

Spotlight on management of hypertrophic cardiomyopathy

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Submitted: 4 September 2014

Accepted: 23 September 2014

Published online: 14 November 2014

Abstract Hypertrophic cardiomyopathy (HCM) is the commonest inherited cardio-myopathy. Prevalence 1/500 individuals. The disease has variable expressivity and penetrance, which leads to a diverse phenotypical expression. The aim of this review paper is to shed light on management of HCM.

Keywords Cardiac magnetic resonance imaging • Left ventricular outflow tract obstruction • Hypertrophic cardiomyopathy • Left ventricular hypertrophy • Sudden cardiac death

Imprint Mohammed El-Assaly. Spotlight on management of hypertrophic cardiomyopathy; *Cardiometry*; No.5; November 2014; p.78-88; doi:10.12710/cardiometry.2014.5.7888 Available from: www.cardiometry.net/no5-november-2014/hypertrophic-cardiomyopathy

Introduction

Dr. Robert Donald Teare, a pathologist at St George's hospital in London, described HCM more than fifty years ago. Sudden cardiac death (SCD) may be the first presentation hence the need to identify potential inheritants who may benefit from SCD preventive strategy. Incidence of sudden cardiac death is 2% to 4% per year in adults [1]. The emergence of cardiovascular magnetic resonance imaging (CMR) as an imaging modality aids diagnosis and prognostication.

A cardiomyopathy is:

“A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular dis-ease and congenital heart disease sufficient to cause the observed myocardial ab-normality.” [2]

The heart muscle hypertrophy is the cause of the disease and not a sequela of an-other cardiac (like aortic stenosis) or extra-cardiac pathology (for example acro-megaly).

Genetics:

It is typically autosomal dominant. Autosomal recessive, X-linked, and mito-chondria patterns of inheritance also occur. About 50-60% of patients with a high index of clinical suspicion for HCM will have a mutation identified in at least 1 of 9

sarcomeric genes. In HCM there is no sex or race predilection. New molecular & genetic techniques allow identifying patients & family members with HCM. It can also identify genotypically positive phenotypically negative patients (carrier of the gene without clinical manifestation yet).

Diagnosis:

High index of suspicion is mandatory although may lead to false positive diagnosis of HCM. Causes of false positive diagnosis of HCM are:

Conditions simulating LVH/ASH:

1. Sigmoid septum of elderly.
2. Oblique sections of ventricular walls (off axis views).
3. Left ventricular false tendons.

LVH due to:

1. Infiltrative cardiomyopathy.
2. Anderson-Fabry disease (Skin manifestations may be a clue and enzymatic assays confirms deficiency of alpha-galactosidase).
3. Hypertension with LVH and inferior myocardial infarction.

LVOT gradient is present due to LVH or haemodialysis.

HCM may present with symptoms of Exertional syncope, pre-syncope, palpitations or dyspnea in absence of another disease which could account for the symptom. More fortunate individuals from the diagnosis point of view are those asymptomatic detected during screening.

Hypertrophic obstructive cardiomyopathy (HOCM) may cause Pulsus bisferiens (double peak pulse) due to dynamic left ventricular outflow tract obstruction (LVOTO). Aortic stenosis or subvalvular aortic membrane (fixed LVOTO) gives low pulse volume, Pulsus parvus et tardus.

A systolic murmur in left parasternal edge increases with valsalva. In contrast to other causes of LVOTO the systolic murmur is decreased with valsalva due to decreased preload.

LVOTO is caused by septal hypertrophy, SAM and anterior displacement of mitral valve apparatus.

ECG showing LVH usually triggers imaging modality like trans-thoracic echocardiography (TTE) for the first instance. Cardiac imaging demonstrates asymmetrical septal hypertrophy (ASH), systolic anterior motion of mitral valve (SAM), left ventricular cavity obliteration and/or blood flow acceleration. Up to 42% of HCM cases show symmetrical (concentric) hypertrophy with no regional wall preference.

