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Cardiogenetics of Hypertrophic Cardiomyopathy: A Short Review

Sambhav Kumar[1], Ashish K Nayyar[2]

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Abstract

Hypertrophic cardiomyopathy is an 'umbrella' term that encompasses a diverse and complex spectrum of genetic and acquired diseases. It is the most common familial heart disease (1:500) with vast heterogeneity with histological features of myocardial hypertrophy, myofibrillar disarray and interstitial fibrosis. The penetrance is incomplete and is age and gender dependent and has been accepted to be a disease of the sarcomere. Sixty percent of HCM carry mutations in one of eight sarcomere protein genes, mainly MYBPC3 and missense MYH7 variants. It is characterised by thickening of the wall of the heart, predominantly left ventricle (LV) and Inter ventricular septum (IVS). Due to the morphological and pathological heterogeneity of the disease, the appearance and progression of symptoms is not straightforward. Most HCM patients are asymptomatic, but up to 25% develop significant symptoms, including chest pain and sudden cardiac death. Sudden cardiac death is a dramatic event, since it occurs without warning and mainly in younger people, including trained athletes. Molecular diagnosis of HCM is of the outmost importance, since it may allow detection of subjects carrying mutations on HCM-associated genes before development of clinical symptoms of HCM. However, due to the genetic heterogeneity of HCM, molecular diagnosis is difficult. Currently, there are mainly four techniques used for molecular diagnosis of HCM, including Sanger sequencing, high resolution melting, mutation detection using DNA arrays, and next-generation sequencing techniques. Current pharmalogical treatment only focusses on symptom alleviation and prevention of complications. This short review on the current status of HCM highlights the importance of genetic implications and the importance of regenerative medicine to alleviate the gaps, together with new therapeutic drugs and delivery systems.

Keywords: Hypertrophic cardiomyopathy; Inter ventricular septum (IVS); Left ventricle (LV).

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common familial heart disease with vast genetic heterogeneity affecting over 1 in 500 people worldwide typically inherited in an autosomal dominant pattern (60%) with a small male preponderance.[1–3] The hallmark of the disease is left ventricular hypertrophy (LVH) not explained by abnormal loading conditions.[4] The disease can present at any age and is highly variable in clinical expression. Patientscan remain asymptomatic throughout their life, but upto 25% will develop significant symptoms.[2] HCM is also associated with premature mortality from heart failure, stroke, and sudden cardiac death (SCD) which maybe the first manifestation of the disease.[2,4] Five to ten percent of adult cases are caused by other genetic disorders including inherited metabolic and neuromuscular diseases, chromosome abnormalities and genetic

Author's Affiliation: [1]Junior Resident, [2]Associate Professor, Department of Anatomy, All India Institute of Medical Sciences, Jodhpur, Rajasthan 342005, India.

Corresponding Author: Ashish K Nayyar, Associate Professor, Department of Anatomy, All India Institute of Medical Sciences, Jodhpur, Rajasthan 342005, India.

E-mail: drashishknayyar@gmail.com

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syndromes[5,6] Some patients have non-genetic disorders that mimic genetic forms of the disease, for example, senile (TTR) and (AL) amyloidosis.[3]

Age is one of the most important factors to take into account when considering the possible causes for HCM. For example, inherited metabolic disorders and congenital dysmorphic syndromes are much more common in neonates and infants than in older children or adults, whereas wild-type TTR-related amyloidosis is a disease mostly of men over the age of 65 years.[3]

The ECG is a sensitive though non-specific early marker of disease in relatives.[7] ECG is recommended at the first clinic visit in all individuals with known or suspected HCM and should be repeated whenever there is a change in symptoms in patients with an established diagnosis. Echocardiography is central to the diagnosis and monitoring of HCM. Transoesophageal echocardiography (TTE) should be considered inpatients with poor transthoracic echo windows, as an alternative or complementary investigation to CMR. Cardiovascular magnetic resonance imaging embraces several modalities that provide detailed information on cardiac morphology, ventricular function and myocardial tissue characteristics.[8] Many of the genetic and non-genetic causes of HCM have characteristic histological appearances, but the diagnosis of HCM is clinical andrelies on non-invasive testing in the first instance. Conventional genetic practice uses pedigree analysis and clinical evaluation to target molecular testing to the most likely diagnosis. New, high-through put sequencing (HTS) technologies, capable of analysing entire exomes at similar cost and accuracy to conventional sequencing methods, offer an alternative approach in which no a priori assumptions are made about the cause of disease.

