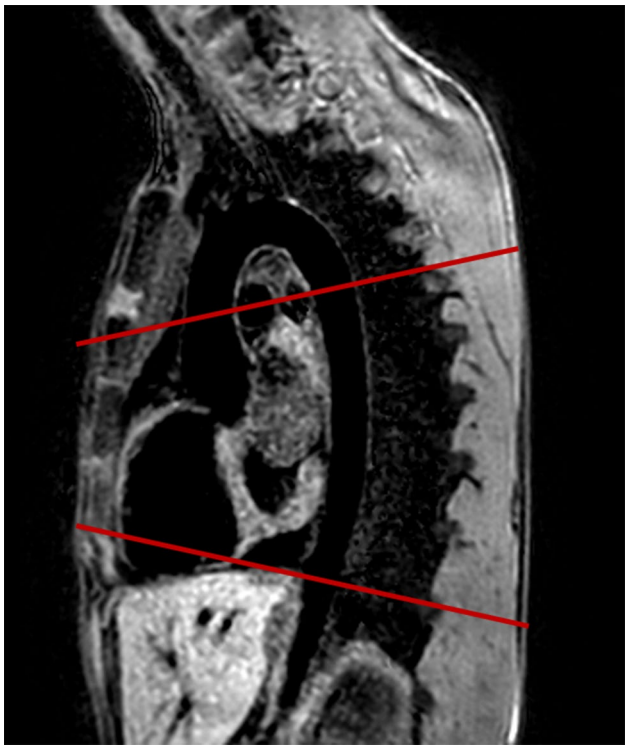

Fig. 2 Location of aortic measurements. This sagittal black blood view of the aorta depicts the location of aortic measurements for pulse wave velocity, aortic wall thickness, and aortic distensibility. The superior red line encompasses the ascending and descending aorta. The inferior red line encompasses the diaphragmatic aorta

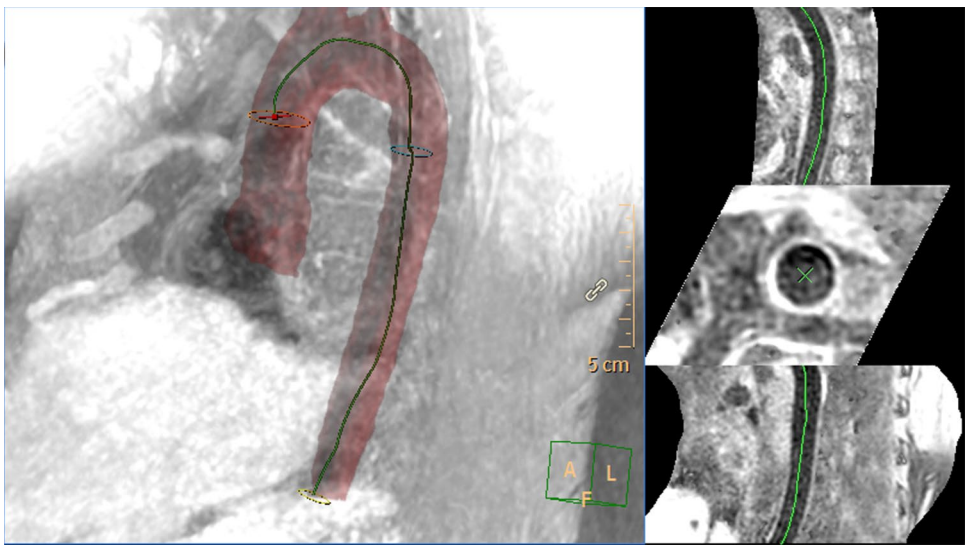

Fig. 1 3D-centerline tracking of the aorta. Aortic length was determined using automated 3D-centerline tracking as depicted by the green line for pulse wave velocity calculation. The ascending aorta (red circle), descending aorta (blue circle), and diaphragmatic aorta (yellow circle) are depicted. A red overlay of the aorta is provided on the left panel for clarity

