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REVIEW

Cardiomyopathies: Evolution of pathogenesis concepts and potential for new therapies

Hamayak Sisakian

Hamayak Sisakian, Department Cardiology, Clinic of General and Invasive Cardiology, University Hospital 1, Yerevan State Medical University, Yerevan 0025, Armenia
Author contributions: Sisakian H solely contributed to this paper.
Correspondence to: Hamayak Sisakian, Professor, Department Cardiology, Clinic of General and Invasive Cardiology, University Hospital 1, Yerevan State Medical University, 2 Koryun street, Yerevan 0025, Armenia. hamayak_sisakyan@hotmail.com
Telephone: +374-10-582023 Fax: +374-10-541350
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Abstract

Cardiomyopathies are defined as diseases of the myocardium with associated structural and functional abnormalities. Knowledge of these pathologies for a long period was not clear in clinical practice due to uncertainties regarding definition, classification and clinical diagnosis. In recent decades, major advances have been made in the understanding of the molecular and genetic issues, pathophysiology, and clinical and radiological assessment of the diseases. Progress has been made also in management of several types of cardiomyopathy. Advances in the understanding of these diseases show that cardiomyopathies represent complex entities. Here, special attention is given to evolution of classification of cardiomyopathies, with the aim of assisting clinicians to look beyond schematic diagnostic labels in order to achieve more specific diagnosis. Knowledge of the genotype of cardiomyopathies has changed the pathophysiological understanding of their etiology and clinical course, and has become more important in clinical practice for diagnosis and prevention of cardiomyopathies. New approaches for clinical and prognostic assessment are provided based on contemporary molecular mechanisms of contribution in the pathogenesis of cardiomyopathies. The genotype-phenotype complex approach for assessment improves the clinical evaluation and management strategies of these pathologies. The review covers also the important role of imaging methods, particularly echocardiography, and cardiac magnetic resonance imaging in the evaluation of different types of cardiomyopathies. In summary, this review provides complex presentation of current state of cardiomyopathies from genetics to management aspects for cardiovascular specialists.

Key words: Dilated cardiomyopathy; Hypertrophic cardiomyopathy; Restrictive cardiomyopathy; Arrhythmogenic cardiomyopathy; Secondary cardiomyopathy

Core tip: Cardiomyopathies represent a different group of disorders in which myocardium is itself structurally and functionally abnormal. During recent decades, the genetics, pathophysiology and diagnosis of cardiomypathy have advanced from the traditional methods of clinical presentation to new genetic and imaging techniques. Nevertheless, the differences in definition, classification, pathophysiological mechanisms and diagnosis are controversial issues in clinical practice. The purpose of this review is to present the current state of classification, genetics, diagnostic approaches and management in order to provide useful instructions for clinical practice.

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INTRODUCTION

Cardiomyopathies are defined as myocardial disorders in

Table 1 American Heart Association classification for cardiomyopathies

Primary cardiomyopathies	Genetic	HCM/ARVC/LVNC/Conduction defects/Mitochondrial myopathies/ion channel disorders
	Mixed	DCM/restrictive
	Acquired	Inflammatory/Tako-Tsubo/Peripartum/Tachycardia induced/Infants of IDDM mothers
Secondary cardiomyopathies	Infiltrative	Amyloidosis, Gauchers, Hurler's, Hunter's
	Storage	Fabry's, Glycogen storage disease, Niemann-Pick disease, haemochromatosis
	Toxicity	Drugs, heavy metals
	Endomyocardial	EMF, Loeffler's endocarditis
	Inflammatory	Sarcoidosis
	Endocrine	Diabetes, hyperthyroidism, hypothyroidism, hyperparathyroidism
	Cardiofacial	Noonan's, lentiginosis
	Neuromuscular	Friedreich's ataxia, Duchenne-Becker muscular dystrophy, myotonic dystrophy
	Nutritional	Beriberi, scurvy, selenium
	Autoimmune	SLE, dermatomyositis, scleroderma
	Consequence of cancer therapy	Anthracyclines, radiation, cyclophosphamide,

ARVC: Arrhythmogenic right ventricular cardiomyopathy/dysplasia; DCM: Dilated cardiomyopathy; HCM: Hypertrophic cardiomyopathy; LVNC: Left ventricular non-compaction; EMF: Endomyocardial fibrosis.

which the myocardium is structurally and/or functionally abnormal in the absence of definite disease able to cause the myocardial pathology. Cardiomyopathies are classified traditionally according to morphological and functional criteria into four categories: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM) and arrhythmogenic right ventricular (RV) cardiomyopathy/dysplasia (ARVC/D). DCM is the most common form of heart muscle disease, comprising approximately 60% of all cardiomyopathies and characterized by left ventricular (LV) dilation and systolic dysfunction. The dilated cardiomyopathy is often assumed as a common pathway of several cardiovascular pathologies.

EVOLUTION OF CLASSIFICATIONS

Cardiomyopathies are classified as either primary or secondary. Primary cardiomyopathies consist of disorders namely or predominantly confined to the heart muscle, which have genetic, nongenetic, or acquired causes. Secondary cardiomyopathies are disorders that have myocardial damage as a result of systemic or multi-organ disease[1]. These cardiomyopathies can be primary myocardial disorders or develop as a secondary consequence of a variety of conditions, including myocardial ischemia, inflammation, infection, increased myocardial pressure or volume load and toxic agents.

In the 1980 World Health Organization (WHO) classification, cardiomyopathies were classified as "heart muscle diseases of unknown cause", reflecting a general lack of etiologic factors which may cause heart failure. The next WHO classification published in 1995 proposed "diseases of myocardium associated with cardiac dysfunction" and included for the first time ARVC/D, as well as primary RCM[2,3].

A more recent definition and classification of cardiomyopathies was proposed by the American Heart Association (AHA) Scientific Statement Panel, which divides cardiomyopathies as follows: "Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction, which usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation, due to a variety of etiologies that frequently are genetic. Cardiomyopathies are either confined to the heart or are part of generalized systemic disorders, and often lead to cardiovascular death or progressive heart failure-related disability"[1].

So far as the classification of cardiomyopathies is difficult, because the etiology or pathophysiology is not always clarified, there is no agreement on classification approaches in regular clinical practice.

For promoting standard nomenclature, recent knowledge on underlying causes and pathophysiology of cardiomyopathies has been implemented in a cardiomyopathy classification system both on behalf of the AHA and European Society of Cardiology (ESC)[4].

The AHA divides cardiomyopathies into two major groups based on predominant organ involvement. Primary cardiomyopathies (genetic, nongenetic, or acquired) are those solely or predominantly confined to heart muscle and are relatively less common. Secondary cardiomyopathies show pathological myocardial involvement as part of a several number of systemic pathologies (Table 1)[5].

In 2013, the MOGE(S) classification for a phenotype-genotype nomenclature of cardiomyopathies was proposed by the World Heart Federation[6]. This classification suggests a nosology that addresses five characteristics of cardiomyopathic disorders: morphofunctional state (M), organ involvement (O), genetic inheritance (G), etiologic annotation (E) and functional state (S) according to ACC/AHA A-D stage and New York Heart Association (NYHA) I -IV functional class. The description of five characteristics provides classification in MOGE(S) designation. The MOGE(S) classification has several advantages with regard to simultaneous maximal description of disease from clinical and genetic points. However, this classification does not fulfill the diagnostic criteria of cardiomyopathies in several clinical situations and may not be always applied in clinical practice, because of the lack of genetic testing in many clinical centers. On the other hand, the classification based on systematically genetic

testing and monitoring may cause overdiagnostic states without clinically evident signs of cardiomyopathies and absence of clinical phenotype. Further genetic research and development of multicenter registries are needed to clarify the clinical advantages and to make more practical of MOGE(S) classification of cardiomyopathies.

