Chapter

Sudden Cardiac Death in Hereditary Dilated Cardiomyopathy

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Abstract

Dilated cardiomyopathy (DCM) is characterized by the phenotype of a dilated left ventricle with systolic dysfunction. It is classified as hereditary when it is deemed of genetic origin; more than 50 genes are reported to be related to the condition. Symptoms include, among others, dyspnea, fatigue, arrhythmias, and syncope. Unfortunately, sudden cardiac death may be the first manifestation of the disease. Risk stratification regarding sudden death in hereditary DCM as well as preventive management poses a challenge due to the heterogeneity of the disease. The purpose of this chapter is to present the epidemiology, risk stratification, and preventive strategies of sudden cardiac death in hereditary DCM.

Keywords: cardiomyopathy, dilated cardiomyopathy, heart failure, implantable cardioverter defibrillator, risk stratification

1. Introduction

Cardiomyopathies are categorized based on their phenotype. In that context, dilated cardiomyopathy (DCM) is characterized by a dilated left ventricle (LV), typically with thin walls, and systolic dysfunction (**Figure 1**). Sometimes the dysfunction is not limited to the left ventricle but also affects the right ventricle. It is estimated that approximately 1 in 2500 people suffer from DCM [1]. The causative pathways are often complex, and several risk factors work together. In the vast majority of patients, there is a history of hypertension. Other well-known etiologies are myocarditis, chemotherapy, toxins, radiation, and coronary artery disease. However, when a causative reason for the dilation of the heart cannot be identified, DCM is considered idiopathic. About 20–50% of idiopathic DCM is considered to be of a genetic origin, being consequently hereditary [2]. Interestingly, only in 30–40% of cases of familial DCM can a specific gene be identified [3].

In hereditary DCM, there is variability among phenotypes, and the manifestation of LV dysfunction is heterogeneous. More than 50 genes are associated with the disease [4] (**Table 1**). Many of the gene mutations responsible for DCM affect the cell structure called sarcomere, which is involved in cardiac contractility. That is why some of those genes may be responsible for the development of hypertrophic cardiomyopathy as well. In 20% of the cases of hereditary DCM, mutations of the titin (TTN) gene are found, which encodes the protein titin found in the sarcomere [5].

