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Early Segmental Relaxation Abnormalities in Hypertrophic Cardiomyopathy for Differential Diagnostic of Patients with Left Ventricular Hypertrophy

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1. Original Article

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WILEY CLINICAL CARDIOLOGY

CLINICAL INVESTIGATIONS

Early segmental relaxation abnormalities in hypertrophic cardiomyopathy for differential diagnostic of patients with left ventricular hypertrophy

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Background: Hypertrophic cardiomyopathy (HCM) is characterized by asymmetric left ventricular hypertrophy (LVH). However, clinical signs can be subtle and differentiation from other causes of LVH is challenging.

Hypothesis: As diastolic dysfunction (DD) is an early sign in HCM, we aimed to find regional changes in relaxation pattern for differentiation from other entities of LVH.

Methods: In 148 patients (81 HCM, 55 arterial hypertension (AHT), 12 Fabry disease) and 63 healthy controls, relaxation patterns were assessed using regional tissue Doppler imaging. In 42 HCM patients, myocardial mass and fibrosis were quantified by cardiac magnetic resonance imaging and correlated with relaxation parameters.

Results: In HCM the septal to lateral isovolumic relaxation time (s/l IVRT) ratio was higher (1.5 ± 0.4) compared with AHT (1.1 ± 0.2), Fabry disease (1.0 ± 0.1), and controls (1.1 ± 0.2; $P < 0.001$), showing 77% sensitivity and 79% specificity to discriminate HCM-related LVH from other entities. The s/l IVRT ratio was independent of global DD in HCM (HCM with DD: 1.5 ± 0.5, n = 52; HCM without DD: 1.5 ± 0.3, n = 29) and remained significantly different from other entities in a subgroup of HCM patients with maximum wall thickness < 20 mm (s/l ratio: 1.5 ± 0.5, n = 28). Regional IVRT did not correlate with the corresponding segmental myocardial mass or amount of fibrosis in cardiac magnetic resonance imaging.

Conclusions: HCM patients show a prolonged septal IVRT irrespective of the extent of LVH and even before developing global DD. The s/l IVRT ratio is significantly higher in HCM compared with AHT or Fabry disease, thus establishing segmental IVRT analysis as a potential parameter for differential diagnosis in LVH.

KEYWORDS

Hypertrophic Cardiomyopathy, Arterial Hypertension, Fabry's Disease, Isovolumic Relaxation Time, Tissue Doppler Imaging

1 | INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common monogenetic cardiovascular disease, with a prevalence of ≥1:500, and is the most frequent cause of sudden cardiac death in the young, especially in athletes.[1] The disease is characterized by left ventricular hypertrophy (LVH) with asymmetric thickening predominantly of the septal wall,[2] leading to left ventricular (LV) outflow tract obstruction in almost 25% of patients. Diagnosis of HCM is primarily based on the magnitude of LVH with a maximum wall thickness of ≥15 mm in the absence of abnormal loading conditions or other cardiac or systemic disease that could produce the magnitude of hypertrophy evident.[3] However, it often remains difficult to distinguish, especially between the nonobstructive form of HCM and other causes of LVH, such as arterial hypertension (AHT)[4] or storage disorders.[5] Due to its relatively high prevalence and potentially fatal outcome, early diagnosis of HCM and reliable distinction from phenotypes of similar disorders is crucial.

As impaired myocardial relaxation has been identified as an early manifestation of HCM,[6] a variety of echocardiographic parameters for evaluation of diastolic dysfunction (DD), such as tissue Doppler

imaging (TDI) and strain imaging, were recently shown to be useful in differentiation and early detection of the disease, even in mutation carriers without a clinical phenotype.[7–9] Regional differences between the septal and lateral mitral annulus velocities showing longer IVRT, lower E′ and higher E/E′ ratios in the septal annulus can be observed in different entities of LVH.[10] These TDI parameters have already been shown to be useful for discrimination between HCM and AHT and a prolonged IVRT has been proposed to be useful for discrimination from other entities.[11] Likewise, we observed septal pronounced isovolumic relaxation time (IVRT) prolongation in HCM patients in our outpatient clinic. However, to date a differential analysis even in HCM patients without apparent DD has not been performed yet.

This study was designed to answer the following questions:

- Are regional relaxation abnormalities in HCM visible before development of global DD?
- Do echocardiographic changes in myocardial relaxation follow the same asymmetrical distribution as LVH in HCM patients, and are these relaxation patterns correlated with the amount of LVH and/or the amount of myocardial fibrosis?
- Can echocardiographic parameters of regional diastolic impairment be used for discrimination of HCM from other LVH entities?

2 | METHODS

2.1 | Study population

A total of 211 individuals were retrospectively studied. All patients were recruited during a routine visit at the outpatient clinic at the University Heart Center Hamburg between July 2010 and September 2013. Medical histories were recorded, a 12-lead electrocardiogram was performed, and patients were examined physically and by echocardiography.

The HCM group consisted of 81 patients with a clinical phenotype. In 20 patients a pathogenic mutation was genetically confirmed. According to current guidelines, HCM was defined as a maximum wall thickness of ≥15 mm in the absence of abnormal loading conditions or another cardiac or systemic disease that could produce the magnitude of hypertrophy evident.[3,12] Hypertrophy was either septal pronounced or concentric. Patients with other types of hypertrophy (eg, apical hypertrophy) were excluded.

The Fabry group included 12 patients with genetically confirmed Fabry disease and echocardiographic evidence of cardiac manifestation.

Fifty-five patients with known AHT receiving antihypertensive medication were also recruited. These patients showed mild to moderate cardiac hypertrophy (wall thickness 11–15 mm) in the absence of any other disease that could have influenced the cardiac phenotype. Excluded were patients with a history of myocardial infarction, significant coronary heart disease, ventricular conduction asynchrony, moderate or severe valvular disease, left ventricular ejection fraction (LVEF) ≤45%, atrial fibrillation at the time of investigation, or systemic diseases with potential cardiac involvement. Also, 63 individuals without any cardiac pathology were included.

The study protocol was in line with the principles outlined in the Declaration of Helsinki and approved by the local ethics committee.

2.2 | Echocardiographic studies

Two-dimensional transthoracic echocardiography was performed using a Philips iE33 system (Philips Healthcare, Best, The Netherlands) and data were analyzed with Syngo Dynamics (Siemens Healthcare, Erlangen, Germany). LVEF was obtained with the Simpson method from 2-dimensional apical images. 2D images were obtained from parasternal short axis to measure septal (SW) and lateral wall (LW) thickness. Left atrial diameter (LAD), as well as left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) were measured using M-mode in the same orientation. Peak early (E wave) and late (A wave) transmitral filling velocities and deceleration time of E (DT of E wave) were measured using pulsed-wave Doppler of transmitral flow in the apical 4-chamber view. TDI was used in the color-guided pulsed-wave Doppler mode to assess peak early (E′) and late diastolic (A′) mitral annulus velocities at the septal and lateral mitral valve annulus in the apical 4-chamber view. The same tracing was also used to measure isovolumic contraction time and IVRT intervals. For each measurement, 2 to 3 beats were averaged and analyzed by 2 independent observers. DD was defined by published criteria.[13] There were no patients with restrictive filling pattern in either group.

2.3 | Cardiac MRI

A subset of 42 HCM patients underwent cardiac magnetic resonance (CMR) imaging using a 1.5-T scanner (Achieva; Philips Healthcare). Images were obtained in the cardiac short-axis, vertical long-axis, and horizontal long-axis planes using a breath-hold balanced fast field sequence. After injection of 0.2 mL/kg body weight gadobenate dimeglumine (MultiHance; Bracco Diagnostics, Monroe Township, NJ), late gadolinium enhancement (LGE) images were acquired using a phase-sensitive inversion recovery sequence. LGE images were acquired in the LV short-axis orientation as well as in 2-, 3-, and 4-chamber views. Endocardial and epicardial borders were manually traced in each slice. A region of interest was placed in normal-appearing myocardium typically in the lateral LV wall, which was defined as a nonhypertrophied region without apparent LGE. LGE quantification was performed using a threshold method >2 SD above the signal intensity of normal-appearing myocardium. The amount of fibrotic tissue of each patient was assessed in percent of LV myocardial mass (%LV) using the in-house–developed Heart Analysis Tool (HeAT) software.[14] Measurements were performed by 2 independent radiologists who were blinded to the echocardiographic results, patients' diagnoses, and the measurements performed by their colleague. To determine segmental distribution of myocardial mass and fibrosis detected by LGE, data were obtained for septal segments 3 and 9 as well as for lateral segments 6 and 12, following published recommendations.[15]

2.4 | Statistical analysis

Continuous variables are reported as mean ± SD and categorical variables are presented as frequencies and percentages. To determine differences between HCM patients and all other patient groups (AHT, Fabry disease, control) in echocardiographic parameters, linear

models adjusted for age, sex and quotient of septal to lateral wall thickness were used. Parameters were logarithmized if necessary.