Pharmacological therapy of HCM consists of β-blockers and calcium channel blockers. β-Blockers and calcium channel blockers are used to improve diastolic function in patients with HCM. Invasive treatment includes Ventricular septal myectomy, Alcoholic septal ablation, Implantable Cardiac Defibrillator.[9]

The power of HCM mutational analysis, albeit a more limited role than initially envisioned, lies most prominently in screening family members at risk for developing disease and excluding unaffected relatives, which is information not achievable otherwise.[1]

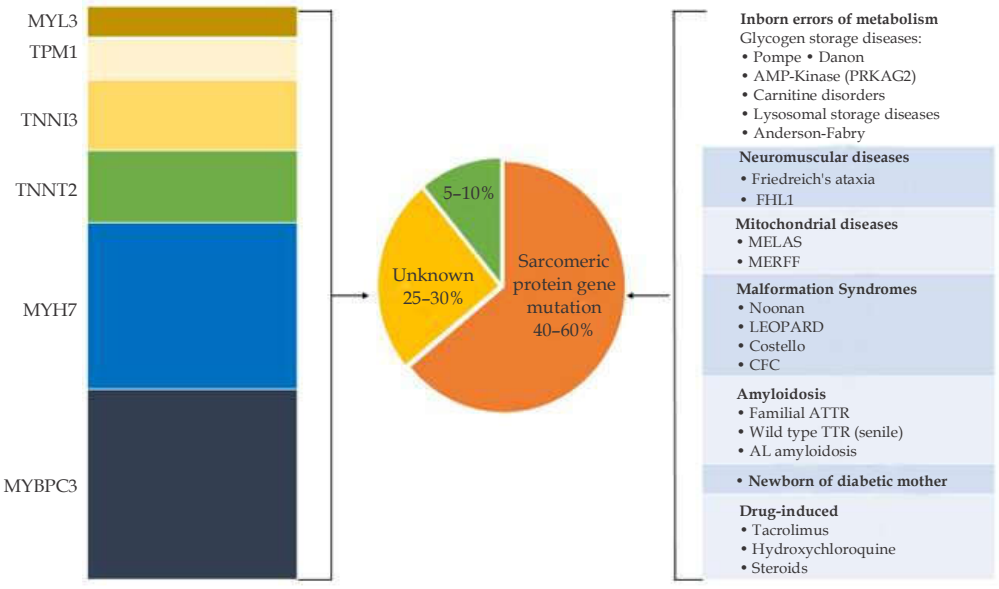

Fig. 1: Diverse aetiology of Hypertrophic Cardiomyopathy(3)

The majority of cases in adolescents and adults are caused by mutations in sarcomere protein genes. AL = amyloid light chain; ATTR = amyloidosis, transthyretin type.
CFC = cardiofaciocutaneous; FHL-1 = Four and a half LIM domains protein 1; LEOPARD = lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF = myoclonic epilepsy with ragged red fibres; MYL3 = myosin light chain 3; MYBPC3 = myosin-binding protein C, cardiac-type; MYH7 = myosin, heavy chain 7; TNNI3 = troponin I, cardiac; TNNT2 = troponin T, cardiac: TPM1 = tropomyosin 1 alpha chain; TTR = transthyretin.

