The Heart Surgery Forum 2021-3977
24 (4), 2021 [Epub August 2021]
doi: 10.1532/hsf.3977

Online address: http://journal.hsforum.com

Right Ventricle Involvement in Hypertrophic Cardiomyopathy and Role of Cardiac Magnetic Resonance in Hypertrophic Cardiomyopathy: Review Article

Weihao Ding,[1] Sandeep Bhushan, PhD,[2] Chen Ma,[1] Yifan Yan,[1] Xiao Zongwei [3]

[1]Zunyi Medical University, Zunyi, Guizhou, China; [2]Department of Cardiothoracic Surgery, Chengdu Second People's Hospital, Chengdu, Sichuan, China; [3]Department of Cardiothoracic Surgery, Zunyi Medical University, Chengdu Second People's Hospital, Chengdu, Sichuan, China

ABSTRACT

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disease, and its main characteristic is symmetrical or asymmetrical hypertrophy of the left ventricle and/or right ventricle. Most previous studies mainly include the left ventricle for definition of HCM, thus neglecting the right ventricle. But recently, many studies have reported the right ventricular involvement in HCM. Histopathological results showed that similar pathogenic changes in both the right and left ventricles, which suggests common myopathic processes and sarcomere genetic mutations.

Cardiovascular magnetic resonance (CMR) is a gold standard imaging modality to assess heart anatomy and function and provides highly accurate and reproducible measurements. CMR is very useful in characterizing the various phenotypes of right and left ventricles in HCM. CMR also can be useful in detecting early and dominant phenotypic expression of HCM. Due to the complex geometry of the right ventricle and its retrosternal position, echocardiography may not provide accurate measurements. CMR also provides more accurate and repeatable right ventricular measurements. Thus, right ventricle evaluation along with left ventricle should routinely be done for better assessment of HCM patients.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common hereditary heart disease, and it is characterized by symmetrical or asymmetrical hypertrophy of the left ventricle and/or right ventricle, mainly associated with sarcomere gene mutations. Its estimated prevalence is approximately 1:500 (0.2%) in the general population [Kawashiri 2014]. HCM has now been recognized as a global disease with reported cases on all continents affecting both sexes and people of all races and origins [Elliott 2004]. HCM inheritance is a Mendelian autosomal dominant trait, and this is caused by a mutation in one of 13 or more genes that encode cardiac sarcomere protein and more than 600 genetic mutations have been identified [Maron 2002]. HCM has varied clinical presentation, but has similar genotypic abnormalities. Most of the HCM patients remain asymptomatic with a normal life expectancy, but some have severe complications and worse prognosis. The symptoms of HCM are dyspnea on exertion, chest pain, syncope and pre-syncope; these symptoms are the result of various degree of left ventricular outflow tract (LVOT) obstruction, left ventricular diastolic dysfunction, left ventricular systolic dysfunction, and various cardiac arrhythmias [Maron 2004]. There are many complications of HCM, such as heart failure, sudden cardiac death (SCD), various arrhythmias, and left ventricular outflow tract (LVOT) obstruction. In some asymptomatic or less symptomatic young HCM patients, SCD may be the first feature [Alcalai 2008]. Most of the clinical evaluations regarding HCM have mainly focused on left ventricular function and have ignored the right ventricular function. But recently, due to the emergence of anatomical proximity, a clear functional relationship has been shown between the right and left ventricles and the genetic basis of the disease has shown the involvement of the whole myocardium. Thus, it indicates that right ventricular functional impairment also may accompany HCM disease [Ashrafian 2007]. At present, echocardiography is the most commonly and widely used imaging technique for evaluation of heart function. However, accurate assessment of right ventricular function parameters using conventional echocardiographic techniques is difficult because of complex geometry of the right ventricle [Rowin 2016].

Among all kinds of heart diseases with right ventricular involvement, cardiac magnetic resonance (CMR) imaging has been recognized as the gold standard for evaluating the structure and function of the right ventricle, due to its high spatial and temporal resolution [Marian 2001]. CMR even can identify hypertrophic areas that echocardiography cannot display well and provide more accurate wall thickness measurements, thus helping to distinguish HCM from various other left ventricular hypertrophy etiology. CMR also is useful to characterize the many different phenotypes of HCM. CMR with late-gadolinium enhancement (LGE) is very helpful in detecting areas of myocardial fibrosis.

Definitions of right ventricular involvement: The involvement of the right ventricle in HCM is related to structural and functional changes associated with hypertrophic ventricle. At present, there is no standard diagnostic criterion

Received May 15, 2021; accepted June 16, 2021.