DCM

DCM represents the most common cardiomyopathy worldwide. It is a heart muscle disorder defined by the presence of a dilated and poorly functioning left or both ventricles. It can be primary (genetic, mixed or predominantly familial nongenetic, or acquired) or secondary (inflammatory, autoimmune, or thyrotoxic). This disease can be diagnosed in association with recognized cardiovascular disease; however, to qualify as DCM, the extent of myocardial dysfunction cannot be explained exclusively by abnormal loading conditions (hypertension or valve disease) or ischemic heart disease[4,7]. A large number of cardiac and systemic diseases can cause systolic dysfunction and LV dilatation, but in the majority of cases no definite cause is found. This has led to the common terminology idiopathic dilated cardiomyopathy (IDC).

PREVALENCE

Prevalence in the general population remains undefined. This disorder develops at any age, in either sex, and in people of any ethnic origin[8,9]. In adults, DCM arises more commonly in men than in women. In children, the yearly incidence is 0.57 cases per 100000, but is higher in boys than in girls (0.66 *vs* 0.47 cases per 100000, $P < 0.006$). Two-thirds of children are thought to have idiopathic disease[4]. In adults, the prevalence is 1 in 2500 individuals, with an incidence of 7 per 100000 per year (but it could be underdiagnosed). The prevalence of DCM in the United States (adjusted for age) is 36 per 100000 of the population[8]. The etiology includes genetic transmission (estimated at 30%-40%) identifying familial DCM, cytotoxic agents (*e.g.*, anthracycline derivatives), malnutrition (*e.g.*, protein deficiency), myocarditis (viral etiology), and autoimmune disease. In many cases, the disease is inherited, and is called familial dilated cardiomyopathy (FDC). The familial type might account for 20%-48% of all cases[10].

FAMILIAL (GENETIC) DILATED CARDIOMYOPATHY

Prominent progress has been made in studies of the genetics of DCM. Most of the genes involved in the development of DCM encode structural elements of the cardiomyocytes, particularly dystrophy associated glycoprotein complex or components of the sarcomeric complex. Genetic predisposition may have a decisive role in the development of primary and secondary DCM. Currently, > 30 autosomal and 2-X-linked genes have been shown to predispose to DCM and the number of these genes will continue to increase. There are sufficient data that with new diagnosis of IDC the clinical screening of first-degree family members will reveal familial (genetic) DCM in 20%-35% of those family members. Recent guidelines recommend that genetic testing should be provided in families in whom familial DCM is suspected for early diagnosis of cardiomyopathy in family members[4].

The diagnosis of FDC is made when IDC is diagnosed in two closely related family members. About 20%-48% of DCM has been reported as familial, although with incomplete and age-dependent penetrance, and linked to a diverse group of > 20 loci and genes[10]. Although genetically heterogeneous, the predominant mode of inheritance for DCM is autosomal dominant, with X-linked autosomal recessive and mitochondrial inheritance being less frequent. Thus, when taking a family history, specific attention should be given to a history of muscular dystrophy, features of mitochondrial disease (*e.g.*, familial diabetes, deafness, epilepsy, or maternal inheritance), and signs and symptoms of other inherited metabolic diseases[10]. Several of the mutant genes linked to autosomal dominant DCM encode the same contractile sarcomeric proteins that are responsible for HCM, including α-cardiac actin; α-tropomyosin; cardiac troponin T, I and C; β- and α-myosin heavy chain; and myosin binding protein C. Z-disc protein-encoding genes, including muscle LIM protein, α- actinin-2, ZASP, and titin, also have been identified. DCM is also caused by a number of mutations in other genes encoding cytoskeletal/sarcolemmal, nuclear envelope, sarcomere, and transcriptional coactivator proteins. The most common of these probably is the lamin A/C gene, also associated with conduction system disease, which encodes a nuclear envelope intermediate filament protein. Mutations in this gene also cause Emery-Dreifuss muscular dystrophy[11-13]. Other DCM genes of this type include desmin, caveolin, and β- and α-sarcoglycan, as well as the mitochondrial respiratory chain gene[1]. X-linked DCM is caused by the Duchenne muscular dystrophy (dystrophin) gene, whereas G4.5 (tafazzin), a mitochondrial protein of unknown function, causes Barth syndrome, which is an X-linked cardioskeletal myopathy[10,13].

PATHOLOGY

Macroscopic examination

Macroscopic examination of heart reveals ventricular chamber dilation with thickened or normal thickness walls. Valvular changes are not typical, although dilation of valvular orifices may be present as secondary changes due to dilation of chambers. Coronary anatomy is most commonly normal, although the presence of nonocclusive atherosclerotic plaques may be present. Thrombi are found most frequently in ventricles and atrial appendages.

Histological examination

The most typical DCM pattern is the development of

interstitial and perivascular fibrosis of varying degree[14]. Myocardial necrosis predominantly is present at subendocardium. Our study group investigated noninvasively using the Shirani method[15] the degree of myocardial fibrosis in patients with IDC and ischemic dilatation cardiomyopathy. The percentage of volumic collagen fraction in the LV myocardium was significantly higher in DCM patients compared to those with ischemic cardiomyopathy. Increase of collagen fraction correlated with the degree of dilation of the left ventricle[16].

Clinical manifestations

The most common clinical manifestations of DCM are congestive heart failure symptoms and thromboembolic complications. The disease commonly has a progressive course. The determination of time of manifestation is not easy, because the disease course for a long period is not symptomatic. Patients are admitted to hospital in cases with expressed heart failure symptoms. A careful history taking and physical examination with diagnostic studies are essential for differential diagnosis of DCM. More commonly, DCM manifests without any history and provoking factor. Cardiomegaly at radiological examination or on abnormal electrocardiography (ECG) may be the first findings in an asymptomatic patient. The left ventricle is dilated, and more spherical than usual with raised wall stress and depressed systolic function. As the disease progresses, definite symptoms of congestive heart failure present. Chest discomfort may occur in some cases, however this discomfort is not relieved by nitroglycerin. Physical examination may reveal gallop rhythm in decompensated patients. The jugular venous pulse is normal until right heart decompensation is present. The clinical course of DCM may be variable both with slow progression and rapidly progressive over several months. Cachexia and peripheral edema typically arise late in the course. Sudden death, presumably due to ventricular fibrillation may be the first manifestation. Some cases of DCM most probably develop due to viral myocarditis and these patients may have a history viral infection prior to deterioration of heart failure symptoms. An acute systemic febrile infectious disease (such as influenza) is followed by a latent period during which time the patient may be asymptomatic. It is reported also that in 20%-25% of patients with new-onset DCM may have cardiac recovery[17].

Several clinical, laboratory and instrumental factors may have prognostic significance in DCM patients. These factors are symptomatic ventricular arrhythmias, persistent gallop rhythm, persistent jugular venous distention, systemic hypotension, persistently elevated B-type natriuretic peptide, left bundle branch block, pulmonary capillary wedge pressure > 20 mmHg, cardiac index < 2.5 L/min per square meter, severely reduced ejection fraction, restrictive diastolic filling pattern, and severe mitral regurgitation[18].

ECG

ECG in patients with idiopathic DCM has no specific diagnostic role, and abnormalities ranging from isolated T wave and ST segment changes to septal pathological Q waves, wide QRS complex in patients with LV fibrosis might be present. Prolongation of atrioventricular (AV) conduction, and bundle branch block can be observed. Sinus tachycardia and supraventricular arrhythmias are common, in particular atrial fibrillation. Approximately, 20%-30% of patients have nonsustained ventricular tachycardia and a small number present with sustained ventricular tachycardia. ECG is utilized as a first-line screening and diagnostic tool for detecting conditions associated with sudden death. Idiopathic DCM patients with a prolonged QRS have significantly worse survival than other patients[19].

ECHOCARDIOGRAPHY

Echocardiography in DCM has characteristic patterns, although it is not possible to make differential diagnosis by echocardiography between idiopathic and other secondary LV dilation with dysfunction. M-mode echocardiography shows LV dilation with diffuse hypokinetic walls (Figure 1). Although cardiomyopathy is diffuse pathology, there may be segmental differences of the degree of hypokinesis revealed by two-dimensional echocardiography, which causes difficulties for differentiation from ischemic cardiomyopathy. Ventricular dilation usually is not accompanied by sufficient hypertrophy, which causes increase of volume-to-mass ratio[20]. Doppler echocardiography shows frequently functional mitral and tricuspid regurgitation and a different degree of diastolic dysfunction, depending on severity of intracardial hemodynamic abnormalities.