Risk

Stratification:

The aim is to identify individuals in whom pre-emptive implantation of AICD is warranted to prevent SCD due to VF/VT.

Major risk factors for SCD are:

- Left ventricular hypertrophy (LVH) ≥ 30 mm or more.
- Previous cardiac arrest.
- Fall of systolic blood pressure on symptom limited ETT.
- First degree relative with SCD.
- Unexplained syncope or pre-syncope (non vasovagal).
- Non-sustained ventricular tachycardia (NSVT) on ECG monitoring.

NSVT:

Is defined as 3 or more consecutive beats arising below the atrio-ventricular node with a rate >120 beats/min and lasting less than 30 seconds.

NSVT can be precipitated by vasodilatation, dynamic LVOTO, myocardial ischemia driven by epicardial coronary artery stenosis and/or small vessel disease.

The stimulus may be atrial and/or ventricular non malignant arrhythmia. VT is maintained via reentry. Programmed electrical stimulation rarely induces VT hence EP is of benefit in ablating atrio-ventricular accessory pathway if present.

LVH ≥ 30 mm:

Any myocardial segment can be involved. LVH of HCM is 15 mm or more usually involving inter-ventricular septum or ratio of septum to lateral wall 1.3 or more. A septal to posterior wall thickness ratio >1.5 can point towards diagnosis of HCM in hypertensive patients.

However Maron et al. [3] stated that virtually any LV wall thickness can be consistent with the presence of an HCM-causing mutant gene.

CMR usually quantifies LV mass accurately.

Abnormal blood pressure response to exercise (ABPR):

ABPR is failure of blood pressure to rise, or a fall in blood pressure during exercise. Patient should not be on any cardio-active medications for 5 pharmacokinetic half lives. The mechanism of ABPR in patients with HCM is still debated. Counihan et al. and Frenneaux et al. [4] reported that excessive fall in systemic vascular resistance during exercise occurs due to a peripheral vasodilatory mechanism. Yoshida N, Ikeda H, Wada T, et al [5] suggested sub-endocardial ischemia in patients with HCM causes decline in LV systolic function and ABPR.

ABPR can be detected in 25% of HCM patients and thus its positive predictive accuracy for sudden death is low. It is a more sensitive indicator of SCD risk in younger patients (< 40 year old).

Family history of first degree relative with SCD (FHSCD):

SCD is defined as unexpected natural death from a cardiac cause within a short time period, generally <1 hour from the onset of symptoms, in a person without any prior condition that would appear fatal.

FHSCD is fulfilled as a major risk factor if:

1. First degree relative <50 years of age died suddenly whether or not had the diagnosis of HCM and/or:
2. First degree relative with diagnosis of HCM died suddenly at any age.

The diagnosis of HCM may be suggested by postmortem examination. Causes of unexplained syncope and pre-syncope are as follows: a broad differential diagnosis should be considered including vasovagal syncope, atrial tachyarrhythmias with rapid ventricular response with or without accessory pathway, VT, bradyarrhythmia and atrio-ventricular nodal block. LVOTO, orthostatic hypotension or carotid sinus hypersensitivity may cause syncope or presyncope.

The utilization of ambulatory ECG monitoring and ambulatory blood pressure (ABP) recording may reveal diagnosis and guide subsequent therapy. PPM can be used for treatment of bradyarrhythmias. Radiofrequency (RF) ablation used to ablate accessory pathway. AICD is indicated if NSVT is revealed. If syncope or pre-syncope cannot be explained it is best regarded as a major risk factor for SCD and AICD is warranted.

Previous cardiac arrest:

History taking may be rewarding if there is family history of diagnoses of HCM. The first presenter in any family poses the greatest challenge. Once diagnosed the rest of first degree relatives will be under medical surveillance.

Factors associated with increased risk of SCD in HCM are as listed below:

- Young age;
- Left ventricular outflow tract obstruction;
- Atrial fibrillation;
- Myocardial ischemia;
- Genetic mutations.

