Pediatr Cardiol
DOI 10.1007/s00246-015-1107-7

ORIGINAL ARTICLE

Quantification and Significance of Diffuse Myocardial Fibrosis and Diastolic Dysfunction in Childhood Hypertrophic Cardiomyopathy

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Received: 8 October 2014 / Accepted: 13 January 2015

Abstract The purpose of this study was to evaluate the presence of diffuse myocardial fibrosis in children and adolescents with hypertrophic cardiomyopathy (HCM) and to assess associations with echocardiographic and clinical parameters of disease. While a common end point in adults with HCM, it is unclear whether diffuse myocardial fibrosis occurs early in the disease. Cardiac magnetic resonance (CMR) estimation of myocardial post-contrast longitudinal relaxation time (T1) is an increasingly used method to estimate diffuse fibrosis. T1 measurements were taken using standard multi-breath-hold spoiled gradient echo phase-sensitive inversion-recovery CMR before and 15 min after the injection of gadolinium. The tissue–blood partition coefficient was calculated as a function of the ratio of T1 change of myocardium compared with blood. An echocardiogram and blood brain natriuretic peptide (BNP) levels were obtained on the day of the CMR. Twelve controls (mean age 12.8 years; 7 male) and 28 patients with HCM (mean age 12.8 years; 21 male) participated. The partition coefficient for both septal (0.27 ± 0.17 vs. 0.13 ± 0.09; $p = 0.03$) and lateral walls (0.22 ± 0.09 vs. 0.07 ± 0.10; $p < 0.001$) was increased in patients compared with controls. Eight patients had overt areas of late gadolinium enhancement (LGE). These patients did not show increased partition coefficient compared with those without LGE (0.27 ± 0.15 vs. 0.27 ± 0.19 and 0.22 ± 0.09 vs. 0.22 ± 0.09; $p = 0.95$ and 0.98, respectively). However, patients who were symptomatic (dyspnea, arrhythmia and/or chest pain) had higher lateral wall partition coefficient than asymptomatic HCM patients (0.27 ± 0.08 vs. 0.17 ± 0.08; $p = 0.006$). Similarly, patients with raised BNP (>100 pg/ml) had raised lateral wall coefficients (0.27 ± 0.07 vs. 0.20 ± 0.07; $p = 0.03$), as did those with traditional risk factors for sudden death (0.27 ± 0.06 vs. 0.18 ± 0.08; $p = 0.007$). Diffuse fibrosis, measured by the partition coefficient technique, is demonstrable in children and adolescents with HCM. Markers of fibrosis show an association with symptoms and raised serum BNP. Further study of the prognostic implication of this technique in young patients with HCM is warranted.

Keywords Child · Adolescent · Hypertrophic cardiomyopathy · Cardiovascular magnetic resonance imaging · Echocardiography

Abbreviations

HCM	Hypertrophic cardiomyopathy
CMR	Cardiac magnetic resonance
T1	Longitudinal relaxation time
BNP	Brain natriuretic peptide
LGE	Late gadolinium enhancement
LV	Left ventricle

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Published online: 21 January 2015

E/A	Mitral inflow early-to-late diastolic flow ratio
IVRT	Isovolumic relaxation time
S/D	Pulmonary venous systolic-to-diastolic peak velocity ratio
E′lat	Mitral lateral early diastolic tissue velocities
E′med	Septal peak early diastolic tissue velocities
NYHA	New York Heart Association

Introduction

Inappropriate myocardial hypertrophy, macroscopic scarring, myocyte disarray and interstitial diffuse fibrosis are histopathological features of hypertrophic cardiomyopathy (HCM) [32]. Macroscopic scarring, as demonstrated by late gadolinium enhancement (LGE), has been shown to be associated with adverse outcomes in adults with HCM [1, 11, 23, 27]. Diffuse interstitial fibrosis occurs alongside this macroscopic scarring as a distinct histopathological process and has been shown to have independent clinical sequelae [32]. It is postulated that diffuse fibrosis is the morphological culprit of impaired diastolic function and symptoms of heart failure [6].

