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REVIEW

DILATED CARDIOMYOPATHY: EVOLUTION OF PATHOGENESIS CONCEPTS AND POTENTIAL FOR NEW THERAPIES

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ABSTRACT

Cardiomyopathies are classified as either primary or secondary. Primary cardiomyopathies consist of disorders namely or predominantly confined to the heart muscle, which have genetic, non-genetic, or acquired causes. Secondary cardiomyopathies are disorders, which have myocardial damage as a result of systemic or multi organ disease. 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.

Cardiomyopathies are defined as cardiac diseases of myocardium with associated structural and functional abnormalities. The knowledge of these pathologies for a long period was not clear in clinical practice due to uncertainties regarding definition, classification and clinical diagnosis. In the past decades great advances have been made in the understanding of the molecular and genetic issues, pathophysiology, clinical and radiologic assessment of these diseases.

Dilated cardiomypathy represents the most common form of all cardiomyopathies and this review provides advances in the studies of dilated cardiomyopathy genetics, genotype-phenotype approach, imaging diagnostics, and management strategies.

Cardiomyopathies are defined as myocardial disorders in 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, hypertrophic cardiomyopathy, restrictive cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy/dysplasia. Dilated cardiomyopathy is the most common form of heart muscle disease, comprising approximately 60% of all cardiomyopathies and characterized by left ventricular dilation and systolic dysfunction. The dilated cardiomyopathy is often assumed as a common pathway of several cardiovascular pathologies.

KEYWORDS: dilated cardiomyopathy, secondary cardiomyopathy, echocardiography, magnetic resonance imaging, classification.

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, non-genetic, or acquired causes. Secondary cardiomyopathies are disorders, which have myocardial damage as a result of systemic or multi organ disease [*Maron BJ et al., 2006*]. 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.

A more recent definition and classification of cardiomyopathies was proposed by 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 ven-

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tricular 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" [*Maron BJ et al., 2006*].

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 American Heart Association (AHA) and of the European Society of Cardiology (ESC) [*Jefferies JL, Towbin JA, 2010*].

The AHA divided cardiomyopathies into 2 major groups based on predominant organ involvement. Primary cardiomyopathies (genetic, nongenetic, 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) [*Elliott P et al., 2008*].

In 2013 the MOGE(S) classification for a phenotype- genotype nomenclature of cardiomyopathies is proposed by World Heart Federation [*Arbustini E et al., 2013*]. 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 American College of Cardiology, AHA A-D class and New York Heart Association (NYHA) I-IV functional classes. 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

Table 1.

Classification for cardiomyopathies by American Heart Association

Primary cardiomyopathies	Genetic	Hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, left ventricular non compaction, conduction defects, mitochondrial myopathies, ion channel disorders
	Acquired	Inflammatory, takotsubo, peripartum, tachycardia induced, infants of mothers with insulin-dependent diabetes mellitus
	Mixed	Dilated cardiomyopathy, restrictive
Secondary cardiomyopathies	Infiltrative	Amyloidosis, Gaucher's, Hurler's, Hunter's
	Storage	Fabry's, glycogen storage disease, Niemann-Pick disease, hemochromatosis
	Toxicity	Drugs, heavy metals
	Endomyocardial	Endomyocardial fibrosis, 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	Systemic lupus erythematosus, dermatomyositis, scleroderma
	Consequence of cancer therapy	Anthracyclines, radiation, cyclophosphamide

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.

Dilated cardiomyopathy

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 non-genetic, or acquired) or secondary (inflammatory, autoimmune, 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, valve disease) or ischemic heart disease [*Rosamond W et al., 2008; Jefferies JL, Towbin JA, 2010*]. A large number of cardiac and systemic diseases can cause systolic dysfunction and left ventricular dilatation, but in the majority of cases no definite cause is found. This led to the common terminology "idiopathic dilated cardiomyopathy".

