Chapter 9

Recent Advances in Hypertrophic Cardiomyopathy: A System Review

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Abstract

Hypertrophic cardiomyopathy (HCM) is a common genetic cardiovascular disease present in 1 in 500 of the general population, leading to the most frequent cause of sudden death in young people (including trained athletes), heart failure, and stroke. HCM is an autosomal dominant inheritance, which is associated with a large number of mutations in genes encoding proteins of the cardiac sarcomere. Over the last 20 years, the recognition, diagnosis, and treatment of HCM have been improved dramatically. And moreover, recent advancement in genomic medicine, the growing amount of data from genotype-phenotype correlation studies, and new pathways for HCM help the progress in understanding the diagnosis, mechanism, and treatment of HCM. In this chapter, we aim to outline the symptoms, complications, and diagnosis of HCM; update pathogenic variants (including miRNAs); review the treatment of HCM; and discuss current treatment and efforts to study HCM using induced pluripotent stem cell–derived cardiomyocytes and gene editing technologies. The authors ultimately hope that this chapter will stimulate further research, drive novel discoveries, and contribute to the precision medicine in diagnosis and therapy for HCM.

Keywords: cardiac sarcomere, gene, hypertrophic cardiomyopathy, microRNA, pharmacology

1. Introduction

Hypertrophic cardiomyopathy (HCM) is a heterogeneous cardiac disease with a diverse clinical presentation and course, presenting in all age groups from infancy to the very elderly,

which was first described in 1868, its functional consequences in 1957, left ventricular (LV) asymmetric and especially septal hypertrophy in 1958, and its familial nature in 1960 [1, 2]. HCM is a global disease, affecting 1 in every 500 people [3]. And, the existing epidemiological studies might have underestimated the prevalence of HCM because majority of the original prevalence studies enrolled unrelated adults only and employed a diagnostic criterion of maximal wall thickness (MWT) ≥15 mm, or both, thereby resulting in under-recognition of early, familial disease [1, 4]. Enhanced recognition of HCM is important, allowing more timely diagnosis and the implementation of appropriate treatment options for many patients.

HCM is characterized by left ventricular hypertrophy with histological features of myocyte hypertrophy, myofibrillar disarray, and interstitial fibrosis [5]. The thickened and stiff ventricle reduces the compliance of the heart muscle, decreases preload, and leads to the most frequent cause of sudden death in young people (including trained athletes), heart failure, and stroke [6].

Since its first description in the 1950s, much progress has been made in elucidating the extremely heterogeneous genetic, morphogenic, diagnosis, and patient management. The goals of this chapter are to outline the symptoms, complication, and diagnosis of HCM; update published pathogenic variants; and discuss current treatment and efforts to study HCM by using induced pluripotent stem cell-derived cardiomyocytes, next-generation sequencing, and gene editing technologies.

2. Symptoms and complications

HCM is a common inherited cardiomyopathy with a diverse clinical presentation. Most patients with HCM are asymptomatic and have a normal life span but some develop symptoms. The most frequent symptoms of HCM included chest pain, dizziness, shortness of breath, palpitations, fatigue, and inability to perform vigorous exercise. Another devastating manifestation of HCM is sudden cardiac death (SCD) [7].

Furthermore, HCM is related with disease complications that may be profound, with the potential to result in disease progression or premature death [8, 9]. Atrial fibrillation (AF) is the most common sustained arrhythmia in HCM. Paroxysmal episodes or chronic AF ultimately occur in 20–25% of HCM patients, increase in incidence with age, and are linked to left atrial enlargement [10]. AF is a precursor of stroke (incidence, about 1% annually; prevalence, 6%), which is associated with death as well as disability most frequently in the elderly, and progressive heart failure, particularly for patients who have AF before 50 years old and accompanied basal outflow obstruction [11, 12].

Heart failure is another severe complication of HCM. Symptoms of chronic heart failure are frequent; however, the clinical profile of advanced heart failure varies between patients. In some, the thickened and stiff ventricle reduces the compliance of the heart muscle, decreases preload, and contributes to diastolic heart failure [6]. On the other end of the spectrum, typical DCM cases show chamber volume dilatation and thin walls, which reduces contractile force and causes systolic heart failure [13].

Myocardial ischemia: the other common pathologic features of HCM are the thickened and narrowed intramural coronary arteries and myocardial fibrosis by increased collagen deposition, leading to symptoms related to myocardial ischemia [14].