CMR in cardiomyopathy:

Whether ischemic cardiomyopathy (ICMP) or non-ischemic cardiomyopathy (NICMP), CMR provides an imaging modality which is quite unique: no ionizing radiation is available, it is non-invasive, independent of patient habitus and significant operator variability.

In CMR the contrast agent used is gadolinium. Caution is advised if estimated glomerular filtration rate (eGFR) is less than 30 due to increasing incidence of nephrogenic systemic fibrosis. Limitations include claustrophobia, which may be managed by prone positioning of patient. The presence of non-MRI compatible cardiac device or metal clips remains a hurdle. CMR scan usually takes 40 to 60 minutes according to protocol. When clinical suspicion of HCM is present HCM protocol is utilized.

CMR in HCM [6, 7]:

Resting cardiac functions:

Breath-holding cine steady state free precision (SSFP) imaging is the gold standard for accurate non-operator depended quantification of cardiac volumes, mass and biventricular systolic function.

Mostly the presence of LVH is the cornerstone of consideration of the diagnosis of HCM. In end stage HCM LV exhibits dilatation, LVH may be absent.

LVH may be asymmetrical commonly affecting inter-ventricular septum (ASH). Sometimes concentric hypertrophy is noted but out of proportion to loading conditions. LVH > 15 mm even in presence of afterload increasing disease argues strongly for diagnosis of HCM. Systolic anterior motion of mitral (SAM) valve apparatus participates in left ventricular out flow tract obstruction (LVO-TO).

CMR can quantify accurately LV mass and localize hypertrophied segments.

Maximal LV thickness ≥ 30 mm is a major risk factor for SCD. LV maximal hypertrophy may be under appreciated by transthoracic echocardiography (TTE). The increase of LV mass points towards progression of HCM. A reduction of LV mass and LV dilatation in an established diagnosis of HCM could mean end stage HCM.

Right ventricular hypertrophy (RVH) and apical HCM can be readily identified by CMR yet pose an imaging challenge to trans-thoracic echocardiography.

A hyper-contractile LV is usually present. Accurate quantification of LV ejection fraction is needed for follow up of HCM patients. Cavity obliteration and flow acceleration are readily demonstrated by CMR. LVOT gradients, whether dynamic or resting, are accurately quantified by echocardiography. Resting cardiac functions evaluating end diastolic (EDV) and end systolic (ESV) volumes are used to monitor progression of HCM. Abnormality of mitral valve apparatus and SAM is easily demonstrated by CMR along with mitral regurgitation for which TTE is validated for quantification.

In up to 42 % of HCM cases concentric LVH is present, which should be more meticulously differentiated from other causes of concentric LVH.

Apical HCM:

It is more common in Japan. Apical wall thickness of > 15 mm gives imaging feature of HCM. A ratio of apical LVH to basal LVH ≥ 1.3 –1.5 is another imaging clue. The characteristic spade like configuration of the left ventricular cavity initially described in angiographic studies is well appreciated on left ventricular vertical long-axis views on MRI. Right ventricular apical ventricular hypertrophy is well demonstrated by CMR paving the way to picking right ventricular involvement in HCM. RVH may lead to RVOTO and RV diastolic dysfunction.

Non-contrast tissue characterization

T2-weighted sequence, Short-Tau Inversion Recovery (STIR):

It is a sensitive sequence to detect myocardial edema. Although myocardial edema was first noticed on STIR for ICM it has been extended to NICP as well. As it suppresses the signal from flowing blood and fat it enhances sensitivity to tissue fluid. There is growing interest in myocardial edema which acts as a substrate to facilitate re-entry mechanism that sustains arrhythmias in HCM.

T1 mapping in HCM a histopathological sample of the myocardium:

T1 mapping without contrast shows myocardial cells versus extracellular volume (ECV). ECV is the space in the myocardium not occupied by myocytes. In non-ischemic myocardial insult T1 mapping is superior to LGE in quantifying extra-cellular matrix expansion (ECM). ECV can detect subtle myocardial fibrosis not necessary detected by LGE. Hence CMR evidence of subclinical HCM may be demonstrated by T1 mapping enabling initiation of management.