CARDIAC CATHETERIZATION

Catheterization for exclusion of coronary artery disease is important for following management of DCM patients. Catheterization also may reveal increased LV end-diastolic pressure and pulmonary artery wedge pressure. Left ventriculography may show ventricular dilation with global hypokinesis.

CARDIAC MAGNETIC RESONANCE IMAGING AND DILATED CARDIOMYOPATHY

Cardiac magnetic resonance imaging (MRI) can differentiate ischemic from non-ischemic cardiomyopathies through use of late gadolinium imaging, even when the heart is globally dilated and dysfunctional (Figure 2). Infarction is characteristic in that it always causes subendocardial late gadolinium enhancement (LGE), which extends variably transmurally to the epicardium. It also follows a coronary territory distribution. The absence of LGE in a dysfunctional segment of myocardium implies the potential for recovery with time (stunning), medical treatment or revascularization (hibernation), biventricular pacing (dyssynchrony)[21]. Nonischemic DCM may dem-

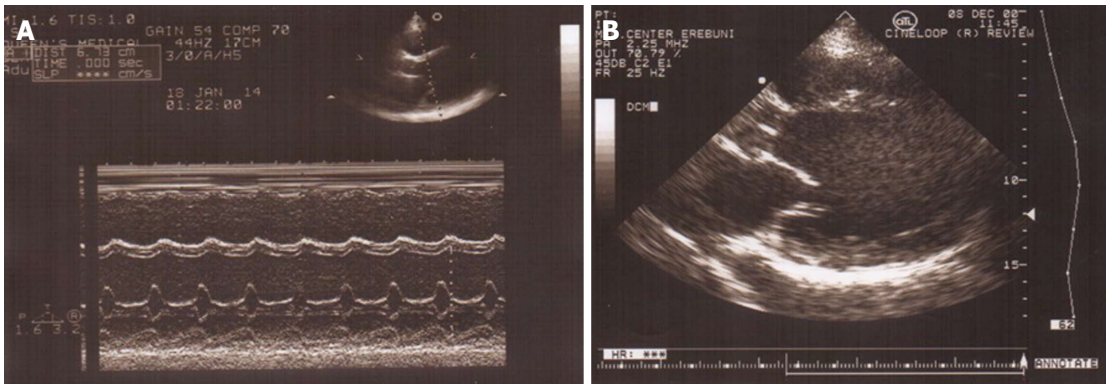

Figure 1 M mode and B mode echocardiogram of patient with idiopathic dilated cardiomyopathy. A: M mode echocardiogram shows dilated left ventricle with hypokinesis of interventricular septum and posterior wall; B: Parasternal long axis view of B mode echocardiogram showing remodeled left ventricular shape with loss of elliptical form.

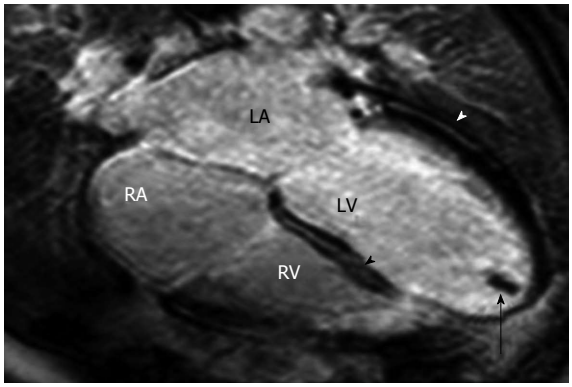

Figure 2 Dilated cardiomyopathy in a 36-year-old male soccer player with fatigue and a 3-5-d history of burning epigastric pain associated with nausea, vomiting, and early satiety[105]. Horizontal long-axis late contrast-enhanced magnetic resonance imaging shows an apical thrombus (arrow) in the left ventricle (LV) and midwall enhancement in the lateral left ventricular wall (white arrowhead) and the interventricular septum (black arrowhead). RA: Right atrium; RV: Right ventricle; LA:Left atrium.

onstrate either no LGE or mid-wall LGE in areas not corresponding to a coronary territory. Additional features that can be detected using cardiac MRI include valvular regurgitation, apical thrombus, dyssynchrony with or without posterior scar, signs of decompensation, cardiac iron, LV hypertrophy (LVH), RV involvement and atrial size.

CHRONIC MYOCARDITIS AND DCM

The major long-term consequence of myocarditis is inflammatory dilated cardiomyopathy, but the pathways that lead to myocardial fibrosis are poorly understood.

The gold standard of diagnosing the underlying causes of myocarditis and inflammatory cardiomyopathy is the histological, immunohistological and polymerase chain reaction-based analysis of cardiac MRI-guided endomyocardial biopsy (EMB) specimens. Persistent viral infections and infection-associated or postinfectious inflammatory processes of the myocardium may be key pathological mechanisms of progression of myocarditis to cardiomyopathy.

ANTIVIRAL THERAPY APPROACH

Several recent studies have investigated endomyocardium-based etiological antiviral treatment of inflammatory cardiomyopathies.

Interferons serve as a natural defense against many viral infections. Their innate production is associated with clinical recovery from viral infection and subsequent sequelae, while exogenous administration is protective. Type I interferons are a promising choice for treatment of chronic viral myocarditis. Currently, there is no approved treatment for chronic viral heart disease, but data from open-label phase II studies have demonstrated that subgroups of patients, who had not improved upon regular heart failure medication, may have significant benefit even years after onset of chronic disease. In the study of a 6-mo interferon-β1a therapy of patients with persistent enteroviral and adenoviral myocarditis, complete elimination of enteroviral and adenoviral genomes was demonstrated by follow-up biopsies taken 3 mo after termination of antiviral therapy. Virus clearance was paralleled by an improvement of mean LV function, a decrease in ventricular size, amelioration of heart failure symptoms, and a decrease of infiltrating inflammatory cells. No patient deteriorated and patients with severely affected LV dysfunction gained most benefit. Viral elimination after antiviral treatment suggests that early biopsy-based diagnosis and timely treatment may prevent disease progression and thereby improve the outcome of chronic viral cardiomyopathy. However there are limited data on efficacy of specific antiviral therapies and more studies are needed to identify patient cohorts who will benefit from targeted antiviral or immunosuppressive therapy. Treatment of myocarditis in current regular clinical practice remains supportive including the need for ventricular assist devices and heart transplantation[22].

EMB

In recent years, EMB has become a useful diagnostic tool for the investigation and treatment of myocardial diseases. However, its routine use is criticized by some

authors for the lack of therapeutic usefulness[23]. The techniques enable us to obtain multiple tissue samples from both ventricles with a low incidence of procedural complications. In addition to several clinical states such as after heart transplantation, specific myocardial diseases, the more frequent indication for EMB is suspected myocarditis in patients with progressive heart failure. In such cases, the correct analysis of tissue samples represents an important point to diagnosis. Although EMB provides suggestive findings in DCM, these findings may not always be revealed due to the technical difficulties of procedure and biopsy specimens may not contain pathological changes. The diagnostic performance of EMB is superior if the procedure is provided with a cardiac MRI-guided target area[24]. Diagnostic findings that show absence of inflammation may assist in further management strategies for DCM. Thus, in selected cases, EMB represents a useful method for correct prognostic and therapeutic evaluation of DCM.