3. Diagnosis

Accurate diagnosis is vital for the management of HCM patients. Echocardiography is the primary method of diagnosis of HCM by determination of left ventricular hypertrophy (LVH) [15], left ventricular outflow tract gradients [16], systolic and diastolic function, as well as mitral valve anatomy and function. Cardiac magnetic resonance imaging (MRI) is becoming more widely used in diagnosis of HCM by determining the extent and location of LVH and the anatomic abnormalities of the mitral valve and papillary muscles [17]. Besides, genetic testing that is now commercially available is currently used most effectively in the identification of affected relatives in families known to have HCM.

3.1. Echocardiography

Echocardiography (echo) was first used to aid diagnosis in HCM in 1969 [18]. Forty years later, echo is central to diagnosis and monitoring of HCM. Diagnostic criteria of HCM by echo: in an adult, HCM is defined by a wall thickness ≥15 mm in one or more LV myocardial segments. However, in some cases, genetic and nongenetic disorders may present with a lesser degrees of wall thickening (13–14 mm); for these patients, the diagnosis of HCM requires evaluation of other factors including electrocardiogram (ECG) abnormalities, laboratory tests, and MRI, as well as family history [19]. For children, HCM diagnosis requires an LV wall thickness more than two standard deviations greater than the predicted mean (z-score > 2, where a z-score is defined as the number of standard deviations from the population mean) [19, 20].

HCM typically can be classified in three categories (**Table 1**), "nonobstructive," "labile," or "obstructive at rest" depending on their degree of left ventricular outflow tract obstruction (LVOTO), which result from a hypertrophied interventricular septum and/or abnormal mitral valve morphology. About one-third of patients will have obstruction at rest (peak gradient >30 mm Hg), and one-third will have labile obstruction (peak gradient >30 mm Hg only

Hemodynamic state	Conditions	Outflow gradients*
No obstruction	Rest	<30 mm Hg
	Physiologically provoked	<30 mm Hg
Labile obstruction	Rest	<30 mm Hg
	Physiologically provoked	≥30 mm Hg
Basal obstruction	Rest	≥30 mm Hg

*Gradients are the peak instantaneous continuous wave Doppler gradient.

Table 1. Definition of dynamic left ventricular outflow tract obstruction [2].

during provocation, which includes the Valsalva maneuver, administration of a potent inhaled vasodilator, such as amyl nitrite, and exercise treadmill testing [7]. Another one-third will have no obstruction under provocation or resting conditions (peak gradient <30 mm Hg). It is clinically important to distinguish between the obstructive and nonobstructive forms of HCM because management strategies are largely dependent on the presence or absence of symptoms caused by obstruction.

3.2. Cardiovascular magnetic resonance

Magnetic resonance imaging (MRI) and computed tomography imaging are being used increasingly to evaluate patients with HCM. Cardiovascular magnetic resonance (CMR), with its superior spatial resolution as well as tomographic imaging capability, has provided the opportunity to more accurately characterize the diverse phenotypic expression of HCM [21]. CMR is mainly used in the following situations: (1) the patients are suspected with HCM, but the echocardiogram is inconclusive, mostly because of suboptimal imaging from poor acoustic windows or when hypertrophy is localized to regions of the LV myocardium not well visualized by echocardiography [22]. (2) Hypertrophy confined to the apex (i.e., apical HCM) may be difficult to visualize with echocardiography but is evident with CMR [23]. (3) CMR can more readily detect the presence of apical aneurysms, which are potential implications for management with ICDs and/or anticoagulation; then CMR may identify high-risk status on the basis of massive hypertrophy [24].

4. Hypertrophic cardiomyopathy-associated genes

Hypertrophic cardiomyopathy is a common genetic cardiovascular disease. Genetic disorders account for 60–70% of HCM etiology. Since the identification of the first locus for familial HCM and the first mutation in MYH7-encoded beta-myosin heavy chain 20 years ago [25], over 1500 causal mutations associated with HCM encode sarcomeric proteins have been revealed [26]. 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 [13]. Recently, large genotype-phenotype analysis correlation studies established implications for septal morphology, disease onset, and prognosis of certain sarcomeric genes, which may further facilitate commercialized genetic testing. On the other hand, unexplained left ventricular hypertrophies that mimic HCM appear in some syndromic diseases. These diseases are usually called phenocopies and may contain rare variants in metabolism genes. These mutations alter myocardial metabolism, resulting in increased wall thickness, cardiac storage abnormalities, and conduction irregularities second to multiple systematic disorders. The information of HCM susceptibility genes and HCM phenocopies are listed in **Tables 2** and **3** [13, 27, 28].