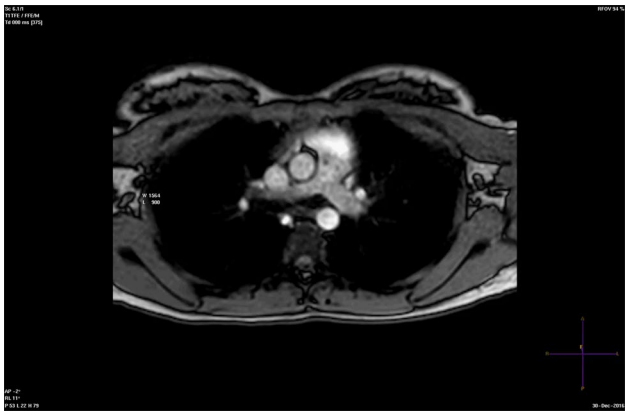

Fig. 3 Aortic distensibility of the ascending and descending aorta. Magnitude images of the phase contrast MRI were used to determine aortic distensibility

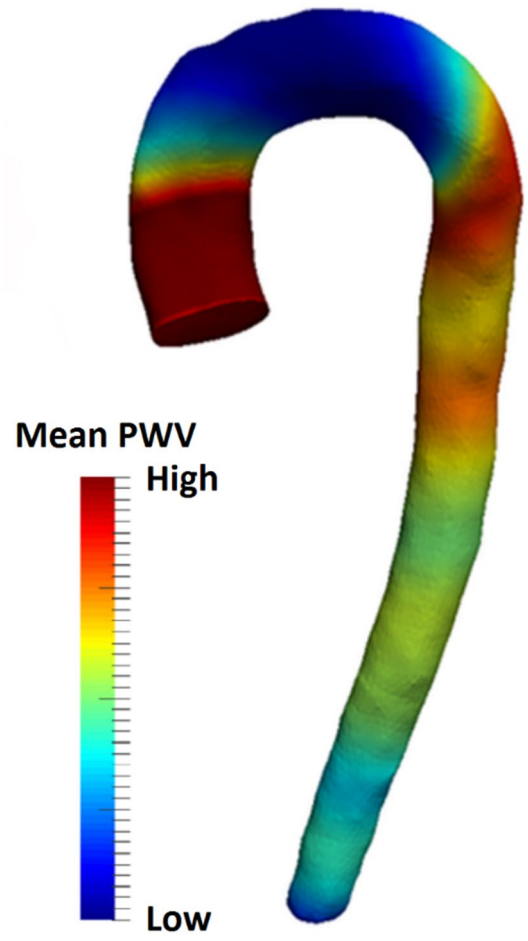

Fig. 4 4D-Flow mean aortic pulse wave velocity in FH patients. The 4D-Flow through the aorta for 25 patients with FH is represented here showing increased mean pulse wave velocity (PWV) in the ascending aorta

the local minimum. PWV was then calculated by dividing the centerline length between two locations by the transit time between those locations. For each subject, PWV calculations (Fig. 2) were performed for the segments ASC-DESC, DESC-DIAPH and for the entire thoracic aorta (ASC-DIAPH). Aortic distensibility was determined using semiautomated aortic area measurements using the CVI42 software (Circle Cardiovascular Imaging, Calgary, AB, Canada) at the ascending aorta, proximal descending aorta, and diaphragmatic aorta from the magnitude images of the PCMRI (Fig. 3).

Additionally, local PWV measurements for quantifying local alterations due to variation in aortic distensibility were calculated using 4D flow data (Fig. 4). The sequence was performed with a 3D fast field echo phase-contrast during free breathing and retrospective cardiac gating (25 time frames per cardiac cycle, resulting in a temporal resolution of 25–35 ms, reconstructed voxel size of 2–2.55 mm on each side, TR(ms)/TE(ms) = 4.8/2.7, average acquisition duration 7–9 min) [24]. Local PWV was determined using an algorithm to calculate flow waveforms accurately over isosurfaces without manual interpolations over a number of arbitrary flat planes [25]. To improve the analysis, each waveform was perturbed with random noise of 5% with respect to the maximal amplitude, generating 10 new realizations for each waveform. The cross-correlation was performed regarding all possible combinations.