MANAGEMENT

There is no specific etiology-based therapy in DCM. The main principles of DCM treatment are general concepts of chronic heart failure treatment. Although conventional pharmacotherapy is not specific with regard to etiopathogenesis, it decreases mortality in such patients. Common treatment includes β-blockers, angiotensin-converting enzyme (ACE) inhibitors, spironolactone in patients with NYHA class Ⅱ-Ⅳ heart failure. Diuretic therapy may have a beneficial effect on symptoms without a prominent effect on long-term outcome. β-Blockers and amiodarone can be used for management of supraventricular and ventricular arrhythmia. However, their long-term effect did not reduce mortality conditioned by sudden cardiac death (SCD)[25]. An implantable cardioverter defibrillator (ICD) and biventricular pacemakers are indicated in appropriate patients with both idiopathic and secondary dilated cardiomyopathies with LV dysfunction for secondary prevention of SCD. ICD can be combined with cardiac resynchronization therapy in patients with prolonged QRS duration and LV dys-synchrony[26]. However, the benefits of ICD were established in patients with systolic dysfunction of ischemic etiology[25,27]. Individual studies in patients with nonischemic cardiomyopathy failed to show significant reduction of total mortality[28-30], although a meta-analysis of five trials showed 31% mortality reduction[31].

Surgical approaches to restore LV shape by reverse remodeling include LV reconstruction and implantation of external restraint devices. The aims of ventricular reconstruction procedures are to restore elliptical ventricular chamber to decrease wall stress, end systolic volume and mitral regurgitation[32]. Most of these reconstruction procedures and trials have been estimated in patients with ischemic origin DCM.

The selected ventriculoplasty in combination with mitral annuloplasty is a useful option for patients with an extremely dilated left ventricle in IDC. Surgery should be considered before inotropic dependency occurs when prior medical treatment has failed[33].

In carefully selected patients, partial ventriculectomy combined with mitral valve reconstruction achieves short-term results comparable to those after heart transplantation[34]. However, long-term results and multicenter evaluation are needed to define its place in the treatment of advanced heart failure. With studies directed to patient selection and surgical modification, ventriculoplasty will become a realistic option in the treatment of heart failure caused by nonischemic cardiomyopathy.

Stem cell therapy has shown moderate effects in clinical trials for ischemic cardiomyopathy, but it remains to be determined if these results are applicable to idiopathic DCM patients. There is a need for methodologically sound studies to elucidate underlying mechanisms and translate those into improved therapy for clinical practice. In a single center study with 110 patients with nonischemic DCM, intracoronary $CD34^+$ stem cell transplantation was associated with improved ventricular function, exercise tolerance, and long-term survival[35]. Higher intramyocardial homing in this study was associated with better stem cell therapy response.

To prove safety and efficacy of cell therapy for DCM, adequate randomized (placebo) controlled trials using different strategies are mandatory. The REGENERATE-DCM trial is the first ongoing randomized, double-blind, placebo-controlled trial worldwide to investigate the role of granulocyte-colony-stimulating factor and autologous bone-marrow-derived stem/progenitor cell therapy to improve cardiac function in patients with DCM[36].

The 5-year survival averages 30%-40% and is improved by contemporary heart failure therapy, but not all patients respond well to therapy and some patients rapidly deteriorate no matter the therapeutic approach, and for them, heart transplantation remains the only option.

CARDIOMYOPATHIES WITH DILATED PHENOTYPE

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a rare but potentially life-threatening condition that occurs in previously healthy women during the last month of pregnancy and up to 5-6 mo postpartum. The etiology and pathophysiology remain uncertain, although recent observations strongly suggest the specific role of prolactin cleavage secondary to unbalanced peri-/postpartum oxidative stress[37]. PPCM is a diagnosis of exclusion, because it shares many clinical characteristics with other forms of systolic heart failure secondary to cardiomyopathy. The heart failure management requires a multidisciplinary approach during pregnancy, considering the possible adverse effects on the fetus. Some novel therapies, such as prolactin blockade, are proposed to either prevent or treat the patients with PPCM[38]. A critical individual approach concerning the risks of subsequent pregnancy must be considered. As a result of its rare incidence, geographical

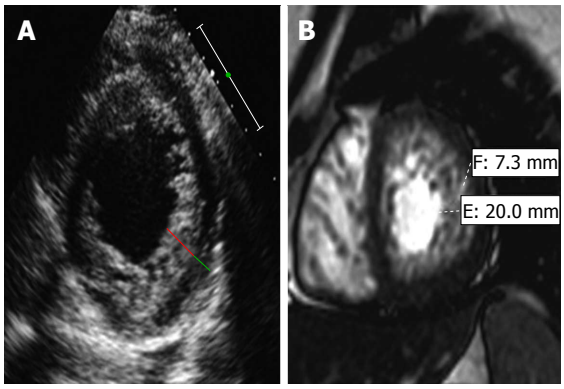

Figure 3 Non-compaction cardiomyopathy in two patients[105]. A: Dilated cardiomyopathy in a 60-year-old man with new-onset congestive heart failure. Short-axis echocardiogram obtained in systole at the level of the left ventricle (LV) shows a two-layered myocardium with a noncompacted (red line) and com¬pacted (green line) layer along the lateral, inferior, and anterior walls and a maximal end-systolic NC: C ratio > 2; B: Symptoms of New York Heart Association Class Ⅲ heart failure and severely reduced (≤ 35%) LV ejection fraction in a 35-year-old woman. Short-axis 2D SSFP cardiac magnetic resonance imaging obtained in end diastole shows thickening of the noncompacted layer of the LV myocardium, with an NC: C ratio of 2.9. The patient underwent subsequent implantable cardioverter-defibrillator placement for primary prevention of sudden cardiac death.

differences, and heterogeneous presentation, PPCM continues to be incompletely characterized and understood. For all these reasons, PPCM remains a challenge in clinical practice, so future epidemiological trials and national registries are needed to learn more about the disease.

Classic criteria of PPCM include development of heart failure in the last month of pregnancy or within the first 5 mo postpartum, absence of an identifiable cause of heart failure, and absence of recognizable heart disease prior to the last month of pregnancy[39].

LV non-compaction

LV non-compaction (LVNC) is a cardiomyopathy resulting from arrest of fetal development of the heart. This leads to altered myocardial architecture that is seen as a two-layered myocardium with a thin, compacted epicardial layer and a thick, noncompacted endocardial region. The noncompacted myocardial region is comprised of prominent trabeculations and deep intertrabecular recesses that directly communicate with the LV cavity. The condition may present without any associated cardiac malformation and is then labeled isolated LVNC. Noncompacted myocardium is also seen in conjunction with other cardiac abnormalities including cyanotic congenital heart disease, Ebstein's anomaly, and other cardiomyopathies. Clinical presentation in LVNC is seen with congestive heart failure, ventricular arrhythmia, and systemic thromboembolism. The condition is listed as an unclassified cardiomyopathy in the WHO and ESC classification of cardiomyopathies[4] and as a primary genetic cardiomyopathy in the AHA classification[5].

Both sporadic and familial forms are described.

The presence of significant non-compaction is estimated at 1:2000 in the general population. The condition is, however, more prevalent in heart failure patients. More frequent use of cardiac imaging in clinical practice has increased recognition of this condition[40].

Non-compaction myocardium clinically may represent from asymptomatic individuals to those with severe disease presenting with heart failure, ventricular arrhythmia, and systemic thromboembolism. Noncardiac features may include facial dysmorphism and neuromuscular disorders.

Echocardiography may reveal trabeculation in the LV wall. However in healthy persons this can be also found. To separate benign LV trabeculation from pathological LVNC following diagnostic criteria is proposed[41].

Echo: Ratio of noncompacted to compacted myocardium in end-systole of > 2:1.

Cardiac MRI: Ratio of noncompacted to compacted myocardium in end-diastole of > 2.3:1. Cardiovascular imaging is important in the diagnosis of LV noncompaction. Cardiac MRI (Figure 3) has better resolution compared to echocardiography, which makes it a preferred imaging modality in such patients. Cardiac MRI is also reliable in distinguishing LVNC from other causes of LV apical deformity, including apical variant of hypertrophic cardiomyopathy, endomyocardial fibrosis (EMF) and apical thrombus[42]. Pharmacological management of LVNC is mainly symptomatic and directed to relief of heart failure symptoms. Heart transplantation remains an option in patients with treatment-tolerant high functional class patients. Ventricular arrhythmia is not directly related to severity of LV dysfunction and a prophylactic ICD is recommended. Anticoagulation to prevent thromboembolic complications is recommended, particularly in patients with severe contractile dysfunction.