Although more than 1500 mutations linked to hypertrophic cardiomyopathy, most of which are unique to individual families and less evident for pathogenicity. There are four sarcomeric

Gene	Chromosomal position[a]	Protein	HCM-associated mutations	Location or function[b]
ACTA1	1q42.13–q42.2	Actin, alpha 1	1	Sarcomere, skeletal muscle
ACTC1	15q11–q14	Actin, alpha, cardiac muscle 1	25	Actin, alpha, cardiac muscle 1
ACTN2	1q42–q43	Actinin, alpha 2	5	Z-disk
ANKRD1	10q23.33	Ankyrin repeat domain 1	3	Z-disk and nucleus (transcription factor)
BRAF	7q34	v-Raf murine sarcoma viral oncogene homolog B1	1	
COA5	2q11.2	Cytochrome c oxidase assembly factor 5	1	Mitochondrial
CALM3	19q13.2–q13.3	Calmodulin 3 (phosphorylase kinase, delta)	1	Calcium sensor and signal transducer
CALR3	19p13.11	Calreticulin 3	2	endoplasmic reticulum chaperone
CASQ2	1p13.3–p11	Calsequestrin 2	1	Sarcoplasmic reticulum; calcium storage
CASQ2	1p13.3–p11	Calsequestrin 2	1	Sarcoplasmic reticulum; calcium storage
CAV3	3p25	Caveolin 3	1	Plasma membrane
COX15	10q24	Cytochrome c oxidase assembly homolog 15	2	Mitochondrial respiratory chain
CSRP3	11p15.1	Cysteine and glycine-rich protein 3	15	Z-disk
DES	2q35	Desmin	1	Intermediate lament
FHL1	Xq26	Four and a half LiM domains 1	3	Biomechanical stress sensor
FHOD3	18q12	Formin homology 2 domain containing 3	1	Actin-organizing protein
FXN	9q13–q21.1	Frataxin	1	Mitochondrial iron transport and respiration
GLA	Xq22	Galactosidase, alpha	765	Lysosome
JPH2	20q13.12	Junctophilin 2	6	Junctional membrane complexes; calcium signaling
KLF10	8q22.2	Kruppel-like factor 10	6	Transcriptional repressor; inhibits cell growth
MAP2K1	15q22.1–q22.33	Mitogen-activated protein kinase kinase 1	1	MAP kinase kinase; signal transduction
MAP2K2	19p13.3	Mitogen-activated protein kinase kinase 2	1	MAP kinase kinase; signal transduction
MRPL3	3q21–q23	Mitochondrial ribosomal protein L3	1	Mitochondrial ribosomal protein

Gene	Chromosomal position[a]	Protein	HCM-associated mutations	Location or function[b]
MTO1	6q13	Mitochondrial tRNA translation optimization 1	2	Mitochondrial tRNA modi cation
MYBPC3	11p11.2	Myosin-binding protein C, cardiac	506	Sarcomere
MYH6	14q12	Alpha-myosin heavy chain	3	Sarcomere
MYH7	14q12	Beta-myosin heavy chain	491	Sarcomere
MYL2	12q23–q24.3	ventricular myosin regulatory light chain	20	Sarcomere
MYL3	3p21.3–p21.2	Myosin light chain 3	16	Sarcomere
MYLK2	20q13.31	Myosin light chain kinase 2	2	Calcium/calmodulin-dependent kinase
MYO6	6q13	Myosin VI	1	Actin-based reverse-direction motor protein
MYOM1	18p11.31	Myomesin 1	1	Sarcomere
MYOZ2	4q26–q27	Myozenin 2	2	Z-disk
MYPN	10q21.3	Myopalladin	8	Z-disk
NDUFAF1	15q11.2–q21.3	NADH dehydrogenase (ubiquinone) complex I, assembly factor 1	2	Mitochondrial chaperone
NDUFV2	18p11.31–p11.2	NADH dehydrogenase (ubiquinone) avoprotein 2	1	Mitochondrial respiratory chain
NEXN	1p31.1	Nexilin	2	Z-disk
OBSCN	1q42.13	Obscurin	1	Sarcomere
PDLIM3	4q35	PDZ and LiM domain 3	1	Z-disk
PRKAG2	7q36.1	5′-AMP-activated protein kinase subunit gamma-2	7	energy sensor protein kinase
PLN	6q22.1	Phospholamban	7	Sarcoplasmic reticulum; regulates Ca^{2+} -ATPase
RAF1	3p25	v-Raf-1 murine leukemia viral oncogene homolog 1	1	Serine/threonine-protein kinase; signal transduction
SLC25A3	12q23	Solute carrier family 25, member 3	1	Phosphate carrier protein (cytosol to mitochondria)
SLC25A4	4q35	Solute carrier family 25, member 4	2	Adenine nucleotide translocator (cytosol/ mitochondria)
SOS1	2p22–p21	Son of sevenless homolog 1	1	Guanine nucleotide exchange factor for RAS proteins; signal transduction
SRI	7q21.1	Sorcin	2	Calcium-binding; modulates

