VIA MEDICA

REVIEW ARTICLE

Cardiology Journal
2016, Vol. 23, No. 3, 250–263
DOI: 10.5603/CJ.a2016.0019

ISSN 1897–5593

Cardiovascular magnetic resonance imaging in hypertrophic cardiomyopathy: Current state of the art

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Abstract

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiomyopathy with a prevalence of 1:500 (0.2%) in the general population. Sudden cardiac death (SCD) is the most feared presentation of HCM. Therefore, it is essential to identify individuals at high risk in order to prevent SCD. The absence of conventional risk factors does not nullify the risk of HCM related SCD. Although echocardiography is currently the most widely used imaging modality, cardiac magnetic resonance (CMR) allows detailed characterization of the HCM phenotype, which makes it possible to differentiate HCM from other causes of left ventricular hypertrophy. CMR has the potential to further refine risk stratification. Late gadolinium enhancement (LGE) on CMR is a high-risk feature and there is emerging data to suggest that the presence of LGE should be employed as a marker for major adverse outcomes such as SCD, arrhythmias, systolic and diastolic heart failure. Hence, LGE on CMR may be considered an additional risk factor for SCD in HCM patients and should be incorporated in decision-making for implantable cardioverter defibrillator implantation to aid primary prevention. Novel markers such as the extent of myocardial fibrosis on CMR must be accounted for comprehensive risk stratification of HCM patients. The purpose of this review is to discuss the current status and emerging role of CMR in HCM. (Cardiol J 2016; 23, 3: 250–263)

Key words: hypertrophic cardiomyopathy, sudden cardiac death, myocardial fibrosis, cardiovascular magnetic resonance, T1-mapping, gadolinium contrast

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiomyopathy with a prevalence of 1:500 (0.2%) in the general population [1]. It is characterized by inappropriate myocardial wall thickening and is usually caused by mutations in genes encoding proteins of the cardiac sarcomere. It is transmitted by an autosomal dominant pattern of inheritance in 60% of cases. The heterogeneity in penetrance, phenotypic expression, and clinical presentation suggests a role of additional genetic, epigenetic and environmental factors in the pathogenesis. Defective sarcomere proteins impair the function of cardiac myocytes, ultimately resulting in left ventricular hypertrophy (LVH) with asymmetric ventricular septal hypertrophy being the most common phenotype [2, 3]. HCM has a broad range of clinical manifestations of HCM. Most patients remain undiagnosed or asymptomatic with normal life expectancy [4]. However, symptomatic patients present with palpitations, chest

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Received: 01.02.2016 Accepted: 08.02.2016

pain, exertional dyspnea, or sudden cardiac death (SCD). It is the most common cause of SCD in the young and one of the leading causes of heart failure (HF) disability at 5–10 years of age [5]. The symptoms occur due to systolic or diastolic dysfunction, left ventricular (LV) outflow tract obstruction, microvascular ischemia or ventricular/ /supraventricular arrhythmias [6]. Although annual mortality rates range from 1% to 5%, a significant number of patients are at risk for adverse outcomes [7]. Therefore, it is essential to identify the risk of SCD and plan implantable cardioverter defibrillator (ICD) in those patients who are at high risk. Although echocardiography is commonly used, cardiac magnetic resonance (CMR) is considered to be the gold standard for evaluating ventricular mass, volumes, and ejection fraction (EF). Unlike echocardiography, CMR has an advantage in that there are no limitations from poor acoustic windows. The purpose of this review is to discuss the current status and emerging role of CMR in HCM.

Diagnosis of HCM

Echocardiography has been the most valuable screening tool to evaluate HCM, as it is widely available, bedside technique, which is relatively cheap and non-ionizing. In addition, it provides useful information for risk stratification, treatment, and follow-up of patients.

Cardiac magnetic resonanse for diagnosis of LVH

Although asymmetrical septal hypertrophy is a common phenotype, accurate assessment of LVH by echocardiography may not be possible in all segments in all patients. It is hard to differentiate the lateral epicardial border of the LV myocardium from the adjacent thoracic parenchyma and the epicardial border of the posterior septum in the area of insertion of the right ventricular (RV) free wall by echocardiography due to loss of spatial resolution. CMR is not limited by such constraints and it is superior to echocardiography for assessing LV wall thickness on the anterior wall, posterior septum and apex of the heart due to its tomographic imaging capability and higher spatial resolution [3, 8]. Maron et al. [8] described different patterns of LVH in 333 HCM patients utilizing CMR. The most common location of hypertrophy (in 70% patients) was the confluence of the basal anterior septum with the adjacent anterior free LV wall. The next most common site was the posterior septum at the mid-ventricular level [3]. Thus, CMR allows detailed characterization of the HCM phenotype (Figs. 1, 2) and helps differentiate HCM from other causes of LVH.