Recently, gadolinium myocardial longitudinal relaxation time (T1) mapping using cardiac magnetic resonance (CMR) has been used to noninvasively detect and quantify interstitial myocardial fibrosis [8, 12]. With this technique, Ellims et al. [6] showed an association between diastolic dysfunction and the presence of diffuse myocardial fibrosis but not with the presence macroscopic scarring in adult HCM patients. It is unclear, however, whether and to what extent pathological diffuse fibrosis occurs in childhood HCM. The purpose of this study was to determine whether diffuse myocardial fibrosis occurs in children with HCM using quantification of T1 changes after gadolinium administration and to assess associations with echocardiographic assessment of diastolic function and with clinical symptoms.

Methods

Children and adolescents with a clinical diagnosis of hypertrophic cardiomyopathy, who underwent CMR for clinical purposes between October 2009 and October 2012, participated in this study. Institutional clinical practice during this period was for HCM patients to undergo CMR every 2 years. Children underwent CMR, transthoracic echocardiography and measurement of serum brain natriuretic peptide (BNP) on the day of study. The clinical records were reviewed for a history of any symptoms that were reported prior to CMR (dyspnea, exertional chest pain, arrhythmia or unexplained syncope). Patients were also dichotomized according to the traditional risk factor for sudden cardiac death (unexplained syncope, non-sustained VT, previous arrest, family history of sudden cardiac death or family history of internal cardiac defibrillator with appropriate shock). As a control group, healthy asymptomatic children with normal echocardiograms and electrocardiograms undergoing CMR for screening purposes were invited to participate. CMR examinations with abnormal clinical findings were excluded from the control group. Institutional Review Board approval and patient and/or parental consent were obtained.

Cardiac Magnetic Resonance

The CMR examination was performed at 1.5 T (Avanto, Siemens Medical Solutions, Erlangen, Germany) using a phased-array multichannel surface receiver coil. Sequences were acquired using consecutive breath-holds. Left ventricular mass and function were assessed using a multislice, multiphase steady-state free precession pulse sequence in short axis [2]. The presence of LGE was determined using standard 4-chamber, 2-chamber, 3-chamber and multislice short-axis stack phase-sensitive inversion-recovery acquisitions 10 min after administration of 0.2 mmol/kg of gadopentetate dimeglumine (Magnevist, Bayer, Leverkusen, Germany) [16]. T1 measurements were taken at the identical location before and 15 min after 0.2 mmol/kg of gadopentetate dimeglumine, using a single mid-ventricular short-axis slice orientation. Measurements were based on standard spoiled gradient echo phase-sensitive inversion-recovery acquisitions with increasing inversion times (150, 400, 800 and 3,200 ms) and the following settings: slice-thickness = 6 mm; TR = 3.1 ms, TE = 1.3 ms; acquired in-plane resolution = 1.4 × 1.4 mm, imaging alternate heart beats; flip angle = 45°; each slice acquired over a separate breath-hold of 10–14 s duration. The images were analyzed using commercially available software with heart rate correction for T1 values (CMR42, Circle Cardiovascular Imaging, Calgary, AB, Canada). For analysis, regions of interest were drawn in the interventricular septum, left ventricular (LV) blood pool and LV lateral wall, incorporating as much of the relevant segments as possible while taking care to avoid the luminal trabeculations, epicardial fat and myocardium known to have overt macroscopic scarring, as evidenced by LGE. A 3-parameter curve-fitting technique was used to derive the T1 time constant (Fig. 1). The "goodness" of the curve fit was measured using R^2. Values of 0.99 or higher suggested a good fit. Cases with poor curve fit were excluded from the analysis. The tissue–blood partition coefficient (λ) was calculated as a function of the ratio of T1 change of myocardium compared with

blood. Higher partition coefficient values indicate greater fibrosis [7]. Tissue–blood partition coefficient (λ) = $\Delta R1_{muscle}/\Delta R1_{blood}$, where $\Delta R1 = 1/T1_{post\text{-}gadolinium} - 1/T1_{pre\text{-}gadolinium}$

Echocardiography

Echocardiography studies were performed using either a GE Vivid 7 or a GE E9 echocardiography machine (General Electric Medical Systems, Wisconsin, USA). The following parameters were measured from the stored digital data by a single investigator (A.D.): mitral inflow early-to-late diastolic flow (E/A) ratio, isovolumic relaxation time (IVRT), pulmonary venous systolic-to-diastolic peak velocity ratio (S/D), pulmonary venous atrial wave reversal amplitude and duration, time difference between pulmonary vein atrial wave reversal and mitral A duration, mitral lateral and septal peak early diastolic tissue velocities (E′lat, E′med), mitral E-to-mean E′ ratio, peak systolic tissue velocity at the lateral mitral annulus, left atrial volume (by the area length method) indexed to body surface area, maximal septal thickness, global radial strain using speckle tracking, global circumferential strain using speckle tracking and net torsion angle using speckle tracking. All measurements were taken using standard views and according to the current guidelines [20].