Prevalence

Prevalence in the general population remains undefined. This disorder develops at any age, in either sex, and in people of any ethnic origin [*Taylor MR et al., 2006; Towbin JA et al., 2006*]. In adults, DCM arises more commonly in men than in women. In children, the yearly incidence is 0.57 cases per 100,000 per year overall, but is higher in boys than in girls (0.66 vs. 0.47 cases per 100,000, $P<0.006$). Two thirds of children are thought to have idiopathic disease [*Towbin JA et al., 2006; Jefferies JL, Towbin JA, 2010*]. In adults, the prevalence is 1 in 2500 individuals, with an incidence of 7 per 100,000 per year (but it could be underdiagnosed). The prevalence of DCM in the United States (adjusted for age) is 36 per 100,000 of the population [*Towbin JA et al., 2006*]. 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 [*Hershberger RE et al., 2009*].

Familial (Genetic) dilated cardiomyopathy

Prominent progress has been made in studies the genetics of DCM. Most of genes involved in the development of DCM encode structural elements of the cardiomyocytes particularly dystrophic 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 more than 30 autosomal and 2-X linked genes shown to predispose to DCM and number of these genes will continue to increase. There are sufficient evident data that with new diagnosis of idiopathic dilated cardiomyopathy 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 far early diagnosis of cardiomyopathy in family members [*Jefferies JL et al., 2010*].

The diagnosis of FDC is made when idiopathic dilated cardiomyopathy is diagnosed in two closely related family members. About 20-48% of DCM have been reported as familial, although with incomplete and age dependent penetrance, and linked to a diverse group of >20 loci and genes [*Hershberger RE et al., 2009*]. Although genetically heterogeneous, the predominant mode of inheritance for DCM is autosomal dominant, with X-linked autosomal recessive and mitochondrial inheritance 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, maternal inheritance), and signs and symptoms of other inherited metabolic diseases [*Hershberger RE et al., 2009*]. 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 [*Arbustini E et al., 2002; Hermida-Pieto M et al., 2004; McNair WP et al., 2004*]. Other DCM genes of this type include desmin, caveolin, and β- and α-sarcoglycan, as well as the mitochondrial respiratory chain gene [*Maron BJ et al., 2006*]. 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 [*McNair WP et al., 2004; Hershberger RE et al., 2009*].

Pathology

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 dilated 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.

Histologic examination: the most typical DCM pattern is the development of interstitial and perivascular fibrosis of varying degree [*Sanderson JE et al., 1993*]. Myocardial necrosis predominantly is present at subendocardium.

Our study group noninvasively investigated myocardial fibrosis degree in patients with idiopathic and ischemic dilatation cardiomyopathy by Shirani method [*Shirani J et al., 1992*]. The percentage of volumic collagen fraction in the left-ventricular myocardium was significantly higher in DCM patients compared to those with ischemic CMP. Increase of collagen fraction correlated with the degree of dilation of left ventricle [*Sisakian A et al., 2001*].

Clinical manifestation

The most common clinical manifestations of DCM are congestive heart failure symptoms and thromboembolic complications. The disease commonly has progressive course. The determination of time of manifestation is not easy, because the disease course for a long period is not symptomatic. Patients admit to hospital in cases of expressed heart failure symptoms. A careful history taking and physical examination with diagnostic studies are very essential for differential diagnostics of DCM. More commonly, DCM manifests without any history and provoking factor. Cardiomegaly at radiologic examination or on abnormal electrocardiogram (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 transpire. 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 oedema 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 % patients with new-onset DCM may have cardiac recovery [*McNamara DM et al., 2001*].

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 *mm Hg*, cardiac index <2.5 $l/min/m^2$, severely reduced ejection fraction, restrictive diastolic filling pattern, and severe mitral regurgitation [*Topol E, 2007*].

Electrocardiography

The ECG in patients with idiopathic DCM has no specific diagnostic role, and abnormalities ranging from isolated T wave and ST segment changes to septal pathologic Q waves, wide QRS

complex in patients with left ventricular fibrosis may 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 non-sustained ventricular tachycardia and a small number present with sustained ventricular tachycardia.The electrocardiography is utilized as a first-line screening and diagnostic tool for detecting conditions associated with sudden death. Idiopathic DCM patients with a prolonged QRS had significantly worse survival than other patients [*Silverman ME et al., 1995*].