The adjusted septal/lateral (s/l) IVRT ratio was estimated from the linear model for each group as well as in the setting in which the HCM patients were further divided into the subgroups "with DD" and "without DD" and septal wall thickness < 20 and ≥20 mm. A receiver operating curve (ROC) was created to evaluate the ability of the s/l IVRT ratio to discriminate patients suffering from HCM from those with LVH caused by AHT or Fabry disease. The area under the curve was determined, and specificity and sensitivity of the IVRT ratio were calculated at various cutoffs.

For the subgroup of HCM patients where CMR data were available, a linear model adjusted for age and sex was estimated to examine if IVRT was associated with myocardial fibrosis and/or mass.

A 2-tailed *P* value <0.05 was considered statistically significant. As this analysis was performed in an explorative way, no adjustment for multiple testing was made. All analyses were carried out using Stata version 14.1 (StataCorp LP, College Station, TX).

3 | RESULTS

3.1 | Patients

HCM and AHT patients were older than patients with Fabry disease or controls. Aside from the control group, all patient groups comparably suffered from concomitant diseases. Baseline characteristics are listed in Table 1.

3.2 | Echocardiography

Apart from 3 HCM patients with a moderately reduced LVEF, all patients in the disease groups showed LVH with a normal ejection fraction. SW thickness and the ratio of SW to LW thickness were higher in all HCM patients compared with the other groups. LADs were highest in HCM but were also increased in AHT and Fabry disease compared with controls. The diameters of the LV chamber were similar among all 4 groups (Table 1).

3.3 | Diastolic function

Markers of DD, such as E/A ratio, DT of E wave, E′, E/E′ ratio, and IVRT were significantly altered in all disease groups compared with healthy controls. Mean E′ was significantly reduced in HCM compared with healthy controls and AHT patients due to a significant reduction in septal E′. However, the ratio of septal to lateral E′ did not show any significant differences between groups. In HCM patients E/E′ was significantly higher in both, septal and lateral TDI in comparison to AHT and controls but not to Fabry disease, probably due to the small number of Fabry patients (Table 2).

TABLE 1 Patient characteristics and baseline echocardiographic characteristics

	HCM, n = 81	AHT, n = 55	Fabry, n = 12	Control, n = 63	*P* Value, Group	*P* Value for HCM vs		
						AHT	Fabry	Control
Age, y	54.1 ± 15.2	60.1 ± 12.4	48.3 ± 9.5	42.3 ± 12.7	<0.001	0.011	0.165	<0.001
Male sex	44 (54.3)	33 (60.0)	6 (50.0)	29 (46.0)	0.495	—	—	—
At least 1 concomitant disease:	41 (50.6)	55 (100.0)	8 (66.7)	0 (0.0)	0.305	—	—	—
AHT	37 (45.7)	55 (100.0)	6 (50.0)	0 (0.0)	0.780	—	—	—
CAD	7 (8.6)	7 (12.7)	2 (16.7)	0 (0.0)	0.604	—	—	—
AF	6 (7.4)	4 (7.3)	1 (8.3)	0 (0.0)	0.992	—	—	—
DM	6 (7.4)	11 (20.0)	0 (0.0)	0 (0.0)	0.036	0.035	NE	NE
At least 1 medication:	68 (84.0)	52 (94.5)	8 (66.7)	0 (0.0)	0.039	0.072	0.159	NE
β-Blocker	47 (58.0)	35 (63.6)	4 (33.3)	0 (0.0)	0.177	—	—	—
Ca blocker	23 (28.4)	29 (52.7)	3 (25.0)	0 (0.0)	0.012	0.005	0.807	NE
ACEI/ARB	26 (32.1)	43 (78.2)	6 (50.0)	0 (0.0)	<0.001	<0.001	0.230	NE
Diuretic	12 (14.8)	26 (47.3)	1 (8.3)	0 (0.0)	<0.001	<0.001	0.552	NE
Other	7 (8.6)	20 (36.4)	0 (0.0)	0 (0.0)	<0.001	<0.001	NE	NE
LVEF >55%/45%–54%	78/3	55/0	12/0	63/0	NE	NE	NE	NE
SW, mm	22.5 ± 5.4	13.9 ± 2.4	15.3 ± 3.4	9.6 ± 1.2	<0.001	<0.001	<0.001	<0.001
LW, mm	15.3 ± 3.7	13.2 ± 2.4	14.3 ± 2.5	9.2 ± 1.3	<0.001	<0.001	0.286	<0.001
SW/LW	1.5 ± 0.4	1.1 ± 0.1	1.1 ± 0.1	1.0 ± 0.1	<0.001	<0.001	<0.001	<0.001
LVEDD, mm	45.1 ± 7.6	50.8 ± 5.7	47.3 ± 7.2	48.8 ± 4.6	<0.001	<0.001	0.278	<0.001
LVESD, mm	25.3 ± 7.7	30.6 ± 5.4	26.8 ± 7.1	31.3 ± 3.9	<0.001	<0.001	0.458	<0.001
LAD, mm	47.1 ± 8.8	41.6 ± 5.2	41.4 ± 8.0	34.2 ± 4.8	<0.001	<0.001	0.009	<0.001
DD grade, 0/1/2/3	29/13/37/0	0/26/29/0	8/1/3/0	63/0/0/0	0.051	—	—	—

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AHT, arterial hypertension; ARB, angiotensin II receptor blocker; Ca, calcium; CAD, coronary artery disease; DD, diastolic dysfunction; DM, diabetes mellitus; HCM, hypertrophic cardiomyopathy; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LW, lateral wall thickness; NE, not estimable; SD, standard deviation; SW, septal wall thickness.

Data are presented as n (%) or mean ± SD.

TABLE 2 Echocardiographic parameters of DD

	HCM, n = 81	AHT, n = 55	Fabry, n = 12	Control, n = 63	*P* Value for HCM vs		
					AHT	Fabry	Control
E wave, m/s	85.7 ± 28.3	83.6 ± 26.4	88.4 ± 21.6	84.0 ± 14.5	0.590	0.778	0.716
A wave, m/s	80.8 ± 30.0	85.7 ± 26.7	74.8 ± 18.0	60.3 ± 17.4	0.385	0.255	<0.001
E/A	1.2 ± 0.6	1.1 ± 0.6	1.2 ± 0.4	1.5 ± 0.6	0.837	0.337	0.002
DT of E wave, ms	241.8 ± 76.8	221.4 ± 49.6	208.5 ± 29.2	188.6 ± 38.1	0.038	0.109	<0.001
Septal E′, cm/s	5.1 ± 1.9	5.7 ± 1.9	6.0 ± 1.3	10.2 ± 2.3	0.004	0.081	<0.001
Lateral E′, cm/s	7.9 ± 3.2	8.2 ± 3.3	9.5 ± 4.2	14.9 ± 3.7	0.064	0.366	<0.001
Septal E′/lateral E′, cm/s	0.7 ± 0.2	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.2	0.690	0.942	0.388
Mean E′, cm/s	6.5 ± 2.4	7.0 ± 2.4	7.8 ± 2.3	12.6 ± 2.6	0.025	0.311	<0.001
Septal E/E′, cm/s	19.0 ± 9.3	16.2 ± 7.4	15.3 ± 4.3	8.5 ± 2.0	0.009	0.345	<0.001
Lateral E/E′, cm/s	12.8 ± 7.1	11.8 ± 6.6	10.6 ± 4.7	5.9 ± 1.6	0.031	0.404	<0.001
Mean E/E′, cm/s	15.0 ± 7.5	13.3 ± 6.4	12.1 ± 4.1	6.9 ± 1.6	0.010	0.303	<0.001
Septal IVRT, ms	152.5 ± 49.3	111.1 ± 29.9	113.3 ± 20.1	81.5 ± 15.8	<0.001	0.021	<0.001
Lateral IVRT, ms	106.5 ± 37.3	105.1 ± 30.9	111.2 ± 16.7	76.8 ± 17.7	0.570	0.079	0.006
Mean IVRT, ms	129.5 ± 40.3	108.1 ± 28.3	112.2 ± 17.3	79.1 ± 15.6	0.004	0.580	<0.001
Septal/lateral IVRT, s/l ratio	1.5 ± 0.4	1.1 ± 0.2	1.0 ± 0.1	1.1 ± 0.2	<0.001	<0.001	<0.001