Doppler waveform patterns were classified as abnormal if there was evidence of early relaxation abnormality or pseudonormal filling (i.e., either mitral E:A reversal and pulmonary S-wave peak velocity >2× pulmonary venous D-wave or large pulmonary venous A-wave (>35 cm/s) and S-wave peak velocity <1/2 D-wave), or if there was evidence of decreased compliance (mitral E:A ratio >2 and pulmonary venous S-wave peak velocity <1/2 D-wave and

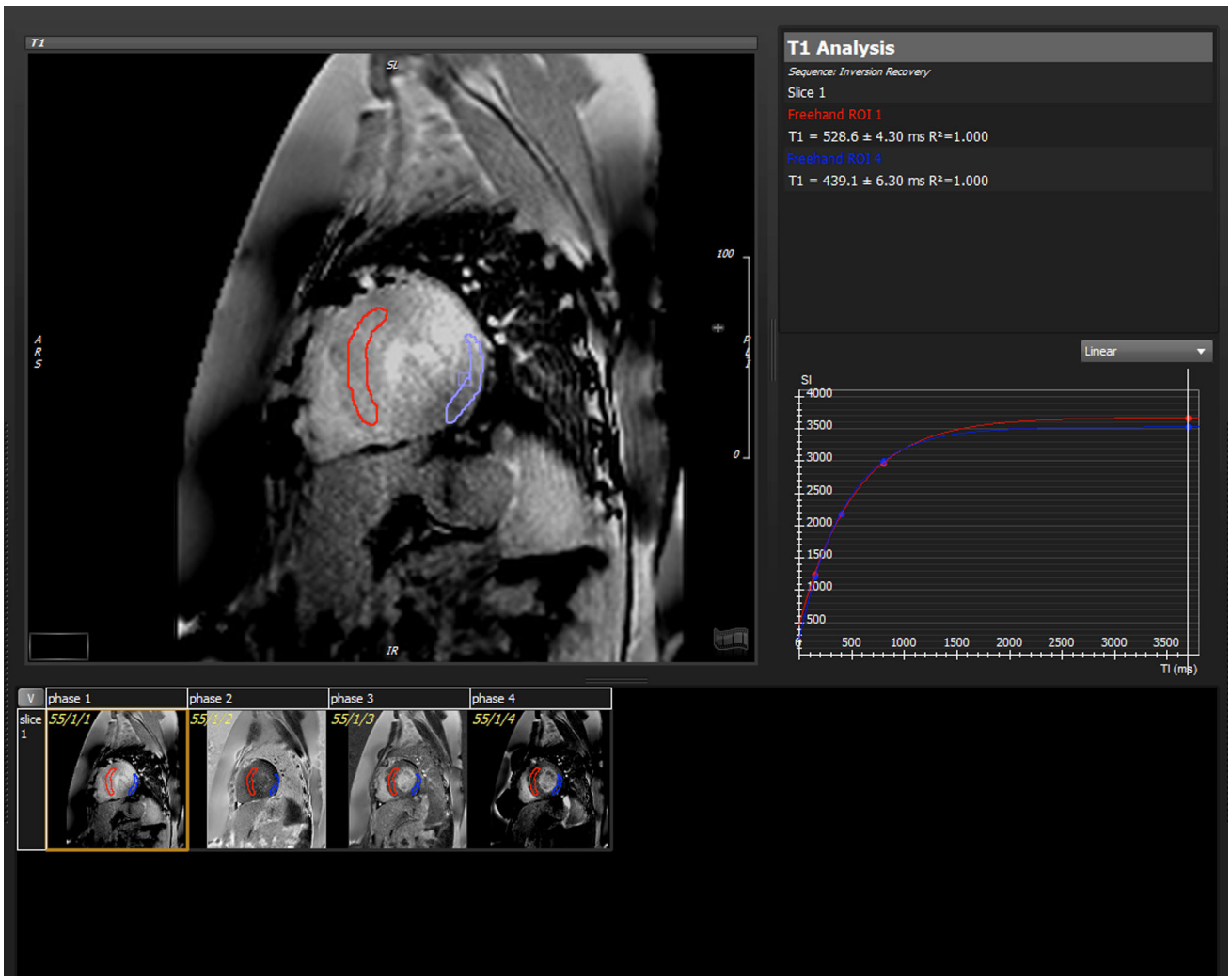

Fig. 1 Assessment of myocardial T1 time A single mid-ventricular slice imaged over multiple inversion times. A curve-fitting technique was used to create a T1 map of the myocardium. Individual regions of interest in the septum and lateral wall are sequentially drawn and recorded

the pulmonary vein A-wave duration was prolonged >30 ms compared with mitral valve A-wave duration) [4]. An estimated resting LVOT peak gradient ≥30 mmHg was defined as significant obstruction.

Finally, in order to amalgamate echocardiographic analyses of diastolic function, patients were classified as having either clear evidence of or no abnormality of diastolic function. A clear abnormality of diastolic function was defined by having one of the three following findings: (1) E/E' > 15, (2) indexed LA volume >45 ml/m^2 or (3) an abnormal mitral and pulmonary venous Doppler pattern. These definitions were taken by extrapolating scatter plots from recently published pediatric cardiomyopathy data [5].

Statistical Methods

Results are expressed as mean ± standard deviation where appropriate. Continuous variables were tested for normality using Kolmogorov–Smirnov tests. Independent samples *t* tests were used for normally distributed continuous variables and χ^2 testing or Fisher's exact test, as appropriate, for categorical variables, comparing patients to controls. Patients were further divided into categories comparing symptomatic (exertional dyspnea or chest pain NYHA grade ≥2/4, previous cardiac arrest or unexplained syncope) to