Echocardiography

Echocardiography in DCM has characteristic pattern, although it is not possible to make differential diagnosis by echocardiography between idiopathic and other secondary left ventricular dilation with dysfunctions. M-mode echocardiography shows dilated LV with diffuse hypokinetic walls (Fig. 1a,b). 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 is usually not accompanied by sufficient hypertrophy, which causes increase of volume-to-mass ratio [*Elliott P, 2000*]. Doppler echocardiography shows frequently functional mitral and tricuspid regurgitation and different degree of diastolic dysfunctions 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 left ventricular end diastolic pressure and pulmonary artery wedge pressure. Left ventriculography may show ventricular dilation with global hypokinesis.

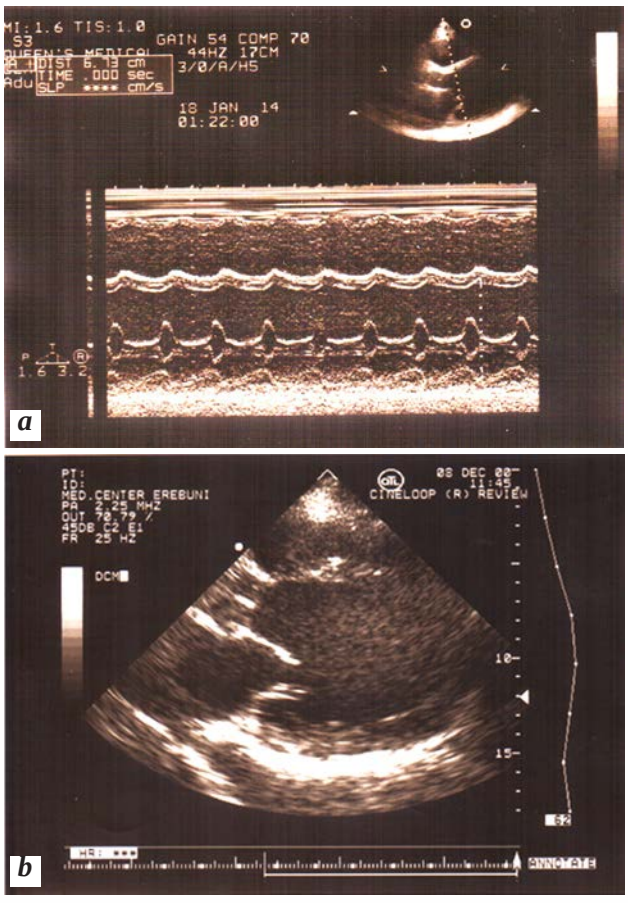

Figure 1. *M mode and B mode echocardiogram of patient with idiopathic DCM.*
a) *M mode echocardiogram shows dilated left ventricle with hypokinesis of interventricular septum and posterior wall,*
b) *parasternal long axis view of B mode echocardiogram showing remodeled left ventricular shape with loss of elliptical form.*

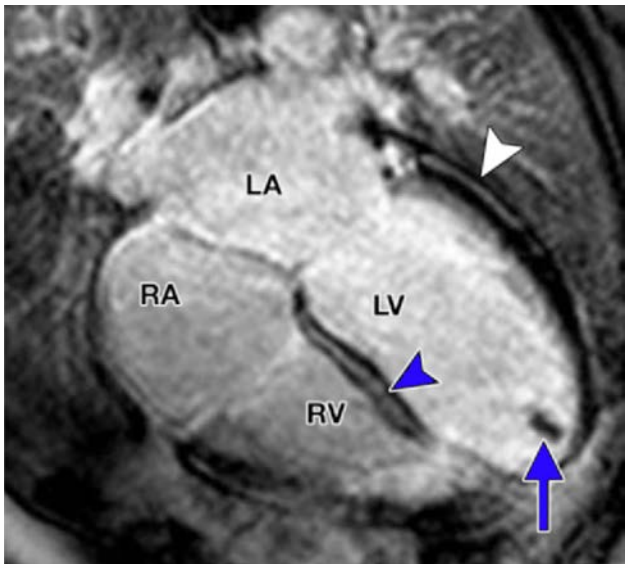

Figure 2. *Dilated cardiomyopathy in a 36-year-old male soccer player with fatigue and a 3-5-day history of burning epigastric pain associated with nausea, vomiting, and early satiety. Horizontal long-axis late contrast-enhanced MR image shows an apical thrombus (arrow) in the left ventricle and midwall enhancement in the lateral left ventricular wall (white arrowhead) and the interventricular septum (black arrowhead) [Stojanovska J et al., 2013].*