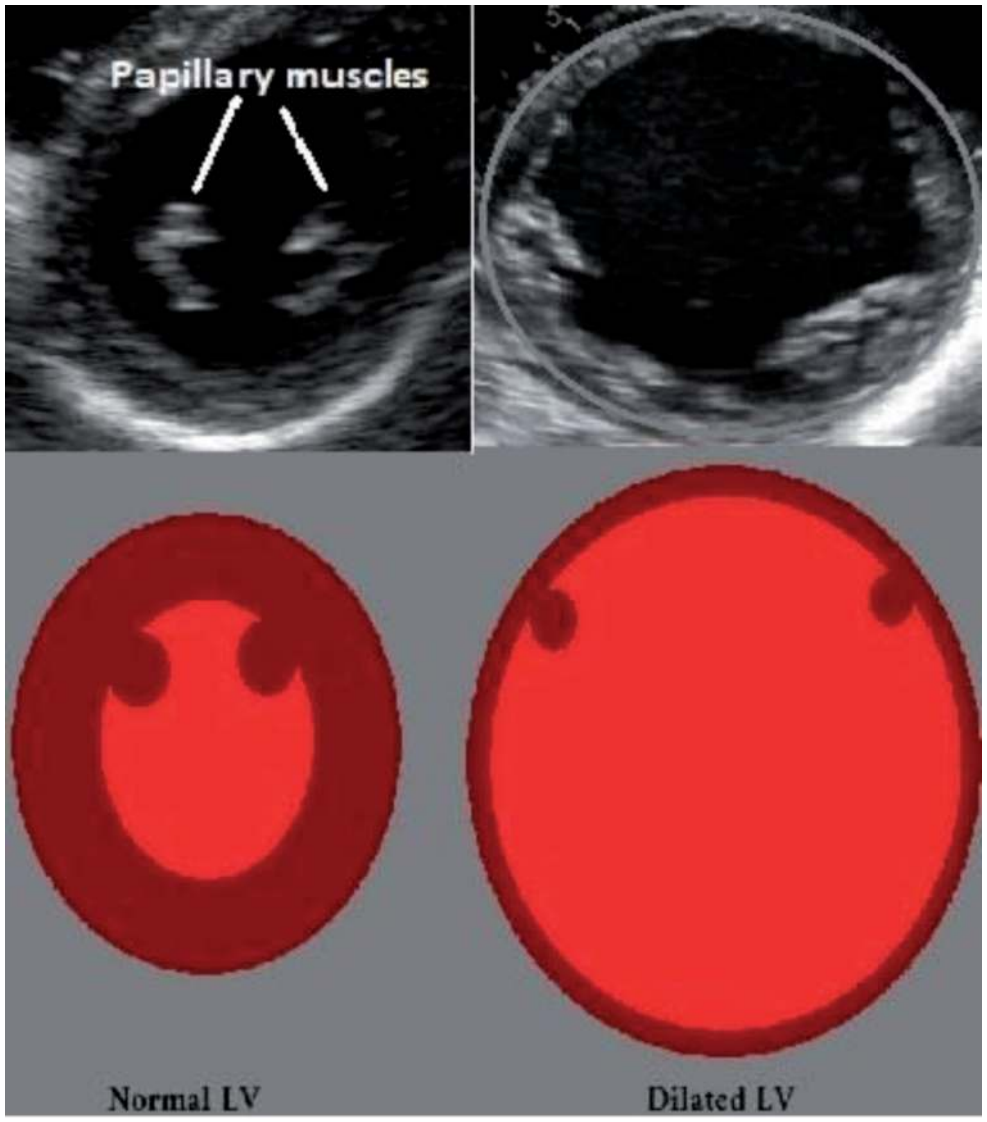

Figure 1.
Normal and dilated left ventricle in parasternal short-axis view.

The inheritance pattern is autosomal dominant in the vast majority of the cases, which means that an individual has a 50% chance to inherit the gene if one of the parents carries it. In other cases, the pattern is autosomal recessive, which means that if both parents are affected, there is a 25% chance of inheriting the disease genotype. X-linked patterns, in which the gene is inherited through an X chromosome, have also been reported. In some cases, it is possible that the carrier may not develop the phenotype of the disease due to variable penetrance of the disease.

Inherited DCM is defined by (a) the presence of two or more affected individuals in a single family who fulfill DCM criteria; fractional shortening <25% and/or ejection fraction <45% and left ventricular end diastolic diameter > 117% of the upper reference level corrected for age and body surface area based on Henry's formula or (b) the presence of a first-degree relative with unexplained sudden death before the age of 35 years [6].

Symptoms of DCM are due to ventricular dysfunction and compensatory left ventricular remodeling as well as the involvement of the electrical conduction system of the heart [7]. Symptoms vary among patients, even if they are members of

Gene	Cellular structure
ABCC9	Calcium/sodium handling
ACTC1	Sarcomere and cytoskeleton
ACTN2	Sarcomere and cytoskeleton
ANKRD1	Sarcomere and transcription factor
BAG3	Sarcomere
CRYAB	Cytoskeleton
CSRP3	Sarcomere and cytoskeleton
DES	Cytoskeleton
DMD	Cytoskeleton
DSG2	Desmosome
EYA4	Other
FLNC	Cytoskeleton
GATAD1	Other
LAMA4	Extracellular matrix proteins
LCB3	Cytoskeleton
LMNA	Nuclear envelope
MYBPC3	Sarcomere
MYH6	Sarcomere
MYH7	Sarcomere
MYPN	Cytoskeleton
PLN	Calcium/sodium handling
PSEN1	Other
PSEN2	Other
RBM20	Other
SCN5A	Calcium/sodium handling
SGCD	Cytoskeleton
TAZ	Other
TCAP	Sarcomere and cytoskeleton
TMPO	Nuclear envelope
TNNC1	Sarcomere
TNNI3	Sarcomere
TNNT2	Sarcomere
TPM1	Sarcomere
TTN	Sarcomere
VCL	Sarcomere and cytoskeleton

Table 1.
The main genes associated with hereditary dilated cardiomyopathy and the cellular structure that they regulate.

the same family [5]. Symptoms can occur at any age; typically, they first appear in mid-adulthood. Patients often report breathlessness, swelling of the legs, fatigue, chest pain, and arrhythmias, ranging from palpitations and syncope to fatal

arrhythmias that cause SCD. Unfortunately, SCD is sometimes the first manifestation of the disease.