Genetic Basis

The molecular era emerged more than 20 years ago with identification of disease-causing mutations in genes coding for proteins of the cardiac sarcomere.[10–12] The first gene for familial HCM (FHCM) was mapped to chromosome 14q1.[13] More than 25 genes are known to cause HCM till date, and around 1500 mutations are reported to be associated with HCM.[13]

Construction of a three- to four-generation family pedigree helps to confirm a genetic origin of disease and identifies other family members that are at risk of disease development. Specific features to note in the family history include sudden cardiac deaths, unexplained heart failure, cardiac transplantation, pacemaker and defibrillator implants, and evidence for systemic disease (stroke at a young age, skeletal muscle weakness, renal dysfunction, diabetes, deafness, etc.). Pedigree analysis can also determine the likely mode of inheritance. Most genetic forms of HCM are autosomal dominant and are therefore characterized by the presence of affected individuals in every generation, with transmission from parents of either sex (including male to male) and a 50% risk to offspring. X-linked inheritance should be suspected if males are the only or most severely affected individuals and there is no male-to-male transmission. Autosomal recessive inheritance, the least common pattern, is likely when both parents of the proband are unaffected and consanguineous. When women—but not men—transmit the disease to children of either sex, mitochondrial DNA mutations should be considered.[3]

More recently, striking scientific advances in molecular genetics have resulted in availability of comprehensive commercial genetic testing to the practicing cardiovascular community, while paradoxically creating many unanswered questions, and communication gaps surrounding translation of genetic information to clinical decision making. Therefore, it is timely to place the benefits and challenges of genotyping in HCM into perspective, for a disease that epitomizes application of genetic science to cardiovascular medicine.

Because of the hereditary nature of the disease, first degree relatives are advised to undergo periodic cardiac evaluation for the presence of LVH. In about half of all patients, a disease causing mutation can be detected in one of the genes encoding for sarcomeric proteins. Detection of a disease causing mutation allows predictive genetic testing in relatives, and facilitates identification of relatives at risk of developing HCM and associated disease related complications.[14]

Offspring of an affected individual have a 50% probability of inheriting a mutation and risk for disease; alternatively, sporadic cases may be due to de novo mutations in the proband but absent from the parents.

Introducing basic science to HCM, by interfacing deoxyribonucleic acid (DNA)– based methodologies and classical segregation linkage analysis with echocardiography, allowed mapping HCM to a causative locus on chromosome 14 in 1989.[8] In 1990, sequence analysis of a candidate gene revealed a pathogenic missense mutation in the beta-myosin heavy chain gene (MYH7Arg 403 Gln) to be responsible for HCM.[9]

Mutational Basis

According to gene susceptibility, HCM can be divided to "myofilament (sarcomeric) HCM," "Z-disk HCM," and "calcium-handling HCM," with "myofilament (sarcomeric) HCM" being the most common genetic form of HCM, account for 50% of all HCM cases.[9] 11 or more causative genes[10,15–21] with >1,400 mutations expressed primarily or exclusively in the heart. 70% of those patients with positive genetic tests are found to have mutations (of either definite or uncertain pathogenicity) in the 2 most common genes, MYH7 and myosin binding protein C (MBPC3) which together account for 75–80% of sarcomere mutations in HCM, while an additional 10% come from cardiac troponin T type 2 (TNNT2) and cardiac troponin I type 3 (TNNI3).[1,9]

Missense Mutations comprise 90% of pathogenic mutations altering physical and functional properties of proteins in which a single amino acid is exchanged for another. Alternatively, Frameshift mutations cause more substantial clinical consequences due to more radical mutations affecting many amino acids resulting in a different product. It is frequently found in MYBPC gene or abnormal splicing of mRNA.[1]

In general, patients with a sarcomere protein mutation present earlier and report a higher prevalence of family history of HCM and sudden cardiac death (SCD) than those without a mutation.[22,23] They also tend to have more severe hypertrophy, microvascular dysfunction and myocardial fibrosis.[24] Several studies have suggested that some sarcomeric protein mutations are associated with a poorer prognosis than others, but these observations are based on small numbers

of affected individuals, are sometimes inconsistent between studies, and are limited by the rarity of individual mutations.[25-31] VUS (Variants of Uncertain significance) are benign polymorphisms not considered to be capable of causing disease are however placed in an ambigious category as their relevance remains unclear with virtually no clinical utility for family screening. Distinguishing pathogenic mutations from VUS, or rare nonpathogenic variants, has increasingly emerged as a dilemma for interpreting testing results in HCM, and has been regarded as the "Achilles heel" of this diagnostic strategy.[1,16]