STRESS-INDUCED OR "TAKOTSUBO" CARDIOMYOPATHY

Stress-induced cardiomyopathy was termed Takotsubo cardiomyopathy by Japanese cardiologists in 1991[43]. Advances in diagnostic imaging and emergency coronary angiography have contributed to increased recognition of stress-induced cardiomyopathy, and increasing numbers of reports have been published since then.

A history of intense emotional or physical stress and a typical pattern of LV contractile dysfunction on cardiac imaging are suggestive of the diagnosis. The most common abnormality on ECG is ST-segment elevation resembling ST segment elevation myocardial infarction[44]. This cardiomyopathy is transient and reversible. Clinical presentation may be indistinguishable from acute coronary syndrome, invariably necessitating coronary angiography for exclusion of obstructive coronary artery disease. Prevalence is in 1%-2% of patients undergoing coronary angiography for acute coronary syndrome. Based on morphological features of the LV, presumed causative role of stress and catecholamine excess and transient nature of the contractile dysfunction, other

nomenclature used to describe this cardiomyopathy include ampulla cardiomyopathy, stress cardiomyopathy or catecholamine cardiotoxicity and transient LV apical ballooning syndrome[45].

Distinct pattern of contractile abnormality is noted in the left ventricle. In the typical case the LV apex is dyskinetic and expanded and may be associated with hyperdynamic contractility of the basal LV segments. The shape of left ventricle in systole resembles a Japanese octopus trap (Takotusbo), which has a narrow neck and a wide base. The condition is associated with markedly elevated circulating catecholamine, which is assumed to be central in the pathophysiology of this condition though exact mechanism at the cellular level is not fully understood. In a report by Wittstein *et al*[46], two to three times higher plasma catecholamine concentrations were found in 13 patients with transient LV apical ballooning syndrome compared with seven controls hospitalized for acute myocardial infarction with Killip class Ⅲ heart failure. Preponderance of females afflicted by this condition is unclear.

Estrogen deficiency in the postmenopausal state may play a role[47]. Of particular interest, in other conditions with elevated catecholamine levels like subarachnoid hemorrhage, segmental wall motion abnormality is also predominantly seen in women. A reverse pattern of contractile abnormality with apical sparing has also been reported. Cardiac MRI is helpful in diagnosing and monitoring clinical recovery. Absence of delayed hyperenhancement on cardiac MRI is particularly important in differentiating this condition from ischemic and other types of nonischemic cardiomyopathy and acute myocarditis: normal first-pass contrast enhanced rest myocardial perfusion, reversible myocardial edema in regions of contractile dysfunction, and absence of late gadolinium enhancement is strongly indicative of the diagnosis of Takotsubo cardiomyopathy. Resolution of contractile dysfunction, days to weeks after initial presentation, is confirmatory of the diagnosis.

DRUG-INDUCED CARDIOMYOPATHIES

Several drugs may cause acute and chronic cardiac systolic dysfunction with the development of myocardial remodeling. Many of drugs administered chronically are cardiotoxic and may trigger the development of cardiac injury even when used appropriately. ESC guidelines emphasize some specific drug groups, which are strongly related to development of heart failure[48].

Anthracyclines are highly effective antineoplastic agents with wide application. However, one of the major complications in their long-term pharmacotherapy is cardiac dysfunction. Three distinct types of anthracycline-induced cardiotoxicity have been described[49]. Acute or subacute injury can occur immediately after treatment with transient arrhythmias, pericarditis and myocarditis. These manifestations usually respond rapidly with interruption of anthracycline infusion. Long-term therapy may be associated with chronic cardiotoxicity resulting in cardiomyopathy. Late-onset anthracycline cardiotoxicity may cause ventricular dysfunction and arrhythmias, which manifest years to decades after anthracycline treatment has been completed.

Echocardiography may serve as excellent diagnostic tool both for diagnosing and for screening, monitoring of patients on antineoplastic therapy.

A clinical study estimating the cumulative percentage of patients who developed doxorubicin-induced congestive heart failure found that cumulative dose of 400 mg/m^2 was 3%, increasing to 7% at 550 mg/m^2 and to 18% at 700 mg/m^2. Current anthracycline regimens typically contain less than the cumulative dose associated with increased risk of cardiomyopathy[50,51].

Standard treatment for systolic heart failure is indicated for treatment for both asymptomatic and symptomatic cases, with ACE inhibitors, β-blockers, spironolactone.

Several agents have been studied to decrease cardiotoxicity in such patients. Dexrazoxane (also known as cardioxane) is the most investigated agent[52,53]. It is the only approved cardioprotective agent in anthracycline chemotherapy, but there is no evidence for a difference in response rate or survival[54]. Other agents such L-carnitine, coenzyme Q10, N-acetylcysteine, vitamin E, and trimetazidine, have been investigated as metabolic cardioprotective agents[55-62]. Unfortunately, none of them showed prominent clinical efficacy in preventing anthracycline toxicity.

The alkylating agent cyclophosphamide is mainly cardiotoxic at high doses in bone marrow transplantation protocols[63]. Cardiotoxicity is expressed from transient electrocardiographic changes and asymptomatic increases of serum levels of cardiac enzymes to severe cardiotoxicity such as exudative pericardial effusion, ventricular hypertrophy and fatal myopericarditis and (hemorrhagic) myocardial necrosis[64].

ALCOHOLIC CARDIOMYOPATHY

Alcoholic cardiomyopathy represents one of the most common forms of secondary cardiomyopathies resembling IDC. The risk of development of alcoholic cardiomyopathy depends on both duration and doses of alcohol consumption. The clinical course and prognosis in alcoholic cardiomyopathy in withdrawal of alcohol consumption is better compared to those with idiopathic DCM[65,66]. The diagnosis of alcoholic cardiomyopathy may have several difficulties with regard to widespread consumption of alcohol in many countries, including patients with idiopathic DCM and similarities of radiological patterns of myocardial remodeling in both idiopathic and alcoholic cardiomyopathy[67].

ARRHYTHMOGENIC CARDIOMYOPATHY

Arrhythmogenic cardiomyopathy/RV dysplasia is the genetic form of cardiomyopathy characterized by fibrosis and fatty infiltration of RV myocardium and by manifestation of ventricular tachycardia/ventricular fibrillation. Lately, it has been shown that the disease is not confined

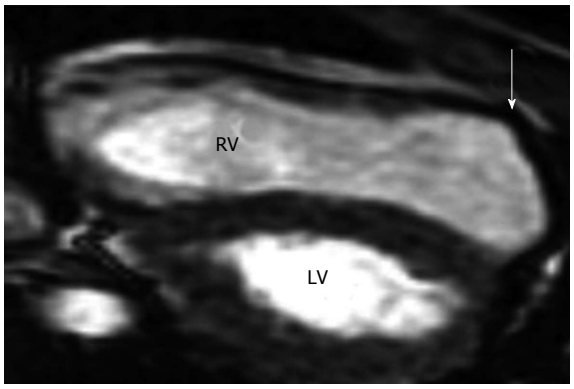

Figure 4 Arrhythmogenic right ventricle cardiomyopathy in a 17-year-old boy who experienced sudden cardiac death from sustained ventricular tachycardia during a soccer match and was revived with on-site defibrillation[105]. Parasternal long-axis 2D echocardiograms obtained in end systole show a dilated right ventricle (RV) and regional dyskinesis at the RV outlet tract (arrow). LV: left ventricle.

only to the right ventricle as the name suggests, because the left ventricle may be affected in up to 75% of patients[68]. This disease accounts for 20% of cases of SCD and mainly among young athletes dying suddenly, the prevalence of this cardiomyopathy is higher. In 30%-50% of cases arrhythmogenic cardiomyopathy represents family disease with autosomal-dominant inheritance of gene mutations encoding desmosomal proteins[69]. Presenting symptoms range from palpitation to syncope and SCD. Myocardial electrical instability comprises the main clinical manifestation with ventricular ectopics and ventricular tachycardia. Biventricular or RV failure is less common and observed mainly in patients with long-term disease protected from SCD by ICD implantation.

