Hypertrophic cardiomyopathy

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Hypertrophic Cardiomyopathy

GRADUATE THESIS

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Summary

Title: Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is a disease of a thickened, but not dilated, left ventricle, that is not attributable to loading conditions. With a prevalence of around 1 in 500, HCM is the most common inherited condition of the cardiovascular system. In the majority of cases the disease is caused by one or more mutations of genes encoding for proteins of myocytic sarcomeres. These mutations are mostly inherited autosomal-dominantly, but can also arise *de novo.* Inherited metabolic diseases, neuromuscular disorders, amyloidoses, and adverse drug reactions are further possible etiologies of HCM. The pathophysiology of the disease is based on abnormalities of the myocytes, the interstitium and the microvasculature. Due to arrhythmias and hemodynamic abnormalities, which are shaped mainly by diastolic dysfunction and left ventricular outflow tract (LVOT) obstruction, patients develop the clinical manifestation of syncope, heart failure, as well as chest pain. Of special note is the occurrence of sudden cardiac death (SCD), which is often the first and only manifestation of the disease. In fact, HCM is the most common cause of SCD in the young. The diagnosis of HCM starts with the patient's history, physical examination, and electrocardiogram (ECG) but it is mainly confirmed by echocardiographic findings. Further diagnostic modalities, which help in differentiating HCM from physiologic ventricular hypertrophy, fixed aortic stenosis, and other conditions, are cardiovascular magnetic resonance imaging (CMR), nuclear imaging, and genetic testing. As there is no cure of the underlying cause of the disease, the management focuses on the control of symptoms, improvement of the patients' functional status, and prevention of SCD. Patients with HCM are advised to avoid competitive sports and intense physical exercise. Beta-blockers and calcium-channel blockers are the mainstay of medical management of heart failure symptoms, and chest pain. If the symptoms cannot be controlled adequately by medication, ventricular septal myectomy and alcohol septal ablation are two possible invasive procedures, which improve the functional status of the patient by relieving the outflow tract obstruction. Dual-chamber pacing using a short-programmed atrial ventricular delay is another modality for treatment of heart failure symptoms. The occurrence of a SCD can be prevented by implantation of an implantable cardioverter defibrillator (ICD).

Keywords: • Hypertrophic Cardiomyopathy • Genetic disease • Sudden Cardiac Death • Heart Failure • Alcohol Septal Ablation

Sažetak

Naslov: Hipertrofična kardiomiopatija

Autor: Luka Utrobičić

Hipertrofična kardiomiopatija (HCM) je bolest zadebljane, ali ne i proširene lijeve klijetke koja se ne može pripisati uvjetima njenog povećanog opterećenja. Sa učestalošću od oko 1:500, HCM je najčešća nasljedna bolest kardiovaskularnog sustava. U većini slučajeva bolest je uzrokovana mutacijom jednog ili više gena koji kodiraju proteine sarkomera kardiomiocita. Ove mutacije uglavnom se nasljeđuju autosomno-dominantno, ali mogu nastati i *de-novo*. Nasljeđene metaboličke bolesti, neuromuskularni poremećaji, amiloidoza i nuspojave nekih lijekova su rijeđi uzroci HCM-a. Patofiziologija bolesti se temelji na abnormalnostima kardiomiocita, intersticija i mikrocirculacije. Ritmološka nestabilnost, i poremećaj hemodinamike, koji je posljedica dijastoličke disfuncije miokarda i/ili opstrukcije izgonskog trakta lijeve klijetke (LVOT), uzrokuju kliničku sliku sinkope, zatajivanja srca i bolova u prsima. Posebno treba istaknuti iznenadnu srčanu smrt (SCD) kao posljedicu HCM-a. SCD je često prva i jedina manifestacija ove bolesti. Zapravo, HCM je najčešći uzrok SCD kod mladih. Dijagnoza HCM započinje anamnezom bolesnika, fizikalnim pregledim i elektrokardiogramom (EKG), a potvrđuje se uglavnom ehokardiografijom. Daljnji dijagnostički modaliteti koji pomažu u razlikovanju HCM-a od fiziološke hipertrofije ventrikula, fiksne aortne stenoze i drugih uzroka su magnetska rezonanca srca (CMR), nuklearno snimanje i genetičko testiranje. Kako se bolest u pravilu ne može etiološki lječiti, liječenje se fokusira na kontrolu simptoma, poboljšanje funkcionalnog stanja pacijenata i prevenciju SCD-a. Pacijentima s HCM-om preporučuje se izbjegavati natjecateljske sportove i intenzivnu fizičku aktivnost. Beta blokatori i blokatori kalcijevih kanala osnova su konzervativnog liječenja simptoma zatajenja srca i boli u prsima. Ako se simptomi ne mogu adekvatno nadzirati lijekovima, ventrikularna septalna miektomija i alkoholna septalna ablacija dva su invazivna postupka koja mogu poboljšati funkcionalni status pacijenta umanjujući opstrukciju LVOT-a. Dvokomorska elektrostimulacija s programiranjem kratkog atrioventrikulskog kašnjenja je mogući način liječenja bolesnika s opstrukcijom LVOT koji nisu reagirali na medikamentno liječenje, a nisu kandidati za ostale invazivne postupke. SCD se može spriječiti ugradnjom implantabilnog kardioverter defibrilatora (ICD).

Ključne riječi: • Hipertrofična kardiomiopatija • Genetska bolest • Iznenadna srčana smrt • Zatajenje srca • Alkohol septalna ablacija

1. Introduction

Hypertrophic cardiomyopathy (HCM) is a disease of a thickened, but not dilated, left ventricle, that is not attributable to loading conditions.

It was first described in 1958 by Teare in his article *Assymmetrical hypertrophy of the heart in young adults* (1), and has ever since been subject to a lot of research, also driven by the sometimes dramatic presentation of an unexpected death of a young person or athlete. Nowadays we know that hypertrophic cardiomyopathy is the most common genetic cardiovascular disease, as well as the most common cause of sudden cardiac death (SCD) in the young. (2, 3) Also in regards to therapy of the disease a lot of progress has been made. The mortality rate has decreased from six percent 40 years ago to 0.5% per year, and HCM is now no longer a death sentence, but a disease which is compatible with a normal longevity, if diagnosed and treated adequately. (4)

Despite the improved understanding and knowledge of the genetics, clinical course, diagnostics, and management of the disease, there is still a controversy about the exact definition: The European Society of Cardiology (ESC) defines cardiomyopathies according to morphological and functional criteria, and then groups them according to genicity, independently of the presence of an extra-cardiac disease. Thus, the ESC defined HCM in their 2014 guidelines on diagnosis and management of hypertrophic cardiomyopathy as follows:

> „Hypertrophic cardiomyopathy (HCM) is defined by the presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions.“ (5)

On the contrary, the most recent guideline from the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) task force on diagnosis and treatment of hypertrophic cardiomyopathy from 2011 still defines HCM as

> “[…] a disease state characterized by unexplained LV hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient […]” (6)

According to this definition, conditions which cause the same morphologic and clinical picture, such as metabolic or infiltrative disorders, are only “mimicking” HCM caused by sarcomeric protein mutations and thus should not be termed HCM. (6)