Correspondence: Zongwei Xiao, Department of Cardiothoracic Surgery, Zunyi Medical University, Chengdu Second People's Hospital, Chengdu, Sichuan 600017, China, Telephone +86-18908178146 (e-mail: zongweixiao@163.com).

for right ventricular hypertrophy and right ventricular dysfunction. A study by Foale et al. regarding the echocardiographic evaluation of the right ventricle defined normal thickness of right ventricle wall as ≤7 mm [Foale 1986]. A study by McKenna et al. classified right ventricular hypertrophy as (a) mild: 6-8 mm thickness of right ventricle wall, (b) moderate: 9-12 mm thickness of right ventricle wall, and (c) severe: >12 mm thickness of right ventricle wall. Maron et al. defined right ventricular hypertrophy as right ventricle wall thickness (anterior, free, or apical wall) during end-diastole as ≥5 mm, and severe right ventricular hypertrophy if ≥ 10 mm. Right ventricular systolic dysfunction (RVSD) is defined as CMR measured right ventricular ejection fraction (RVEF) ≤ 45%, based on a guideline proposed by the modified Task Force Criteria.

Prevalence of right ventricle involvement: There is a great variance in the prevalence of right ventricle involvement in HCM, as reported by various studies. The prevalence of right ventricular hypertrophy is in 30% of HCM patients, based on various studies by cardiac magnetic resonance, whereas echocardiography studies have reported prevalence of right ventricular hypertrophy to be 44% of HCM patients [Dhillon 2011]. The prevalence of severe right ventricular hypertrophy is very rare (1.3%).

Structural changes of the right ventricle in HCM: Various patterns of ventricular and septal wall thickening have been observed in HCM, such as concentric to diffuse hypertrophy of mid septum, basal septum, apex, and/or the right ventricle wall. Right ventricular hypertrophy can occur in isolated form and as well as in combination with left ventricular hypertrophy [Gersh 2011]. Maron MS et al. reported a strong correlation between maximum thickness of the right and left ventricle walls and between right and left ventricular mass. Hypertrophied crista supraventricularis is a common finding in right ventricular hypertrophy and the thickness of right ventricular wall is associated to the cross-sectional area crista supraventricularis.

The causes of right ventricle structural remodeling in HCM are due to systolic intraventricular gradient, and occurrence of RV systolic obstruction has been reported 15% to 92% by catheterization studies [Elliott 2004]. There may be outflow tract obstruction, mid-base obstruction and apical obstruction in the right ventricle. Right ventricular outflow tract (RVOT) obstruction has been defined as resting outflow tract pressure gradient > 25 mmHg or > 16 mmHg [Shimizu 2003]. Most of RVOT obstruction commonly is because of the consequence of LVOT obstruction, but there also are few isolated right ventricular obstruction cases.

The pathophysiology of right ventricle remodeling in HCM still remains unclear. In pulmonary hypertension, causes of right ventricle hypertrophy are a primary myopathic process rather than a secondary to left ventricle dysfunction [Weissler-Snir 2017]. There is a close relationship between right and left ventricular remodeling, which can suggest myopathic process in HCM can affect both ventricles.

Histopathologic findings suggest that the myocardial disarray and fibrosis that occurs in HCM is identical in both the left and right ventricle [Redington 2002]. Thus, we can say that there is a similar pathogenesis of structural changes in both the right and left ventricles in HCM [Harris 2006]. By CMR imaging, fibrosis and scarring has been observed in the right ventricle wall, which supports the histopathological findings and explains the right ventricle functional impairment in HCM [Prinz 2012].

RVH and RV dysfunction in HCM is related to sarcomere gene mutations. In a study of severe right ventricular hypertrophy, TTN, MYH7, and MYBPC3 genes genetic mutations commonly were reported [Maron 2002].