The aorta was visualised by obtaining thirty-three transverse slices (no slice gaps) spanning from the aortic arch to the aortic bifurcation using zoom imaging (free-breathing, double inversion, black-blood, two-dimensional proton density weighted, turbo-spin-echo sequence) as previously described [26]. To maximize signal-to-noise, the cardiac coil was centered over the thoracic and abdominal aorta, respectively. Other imaging parameters included: pixel bandwidth 416 Hz, repetition time of 2 heart beats, shortest trigger delay (~ 500 ms), inversion time ~ 500 ms, echo time 5 ms, 60 ms acquisition window, 12 lines per heartbeat, field of view 220 × 67, acquired matrix size 224 × 208 (acquired resolution 0.98 × 1.06 mm), slice thickness 5 mm and partial Fourier imaging factor = 0.75 [26]. Compensation for respiratory motion in the aorta was achieved using two signal averages. For each cross-sectional slice, a circular region of interest was drawn around the inner and outer aortic walls using the CVI42 software and the area for both recorded. Aortic lumen and outer adventitial diameters were calculated from the inner and outer areas assuming a circular cross-section and average aortic wall thickness calculated as the difference between inner and outer diameters divided by two (Fig. 5). The presence of an atherosclerotic plaque was defined as a luminal protrusion > 1 mm. Aortic wall thickness was measured at the ascending aorta and proximal

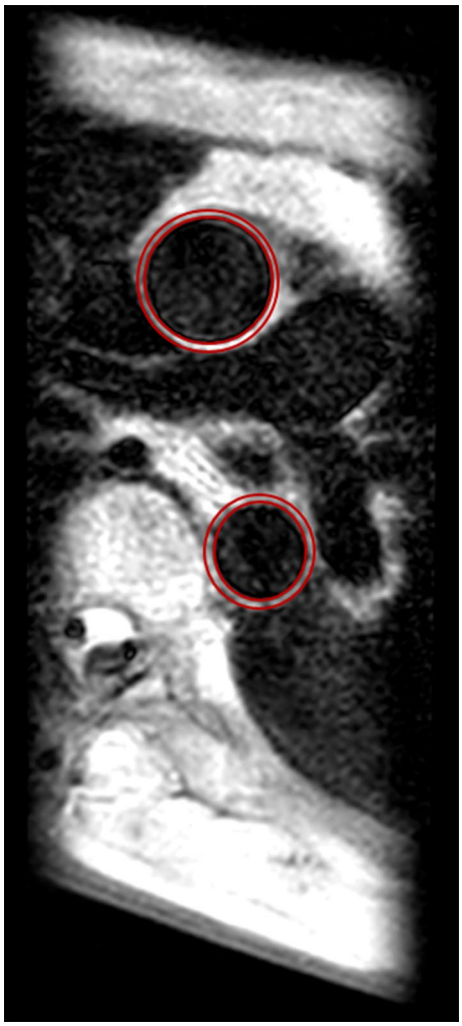

Fig. 5 Zoom imaging of the ascending and descending aorta for aortic thickness measurements. This transverse view through the ascending and descending aorta depicts the aortic lumen and outer adventitial measurements obtained to determine aortic wall thickness

descending aorta. As the measurement of aortic wall thickness required manual segmentation, the reproducibility of this measurement was evaluated by two independent and blinded observers.