Cardiac magnetic resonance imaging (CMR) and dilated cardiomyopathy

CMR can differentiate ischemic CMP from non- ischemic CMPs through use of late gadolinium imaging, even when the heart is globally dilated and dysfunctional (Fig. 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 revascularisation (hibernation), biventricular pacing (dyssynchrony) [*Arai AE, 2011*]. Non-ischemic DCM may demonstrate either no LGE or mid-wall LGE in areas not corresponding to a coronary territory. Additional features that can be detected using CMR include valvular regurgitation, apical thrombus, dyssynchrony with or without posterior scar, signs of decompensation, cardiac iron, left ventricular (LV) hypertrophy, Right ventricular (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 (DCM) is the histological, immunohistological and polymerase chain reaction (PCR)-based analysis of CMR guided endomyocardial biopsy (EMB) specimens. Persistent viral infections and infection-associated or postinfectious inflammatory processes of the myocardium may be key pathologic mechanism of progression of myocarditis to cardiomyopathy.

Antiviral therapy approach

Recently several studies undertaken for endomyocardial based etiologic 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 promising choice for treatment of chronic viral myocarditis. Currently, there is no approved treatment for chronic viral heart disease, but data from open labelled 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-months interferon-beta (IFN-β1a) therapy of patients with persistent enteroviral and adenoviral myocarditis complete elimination of enteroviral and adenoviral genome was proved by follow-up biopsies taken 3 month after termination of the antiviral therapy. Virus clearance was paralleled by an improvement of mean left ventricular function, a decrease in ventricular size, an 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 needed to identify patient cohorts who will benefit from target antiviral or immunosuppressive therapy. Treatment of myocarditis in current regular clinical practice remains supportive including the need for ventricular assist devices and heart transplantation [*Kühl U et al., 2003*].

Endomyocardial biopsy

In the last 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 [*Perkan A et al., 2002*]. Actual techniques enable to perform multiple drawings of tissue samples from both ventricles with low incidence of procedural complications. In addition to several clinical states such as after heart transplantation, specific myocardial diseases, the more frequent indication to 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 dif-

ficulties of procedure, and biopsy specimens may not content pathologic changes. The diagnostic performance of EMB is superior if procedure is provided with CMR guided target area [*Yoshida A et al., 2013*]. Diagnostic findings which show absence of inflammation may assist in further management strategy of DCM. Thus, in selected cases EMB represents a useful method for a 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 beta-blockers, ACE inhibitors, spironolactone in patients with NYHA class II to IV heart failure. Diuretic therapy may have beneficial effect on symptoms without prominent effect on long-term outcome. Beta- 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) [*Bardy GH et al., 2005*]. An implantable cardioverter-defibrillator (ICD) and biventricular pacemakers are indicated in appropriate patients with both idiopathic and secondary dilated cardiomyopathies with left ventricular dysfunction for secondary prevention of sudden cardiac death. ICD can be combined with cardiac resynchronization therapy (CRT) in patients with prolonged QRS duration and left ventricular dyssynchrony [*Chung ES et al., 2008*]. However the benefits of ICD were established in patients with systolic dysfunction of ischemic etiology [*Moss AJ et al., 2002; Bardy GH et al., 2005*]. Individual studies in patients with nonischemic CMP failed to show significant reduction of of total mortality [*Bänsch D et al., 2002; Wijetunga M, Strickberger SA, 2003; Kadish A et al., 2004*], although meta-analysis of five trial showed 31% mortality reduction [*Desai AS et al., 2004*].