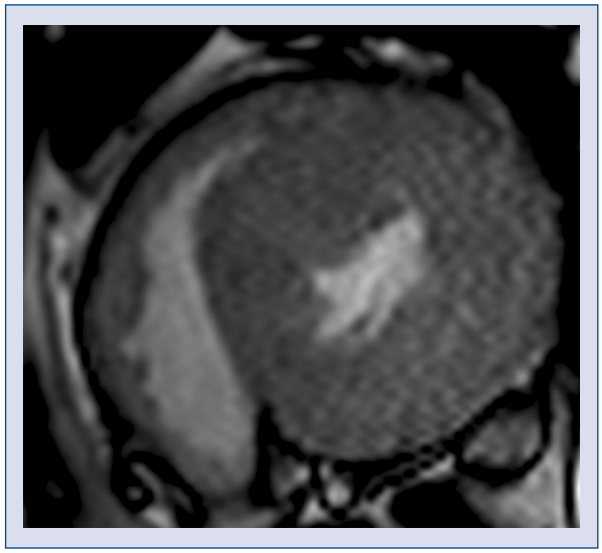

Figure 1. Short axis view on cardiac magnetic resonance demonstrating concentric left ventricular hypertrophy.

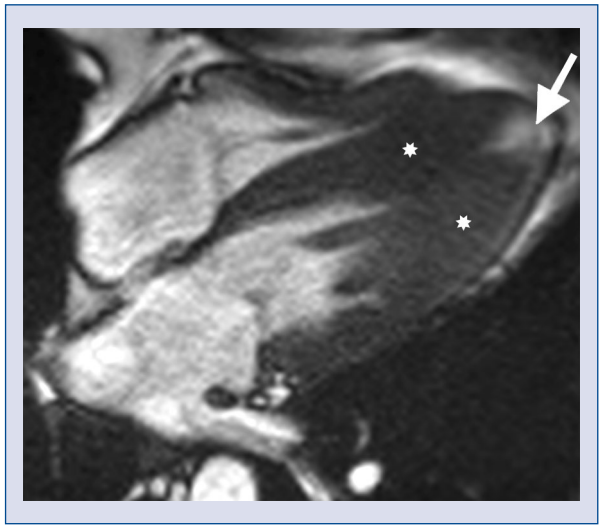

Figure 2. Four chamber view on cardiac magnetic resonance demonstrating mid-ventricular hypertrophy (white asterisk) and an apical aneurysm (white arrow).

Differentiating HCM from athlete's heart

Cardiac magnetic resonanse has several advantages as compared to echocardiography for the evaluation of LVH in trained athletes. If there is an ambiguity regarding the borderline LV wall thick-

ness either due to athletic training or HCM, the presence of scar/enhancement on CMR would suggest the presence of HCM. Interruption or cessation of intense physical activities in trained athletes (deconditioning) for short [9] or long periods [10] of time results in restoration of normal LV cavity size due to regression of LVH. However, alteration in physical activity does not affect LV wall thickness in HCM. CMR can be used to detect serial changes in LV wall thickness during deconditioning of the heart in athletes [10].

Detection of myocardial fibrosis with late gadolinium enhancement using CMR

Myocardial fibrosis is defined as a significant increase in the collagen volume fraction of myocardial tissue, which is common in advanced cardiac disease [11]. Replacement (focal and diffuse) fibrosis or interstitial fibrosis are two types of myocardial fibrosis commonly seen in HCM. Scarring or replacement fibrosis is the accumulation of collagen corresponding to necrotic or damaged myocyte. Interstitial fibrosis is diffusely distributed in the extracellular space. It is predicted that transforming growth factor-beta 1 triggers production of extracellular matrix proteins leading to myocardial fibrosis in HCM [12]. Myocardial fibrosis has been recognized as a predictor of adverse clinical outcomes in HCM patients and therefore its quantification has gained great importance. Endomyocardial biopsy, the gold standard invasive method, is used to assess interstitial collagen accumulation. CMR is emerging as a gold standard among the non-invasive imaging modalities to visualize the extracellular compartment of myocardium and quantify myocardial fibrosis. In a study of 29 patients by Moravsky et al. [13], the significant correlation was seen between quantitative assessment of myocardial fibrosis by histological methods and late gadolinium enhancement (LGE). The gadolinium contrast distributes preferentially to the extracellular compartment of the myocardium because it is small enough to pass through the capillary wall yet large enough to preclude its entry into the cell membrane (Fig. 3) [13]. The role of LGE on CMR for the prediction of major adverse outcomes such as SCD, arrhythmias, systolic and diastolic HF may be supported by some emerging data [14–16].

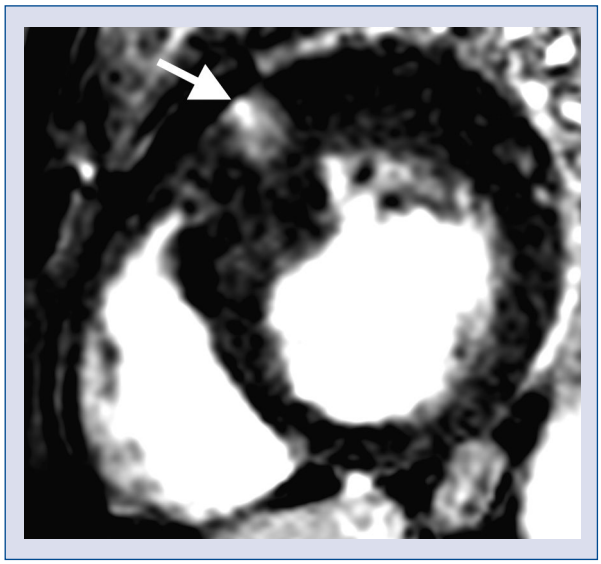

Figure 3. Short axis view on cardiac magnetic resonance with late gadolinium enhancement demonstrating patchy enhancement especially prominent in the anterior right ventricle insertion point (white arrow).