Ventricular volumetric analysis and LV myocardial mass were measured using retrospectively ECG-gated balanced-steady state-free precession (bSSFP) cine images taken in a short-axis orientation planned parallel to the atrio-ventricular valve plane as previously described [27]. Images were acquired contiguously during end expiratory breath-holds covering apex to base. Typical imaging parameters: TR = 3.0–3.6 ms; TE = 1.5–1.8 ms; parallel imaging (SENSE) factor 2; flip angle 60°; field of view 280–400 mm, slice thickness 10 mm, in-plane resolution 1.5–2.0 mm; acquired temporal resolution 20–30 phases, breath-hold duration 5–7 s per slice, 10–14 slices to cover the heart.

Table 1 Characteristics of FH patients

Characteristics	FH patients (n = 33)
Sex, M/F (% male)	14/19 (42.4%)
Age, years (range)	14.6 ± 3.3 (7.3–19.8)
Race	
White Hispanic or Latino	45.4% (n = 15)
White non-Hispanic or Latino	42.4% (n = 14)
Black	9.1% (n = 3)
Asian	3.0% (n = 1)
BMI (kg/m^2)	23.4 ± 6.7
BMI Z-score	0.65 ± 1.43
Systolic blood pressure (mmHg)[a]	117.2 ± 12.7
Diastolic blood pressure (mmHg)[a]	65.1 ± 11.0
Family history of CAD (%)	51.5% (n = 17)
Total cholesterol years (mg-year/dL)	3920.3 ± 1216.1

Where appropriate, data is expressed as mean and standard deviation

FH familial hypercholesterolemia, *M* male, *F* female, *BMI* body mass index, *CAD* coronary artery disease

[a]Blood pressure data was obtained for 32 patients

Statistical analysis

Descriptive analyses of the data were performed using mean, standard deviation, and proportion as appropriate. For each variable, we took the difference between the observed value and the expected value and conducted a 1 sample T-test to assess whether the difference was statistically significant using a p-value of < 0.05. Pearson correlation coefficients were calculated for the patients to examine association between patient characteristics and outcome variables. The analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Thirty three patients with heterozygous familial hypercholesterolemia were recruited for the study. Patient characteristics are shown in Table 1. The majority of the patients were on statin treatment except for 7 patients having been recruited at initial diagnosis of FH and so not yet having started statin therapy. While none of the patients had prior diagnosis of hypertension, 7 patients (21.9%) had blood pressure readings at recruitment that were above thresholds for stage 1 systolic hypertension and 3 additional patients (9.4%) were above thresholds for stage 2 systolic hypertension [28]. Out of the aforementioned 10 patients, two patients (6.3%) were additionally above thresholds for stage 1 diastolic hypertension.

Table 2 PWV, aortic distensibility, aortic cross-sectional area, aortic wall thickness, and ventricular parameters in FH and reference patients

	FH (n = 33)	Reference cohort (n = 33)	p-value
PWV (m/s)[a]	4.5 ± 0.8	3.5 ± 0.3	< 0.001
Distensibility, 10^{-3} $(mmHg)^{-1}$[a]			
Ascending aorta	12.9 ± 5.5	8.4 ± 1.5	< 0.001
Descending aorta	9.1 ± 4.3	6.9 ± 0.9	0.003
Diaphragmatic aorta	12.0 ± 5.2	8.4 ± 1.0	< 0.001
Cross-sectional area (mm^2)			
Ascending aorta	506.8 ± 115.3	488.7 ± 84.9	0.153
Descending aorta	262.8 ± 64.2	246.0 ± 45.4	0.107
Diaphragmatic aorta	199.0 ± 41.8	207.3 ± 38.0	0.404
Aortic wall thickness (mm)			
Ascending aorta	1.37 ± 0.18	1.30 ± 0.02	0.026
Descending aorta	1.07 ± 0.14	1.09 ± 0.02	0.594
LVEDV/BSA, mL/m^2	76.5 ± 12.9	81.2 ± 5.3	0.032
LVESV/BSA, mL/m^2	28.6 ± 6.9	29.9 ± 2.9	0.200
LV myocardial mass/BSA (g/m^2)	50.0 ± 7.5	58.3 ± 8.3	< 0.001
RVEDV/BSA (mL/m^2)	81.1 ± 13.9	88.0 ± 8.0	0.012
RVESV/BSA (mL/m^2)	35.4 ± 8.3	36.1 ± 5.6	0.656