Functional changes of right ventricle in HCM:

1. Systolic dysfunction of the right ventricle in HCM: The RV systolic and diastolic dysfunction also can occur in HCM beside LV dysfunction. There are many echocardiographic indices for evaluation of right ventricular systolic function, such as ejection fraction, TAPSE, fractional area change (FAC), and tissue Doppler. These echocardiographic right ventricular systolic function indices are usually within normal limits and fail to show subclinical right ventricular dysfunction. Longitudinal strain can identify right ventricular longitudinal dysfunction and global systolic strain is an important index to measure systolic function of the right ventricle. Eighty percent of the total stroke volume of right ventricle is due to longitudinal shortening [Zemanek 2010]. Right ventricular ejection fraction is caused by longitudinal shortening and compression of the free wall of the right ventricle against the interventricular septum. Right ventricular remodeling in HCM at the early stage involves reduced longitudinal function and consequently increases in transverse function as a result of shortening of circumferential fibers. Thus, right ventricular longitudinal strain can be helpful in identifying initial dysfunction of the right ventricle in HCM.
2. Diastolic dysfunction of the right ventricle in HCM: Right ventricular diastolic dysfunction also can occur in HCM, as a result of fibrosis of the right ventricle wall [Kuehne 2004]. CMR-LGE can detect ventricular fibrosis. Efthimiadis et al. showed that compared with controls, HCM patients had significantly lower right ventricular E/A ratio and prolonged right ventricular deceleration time (DT) and isovolumetric relaxation time (IVRT). Right ventricular diastolic dysfunction can lead to elevated right ventricular end-diastolic pressure, which further leads to venous congestion and heart failure [Greupner 2012]. Some studies have reported that there is increased morbidity and mortality with the presence of right ventricular dysfunction.

CMR and HCM diagnosis: HCM is diagnosed on the presence of LVH, which is not explained by any other cardiac or systemic disease [Guo 2010]. Thus, clinical diagnosis of HCM primarily is based on accurate and non-invasive assessment of the LV wall thickness [Lang 2006]. Although echocardiography has been used as a primary imaging method to assess HCM patients, there are some drawbacks, such as poor acoustic windows, incomplete visualization of the LV wall, and inaccurate measurements of LV mass. CMR enables more accurate evaluation of wall thickness and the disease distribution better than echocardiography. CMR can more accurately

evaluate LV wall thickness, which is important in evaluating myocardium >30 mm thick and is one of the important prognostic indicators of HCM [Galea 2013]. CMR enables more accurate evaluation of LV mass, LV volumes, and LV function than echocardiography and also evaluation for areas of regional wall motion abnormalities (RWMA), aneurysms, and focal areas of LGE [Kukulski 2000]. CMR also can identify individuals at-risk with a family history of HCM and be used for screening purposes.

Morphologic variants of HCM identified by CMR – Asymmetric HCM with sigmoid septal contour: Among different HCM morphologic types, asymmetric morphologic form is the most common one, and it accounts for about 2/3rd of the HCM [Foale 1986]. The hypertrophy of anterior septum of myocardium results in sigmoidal shape of the interventricular septum [McKenna 1988]. The sigmoidal septum type of HCM results in SAM of the mitral valve and causes mitral leaflet to septal contact and subaortic LVOT obstruction. LVOT obstruction occurs in about 20–30% of the HCM cases [Guo 2017]. Peak instantaneous LVOT gradients can be estimated by phase-contrast CMR. Peak LVOT gradient of ≥30 mmHg is considered an important factor for pathophysiology and prognosis of HCM.

Asymmetric HCM with reversed septal contour: In this type of HCM, the hypertrophy of interventricular septum presents a reverse S-shaped curve that doesn't cause LVOT obstruction [Mittal 2010]. Asymmetric HCM is diagnosed on the basis of short-axis images of CMR, which is characterized by the ratio of interventricular septum to left ventricular free wall thickness > 1.3.

HCM with mid-ventricular obstruction: In this type of HCM, there is prominent hypertrophy of the mid-ventricle along with narrowing of the mid-cavity, which gives a 'dumbbell' shape of the left ventricle [Frank 1968]. Severe narrowing of the left ventricle may lead to apical dilatation and in 10% of cases, there is apical aneurysm and late gadolinium enhancement (LGE), which may be result of ischemia due to reduced capillary density, arterial media hyperplasia, myocardial bridging, and increased perivascular fibrosis [Shimizu 2003].

Apical HCM: In apical type of HCM, the left ventricular cavity at the apex is obliterated, and the cavity has a characteristic spade-like shape on vertical long axis views [Maron 2002]. The diagnosis of apical HCM is based on thickness of the apical wall greater than 15 mm or a ratio of apical wall to basal left ventricular wall thicknesses ≥ 1.3, and CMR accurately can help in diagnosing apical HCM [Nagata 2015].