asymptomatic patients, and those with elevated BNP (>100 pg/ml) [10] versus a normal BNP. A binary logistic model was then constructed using age and sex along with previously proven prognostic markers (the presence of resting outflow obstruction and macroscopic scar) [17, 23] and any parameters identified from above analyses as potentially differentiating between symptomatic and asymptomatic patients. Forward stepwise regression was employed with the presence of symptoms as the dependent variable. Finally, echocardiographic variables were tested against the tissue–blood partition coefficient to investigate any relationship between abnormal diastolic function and diffuse fibrosis. A p value <0.05 was considered significant. Statistical analyses were performed on SPSS version 19 (Release 19.0.0, IBM Software Group, New York, USA).

Results

Cohort Characteristics

Twelve controls [mean age 12.8 year. (range 9–16 years); 7 male] and 28 patients [mean age 12.8 year (range 8–18 years); 21 male) were included in the study. Two cases were excluded from the analyses (one patient and one control) as CMR image quality was inadequate to analyze myocardial T1 times. There were no significant differences between controls and patients for age and sex ($p = 0.95$ by independent *t* test and $p = 0.25$ by Fisher's exact test, respectively). Twenty out of the 28 HCM patients (71 %) had pathogenic mutations for sarcomeric HCM (eight had mutation in the MYBPC3 gene; 11 in MYH7; one in TPM1 and one in VCL). One patient had a reduced LV ejection fraction (<54 %) and three demonstrated septal hypertrophy >3 cm on CMR. Eight patients (28 %) had macroscopic scarring on LGE images and eight (28 %) had LV outflow obstruction at rest. Of those with outflow obstruction, the mean gradient was 57 ± 20 mmHg (range 35–100 mmHg). No patient had documented VT on Holter monitoring. Six patients had a family history of sudden cardiac death or of internal cardiac defibrillator with appropriate shock delivery.