Gene	Chromosomal position[a]	Protein	HCM-associated mutations	Location or function[b]
TCAP	17q12	Telethonin	7	Z-disk
TNNC1	3p21.3–p14.3	Troponin C	14	Sarcomere
TNNI3	19q13.4	Troponin I	70	Sarcomere
TNNT2	1q32	Troponin T	90	Sarcomere
TPM1	15q22.1	Alpha-tropomyosin	38	Sarcomere
TRIM63	1p34–p33	Tripartite motif-containing 63	3	Sarcomere; regulates protein degradation
TTN	2q31	Titin	6	Sarcomere
VCL	10q22.1–q23	Vinculin	1	Sarcomere

[a]Human genome mutation database (http://www.hgmd.cf.ac.uk/ac/index.php).

[b]National Center for Biotechnology information (http://ncbi.nlm.nih.gov/). Abbreviations: HCM, hypertrophic cardiomyopathy;tRNA, transfer RNA; AMP, adenosine monophosphate; ATP, adenosine triphosphate.

Table 2. HCM susceptibility genes [28].

Gene	Locus	Protein	Syndrome
TAZ	Xq28	Tafazzin (G4.5)	Barth syndrome/LVNC
DTNA	18q12	Alpha-dystrobrevin	Barth syndrome/LVNC
PRKAG2	7q35–q36.36	AMP-activated protein kinase	WPW/HCM
LAMP2	Xq24	Lysosome-associated membrane protein 2	Danon's syndrome/WPW
GAA	17q25.2–q25.3	Alpha-1,4-glucosidase deficiency	Pompe's disease
GLA	Xq22	Alpha-galactosidase A	Fabry's disease
AGL	1p21	Amylo-1,6-glucosidase	Forbes disease
FXN	9q13	Frataxin	Friedrich's ataxia
PTPN11	12q24.1	Protein tyrosine phosphatase, nonreceptor type 11, SHP-2	Noonan's syndrome, LEOPARD syndrome
RAF1	3p25	V-RAF-1 murine leukemia viral oncogene homolog 1	Noonan's syndrome, LEOPARD syndrome
KRAS	12p12.1	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	Noonan's syndrome
SOS1	2p22–p21	Son of sevenless homolog 1	Noonan's syndrome

AMP, adenosine monophosphate; HCM, hypertrophic cardiomyopathy; LEOPARD, mnemonic for syndrome with clinical characteristics of lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary hypertension, abnormal genitalia, retarded growth, deafness; LVNC, left ventricular noncompaction; WPW, Wolff-Parkinson-White syndrome

Table 3. HCM phenocopies [29].

genes that carry the majority of HCM-related mutations and encode the proteins: myosin heavy chain (*MYH7*) and myosin-binding protein C3 (MYBPC3) are most common, 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) (**Figure 1**) [3].