Data is expressed as mean and standard deviation. p-values are from the paired two sample t-test

PWV pulse wave velocity, *FH* familial hypercholesterolemia, *LVEDV* left ventricular end diastolic volume, *BSA* body surface area, *LVESV* left ventricular end systolic volume, *LV* left ventricle, *RVEDV* right ventricular end diastolic volume, *RVESV* right ventricular end systolic volume

[a]Aortic distensibility and PWV values were obtained for 32 patients

The mean total cholesterol-years score for the patients was 3920.3 ± 1216.1 mg/dL.

The 2D phase contrast pulse wave velocity for the FH patients was significantly higher than the expected value (Table 2). 4D flow data was able to be obtained on 25 patients with increased PWV seen in the ascending aorta (Fig. 4). Aortic distensibility was also significantly higher in FH patients compared to reference in the ascending aorta, aortic isthmus, and diaphragmatic aorta, but there was no difference in aortic cross-sectional area (Table 2). Measurements of aortic wall thickness found that the ascending aorta was significantly thicker in FH patients compared to reference values. There was no difference in the descending aorta (Table 2). The inter-rater reproducibility for aortic wall thickness measurements was high with an intra-class correlation coefficient of 94%. The coefficient of variance (CV) for this measurement in our cohort was very low (13%). No aortic plaques were found in the patients. Ventricular function was normal in the FH group; however, while LVEDV/BSA, LV Myocardial Mass/BSA, and RVEDV/BSA were within the normal range, they were significantly lower than age and sex-matched references (Table 2).

There was no significant correlation between cholesterol-years and pulse wave velocity when taking all FH patients into account (0.2254, p = 0.2228). Similarly, dividing the cohort further to look specifically at treated and untreated FH patients did not show a significant correlation between cholesterol-years and pulse wave velocity (Treated FH 0.204, p = 0.287; Untreated FH 0.353, p = 0.434).

Discussion

Our findings suggest the presence of early aortic changes in young FH patients. Aortic pulse wave velocity was significantly higher than expected and there was increased distensibility in the ascending aorta, aortic isthmus, and diaphragmatic aorta. The ascending aortic wall was significantly thicker than expected with no difference in wall thickness in the descending aorta.

Aortic pulse wave velocity has multiple determinants and can be dynamic. Farrar et al. studied cynomolgus monkeys on a high cholesterol diet and found an initial decrease in PWV followed by a linear increase after a period of 30 months [29]. The monkeys that were taken off of the high cholesterol diet experienced a decrease in PWV after 12 months. Riggio et al. evaluated asymptomatic pediatric patients with untreated hypercholesterolemia (including 18 heterozygous FH patients) by ultrasound and found significantly higher pulse wave velocity and augmentation index compared to control patients [30].

Increased aortic compliance in the setting of hypercholesterolemia has been seen in several studies. Lehmann et al. studied 20 young patients (aged < 24 y.o.) by Doppler ultrasound finding that FH patients had significantly more compliant aortas than their normal counterparts [31]. Newman et al. found that cockerels fed an atherogenic diet also had increased aortic compliance [32]. Soljanlahti et al. more recently found a trend towards significance with greater aortic compliance in heterozygous FH patients compared to controls when evaluated by cardiac MRI [14]. The findings of our study support this as the patients in our cohort were young and with high cholesterol burden.

The patients in our study had significantly increased ascending aortic wall thickness suggesting possible early cholesterol deposition. The ascending aorta appears to be a key site of possible cholesterol deposition as past studies of homozygous and heterozygous FH patients found evidence of supravalvar aortic stenosis and aortic root thickening [33, 34]. However, patients with FH have also been shown to have involvement in the descending and abdominal aorta and increased aortic wall volume [13, 35].