Controls Versus HCM Patients

Comparisons between controls and HCM patients are given in Table 1. As expected, CMR-derived mean myocardial mass, ejection fraction and tissue–blood partition coefficients were all increased in HCM patients. Specifically, the partition coefficient for both septal (0.27 ± 0.17 vs. 0.13 ± 0.09; $p = 0.03$) and lateral walls (0.22 ± 0.09 vs. 0.07 ± 0.10; $p < 0.001$) was increased in patients compared with controls. Post-contrast T1 times are similar to those previously given for children, although native T1 times are lower than that previously reported [30]. On echocardiography, despite an increased ejection fraction, peak global circumferential and peak global radial strain values were significantly reduced in the patient cohort (Table 1). Other parameters of systolic function were not different between controls and patients. Regarding markers of diastolic function, E/E' was significantly greater in patients and mitral and pulmonary venous Doppler patterns were abnormal in four patients, but were normal in all controls. Indexed left atrial volume showed a trend toward enlargement in patients ($p = 0.05$). Regarding the described amalgamated parameter of "clear diastolic dysfunction," 12 of 28 (43 %) patients showed an abnormality while no control showed an abnormality.

Symptomatic Versus Asymptomatic Patients

Thirteen patients exhibited symptoms (three with previous cardiac arrest requiring resuscitation, two with a history of unexplained syncope, three with chest pain (NYHA ≥2) and five with dyspnea (NYHA ≥2). Symptomatic patients were compared with those who were asymptomatic ($n = 15$). The only parameters that were significantly associated with symptoms were lateral wall partition coefficient (0.27 ± 0.08 vs. 0.17 ± 0.08; $p = 0.006$) and the presence of a clear abnormality of diastolic function on

Table 1 Control versus HCM characteristics

	Controls (mean ± SD) $N = 12$	HCM patients $N = 28$	p value (* < 0.05)
Sex (male)	7	21	
Age (years)	12.8 ± 2.2	12.8 ± 2.6	0.95
Height (cm)	156 ± 12	158 ± 16	0.75
Weight (kg)	56 ± 12	55 ± 25	0.8
Native T1 septum (ms)	686 ± 65	748 ± 99	0.09
Native T1 lateral (ms)	686 ± 102	735 ± 102	0.22
Post-contrast T1 septum (ms)	619 ± 74	579 ± 90	0.23
Post-contrast T1 lateral (ms)	629 ± 40	590 ± 87	0.19
Septum partition coefficient	0.13 ± 0.09	0.27 ± 0.17	0.03*
Lateral wall partition coefficient	0.07 ± 0.10	0.22 ± 0.09	<0.001*
Ejection fraction (%)	57 ± 3	68 ± 10	<0.001*
Myocardial mass index (g/m^2)	54 ± 7	103 ± 40	<0.001*
Lat MV peak S (cm/s)	11.6 ± 2.3	9.9 ± 2.4	0.97
E/E′	6.40 ± 1.40	10.53 ± 6.00	0.04*
IVRT (ms)	74.7 ± 13.8	82.9 ± 24.1	0.21
Indexed LA volume (ml/m^2)	29.1 ± 7.8	41.0 ± 18.2	0.05
Global longitudinal strain	−18.2 ± 14.1	−15.2 ± 3.9	0.349
Global circumferential strain	−25.6 ± 2.6	−21.2 ± 5.0	<0.001*
Global radial strain	56.8 ± 8.1	38.0 ± 11.1	0.01*
Torsion (degrees)	15.7 ± 5.5	17.9 ± 7.3	0.41

* Significant difference between controls versus HCM patient, testing by independent samples t test

E/E′ mitral valve inflow E-wave Doppler peak velocity/tissue Doppler-derived peak mean early diastolic velocity, *IVRT* isovolumetric relaxation time, *LA* left atrial, *Lat MV Peak S* tissue Doppler-derived peak systolic velocity at lateral mitral valve annulus, *MPI* myocardial performance index

echocardiography (nine of 12 patients with diastolic dysfunction were symptomatic vs. four of 16 patients with normal diastolic function; $p = 0.02$). Indexed myocardial mass and left atrial volume did show a trend toward increase in symptomatic individuals [117 ± 45 vs. 90 ± 30 g/m^2 in asymptomatic patients ($p = 0.08$) and 47.0 ± 21.3 vs. 35.8 ± 13.8 ml/m^2 ($p = 0.10$)]. The presence of circumferential strain and radial strain was not significantly different between symptomatic and asymptomatic individuals with HCM. There was no difference between symptomatic and asymptomatic patients in regard to the left ventricular end diastolic volume, left ventricular end systolic volume, lateral wall thickness, septal wall thickness, ejection fraction, circumferential strain, radial strain, presence of macroscopic scarring, presence of a resting outflow tract gradient >30 mmHg or presence of an abnormal mitral/pulmonary vein Doppler.