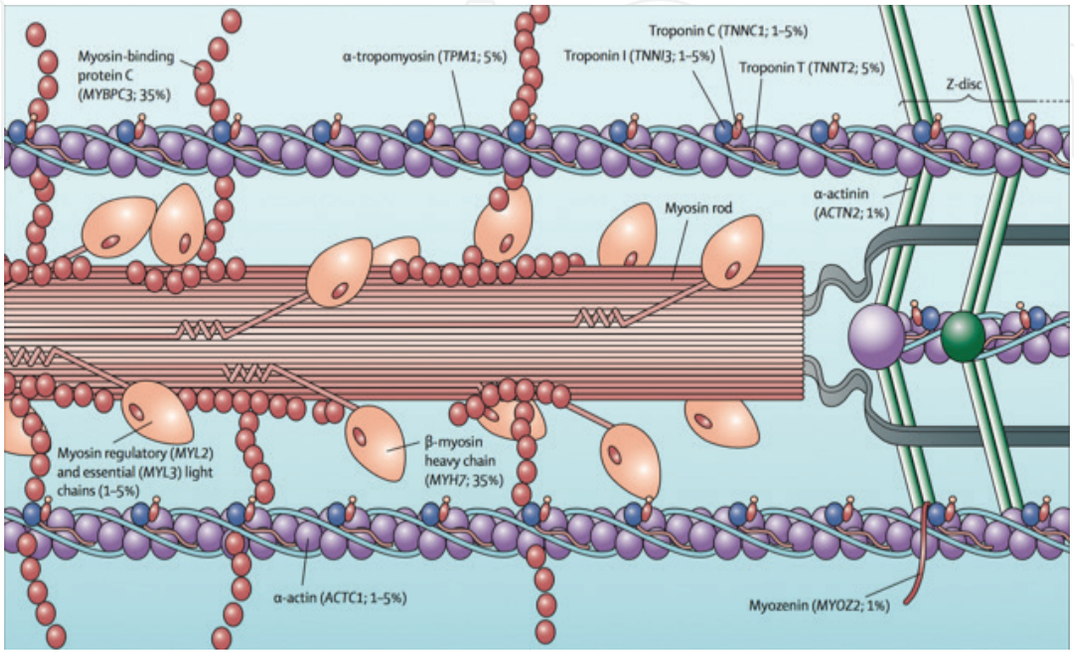

Figure 1. Locations of genes within the cardiac sarcomere known to cause hypertrophic cardiomyopathy [3].

5. Hypertrophic cardiomyopathy-associated miRNA

Despite extensive exploration of many genes, potential genetic associations remain to be found in approximately 30% of HCM patients. The recent newly developed field that has won extensive attention is microRNAs (miRNAs) in cardiovascular biology. miRNAs are noncoding RNAs with a length of approximately 22 ribonucleic acid molecules that bind mRNAs and regulate their expression through posttranslational repression or mRNA cleavage and degradation [30, 31]. It is estimated that the human genome contains more than 1000 miRNAs, which regulate at least 30–60% of protein-coding genes [32]. Multiple studies revealed that single or combined function of miRNAs is directly involved in the pathophysiology of cardiac hypertrophy, fibrosis, and electrical remodeling in vivo and in vitro [33]. The biological functions regulated by miRNAs affecting HCM are listed below (**Table 4** and **Figure 2**). Since miRNAs play a more and more important role in the development of HCM, they are being studied for potential diagnostic biomarkers and a promising therapeutics for HCM.

The schematic shows the miRNAs and their targets involving in cellular hypertrophy, gene switching, electrical remodeling, as well as fibrosis during cardiac hypertrophy. An upward

miRNA	Target	Biological effect	References
miR-340	Dystrophin	Cardiac eccentric	[34]
		Cardiac hypertrophy	
		Heart failure	
miR-133	RhoA	Cardiac hypertrophy	[35, 36]
	Cdc42	Heart failure	
	Nelf-A/WHSC2		
	HCN2		
miR-1	IGF-1	Cardiac hypertrophy	[35, 37, 38]
	calmodulin	Dilated cardiomyopathies	
	Mef2a	Heart failure	
	RasGAP		
	Cdk-9		
miR-208	Thrap1	Cardiac hypertrophy	[39]
	Myostatin		
miR-21	sprouty1	Cardiac hypertrophy	[40]
		Cardiac fibrosis	
miR-23a	MuRF1	Cardiac hypertrophy	[41]
miR-195		Cardiac hypertrophy	[42]
		Heart failure	
miR-99a	mTOR	Cardiac hypertrophy	[43]
	FGFR3	Heart failure	
miR-199a	NFAT	Cardiac hypertrophy	[44]
		Cardiac fibrosis	
		Heart failure	
miR-30	CTGF	Cardiac fibrosis	[35]
miR-29		Cardiac hypertrophy	[45]
		Cardiac fibrosis	

Thrap1, thyroid hormone receptor-associated protein 1; MuRF1, myostatin, muscle-specific ring finger protein 1; RasGAP, Ras GTPase-activating protein; Cdk9, cyclin-dependent kinase 9; Mef2a, calmodulin, myocyte enhancer factor 2A; IGF1, insulin-like growth factor 1; CTGF, connective tissue growth factor; HCN2, hyperpolarization-activated, cyclic nucleotide-gated K þ 2; FGFR3, fibroblast growth factor receptor 3; NFAT, nuclear factor of activated T-cells

Table 4. MiRNA in cardiac hypertrophy.