2. Epidemiology

The prevalence of hypertrophic cardiomyopathy has for the past 20 years been estimated to be around 1 in 500, making it the most common inherited cardiac disease. (2) This estimate mainly stems from the Coronary Artery Risk Development in (Young) Adults (CARDIA) study, which was the first study to research the prevalence of HCM in a large group of subjects. The CARDIA study demostrated echocardiographic evidence of HCM in seven out of 4111 participants (0.17%). (2) This number has been supported by a variety of studies of chinese, tanzanian, japanese, and american Indian populations, showing prevalences of 0.16%, 0.19%, 0.17%, and 0.23%, respectively. All of these results were based on echocardiographic findings. (7–10) However, in 2015 Semsarian et al. suggested that the minimal prevalence of gene carriers for HCM should be considered to be 1 in 200 or higher. (11) This estimation is based on a genetic analysis published in 2012, which demonstrated disease-causing sarcomere gene variants in 0.6% of the 3600 screened participants. (12)

The prevalence of the disease among different ethnicities is similar. Similarly an equal gender distribution is expected, however many studies showed a slightly higher prevalence in the male subjects. (7–10, 13) This might be due to a difference in the expression of sex hormone receptors. (14) Another possible explanation lies in the higher prevalence of hypertension in males, which leads to more frequent echocardiographic examinations and thus a higher rate of diagnosis. (13)

3. Etiology

HCM is widely regarded to be a genetic disease of sarcomeric proteins, but the European Society of Cardiology defines HCM according to its morphology and thus also includes other etiologies. (5) Therefore, the etiology can be divided into gene mutations and other genetic and non-genetic causes.

3.1 Sarcomeric protein gene mutations

Hypertrophic cardiomyopathy is largely a genetic disease, with up to 60% of cases being due to inherited mutations of sarcomeric protein genes. (15–17) The inheritance follows an autosomal dominant pattern, giving the offspring of the affected a 50% probability of inheriting the mutation. (18) Additionally, *de novo* gene mutations leading to sporadic cases of HCM have also been observed. (19) The HCM-causing mutations show a variable expressivity and an incomplete penetrance, which appears to be age-related. (20) Mutations in at least 14 different genes, all of which encode proteins present in the thick or thin sarcomeric

myofilaments, as well as in the Z-disk, can be the cause of HCM. (18) More than 1,400 different mutations affecting these genes have been identified, out of which around 90% are due to an amino acid substitutions, leading to missense mutations. (6) There are also nucleotide insertions or deletions, leading to a frameshift type of mutation, which seem to lead to more severe clinical consequences. (18)

Out of the eleven possible genes, whose mutation have been identified as HCM-causing, the most frequently affected ones are MYH7, which encodes the beta-myosin heavy chains, and MYBPC3, encoding myosin-binding protein C. Each of these two genes is affected in approximately 25 to 40% of patients with identified mutations. TNNT2 and TNNI3, encoding Cardiac Troponin T and I, respectively, as well as the regulatory myosin light chain-encoding gene MYL2 are the next most frequent genes, each of them with a prevalence between 1 and 5% (Figure 1). (18, 21) In around 50 to 60% of patients with HCM a sarcomeric protein gene mutation can be identified. (22)

Frequency distribution of gene mutations

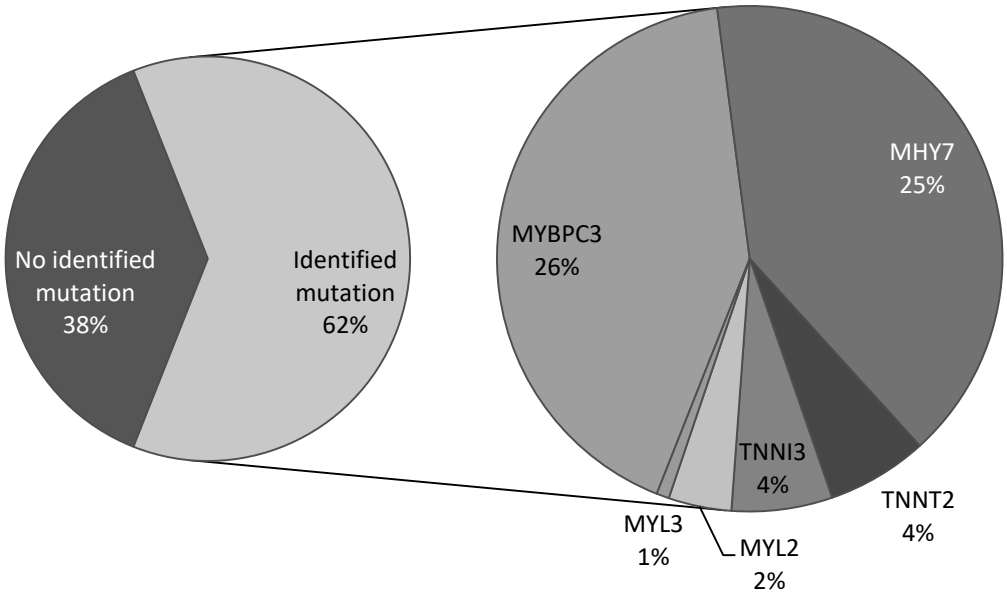

Figure 1. Frequency distribution of gene mutations. Data from Richard et al.: Hypertrophic cardiomyopathy: Distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. (21)

Up to 5% of the affected have more than one gene mutation, and these patients tend to have a more severe clinical phenotype, consisting of a more significant left ventricular hypertrophy, as well as higher risks for developing heart failure and sudden cardiac death, compared to those with only one identified mutation. (23) There have been many attempts to correlate specific mutations, or mutations of specific genes, with a disease phenotype and a

consistent clinical outcome, but there appear to be a number of modulating factors which influence the development of the disease and thus hinder the development of a reliable prognosis. (24) Besides epigenetic changes, one of the causes of this discrepancy between genotype and phenotype of HCM seems to be a variation in the genotype of the renin-angiotensin-aldosterone system (RAAS) with its components angiotensin-converting enzyme, angiotensinogen, and aldosterone. (25) Only mutations of the cardiac troponin T-encoding TNNT2 gene have been shown to produce a consistent phenotype: these gene mutations cause only a mild or undetectable hypertrophy, but are nevertheless associated with a poor prognosis, due to a high incidence of sudden cardiac death. (26)

3.2 Other genetic and non-genetic causes

Apart from gene mutations of sarcomeric proteins, hypertrophic cardiomyopathy can also be a consequence of other genetic diseases, for instance certain inherited metabolic diseases. Anderson-Fabry disease, an X-linked lysosomal storage disease characterized by the deficiency of the enzyme alpha-galactosidase A (a-GAL A) and subsequent accumulation of sphingolipids, is the most common metabolic disease in adults with HCM, with mutations of a-GAL A being present in up to 2% of HCM-patients. (27, 28) Danon disease, which is caused by a mutation of the lysosome associated membrane protein 2 (LAMP2) gene, is another inherited metabolic disease associated with hypertrophic cardiomyopathy, with this mutation being present in approximately 1% of the investigated population with HCM. (29) Furthermore a mutation of the PRKAG2 gene encoding the γ-subunit of the adenosine monophosphate-activated protein kinase, and leading to pathologic glycogen accumulation, was found in 1% of a patient group with HCM. (30, 31)

Additionally, hypertrophic cardiomyopathy can be a manifestation of neuromuscular diseases. One example of this is the autosomal recessive disorder Friedreich's Ataxia. The vast majority of patients with this condition develop cardiac manifestations, usually in the form of left ventricular hypertrophy, characterized by muscle fiber hypertrophy and interstitial fibrosis. (32) In fact, cardiac complications are the most common cause of death in patients with Friedreich's ataxia. (33)