Symmetric (concentric) HCM: In this variant, there is symmetrical hypertrophy of the ventricular wall with no regional preferences, and the left ventricular cavity is reduced in a concentric fashion [Frank 1968]. It accounts for up to 40% cases of HCM. Symmetric LVH may also be present in various other conditions, such as longstanding hypertension, aortic stenosis, amyloidosis, and athlete's heart. Athletes have mild to moderate cardiac hypertrophy and normal to enlarged LV chamber size. However, in HCM, the LV chamber size usually is smaller, and there may be diastolic dysfunction and LGE, whereas diastolic dysfunction and LGE are not visible in the athlete's heart.

Focal HCM: Sometimes, HCM may present with focal, mass-like hypertrophy of the LV, and CMR may help to distinguish it from other causes of cardiac mass by using special CMR tagging technique.

Left ventricular mass: CMR is considered the most precise and reproducible imaging method for quantification of overall left ventricular mass. Contrast-enhanced SSFP (Steady State Free Precession) cine CMR has unrestricted field of view and the interface between blood vessels and myocardium is very much improved, thus it makes CMR the reference standard imaging method for left ventricular wall thickness measurement and measurements usually taken from the LV short axis plane at diastolic end phase [McKenna 1988]. Variability in distribution of LVH and LV mass derived from CMR can more accurately evaluate the overall degree of LVH in HCM patients. If the left ventricle mass identified by CMR is greater, there is less chance of favorable clinical outcome, which may be related to LVOT obstruction and advance heart failure. The normal ranges for left ventricular mass index for male are 62.5 ± 9 g/m2 and for female is 54.6 ± 12 g/m2. Thus, LV mass may be an important marker for adverse risk prediction and can be helpful in risk stratification of HCM [Kukulski 2000].

Left ventricular apical aneurysms: Some patients with HCM have thin-walled apical aneurysms accompanied by mid-ventricular hypertrophy, which is an important subset of HCM. These HCM patients previously were under diagnosed before the use of CMR to HCM [Galea 2013]. The reason is that echocardiography may not reliably detect apical aneurysms, which are small- to moderate-sized and similarly, apical hypertrophy also can be missed [Lang 2006]. Contrast-enhanced CMR has shown that apical aneurysms mainly consist of fibrosis and LGE that usually extends from the aneurysm to the interventricular septum and free wall near to these areas, and it causes ventricular tachyarrhythmia [Greupner 2012].

Diastolic dysfunction: Usually, most of the HCM patients have diastolic dysfunction, which may be due to myocardial stiffness and delayed relaxation [Kuehne 2004]. Diastolic dysfunction may be caused by increased ventricular muscle mass, abnormal function of cardiac act in and myosin filament in the early diastolic stage, in the early stage of the disease [Maron 2002]. So, diastolic dysfunction may be an important functional marker of HCM at an early stage. CMR can precisely and accurately help to assess diastolic dysfunction in HCM.

There are different CMR methods for assessing diastolic dysfunction [Sandeep 2019]. The ventricular time-volume curve assesses overall diastolic function. In the hypertrophied portion of the left ventricle, there is reduced early diastolic filling velocity, and the rate of LV relaxation is decreased [Bhushan 2020]. Mitral valve flow velocity and pulmonary artery flow velocity are derived from phase contrast CMR (PC-CMR), and it allows calculation of flow velocity and pressure gradient and provides highly accurate and repeatable values [Kuehne 2004]. Myocardial motion velocity also can be assessed by using PC-CMR. CMR also can assess diastolic function directly using myocardial tissue tagging, which can show decreased diastolic relaxation rate and decreased

early diastolic filling velocity [Shimizu 2003]. The reduction of E/A ratio indicates mild diastolic dysfunction, and there is pseudo normalization as the dysfunction progresses, and finally, E/A ratio is increased and is in the restrictive phase of diastolic dysfunction [Bhushan 2020].

Right ventricular involvement in HCM: CMR has shown increased maximal thickness of the right ventricle wall (>8 mm) in about 20% of patients with HCM [Sandeep 2019]. The thickness of the right ventricular wall in HCM commonly occurs around the junction of the anterior or posterior septal insertion of the right ventricular wall, and rarely there may be involvement of the entire right ventricle. The right ventricular wall thickness is most commonly observed around the junction of the insertion of the right ventricular wall into anterior or posterior interventricular septum, although entire right ventricle involvement can occur [Shimizu 2003]. CMR images of HCM patients showed that right ventricular hypertrophy had a greater risk of cardiovascular events compared with non-right ventricular hypertrophy. CMR also can identify crista supraventricularis, which is commonly located adjacent to the ventricular septum on the basal short-axis images. The CMR of these patients can accurately show the location and extent of hypertrophy, which is helpful to surgeons with planning for operation of RVOT obstruction [Bhushan 2020].