or a downward arrow is used to represent the upregulation or downregulation of a specific miRNA, respectively. All listed targets have been validated: Thrap1, thyroid hormone receptor-associated protein 1; MuRF1, myostatin, muscle-specific ring finger protein 1; RasGAP, Ras

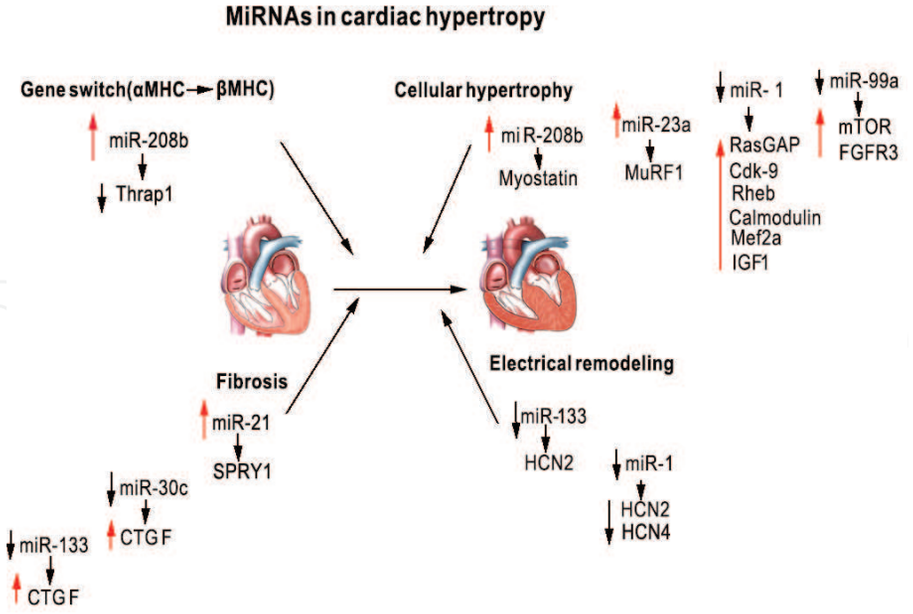

Figure 2. MiRNAs in hypertrophic cardiomyopathy.

GTPase-activating protein; Cdk9, cyclin-dependent kinase 9; Rheb, Ras homolog enriched in the brain; Mef2a, calmodulin, myocyte enhancer factor 2A; IGF1, insulin-like growth factor 1; SPRY1, sprouty 1; CTGF, connective tissue growth factor; HCN2/4, hyperpolarization-activated, cyclic nucleotide-gated K þ 2/4; and FGFR3, fibroblast growth factor receptor 3.

6. Treatment of HCM

As is typical for many forms of CVD, many current therapeutic strategies for HCM try to alleviate symptoms and prevent complications. Although once considered rare and terminal with annual mortality rates of up to 6%, HCM has now emerged as a very treatable form of heart disease [46]. Due to contemporary management strategies and treatment interventions, including ICDs for SD prevention, a variety of available surgical HCM mortality rates have dropped to 0.5% per year [47].

6.1. Pharmacology management

It has been clearly demonstrated that left ventricular outflow tract obstruction at rest in HCM patients is a strong, independent predictor of progression to severe symptoms of heart failure and of death [48]. Considering the mechanisms underlying myocardial contraction (calcium ions binding to troponin C and excitation-contraction coupling), a number of medical regimens have been used in these patients with the goal of lessening or eliminating the LVOT gradient through negative inotropy [7].

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. Small and mostly retrospective studies suggest that oral propranolol can abolish or reduce resting and provocable LVOTO and provide symptomatic benefit [49, 50]. Donald et al.'s study showed that β-blocker abolished the increase in gradient caused by isoproterenol and, more importantly, halved the increase in gradient caused by exercise [51]. In a 5-year follow-up, a study demonstrated that propranolol significantly improved the HCM patient's syndrome (dyspnea, angina, palpitations, dizziness, and syncope) by 58–100% [52].

Calcium channel blockade is used to HCM patients since it might ameliorate the hypercontractility characteristic of HCM. Verapamil, which has the best profile of the calcium antagonists, has been widely used in the treatment of HCM. A double-blind, placebo-controlled crossover trial studied oral propranolol, verapamil, and placebo, to 19 patients with HCM (17 with hypertrophic obstructive cardiomyopathy). Most patients derived symptomatic benefit from drug therapy, especially with verapamil [53]. In a recent study, the calcium channel blocker diltiazem was used to treat 38 HCM patients carrying *MYBPC3* mutation; results showed that diltiazem is safe and may improve early LV remodeling in HCM [54].