Genetic Testing and Screening

Currently, there are mainly four techniques used for molecular diagnosis of HCM, including Sanger sequencing, high resolution melting, mutation detection using DNA arrays, and next-generation sequencing techniques. Application of these methods has proven successful for identification of mutations on HCM-related genes.[2] In 2003, molecular genetic testing entered the mainstream of the health care system, with automated DNA Sanger sequencing providing more rapid, reliable, and comprehensive molecular diagnosis. Due to its well defined chemistry and sequencing precision, Sanger (dideoxy) sequencing has been considered the "gold standard" for clinical genetic testing. screened 5–10 more frequently mutated sarcomere genes (MYH7, MYBPC3, TNNI3, TNNT2, MYL2, TPM1, TNNI3, MYL2, MYL3, ACTC, CSRP3, and TCAP).[6,51,55] The order of the genes to be screened was MYBPC3 and MYH7, and if no mutations were found, TNNT2, TPM1, TNNI3, MYL2, MYL3, ACTC, CSRP3, and TCAP were sequenced in this order.

The necessity for electrophoretic separation of DNA fragments is the major obstacle with in Sanger sequencing increasing experimental time and limiting the number of reactions that can be run in parallel, thus making the technology relatively expensive.

Genetic testing should be performed in patients with an atypical clinical presentation of HCM, or when another genetic condition is suspected of causing it.[32] Genetic testing of the index patient may help identify first-degree family members who are at risk of developing HCM. Clinical screening, with or without genetic testing, is recommended in first-degree relatives of patients who have HCM. Genetic testing is not indicated in relatives of index patients who do not have a definite pathogenic mutation. Relatives who are members of families with HCM, but who have negative genetic test results, do not require ongoing clinical screening. The usefulness of genetic evaluation in assessing the risk of sudden cardiac death in HCM has not been determined.

According to ESC Guidelines, Genetic counselling is recommended in all patients when HCM cannot be explained solely by a non-genetic cause. Pedigree analysis helps to determine the probability of familial disease and the likely mode of inheritance, and provides clues to the underlying aetiology. When a definite causative genetic mutation is identified in a patient, his or her relatives should first be genetically tested, and then clinically evaluated if they are found to carry the same mutation. cascade genetic testing can be offered toall relatives when a definite mutation is identified in the proband.[3]

It should be underscored that the likelihood of obtaining a positive test in the proband is only about 50%, as all genes causing HCM have not yet been identified, and are absent from testing panels.

Genetic testing for the screening of healthy populations or for hypertensive patients with mild hypertrophy is not recommended.[3,4] There are important implications of genetic testing not only for affected but also for asymptomatic carriers. A positive genetic testing in athletes would have an impact on their sports career and might lead to cessation of competitive sport, even in the absence of overt disease.[4,33,34] Two genotype predictor scores have been published recently, which, based on seven clinical variables, estimate the yield of genetic testing in patients with HCM, thus helping the patients and their clinicians to decide whether toundergo genetic testing.

Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM to enable cascade genetic screening of their relatives.[2,35] Genetic analysis of post-mortem tissue or DNA samples can be valuable in the assessment of surviving relatives, but must be interpreted in the light of detailed post-mortem examination of the heart and in accordance with conventional rules for assigning pathogenicity to genetic variants.

Genetic testing in individuals with an equivocal clinical diagnosis (e.g. athletes and hypertensives), should only be performed after detailed clinical and family assessment as the absence of a sarcomere mutation does not exclude familial HCM and variants of uncertain significance are difficult to interpret.[3,7]

Pre-natal genetic diagnosis can be performed at

Table 1: Techniques currently used in diagnosis of hypertrophic cardiomyopathy: advantages, disadvantages and major providers(2)