Abbreviations: AHT, arterial hypertension; DD, diastolic dysfunction; DT, deceleration time; E, early transmitral filling velocity; E′, peak early mitral annulus velocity; HCM, hypertrophic cardiomyopathy; IVRT, isovolumic relaxation time; l, lateral; s, septal; SD, standard deviation.

Data are presented as mean ± SD.

P values result from linear models.

3.4 | Segmental differences in IVRT

Comparison of IVRT in septal and lateral mitral valve annulus TDI revealed most prominent prolongation in the septal wall resulting in a significantly higher s/l IVRT ratio in HCM patients compared with all other groups (Table 2; Figure 1). ROC analysis was performed to demonstrate that the s/l IVRT ratio allows discrimination of patients suffering from HCM from those with LVH caused by AHT or Fabry disease (Figure 2).

Subgroup analysis of 52 HCM patients with echocardiographic evidence of global DD and 29 HCM patients without DD revealed that, even in HCM patients without global DD, septal IVRT was >100 ms, which is usually ascribed to mild to moderate DD.[16] The s/l IVRT ratio in this subgroup of HCM patients was as high as in HCM patients with global DD and differed from AHT, Fabry, and healthy controls, respectively (Table 3). The same calculations were repeated with 27 genetically positive HCM patients. We found that these patients also had a mean s/l IVRT ratio of 1.5 ± 0.3, which did not differ from the IVRT ratio in the whole HCM cohort.

As patients with AHT or Fabry disease had thinner septum diameters than HCM patients, we further analyzed a subgroup of HCM patients with a septum thickness of <20 mm (n = 28). The s/l IVRT ratio also showed the ability to differentiate these HCM patients with a thinner septum from other causes of LVH (Table 3, Figure 1). Of note, medial wall thickness in this group was, at 17.3 mm (SD, 2.2 mm), significantly smaller than medial wall thickness of the remaining HCM patients with thicker LV walls (25.3 mm; SD, 4.4 mm; $P < 0.001$), whereas the s/l IVRT ratio was identical in both groups. The observation that a prolonged septal IVRT was independent of a regional increase in myocardial mass was supported by the results obtained in a subgroup of 42 HCM patients who underwent CMR imaging. No significant association was observed between septal and lateral IVRT with segmental myocardial mass (septal: 1.01, 95% confidence interval [CI]: 1-1.02, $P = 0.09$; lateral: 1.03, 95% CI: 0.99-1.01, $P = 0.62$) or fibrosis visualized by LGE in CMR (septal: 1.02, 95% CI: 1-1.05, $P = 0.09$; lateral: 1.03, 95% CI: 0.99-1.08, $P = 0.14$).

4 | DISCUSSION

4.1 | Regional changes of myocardial relaxation in HCM are independent of overall DD

This echocardiographic study of diastolic relaxation in different entities of LVH revealed a significantly prolonged IVRT in septal mitral annulus TDI in all HCM patients, irrespective of their global diastolic function. Most interesting, a prolongation of septal IVRT is already prominent in HCM patients with an overall still-normal diastolic function. These results are in line with the idea of subtle regional changes in diastolic function prior to the evidence of global diastolic dysfunction.[7] According to previous studies, IVRT is prolonged in HCM patients, particularly in the septal mitral annulus,[11,17] and regional differences in relaxation abnormalities in HCM patients have already been reported by others. In line with our data, Saccheri et al. described a septal pronounced decrease of E′ in HCM patients[18] compared with healthy individuals. Further, heterogeneous IVRT intervals both in patients with HCM as well as in AHT were reported by Nunez et al.[11] However, we could not find any septal-to-lateral differences for E′, E/E′, and E′/A′ among different entities of LVH.

4.2 | Regional changes in IVRT are not associated with LVH or fibrosis

Our data provide evidence that IVRT prolongation is not confined only to hypertrophied segments. Hence, as also shown

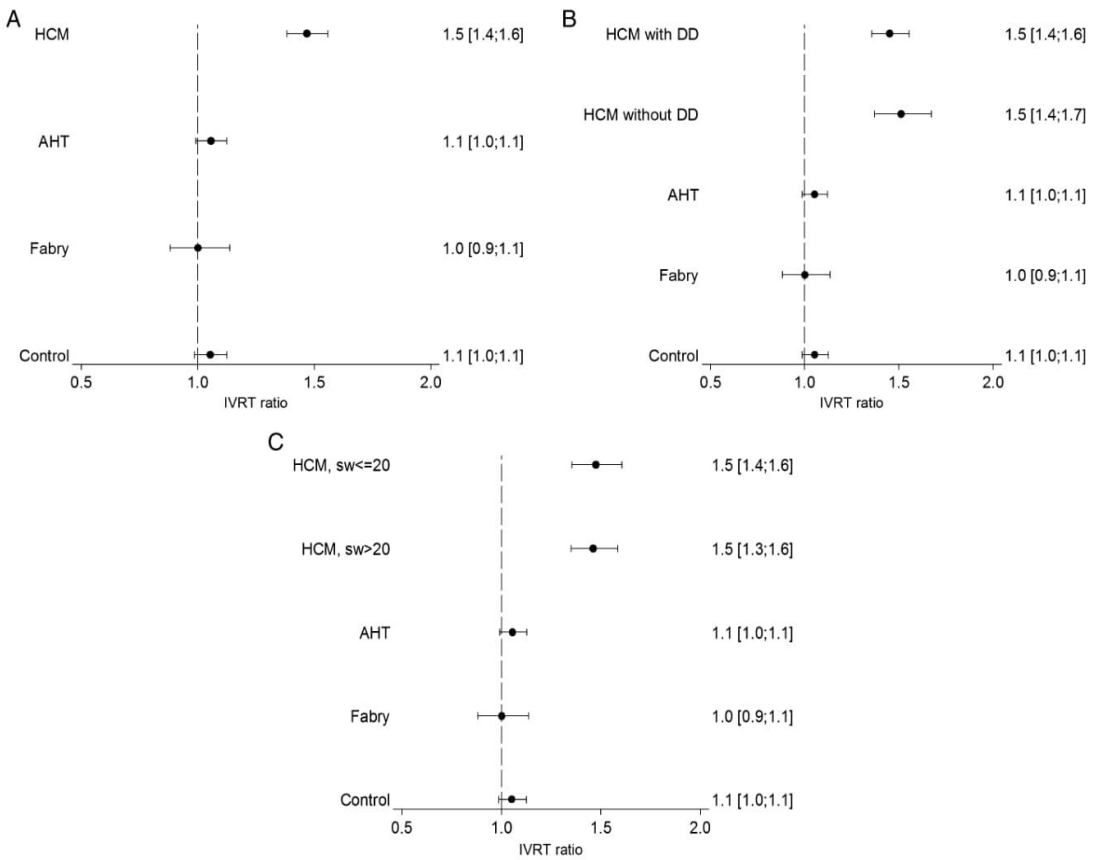

FIGURE 1 Forest plots for segmental IVRT. Adjusted IVRT ratios from linear models together with 95% CIs are presented for (A) all HCM patients, (B) HCM patients with and without DD, and (C) HCM patients with a septal wall thickness of ≤20 mm or >20 mm compared with patients with AHT, Fabry disease, and healthy controls. Abbreviations: AHT, arterial hypertension; CI, confidence interval; DD, diastolic dysfunction; HCM, hypertrophic cardiomyopathy; IVRT, isovolumic relaxation time; sw, septal wall