Noonan syndrome is the most common genetic cause of infantile hypertrophic cardiomyopathy, with HCM being a manifestation in around 10% of patients affected by Noonan syndrome. (34)

Apart from the previously mentioned genetic causes, hypertrophic cardiomyopathy can also be a manifestation of non-genetic, systemic diseases such as the cardiac amyloidoses. This group of diseases is characterized by extracellular deposition of amyloid fibrils. Light chain amyloid (AL), which is derived from immunoglobulin light chains, is the most common type of amyloidosis. It is usually systemic in distribution, and affects the heart in around 50% of the cases. (35) If the heart is involved in patients with systemic AL amyloidosis, this involvement represents the worst prognostic indicator for patients with this condition. (36) In only around 4% of patients suffering from AL amyloidosis, the fibril deposition is isolated to the heart. (36) Hereditary amyloidosis is another type of systemic amyloidosis. It is caused by an autosomal dominantly inherited mutation and subsequent deposition of the transthyretin protein (TTR) in the myocardium. TTR is also the cause of systemic senile amyloidosis, however in this disease the protein is not mutated, but it is deposited in its wildtype structure. It affects predominantly men and up to 25% of the population older than 80 years. (37) Secondary, or AA amyloidosis, is characterized by systemic depositions composed of fibrils derived from the acute phase proteins serum amyloid A, and develops in response to chronic inflammation caused by auto-immune disorders, such as rheumatic diseases. (38) While secondary amyloidosis shows similar electrocardiographic and echocardiographic findings like the AL type, the cardiac infiltrations do not appear to be clinically significant. (39) In general the cardiac amyloidoses cause heart disease by myocardial infiltration of the fibrils, which leads to infiltrative/restrictive cardiomyopathy and subsequent left and/or right ventricular hypertrophy. (35)

Some medications have also been identified as causes of HCM. The immunosuppressive agent tacrolimus has been shown to cause congestive heart failure in combination with hypertrophic obstructive cardiomyopathy in pediatric transplant patients. This seems to be dose-related and related to increased calcium release from the sarcoplasmic reticulum, inducing myocardial hypertrophy. (40) Hydroxychloroquine is another medication which has been associated with ventricular hypertrophy and subsequent development of heart failure. (41)

4. Pathology

The underlying pathology in hypertrophic cardiomyopathy is a disarray of myocytes. The individual cardiac myocytes are hypertrophied and distorted, which leads to a loss of the parallel alignment of the cells, and instead formation of a disorganized pattern. This chaotic pattern is present in the hypertrophied, as well as in the nonhypertrophied parts of the

ventricular wall. Myocardial hypertrophy is a consequence of the changes in the architecture of the individual myocytes, their hypertrophy, as well as of the expansion of the extracellular matrix, which is caused by interstitial and replacement fibrosis due to focal ischemia. In addition to the myocytes and the interstitium, the coronary vessels are also affected by histopathological changes: The intramural arterioles exhibit a narrowed lumen due to hyperplasia of the smooth muscle of the media. (42)

Increased thickness of the left ventricular wall is the main morphologic finding of HCM. The pattern of hypertrophy is often asymmetric, and also variable between different patients, even in the inherited form. It usually develops during adolescence and ends up affecting the septal as well as the free wall of the left ventricle (LV), however it can also be present in the apical or midventricular region of the LV, or even in the right ventricle. (42) Furthermore the left atrium is dilated. (42)

5. Pathophysiology

The hypertrophy of the myocardium and subsequent increase in muscle mass causes the wall/lumen ratio of the myocardium to increase and thus leads to a mismatch of oxygen and nutrient supply and demand (Figure 2). This effect is further aggravated by the microvascular changes in the intramural arterioles, which exhibit an impaired vasodilation. The combination of these two factors predisposes for myocardial ischemia, which further leads to replacement fibrosis and scarring, as well as angina chest pain under exertion. (20,42)

One of the main pathophysiologic components in HCM is the obstruction of the left ventricular outflow tract (LVOT). The hypertrophy is usually asymmetric and mostly pronounced at the anterior septum and neighboring anterior free wall. (43) However there can also be hypertrophy of the apex or a mid-cavity obstruction. (44) The hypertrophy causes the septum to bulge beneath the aortic valve and narrow the outflow tract of the ventricle. Another, possibly even greater contributor to the left ventricular outflow tract obstruction (LVOTO) is the prolapse of the anterior leaflet of the mitral valve into the LVOT. This systolic anterior motion (SAM) of the leaflet is caused by high-velocity blood flow due to the narrowing of the outflow tract, against the mitral valve apparatus according to the Venturi effect. It is precipitated by morphological abnormalities of either the valve, such as elongated leaflets, or the papillary muscle, such as hypertrophy or direct anomalous insertion of the muscle directly into the anterior mitral leaflet. (45) The SAM of the anterior leaflet also prevents complete coaptation of the mitral valve and consequently leads to mitral regurgitation (MR). The LVOTO leads to an elevated systolic pressure in the ventricle, which

in turn leads to a prolonged ventricular relaxation and thus also an increased end-diastolic pressure. Together with the MR this contributes to a decrease in cardiac output. (46)