From the above analyses, lateral wall partition coefficient, presence of echocardiographic diastolic dysfunction and indexed LV mass were individually either significantly different between symptomatic and asymptomatic patients or were trending toward significance and therefore were added to a binary logistic regression model (along with age, sex, scar and outflow gradient as in methods section). Model fit was confirmed by the omnibus test for model coefficients ($\chi^2 = 17.54$; $p < 0.001$). After forward stepwise exclusions, only the lateral wall partition coefficient (hazard ratio 20.9, $p = 0.04$) and the presence of significant echocardiographic diastolic dysfunction (hazard ratio 3.8; $p = 0.02$) were independent predictors of clinical symptoms.

BNP

Four patients did not have BNP levels assessed during the imaging portion of the study and were excluded from the analyses. Only indexed LV mass (mean 132 ± 37 vs. 90 ± 31 g/m^2; $p = 0.01$) and lateral wall partition coefficient (mean = 0.34 ± 0.21 vs. 0.22 ± 0.10; $p = 0.03$) were significantly increased in patients with increased BNP (>100 pg/ml) versus those with a concentration ≤100 pg/ml. The presence of a resting outflow tract gradient >30 mmHg and echocardiographic diastolic dysfunction showed a nonsignificant trend toward association with raised BNP ($p = 0.06$ and 0.09, respectively, Fisher's exact test).

Function, Morphology and Diffuse Fibrosis

Patients with echocardiographic evidence of diastolic dysfunction did not have a significantly higher lateral wall partition coefficient than those without (0.24 ± 0.10 vs. 0.20 ± 0.08, $p = 0.24$). Patients with a septal thickness >12 mm had a significantly higher septal partition coefficient than those with a septal thickness <12 mm (0.33 vs. 0.16, $p = 0.029$). This relationship did not exist for the lateral wall, but only four patients had a lateral wall thickness >12 mm. No other significant relationships between echocardiographic variables and indices of diffuse fibrosis were identified in HCM patients. No significant difference was detected in the amount of diffuse fibrosis between patients with macroscopic scars and those without (lateral partition coefficient 0.22 vs. 0.22, $p = 0.98$ and septal partition coefficient 0.27 vs. 0.27, $p = 0.95$). No difference was detected in the amount of diffuse fibrosis between patients with identified sarcomeric mutations and those without (lateral partition coefficient 0.22 vs. 0.21, $p = 0.89$ and septal partition coefficient 0.26 vs. 0.29, $p = 0.78$).

Looking separately in patients with traditional risk factors for sudden cardiac death (unexplained syncope, non-sustained VT, previous arrest, family history of sudden cardiac death or family history of internal cardiac defibrillator with appropriate shock), these patients also had increased partition coefficients in the lateral wall (0.27 ± 0.06 for those with risk factors vs. 0.18 ± 0.08 for those without; $p = 0.007$) but not septal wall (0.31 ± 0.15 vs. 0.24 ± 0.19; $p = 0.39$).

Discussion

This study shows that post-gadolinium myocardial T1 mapping techniques to identify interstitial fibrosis are feasible in children with HCM. Using post-contrast myocardial relaxation time mapping, children with HCM were shown to have increased partition coefficients, suggesting that diffuse LV fibrosis is present in children with HCM. This study also demonstrates that diffuse fibrosis and diastolic dysfunction are independent predictors of symptoms in patients with HCM. Furthermore, as previously demonstrated in adult studies [14, 19, 28], this study confirms that echocardiographic techniques in children are able to demonstrate a reduction in diastolic and systolic function before a reduction in ejection fraction is noted.