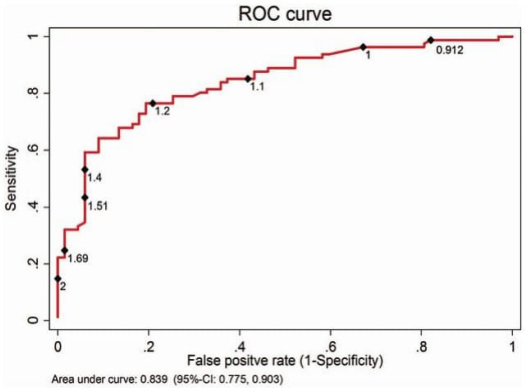

FIGURE 2 ROC curve for predicting HCM in patients with LVH by s/l IVRT ratio. Abbreviations: CI, confidence interval; HCM, hypertrophic cardiomyopathy; IVRT, isovolumic relaxation time; l, lateral; LVH, left ventricular hypertrophy; ROC, receiver operating characteristic; s, septal

previously, regional differences in IVRT in HCM can be interpreted as a sign of relaxation abnormalities occurring independently of LVH.[17]

The influence of LVH on diastolic function has been discussed controversially. As De Marchi et al. reported an association,[19] several studies claimed that relaxation abnormalities precede the development of LVH,[8,9,18,20] which is consistent with experimental data and theoretic reflections.[2,21] Based on our observations, we could not confirm an association of regional myocardial relaxation abnormalities in HCM patients with the corresponding segmental myocardial mass in CMR. Furthermore, we could not find any significant correlation between IVRT and fibrosis visualized by LGE, although an association between diastolic function and myocardial fibrosis was suggested by others.[22,23] In this regard, reduced myocardial velocities may reflect impairment of sarcomeric function rather than fibrosis.

4.3 | The s/l IVRT ratio for discrimination of different entities of LVH

The s/l IVRT ratio in HCM was significantly higher compared with patients with LVH in AHT and/or Fabry disease. These data raise evidence that a higher s/l IVRT ratio reflects a unique HCM-specific phenotype that differs from normal hearts as well as from other entities of LVH, such as AHT and Fabry disease. The best threshold according to ROC analysis lies between 1.2 (sensitivity 76.5%,

TABLE 3 Segmental IVRT in HCM subgroups

	HCM			
	With DD, n = 52	Without DD, n = 29	≤20 mm, n = 28	>20 mm, n = 53
Septal IVRT, ms	164.7 ± 47.5	130.7 ± 45.5	143.0 ± 35.8	157.6 ± 54.8
Lateral IVRT, ms	116.6 ± 39.6	88.3 ± 24.1	99.0 ± 30.5	110.5 ± 40.1
Mean IVRT, ms	140.7 ± 40.1	109.5 ± 32.6	121.0 ± 28.5	134.0 ± 44.9
Septal/lateral IVRT	1.5 ± 0.5	1.5 ± 0.3	1.5 ± 0.5	1.5 ± 0.3

Abbreviations: DD, diastolic dysfunction; HCM, hypertrophic cardiomyopathy; IVRT, isovolumetric relaxation time; SD, standard deviation.
Data are presented as mean ± SD.

specificity 79.1%) and 1.3 (sensitivity 63%, specificity 91%; Figure 2). Supposing that in a clinical setting a higher specificity would be of greater value than a high sensitivity, we recommend an s/l IVRT ratio of 1.3 as a possible lower threshold for discrimination of HCM from other causes of hypertrophy. Although clinical diagnosis of HCM was performed thoroughly, the HCM genotype was known only in 27 patients. However, medial IVRT ratio in these genetically positive patients was comparable with the IVRT ratio of the entire HCM cohort underlining our result.

As in patients with AHT or Fabry disease, hypertrophy was less pronounced than in the majority of HCM patients, a subgroup analysis in HCM patients with less hypertrophy (15–19 mm) was performed. Even in these patients, a significantly higher s/l IVRT ratio was prominent, suggesting this ratio as a potential parameter for differential diagnosis of LVH even in earlier stages of the disease.

4.4 | Study limitations

HCM and AHT patients with DD were older than patients without DD, which is probably because DD increases with age. Younger age in the HCM group without DD might also account for less frequent concomitant diseases. Differences in medication among groups are explained by divergent treatment options for the specific diseases. In this context a potential limitation of this study is the continuous administration of cardiac drugs, which may alter diastolic function throughout all disease groups.

CMR was only performed in a subgroup of HCM patients and not in the other groups; therefore, general conclusions based on our observations from CMR imaging are limited.

We would further like to stress that the American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines recommend a different approach for the evaluation of diastolic function in patients with HCM than we chose. However, the aim of our study was to compare parameters of diastolic function in patients with LVH to differentiate between the different entities, which was only possible when using the same method for all patients.

5 | CONCLUSION

HCM patients with asymmetric septal LVH show a septal pronounced IVRT prolongation, which occurs independent of global DD and which is independent of regional myocardial mass and fibrosis. The s/l IVRT ratio is significantly higher in HCM patients compared with other entities of LVH, such as AHT or storage disorders, and also differs from healthy individuals. Hence, the s/l IVRT ratio might be a useful additional parameter for differential diagnosis of LVH, especially in HCM patients with lesser extent of hypertrophy and irrespective of their global diastolic function. Furthermore, these results may shed more light on the pathophysiologic understanding of DD in HCM.

Author contributions

Christian Voigt and Julia Münch contributed equally to this article.

Conflicts of interest

The authors declare no potential conflicts of interest.

REFERENCES

1. Maron BJ. Hypertrophic cardiomyopathy [published correction appears in *Lancet*. 1997;350:1330]. *Lancet*. 1997;350:127–133.
2. Marian AJ, Roberts R. The molecular genetic basis for hypertrophic cardiomyopathy. *J Mol Cell Cardiol*. 2001;33:655–670.
3. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2011;58:e212–e260.
4. Lewis JF, Maron BJ. Diversity of patterns of hypertrophy in patients with systemic hypertension and marked left ventricular wall thickening. *Am J Cardiol*. 1990;65:874–881.
5. Sachdev B, Takenaka T, Teraguchi H, et al. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. *Circulation*. 2002;105:1407–1411.
6. Michels M, Soliman OI, Kofflard MJ, et al. Diastolic abnormalities as the first feature of hypertrophic cardiomyopathy in Dutch myosin-binding protein C founder mutations. *JACC Cardiovasc Imaging*. 2009;2:58–64.
7. Ho CY, Sweitzer NK, McDonough B, et al. Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical hypertrophic cardiomyopathy. *Circulation*. 2002;105:2992–2997.
8. Cardim N, Perrot A, Ferreira T, et al. Usefulness of Doppler myocardial imaging for identification of mutation carriers of familial hypertrophic cardiomyopathy. *Am J Cardiol*. 2002;90:128–132.
9. Nagueh SF, Bachinski LL, Meyer D, et al. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. *Circulation*. 2001;104:128–130.