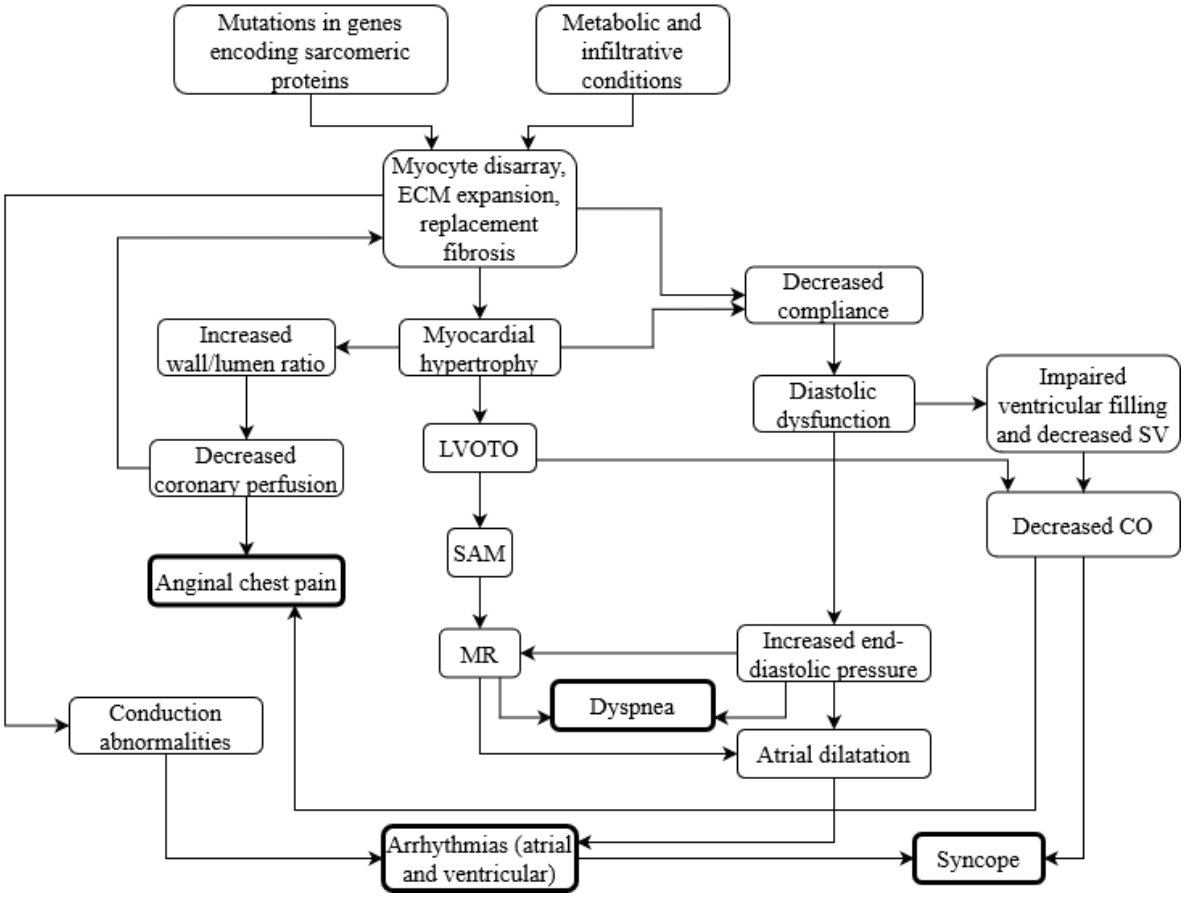

Figure 2. Pathophysiology of Hypertrophic cardiomyopathy. ECM Extracellular matrix, LVOTO left ventricular outflow tract obstruction, SAM systolic anterior motion of leaflet, MR mitral regurgitation, SV stroke volume, CO cardiac output

Diastolic dysfunction is an important component in the pathophysiology of HCM. This is caused by the hypertrophy and scarring (due to ischemia) of the myocardium, extracellular fibrosis, and disorganization of myocytic arrangement, all of which lead to impaired relaxation, increased stiffness, and reduced compliance of the ventricle. (20) With exertion and acceleration of the heart rate, the diastolic filling time decreases. This leads to development of an increased pulmonary capillary wedge pressure, and precipitation of dyspnea, i.e. symptoms of heart failure. (46) The diastolic dysfunction leads to an increased requirement of atrial contraction in order to fill the ventricle, which in turn causes a dilation of the atrium and predisposes for atrial fibrillation. (47)

The combination of a disarray of myocytes, interstitial fibrosis and myocardial scarring also leads to a disordered conduction pattern in the ventricles and thus predispose for the occurrence of ventricular tachyarrhythmias. (20)

6. Clinical presentation

HCM can manifest at any age, or patients can remain asymptomatic for their whole life. (48) Around 50% of patients are diagnosed incidentally due to the discovery of a murmur or during screening, after a family member has been diagnosed with HCM, while the other half presents with symptoms. (49) In patients who do develop symptoms, this usually occurs after the LVOT obstruction develops, which tends to be around young adulthood or middle age. (50) Once symptoms start developing, they are usually caused by heart failure. Exertional dyspnea due to progressive heart failure is usually the first symptom. This is due to the diastolic dysfunction, while systolic function is preserved. The dyspnea can later be further exacerbated by the occurrence of mitral regurgitation and atrial fibrillation. (46)

Another common presenting symptom is anginal chest pain, which is caused both by a mismatch of oxygen supply and demand with subsequent focal myocardial ischemia, as well as by the increased LV wall stress and the LVOTO directly. (51) Both the outflow obstruction and the chest pain have been shown to be exacerbated by a heavy meal. (52)

Lightheadedness, or presyncope, as well as syncopes are further possible presentation of HCM. The decreased cerebral perfusion is due a reduced cardiac output, which can be caused by the outflow obstruction itself or by arrhythmias such as a complete heart block, sustained ventricular tachycardia, or atrial fibrillation (AF) with a fast ventricular response. Atrial fibrillation is the most common arrhythmia in HCM patients, with a prevalence of about 22%. Besides precipitating syncopes and causing palpitations, AF can also lead to thromboembolic events. (53)

Sadly, often the first and only presentation of HCM is sudden cardiac death (SCD), in previously asymptomatic patients younger than 45 years of age. (3) It is usually caused by ventricular tachyarrhythmias. (42) SCD is assumed to be the most common cause of death in HCM, and HCM is the most common cause of SCD in the young. (3) For many years the incidence of SCD in HCM patients has been estimated to be around 0.5% to 1% per year (5 to 10 per 1000 HCM person-years) (54, 55), however in a study published in October 2019 Weissler-Snir et al. demonstrated an incidence of HCM-related SCD of only 0.31 per 1000 HCM person-years in a large, unselected population (estimated 140,740 observed HCM person-years). SCD seems to occur more frequently during physical activity and in previously asymptomatic patients. (56)

7. Diagnosis

7.1 Diagnostic criteria

Since the European Society of Cardiology (ESC) does not differentiate between the genetic disease of inherited mutations of sarcomeric protein genes and other causes in its definition of HCM, the diagnosis can be based on an increased thickness of the left ventricular (LV) wall that is not explained by abnormal loading conditions. Once this unexplained LV hypertrophy has been identified, a further systematic workup should be conducted in order to determine the underlying cause of the disease. (5)

Consequently, the ESC composed the following diagnostic criteria for adults (5):

- Myocardial thickness ≥ 15 mm in one or more segments of the left ventricle seen on echocardiography, cardiac magnetic resonance imaging, or computed tomography (CT)
- LV wall thickness 13-14 mm, if family history, non-cardiac signs and symptoms, electrocardiogram (ECG) abnormalities, or laboratory abnormalities are present

In children the diagnosis of HCM is also based on an LV wall thickness in relation to the predicted mean of the respective age. (5)

In first-degree relatives of patients with definite HCM, an unexplained thickness of the LV wall of ≥ 13 mm seen on any of the mentioned cardiac imaging modalities is sufficient for diagnosis of the disease. (5)

7.2 History and Physical Examination

The extent of findings in the physical examination as well as the symptomatology depend mainly on the hemodynamic state, meaning whether a left ventricular outflow tract (LVOT) obstruction is present or not. (42) Between 20% and 30% of patients with HCM have obstruction of the LVOT at rest; a similar proportion has a dynamic obstruction, while the rest of the HCM patients have no provocable obstruction. (20)

In advanced disease, when diastolic dysfunction and/or a LVOT obstruction are present, patients may have symptoms related to heart failure (dyspnea, paroxysmal nocturnal dyspnea [PND], orthopnea), outflow obstruction (syncope), myocardial ischemia (angina), or to arrhythmias (palpitations).