Diagnosis of this condition may cause difficulties with nonspecific abnormalities on echocardiographic and angiographic examinations. EMB has a low sensitivity, because samples are usually taken from the septum; a region that is infrequently involved[70]. ECG may have a diagnostic role with the following typical characteristics: wide QRS complexes in right chest leads, T wave inversion, and ε wave after QRS complex as a prototype of late ventricular potentials. The task force determined diagnostic criteria for arrhythmogenic cardiomyopathy, which involve data for cardiac MRI, ECG, positive family history, and arrhythmia clinics[71].

Contrast-enhancement-cardiac MRI may help to guide targeted EMBs (Figure 4).

Predilection patterns with midwall contrast enhancement are found in the basal anterior region and/or the RV outflow tract. These patterns of fibrosis correlate with fibrofatty replacement of the myocardium at histological assessment and predict induction of ventricular tachycardia during electrophysiological studies[69,71].

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is a clinically heterogenous autosomal dominant heart muscle disorder with inherited etiology, primarily by mutations of genes encoding the cardiac sarcomere myofilament proteins. HCM prevalence is 0.2% and one-third of patients show no obstruction of LV outflow tract (LVOT), whereas two-thirds develop a significant gradient under resting conditions and/or on exertion[72]. HCM was hardly diagnosed in the pre-echocardiographic era and abnormal electrocardiographs suggestive of LVH were attributed by clinicians to hypertensive heart disease. The etiology of HCM has similarly been sorted and HCM is an autosomal dominant genetic disorder, caused by mutations in at least 10 different genes, which code for sarcomeric proteins[73]. Mutations in the β-myosin heavy chain gene, myosin binding protein C and troponin T account for 70%-80% of all cases. The total number of mutations is > 100 and new mutations are being discovered[74]. These developments in the etiology of HCM resulted in a change of definition and HCM eventually was no longer a heart muscle disease of unknown cause.

GENETICS IN HCM

Sarcomere mutations are found in 60%-70% of adult and pediatric patients with a family history of HCM and in 30%-40% of apparently sporadic cases[69]. Mutations in myosin heavy chain (MYH7) and myosin binding protein C (MYBPC3) are the most frequent and comprise up to 8% of cases of sarcomeric HCM. Several studies[74] have demonstrated that cardiovascular deaths, progressive symptoms, and ventricular arrhythmias appear more prominent in HCM patients with sarcomeric mutations than in patients without mutations. Moreover, patients with more than one mutation have more severe symptomatology[74]. However the phenotypic presentation and penetrance of mutations may be variable and dependent on several other factors such as presence of hypertension and age. The presence of LVH frequently cannot be diagnosed before adolescence. Thus, the interpretation of genetic testing should be complex including clinical assessment.

The clinical application of genetic testing depends on the confidence of the prediction of disease. Genetic testing must be conducted also as a family test, because its advantages are greatest in larger families with both disease presentations and healthy individuals.

PATHOLOGY IN HCM

HCM is characterized by asymmetrical or symmetrical hypertrophy of the left ventricle with increased LV mass. Asymmetrical hypertrophy is presented by comparing the thickness of the septum with the LV free wall and by presence of septal to free wall thickness ratio > 1.3. Asymmetric hypertrophy of interventricular septum is the most frequent form of HCM. Other presentations include symmetric, apical forms. RV involvement occurs in 17.6% of all cases of HCM, most frequently affecting the middle to apical portion of the right ventricle[75,76].

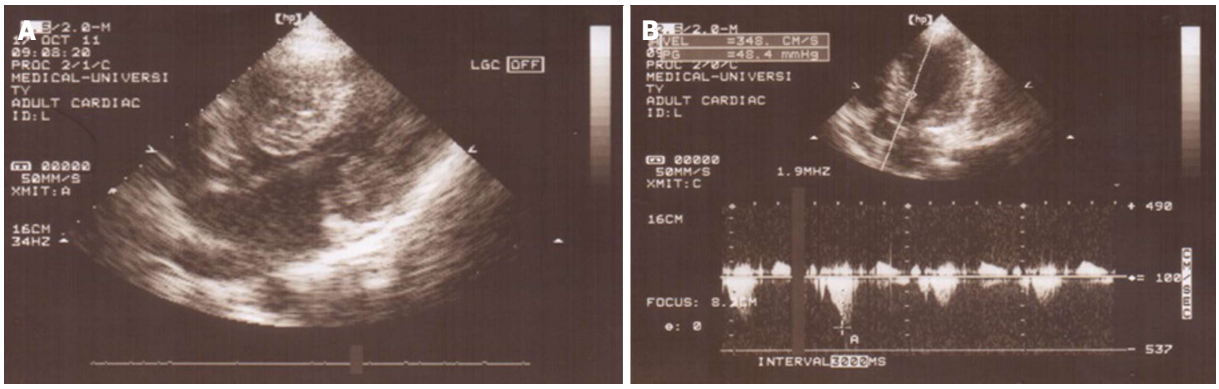

Figure 5 Patient with hypertrophic cardiomyopathy and subaortic stenosis. A: Parasternal long axis view showing expressed left ventricular (LV) hypertrophy at the region of the LV outflow tract; B: Doppler echocardiogram reveals the high subaortic gradient (ΔP = 48 mmHg).

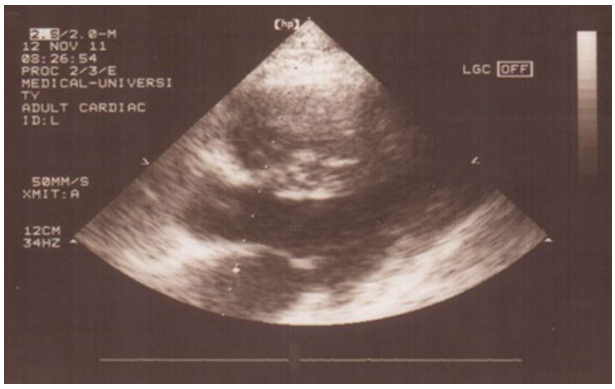

Figure 6 Echocardiogram of a 35-year-old patient with hypertrophic cardiomyopathy: massive hypertrophy of the interventricular septum with wall thickness 37 mm compared to posterior wall; hyperechogenic septal myocardium.

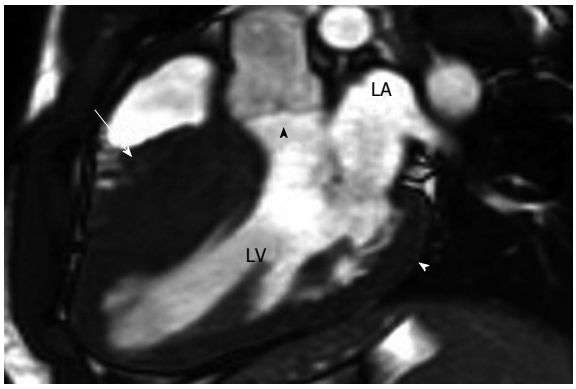

Figure 7 Hypertrophic cardiomyopathy[105]. A: 2D SSFP cardiac magnetic resonance imaging, obtained in end diastole in the long-axis plane of the LV outflow tract (LVOT) in a 17-year-old boy with Hypertrophic cardiomyopathy found at family screening, shows marked asymmetric septal hypertrophy with a ratio of ventricular septal thickness (27 mm, arrow) to inferiolateral wall thickness (9 mm, white arrowhead) of 3:1. Note that the hypertrophied septum encroaches on the LV lumen, causing mild narrowing of the LVOT (black arrowhead). LA: Left atrium; LV: Left ventricle.

Pathological changes in HCM at the histological level are characterized by cardiomyocyte hypertrophy and disarray with bizarre enlarged nuclei, hyperchromasia and pleomorphism. Increased content of interstitial collagen volume may also be present[77].