10. Galderisi M, Caso P, Severino S, et al. Myocardial diastolic impairment caused by left ventricular hypertrophy involves basal septum more than other walls: analysis by pulsed Doppler tissue imaging. *J Hypertens.* 1999;17:685–693.
11. Núñez J, Zamorano JL, Pérez De Isla L, et al. Differences in regional systolic and diastolic function by Doppler tissue imaging in patients with hypertrophic cardiomyopathy and hypertrophy caused by hypertension. *J Am Soc Echocardiogr.* 2004;17:717–722.
12. Maron BJ, Maron MS. Hypertrophic cardiomyopathy. *Lancet.* 2013;381:242–255.
13. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2016;17:1321–1360.
14. Säring D, Ehrhardt J, Stork A, et al. Computer-assisted analysis of 4D cardiac MR image sequences after myocardial infarction. *Methods Inf Med.* 2006;45:377–383.
15. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Int J Cardiovasc Imaging.* 2002;18:539–542.
16. Nagueh SF. Echocardiographic assessment of left ventricular relaxation and cardiac filling pressures. *Curr Heart Fail Rep.* 2009;6:154–159.
17. Severino S, Caso P, Galderisi M, et al. Use of pulsed Doppler tissue imaging to assess regional left ventricular diastolic dysfunction in hypertrophic cardiomyopathy. *Am J Cardiol.* 1998;82:1394–1398.
18. Saccheri MC, Cianciulli TF, Lax JA, et al. Impaired myocardial function in hypertrophic cardiomyopathy. *Echocardiography.* 2009;26:657–664.
19. De Marchi SF, Allemann Y, Seiler C. Relaxation in hypertrophic cardiomyopathy and hypertensive heart disease: relations between hypertrophy and diastolic function. *Heart.* 2000;83:678–684.
20. Nagueh SF, McFalls J, Meyer D, et al. Tissue Doppler imaging predicts the development of hypertrophic cardiomyopathy in subjects with subclinical disease. *Circulation.* 2003;108:395–398.
21. Nagueh SF, Kopelen HA, Lim DS, et al. Tissue Doppler imaging consistently detects myocardial contraction and relaxation abnormalities, irrespective of cardiac hypertrophy, in a transgenic rabbit model of human hypertrophic cardiomyopathy. *Circulation.* 2000;102:1346–1350.
22. Ellims AH, Taylor AJ, Mariani JA, et al. Evaluating the utility of circulating biomarkers of collagen synthesis in hypertrophic cardiomyopathy. *Circ Heart Fail.* 2014;7:271–278.
23. Zhu Y, Park EA, Lee W, et al. Extent of late gadolinium enhancement at right ventricular insertion points in patients with hypertrophic cardiomyopathy: relation with diastolic dysfunction. *Eur Radiol.* 2015;25:1190–1200.

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2. Summary and Description of Paper

2.1 Background and Rationale

Hypertrophic Cardiomyopathy (HCM) was first defined in 1907 by a German pathologist as a “diffuse muscular hypertrophy of the left ventricular outflow tract” (Schmincke 1907). In 1958 HCM was still considered to describe an asymmetric hypertrophy (Teare 1958), but six years later the definition of the term changed. Henceforth it denoted an “idiopathic hypertrophic subaortic stenosis” (Braunwald et al. 1964), meaning HCM de facto became a synonym for Hypertrophic Obstructive Cardiomyopathy by putting a stronger emphasis on the potentially occurring obstruction of the left ventricular outflow tract (LVOTO). Due to the fact that one third of patients do not show signs of LVOTO, HCM is now commonly used as a generic term that refers to all genetically affected patients (Elliott et al. 2014). This is also how HCM will be understood in the context of this dissertation.

HCM is an inherited monogenetic cardiac disorder with causative mutations in more than a dozen genes coding for sarcomere-associated proteins. These not only cause myocardial hypertrophy, but also myocyte disarray, increased fibrosis and altered cardiac physiology (Marian et al. 2017, Alcalai et al. 2008). HCM affects 1 in 500 people, as measured by echocardiographic criteria (Maron et al. 1995). Taking into consideration more sensitive imaging techniques and more widely used genetic testing, the prevalence of HCM has even been described to be as high as 1:167 (Marian and Braunwald 2017). Despite this relatively high genetic prevalence, the majority of cases most likely remain undiagnosed due to the diverse and often subclinical cardiac manifestation (Maron BJ and Maron MS 2013). Additionally, already by 1997 HCM was recognized as the most common cause of sudden cardiac death in young people (Maron 1997) emphasizing its potentially fatal sequela.

Diagnostic criteria detail a “maximal end-diastolic wall thickness of ≥15 mm anywhere in the left ventricle, in the absence of another cause of hypertrophy in adults“ (Ommen et al. 2020, cf. Elliott 2014), as seen in echocardiography, cardiac magnetic resonance imaging (CMR) or computed tomography. This hypertrophy

can cause an obstruction in the left ventricular outflow tract (the defining feature of the obstructive form of HCM) and lead to more severe symptoms. However, in spite of a typically asymmetrical distribution and pronunciation of the septal wall, the disease's clinical expression is diverse in every possible magnitude, including every possible distribution of left ventricular thickening (Klues et al. 1995, Maron 1997). This instance makes it difficult to distinguish hypertrophy caused by HCM from that of other causes, such as arterial hypertension (Lewis and Maron 1990) or storage disorders (Sachdev et al. 2002).

The pathogenesis mentioned above also contributes to changes in diastolic function – leading to symptoms of heart failure (Ommen et al. 2020, Briguori et al. 1999). It has been noted that diastolic dysfunction can develop independently of, or sometimes precede, cardiac hypertrophy (Marian and Roberts 2001, Nagueh et al. 2000, Nagueh et al. 2001). Regional differences have been described between the septal and lateral mitral annulus, namely in their isovolumic relaxation times (IVRT), their peak early mitral annulus velocities (E'), as well as the quotient of early transmitral filling velocity and peak early mitral annulus velocities (E/E') (Galderisi et al. 1999). Likewise, regional changes in diastolic parameters at septal and lateral mitral annulus appear to be of use in distinguishing between different causes of hypertrophy – for example between arterial hypertension and HCM. The septal annulus appears to be particularly involved in this, and may therefore be useful (Núñez et al. 2004).

Furthermore, genetic mutations associated with HCM can also lead to myocardial fibrosis – which can be associated with the occurrence of ventricular arrhythmia – (Prinz et al. 2013) and can heighten the risk of all-cause and cardiac mortality in these patients (Bruder et al. 2010). It has previously been shown that myocardial fibrosis, defined by late gadolinium enhancement (LGE) in cardiac magnetic resonance imaging (CMR) (Jan and Tajik 2017), can also alter diastolic function (Marian and Braunwald 2017). Therefore, in a subset of the HCM patients in this study the extent of regional myocardial fibrosis was correlated with regional changes in diastolic function.

Discerning precisely between the different underlying disorders of cardiac left ventricular hypertrophy (LVH) is of utmost clinical relevance due to the many consequences concerning therapeutic strategies and risk management. However, an echocardiographic criterion that clearly diagnoses patients with LVH, with or without symptoms of global diastolic dysfunction, has yet to be established. This paper is therefore aimed at establishing parameters to distinguish different causes of LVH by studying the aforementioned features, with particular emphasis on regional parameters of diastolic function.

2.2 Material and Methods

Patients were recruited over a number of routine visits to the outpatient clinic at the University Heart Center Hamburg between July 2010 and September 2013. The patients' echocardiographic data as well as, in a subset of patients, CMR data was retrospectively analyzed. HCM was then diagnosed in 81 patients by the echocardiographic criteria mentioned above, and was additionally confirmed by genetic testing in approximately a quarter of these cases. Two further groups, one consisting of 12 patients with genetically confirmed Morbus Fabry and evidence of cardiac involvement, the other of 55 patients with confirmed arterial hypertension (AHT) and signs of LVH, were also included in the study. An additional 63 patients without a known history or signs of cardiac pathology in physical examination, electrocardiogram or echocardiography were selected as a control.

Several echocardiographic parameters – mostly concerning diastolic function – were assessed in all of the selected patients and subsequently analyzed. The chosen parameters encompassed numerous routine data types such as left ventricular ejection fraction, septal and lateral wall thicknesses, as well as a survey of the global diastolic function, which was examined in greater detail. The peak early (E wave) and late (A wave) transmitral filling velocities for E/A ratio and the deceleration time of E wave (DT of E wave) were among the factors measured. Specific emphasis lay on regional (septal to lateral) changes in isovolumic relaxation time (IVRT), peak early (E') and late (A') mitral annulus velocities, the ratio of these two parameters and the quotient of early transmitral filling velocity and peak early mitral annulus velocities (E/E'). Septal to lateral quotients were

calculated and cross-compared between groups when possible. In addition, the septal to lateral ratio of IVRT was analyzed in the HCM subgroups with and without global diastolic dysfunction, as well as the HCM subgroups, in which the septal wall thicknesses were less and greater than 20mm. Linear models adjusted for age, sex and quotient of septal to lateral wall thickness were used. In the case of septal to lateral IVRT ratio, a receiver operating curve was created in order to evaluate the definition of a cut off value differentiating HCM patients from other groups.