Post-gadolinium Myocardial Longitudinal Relaxation Time (T1) Mapping

Our findings show that it is feasible to derive post-gadolinium myocardial T1 time constants in children. Gadolinium-based contrast agents have a low molecular weight, enabling them to pass through the capillary walls into the extracellular space of the myocardium but are too large to pass into the cells. Hence, these contrast agents accumulate passively in the extracellular space of the myocardium. Diffuse myocardial fibrosis results in the expansion of the interstitial space, hence increasing the proportion of extracellular space within the myocardial volume. This increases the volume of distribution for the gadolinium chelates and results in a reduction in the T1 time of the myocardium. In our study, there was a significant difference in the derived partition coefficient between healthy controls and children with HCM, suggesting that even young patients with this condition have an increased "extracellular volume," commonly thought to represent fibrosis.

The technique of post-contrast myocardial T1 mapping has been refined over the last few years. The partition coefficient technique, using a ratio change in T1 time, was used in this study [7]. This has fewer assumptions than earlier techniques measuring myocardium alone [12, 29]. Such studies using post-contrast T1 times alone as a marker for increased extracellular volume assume that body composition is similar from one individual to the next (which is untrue, e.g., a higher percentage of body fat caused by a disease process will result in relatively less extra-cellular water and a falsely low T1). These studies also assume a similar clearance of contrast agent among different individuals, which is not the case if, for example, renal function is impaired. The partition coefficient technique reduces these concerns by taking a ratio of the myocardium to the blood pool. However, this technique does not account for differences in hematocrit between patients, and calculation of the volume of distribution by measuring and correcting for hematocrit is now thought to be more accurate [8]. Newer imaging techniques also reduce errors that may be caused by inflow effects on blood T1 times, and there may be some justification for using such sequences in preference to the technique used in this study [3]. Another limitation of the technique is that it relies on a dynamic equilibrium of contrast exchange to be reached between the blood pool and the myocardium. Recent reports suggest that this will occur at around 15 min post-contrast, but this depends, to some degree, on the type of contrast agent and the dose given [33]. In adults, post-contrast T1 mapping techniques have been validated using biopsy histology to confirm the findings [8, 12]. In our study, as a corroboration of the technique, those patients with a septal thickness >12 mm showed greater diffuse fibrosis in this area.

It should be noted that, although the post-contrast T1 times reported in this study are similar to those reported with current techniques, native T1 times were lower [30].

As a result of lower native T1 times with our technique, the partition coefficient is lower than that measured with previous studies. However, published studies already have widely varying partition coefficients. Flacke et al. [7] reported a partition coefficient in healthy adult volunteers of 0.56 using a Look–Locker sequence with a low flip angle. Raman et al. and Puntmann et al. both quote a partition coefficient of 0.47 using a modified Look–Locker (MOLLI) sequence in healthy adults [25, 26]. Chow et al. [3] reported normal healthy adults as having a partition coefficient of 0.38 using the saturation-recovery single-shot acquisition technique. It has also been shown that the partition coefficient increases with age [15]. Normal values in children would therefore be expected to be lower, and the value would depend on the sequence used. However, these data are lacking in children. Values from children after anthracycline treatment are published in the literature by Tham et al. [30] using a saturation-recovery single-shot acquisition technique. They suggest that the partition coefficient in these individuals was 0.36. It can be expected that normal children would have a value substantially lower than this if we extrapolate from other studies in childhood cancer survivors that received anthracyclines [31]. In short, our partition coefficient values remain below the quoted means for adults, but our patient age precludes robust comparisons given the dependence on the technique used and the scarcity of comparative data in the published literature. Regarding HCM patients, there are even less comparative pediatric data, but Puntmann et al. as with our data in children also show an absolute rise in the partition coefficient in adult HCM patients compared with healthy controls.

Systolic and Diastolic LV Function

Systolic function, measured by ejection fraction, was above normal in the HCM patients studied here, as has been previously reported [34]. Systolic function as measured by peak global systolic circumferential or radial strain however was reduced. This finding suggests that for HCM patients, peak strain analysis may be a more sensitive marker of systolic dysfunction than ejection fraction, which is often paradoxically increased [14, 19, 28].

In this study, a number of descriptors of diastolic function differed between patients and healthy controls, i.e., mitral and pulmonary venous Doppler patterns, E/E′ and indexed LA volume. Despite the proven utility of these techniques in other causes of diastolic dysfunction, investigators have found a lack of reliability of these individual parameters to predict diastolic dysfunction in the setting of hypertrophic cardiomyopathy [9, 21]. This is supported by a recent relevant echocardiographic study in children with all forms of cardiomyopathy [5]. This may explain why it was that, in our study, these parameters individually failed to show any differentiation between symptomatic and asymptomatic patients [5].