Surgical approaches to restore left ventricular shape by reverse remodeling include left ventricular 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 [*Mann DL, Willerson JT, 1998*]. 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 idiopathic dilated cardiomyopathy. Surgery should be considered before inotropic dependency occurs when prior medical treatment has failed [*Suma H et al., 2007*].

In carefully selected patients, partial ventriculoectomy combined with mitral valve reconstruction achieves short-term results comparable to that after heart transplantation [*Wilhelm MJ et al., 2005*]. However, long-term results and multicenter evaluation will be 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 can be 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 the single center study with inclusion of 110 patients with nonischemic DCM intracoronary CD 34+ stem cell transplantation associated with improved ventricular function, exercise tolerance, and long-term survival [*Vrtovec B et al., 2013*]. 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. 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 cells therapy to improve cardiac function in patients with DCM [*Arnous S et al., 2011*].

The five-year survival averages 30–40% and 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 the 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 months 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 [*Ntusi NBA, Mayosi BM, 2009*]. PPCM is a diagnosis of exclusion, as 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 [*Abboud J et al., 2007*]. A critical individual approach concerning the risks of subsequent pregnancy must be considered. Because of its rare incidence, geographical 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 months postpartum, the absence of an identifiable cause for heart failure, the absence of recognizable heart disease prior to the last month of pregnancy [*Demakis JG et al., 1971*].

Left ventricular non-compaction

Left ventricular 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, non-compacted endocardial region. The non-compacted myocardial region is comprised of prominent trabeculations and deep intertrabecular recesses that directly communicate with the left ventricular cavity. The condition may present without any associated cardiac malformation and is then labelled isolated left ventricular non compaction. Non compacted 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 [*Jefferies JL, Towbin JA, 2010*] and as a primary genetic cardiomyopathy in the American Heart Association classification [*Elliott P et al., 2008*].

Both sporadic and familial forms are described. The presence of significant non compaction is estimated at 1:2.000 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 [*Udeoji DU et al., 2013*].

Non-compaction myocardium clinically may represent from asymptomatic individuals to those with severe disease presenting with heart failure, ventricular arrhythmia and systemic thromboembolism. Non cardiac 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 [*Nikolić A et al., 2012*].

- Echo: ratio of non-compacted to compacted myocardium in end-systole of > 2:1

- Cardiac MRI: ratio of non-compacted to compacted myocardium in end-diastole of > 2.3:1. Cardiovascular imaging is important in the diagnosis of left ventricular non compaction. Cardiac MRI (Fig. 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 and apical thrombus [*Cheng H et al., 2011*]. Pharmacological management of LVNC mainly is symptomatic and directed to heart failure symptoms relief. Heart transplantation re-