If an obstruction is present, a medium-pitch systolic ejection murmur at the left lower sternal border, which may radiate to the right sternal border and to the apex (5), and whose intensity varies with the degree of the LVOT pressure gradient, can be appreciated. (42) Once the murmur can be identified as grade 3/6, the patient likely has an LVOT pressure gradient of

more than 30 mmHg. (42) The murmur can be enhanced by the Valsalva maneuver. In this test the patient decreases the cardiac preload by increasing intrathoracic pressure. While most murmurs of other causes are diminishes by this maneuver, the LVOTO of HCM is exacerbated by the decreased volume and the intensity of the murmur increases. With advanced disease, signs of mitral regurgitation are also present. (5)

Taking the patients' history and physical examination can also give clues about the possible cause of HCM. For example, the family history is important in identifying the genetic variant of HCM. Here, creating a family pedigree is useful, also to identify family members who are not diagnosed with HCM but might be at risk. (5) Furthermore in regards to age it is noteworthy that HCM in the context of metabolic disorders is more common in young children, while HCM in senile systemic amyloidosis affects older men. Learning difficulties and mental retardation can steer the diagnosis toward Danon disease and sensorineural deafness toward Anderson-Fabry disease, while both of these clues can also indicate a mitochondrial disease. Similarly, visual impairment can accompany mitochondrial diseases, TTR-related amyloidosis, as well as Danon and Anderson-Fabry disease. Gait disturbance and muscle weakness are hallmark signs of Friedreich's ataxia. (57)

7.3 Electrocardiography

Due to its wide availability, low cost, and high sensitivity, the electrocardiography (ECG) remains one of the best modalities for the diagnosis of HCM. More than 90% of the patients with HCM show abnormalities in the ECG, as well as 75% of their asymptomatic relatives. (42) While ECG is sensitive in showing abnormalities in HCM, none of the abnormalities are specific. Generally speaking, the most common ECG changes in HCM are increased voltages representing the ventricular hypertrophy, T wave inversion, signs of left atrial enlargement, as well as deep and narrow Q waves (Figure 3). (42) Lyon et al. suggest that the first two changes mentioned, increased voltage and T wave inversion, occurring independently from one another, provide basis for division of HCM into two ECG-based phenotypes: The QRS abnormalities with wide and deep S waves in the lateral leads are explained by an abnormal coupling of the Purkinje branches to the endocardium, whereas heterogeneities in the apico-basal repolarization were shown to produce T wave inversions without changes in the QRS complex, even in the presence of septal and apical hypertrophy. (58) This is supported by previous observations that the extent of increased voltage in the ECG does not correlate with the extent of LV hypertrophy. (42)

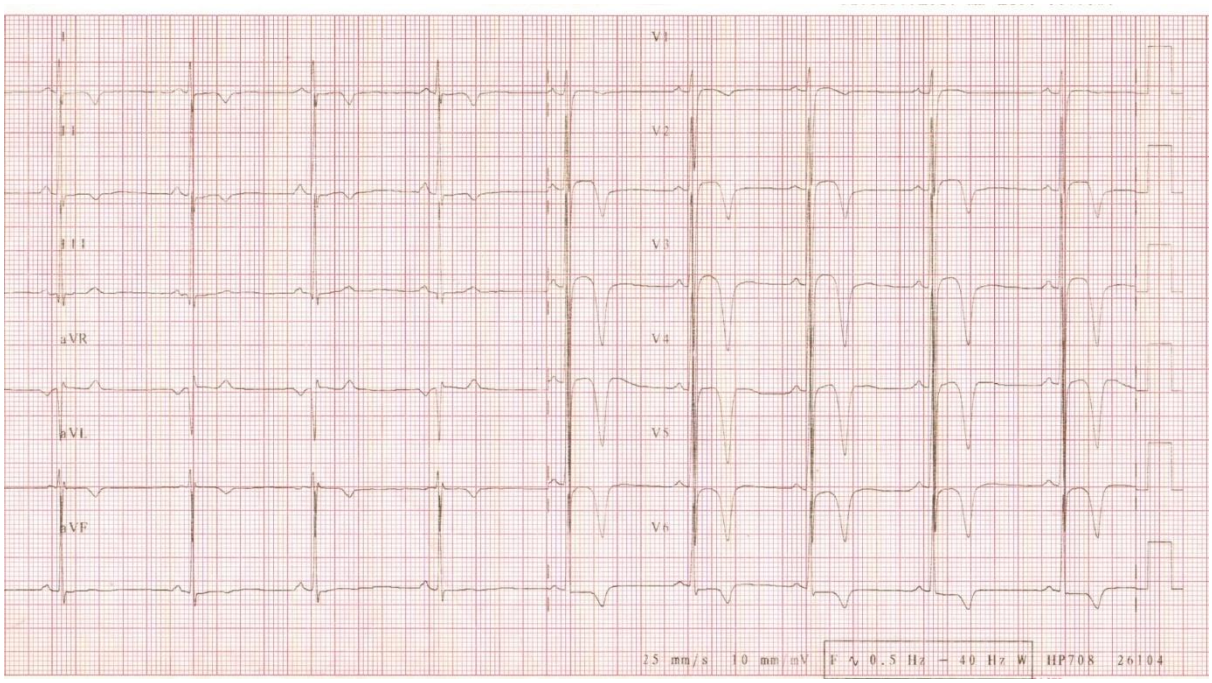

Figure 3. ECG of a patient with HCM showing increased voltage and T wave inversion

In syndromic HCM there are some disease-specific abnormalities to be noted on ECG. Danon disease, Anderson-Fabry disease, and amyloidosis can all cause a short PR interval and ventricular pre-excitation, as well as an AV block. Danon disease and amyloidosis can also induce a change in the QRS voltage, more specifically the former an extreme increase, and the latter a decrease. (35, 59–61) The decrease in QRS voltage in amyloidosis is an especially useful diagnostic feature, since this pattern is uncommon in HCM due to sarcomeric gene mutations. HCM in Noonan syndrome also shows one characteristic finding, that is an extreme superior axis deviation. (57)

Arrhythmias represent another manifestation of HCM that can be detected and monitored on ECG. Couplets, supraventricular tachycardia (SVT), and non-sustained ventricular tachycardia (nsVT) are common and related to the patients' age. nsVT is also associated with greater ventricular hypertrophy and more severe clinical symptoms, while SVT is related to outflow obstruction. (62) Due to the high prevalence of nsVT (up to 30%) (62), ambulatory monitoring with a Holter ECG is recommended in the initial assessment of HCM patients. (5)

6% of HCM patients exhibit a normal ECG. These patients seem to have a less severe phenotype of the disease and a better prognosis than those with ECG changes. (42, 63)

7.4 Echocardiography

Since the diagnosis of hypertrophic cardiomyopathy is based on imaging of the ventricular wall thickness, echocardiography as the most readily available imaging methods has central diagnostic utility for HCM. (5) In order to assess the ventricular wall thickness, it is important to visualize all segments of the LV wall, since different parts of the septum, the apex, the lateral wall, as well as the myocardium at the mid-ventricular level and at the level of the mitral valve might be affected. Especially apical hypertrophy might be difficult to visualize. In this case it is recommended to utilize intravenous ultrasound contrast agents. (64) The measurements should be performed at the end of diastole and using short-axis views. (5) Echocardiography can also be utilized to assess the extent of the LVOT obstruction (LVOTO). It is usually dynamic, meaning that most patients do not have an obstruction during rest, but will develop it during the provocative maneuvers, which decrease either the preload or the afterload of the left ventricle, increase the heart rate and/or contractility, such as the Valsalva maneuver or exercise. LVOT obstruction is defined by an outflow tract pressure gradient $\geq$ 30 mmHg. Once the gradient reaches or exceeds 50 mmHg, it becomes hemodynamically significant. (20) The LVOTO can be usually assessed by Doppler echocardiography, but in case it cannot be sufficiently visualized, transesophageal echocardiography (TEE) might be necessary. (5) The factors contributing to the LVOTO can also be determined on echocardiography, such as SAM of the anterior mitral valve leaflet, or structural abnormalities of the leaflets or the papillary muscles. Additionally, MR occurring as a consequence of the SAM is assessed using Doppler echocardiography. It is important to differentiate between MR caused by the SAM, resulting in a posteriorly directed regurgitation, and regurgitation due to other mitral valve abnormalities such as prolapse, which is directed anteriorly or centrally into the atrium. (65) In case the peak LVOT pressure gradient at rest, during the Valsalva maneuver, and at standing is lower than 50 mmHg in a symptomatic patient, it is recommended to perform exercise echocardiography, in order to identify any dynamic LVOTO. (5)