However, referring to the aforementioned echocardiographic study, it also provides us with a comparison of values between control children and children with HCM [5]. This is helpful as it shows that both early relaxation abnormalities and pseudonormal filling patterns do occur almost exclusively in a small subgroup of patients with hypertrophic cardiomyopathy (but not in dilated or restrictive cardiomyopathy). Furthermore, this data show that an indexed LA volume >45 mls/m^2 and E/E′ >15 both have 100 % specificity for cardiomyopathy in comparison with healthy controls [5]. This explains our rationale behind choosing these values for the amalgamated analysis of diastolic function. Given the discrepancies noted by the study between criteria within individual patients, [5] we have also taken a combination of the three echocardiographic markers of diastolic dysfunction in order to improve the sensitivity to detect diastolic dysfunction. In doing so, in our study, we found a significant association between the amalgamated "clear diastolic dysfunction" and clinical symptoms in HCM. This suggests that, in the setting of pediatric HCM, it is important to assess a comprehensive evaluation of diastolic function rather than relying on any single parameter.

In adult studies, it has been shown that diffuse fibrosis is associated with diastolic dysfunction and a causal relationship between the two has been postulated [6]. In contrast, our data did not show any evidence of a correlation between diastolic dysfunction and diffuse fibrosis [6], perhaps related to the small overall sample size.

Predictors of Clinical Symptoms

In this study, patients with symptoms had significantly increased lateral wall partition coefficients, and in the multivariable analysis, only diastolic dysfunction on echo and the lateral wall partition coefficient were independent predictors of symptoms. This suggests that lateral wall diffuse fibrosis may be an important prognostic indicator, although longitudinal studies are required for confirmation. Interestingly, although lateral wall fibrosis was related to symptoms, septal diffuse fibrosis was not. This may be because septal involvement is known to occur early in the natural history of HCM, it may be a less potent discriminator later in symptomatic disease. This notion is supported by the fact that in seven of eight patients with macroscopic scarring, it occurred in the septum and that the amount of diffuse fibrosis in the septum was greater than in the lateral wall ($p = 0.007$).

In our study, those patients with an elevated BNP had a significantly higher lateral wall partition coefficient. An elevated serum BNP level has been shown to be a predictor

of mortality and functional status in adults with HCM [10]. It has also been associated with progression to end-stage disease, diastolic dysfunction and left ventricular outflow obstruction [22, 24]. In children, raised BNP levels have been shown to correlate with disease severity [10, 13, 18]. Our findings are also supported by our data taking into consideration known traditional risk factors for sudden cardiac death. We showed again that those with a known traditional risk factor had higher lateral wall coefficients than those without any risk factor. Taken together with these findings and other studies, the lateral wall partition coefficient deserves further evaluation as a prognostic marker.

Limitations

As a pediatric series of overt phenotypic HCM, this study is relatively large. However, absolute numbers are small, and this may have obscured further associations. For example, there are certain known indicators of poor outcome such as gross septal hypertrophy and end-stage disease with reduced ejection fraction, which were uncommon in our patient group. In addition, diffuse fibrosis of the LV was only assessed at the mid-ventricular level. It is possible that the distribution of fibrosis is inhomogeneous and that the data gathered are not representative of other parts of the myocardium. Furthermore, during the course of this study, there have been improvements to the technique of T1 mapping [8]. For example, the volume of distribution depends on the patient's hematocrit, which was not measured in this cohort.

Conclusions

A detailed echocardiographic evaluation is helpful in the setting of childhood and adolescent HCM because circumferential and radial strain appear to be sensitive markers of systolic dysfunction and diastolic dysfunction correlates with symptoms. Diffuse fibrosis in the lateral wall may prove to be an important predictor of disease progression and, perhaps, of adverse outcome.

Acknowledgments Andreas Greiser is an employee of Siemens Healthcare, Erlangen, Germany. All the other authors were not consultants or employees for Siemens Healthcare and had control of inclusion of any data and information that might present a conflict of interest for Andreas Greiser. We thank Judith Wilson and Sandra Aiello for their help with the data collection.

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