

DILATED CARDIOMYOPATHY

Definition

Dilated cardiomyopathy (DCM) refers to a spectrum of heterogeneous myocardial disorders that are characterized by ventricular dilation and depressed myocardial performance in the absence of hypertension, valvular, congenital, or ischemic heart disease.¹ Left ventricular dilatation is defined by LV end-diastolic dimensions or volumes >2 z-scores above population mean values corrected for body size, sex, and/or age. For adults this represents an LV end-diastolic diameter >58 mm in males and >52 in females and an LVEDV index of ≥ 75 mL/m² in males and ≥ 62 mL/m² in females by ECHO.² Left ventricular diastolic dysfunction may coexist, and atrial dilation as well as right ventricular dilation and dysfunction can also develop. In essence, dilated cardiomyopathy is an ‘umbrella’ term that describes the final common pathway of different pathogenic processes and gene–environment interactions.³

Epidemiology

Dilated cardiomyopathy is the most common cardiomyopathy worldwide and accounts for 25% of heart failure cases in the US. The estimated prevalence is 0.04-0.4%.^{1,2} It is lower in Japan and higher in Africa and Latin America. Blacks have a 3-fold increase in risk of developing DCM compared with whites.¹ This disorder develops at any age, and in either sex, but more commonly in men than in women. In children, two-thirds of cases are idiopathic.

Aetiology and Pathophysiology

Dilated cardiomyopathy is the final common response of myocardium to diverse genetic and environmental insults.⁴ Non-generic causes are presented in Table 1. Phenomapping based upon clustering of clinical data by machine learning may help to create homogeneous DCM subgroups, called phenogroups. Four distinct phenogroups have been identified (mild and severe systolic dysfunction, auto-immune and arrhythmias).⁵ They are associated with significant differences in clinical presentation, and outcome, paving the way for a more personalized treatment approach.

Familial and Genetic

Inherited dilated cardiomyopathy accounts for 20-35% of all cases. Approximately 40% of familial DCM cases have an identifiable monogenic cause, or at least a rare variant of large effect size as the primary determinant of risk.⁶ The prevalence is estimated to 0.036-0.4%.² Most mutations are private missense, nonsense or short insertion/deletions. Autosomal

dominant inheritance is the predominant pattern of transmission. X-linked, autosomal recessive, and mitochondrial inheritance are less common. At presentation, a family history and screening of first-degree relatives (for ventricular dilation, conduction disturbances and skeletal myopathy) should be considered.^{4,7}

Idiopathic DCM, compared to other genetic cardiomyopathies, demonstrates marked locus heterogeneity, with many genes proposed to have a role in the phenotype. However, while clinical DCM genetic testing panels include an average of ~100 genes, in large cohorts and a study that has curated published evidence, a total of 12 genes were classified as a definitive or strong relationship (**BAG3, DES, DSP, FLNC, LMNA, MYH7, PLN, RBM20, SCN5A, TNNC1, TNNT2, TTN**). Additional genes of moderate evidence are presented in Table 2 and Appendix 1.⁸⁻¹¹ Causative genes in dilated cardiomyopathy seem to predominantly encode sarcomeric proteins with subsequent defects of force generation and transmission. Certain DCM-associated genes (LMNA, FLNC, desmosomal, PLN, TMEM43, RBM20) exhibit a predominantly arrhythmogenic phenotype, while other genotypes (TTN, MYH7, and BAG3) have been described to exhibit a predominant heart failure phenotype in which arrhythmic events are less common.^{2,12}