DIAGNOSIS OF HCM

Diagnosis relies on the electrographic and echocardiographic demonstration of hypertrophy patterns. LVH may be diffuse or more segmentally distributed (proximal and/or midportion of the interventricular septum, apex, anterior or lateral wall), but no single morphologic expression appears to be specific[78].

In fact, differentiation of LVH secondary to HCM may be difficult from other diseases affecting the ventricles, for example, hypertrophy secondary to infiltrative diseases (*e.g.*, amyloidosis), Fabry's disease[79], glycogen storage disorders[80], or systemic arterial hypertension. These diagnostic difficulties may rise with advanced age (Figures 5-8).

Besides LVH, LV outflow obstruction is one of the most common features of this disease. Asymmetric basal septal hypertrophy and the systolic anterior motion of the anterior leaflet of the mitral valve are the major contributors of LV outflow obstruction and the more or less significant accompanying mitral regurgitation[81]. In a series of 320 consecutive HCM patients, this obstructive pathology at resting conditions (defined as a gradient $\geqslant$ 50 mmHg at rest) was found in 37% of patients[82]. In the remaining patients, 52% developed dynamic outflow gradients during exercise or maneuvers which decrease afterload or increase contractility. Abnormal diastolic function is typical pattern of HCM. It may be present at early stages of HCM, even before morphological evidence of hypertrophy occurs[83,84].

The clinical presentation of HCM patients shows remarkable diversity: some individuals experience none or minor symptoms, others may develop dyspnea at exercise or at rest, angina pectoris, palpitations, atrial fibrillation, dizziness, presyncope and syncope, fatigue or finally end-stage heart failure requiring cardiac transplantation[85].

The changes on ECG are variable and include left axis deviation, occurrence of Q waves, a positive Sokolow index for hypertrophy, conduction abnormalities, ST-T depression or other abnormalities, negative T waves and giant T waves (particularly observed in Japanese

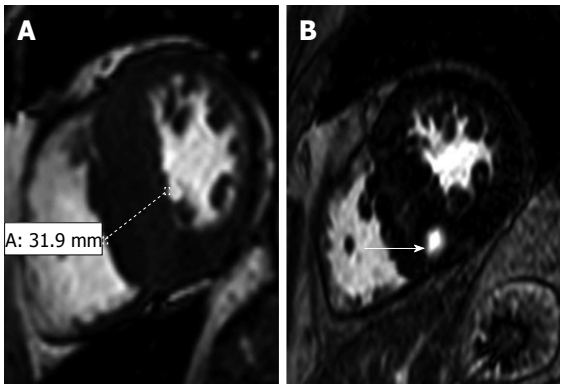

Figure 8 Hypertrophic cardiomyopathy in a 57-year-old man with a 2-year history of exertional dyspnea and chest discomfort who underwent implantable cardioverter-defibrillator placement for primary prevention of sudden cardiac death[105]. A: Short-axis 2D SSFP magnetic resonance imaging (MRI) performed in end diastole shows asymmetric septal hypertrophy with a maximal thickness of 31.9 mm encroaching on the ventricular lumen; B: Short-axis late contrast-enhanced MRI shows a patchy nodular area of enhancement in the hypertrophied septum (arrow) that does not correspond to a coronary artery territory and, therefore, is distinctly different from an infarct scar.

patients with apical type of HCM[86]. The ECG abnormalities may not parallel hypertrophy in all cases. Konno *et al*[73] observed ECG abnormalities (in particular ST-T abnormalities) in about 54% of genetically affected, but nonhypertrophic patients at echocardiography. A normal ECG does not exclude the presence of HCM but suggests a mild manifestation of the disease[87].

Risk stratification

Identification of high-risk HCM patients is important because of the need to implant an ICD. Several major risk factors of sudden death have been identified to date and these factors are: positive family history of premature SCD caused by HCM, documented nonsustained ventricular tachycardia, syncope at rest or during exercise, abnormal blood pressure response during exercise with increase in the systolic blood pressure of < 20 mmHg from the baseline value, and progressive fall in blood pressure during exercise or a fall in the systolic value by 20 mmHg after an initial increase, particularly in younger patients (< 40 years of age), expressed LVH with wall thicknesses > 30 mm[88]. The highest rate of cases of SCD in adolescents was linked with pronounced hypertrophy[88]. Potential additional risk factors include marked fibrosis on cardiac MRI, LV apical aneurysm, LVOT with gradient > 30 mmHg at rest, obstructive sleep apnea[88].

MANAGEMENT OF HCM

Medical therapy

Many patients with LVOT gradients > 50 mmHg may still be asymptomatic, but most HCM patients have symptoms that need to be managed. β-Blockers represent the cornerstone of therapy and have proved effective in patients with angina or dyspnea on effort, particularly when associated with LVOT obstruction, and are often administered to decrease the frequency of nonsustained ventricular arrhythmias. These beneficial effects are mediated by negative inotropic, chronotropic effects, improved ventricular relaxation, and increased time for diastolic filling. Despite these advantages, whether long-term treatment with β-blockers ultimately affects outcome in HCM patients remains undefined. By virtue of their efficacy in reducing LVOT obstruction and myocardial ischemia, current guidelines recommend β-blockers as first-line agents in symptomatic patients, both with and without resting obstruction. Two recent studies have consistently shown marked reduction or abolition in exercise-induced LVOT obstruction[83]. In patients intolerant to β-blockers, verapamil may be a good alternative for treatment of HCM patients. Verapamil and diltiazem have been administered in symptomatic patients with non-obstructive HCM. HCM guidelines suggest caution in using calcium channel blockers in patients with significant LVOT obstruction and elevated pulmonary artery wedge pressure, due to their potentially adverse hemodynamic effects and risk of precipitating edema. The beneficial effects of calcium channel blockers are largely mediated by their negative inotropic and chronotropic effects, leading to prolonged LV filling time and improved redistribution of flow towards the subendocardial layers of the left ventricle. To date, there is no definite evidence that verapamil effectively improves functional capacity in HCM, although the drug has been used for decades to ameliorate quality of life in nonobstructive patients, and is considered standard treatment[89]. Diltiazem was shown to improve LV diastolic parameters, either acutely or at mid-term administration[84].

The class IA antiarrhythmic drug disopyramide has been used successfully to attenuate the pressure gradient and improve symptoms in patients with LVOT obstruction, generally in association with β-blockers. The beneficial effect of disopyramide is conditioned by negative inotropic effects, resulting in symptomatic improvement[90]. Nevertheless, concerns regarding QTc prolongation and significant anticholinergic side effects may limit its long-term use.

Previously it was considered that amiodarone may have a protective role in HCM, with regard to ventricular arrhythmias. However, its efficacy in preventing sudden death is now considered not evident based on the fact that 20% of patients dying suddenly in one retrospective study were on active amiodarone treatment at the time of death[91].

Several studies showed that approximately two-thirds of patients can be successfully managed by medical therapy with resulting symptoms limitation and decrease of LVOT gradient > 50[89,91,92].

INTERVENTIONAL THERAPY AND SURGERY

Despite advances and efficacy of medical management of patients with HCM, many patients remain symptomatic and at high risk of SCD, which requires interven-

tional approaches to relieve LVOT obstruction. Alcohol septal ablation may be a suitable approach for patients with advanced age and high surgical risks. The procedure involves injecting 1-3 mL 96% ethanol into one of the septal branches supplying the hypertrophied myocardium, causing acute regional contractile dysfunction and leading to a thinning over the long term. This approach leads to reduction or elimination of the obstruction in 90% of cases. Mortality associated with the procedure is similar to that for myectomy (1%-2%) in experienced centers. High-grade AV block as a complication requiring implantation of a pacemaker is registered in experienced centers in 5% of cases[93].