Late gadolinium enhancement and SCD

The performance of conventional risk factors for risk stratification of SCD in HCM is known to be suboptimal. Hence, it can be challenging to accurately identify risk factors which can improve the patient selection for prophylactic ICD therapy [17]. Contrast-enhanced CMR has emerged as an excellent tool for improving risk stratification of HCM patients. Although the data are still limited in this regard, there are several studies which have highlighted that the presence and extent of LGE can improve risk stratification of HCM patients [14, 18–20]. The relevant studies are summarized in Tables 1–4.

The presence and extent of LGE as a marker of myocardial fibrosis is a risk factor for SCD in HCM patients. Moon et al. [18] showed that greater area of LGE ($p < 0.001$) and the presence of two or more risk factors for sudden death ($p < 0.02$) are directly proportional to disease progression in HCM patients. Progressive disease was defined as a decrease in maximal LV wall thickness by ≥ 5 mm and an increase in LV end-systolic dimension by ≥ 5 mm during 5 or more years of serial follow-up with an echocardiogram. In a recent study, Ismail et al. [21] have shown that even small increments in fibrosis, such as an increase in LGE by 5%, significantly increase the risk of SCD. Another recent study by Chan et al. [22] virtually establishes that the extent of LGE is a strong predictor of SCD events. When compared with conventional risk factors, the extent of LGE was by far the best predictor of SCD events. When used in combination

Table 1. Study characteristics.

Author (year)	No. of patients	Type of study	Location of study	Clinical outcomes	Duration of study	NYHA mean n (%)	RF for SCD mean n (%)
Motoyasu et al. (2008)	17	Prospective cohort study	Tsu, Japan	Relationship between LGE and diastolic dysfunction	–	–	–
Chan et al. (2014)	1,293	Prospective cohort study	Massachusetts and Minnesota	SCD end-stage HCM with systolic dysfunction	November 2001 and February 2010	1.6 ± 0.7 I: (57) II: 380 (29) III/IV: 178 (14)	0.5 ± 0.6 0 RF: 782 (60) 1 RF: 415 (32) 2 RF: 90 (7) 3 RF: 6 (0.5) 4 RF: 0 (0)
Ismail et al. (2014)	711	Prospective cohort study	London, United Kingdom	SCD or aborted SCD	September 2000 to June 2011	I: 439 (62.7) II: 210 (30.0) III: 47 (6.7) IV: 4 (0.6)	–
Adabag et al. (2008)	177	Prospective cohort study	Minneapolis, Minnesota, and Boston, Massachusetts	Arrhythmias	January 2003 to January 2007	I: 137 (77) II: 31 (18) III: 9 (5) IV: 0 (0)	–
Olivotto et al. (2010)	310	Prospective cohort study	Mass/Minnesota	Systolic dysfunction	2001 to 2008	1.3 ± 0.6 I: 221 (71%) II: 43 (14%) III: 46 (15%) IV: 0	–
Conte et al. (2011)	124	Prospective cohort study	Torino and Asti, Italy, and London, United Kingdom	Relationship of LGE with EF, NSVT, LAD	January 2005 to August 2009	I: 76 (61%) II: 45 (36%) III/IV: 3 (3%)	0 RF: 63 (51%) 1 RF: 42 (34%) 2 RF: 14 (11%) 3 RF: 4 (3%) 4 RF: 1 (0.8%)
Soler et al. (2006)	53	Cohort study	La Coruna, Spain	Left ventricular perfusion and contractile defects	–	–	0 RF: 18 (34%) 1 RF: 21 (40%) 2 RF: 9 (17%) 3 RF: 4 (7%) 4 RF: 1 (2%)
Maron et al. (2008)	202	Prospective cohort study	Massachusetts and Minnesota	Heart failure	April 2002 and November 2006; followed up for 681,249 days	1.5 ± 0.7 I: 123 (61) II: 54 (27) III/IV: 25 (12)	–
Hen et al. (2014)	345	Retrospective cohort study	Tokyo, Japan	Heart failure arrhythmias cardiovascular events	January 2006 and December 2010	III/IV: 42 (12.2)	–

Table 1. cont. Study characteristics.