Titin gene (**TTN**) truncating mutations represent the largest single genetic contributor to DCM, they have been detected in approximately 25% of familial cases of idiopathic dilated cardiomyopathy and in 18% of sporadic cases,¹³ and are also common in families with both dilated and peripartum cardiomyopathy.¹⁴⁻¹⁷ It should be noted, however, that clinical manifestations of TTN -gene-positive familial cardiomyopathy are not solely genetically determined and are influenced by risk factors.¹⁸ In patients with TTN cardiomyopathy and ventricular arrhythmias, the arrhythmogenic substrate mainly involves the basal septal and perivalvular regions. The most common ECG morphology is characterized by a left bundle branch block or right bundle branch block pattern with inferior QRS axis, and ventricular arrhythmias are usually fast and poorly tolerated.¹⁹ A high overlap between mutations causing dilated and hypertrophic cardiomyopathies, and genetic channelopathies has been observed in next-generation sequencing studies.²⁰ The same sarcomeric genes identified for hypertrophic cardiomyopathy seem to be responsible and support the concept of a ‘final common pathway’ of genetically-determined cardiomyopathies. Truncating genetic variants in Titin have been associated with cardiomyopathy and arrhythmia, especially in individuals of European ancestry.²¹ The heart is commonly involved in inherited muscle and cardiac phenotypes (cardiomyopathies and rhythms disorders) can be the first or predominant manifestations.²² Mutations in the TTN gene are prevalent in preeclampsia, dilated cardiomyopathy, and peripartum cardiomyopathy.²³

When the disease is associated with atrioventricular block with or without limb-girdle muscular dystrophy, the most frequently identified mutations are in the **LMNA** gene

encoding for lamin proteins A and C, and that is integral to nuclear structural integrity, which account for approximately 5-8% cases of familial DCM.^{24,25} These mutations also cause Emery–Dreifuss muscular dystrophy and limb-girdle muscular dystrophy (Erb’s). Emery–Dreifuss muscular dystrophy (EDMD) is a rare, progressive genetic disorder characterized by early joint contractures, progressive muscle atrophy, and cardiac abnormalities. In most cases, EDMD is inherited as an X-linked or autosomal dominant disease caused by variants in genes encoding one or more of the proteins comprising the nuclear envelope. The two most commonly implicated genes are *EMD* (EDMD1) and *LMNA* (EDMD2).²⁶ Patients with the *LMNA* gene are also prone to AF and subsequently thromboembolism, and ventricular arrhythmias and sudden death. Male *EMD* variant-carriers have a risk of progressive heart failure and ventricular arrhythmias similar to that of male *LMNA* variant-carriers.²⁶

RNA-binding motif protein 20 (***RBM20***) mutation carriers with dilated cardiomyopathy also present with a fast progression of heart failure and high risk for arrhythmias.²⁰ Other mutations with pleiotropic cardiac manifestations such as of the ***SCN5A*** gene have been implicated in various arrhythmia syndromes (long QT, Brugada, idiopathic VF, conduction system disease, sick sinus syndrome and AF).²⁷ Mutations in the ***FLNC*** gene (encoding filamin C) cause an overlapping phenotype of dilated and left-dominant arrhythmogenic cardiomyopathies complicated by frequent premature sudden death.²⁸

Infectious Causes

Myocarditis is characterised by pathological inflammation of the myocardium, leading to chronic heart failure in a substantial number of patients younger than 40 years. Bacterial, fungal, parasitic, rickettsial, and spirochetal infections may be implicated, but the more common cause in the western world are viral infections. Although the causative relationship between viral infection and myocarditis is not unequivocally established, identification of the causative virus with polymerase chain reaction (PCR) indicates that some cases of dilated cardiomyopathy are the result of chronic myocarditis and subsequent cardiac injury either due to autoimmune reactions or direct viral tissue injury. Viral persistence in the myocardium has been associated with progressive cardiac dysfunction.^{29,30} The most common viruses are ***coxsackie B*, *parvovirus B19*, *adenovirus*, and other enteroviruses**.^{30,31} Presentation of disease can vary, ranging from minor symptoms of malaise to acute heart failure. ***Chagas’ cardiomyopathy***, an enzootic disease caused by the protozoan *Trypanosoma cruzi* and transmitted by the Triatomine insect, remains the leading cause of chronic systolic heart failure in endemic areas.³² Traditionally regarded as a tropical disease found only in Central America and South America, Chagas disease is growing in prevalence in other traditionally nonendemic areas. In 2018 it had been estimated to affect at least 300 000 residents of the United States.³³ In acute Chagas disease, a widespread immunological reaction is