Contrast tissue characterization:

Mid wall T2 late gadolinium enhancement of LV myocardium points to myocardial fibrosis. Disarray of myocyte and fibrosis leads to delayed wash out of Gadolinium and hyper-enhancement. In HCM commonest site of LGE is in the ven-tricular septum and LV free wall. A less frequent pattern of LGE is restricted to the LV free wall or septum only. A less common pattern is LGE at RV insertion into the ventricular septum. Lastly LGE confined to the LV apex. It is uncommon to find LGE without LVH in HCM, although this is usually the case in pre-clinical HCM. Anecdotal data correlating extent of LGE and severity of LVEF reduction exist. Extent of LGE is associated with cardiac mortality.

In HCM late gadolinium enhancement of LV myocardium is not subendo-cardial nor transmural. LGE is not restricted to a coronary artery territory. In HCM LGE is typically mid-wall and mid-segment enhancement. Sub-endocardial LGE is present if myocardial infarction occurs due to coexisting epicardial coronary artery stenosis leading to myocardial infarction. Thromboembolic led epi-cardial coronary occlusion usually causes myocardial infarction in apical LV segments. Increasing amount of LGE in comparison to previous CMR is an indicator of progression of HCM. Progression of LGE is not yet validated as a major risk factor for SCD.

Stress perfusion study:

Adenosine is used to induce hyperaemia which demonstrates hypo-perfusion in myocardial segments. In HCM hypo-perfusion may co-localize to segments of maximal hypertrophy. Stress induced perfusion may be due to epicardial to endocardial gradients because of micro vascular dysfunction. Rest perfusion defect is due to micro-vascular disruption as a result of myofibril disarray and fibrosis. Mixed defects may exist.

Pharmacological therapy:

Diastolic and possibly systolic dysfunction is present in HCM. Beta blockers (BB) can increase diastolic time and allow LV more time for filling. If BB do not provide full symptomatic improvement in way of dyspnea non-dihydropyridine calcium channel blockers (CCB) such as verapamil can be added. Amiodarone can be used as a sinus rhythm maintain drug after AF cardioversion. Pharmacological antiarrhythmic are not a replacement for AICD when indicated.

Careful use of diuretics may also relieve symptoms of pulmonary venous congestion. Judicial use of diuretics is needed to avoid decreasing preload and increasing LVOT gradient.

Aspirin can be used for thromboprophylaxis in patients not known to have atrial fibrillation/flutter. Warfarin is needed if AF is diagnosed regardless of type of AF, (paroxysmal, persistent, longstanding persistent or permanent). Patients with HCM tolerate tachyarrhythmias poorly due to reduced diastolic time. Chemical or DC cardioversion is needed for atrial fibrillation/flutter.

The major risk factors for SCD are used to decide which patient need AICD to guard against VT/VF induced SCD [8]. During AICD implantation a challenge in testing for VF threshold may arise. VF threshold may be increased by amiodarone and BB.

Single chamber ICD is usually preferred especially in young patients. Patients should be well informed about possibility of inappropriate shocks (around 25%), restriction on driving and occupational implications. Anti tachycardia pacing is usually effective in terminating VT. Device therapy is not without complications among which cardiac device related infective endocarditis and device malfunction (inappropriate shocks, failure of sensing or capturing, pacemaker mediated tachycardia).

Disopyramide is a class IA anti arrhythmic with sodium channel blocking effect and a weak calcium channel blocking activity. It can be used to reduce symptoms of LVOTO [9]. Disopyramide may be used to maintain sinus rhythm after cardioversion of A.fibrillation/Aflutter. Pollick and coworkers reported a decrease in LVEDP in response to intravenous disopyramide in their patients with HOCM. In 10 patients with HCM (6 with HOCM), Fifer et al reported intravenous disopyramide caused a universal increase in LVEDP. τ (the relaxation time constant), an index for the active diastolic LV properties, was unchanged. Mastubara and coworkers demonstrated LVEDP lowering effect of disopyramide along with shortened τ in patients with LVOT obstruction but raised LVEDP and lengthened τ in patients without LVOT obstruction.