Another medicine used in hypertrophic obstructive cardiomyopathy (HOCM) patients is disopyramide, which is an effective negative inotropic agent by mediating sodium-calcium exchange [55]. Pollick et al. administered intravenous disopyramide to 43 patients with HOCM. The LVOT gradient was abolished or reduced; the effect was greater than that seen previously for either propranolol or verapamil [56]. By virtue of its atrial antiarrhythmic properties, disopyramide may be of particular benefit in HOCM patients with atrial fibrillation. Then, the ESC guideline recommended disopyramide, as Class IA anti-arrhythmic drug, which may be added to a maximum tolerated dose (usually 400–600 mg/day), if β-blockers alone are ineffective [19]. It can improve exercise tolerance and functional capacity as well as abolish basal LV outflow pressure gradients without proarrhythmic effects or an increased risk of sudden cardiac death.

6.2. Invasive treatment of LVOTO

Invasive treatment should be considered in patients with an LVOTO. The American and European colleges of cardiology recommend invasive treatment to (1) patients with labile obstruction and peak LVOT pressure gradients ≥50 mm Hg during exercise or provocation and resting gradients >30 mm Hg and (2) patients with moderate-to-severe symptoms (New York Heart Association (NYHA) functional classes III–IV) refractory to medical therapy [7, 19]. Two common surgical procedures performed in about 3% of obstructive HCM patients are septal myectomy and alcohol septal ablation [28].

6.2.1. Ventricular septal myectomy

Since the time of the first myectomy through the aortic root by Cleland in Great Britain in November 1958 [57], ventricular septal myectomy (Morrow procedure) is the most commonly performed surgical procedure used to treat LVOTO [58]. In a 10-year follow-up in 185 patients, the patients with hypertrophic cardiomyopathy (HCM) were treated with septal myotomy-myomectomy (MM) with a significant reduction in left ventricular outflow gradient at rest,

which improves exercise capacity and symptoms. Long-term symptomatic benefit is achieved in 70–80% of patients with a long-term survival compared to that of the general population [59]. Notably, operative mortality at surgical centers is now low, reduced to less than 1%.

6.2.2. Alcohol septal ablation

Percutaneous alcohol septal ablation is an alternative to surgical myectomy, which is a selective injection of alcohol into a septal perforator artery to create a localized septal scar. There are no randomized trials comparing surgery and septal alcohol ablation (SAA), but several meta-analyses have shown that SAA procedures improve functional status with a similar surgery in terms of gradient reduction, symptom improvement, and exercise capacity [60]. The main nonfatal complications are AV block in 7–20% of patients and a procedural mortality of about 2% [3]. Alcohol ablation has been recommended as a selective alternative for older patients, those with comorbidities, or patients with an absolute reluctance toward surgery.

6.2.3. Implant cardiac defibrillator

In addition to myectomy, the implantable cardioverter-defibrillator (ICD) has proven to be effective in terminating life-threatening ventricular tachyarrhythmia in HCM, altering the natural course of the disease and prolonging life [61, 62]. The indications for ICD placement are (1) positive family history of several sudden cardiac deaths in a distant family member, (2) nonsustained ventricular tachycardia on Holter monitoring, (3) LVH >30 mm, (4) prior unexplained syncope during exercise or at rest, and (5) an abnormal blood pressure response during exercise, which can be described as progressive decrease in the systolic value by 20 mm Hg after an initial increase or an increase in systolic blood pressure of <20 mm Hg from the baseline value or a [2, 63, 64]. The decision for placement of primary prevention of ICD in HCM often involves a large measure of individual clinical judgment, particularly when the evidence for risk is ambiguous.

7. Recent advances toward precision medicine for HCM

7.1. iPSC-CMs

Induced pluripotent stem cells (also known as iPS cells or iPSCs) are a type of embryonic stemlike cells that can be generated directly from adult cells [65–67]. The emergence of patient-derived induced pluripotent stem cells (iPSCs), which can be differentiated into functional cardiomyocytes (CMs) in vitro, may provide an exciting new approach to understand disease mechanisms underpinning inherited heart diseases (**Figure 3**) [26, 68].

iPSC-CMs derived from a patient with HCM caused by the MYH7 mutation p.Arg442Gly and mutation p.Arg663His have demonstrated the pathogenic effects [69, 70]. HCM iPSC-CMs exhibited structural abnormalities consistent with the HCM phenotype. Similar calcium-handling abnormalities were identified, consistent with observations made from animal models [70]. These studies explored the possible patient-specific and mutation-specific disease mechanism of HCM and demonstrated the potential of using HCM iPSC-CMs for future development of therapeutic strategies.