2. Sudden cardiac death in hereditary DCM

2.1 Definition of sudden cardiac death

Sudden cardiac death (SCD) is defined as the sudden and unexpected death of a person who was otherwise stable prior to the event [8]. If the death is witnessed and occurs within 1 hour of onset of symptoms, it is classified as SCD. If the sudden and unexpected death is not witnessed, then SCD is declared if it occurs within 24 hours of the person last being seen alive and well.

2.2 Mechanisms

In the case of hereditary cardiomyopathies, such as DCM, SCD occurs due to the development of fatal ventricular arrhythmias: ventricular tachycardia (VT) and ventricular fibrillation (VF) are most common, but prolonged bradycardia does occur. Possible underlying mechanisms for the initiation of a fatal re-entry arrhythmia in a DCM patient may include: (a) conduction block caused by a reduction of myocytes and hypertrophy and (b) continuous re-entry regeneration due to increased fibrosis, interstitial, and perivascular as well as post-necrosis fibrosis [9, 10]. Non re-entry mechanisms, such as focal automaticity, electrolyte disturbances, and stretch-induced arrhythmias, also contribute to the presentation of arrhythmias [10]. In particular, focal automaticity predisposes a patient to nonsustained VT (NSVT) [11].

2.3 Epidemiology

DCM ranks third as the cause of SCD among cardiomyopathies, after arrhythmogenic right ventricular cardiomyopathy (ARVC) and hypertrophic cardiomyopathy. SCD accounts for roughly a third of all-cause mortality among hereditary DCM patients. Rates of SCD vary among the patients in regard to their New York Heart Association (NYHA) functional status (**Table 2**). Notably, in patients with NYHA class I and II, 50–60% of deaths are classified as sudden, while in NYHA class IV patients, only 20–30% of deaths are sudden [10]. This is explained by the fact that in NYHA class IV, most patients die from progressive heart failure [12]. In most cases, potentially fatal arrhythmias present in a setting of systolic ventricular dysfunction, although the proportion of SCD is higher among patients with lower NYHA status. However, there is a subset of patients (reported to vary from 2% to one third of the DCM population) who present early in the disease course with

NYHA	Risk of SCD
Class I	50–60%
Class II	50–60%
Class III	20–30%
Class IV	20–30%

Table 2.
Risk of sudden cardiac death as a proportion of overall mortality according to New York Heart Association classification.

Factors associated with a high risk of arrhythmias	
Clinical	Low LVEF (<25–30%) Absence of beta-blockers AR-DCM Family history of SCD
Ambulatory	QRS duration QT dynamicity T-wave alternans NSVT on Holter monitoring
Imaging	Midwall late gadolinium enhancement Impaired global longitudinal strain Mechanical dispersion
Genetic	Desmosomal mutations LMNA mutation SCN5A mutation FLNC mutation RBM20 mutation PLN mutation

Table 3.
Factors associated with a high risk of life-threatening arrhythmias.

life-threatening arrhythmias (**Table 3**) or unexplained syncope that are not related to the severity of LV dysfunction [13, 14]. This specific entity is referred to as arrhythmogenic DCM (AR-DCM). Patients who suffer from AR-DCM, compared to other DCM patients, have a higher risk of experiencing major arrhythmic events and SCD. Thus, a family history of SCD in an AR-DCM patient results in a higher burden of life-threatening arrhythmias and a higher risk of SCD [7]. It is important to mention that DCM patients, due to their high incidence of atrial fibrillation, also have a higher risk for ischemic stroke. However, it should be noted that if a cause of death other than arrhythmia is confirmed, the death will not be classified as sudden.