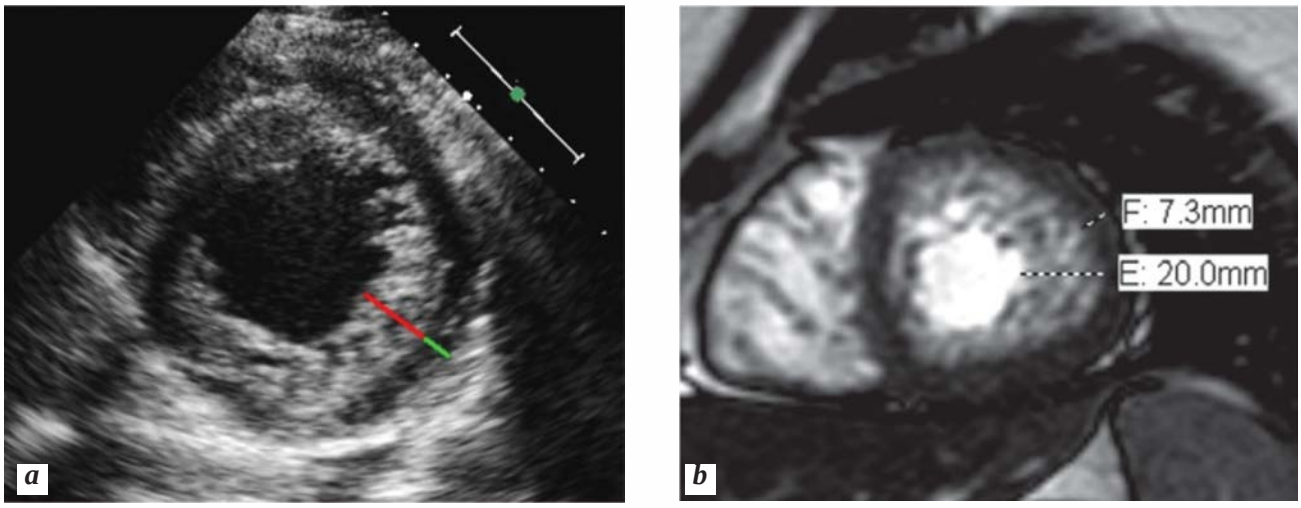

Figure 3. *Noncompaction cardiomyopathy in two patients.*
a) *Dilated cardiomyopathy in a 60-year-old man with new-onset congestive heart failure. Short-axis echocardiogram obtained in systole at the level of the left ventricle shows a two-layered myocardium with a noncompacted (red line) and compacted (green line) layer along the lateral, inferior, and anterior walls and a maximal end-systolic NC:C ratio of more than 2,*
b) *Symptoms of New York Heart Association Class III heart failure and severely reduced (35% or less) left ventricular ejection fraction in a 35-year-old woman. Short-axis 2D SSFP cardiac MR image obtained in end diastole shows thickening of the noncompacted layer of the left ventricular myocardium, with an NC:C ratio of 2.9. The patient underwent subsequent ICD placement for primary prevention of sudden cardiac death [Stojanovska J et al., 2013].*

mains 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 [*Dote K et al., 1991*]. 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.

History of intense emotional or physical stress and a typical pattern of left ventricular contractile dysfunction on cardiac imaging are suggestive of the diagnosis. The most common abnormality on ECG is ST-segment elevation resembling STEMI [*Prasad A et al., 2008*]. This cardiomyopathy is a transient and reversible cardiomyopathy. 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 morphologic features of the left ventricle, 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 left ventricular apical ballooning syndrome [*Zeb M, 2011*].

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 (takotsubo), 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 IS (*2012*), two to three times higher plasma catecholamine concentrations were found in 13 patients with transient LV apical ballooning syndrome compared with 7 controls hospitalized for acute myocardial infarction (MI) with Killip class III heart failure. Preponderance of females afflicted by this condition is unclear.

Estrogen deficiency in the post-menopausal state may play a role [*Brenner R et al., 2012*]. 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 diagnosis and in monitoring clinical recovery. Absence of delayed hyperenhancement on cardiac MRI is particularly important in differentiating this condition from ischemic and other types of non-ischemic 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 [*Dickstein K et al., 2008*].

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 [*Shan K et al., 1996*]. 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.

Clinical study estimating doxorubicine induced cumulative percentage of patients, who developed 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 [*Carver JR et al., 2008; Wu AH, 2008*].

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

Several agents have been studied to decrease cardiotoxicity in such patients. Dexrazoxane (also known as cardioxane) is the most investigated agent [*Wexler LH et al., 1996; Swain SM et al., 1997*]. It is the only approved cardioprotective agent in anthacycline chemotherapy, but there is no evidence for a difference in response rate or survival [*van Dalen EC et al., 2011*]. Other agents such L-carnitine, coenzyme Q10, N-acetylcysteine, vitamin E, trimetazidine, have been investigated as metabolic cardioprotective agents [*Unverferth DV et al., 1983; De Leonardis V et al., 1985; Kawasaki S et al., 1992; Iarussi D et al., 1994; Elihu N et al., 1998; Singal PK, Iliskovic N, 1998; van Acker FA et al., 2000; Silber JH et al., 2004*]. Unfortunately, none of them showed prominent clinical efficacy in preventing antracycline toxicity.