In order to gain information about the extent of the diastolic dysfunction in a patient with HCM, it is recommended to assess the pulmonary vein flow velocities, pulmonary artery systolic pressure, LA size and volume, LV size and volume, Doppler of mitral valve inflow and perform tissue Doppler imaging. (66)

7.5 Other imaging modalities

Cardiovascular magnetic resonance (CMR) imaging is another imaging method that should be used in the initial evaluation of HCM if the local resources permit. (5) CMR is similar to transthoracic echocardiography (TTE) in visualizing the morphology and function of the LV, if good images have been obtained on TTE. (67) However if that is not the case, and especially in the presence of apical and the anterolateral LV wall involvement, CMR is capable of identifying areas of hypertrophy, which were not visible on TTE. (68) Furthermore CMR is valuable for the detection of aneurysms, thrombi and papillary muscle abnormalities. (69–71) Using gadolinium-based contrast agents, CMR is also useful in the assessment of the expansion of the interstitium, which occurs due to fibrosis, as well as of the accompanying myocardial stiffness and wall motion abnormalities. The extent of interstitial fibrosis detected by CMR might be used as a predictor for malignant arrhythmias. (72) In patients with contraindications for CMR and if echocardiography was not sufficient, cardiac CT can be considered as an alternative imaging method. (73)

Nuclear imaging is useful in the identification of the transthyretin (TTR)-related amyloidoses as cause of HCM. TTR has been shown to retain ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) in both its wild-type configuration (present in systemic senile amyloidosis) as well as in the mutated form, that is the cause of hereditary transthyretin amyloidosis. The light chains of primary (AL) amyloidosis however do not take up ^{99m}Tc-DPD. (74) In HCM patients, in whom amyloidosis is more likely the cause of the disease than sarcomeric protein gene mutations, such as those with absent family history of HCM or sudden cardiac death, as well as the presence of other signs or symptoms consistent with amyloidosis, nuclear scintigraphy should therefore considered as a diagnostic tool.

7.6 Genetic testing

Genetic testing using high-throughput sequencing (HTS) is recommended in patients who fulfill the diagnostic criteria for HCM and do not an underlying systemic disease. (5) While the identification of a specific sarcomeric gene mutation does not have many implications on the management or the prognosis of the disease, (24) the confirmation of one or more mutations is valuable for establishing a screening program for the relatives of the patients, since these mutations are usually inherited in an autosomal dominant pattern. (15)

8. Differential Diagnosis

Since fixed valvular aortic stenosis (AS) usually presents similarly to HCM with syncope and signs of heart failure, it is important to differentiate it from the functional stenosis caused by the dynamic LVOTO of HCM. In both cases there is a systolic ejection murmur at the left lower sternal border, but a detailed physical examination can easily distinguish these two conditions: In the case of HCM the murmur increases with performing the Valsalva maneuver, during or after exercise, or while standing up. Another difference is that the murmur of a fixed aortic stenosis usually radiates along the carotid arteries to the neck, whereas the murmur of the dynamic outflow obstruction in HCM does not. (42) Furthermore, valvular aortic stenosis usually results in a symmetric (concentric) hypertrophy of the left ventricle, whereas in HCM the hypertrophy has a more focal distribution, as seen on echocardiography. (75)

Another condition, which is difficult to differentiate from HCM, is the physiologic LV hypertrophy that can arise in elite athletes, the so-called *Athlete's heart*. Patients with this condition may also meet the diagnostic criteria defined by the ESC for HCM. In elite athletes a LV wall thickness of 13 to 16 mm has been described. (76, 77) In order to differentiate between physiologic and pathologic hypertrophy, a few indicators can be assessed: Reduction of LV mass after periods of deconditioning, a maximal oxygen consumption > 110% of predicted, and a LV cavity > 55 mm steer the diagnosis towards physiologic hypertrophy, whereas unusual (i.e. focal) patterns of LV hypertrophy, a LV cavity < 45 mm, abnormal diastolic filling, and a positive family history indicate HCM. (76, 77) Cardiac magnetic resonance imaging provides another method for differentiation between the two conditions: In the case of HCM, the myocardial interstitium is expanded and demonstrates areas of fibrosis, as detected by late gadolinium enhancement. (78)

Another differential diagnosis to consider is hypertensive heart disease (HHD). In this condition the myocardium can also show an end-diastolic wall thickness of > 15 mm with a similar asymmetric pattern like that of HCM. However, the presence of systolic anterior motion of the mitral valve leaflet, of late gadolinium enhancement, and the absence or presence of an only slightly elevated indexed left ventricular mass have been shown to be good predictors to steer the diagnosis towards HCM instead of HHD. (79)

Left ventricular noncompaction cardiomyopathy (LVNC) is a rare genetic disease, which may be similarly to HCM caused by sarcomeric protein gene mutations and result in LV wall thickening with poor diastolic function in combination with preserved systolic function. The hallmark feature of this disease, which can be used to differentiate it from

HCM, is an increased thickness of the trabeculations in relation to the underlying myocardium, seen on echocardiography or other imaging modalities. (80) Despite the distinct definitions of these two diseases, their differentiation may be complicated by the fact that they can coexist in the same patient and be co-inherited in one family. (81) In one study, the diagnostic criteria of LVNC were met in 70% of examined HCM patients. (82) This raises the question if these two diseases are different manifestations of the same spectrum. (83)

9. Management

The management of HCM focuses mainly on the control of symptoms and complications, as well as the improvement of the functional status of the patients, since there is typically no cure for the underlying cause.

9.1 Medical therapy

The treatment of left ventricular outflow tract obstruction (LVOTO), which is one of the central symptom-causing abnormalities in HCM, is the cornerstone of the management of HCM. Generally, dehydration, strenuous exercise, competitive athletics, excess alcohol consumption, arterial and venous dilators such as nitrates and phosphodiesterase type 5 inhibitors, as well as diuretics should be avoided, since all of these factors can exacerbate LVOTO. (5, 6) Similarly, positive inotropes, such as digoxin, should be avoided. (84) In addition to this, risk factors contributing to coronary artery disease (CAD) should be treated aggressively, since coexisting CAD appears to have a much more significant impact on survival of HCM patients than in the general population. (85) Medicamentous treatment can be used in patients with a maximum LVOT pressure gradient between 30 mmHg and 50 mmHg. The first line of therapy are orally administered beta-blockers: Propranolol has been shown to improve the symptomatic state of patients with LVOTO, specifically shortness of breath, exercise intolerance, and chest pain, however it does not alter the course of the disease. (86, 87) Patients treated with sotalol also exhibited better exercise tolerance, additionally to lowered occurrences of supraventricular and ventricular arrhythmias. (88) Increased exercise tolerance, improvement of symptoms, and improvement of diastolic filling can also be achieved with the calcium channel blocking agents verapamil and diltiazem. (89–91) They can been used in patients who do not tolerate or respond to beta blockers, however in patients with a LVOT pressure gradient ≥ 100 mmHg or elevated systolic pressure in the pulmonary arteries care must be taken in order not to precipitate pulmonary edema. (92) The sodium channel blocker disopyramide can be administered together with beta blockers. This combination is more effective in reducing the LV outflow gradient and improving symptoms

than beta blockers or verapamil alone, however it may be associated with more systemic adverse effects. (93–95) Low dose thiazide diuretics can also be used in order to improve dyspnea, however it is important not to cause hypovolemia, which would lead to a worsening of the LVOTO. (5)