Technique	Advantages	Disadvantages	Reference
Sanger Sequencing*	Accurate Precise Important for validation/ confirmation proposes	Time-consuming (more than 1 month; total time depends on number of regions analyzed) Laborious Expensive	*
dHPLC	Faster than Sanger sequencing (total time depends on number of regions analysed)	Sensitivity and specificity 87.5% and 97.42%, respectively (compared with Sanger sequencing) Optimization laborious Screening of heterozygous/homozygous Require Sanger sequencing for mutation confirmation	(39–42)
High resolution melting	>99% sensitivity and specificity (compared with Sanger sequencing) Closed-tube genotyping approach, reducing contamination risk Much faster than Sanger sequencing; 3 hours for complete gene scanning (96 or 384 plates; total time depends on number of regions anaylzed	Require Sanger sequencing for mutation confirmation	(39,43–45)
PLEX-MassARRAY	48 hours for complete mutation detection (multiplex analysis of more than 10,000 genotypes/384 plate) Accurate	Incapable to detect unknown mutations	(44,46,47)
Next-generation sequencing	Allow simultaneous sequencing of large amount of genes Targeted gene panels – limited gene panels allows high depth of coverage for increased sensitivity and specificity Higher ability to interpret the findings in a clinical context Allows to run more patient samples per instrument cycle (barcoding and pooling) Less amount of data and storage requirements	Genome data analysis is time-consuming High number of VUS Follow-up by Sanger sequencing to fill gaps in the data for regions showing low coverage (eg, GC-rich or repetitive regions)	(22,37,48–57)

Note: *Sanger sequencing is used in all the references provided in this table as the confirmation/validation gold standard technique.

Abbreviations: dHPLC, denaturing high-performance liquid chromatography; VUS, variants of uncertain significance

the beginning of pregnancy using chorionic villus sampling or amniocentesis.[3]

Conventional genetic practice uses pedigree analysis and clinical evaluation to target molecular testing to the most likely diagnosis. New, high-through put sequencing (HTS) technologies, capable of analysing entire exomes at similar cost and accuracy to conventional sequencing methods, offer an alternative approach in which no a priori assumptions are made about the cause of disease.[3,36,37]

These high-through put techniques allowed simultaneously testing of more samples and inclusion of established HCM-causative genes, phenocopy associated genes, and other genes with lesser evidence of pathogenicity.[1,2,38]

Next Generation Sequencing

NGS overcomes the limitations of electrophoretic separation and the detection requirements of Sanger sequencing.[54] NGS technologies are now becoming more and more adopted in clinical settings with three main levels of analysis and increasing degrees of complexity, i.e, disease-targeted gene panels, exome sequencing, and genome sequencing (covering both coding and noncoding regions).[50] NGS is composed of three major tasks, ie, sample preparation, sequencing, and data analysis.[76] The workflow begins with

extraction of genomic DNA from patient samples with targeted panels and exome sequencing requiring enrichment strategies to focus on a subset of genomic targets (usually short DNA fragments [100–500 base pairs] flanked by platform-specific adapters).[50]

However, the huge amount of information generated is simultaneously the greatest advantage and greatest disadvantage of NGS.[58]

NGS data have emerged in HCM, suggesting that double (or triple) or compound pathogenic mutations can be associated with more severe disease expression and an adverse prognosis (eg, heart failure or sudden death, even in the absence of conventional risk markers), with several implications for genetic counselling.[1,38] While it is possible that multiple mutations will prove to be prognostic markers or arbitrators of ambiguous risk profiles, the current evidenceis preliminary and prospective long-term studies in large populations are required.[1] Nevertheless, a major dilemma concerning NGS data for interpreting test results in HCM lies in distinguishing pathogenic mutations from variants of uncertain clinical significance (VUS) or rare non-pathogenic variants.[16] Lopes et al., using their targeted NGS strategy, identified a large number of rare non-synonymous sequence variants in non-sarcomeric genes (such as RYR2, ANK2, CAV3, and SCN5A) that may be potential phenotype modifiers in HCM and could explain the genetic heterogeneity of the disease.[22]

Therefore, application of NGS to HCM stands at a crossroads. If genetic testing is to evolve and have a more substantial role in the management of patients with HCM, future efforts should focus on clarifying precisely the pathogenicity of the substantial number of novel variants that are presently recognized and associated with the clinical heterogeneity of HCM and those that will inevitably be identified by new molecular techniques.[2]