An alkylating agent – cyclophosphamide is mainly cardiotoxic at high doses in bone marrow transplantation protocols [*Meinardi MT et al., 2000*]. 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 [*Chu TF et al., 2007*].

Alcoholic cardiomyopathy

Alcoholic CMP represents one of the most common forms of secondary cardiomyopathies resembling idiopathic dilated cardiomyopathy. The risk of development of alcoholic CMP depends on both duration and doses of alcohol consumption. The clinical course and prognosis in alcoholic CMP in withdrawal of alcohol consumption is better compared to those with idiopathic DCM [*Demakis JG et al., 1974; Guillo P et al., 1997*]. The diagnosis

of alcoholic CMP may have several difficulties with regard to widespread consumption of alcohol in many countries including patients with idiopathic DCM and similarities of radiologic patterns of myocardial remodeling in both idiopathic and alcoholic CMP [*Fauchier L et al., 2000*].

Arrhythmogenic cardiomyopathy

Arrhythmogenic cardiomyopathy/right ventricular dysplasia is the genetic form of cardiomyopathy characterized by fibrosis and fatty infiltration of right ventricular myocardium and by manifestation of ventricular tachycardia/ventricular fibrillation. Lately it has been shown that the disease is not confined only to the right ventricle as the name suggests, because the left ventricle may be affected in up to 75 % of patients [*Falase AO, Ogah OS, 2012*]. 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 genes mutations encoding desmosomal proteins [*McKenna WJ et al., 1994*]. Presenting symptoms range from palpitation to syncope and SCD. Myocardial electrical unstability composes the main clinical manifestation with ventricular ectopics, ventricular tachycardia. Biventricular or right ventricular 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, as samples are usually taken from the septum, a region that is infrequently involved [*Maron BJ et al., 2003*]. Electrocardiography may have diagnostic role with following typical characteristics: wide QRS complexes in right chest leads, T wave inversion and epsilon 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 magnetic resonance (CMR) imaging, electrocardiography, positive family history and clinics of arrhythmias [*Bohl S et al., 2008*].

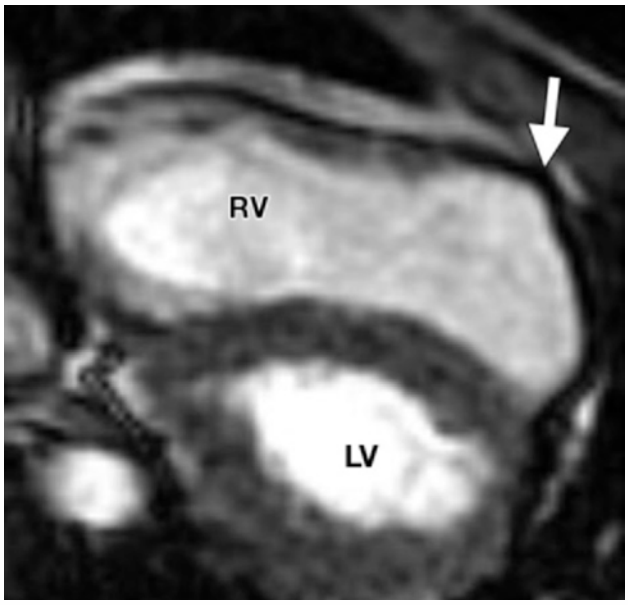

Figure 4. *ARVC in a 17-year-old boy who experienced sudden cardiac death from sustained ventricular tachycardia during a soccer match and was revived with on-site defibrillation. Parasternal long-axis 2D echocardiograms obtained in end systole show a dilated right ventricle and regional dyskinesis at the RVOT (arrow) [Stojanovska J et al., 2013].*

Contrast-enhancement CMR may help guide targeted endomyocardial biopsies (Fig. 4).

Predilection patterns with midwall contrast enhancement are found in the basal anterior region and/or the right ventricular outflow tract. These patterns of fibrosis correlate with fibrofatty replacement of the myocardium at histologic assessment and predict induction of ventricular tachycardia during electrophysiological studies [*McKenna WJ et al., 1994; Bohl S et al., 2008*].

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