characterized by diffuse lymphadenopathy, hepatomegaly, and splenomegaly. However, most patients may be asymptomatic or present with RBBB and LAH and wall-motion abnormalities.³⁴ Although uncommon (<10%), patients can progress directly from acute Chagas disease to the chronic cardiac form. More commonly, chronic Chagas heart disease develops after several decades of the indeterminate form of the disease.³³ An initial myopericarditis that may evolve to dilated cardiomyopathy is the most important and severe manifestation of human chronic Chagas disease and is characterized by heart failure, ventricular arrhythmias, heart blocks, atrial fibrillation, thromboembolic phenomena, and sudden death.³⁴ Chronic Chagas cardiomyopathy is highly arrhythmogenic, with estimated annual rates of appropriate implantable ICD therapies and electrical storm of 25% and 9.1%, respectively.³⁵ The annual incidence of Chagas cardiomyopathy is 1.85% and is driven primarily by mild cardiomyopathy.³⁶ Approximately 25% of asymptomatic, T cruzi-seropositive persons will develop cardiomyopathy within the next 10 years.³⁶ **HIV**-associated cardiomyopathy may present as focal myocarditis, subclinical left ventricular (LV) or right ventricular dysfunction, and symptomatic dilated cardiomyopathy.³⁷

Autoimmunity

Diagnosis for both viral and non-viral causes is based on histological, immunological, and immunohistochemical criteria for endomyocardial biopsy samples. Autoimmune-mediated chronic myocarditis is characterised by autoantibodies to cardiac myosin and other heart antigens.³⁸ Whether patients develop heart disease because they possess harmful antibodies against this receptor or whether they develop these antibodies as a result of cardiac tissue injury remains unclear. However, circulating cardiac autoantibodies are identified in dilated cardiomyopathy and myocarditis patients at a higher frequency than in patients with non-inflammatory heart disease. Furthermore, in healthy relatives of dilated cardiomyopathy patients, serum anti-heart autoantibodies are an independent predictor for development of this disease.³⁹

Cytotoxicity

Chronic alcohol abuse is an important cause of dilated cardiomyopathy in developed countries. The amount of alcohol required to produce cardiomyopathy is generally considered as >80 g/day over 5 years, but there is still some controversy regarding this definition.⁴⁰ The exact mechanism is not known: direct toxicity and increased cellular apoptosis, acetaldehyde-mediated impairment of actin–myosin interaction and mitochondrial dysfunction, and neurohormonal activation have been proposed. A genetic background may also coexist since titin truncating variants predispose to alcoholic cardiomyopathy.⁴¹ The outcome is worse than in idiopathic dilated cardiomyopathy, and the estimated 4-year mortality rate approaches 50% in patients without complete abstinence after diagnosis.⁴² The cardiac toxicity of drugs such as

cocaine, methamphetamines, anthracyclines (doxorubicin and daunorubicin), trastuzumab, and tyrosine kinase inhibitors such as *anti-vascular endothelial growth factor (VEGF)* chemotherapy agents (bevacizumab, sorafenib, sunitinib, pazopanib) is discussed in Cardio-oncology.

Hyper- and hypo-thyroidism, infiltrative disease such as *haemochromatosis, rheumatological and endocrine/metabolic disease* are more rare causes. *Amyloidosis, mitochondrial dysfunction, and metabolic storage diseases* are discussed in the Chapter on Syndromic and Metabolic Cardiomyopathies.

Peripartum cardiomyopathy and tachycardiopathies, and stress-induced cardiomyopathy are discussed in relevant Chapters.

Despite complete evaluation including history, physical examination, echocardiography, coronary angiography, and endomyocardial biopsy, approximately 50% of patients with dilated cardiomyopathy have no etiology identified.⁴³

Presentation

Patients present with SOB and fatigue or signs of overt heart failure. Signs and symptoms that raise suspicion of specific diagnoses are presented in the Chapter on Classification and Diagnosis.

Physical examination

It may be unremarkable or reveal the signs of heart failure as described in the Chapters on Heart Failure.