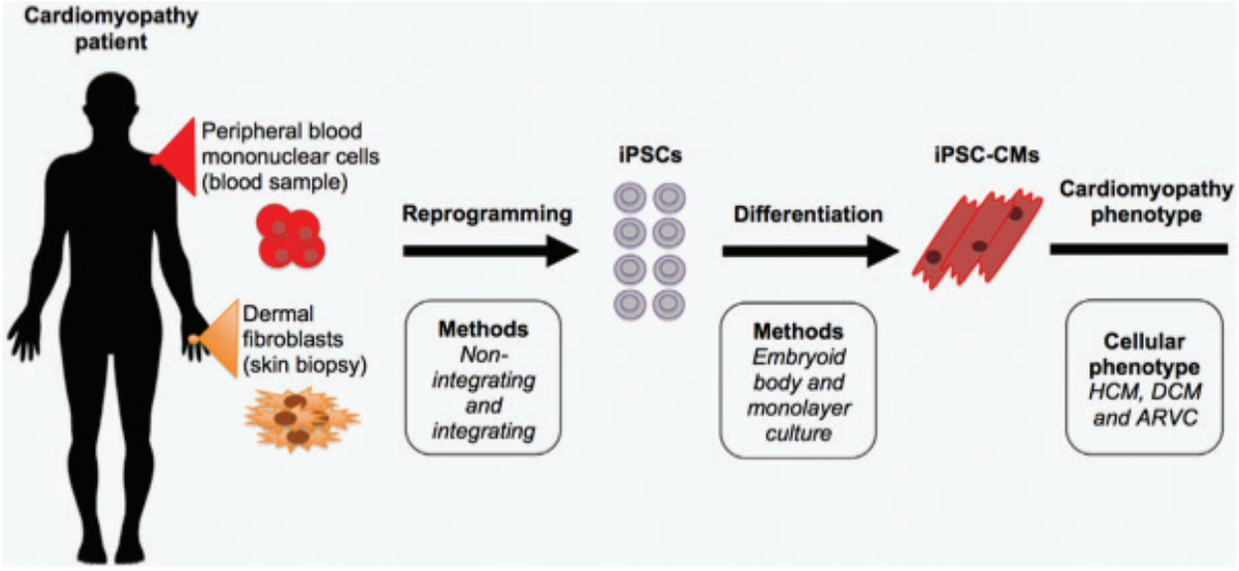

Figure 3. Generation of iPSCs from patients and then the differentiation to cardiomyocytes and then to their use in different cardiomyopaties. HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy.

In vivo direct cardiac reprogramming of somatic cells into cardiomyocytes is a potential offshoot of current reprogramming techniques but has not yet been tested in humans [71]. For HCM in particular, the possibility of converting cardiac fibroblasts into functional cardiomyocytes could theoretically ameliorate hypertrophy and improve diastolic function.

Although still in a nascent stage, direct cardiac reprogramming has undergone great advances and attracted considerable attention, these techniques could offer a renewable source of cardiomyocytes and deliver medicine individually tailored to each patient [72].

7.2. Gene editing technology

Gene editing is rapidly progressing from being a research/screening tool to one that promises important applications downstream in drug development and cell therapy. As primarily inherited cardiomyopathies, HCM is perhaps the strongest candidate for gene editing technologies [73, 74]. 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 [74, 75].

This CRISPR/Cas9 system makes it possible to efficiently, easily, and cheaply modify the genome, which is the current front-runner of these gene modification technologies [76]. To date, the CRISPR/Cas9 system has been used to successfully engineer cardiomyopathy into in zebra fish and mice models and is currently being applied to larger animals such as pigs and nonhuman primates [77]. This new technology promises to provide researchers with more accurate model for studying and treating HCM [78].

8. Conclusion

Hypertrophic cardiomyopathy (HCM) is a global and is considered one of the most common genetic cardiovascular diseases. Genetic variants, molecular mechanisms, and clinical phenotypes of HCM vary on a patient-by-patient basis. 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 in HCM patients and gene editing technology (including CRISPR/Cas9). However, currently, treatments for HCM are directed at symptomatic relief, preventing sudden death. The future goal of research is focused on changing the natural course of the disease and preventing its phenotypic expression. Working group from clinical, translational, and basic science aspects should work together to develop novel treatments to HCM. Then, finally, with the effort of all groups, we will reach the goal of the precision medicine of HCM.

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