CMR findings, including the amount of fibrosis as estimated by LGE (>2 standard deviations above signal intensity of normal-appearing myocardium), were available for a subset of 42 HCM patients. The amount of lateral and septal myocardial mass in defined segments following published recommendations (Cerqueira et al. 2002) and the extent of LGE (in percent of LV mass) in these segments were therefore correlated with the parameters of diastolic dysfunction.

2.3 Results

Patients in the HCM and AHT groups were significantly older than those with Fabry's disease as well as the control group. As expected by classification we observed notable differences in wall thicknesses, with the highest values found in the HCM group, as well as in parameters of diastolic function. Disease groups showed significantly altered values in their transmitral filling velocities, DT of E wave, E', E/E', in comparison to control group but not for A' or E'/A'. The latter therefore were not further examined.

Transmitral filling velocities and DT of E wave showed significant alterations between patient groups and healthy control. However, these parameters were not further analyzed considering the lack of conclusive differences between the HCM group and other patient groups. Mean E' showed a significant reduction in the HCM group compared to healthy control and AHT groups due to a marked reduction mostly in septal E', in line with published data (Núñez et al. 2004). However, no significant divergence between the HCM and Fabry group was observed here – furthermore, the ratio of septal to lateral E' did not display any

significant differences between groups. In HCM patients, E/E' was significantly higher in both septal and lateral Tissue Doppler Imaging (TDI) in comparison to the AHT and control groups, but again not the Fabry group.

IVRT of septal and lateral mitral annulus was prolonged in all three patient groups in comparison to the healthy control group. While the lateral mitral annulus IVRT did not differ significantly between patient groups, a markedly higher prolongation was observed for septal IVRT in the HCM group. This resulted consequently in a higher septal to lateral IVRT ratio, distinguishing the HCM patients significantly from all other groups with a mean value of 1.5, compared to 1.0 or 1.1 respectively. In contrast, mean IVRT was not able to distinguish HCM patients from all other groups.

Furthermore, in an analysis of subgroups of the HCM group, the increased septal to lateral IVRT ratio occurs independently of the presence of global diastolic dysfunction as well as the extent of septal wall thickness. 29 HCM patients with normal global diastolic function displayed shorter IVRT on the septal site of mitral annulus compared to the septal IVRT values of all HCM patients, but were nonetheless still prolonged in comparison to other patient groups and control group. Remarkably, though this HCM patients did not display any signs of global diastolic dysfunction, the septal to lateral IVRT ratio was still significantly increased (mean value of 1.5) – thereby also discriminating this subgroup of HCM patients from all other patient and control groups. Considering the fact that patients in AHT and Fabry groups display a significantly lower septal wall thickness in comparison to HCM patients as a potential confounder, a second subgroup analysis was performed to compare 28 HCM patients with a septal wall thickness of less than 20mm with these groups. The results found here are similar to the aforementioned analysis, with still particularly prolonged IVRT values on the septal mitral annulus in this HCM subgroup, leading once more to a mean septal to lateral IVRT ratio of 1.5 – serving likewise to differentiate also HCM patients with milder extent of septal wall thickness considerably from all other groups.

Ascertaining that the septal to lateral ratio of IVRT is able to discriminate left ventricular hypertrophy due to HCM of LVH due to other entities regardless of either the presence of reduced global diastolic function or excess wall thickness this parameter was further evaluated through a receiver operating curve (ROC) analysis. The optimum cut-off value for distinguishing groups seems to be between 1.2 (sensitivity of 76.5%, specificity 79.1%) and 1.3 (sensitivity 63%, specificity 91%).

In addition to these findings, the CMR data on myocardial mass and LGE of 42 HCM patients was cross-analyzed with the results of IVRT studies. No relevant correlation could be detected in HCM patients between IVRT prolongation and the amount of myocardial mass or the amount of fibrosis as detected by LGE.

2.4 Discussion

This study analyzed various parameters of diastolic function in patients displaying left ventricular hypertrophy of differing aetiologies. The aim of the study was to find parameters herein that distinguish patients with Hypertrophic Cardiomyopathy from those with LV hypertrophy caused by either arterial hypertension or Fabry's disease.

Similar to earlier studies on HCM patients (Núñez et al. 2004), E' was found to have been more altered in the septal mitral annulus compared to the lateral mitral annulus in our HCM group. However, this could also reflect a generally more involved septum in terms of diastolic function, irrespective of the underlying diagnosis (Nagueh et al. 2009). In line with this, we observed that the septal to lateral ratio of E' was equally reduced in all groups, meaning therefore that regional alterations in this parameter cannot be used to differentiate between diseases. E/E' is not reliable enough to distinguish between different disorders for the same reason. Overall neither E' alone nor E/E' seem to be able to differentiate between hypertrophies of varying causes in this study, congruent with previously collected data (De Backer et al. 2005).

An interesting set of results were obtained for IVRT values, especially considering their septal to lateral ratios. It was observed that the prolongation of IVRT, particularly on the septal mitral annulus, may be a regular occurrence in HCM-patients – as previously denoted by other studies (Núñez et al. 2004, Severino et al. 1998). Firstly, these changes occur irrespective of whether overall diastolic dysfunction is present in HCM patients, which is also in alignment with previous findings (Severino et al. 1998), and which is coherent with the idea of early subtle changes in diastolic function in HCM – in this instance predominantly involving the septal annulus for yet unknown reasons. Changes in parameters of diastolic function occuring prior to or independent of conclusive evidence of global diastolic dysfunction have yet been described as rather imprecise or unreliable for identifying HCM patients using the example of E' (Ho et al. 2002), which is possibly attributable to the same reasons discussed above. The underlying idea seems to be nonetheless applicable to IVRT considering the data obtained in this study. In conclusion, a heightened septal to lateral IVRT ratio may reflect an early manifestation of (diastolic dysfunction in) HCM.

Secondly, these findings emphasize that changes in diastolic parameters can occur independently of the extent of left ventricular hypertrophy. By now this independency is only shown for the correlation between LVH and E' (Ho et al. 2002, Nagueh et al. 2001, Nagueh et al. 2003), as well as E/E' (Saccheri et al. 2009). Conversely, others describe a correlation between the extents of LVH and IVRT in HCM patients (De Marchi et al. 2000). This study does not, however, find any evidence of correlation between changes in diastolic function and myocardial wall thickness as measured by echocardiography, as well as myocardial mass as measured by CMR in a HCM subgroup.

Additionally, CMR data in this study reveals no correlation between altered diastolic function in form of prolonged IVRT and myocardial fibrosis as detected by LGE. These findings have been the topic of controversial discussion in literature – with some finding a correlation between the amount of LGE and alterations in E/E' and E/A respectively as parameters for diastolic function (Zhu et al. 2015, Prinz et al. 2012). Others, however, find no correlation between diastolic dysfunction and

regional fibrosis as measured by LGE, but at the same time do describe a correlation with more diffuse interstitial fibrosis as measured through CMR guided measurement of myocardial T1 times (T1-mapping) (Ellims et al. 2014). These results raise the question of whether diastolic dysfunction is caused by diffuse and interstitial fibrosis, rather than by myocardial replacement fibrosis as detected by LGE. T1-mapping, being a relatively well-investigated examination for diffuse fibrosis (Iles et al. 2008), may therefore be a more suitable approach for surveying correlations between fibrosis and diastolic function in HCM patients. However, data from T1-mapping was not available for analysis in this study.

As mentioned above, the septal to lateral IVRT ratio was significantly higher in the HCM group compared with the AHT and Fabry groups. Therefore, a septal pronounced alteration of diastolic function in form of prolonged IVRT may reflect a HCM specific phenotype and may be used as a valuable parameter for discriminating HCM patients from those with LVH of other aetiologies. This characteristic is shown by the results of ROC analysis of the IVRT ratio, finding the optimal cut-off value for discrimination of HCM patients from other patient groups to be between 1.2 and 1.3. Supposing a higher specificity would be more useful than a high sensitivity in a clinical setting, a septal to lateral IVRT ratio of 1.3 (sensitivity 63%, specificity 91%) could be proposed as a possible cut-off value in order to discern HCM from other causes of hypertrophy.