Interventional measures to reduce LVOTO:

In absence of LVOT obstruction, LV systolic pressure = systolic arterial blood pressure.

In HCM LVOT gradient may be resting or on provocation. It can vary from beat to beat and with respiration.

LVOT obstruction is defined as a resting LVOT gradient of ≥ 30 mmHg. Severe obstruction is defined as ≥ 50 mmHg [10].

Septal reduction commonly performed for severely symptomatic patients in spite of optimal medical therapy with severe obstruction ≥ 30 mmHg at rest or ≥ 50 mmHg with provocation.

Alcohol septal ablation (ASA) [11-13]

Criteria for selection:

Symptoms of LVOTO that interfere with lifestyle despite optimal medical therapy; (2) Septal thickness ≥ 15 -16 mm; (3) LVOT gradient ≥ 30 mm Hg at rest or ≥ 50 mm Hg on provocation; (4) accessible septal branch(es); and (5) absence of intrinsic abnormality of the mitral valve and of proximal left anterior descending coronary artery stenosis or severe coronary artery disease.

Complications include CHB requiring PPM. Large volume of alcohol injection, female sex and age >55 y are associated with CHB. Among the criteria, found is presence of LBBB on pre-intervention ECG as a strong predictor of development of post ASA CHB.

Surgical myomectomy [14-16]:

may be misrepresented as a high risk treatment modality if compared to ASA. In North American centers 0 % post-operative mortality was reported for >1500 consecutive isolated myomectomy operations.

Meta-analysis of three retrospective studies demonstrated that surgical myomectomy and ASA showed comparable results on septal hypertrophy and NYHA class improvement.

Dual chamber pacing [17]:

Backed by subjective symptom improvement reported by the patients. It is argued against by lack of consistent objective reduction of LVOT gradient suggesting symptom improvement may be a placebo effect. Cardiac catheterization laboratory studies showed that a decrease in the outflow gradient produced by temporary A-V sequential pacing could be detrimental to ventricular filling and cardiac output.

Advantage of dual chamber pacing was demonstrated in patients receiving dual chamber ICD permitting more aggressive pharmacological intervention without fear of bradyarrhythmia. To obtain best results dual chamber pacing should be carried out in centers highly experienced in both pacemaker therapy and HCM.

Life style modification:

Competitive sports should be discouraged, patients should be educated to report change in severity of shortness of breath or the appearance of red flags like symptoms of pre-syncope or syncope.

Psychological aspect of HCM:

1,297 patients with HCM over period of 16 months reported emotionally triggered:

- Chest pain (60%).
- Syncope/lightheadedness 50%.
- Dyspnea 54%.

Females reported emotion-triggered symptoms more than males (50% vs 35% in males, $P < 0.001$).

As with any chronic disease, especially if life threatening, anxiety and de-pression should not be overlooked.

Infective endocarditis:

Is largely confined to those patients with LV outflow tract obstruction (resting or provoked), with intrinsic mitral valve disease or cardiac device related. The AHA recommendation 212 for antibiotic prophylaxis should be applied at the time of dental or selected surgical procedures.

Family screening:

Family screening for HCM poses a challenge. The customary strategy utilizes 12 lead ECG and TEE on a 12- to 18-month basis, usually beginning at age of 12 years. If no LVH is demonstrated at the age of about 18 to 21 years reassurance that HCM is likely to be absent.

Nevertheless being a disease of variable expressivity and penetrance late on-set HCM can be missed. Extending diagnostic serial transthoracic echocardiogram into mid-life for those family members with a normal echocardiogram and ECG may be advised.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The author read the ICMJE criteria for authorship and approved the final manuscript.

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