HCM patients with mid-ventricular obstruction often exhibit a more severe symptomatology and an increased risk for heart failure and sudden cardiac death than other HCM patients. They should consequently be treated with high dose beta-blockers, verapamil or diltiazem, however invasive treatment is often required. Patients with mid-ventricular obstruction are also prone to the development of LV apical aneurysms, which in turn predisposes the development of thrombi. While the aneurysms themselves usually do not require treatment, long-term oral anticoagulation should be initiated if a thrombus is discovered in the aneurysm, in order to decrease the risk of thromboembolisms. (5, 96, 97)

Beta-blockers, verapamil, diltiazem, and low-dose thiazide diuretics are also recommended for the treatment of heart failure symptoms in the absence of a LVOTO at rest or during provocation (LVOT gradient ≤ 50 mmHg), and preserved LV systolic function (i.e. the ejection fraction (EF) is ≥ 50%). (5) If the systolic function is reduced, i.e. the LVEF is < 50%, beta-blockers and inhibitors of the renin-angiotensin-aldosterone system (RAAS), namely angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonists (MRA), should be utilized. (98)

The anginal chest pain, caused by focal myocardial ischemia due to a supply/demand mismatch, can also be treated by beta-blockers and calcium channel blockers. Being negative inotropes, they reduce the oxygen demand of the myocardium and improve the diastolic function. (99, 100)

Since atrial fibrillation (AF) is the most common type of arrhythmia in HCM patients and it can lead to serious consequences like stroke and peripheral thromboembolisms, it is important to detect it early in order to prevent the formation of thrombi. Because the size of the left atrium (LA) is a good predictor for the development of AF, patients with an increased LA diameter should be regularly evaluated using ambulatory ECG monitoring. (53) The treatment of AF in HCM patients does not differ from the conventional therapy: In the acute setting of new-onset AF, direct current cardioversion should be attempted immediately in hemodynamically unstable patients. In hemodynamically stable patients rhythm control can be attempted using antiarrhythmic drugs or electrical cardioversion if the onset of AF is known to be no longer than 48 hours in the past. Medicamentous rhythm control can be attempted using amiodarone, flecainide, propafenone or sotalol. (88, 101) If the time of onset

is not known, or the AF is known to persist for longer than 48 hours, oral anticoagulation as well as rate control treatment should be initiated and oral beta-blockers or non-dihydropyridine calcium channel blockers, respectively. After at least three weeks of effective anticoagulation has been achieved, or the presence of a thrombus in the atrium has been excluded by transesophageal echocardiography (TEE), cardioversion can be attempted. (101) Because of the high incidence of thromboembolic events in HCM patients with AF (3.75 per 100 patients per year), the recommendations for thromboembolism prophylaxis are stricter in HCM and the usual CHA2DS2-VASc scoring system should not be applied. Instead, all HCM patients with AF should be anticoagulated, even if a sinus rhythm is restored. (5, 53)

One of the most severe consequences of HCM is sudden cardiac death (SCD). In order to estimate the risk of SCD in HCM, a prediction model called *HCM risk-SCD* has been developed. Based on the patient's age, maximal LV wall thickness, LA diameter, LVOT gradient, family history of SCD, non-sustained ventricular tachycardia, and history of unexplained syncope it provides 5 year risk estimates for SCD. (102) This risk should be assessed at the first evaluation of a patient, and then reevaluated every one to two years. To minimize the individual risk of SCD, HCM patients should be discouraged from participating in competitive sports and strenuous physical exercise. Further risk reduction can only be achieved by an intervention, namely the implantation of an implantable cardioverter-defibrillator. (5)

9.2 Invasive treatment

If medicamentous therapy is not sufficient in controlling the symptoms of heart failure and the occurrence of syncopes due to LVOTO, invasive procedures should be considered. The two procedures that are most frequently performed are ventricular septal myectomy and alcohol septal ablation.

Ventricular septal myectomy, also known as Morrow myectomy, is the most common surgical procedure. It involves resection of the bulging muscle of the subaortic septum through a transaortic approach. For midventricular obstruction and apical hypertrophy a transapical approach is preferred. This procedure not only resolves the LVOTO, but also alters the blood flow through the outflow tract enough that the Venturi forces causing the SAM of the mitral valve leaflet are terminated and the mitral regurgitation ceases. (50, 103) Septal myectomy is a safe and effective procedure. It has a procedural mortality of around 1%, and operated patients have a long-term survival on the same level like the general population. In most cases (98%), the LVOT gradient was eliminated, and up to 94% of

patients had an improvement of their heart failure-related symptoms. (104, 105) If the patient has MR not only because of the redirected blood flow, but also due to an intrinsic abnormality of the mitral valve, concomitant valve replacement can be performed in the same procedure. (50) Development of second degree or complete heart block is the most frequent complication, with up to 10% of patients requiring pacemaker implantation postoperatively. Other possible complications are the iatrogenic development of new aortic valve regurgitation, mitral valve regurgitation, and ventricular septal defect (VSD), occurring in up to 5.5%, 1.5%, and 1%, respectively. (105–107) Left bundle branch block (LBBB) is also a frequent finding after this procedure. (50)

Alcohol septal ablation (ASA) is a less invasive septal reduction therapy than myectomy. It involves selective injection of 95-99% ethanol into the isolated first or second septal perforator arteries, branches of the left anterior descending (LAD) artery. The best way to detect the exact target artery for ablation is by intraprocedural myocardial contrast echocardiography. (108) The ethanol injection causes an infarction, and subsequent scarring, thinning, and akinesia of the hypertrophied basal septum, reducing the LV outflow gradient and the SAM of the anterior mitral valve leaflet and thus the mitral regurgitation.

The following case is exemplary for the successful utilization of this procedure:

> **Case 1:** In 2017, a 67 year old patient had presented with increased fatigue and decreased tolerance of physical activity. Arterial hypertension was present for 20 years. On echocardiography she was found to have hypertrophy of the left ventricle with an intraventricular septum thickness of up to 20 mm, an EF of 65%, SAM, mild MR, and an intracavitary gradient of 80-100 mmHg. Cardiac magnetic resonance imaging confirmed the presence of a LVOTO and SAM with subsequent MR. A LVOT gradient of 112 mmHg was measured on left heart catheterization in 2018, before the decision was made to perform ASA.
>
> In March of 2019, when she finally agreed to the procedure, she reported shortness of breath with exertion and being able to walk up one flight of stairs, as well as occasional lightheadedness. She denied having chest pain, paroxysmal nocturnal dyspnea, dizziness or loss of consciousness. Her medications included bisoprolol, amlodipine, indapamid, moxinidin, and atorvastatin. On physical examination a 3/6 systolic murmur with punctum maximum left parasternally could be heard.
>
> For the procedure a temporary pacemaker was placed in the right ventricle through the right femoral vein. A pigtail catheter for the measurement of LV pressure

was inserted through the left femoral artery into the left ventricle. A guide catheter was placed in the left coronary artery through the right femoral artery. After a borderline stenosis of the LAD in the vicinity of the target septal branch was found, the stenosis was evaluated using the instantaneous wave-free ratio (iFR) and it was determined to not cause a significant decrease of pressure (iFR 0.96). A maximal pressure gradient between the aorta and the left ventricle of up to 130 mmHg was measured in postextrasystolic beats. After confirmation of the septal target branch using contrast echocardiography, 1 mL of 96% ethanol was injected. The control postextrasystolic LVOT gradient was decreased to around 25 mmHg.