Author (year)	No. of patients	Type of study	Location of study	Clinical outcomes	Duration of study	NYHA mean n (%)	RF for SCD mean n (%)
Suk et al. (2008)	25	Prospective cohort study	Auckland, New Zealand	–	January 2004 to December 2006	–	–
Bruder et al. (2010)	220	Prospective cohort study	Germany and Philadelphia, USA	All-cause and cardiac mortality	January 2003 and April 2008; follow-up time was 1,090 days	I: 135 (61.4) II: 68 (30.8) III: 17 (7.2)	0 RF: 167 (75.9) 1 RF: 43 (19.5) 2 RF: 7 (3.2) 3 RF: 3 (1.4) 4 RF: 0 (0)
Choudhury et al. (2000)	21	Prospective cohort study	Illinois, Chicago	LGE correlation with EF and ventricular thickness	July 2000 and February 2001	I: 15 II: 5 III: 1	–
Moon et al. (2003)	53	Prospective cohort study	London, United Kingdom	Ventricular dilation and markers of sudden death	–	I: 30 (57) II: 21 (40) III: 2 (3)	0 RF: 19 (35.8) 1 RF: 16 (30.2) 2 RF: 13 (24.5) 3 RF: 3 (5.7) 4 RF: 2 (3.8)
Kwon et al. (2009)	60	–	Cleveland, Ohio	Association between preoperative CMR findings and SICAD on histopathology and VT	–	III: 60 (100)	–
Leonardi et al. (2009)	110	Prospective cohort study	Italy	Ventricular arrhythmias and sudden death	December 2004 to April 2008	–	–

CMR — cardiac magnetic resonanse; HCM — hypertrophic cardiomyopathy; MWT — maximal wall thickness; LGE — late gadolinium enchancement; NYHA — New York Heart Association; SICAD — small intramural coronary arteriole dysplasia; SCD — sudden cardiac death; EF — ejection fraction; NSVT — non-sustained ventricular tachycardia; LAD — left axis deviation; RF — risk factors; VT — ventricular tachycardia

with other established predictors, the percentage of LGE significantly improved the prediction of SCD events. The results showed that increased LGE by 10% increases the risk of SCD events by 40% (HR: 1.46/10% increase in LGE, p = 0.002). The incidence of SCD per 1,000 person years was directly proportional to the percentage extent of LGE: 10 per 1,000 person years with LGE ≤ 10%, 18 per 1,000 person years with 11–19%, and 24 per 1,000 person years with ≥ 20% (p = 0.001 for trend [22]. Hen et al. [23] found a higher rate of cardiovascular events including SCD in the Japanese population with HCM who had LGE as compared to those without LGE (annual events rate, 6.2% per year vs. 0.6% per year, p = 0.003).

It is worthwhile to emphasize that the role of CMR extends even to those genotypically positive patients who have not yet developed the clinical signs or symptoms of disease. The presence of LGE in genotype(+)/phenotype(–) individuals can indicate structural abnormalities in non-hypertrophied muscle [24]. However, there is no established consensus regarding the definitive diagnostic and prognostic role of delayed enhancement for adverse disease outcomes like SCD and arrhythmias in such a setting.

Late gadolinium enhancement and arrhythmias

Myocardial fibrosis serves as an arrhythmogenic substrate for dangerous ventricular arrhythmias. The studies showing the relationship between LGE and arrhythmias are summarized in Tables 1–4. Adabag et al. [15] reported that patients with LGE had a 7-fold increased risk of non-sustained ventricular tachycardia as compared to those without it (relative risk: 7.3, 95% CI 2.6–20.4, p < 0.0001). Hen et al. [23] found a significantly higher percentage of arrhythmias in patients with LGE compared to patients without LGE in a Japanese cohort of HCM patients (annual events rate, 2.5% per year vs. 0% per year, p = 0.037). Suk et al. [25] demonstrated that the risk of ventricular arrhythmias could be indirectly predicted using LV mass. The size of myocardial scar and hence the risk of arrhythmias was found to be correlated with LV mass (r^2 = 0.74) and LV wall thickness (r^2 = = 0.42). A myocardial scar mass of more than 7 g on LGE predicted the risk of developing ventricular tachycardia with 75% sensitivity and 82% specificity. Kwon et al. [16] independently confirmed an increased frequency of arrhythmias using Holter monitoring. It was reported that a greater percentage of patients with LGE had documented arrhythmias compared to those without LGE (27% vs. 5%, p = 0.03). Leonardi et al. [26] devised a scoring system for quantitative assessment of LGE in HCM known as Delayed contrast enhancement score. Points were given to each segment based on the percentage of LGE (i.e. 0 — absence of LGE; 1 — < 25% LGE; 2 — 25–50% of LGE; and 3 — > 50% of LGE). The total score comprised of individual scores from all segments. Patients were divided into two main groups: group R (risk) with risk factors and group LR (low risk) without any risk factors for SCD. Group R was further divided into high-risk (HR) and intermediate risk (IR) subpopulations. The HR subgroup included patients with prior history of cardiac arrest or sustained ventricular tachycardia and the presence of at least two other risk factors, whereas the IR subgroup included patients with only one risk factor. In the analysis conducted by Leonardi et al. [26], using delayed contrast enhancement score, LGE was also the only independent predictor of ventricular arrhythmias (OR: 1.073, 1.023–1.125, p = 0.004) in the multivariable analysis.