Our study paradoxically found increased PWV in the setting of increased aortic compliance in our patients. Typically, one would expect that the aortic PWV would decrease as distensibility increases. However, aortic stiffness is derived by several factors as described by the Moens-Korteweg equation:

$$PWV = \sqrt{\frac{E \cdot h}{2r\rho}}$$

with E being the elastic modulus, h being vessel wall thickness, r being vessel radius, and ρ being blood density [12]. While greater aortic distensibility decreases the elastic modulus in the equation, the patients in our cohort also had increased ascending aortic wall thickness. This could explain the increased PWV in the setting of increased aortic distensibility. Supporting this, our 4D-flow data shows the pulse wave velocity increase being especially prominent in the region of the ascending aorta (Fig. 4). Another explanation for these findings may be hypertension, which is known to cause aortic changes. An adult study by Brandts et al. found that hypertensive patients had increased aortic PWV compared to normotensive subjects and that aortic PWV was associated with aortic wall thickness [36]. Liu et al. found that hypertensive patients had decreased aortic distensibility and increased PWV but contrasted Brandts et al. in finding that the PWV in adult patients was not related to aortic wall thickness [37]. The 10 patients in this current study that had blood pressure readings above thresholds for stage 1 or stage 2 hypertension did not have prior diagnosis of hypertension and could have had blood pressure elevation secondary to white coat hypertension. Since these blood pressures were taken at a single point in time, it is difficult to say if hypertension truly played a role in the aortic wall changes seen in this study.

Interestingly, the mean and patient-specific ventricular volumetric data were all within the normal range. However, in comparison to expected age/sex-matched control data, the ventricular volumes were slightly lower. Whether this represents an early change due to ventricular-vascular coupling or if this finding was due to inadequate pediatric normative data in the worldwide literature, remains to be seen. Indeed, the normal value cohort from Buechel et al. had fewer Hispanic/Latino children with normative data lacking for different ethnicities [15].

This study had a relatively small number of patients; however, it is the largest cohort yet of young heterozygous patients studied by cardiac MRI. Our patient cohort included multiple ethnicities which could have affected our outcomes, but they are a more representative reflection of the patient population at our center. Post-hoc analysis of sample size suggests that to be able to detect the level of difference detected in the aortic wall thickness with 80% power and a significance level of 5%, the study would have required 63 patients. The difference in aortic wall thickness detected by our study is small and should be considered in the context of this. While the majority of our patients were on statin therapy, several patients were recruited prior to initiating lipid lowering medication which could have skewed the cholesterol burden of our cohort upwards. The mean cholesterol-years of the cohort could also have been affected by varying levels of patient adherence to prescribed medications. None of our patients were on PCSK9 inhibitors. Additionally, our patients were diagnosed phenotypically with FH and did not undergo confirmatory genotyping. Therefore, the underlying defects in these patients causing FH are uncertain. Patients with *LDLR*-null alleles would have higher LDL-C levels and more severe phenotype than those with *LDLR*-defective alleles or mutant *APOB* alleles [38–40].

Areas of future study include recruiting larger numbers of heterozygous FH patients and following them longitudinally in order to possibly find differences in disease presentation and course by ethnicity. Genotyping of these patients would also allow for potentially better risk stratification and determination of management goals.

Young asymptomatic patients with heterozygous FH demonstrate early aortic changes even with the majority of the patients on lipid lowering therapy. This unique cohort of patients with high cholesterol burden, presumably without aortic calcification given the young age [41], had increased aortic pulse wave velocity in the setting of increased distensibility, accompanied by increased thickness of the ascending aortic wall. The presence of these early changes in young patients supports enhanced screening and treatment of familial hypercholesterolemia to prevent potential future cardiovascular events.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the insti-

tutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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