On a control echocardiography on day 4 after the procedure a remaining LVOT gradient of 60 mmHg and SAM were noted to be still present. This finding can be explained by the presence of residual edema due to the induced infarction. (109) On a check-up in November of 2019, the patient stated feeling better in general and having a better tolerance of physical activity. A systolic murmur with an intensity of 1-2/6 was noted during Valsalva maneuver. On echocardiography no SAM or MR was found, the thickness of the septum had decreased to 13 mm, and the LVOT gradient was 11 mmHg (17 mmHg during Valsalva maneuver).

The outcomes of ASA are similar to those of septal myectomy: In-hospital mortality lies between 0.6% and 1.5%, long-term survival is similar to that of septal myectomy and the general population, and around 90% of patients have symptomatic improvement. (110–112) The occurrence of post-procedural AV block is higher than in septal myectomy, with up to 20% of patients requiring pacemaker implantation. (113) Also the risk for a right bundle branch block (RBBB) is significantly increased in patients following ASA, with an odds ratio of 56.3. (114)

Since septal myectomy and ASA have similar results regarding improvement of patients' functional status and mortality, the decision for a septal reduction therapy can be based on the patient's age, with ASA, as the less invasive procedure, being favored in older patients, and on the need for a concomitant repair or replacement of the mitral valve or an intervention on the papillary muscle, which is possible only in septal myectomy. (114) It is important to note that patients undergoing septal myectomy after unsuccessful ASA have a high risk (36%) of need for subsequent pacemaker insertion. This high risk stems from the consecutive development of RBBB and LBBB from either procedure. (50, 115) To avoid this

risk, alternative procedures such as endocardial radiofrequency ablation can be utilized after failed ASA. (116)

Sequential dual chamber pacing with a short programmed atrio-ventricular delay of typically around 100 ms is another intervention that has been shown to decrease the LVOT gradient and improve symptoms and the quality of life in patients with HCM. This therapy should be considered in HCM patients who are not willing or suitable to undergo either of the previously mentioned procedures, or who have another indication for pacemaker therapy and thus have a combined benefit. (5)

Interventional treatment is also available for the therapy of heart failure symptoms. Cardiac resynchronization therapy (CRT), which involves biventricular pacing, has been shown to improve the symptoms of heart failure and the ejection fraction (EF) in HCM patients, and to decrease the left ventricular end-diastolic diameter as well as the left atrial diameter significantly in this population. (117) As a result, CRT can be considered as symptomatic treatment in HCM patients with a LVEF < 50% and a LBBB with a QRS duration > 120 ms. (5)

Orthotopic cardiac transplantation is an option for HCM patients who have severe symptoms of heart failure, meaning patients placed in class III or IV of the New York Heart Association (NYHA) classification of heart failure, despite optimal medicamentous or invasive therapy. According to the European Society of Cardiology (ESC), both HCM patients with heart failure symptoms due to diastolic dysfunction (LVEF ≥ 50%) and due to systolic dysfunction (LVEF < 50%) or intractable ventricular arrhythmias can be considered for orthotopic cardiac transplantation. (5) In fact, around 5% of heart transplant recipients are diagnosed as having nondilated HCM. (118)

For patients with advanced heart failure due to dilated cardiomyopathy, mechanical circulatory support in the form of a left ventricular assist device (LVAD) is frequently used as a bridge to transplant or even destination therapy. For HCM patients however, not much data exists yet about the safety and outcomes of LVAD therapy. (119) Two studies analyzing the outcomes of continuous axial flow LVAD implantation in 8 and 104 HCM patients with end-stage heart failure, respectively, have shown similar short term and 4 year survival to patients receiving an LVAD for therapy of dilated or ischemic cardiomyopathy. (120, 121) While Topilsky et al. noted higher rates of right heart failure, prolonged inotropic use, and central venous catheter infections in the patients with HCM, in the larger of the two studies Patel et al. found similar rates of right ventricular assist device requirement, hemolysis, pump dysfunction, and cardiac arrhythmias in the studied populations. It did, however, note a far

inferior survival in patients with very small ventricles (< 5.0 cm). This is likely due to the fact that these patients are very sensitive to volumetric changes and consequently to suction events, which demands fewer revolutions of the device and thus requires anticoagulation therapy to prevent thromboembolic events originating from the device. (122)

Since sudden cardiac death (SCD) due to ventricular tachyarrhythmias is one of the most serious consequences of HCM, the prevention of this event is a major goal in therapy of the disease. The implantation of implantable cardioverter defibrillators (ICDs) has a place in primary and secondary prevention of SCD. For primary prevention the risk of a SCD is estimated according to the previously explained HCM Risk-SCD scoring system. If the 5-year risk is 4% or greater, an ICD implantation can be considered, especially if the risk is 6% or greater. If the 5-year risk of SCD is less than 4%, an implantation should only be considered in exceptional cases, for example if there were multiple young deaths in the family history of the patient. ICDs should be used for secondary prevention in HCM patients who survived a cardiac arrest due to ventricular fibrillation or ventricular tachycardia, or who experienced sustained ventricular tachycardia with syncope or hemodynamic compromise. (5,123)

Case 2: One example of primary SCD prevention using an ICD is the case of a 25-year-old sportsman. In the past he had lost consciousness during physical activity on three occasions, and had additionally experienced episodes lightheadedness multiple times. A routinely performed ECG during his general medical examination showed typical signs of septal HCM (Figure 3), which was confirmed by echocardiography with a septal thickness of 17 mm and a posterior wall thickness of 17 mm. Due to the high risk of malignant arrhythmias and sudden cardiac death, the patient was advised to abandon his sports activities, as well as to undergo the implantation of an ICD. He received a single-chamber ICD, which was placed in a deltopectoral pocket created on the left side, with a lead reaching to the right ventricle through the subclavian vein. He was able to be discharged 2 days after the procedure with the instruction to take bisoprolol.

10. Family Screening

Since HCM typically is an autosomal-dominantly inherited genetic disease with a consequent 50% risk of transmission to the next generation in up to 60% of the cases, it is advised that first-degree adult relatives of patients with HCM are screened for the same disease-causing mutation, which has been identified in the patient. If the mutation is also found in a relative, he/she should be evaluated based on ECG and echocardiography, in order to identify whether the disease is clinically present or not. Due to the variable penetrance of the HCM-causing mutations it is difficult to predict whether the disease will develop in the genotype positive relatives, and thus they should be followed up regularly and long-term. (5, 16, 20, 124)

Similarly, children of patients with HCM-causing mutations should be screened genetically for the mutation and/or clinically for the development of the disease, starting at the age of 10 years. (5)

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Biography

Luka Utrobičić was born in 1995 in Bad Homburg v.d.H., Germany. After studying economics for one year, he decided to follow his dream and began his medical studies in Zagreb in 2014. His interests lie in the fields of internal medicine and cardiology.