Late gadolinium enhancement and systolic dysfunction

Systolic impairment in HCM results from replacement fibrosis, which occurs as a consequence of microvascular ischemia and myocyte death [27]. Sarcomere mutations cause metabolically inefficient contractions and myocyte energy depletion which can further contribute to systolic dysfunction by triggering apoptosis and collagen deposition [28, 29]. Therefore, the extent of LGE can predict the risk of systolic dysfunction. Various studies have analyzed the relationship between LGE and systolic dysfunction, and they are summarized in Tables 1–4.

The systolic dysfunction can occur at any point during HCM. Chan et al. [22] described the risk of development of systolic dysfunction in end-stage HCM patients. Every 10% increase in LGE resulted in a significant decrease in systolic function (HR: 1.80, 1.40–2.40, p < 0.03). In the prospective cohort study conducted by Ismail et al. [21] in HCM patients with LV dysfunction, there was evidence of fibrosis on CMR. Olivotto et al. [30] demonstrated that LGE predicts adverse LV remodeling in HCM patients and it is negatively correlated to EF. A subgroup of HCM patients (NYHA I or II) with EF 50–65% are in the transition phase towards advanced LV remodeling and

Table 2. Patient demographics.

Author (year)	Age (mean ± standard deviation) [years]	Male n (%)	Arrhythmias n (%)	Mortality during follow-up n (%)
Motoyasu et al. (2008)	57.7 ± 9.8	13 (76)	–	–
Chan et al. (2014)	46 ± 17	85 (63)	NSVT 204 (20) AF 159 (12)	HCM related SD 14 (1.0) Aborted arrest 6 (0.5) ICD discharge (VT/VF) 17 (1.3) HF death 6 (0.5) HT 9 (0.7) End-stage HCM 87 (7) NYHA class III/IV 99 (9) NCD 21 (1.6)
Ismail et al. (2014)	56.3 (median)	498 (70)	AF 22 (3.2) NSVT 38 (5.4)	–
Adabag et al. (2008)	41 ± 16	129 (73)	–	
Olivotto et al. (2010)	42 ± 17	218 (70)		–
Conte et al. (2011)	53 ± 17	86 (69)	NSVT 20/182, p = 0.001 AF 17/182, p = 0.19	–
Soler et al. (2006)	49.55 ± 14.24	33 (62)	–	–
Maron et al. (2008)	42 ± 17	144 (71)	–	–
Hen et al. (2014)	59 ± 17	214 (62)	AF 65 (18.8)	–
Suk et al. (2008)	54 ± 8	17 (68)	–	–
Bruder et al. (2010)	58	149 (61.4)	–	All-cause mortality 22 (10.0) Cardiac mortality 16 (7.2)
Choudhury et al. (2000)	39 (median age)	12 (57)	–	None
Moon et al. (2003)	47 ± 16 (range 15–73)	37 (70)	NSVT on Holter monitor 11 (21%) Documented sustained VT/VF 3 (6%)	
Kwon et al. (2009)	51 ± 14	37 (62)		
Leonardi et al. (2009)	42 ± 15	82 (76)		

AF — atrial fibrillation; HCM — hypertrophic cardiomyopathy; ICD — implantable cardioverter defibrillator; HF — heart failure; HT — heart transplantation; NCD — non cardiac death; NSVT — non-sustained ventricular tachycardia; NYHA — New York Heart Association; SD — sudden death; VT/VF— ventricular tachycardia/ventricular fibrillation

systolic failure. Therefore, regular clinical surveillance and prophylactic therapies have fundamental importance in the management of these patients. In another study by Conte et al. [31], patients were divided into three groups according to the number of segments positive for LGE (first group, 0.3 ± ± 0.4; second group, 2.2 ± 0.4; third group, 5.2 ± ± 1.9 segments). The percentage of patients with EF < 50% as assessed by CMR, in these groups was: group 1 (4%), group 2 (4%), group 3 (17%), p = = 0.02. Thus, it was suggested that patients who had a large extent of LGE on CMR had higher risk of systolic dysfunction. While analyzing the relationship between delayed enhancement and contractile functions in 53 HCM patients with CMR, Soler et al. [32] showed that significant correlations existed between delayed enhancement (DE) and hypokinetic segments ($r = 0.3$, $p < 0.05$). Maron et al. [33] demonstrated in a large cohort of HCM patients the association of LGE and presence of HF symptoms ($p = 0.05$) along with LV systolic dysfunction ($p = 0.001$). Hen et al. [23] stratified patients into three groups according to the LGE score (no LGE, 0; mild LGE, 1–3; marked LGE, > 4). LGE was converted to scores on a scale of 0 to 17, as the sum of the segments in the 17-segment

Table 3. Relationship of late gadolinium enhancement (LGE) with adverse clinical outcomes of hypertrophic cardiomyopathy (HCM).