In spite of disagreement over the correlation between diastolic function and myocardial fibrosis/left ventricular hypertrophy, there seems to be a consensus that subtle changes in diastolic function occur earlier in the disease's progression than other clinical features (Ommen et al. 2020). Septal to lateral IVRT ratio may be an accurate parameter to detect these subtle changes at early points when other disease defining pathologies have not yet developed, whilst also providing a more reliable distinction between hypertrophies caused by different entities. Nevertheless, further study into the usability and validity of this proposed diagnostic parameter – especially for yet clinically undiagnosed HCM patients– would be necessary.

2.5 Study Limitations

Limitations of this study include the continued application of cardiac medication, which can potentially interfere with diastolic function and cause differences between groups due to divergent therapeutic regimes for underlying diseases. To discontinue this medication, however, would not have been ethically viable – though having patients to continue their diverse therapeutic regimes at the time of investigation helps to reflect a real-world scenario.

Another limitation is that CMR imaging was only performed in a subgroup of HCM patients and was not compared with any other groups. Therefore, general conclusions based on these observations remain limited. Additionally, a different approach to CMR – such as T1 mapping – may be a more suitable measurement, in that it detects interstitial fibrosis rather than regional replacement fibrosis possibly correlating better with changes in diastolic function. Data derived from this technique was unfortunately not available for the respective patient group at time of survey.

Assessment of DD of HCM patients followed a different approach as recommended by the guidelines of American Society of Echocardiography/European Association of Cardiovascular Imaging. However, this study aimed to find differences in parameters of diastolic dysfunction between several entities of LVH requiring a homogenous approach for comparability.

2.6 Conclusion

Hypertrophic Cardiomyopathy is a relatively common inherited cardiac disorder with a diverse clinical phenotype, with or without left ventricular outflow tract obstruction. The disease can be completely asymptomatic but patients can also suffer from mild to severe signs of heart insufficiency, to potentially fatal sequela through the associated symptoms of terminal heart failure, ventricular tachycardia and sudden cardiac death. The main clinical characteristic is left ventricular hypertrophy, similar to a variety of other cardiac and systemic diseases. Differential diagnosis therefore remains critical, albeit difficult to carry out. Previous studies have already revealed regional changes in diastolic function, differentiating

HCM from other entities of left ventricular hypertrophy. This study found the septal to lateral ratio of IVRT to be significantly higher in patients with HCM than in healthy patients as well as in those with AHT and Fabry's disease. Within the HCM group this change seems to occur independently of either the presence of global diastolic dysfunction or the extent of myocardial hypertrophy as measured by echocardiography, as well as the extent of myocardial mass as measured by CMR and myocardial fibrosis as detected by LGE in CMR.

Accordingly, analyzing the septal to lateral ratio of IVRT may be a useful measure not only in differentiating between diverse entities of cardiac hypertrophy, but may also be an early indicator of HCM in otherwise undiagnosed patients. Further study on the usability and validity of this parameter as a diagnostic tool – especially in genetically confirmed HCM patients displaying otherwise normal echocardiographic results – seems to be necessary.

2.7 Abbreviation Index

A’	Peak Late Mitral Annulus Velocity
AHT	Arterial Hypertension
A wave	Peak Late Transmitral Filling Velocity
CMR	Cardiac Magnetic Resonance Imaging
DT	Deceleration Time
E wave	Peak Early Transmitral Filling Velocity
E/E’	Quotient of Early Transmitral Filling Velocity and Peak Early Mitral Annulus Velocity
E’	Peak Early Mitral Annulus Velocity
HCM	Hypertrophic Cardiomyopathy
IVRT	Isovolumic Relaxation Time
LGE	Late Gadolinium Enhancement
LV	Left Ventricular
LVH	Left Ventricular Hypertrophy
LVOTO	Left Ventricular Outflow Tract Obstruction
ROC	Receiver Operating Curve
T1 mapping	CMR Guided Measurement of Myocardial T1 Times
TDI	Tissue Doppler Imaging

2.8 Bibliography

Alcalai R, Seidman JG, Seidman CE. Genetic basis of hypertrophic cardiomyopathy: from bench to the clinics. *J Cardiovasc Electrophysiol*. 2008;19(1):104-110.

Braunwald E, Lambrew CT, Rockoff SD, Ross J Jr, Morrow AG. Idiopathic HypertrophicSubaorticStenosis. I. A descriptionofthediseasebasedupon ananalysis of 64 patients. *Circulation*. 1964;30:3-119.

Briguori C, Betocchi S, Romano M, et al. Exercise capacity in hypertrophic cardiomyopathy depends on left ventricular diastolic function. *Am J Cardiol*. 1999;84(3):309-315.

Bruder O, Wagner A, Jensen CJ, et al. Myocardial scar visualized by cardiovascular magnetic resonance imaging predicts major adverse events in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2010;56(11):875-887.

Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105(4):539-542.

De Backer J, Matthys D, Gillebert TC, De Paepe A, De Sutter J. The use of Tissue Doppler Imaging for the assessment of changes in myocardial structure and function in inherited cardiomyopathies. *Eur J Echocardiogr*. 2005;6(4):243-250.

De Marchi SF, Allemann Y, Seiler C. Relaxation in hypertrophic cardiomyopathy and hypertensive heart disease: relations between hypertrophy and diastolic function. *Heart*. 2000;83(6):678-684.

Ellims AH, Taylor AJ, Mariani JA, et al. Evaluating the utility of circulating biomarkers of collagen synthesis in hypertrophic cardiomyopathy. *Circ Heart Fail*. 2014;7(2):271-278.

Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35(39):2733-2779.

Galderisi M, Caso P, Severino S, et al. Myocardial diastolic impairment caused by left ventricular hypertrophy involves basal septum more than other walls: analysis by pulsed Doppler tissue imaging. *J Hypertens*. 1999;17(5):685-693.

Ho CY, Sweitzer NK, McDonough B, et al. Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical hypertrophic cardiomyopathy. *Circulation*. 2002;105(25):2992-2997.

Iles L, Pfluger H, Phrommintikul A, et al. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. *J Am Coll Cardiol*. 2008;52(19):1574-1580.

Jan MF, Tajik AJ. Modern Imaging Techniques in Cardiomyopathies. *Circ Res*. 2017;121(7):874-891..

Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. *J Am Coll Cardiol*. 1995;26(7):1699-1708.

Lewis JF, Maron BJ. Diversity of patterns of hypertrophy in patients with systemic hypertension and marked left ventricular wall thickening. *Am J Cardiol*. 1990;65(13):874-881..

Marian AJ, Braunwald E. Hypertrophic Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. *Circ Res*. 2017;121(7):749-770.

Marian AJ, Roberts R. The molecular genetic basis for hypertrophic cardiomyopathy. *J Mol Cell Cardiol*. 2001;33(4):655-670..

Maron BJ. Hypertrophic cardiomyopathy [published correction appears in Lancet 1997 Nov 1;350(9087):1330]. *Lancet*. 1997;350(9071):127-133.

Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. *Circulation*. 1995;92(4):785-789.

Maron BJ, Maron MS. Hypertrophic cardiomyopathy. *Lancet*. 2013;381(9862):242-255.

Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009;10(2):165-193.

Nagueh SF, Bachinski LL, Meyer D, et al. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. *Circulation*. 2001;104(2):128-130.

Nagueh SF, Kopelen HA, Lim DS, et al. Tissue Doppler imaging consistently detects myocardial contraction and relaxation abnormalities, irrespective of cardiac hypertrophy, in a transgenic rabbit model of human hypertrophic cardiomyopathy. *Circulation*. 2000;102(12):1346-1350.

Nagueh SF, McFalls J, Meyer D, et al. Tissue Doppler imaging predicts the development of hypertrophic cardiomyopathy in subjects with subclinical disease. *Circulation*. 2003;108(4):395-398.

Núñez J, Zamorano JL, Pérez De Isla L, et al. Differences in regional systolic and diastolic function by Doppler tissue imaging in patients with hypertrophic

cardiomyopathy and hypertrophy caused by hypertension. *J Am Soc Echocardiogr*. 2004;17(7):717-722.

Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, Evanovich LL, Hung J, Joglar JA, Kantor P, Kimmelstiel C, Kittleson M, Link MS, Maron MS, Martinez MW, Miyake CY, Schaff HV, Semsarian C, Sorajja P. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2020;142:e558–e631

Prinz C, Schwarz M, Ilic I, et al. Myocardial fibrosis severity on cardiac magnetic resonance imaging predicts sustained arrhythmic events in hypertrophic cardiomyopathy. *Can J Cardiol*. 2013;29(3):358-363.

Prinz C, van Buuren F, Faber L, et al. Myocardial fibrosis is associated with biventricular dysfunction in patients with hypertrophic cardiomyopathy. *Echocardiography*. 2012;29(4):438-444.

Saccheri MC, Cianciulli TF, Lax JA, et al. Impaired myocardial function in hypertrophic cardiomyopathy. *Echocardiography*. 2009;26(6):657-664.

Sachdev B, Takenaka T, Teraguchi H, et al. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. *Circulation*. 2002;105(12):1407-1411.

Schmincke A. Ueber linkseitige muskulose conustenosen. *Deutsche Med Wochenschr.*1907;33:2082–2085.

Severino S, Caso P, Galderisi M, et al. Use of pulsed Doppler tissue imaging to assess regional left ventricular diastolic dysfunction in hypertrophic cardiomyopathy. *Am J Cardiol*. 1998;82(11):1394-1398.

Teare D. Asymmetrical hypertrophy of the heart in young adults. *Br Heart J*. 1958;20(1):1-8.

Zhu Y, Park EA, Lee W, et al. Extent of late gadolinium enhancement at right ventricular insertion points in patients with hypertrophic cardiomyopathy: relation with diastolic dysfunction. *Eur Radiol*. 2015;25(4):1190-1200.

3. German summary

Die Hypertrophe Kardiomyopathie (HCM) ist eine genetische Herzerkrankung mit Veränderungen in Genen, die für Proteine des Sarkomers kodieren. Diese führen – oft in subklinischer Ausprägung – zu strukturellen und funktionellen Alterationen wie linksventrikulärer Hypertrophie oder diastolischer Dysfunktion, letztere oft als Frühzeichen. Diese Arbeit untersucht echokardiographische Parameter zur frühen Identifikation und differentialdiagnostischen Abgrenzung von HCM-Patienten. Untersucht wurden 81 HCM-Patienten, 55 Patienten mit arterieller Hypertonie, 12 Patienten mit Morbus Fabry sowie 63 gesunde Kontrollpatienten bezüglich der (regionalen) diastolischen Funktion. Bei 42 HCM-Patienten lagen zusätzlich Daten zu Herzmuskelmasse und -fibrose aus Magnetresonanztomographien (MRT) vor, welche mit den echokardiographischen Ergebnissen korreliert wurden. Die Auswertung der Daten zeigte, dass von den verschiedenen untersuchten Parametern der diastolischen Funktion (E/A, E‘, A‘ E/E‘, E‘/A‘, IVRT) nur die isovolumische Relaxationszeit (IVRT) eine Diskrimination der HCM-Patienten von allen anderen Gruppen zuließ. Eine Verlängerung der IVRT tritt bei HCM-Patienten betont am septalen Mitralanulus auf und führt zu einem erhöhten septalen zu lateralen Quotienten der IVRT. Während dieser für HCM-Patienten unabhängig vom Ausmaß der linksventrikulären Hypertrophie sowie der globalen diastolischen Funktion bei 1,5 lag, zeigten alle anderen Gruppen Werte zwischen 1,0 und 1,1. Eine Analyse mittels Receiver-Operating-Curve zeigte einen optimalen cut-off-Wert für eine Diskrimination bei einem Quotienten zwischen 1,2 (Sensitivität 77%, Spezifität 79%) und 1,3 (Sensitivität 63%, Spezifität 91%). Die regionale IVRT zeigte in einer HCM-Subgruppe keine Korrelation zur Herzmuskelmasse oder dem Ausmaß der Myokardfibrose (detektiert als Late-Gadolinium-Enhancement) aus MRT-Daten. Unter Berücksichtigung, dass auch subtile Veränderungen der diastolischen Funktion ein Frühzeichen der HCM sein können und eine Erhöhung des IVRT-Quotienten ein HCM-typisches Phänomen zu seien scheint, könnte der septale zu laterale IVRT-Quotient ein zukünftiger Diagnose-Parameter sein, um HCM-Patienten früh vor dem Auftreten weiterer Krankheitsmerkmale zu identifizieren und differentialdiagnostisch von anderen Ursachen der linksventrikulären Hypertrophie abzugrenzen. Hierzu sind jedoch noch weitere Untersuchungen zur Nutzbarkeit und Validität notwendig.

4. English summary

Hypertrophic Cardiomyopathy (HCM) is a genetic cardiac disorder with mutations in genes coding for sarcomeric proteins. These mutations lead to structural and functional alterations like left-ventricular hypertrophy and diastolic dysfunction, with the latter often being described as an early sign of the disease. This paper examines echocardiographic parameters for early identification of HCM-patients and differentiation from other disease entities with similar characteristics. 81 HCM patients, 55 patients with arterial hypertension, 12 patients with Morbus Fabry as well as 63 healthy control patients were examined for echocardiographic criteria of (regional) diastolic function. Of 42 HCM-patients, we additionally obtained cardiac magnetic resonance imaging (CMR) data for myocardial mass and extent of fibrosis as detected by late gadolinium enhancement which was correlated with echocardiography data. Analysis of the data showed that of the examined parameters of diastolic function (E/A, E‘, A‘, E/E‘, E‘/A‘, IVRT) only isovolumic relaxation time (IVRT) allowed a discrimination of HCM patients from all other groups. IVRT prolongation in HCM patients particularly occurs at the septal mitral annulus leading to a heightened septal to lateral IVRT ratio. Whilst this ratio was 1.5 in HCM patients independently of the extent of left ventricular hypertrophy as well as the presence of global diastolic dysfunction as determined by subgroup analysis, this value was 1.0 to 1.1 for all other groups. A receiver operating curve analysis has shown the optimal cut off value to be between 1.2 (sensitivity 77%, specificity 79%) and 1.3 (sensitivity 63%, specificity 91%). Regional IVRT neither correlated with the myocardial mass nor with the extent of myocardial fibrosis (as detected by late gadolinium enhancement) measured by CMR in a HCM subgroup. Recognizing that even subtle changes of diastolic function might be an early sign of HCM and that a heightened IVRT ratio seems to be a HCM specific phenomenon, the septal to lateral IVRT ratio might be a potential future parameter for early diagnosis in HCM patients as well as differential diagnosis of left ventricular hypertrophy. However, further examination of this parameter concerning usability and validity is necessary.

5. Explanation of own Contribution

Early segmental relaxation abnormalities in hypertrophic cardiomyopathy for differential diagnostic of patients with left ventricular hypertrophy
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The doctoral candidate together with Dr. Münch equally drafted and adapted the study design in all phases of the clinical investigation and created the script for this publication under supervision and provision of expertise by PD Dr. Patten and additional consultation by Dr. Witzel. Echocardiography studies for HCM patients were performed by Dr. Münch and PD Dr. Patten, studies for all other groups were performed by the team of the Clinic for General and Interventional Cardiology of the University Heart Center Hamburg. Selection of suitable patients for the HCM-group was performed by Dr. Münch. Selection of suitable patients for all other groups was performed by the doctoral candidate. Analysis of the routinely obtained echocardiography studies for this clinical investigation as well as the collection of all clinical data as depicted in tables 1, 2 and 3 were performed by the doctoral candidate. Data of routinely performed MRI scans were analyzed and collected by Prof. Dr. Lund and Dr. Avanesov and put together with other clinical data by the doctoral candidate. Definition of questions and preparation of data for statistical analysis were prepared by the doctoral candidate in cooperation with Dr. Münch after consultation with Dr. Suling. Statistical analysis and creation of figure 1 and 2 were performed by Dr. Suling.

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7. Curriculum Vitae

Lebenslauf wurde aus datenschutzrechtlichen Gründen entfernt.

8. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbstständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
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Unterschrift: .....