2.4 Risk stratification

It is crucial to identify patients at high risk of a fatal arrhythmia. There are clues in the clinical history, electrocardiographic, imaging characteristics, and specific genetic features that need to be taken into account. Factors such as QRS duration, QT-interval dispersion, and T-wave alternans have been suggested as risk markers [15]. A considerable burden of ventricular arrhythmias (runs of VT) is usually present in a setting of advanced ventricular dysfunction with left ventricular ejection fraction (LVEF) <25%, which is a validated risk factor. Survived cardiac arrest and sustained ventricular tachycardia with hemodynamic compromise imply a high risk of recurrent arrhythmia and are classified as secondary prevention for an implantable cardioverter defibrillator (ICD) [16]. Unexplained syncope may be secondary to arrhythmia and constitutes a risk factor [15]. In the Marburg Cardiomyopathy study (MACAS), which excluded patients with a history of sustained VT or VF, unexplained syncope within the previous 12 months, and amiodarone therapy, it was shown that a low LVEF (<30%) was the only independent factor for major arrhythmic events. Patients with NSVT and patients who were not on beta-blockers upon enrollment also run a high risk for ventricular arrhythmias. Thus, the combination of documented NSVT on Holter monitoring with a low LVEF (<30%) increased the arrhythmic risk by eight-fold [17]. Family history of SCD, defined as SCD in a first degree relative <40 years of age or SCD in a relative with confirmed DCM at any age, is also an established risk factor.

2.5 Imaging

Imaging can be used to predict arrhythmia risk. In cardiac magnetic resonance imaging, midwall late gadolinium enhancement (LGE) can detect fibrosis. Even if magnetic resonance imaging is not able to detect fibrosis, it may still be found by advanced T1 mapping techniques before and after gadolinium infusion. This is a prominent finding due to the fact that it corresponds to macroscopic midmyocardial fibrosis on postmortem examination [18]. In echocardiography, an impaired global longitudinal strain, a marker of myocardial regional contractility, may reflect myocardial fibrosis [19]. It has been demonstrated that an impaired global longitudinal strain is associated with increased arrhythmic events [20]. A predictor of arrhythmias is also mechanical dispersion, which is defined as the standard deviation of the time to peak negative strain among the different myocardial segments [20].

2.6 Mutations associated with SCD

Regarding genetic factors, DCM patients who carry a desmosomal or LMNA (lamin A/C) mutation run a higher risk of life-threatening ventricular arrhythmias and SCD, regardless of their LVEF. Patients who carry the LMNA gene, which encodes the type V intermediate filament protein, tend to have more life-threatening arrhythmias compared to other variant carriers and variant-negative patients [21, 22]. LMNA mutations are associated with high morbidity and mortality and with a high clinical penetrance [23]. For the LMNA carriers, various risk factors have been identified. These include NSVT during electrocardiogram monitoring, truncating mutations, LVEF <45–50%, and male sex [24, 25]. More recently, 1st degree AV block has been identified as another risk factor in LMNA carriers [26]. Desmosomal gene mutations are present in around 3% of DCM patients. They are also frequent in ARVC patients, creating a genotype overlap between the two cardiomyopathies. They have been associated with a high risk of potentially fatal arrhythmias, independently from the LVEF [21]. The SCN5A (sodium voltage-gated channel alpha subunit 5) gene, which provides instructions for making sodium channels, is also associated with conduction defects and ventricular arrhythmias [10]. Also associated with a higher risk of arrhythmic events are mutations in the FLNC gene, which encodes filamin proteins; the RNA-binding motif protein 20 gene (RBM20 gene), which encodes a protein that regulates splicing and the phospholamban (PLN) gene, which encodes a protein that inhibits a sarcoplasmic ATPase [21, 27]. In a 2019 study, it was demonstrated that RBM20 mutation carriers were more likely to have NSVT and sustained VT than idiopathic DCM cohorts [28]. The AR-DCM phenotype is associated with a high risk of fatal arrhythmias. Spezzacatene et al. identified the AR-DCM phenotype as well as a family history of SCD or sustained VT/VF as the only early significant predictors for SCD or sustained VT/VF in the overall DCM population. Interestingly, the AR-DCM phenotype is associated with a higher risk of arrhythmias, irrespective of LV dilatation and dysfunction, which is in contradiction to the general DCM population, where a low LVEF is associated with a higher arrhythmic risk [14]. However, AR-DCM is not associated with a poorer prognosis due to non-arrhythmic events, including heart failure [14].