Investigations

Laboratory tests

Hemoglobin, WBC, serum iron and ferritin, liver, renal, and thyroid function tests, and serum electrolytes should be taken at initial assessment. In suspicion of underlying disease specific tests are obtained.⁴⁴ Simple biomarkers (e.g., serum creatine kinase, lactate) should be systematically tested because they can provide preliminary clues for exploring skeletal muscle disease in patients with cardiomyopathies.²²

Electrocardiography No ECG abnormalities are specific for DCM. First or second degree AV block, intraventricular block, ST-T wave changes, Q waves, atrial fibrillation, or ventricular arrhythmias may be seen. New-onset LBBB is associated with an increased risk of all-cause mortality.⁴⁵ Low QRS voltages are the electrocardiographic landmark of phospholamban mutations.⁴⁶ New ventricular arrhythmias or second-degree or third degree heart block in patients with apparently chronic dilated cardiomyopathy suggests sarcoidosis, muscular or myotonic dystrophy, or LMNA disease. AF may also be seen early in patients

with the LMNA gene. Monomorphic sustained VT is due to bundle branch reentry, but is rare and also suggests sarcoidosis, Chagas disease, or LV-dominant ARVC. An artificial intelligence-enabled ECG model enriched with 3 epidemiological questions (AI-ECG-EPI model) as an opportunistic screening for Chagas disease has been found useful for opportunistic screening in endemic regions of Brazil.⁴⁷

Echocardiography The left ventricle is dilated, and more spherical than usual with raised wall stress and depressed systolic function with or without mitral regurgitation. Usually contractility is globally reduced without segmental abnormalities. Additionally, pericardial effusion (especially in myocarditis) and signs of right heart failure may be present.

Cardiac magnetic resonance (CMR) provides the most accurate estimate of ventricular structure and function and allows detection of inflammation and scarring.⁴⁸ Midwall late gadolinium enhancement identifies a group of patients at increased risk of SCD regardless of the LVEF.⁴⁹⁻⁵¹

Combined 18 F-fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (FDG PET-CT) is useful to rule out sarcoidosis.⁵²

Endomyocardial biopsy is controversial. It can be used to distinguish between disease processes that need alternative treatment strategies, such as storage diseases, sarcoidosis, and haemochromatosis. It is reasonable in patients with new-onset cardiomyopathy and fulminant heart failure who may benefit from an early diagnosis. Usually however, microscopic examination reveals areas of interstitial and perivascular fibrosis, and sometimes areas of necrosis and cellular infiltrate. Assessment of myocardial fibrosis predicts both risk of sudden cardiac death and likelihood of LV functional recovery.⁴ Myocardial fibrosis is the presumed substrate of VF in DCM. Thus, myocardial biopsy for electron microscopic detection of myofilament changes in biopsy specimens may also be useful in determining the prognosis of DCM patients presenting initially with decompensated heart failure, since they are strongly associated with mortality and HF recurrence, regardless of the cause.⁵³

Electrophysiology study is indicated in patients with sustained palpitations, wide-QRS-complex tachycardia, presyncope, or syncope, and to diagnose bundle-branch reentrant tachycardia and to guide ablation.

Additionally, **testing for secondary or specific causes** that mimic dilated cardiomyopathy is suggested—with clinical suspicion of *haemochromatosis*, *sleep-apnea*, *HIV infection*, *rheumatological disease*, *storage diseases*, or *pheochromocytoma*. The diagnosis of *Chagas' disease* is generally based on serologic testing for IgG antibodies to *T. cruzi* antigens, but no one of the available assays (ELISA, immunofluorescence assay, and hemagglutination assay) has adequate sensitivity and specificity for the diagnosis. Two tests, in which different antigens or techniques are used, are required to make the diagnosis; when the results are discordant, additional testing must be performed.⁵⁴

Diagnostic strategies for dilated or non-dilated LV cardiomyopathy are presented in Figure 1.