Mutation Detection

When a definite causative genetic mutation is identified in a patient, his or her relatives should first be genetically tested, and then clinically evaluated if they are found to carry the same mutation. Diagnostic distinction between sarcomeric HCM and its phenocopies is crucial, given differences in natural history and management strategies. For example, mutations in LAMP2 are usually associated with rapid and potentially lethal clinical course within the first 3 decades, requiring early consideration for heart transplant.[59,60] In Fabry disease, clinical benefits have been attributed to enzyme replacement therapy with recombinant galactosidase A including regression of LVH and improved myocardial function and exercise capacity.[61,62] Clinical suspicion sufficient to trigger genetic testing can be raised by: Wolff-Parkinson-White pattern in PRKAG2 and LAMP2, or greatly increased precordial voltages and massive LVH in patients with LAMP2 mutations.[59,60,63,36–38] Fabry disease can be suspected by symmetric LVH and late gadolinium enhancement in the posterobasal LV.[61,62]

Mutation detection using the iPLEX Mass ARRAY matrix-assisted laser desorption/ ionization time-of-flight system has been used recently for diagnosis of HCM.[37,44,46,49] In contrast with automated Sanger sequencing, high-through put techniques such as iPLEX MassARRAY allow rapid and cost-effective testing for a large number of mutations simultaneously. iPLEX MassARRAY involves multiplex primary PCR using outer primers that flank HCM mutation sites followed by a homogeneous mass extend reaction with multiple, single, inner primers that together generate fragments of different mass specific for each genotype (iPLEX).[44] An advantage of iPLEX MassARRAY in comparison with other DNA microarray techniques is its capacity for detecting indels.[64,65] iPLEX MassARRAY has been successfully used to iden-tify pathogenic mutations, including indels, in more than 30 genes implicated in HCM.[44] Although this technique only detects known mutations, it has been demonstrated to be a high-through put platform suitable for routine genetic diagnostics, since it allows rapid and relatively inexpensive screening of the most common HCM-related mutations and simultaneous screening of HCM phenocopies.[44] Using an iPLEX MassArray system, Brion et al. were able to routinely analyze 550 mutations of 16 genes.[46,65,75]

Genotype–phenotype relationships/differential diagnosis

A positive genetic test in phenotypically expressed HCM is only confirmatory, but often useful when morphologic features are mild, equivocal, or atypical. Genetic testing can potentially resolve ambiguous clinical diagnoses such as HCM versus athlete's heart or systemic hypertension; however, in this setting anticipated mutational yield is very low, and a negative test is indeterminate and does not exclude HCM.[26]

Prognostic Value of Genetics in HCM

Multiple attempts to identify genes with an unfavourable impact on prognosis have been made without much success. It seems clear that patients in which it is possible to identify a mutation have a worse prognosis than those with negative genetic testing.[46,54] Traditionally, TNNT2 mutations were associated with a mild phenotype but a high risk of SCD. The radical mutations are very common in the MYBPC3 and do not seem to pose a more unfavorable prognosis than missense mutations. There are critical regions in the β myosin heavy chain encoded by MYH7, in particular involving the converter region which have been consistently associated with early disease and high rates of transplant and malignant arrhythmias.[57] Although several reports support that patients with double or triple mutations have a more severe phenotype and adverse prognosis,[58-60] the impact of the number of mutations on severity is weaker than expected.[4]

Recommendations on Pregnancy and Contraception

Adequate and timely counselling on contraception, the risks associated with pregnancy, and the risk of disease transmission to the foetus is important in all women with HCM.[66,67] Infertility treatment is probably safe in low risk HCM patients. Most women with HCM tolerate pregnancy well. The hypertrophied small left ventricle can, in most cases, accommodate the physiological increase in blood volume without undue rise in filling pressures. Deterioration during pregnancy most often occurs in women who are symptomatic before pregnancy. Women with arrhythmias pre-pregnancy are more likely to experience recurrence in pregnancy,[68,69] but pregnancy per se does not seem to substantially increase the risk of arrhythmia. When medication is prescribed, possible harmful effects to the foetus need to be considered.