Papillary muscles: In some HCM patients, there are abnormalities in papillary muscle morphology, such as an increase in the number of papillary muscles (half of them have 3 or 4 papillary muscles), hypertrophy of the papillary muscles (more than half of them have two-fold increased papillary muscle mass) [Sandeep 2019]. In a subgroup of HCM with normal left ventricular mass, there may be an increased localized wall thickness that may be due to hypertrophied papillary muscles (20% of patients), thus, it indicates papillary muscles may be a part of the cardiomyopathic process in HCM [Galea 2013].

Assessment and quantification of myocardial fibrosis: Myocardial fibrosis or scarring can cause impaired diastolic and systolic function of the heart and is associated with adverse cardiovascular events, such as sudden death, NSVT, and systolic dysfunction. LGE-CMR detected myocardial fibrosis in 33-86% of HCM patients [Redington 2002]. LGE-CMR is not a specific finding for HCM, but diffuse LGE mainly localized within the ventricular septum is highly suggestive of HCM [Harris 2006].

One important feature of LGE in HCM is that the right ventricular anterior and posterior insertion points of crossing fibers of the left ventricle and the right ventricle tend to be enhanced. The interventricular septum most frequently involved in LGE is the anterior septum from the middle to basal segments, which is the most common thickening part in asymmetric HCM [Harris 2006].

Role of CMR in early detection of pre-clinical HCM: Pre-clinical HCM patients don't have left ventricular hypertrophy, but they have gene mutation for HCM. SCD might be the only first symptom in an HCM patient, so early detection of HCM mutation carriers is important. CMR can precisely evaluate both anatomic and functional features of HCM, thus, it has an important role in pre-clinical HCM assessment. By CMR assessment in asymptomatic HCM carriers with normal left ventricle wall thickness, Germans et al. showed left ventricle crypts, which was best seen at end of diastole. Diastolic dysfunction has been reported in pre-clinical HCM.

Role of CMR in treatment and prognosis of HCM: In HCM patients, those with LVOT gradient ≥50 mmHg during rest or with provocation and at the same time have advanced heart failure refractory to medical treatment invasive septal reduction therapy (ASA or surgical septal myectomy) can relieve obstruction and improve severe symptoms [Elliott 2004].

Surgical septal myectomy: Surgical septal myectomy is the main treatment to relieve LVOT obstruction in HCM [Gersh 2011]. CMR is helpful in preoperative planning of surgical myectomy as it helps to find morphologic abnormalities associated with LVOT morphology, also mitral valve and submitral apparatus [Dhillon 2011]. In addition, CMR can help to identify other abnormal morphology of the mitral valve and papillary muscles, which also contribute to the pathophysiology responsible for LVOT gradients.

Alcohol septal ablation: Alcohol septal ablation is an important alternative invasive septal reduction treatment method. It involves alcohol that is injected into a septal perforator artery that supplies the basal septum at the SAM-septal contact point and ultimately, this creates a myocardial infarction leading to septal thinning, thus widening the LVOT area and decreasing LVOT gradient [Marian 2001]. CMR can help to accurately assess the tissue necrosis done by ASA, the relationship between the scar location and outflow tract morphology and also help to assess regression of LV mass after the ASA procedure [McKenna 1988]. Therefore, preoperative CMR is helpful to accurately measure the extent of ventricular septal hypertrophy and the relationship between the ventricular septum and sub-valvular apparatus, papillary muscle morphology, and anterior mitral valve leaflet.

Current guidelines indicate that transthoracic echocardiography (TEE) measured left ventricular thickness >30 mm is an important prognostic criterion, and CMR provides more accurate and reproducible measurements of left ventricular thickness and total left ventricular mass.

CONCLUSIONS

Contrast-enhanced CMR is an important imaging tool that is suitable for the characterization of HCM phenotypes. CMR is helpful in the diagnosis of HCM because it can identify hypertrophic areas that cannot be well shown by echocardiography; it provides more accurate measurements of both the right and left ventricle and helps to distinguish other causes of ventricular hypertrophy. Contrast enhanced CMR with LGE has shown that patients with extensive LGE, with involvement of more than 15% of the left ventricular myocardium, are at an increased risk of sudden death. These patients may benefit from primary ICD therapy. These multiple roles of CMR can justify the routine application in clinical evaluation of patients with HCM.

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