2.7 Preventive management

Most DCM patients present with heart failure and are at a high risk of death. The primary management of such patients lies in the stabilization of progressive heart failure. Drugs like renin-angiotensin-aldosterone system (RAAS) antagonists

and beta-blockers are first-line management in patients with DCM and reduce the risk of SCD by preventing ventricular remodeling. Angiotensin converting enzyme inhibitors (ACEs)/angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and beta-blockers are recommended, unless contraindicated or not tolerated. Furthermore, the combination of sacubitril/valsartan has been shown to be superior to ACE inhibitors and tends to replace them in the treatment of patients who are still symptomatic patients despite optimal medical treatment [16]. The anti-diabetic drug, dapagliflozin, seems to reduce the risk of worsening heart failure and death in patients with a reduced LVEF as well, regardless of the presence of diabetes mellitus, as proven in Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) study [29]. In NYHA IV patients, asystolic arrest and pulseless electrical activity are a frequent cause of death [10]. Cardiac resynchronization therapy (CRT) and CRT with defibrillator (CRT-D) treatment also has a place in both symptomatic treatment and preventive management of such patients.

Arrhythmia management in hereditary DCM patients follows the general recommendations as SCD prevention in patients with reduced LVEF (<35%) [7]. Thus, patients with diagnosed DCM must be carefully evaluated for ventricular arrhythmias. Regarding drug management, amiodarone has not been proven to further reduce overall mortality or arrhythmic risk in the Amiodarone versus Implantable Defibrillator (AMIOVIRT) study, which showed that DCM patients who were on amiodarone did not have a statistically significant difference in terms of survival, compared to patients who received an ICD [30]. However, in the Sudden Cardiac Death in Heart Failure trial (SCD-HeFT) which enrolled patients with an LVEF <35% and NYHA II or III despite optimal medical therapy and compared ICD insertion vs. amiodarone vs. placebo, ICD therapy conferred a significant benefit in patients in NYHA class II, but not in class III. Furthermore, amiodarone, when compared to placebo therapy, showed no benefit in NYHA Class II patients and decreased survival among NYHA Class III patients. Results varied among NYHA classes but did not vary between heart failure of ischemic or nonischemic origin [31]. The Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure (DANISH) trial concluded that prophylactic ICD implantation in symptomatic patients with nonischemic heart failure did not offer a significantly lower long-term rate of death from any cause when compared to standard clinical care but decreased the incidence of SCD by 50% [32].

ICD implantation remains the main therapy in preventive management for DCM patients with impaired LV function, who run a high risk of fatal arrhythmias. Guidelines, as well as the Expert Consensus Statement, recommend an ICD implantation in DCM patients with an LMNA gene mutation and risk factors such as NSVT observed during monitoring, male sex, truncating mutations (class IIa, level B), and an LVEF <45%, which is a higher cutoff value than used in heart failure population guidelines [22, 33].

In addition, a primary-prevention ICD should be considered in DCM patients with both an arrhythmogenic phenotype and a family history of SCD or ventricular arrhythmias, irrespective of their LVEF or LV end-diastolic diameter, as they compose a high-risk group for major arrhythmic events and SCD [14]. However, in individual cases, it can be challenging to determine in which particular patients the benefits of ICD implantation would outweigh the risks. The DEFINITE study (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) randomized 458 patients with nonischemic DCM (LVEF <36%) and premature ventricular complexes or nonsustained VT, between standard medical therapy and ICD implantation. SCD by arrhythmias during a mean follow-up of 29 months was far fewer in the ICD group, proving the efficacy of defibrillation [34]. Yet, the use of LVEF

alone is not always helpful in determining which patients would most benefit from an ICD. This was made clear in the Oregon and Maastricht Registries, in which 80% of SCD victims had an LVEF >35% [35, 36].