Author (year)	% LGE in patients	% LGE in myocardium	LGE correlation with LV mass	Regions of LGE in heart	Association of %LGE and SCD	Association of %LGE with systolic function	Association of %LGE with arrhythmias	Perfusion defects
Motoyasu et al. (2008)	13/17 (76%)	97 of the 510 segments (19%)	r = 0.23, p = 0.3	AW 7, LW 3, PW 1, apex 1, other 1	–	r = –0.59, p < 0.05	–	–
Chan et al. (2014)	548 (42%)	9 ± 10% of the LV	–	Septum and LV free wall 89 (16), apex 187 (34), only at RV insertion into LV 134 (25)	HR adj., 1.46/10% increase in LGE; 95% CI 1.12–1.92; wald χ^2 = 9.6; p = 0.002	HR adj., 1.80/10% increase in LGE; p < 0.03	NSVT %LGE (per 10% increase) Univariate HR 1.50 (95% CI 1.22–1.85) Model global wald χ^2 13.894, p < 0.001, bivariate HR 1.46 (95% CI 1.17–1.82), p < 0.001	–
Ismail et al. (2014)	471 (66.2%)	6.3 (9.2%)	–	–	HR 1.24/5% increase in LGE, 95% CI 1.06–1.45; p = 0.007	–	–	–
Adabag et al. (2008)	72 (41%)	8.5 ± 8% (range 0.6–37.6%)	–	VS 6, LVFW 17, at the RV insertion in septum 10, or in a combination of these location (n = 39), SE in 5, MM in 8, EC in 6, or a combination of these (n = 53)	–	–	7-fold higher risk of NSVT (RR 7.3, 95% CI 2.6–20.4, p = 0.0001)	–
Olivotto et al. (2010)	157 (51%)	–	–	VS and LVFW 53 (34%) LVFW 31 (20%) Septum 38 (24%) RV insertion areas 27 (17%) LV apex 8 (5%)	–	LGE showing a strong, inverse relation to the EF (B –0.69, 95% CI –0.86 to –0.52; p < 0.001)	–	–
Conte et al. (2011)	77%	14.70%		IVS (%): 62 (50%) Apex (%): 23 (19%) IW (%): 22 (18%) ALW (%): 13 (11%)	–	EF < 50%, 11/182, p = 0.02		n = 27 (22%), p < 0.01

Table 3. cont. Relationship of late gadolinium enhancement (LGE) with adverse clinical outcomes of hypertrophic cardiomyopathy (HCM).

Author (year)	% LGE in patients	% LGE in myocardium	LGE correlation with LV mass	Regions of LGE in heart	Association of %LGE and SCD	Association of %LGE with systolic function	Association of %LGE with arrhythmias	Perfusion defects
Soler et al. (2006)	30 (56.6%)	79/901 segments (8.8%)	With and without LGE (218.3 ± 79 vs. 193.9 ± 73.2 g, respectively ($p > 0.05$)	Diffuse or confluent patchy mural foci (53.3%) subendocardial (16.6%), small foci (20%) and subepicardial (10%)	–	Correlations between DE and hypokinetic segments ($r = 0.3$, $p < 0.05$)		Correlations between DE and perfusion defects ($r = 0.5$, $p < 0.01$)
Maron et al. (2008)	111 (55%)	9 ± 11%	–	VS and LVFW 35 (32%) LVFW 29 (26%) Septum 27 (24%) The area of RV insertion into the VS 15 (13%) LV apex 5 (5%)	–	LGE was related to occurrence of HF symptoms ($p < 0.05$) and LV systolic dysfunction ($p < 0.001$)	–	–
Hen et al. (2014)	252	6.0 ± 4.1 3.1 ± 3.0	–	–	–	The HF rate in LGE and no LGE groups (4.6%/year vs. 1.0%/year vs. 0.6%/year, $p = 0.008$)	Arrhythmias with LGE and without LGE (annual events rate, 2.5%/year vs. 0%/year, $p = 0.037$)	–
Suk et al. (2008)	16 (64%)	–	Relationship between LV mass [g] and scar mass [g] showing a close correlation ($R2 = 0.74$, $p < 0.05$)	Basal anteroseptal segment (67%) RV insertion sites in 31%	–	–	Scar mass of > 7 g predicted the presence of VT with a sensitivity of 75% and specificity 82%	–
Bruder et al. (2010)	148 (67.2%)	1.3 (0.0–5.5)	–	–	OR of 5.47 for all-cause and OR 8.01 for cardiac mortality, compared with the presence of 1 or 2 clinical risk factors ($p = 0.038$, HR 8.6), respectively	–	–	–

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Table 3. cont. Relationship of late gadolinium enhancement (LGE) with adverse clinical outcomes of hypertrophic cardiomyopathy (HCM).

Author (year)	% LGE in patients	% LGE in myocardium	LGE correlation with LV mass	Regions of LGE in heart	Association of %LGE and SCD	Association of %LGE with systolic function	Association of %LGE with arrhythmias	Perfusion defects
Choudhury et al. (2000)	17/21	8 ± 9% of the LV and 839 out of 4,912 segments (17%)	LGE correlated positively with wall thickness (r = 0.36, p < 0.0001) and the LV mass (r = 0.33, p = 0.15)	–	–	Correlated inversely with EF (r = –0.46, p < 0.04)	LGE correlation with the corrected QT-interval (r = 0.47, p < 0.03)	–
Moon et al. (2003)	42 (79%)	10.9 ± 11%	r = 0.24, p = 0.04	Transseptal 4 (7%) RV septal 4 (7%) Ventricular junction 12 (23%) Multi-focal 9 (17%) Subendocardial 2 (4%) Other 11 (21%)	–	r = –0.64, p < 0.001	–	–
Kwon et al. (2009)	38 (63%)	10.2 ± 11.4%	Correlation between basal IVS thickness and LGE (r = 0.30, p = 0.02)	–	–	–	DHE-MRI had evidence of VT on Holter monitoring (27% vs. 5%, p =0.03)	–
Leonardi et al. (2009)	92/110	–	–	–	Multivariable analysis DCE score, OR = 1.018, 95% CI = 1.003–1.034, p = 0.019	–	Multivariable analysis DCE score, OR = 1.073, 95% CI 1.023–1.125, p = 0.004	–