Genetic Testing

Genetic testing is essential in patients with newly-onset DCM. Large studies have shown a yield varying from 8% to 36% of genetic testing in patients with DCM, depending on aetiology or family history.⁵⁵ The sensitivity for genetic testing has been variable (25–40% for familial DCM, 10–25% for isolated DCM) and there have been limited genetic-prognostic associations that would directly change the management for the proband.⁶ Familial dilated cardiomyopathy demonstrates incomplete penetrance (ie not all mutations carriers are affected by the disease) with variable phenotypic expression, and significant locus and allelic heterogeneity, making genetic diagnosis complex. In addition, many rare genetic variants exist in the general population, and their contributions to cardiovascular disease have not been defined. Arrhythmias and cardiac conduction disease are the most common early manifestations of putative pathogenic variants implicated in DCM, mostly occurring before the development of structural or functional abnormalities. Thus, a genotype-first screening approach for DCM using a large genetic panel is not suitable in the general population because of incomplete understanding of DCM genetic architecture and reduced penetrance of DCM-associated putative pathogenic variants.⁵⁶

Genetic family screening following the detection of a pathogenic or likely pathogenic variant in a proband with DCM is recommended for all first-degree relatives. A systematic strategy has been proposed by ESC groups.⁵⁷ Relatives of patients with DCM should undergo clinical examination, ECG, echocardiographic screening, and genetic testing,⁵⁸ especially when a highly positive family history is present. Other indications have been proposed.⁶ Table 1 presents the genes that are most relevant for DCM genetic testing and those likely to yield interpretable results.⁸ Other genes involved have limited diagnostic value because novel variants will be uninterpretable and their diagnostic yield is minimal. Developments on TTN truncating mutations are exciting in this respect,¹³ particularly in the light of the reported association with both cardiomyopathy and arrhythmia.²¹

In the presence of premature conduction disturbances and ventricular arrhythmias screening for mutations in the SCN5A or LMNA genes may be useful. Recommendations are presented in Table 3.

Risk Stratification

The main risk-stratifier is LVEF, but its ability to predict arrhythmic death is rather limited (see also Chapters on HF and VT). As in other primary myocardial disorders, programmed

ventricular stimulation has no role in predicting SCD, and the independent predictive ability of NSVT is not established.⁵⁹ CMR may be a predictor of SCD by means of detecting myocardial fibrosis.^{48,60} RV systolic dysfunction as assessed by magnetic resonance is also an independent and powerful prognostic factor.⁶¹ Genetic testing for identification of malignant mutations and other electrocardiographic markers may be useful for risk stratification purposes.⁶⁰ Middle-aged adult carriers of rare missense or loss-of-function LMNA variants are at increased risk for arrhythmia and cardiomyopathy.⁶² Titin cardiomyopathy is not associated with worse prognosis compared to other forms of DCM.¹⁷ A prediction score for risk assessment in patients with LMNA mutations has been derived. It is based on male sex, nonmissense LMNA mutation, first degree and higher atrioventricular block, nonsustained ventricular tachycardia, and left ventricular ejection fraction (<https://lmna-risk-vta.fr>).⁶³ Phospholamban (PLN) p.Arg14del mutation has also been associated with ventricular arrhythmias in patients with DCM.⁶⁴ Risk stratification according to genotypes is presented in Table 4.

Therapy

In the last decades, the prognosis of patients with DCM has improved significantly with survival free from death and heart transplantation rising to more than 80% at 8-year follow-up.⁶⁵ Treatment of heart failure has been described in the relevant Chapter. Treatment of heart failure should continue indefinitely, since many patients deemed to have recovered from dilated cardiomyopathy will relapse following treatment withdrawal.⁶⁶ Treatment of myocarditis is described in the relevant Chapter.

The marked genetic heterogeneity of DCM and variable penetrance of mutations, with the exception of *LMNA* mutations, has impeded the direct application of most genotypes to clinical management.¹⁶ *Immunosuppression* with steroids and azathioprine may be useful only in dilated cardiomyopathy patients with evidence of **HLA upregulation** on biopsy samples or **virus-negative myocarditis** and **chronic inflammatory cardiomyopathy**.^{67,68} Intravenous immune globulin is not effective in recent-onset dilated cardiomyopathy.⁶⁹ In chronic dilated cardiomyopathy and **persistent viral genomes**, treatment with *interferon* resulted in the elimination of the viral genomes and improved left ventricular function.⁷⁰ *Immunoadsorption* with subsequent immunoglobulin G substitution is another possibility for patients with **cardiodepressant autoantibodies** detected in myocardial biopsy specimens.⁷¹ **Danicamtiv** is a promising investigational small molecule that binds directly to cardiac myosin and selectively enhances cardiac actomyosin activity. Initial clinical results are favourable.⁷² Recommendations for the management of arrhythmias are presented in Table 8. Independent risk factors for malignant arrhythmias in **lamin A/C mutation** carriers are

NSVT, LVEF<45% at the first clinical contact, male sex, and non-missense mutations (insidel/truncating or mutations affecting splicing).^{73 74} Table 5 presents general recommendations.