However, both doctor and patient should realise that withholding medication from the mother may seriously threaten her health and therefore also the foetus (e.g. treatment of serious ventricular arrhythmias and anticoagulation therapy for AF). Ultimately, the interests of the mother should prevail. When ever ß-blockers are prescribed, monitoring of foetal growth and of the condition of the neonate is recommended.[3]

Hypertension

Most people with HCM lead normal and productive lives, but a small number experience significant symptoms and are at risk of disease-related complications. In clinical practice, it can be a challenge to makea differential diagnosis between hypertensive heart disease on the one hand and HCM associated with systemic hypertension on the other regression of LVH with treatment of hypertension argues against the diagnosis of HCM, but the reverse is not necessarily true.[3]

Therapeutic Implications

Current therapeutics for HCM patients are based on symptomatic alleviation and depend on the clinical features. The pharmacotherapy is mainly based on beta-blockers, calcium channel blockers and disopyramide.[2] A small percentage of HCM patients with severe symptoms require surgical myectomy and alcohol ablation to relieve left ventricular obstruction. The implantation of an internal cardioverter defibrillator is generally limited to avoid the possibility of SCD and hence extend the lifespan of the Patient.[70]

Exon skipping is emerging as a genetic-correction strategy of clinical usefulness. The antisense oligonucleotides (ASO) used for exon skipping are designed to restore reading frame disruption and it is currently being tested in humans with dystrophin gene mutations causing Duchenne muscular dystrophy.[71]

Exon skipping approach could be useful in HCM where the disease is caused as a consequence of a truncating mutation.[72] Recent advances in genetics, molecular mechanisms and physiopathology are leading to the development of new interesting therapeutic agents in HCM. This is the case of ranolazine, which is currently being evaluated in different studies on HCM patients,[73] and also of a promising small molecule MYK-461, which suppresses the HCM development and attenuates hypertrophic gene expression in mice harbouring heterozygous human mutations in MYH7. This indicates that contraction inhibitors could be valuable therapeutic targets for HCM.[4] Current pharmacological therapy is not able to overcome the effects of HCM-induced myocardial disorders and cannot improve the long-term prognosis.[2]

Conclusion and Future Prospects

New genetic biomarkers are necessary to understand this complex and heterogeneous disease. Genetic information would guide the development of therapeutic agents.[4] The dramatic clinical outcomes of HCM, including sudden cardiac death in younger people, including trained athletes, makes early and accurate diagnosis of the pathology essential.[2] The major limitations for new drug designs is the lack of in vitro models human cardiac disorders that accurately reflect disease phenotypes as well as genomic differences between humans and the mouse. One of the most interesting possibilities in cardiac regenerative medicine is the reprogramming of cardiac fibroblasts to become beating cardiomyocytes.[74] This has special importance for HCM patients, since there is a possibility that early reprogramming of fibroblasts into myocytes would reduce the extent of myocardial fibrosis and consequently decrease the risks of development of other pathological HCM-related conditions and sudden cardiac death. HCM is perhaps the strongest candidate for gene editing technologies[75,76] Recently, genome modification technologies, such as TALEN (transcription activator-like effector nucleases), ZFN (zinc finger nucleases), as well as CRISPR/Cas9 nuclease (clustered regularly interspaced short palindromic repeats/Cas9 nuclease systems), allow for specific editing of individual gene mutations.[45,75] This new technology promises to provide researchers with more accurate model for studying and treating HCM.

Cardiac tissue engineering seems to be promising in terms of providing a deeper understanding of the biological mechanisms inherent to HCM and being able to develop new therapeutic approaches for cardiovascular regeneration.[2]

Fifty years ago, HCM was thought to be an obscure disease. Today, however, our understanding and ability to diagnose patients with HCM have improved dramatically, due to improvements in screening and detection of gene defects in the human genome as well as iPSC-CM model (Induced pluripotent stem cells-Functional Cardiomyocytes) in HCM patients and gene editing technology (including CRISPR/Cas9). However, currently, treatments for HCM are directed at symptomatic relief, preventing sudden death.[9] The future goal of research is focused on changing the natural course of the disease and preventing its phenotypic expression.

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