AW — anterior wall; ALW — anterolateral wall; CI — confidence interval; DCE — delayed contrast enhanced; DE — dalayed enhancement; DHE-MRI — delayed contrast enhanced-magnetic resonance imaging; EC — epicardial; EF — ejection fraction; HF — heart failure; HR — hazard ratio; IW — inferior wall; IVS — interventricular septum; LGE — late gadolinium enhancement; LW — lateral wall; LV — left ventricle; LVFW — LV free wall; MM — midmyocardial; NSVT — non-sustained ventricular tachycardia; OR — odds ratio; PW — posterior wall; RR — relative risk; RV — right ventricular; SE — subendocardial; VS — ventricular septum; VT — ventricular tachycardia

Table 4. Left ventricular characteristics in hypertrophic cardiomyopathy patients using late gadolinium enhancement — cardiac magnetic resonance.

Author (year)	LV mass [g]	LV mass index [g/m^2]	LVEF [%]	LV thickness [mm]	LVEDV	LVESV	Percentage with preserved EF > 50%	Pattern of hypertrophy n of segments (%)	LVOT gradient ≥ 30 mm Hg n (%)
Motoyasu et al. (2008)	128.1 ± 57.2	–	61.2 ± 12.8	19.2 ± 3.8	130.7 ± 25.1 mL	56.3 ± 28.4 mL	14/17 (81%)	ASH: 11 (64.7%) AH: 6 (35.2%)	–
Chan et al. (2014)	163 ± 71	83 ± 34	67 ± 9	20 ± 5	–	–	1,235 patients	–	302 (23%),
Ismail et al. (2014)	–	101.9 ± 37.0	74.6 ± 9.0	19.4 ± 5.1	69.1 ± 15.7 mL/m^2	18.2 ± 9.6 mL /m^2	699 (98.3%)	–	208 (29.3%)
Adabag et al. (2008)	–	–	–	21 ± 5	–	–	–	–	40 (23%)
Olivotto et al. (2010)	203 ± 85	103 ± 38	71 ± 10	21 ± 6	161 ± 45 mL 83–18 mL/m^2	47 ± 24 mL 24–12 mL/m^2	295	–	61 (20%)
Conte et al. (2011)	–	100 ± 43	59 ± 7.9	21 ± 6	79 ± 20 mL/m^2	31 ± 9 mL/m^2	113	–	45 (36%)
Soler et al. (2006)	207.5 ± 76.7		74.5 ± 7.8	17.1 ± 5.4	96.2 ± 24.8 mL	24.3 ± 9.4 mL	–	–	–
Maron et al. (2008)	211 ± 80	107 ± 34	–	225	–	–	192	–	–
Hen et al. (2014)		78.3 in LGE(+) patients, 59.8 in LGE(–) patients	66.7	19.6	68.1 ± 18.6	30.8 ± 18.5	–	–	–
Suk et al. (2008)	182 ± 82	–	73 ± 8	–	154 ± 38	43 ± 19	–	Septal: 18 (72%) Apical: 4 (16%) Concentric: 3 (12%) VT: 8 (32%)	–
Bruder et al. (2010)	156 (127–196)	84 (68–97)	71 (65–77)	19 (16–23)	–	–	–	Septal: 185 (84.1%) Apical: 18 (8.2%) Concentric: 17 (7.7%)	69 (31.4%)
Choudhury et al. (2000)	238 ± 88	–	70 ± 11	25 ± 8	–	–	–	ASH: 18 (90%) Apical: 1 (5%) Concentric: 2 (5%)	8 (38%)
Moon et al. (2003)	–	–	–	–	–	–	–	–	9 (17%)
Kwon et al. (2009)	–	–	64 ± 5%	–	–	–	100%	–	60 (100%)
Leonardi et al. (2009)	–	82 g/m^2	62.1 ± 8.8	–	83.6 ± 21.5 mL/m^2	–	–	–	–

AH — apical hypertrophy; ASH — asymmetrical septal hypertrophy; EF — ejection fraction; LGE — late gadolinium enhancement; LV — left ventricular; LVEF — left ventricular ejection fraction; LVESV — left ventricular end systolic volume; LVEDV — left ventricular end diastolic volume; LVOT — left ventricular outflow tract obstruction; VT — ventricular tachycardia