Tables 6 and 7 and Figures 2-4 present indications for ICD implantation.

Benznidazole and nifurtimox are the only drugs with proven efficacy against **Chagas disease** (Table 8).³³ Benznidazole, 150 mg bd for 60 days is the antiparasitic treatment of choice.^{34,75} However, due to side effects up to one third of patients abandon therapy with the resultant development of resistant species, and the addition of posaconazole does not seem to be beneficial.⁷⁶

Beta blockers are avoided in **cocaine-related cardiomyopathy** (unopposed α receptors), and benzodiazepines are used to blunt adrenergic excess in cocaine-associated heart failure.⁷⁷

Left ventricular volume procedures (such as the Batista or Dor) has not offered improved survival. Gene and stem cell therapy are also under investigation.⁷⁸ Indications for ICD and cardiac resynchronization pacing (CRT) are discussed in Chapters on heart failure and VT). Although meta-analyses have indicated potential benefit, no single trial has documented improved survival with primary ICD implantation in dilated, as opposed to ischemic, cardiomyopathy (see Chapters on heart failure and VT). However, ICD is recommended in patients with LVEF $\leq$ 35% and NYHA II-III heart failure, whereas its use in LVEF<35% and NYHA I is controversial. The risk prediction model for ventricular arrhythmias in laminopathies may facilitate the choice of candidates for implantable cardioverter defibrillators in these patients.⁶³

Hypertrabeculation is not associated with embolic risk in patients with dilated cardiomyopathy, including those in sinus rhythm with severe systolic dysfunction, and the low embolic risk observed in a recent study does not support routine anticoagulation.⁷⁹

Recommendations for exercise and participation in Sports are provided in Table 9.^{80,81}

Prognosis

Prognosis is variable depending on the cause of DCM with an average initial annual mortality 10-30%, which, however, becomes consistently lower with time (5-year mortality at 20%). SCD accounts for at least 30% of the overall mortality in DCM.⁸² Approximately 50% of new-onset DCM cases may have substantial recovery, but early relapse is seen in up to 40% of patients and associated with poor clinical outcomes.⁸³ In a nationwide study in Denmark, a family history of premature cardiomyopathy death was associated with an increase in risk of clinically diagnosed cardiomyopathy ranging from 6- to 400-fold, and a 3- to 7-fold increase in risk of ventricular arrhythmia.⁸⁴ Patients with cardiomyopathy due to infiltrative

myocardial diseases, HIV infection, or doxorubicin therapy have an especially poor prognosis.⁴³ *LMNA*-related heart disease is also associated with a high incidence of phenotypic progression and adverse arrhythmic and nonarrhythmic events over long-term follow-up.²⁴ DCM caused by mutations in *BAG3* is characterized by an aggressive clinical course and high rate of heart failure and a high, but incomplete, penetrance in carriers >40 years of age.⁸⁵ Framingham data have suggested that survival is worse in non-ischemic than ischemic cardiomyopathy,⁸⁶ but this is debatable.⁴³ The highest-risk period for children with dilated cardiomyopathy is in the first year after diagnosis, with death or transplantation occurring in 26% of patients, compared with ~1% per year in subsequent years. Survival is worse for subjects diagnosed before 4 weeks and after 5 years of age, those with familial cardiomyopathy, and those who failed to improve left ventricular function during followup.⁸⁷

Pregnancy

It is not absolutely contraindicated, depending on the type of cardiomyopathy and underlying risk factors (Table 10).^{88,89} Careful considerations to maintain normovolemia and lumbar epidural anesthesia are preferred during labor. Caesarian delivery may be needed to avoid the undesirable circulatory effects of the Valsalva maneuver.

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