Septal myectomy using the Morrow procedure has been defined as the therapy standard for many years for patients with HCM, who cannot be adequately treated by pharmacotherapy. The procedure involves removal of a part of the hypertrophied basal septum or thinning of the remaining septum to 5-8 mm. A reduction or elimination of the gradient was achieved in > 90% of patients. The procedure is indicated in patients with symptoms corresponding to NYHA class Ⅲ and gradient > 50 mmHg (rest or provocation). Perioperative mortality in experienced centers is 1%-2% and the rate of complete AV blocks postoperatively is 2%-5%[94].

In patients with HCM, pacing the RV apex and apical septum can cause a decrease in the outflow tract gradient by decreasing the ventricular contractility, with a decrease in systolic movement of the basal septum to the LVOT. Continuous pacing with the development of LV enlargement may further decrease LVOT gradient. Dual chamber pacing has shown modest benefit in randomized controlled trials. It is mostly indicated in patients > 65 years of age, those who have indication for pacemaker or ICD implantation, and those who have a high risk of surgery[95].

RESTRICTIVE CARDIOMYOPATHIES

Restrictive cardiomyopathy is a disease of the myocardium characterized by impaired ventricular filling and reduced diastolic volume of either or both ventricles, with normal or near-normal systolic function.

Unlike DCM and HCM, where the definition is morphological, the definition of restrictive cardiomyopathy is based on hemodynamic abnormalities. Myocardial relaxation abnormality with interstitial fibrosis and calcifications compose the fundamental abnormalities of restrictive cardiomyopathies. Restrictive filling is due to higher diastolic pressure and causes passive venous congestion. Cardiac output can be increased by an increase of heart rate, but becomes ineffective due to shortened filling time.

PREVALENCE

Restrictive cardiomyopathies form 5% of pediatric cardiomyopathies, but several types are more common in certain populations. For example, EMF is a relatively common cause of heart failure in equatorial Africa[96].

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

These conditions result in impaired ventricular filling and primarily diastolic heart failure. They manifest with a clinical heart failure syndrome frequently indistinguishable from that caused by systolic dysfunction. AV block and symptomatic bradycardia can be seen, often indicating pacemaker insertion. Atrial fibrillation is poorly managed by conventional therapy.

Restrictive cardiomyopathies may be classified as primary (*e.g.*, EMF, Löffler's endocarditis, and idiopathic restrictive cardiomyopathy) or secondary. Causes of secondary restrictive cardiomyopathy include infiltrative diseases (*e.g.*, amyloidosis, sarcoidosis, and radiation carditis) and storage diseases (*e.g.*, hemochromatosis, glycogen storage disorders, and Fabry's disease). Fabry's disease, although rare, has assumed a new importance as effective therapy became possible.

Physical examination in restrictive cardiomyopathies may reveal congestive heart failure signs: peripheral edema, jugular vein distensions, and gallop rhythm. Echocardiographic typical signs of restrictive cardiomyopathy are normal ventricular dimensions with dilated atria as a feature of systemic venous congestion, normal or nearly normal systolic function. Myocardial calcifications are typical for EMF. Some patterns revealed by echocardiography may indicate etiology like granular sparkling of myocardium in amyloidosis (Figure 9), endocardial thickening and thrombus in eosinophilic endocardial disease and EMF.

Doppler features of restrictive cardiomyopathy are high early filling E/A wave ratio > 2, short isovolumic relaxation time < 60 ms, short deceleration time < 150 ms, and expressed pulmonary ravenous reversal flow[97]. The treatment of restrictive cardiomyopathy patients is mainly symptomatic with diuretics and aldosterone antagonists. Severity of heart failure symptoms and absence of efficacy are the indications for cardiac transplantation[98].

SPECIFIC TYPES OF RESTRICTIVE CARDIOMYOPATHIES

Amyloidosis

Amyloid heart disease is classified as primary, secondary, familial, or senile. Primary amyloid heart disease is caused by overproduction of amyloid light chain immunoglobulin from a monoclonal population of plasma cells, usually associated with multiple myeloma. Secondary amyloid heart disease is associated with chronic inflammatory conditions such as rheumatoid arthritis, tuberculosis, and familial Mediterranean fever[99,100].

Familial and senile amyloid heart disease is related to the overproduction of transthyretin. Myocardial amyloid

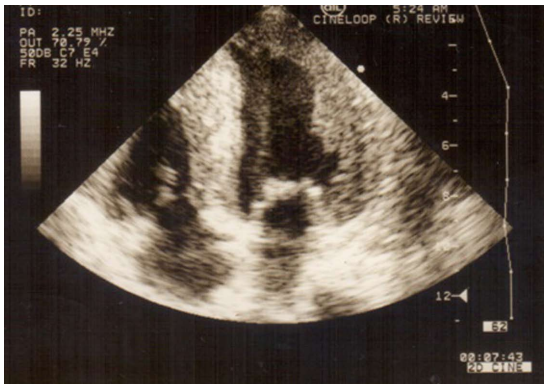

Figure 9 Patient with secondary cardiac amyloidosis due to familial Mediterranean fever. Echocardiogram shows hypertrophic amyloid infiltration and increased hyperechogenic "granular sparkling" myocardium with increased myocardial wall thickness.

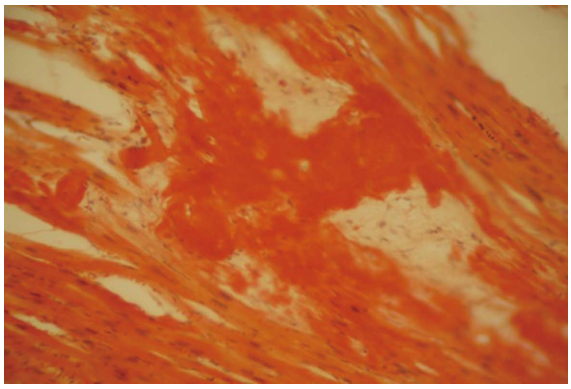

Figure 10 Amyloid deposits in myocardium in patient with secondary amyloidosis due to familial Mediterranean fever. Autopsy study with Congo-Red-positive extracellular deposits, causing disorder of myocardial organization.

heart disease is confirmed by EMB (Figure 10). The presence of near-normal LV dimensions combined with increased myocardial wall thickness, particularly biventricular thickening, should arouse suspicion of an infiltrative cardiomyopathy, especially if accompanied by low-voltage QRS complexes on ECG. Unfortunately, there is no proven treatment for cardiac amyloidosis and the prognosis remains poor.

HEMOCHROMATOSIS

Hemochromatosis ("bronze diabetes") is a disease that results in iron overload and deposition of iron in the sarcoplasmic reticulum of many organs, including the heart. Most commonly it has autosomal recessive type of Mendelian inheritance. Typically, this disorder has multisystem manifestations. Erythropoiesis remains normal, but progressive parenchymal iron deposition causes multi-organ insufficiencies. Excess of cellular iron leads to cellular death and fibrosis[101]. The use of serum ferritin levels as a screen for this condition may be clinically important. Cardiac MRI can have diagnostic value to reveal cardiac involvement. Hemochromatosis may result in a restrictive or dilated cardiomyopathy, with characteristic histological features. Treatment is by repeated phlebotomy. Family screening is advised.

SARCOIDOSIS

Sarcoidosis is a systemic disease resulting in the formation of noncaseating granulomas that can infiltrate the myocardium. It is associated with restrictive cardiomyopathy in 5% of patients, but may later progress to DCM[102]. It is difficult to diagnose unless there is other organ involvement (usually pulmonary). It may be suspected in patients with cardiomyopathy and lymphadenopathy, skin rashes, or splenomegaly. Cardiac sarcoidosis is associated with ventricular tachycardia and conduction abnormalities (especially complete heart block) that can cause syncope and SCD. EMB may show findings specific for sarcoidosis but, because of the patchy nature of the disease, biopsy may miss characteristic lesions, resulting in a low overall sensitivity. Cardiac granulomas may occasionally respond to steroids but turn to scar tissue[103]. Sudden death cannot be prevented by steroids[104]. Regular Holter monitoring is recommended to look for AV blocks, which should be treated with permanent pacemakers.

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