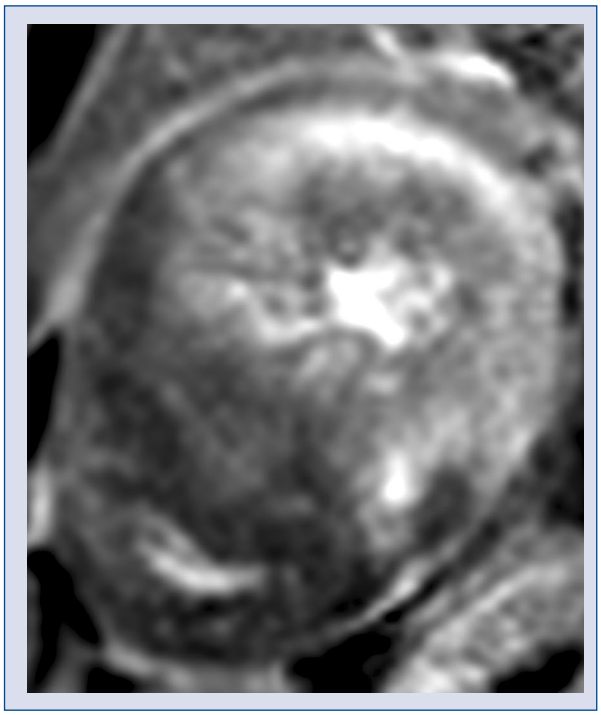

Figure 4. Short axis view on cardiac magnetic resonance with late gadolinium enhancement demonstrating diffuse enhancement of the left ventricular myocardium.

model showing LGE. The HF rate was higher in marked LGE vs. mild LGE groups (4.6% per year vs. 1.0% per year vs. 0.6% per year, $p = 0.008$). According to Choudhury et al. [20], the extent of LGE modestly correlates with EF ($r = –0.64$, $p < 0.001$).

Late gadolinium enhancement and diastolic dysfunction

It is well established that diastolic dysfunction precedes systolic dysfunction in the course of HCM. Motoyasu et al. [34] showed that strong negative correlation exists between LGE and diastolic dysfunction evidenced by decreased peak filling rate ($r = –0.86$, $p < 0.01$).

The role of T1 mapping for detection of diffuse myocardial fibrosis in HCM

Endomyocardial biopsy, the gold standard for myocardial fibrosis, is an invasive procedure associated with morbidity, sampling error and sampling limitations [35]. Therefore, myocardial fibrosis is preferably determined using LGE. Although LGE remains an excellent tool for detecting focal myocardial fibrosis, detection of diffuse fibrosis (Fig. 4) remains challenging since the normal myocardium is used as a reference to highlight patchy areas of focal myocardial fibrosis [36]. Extracellular volume (ECV) quantification by T1 mapping with CMR has overcome this limitation of LGE for detecting diffuse fibrosis in HCM. ECV measures T1 relaxation time, which is based on the molecular environment of water molecules. Every tissue has its characteristic T1 relaxation time, but depending on the pathophysiological state, it can vary within the same tissue. ECV can be measured with and without contrast and has shown promising results for the detection of myocardial fibrosis. Myocardial T1 measurement without the use of gadolinium contrast agents is known as native T1, which shows cellular and extracellular portions of the myocardium. T1 measurement at a point of time after giving a bolus of contrast is known as post contrast T1 and can reveal myocardial properties mostly at the cellular level [37]. Post-contrast T1 values are shorter than pre-contrast or native T1 images due to a small amount of gadolinium contrast being left in the myocardial interstitium during slow renal washout. Renal clearance of gadolinium, hematocrit, contrast dosage and time measurements are potential confounding variables for post contrast T1 [38]. T1 mapping is done systematically in which pixel intensity is directly proportional to T1 relaxation time of the corresponding myocardial voxel. This leads to signal quantification of each myocardial voxel on a standardized scale with high resolution. ECV measurements also hold strong histological validation and closely correlate with collagen volume fraction [39]. ECV quantification by T1 mapping has significant prognostic implications. Wong et al. [40] have demonstrated an association between myocardial extracellular expansion and adverse clinical outcomes using ECV. T1 mapping techniques have another advantage of detecting diffuse fibrosis at early stages of the disease. Compared to LGE images, T1 mapping CMR techniques allow us to eliminate the influences of windowing and variations in signal enhancement by directly measuring the underlying T1 relaxation times. Therefore, it allows signal quantification (in ms) on a standardized scale of each myocardial voxel to characterize myocardial tissue.

Conclusions

Echocardiography is currently the most widely used imaging modality in HCM. Although echocardiography is an excellent non-invasive modality, there are shortcomings in the comprehensive

evaluation and risk stratification of HCM patients if utilized exclusively. SCD is the most feared outcome of HCM. Myocardial fibrosis in HCM can initiate malignant cardiac arrhythmias and SCD even in the absence of conventional risk factors. The extent of LGE on CMR is emerging as a potential risk factor for SCD in HCM patients. CMR has the additional capability of quantifying myocardial fibrosis using novel techniques such as T1 mapping. CMR has incremental value and is complementary to echocardiography in the comprehensive evaluation of patients with HCM.

Conflict of interest: None declared

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