CRT is recommended in patients with sinus rhythm, NYHA class III/IV heart failure, LVEF ≤35%, and QRS >120 ms and/or evidence of mechanical dyssynchrony. It has been shown to offer great survival benefits as well as improvement of LV function in DCM patients [37]. This has been observed especially in women, who seem to benefit more than men from CRT [38]. Furthermore, it has been proven that in patients with nonischemic DCM with an LVEF ≤30%, NYHA class II, and QRS duration ≥130 ms, CRT-D device implantation was also beneficial in reducing the risk of death or heart failure when compared with defibrillation only [39]. On the other hand, patients with low LVEF heart failure and permanent atrial fibrillation do not seem to derive extra benefit from a CRT-D device compared with standard ICD treatment, as suggested by the Resynchronization for Ambulatory Heart Failure Trial (RAFT) trial [40]. Of interest in DCM patients, LGE was proven to be a strong, independent predictor of arrhythmic events and was suggested to improve risk stratification for SCD and better identify the need for ICD therapy [41].

Decisions about ICD therapy should incorporate genetic factors. In patients with mutations, i.e. LMNA mutations, the conventional LVEF-threshold based guidelines for ICD do not apply. In fact, an ICD may be considered for a patient with higher LVEF thresholds [26, 42]. Regarding FLNC mutations, 20% of patients with a primary-prevention ICD who carry the mutation had an appropriate ICD shock, much higher than in unselected DCM populations [43]. Appropriate ICD shocks are also more likely in PLN carriers, especially in R14del variant, along with a family history of SCD before the age of 50 years compared to those who do not carry the mutation [44]. These findings support the hypothesis that genetic factors should be considered early in the disease progression.

The CMR-Guide (Cardiac Magnetic Resonance Guided Management of Mild-Moderate Left Ventricular Systolic Dysfunction) trial, which is expected to be completed in 2020, is randomizing ischemic and nonischemic cardiomyopathy patients with an LVEF between 36 and 50% and presence of LGE to either an ICD or an implantable loop recorder in an attempt to determine whether LGE is a sufficient marker alone or whether genetic characterization is also necessary in risk stratification. In general, a polyparametric integration is being introduced in the primary prevention of SCD through ICD implantation in DCM patients that includes family history of SCD, LVEF, late gadolinium enhancement, and possibly genetic parameters [45].

3. Future perspectives

The evaluation and treatment of hereditary DCM constitutes an emerging field. Still, risk stratification regarding SCD is based on general knowledge. Larger registries and long-term follow-up may elucidate more specific risk markers associated with genotypes in addition to phenotype.

4. Conclusion

Hereditary DCM is a heterogeneous condition, which may lead to advanced HF as well as SCD. Risk stratification and preventive management strategies are challenging. Many factors must be considered in the management of patients with

hereditary DCM. Gene mutations are surfacing and have already been proven to play a very significant role in clinical decisions. Moreover, based on new data and studies, the profile of each DCM patient tends to be better understood. As a result, both therapy and prevention evolve and ameliorate in a way that will become individualized. ICDs are lifesaving but their role in different genotypic settings remains to be elucidated.

Conflicts of interest

Peter Magnusson has received speaker fees or grants from Abbott, Alnylam, Bayer, AstraZeneca, Boehringer-Ingelheim, Lilly, MSD, Novo Nordisk, Octopus Medical, Pfizer, and Zoll. Joseph Pergolizzi is a principal at Native Cardio, Inc. Marianna Leopoulou and Jo Ann LeQuang have no relevant disclosures.

Acronyms and abbreviations

ACE	angiotensin converting enzyme
ARB	angiotensin receptor blocker
AR-DCM	arrhythmogenic dilated cardiomyopathy
ARVC	arrhythmogenic right ventricular cardiomyopathy
CMR	cardiac magnetic resonance
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy defibrillator
DCM	dilated cardiomyopathy
ICD	implantable cardioverter defibrillator
LGE	late gadolinium enhancement
LMNA	lamin A/C
LV	left ventricle
LVEF	left ventricular ejection fraction
NSVT	nonsustained ventricular tachycardia
NYHA	New York Heart Association
RAAS	renin-angiotensin-aldosterone system
PLN	phospholamban
RBM20	RNA binding motif protein 20
SCD	sudden cardiac death
SCN5A	sodium voltage-gated channel alpha subunit 5
TTN	titin
VF	ventricular fibrillation
VT	ventricular tachycardia

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