The concept of isolated, nonischemic disease of the myocardium dates back to 1899 when Fiedler in Dresden published an article entitled Acute Interstitial Myocarditis. He described a series of fatal cases in young adults with cardiomegaly and heart failure. This condition, named Fiedler's myocarditis, is characterized by sudden onset of what was originally thought to be malarial fever, probably of microbial origin, often fatal in 5 to 17 days. Autopsy revealed acute inflammation limited to the myocardium, unrelated to acute rheumatic fever, syphilis, tuberculosis, arteriosclerosis, or septicemia.1

In 1949, Evans2 reported on families with unexplained cardiomegaly, and in 1957, Brigden3 first used the term cardiomyopathy (noncoronary cardiomyopathies) to describe patients with unexplained cardiomegaly. Nearly, 50% of patients dying suddenly in childhood or adolescence or undergoing cardiac transplantation are affected by cardiomyopathies. Novel cardiomyopathies have been discovered (arrhythmogenic, restrictive, and noncompacted) and added to the World Health Organization classification. Myocarditis has also been named inflammatory cardiomyopathy. Extraordinary progress accomplished in molecular genetics of inherited cardiomyopathies allowed establishment of dilated cardiomyopathy as mostly cytoskeleton, force transmission disease; hypertrophic–restrictive cardiomyopathies as sarcomeric, force generation disease; and arrhythmogenic cardiomyopathy as desmosome, cell junction disease. Channelopathies (short and long QT, Brugada, and catecholaminergic polymorphic ventricular tachycardia syndromes) should also be considered cardiomyopathies because of electric myocyte dysfunction. Cardiomyopathies are easily diagnosed but treated only with palliative pharmacological or invasive therapy. Curative therapy, thanks to insights into the molecular pathogenesis, has to target the fundamental mechanisms involved in the onset and progression of these conditions. (Circ Res. 2017;121:722-730. DOI: 10.1161/CIRCRESAHA.117.309711.)
with idiopathic myocardial disease, several of whom had familial disease. Twenty-three years later, a task force of the World Health Organization, chaired by John Goodwin (Figure 1), presented the first classification of the cardiomyopathies which was based on the predominant structural and hemodynamic phenotype, that is, dilated cardiomyopathy (DCM) (Figures 2 and 3), hypertrophic cardiomyopathy (HCM; Figure 4), and restrictive cardiomyopathy. The latter was limited to conditions which impair diastolic function because of obliteration of the ventricular cavities (eg, endomyocardial fibrosis, fibroplastic mural endocarditis—Loeffler disease; Figure 5). All of the cardiomyopathies were initially considered idiopathic, namely heart muscle diseases of unknown cause. Subsequent iterations of the classification updated diagnostic criteria in relation to evolving technology (eg, angiography, M mode, and then 2-dimensional echocardiography) and maintained the focus based on the predominant manifestation, although it was recognized that individual patients often had overlapping phenotypes; an example is HCM with restrictive physiology.

The discovery in 1990 of a mutation in the \( \beta \)-myosin heavy chain gene in all 20 surviving affected members of a French Canadian family with HCM led, over the ensuing decade, to the recognition of disease-causing genes not only for HCM but later of DCM as well.

Thus, in many patients, these cardiomyopathies were no longer idiopathic. In the 1996 World Health Organization classification of the cardiomyopathies, the unknown was deleted, and the cardiomyopathies were redefined as diseases of the myocardium associated with cardiac dysfunction. Arrhythmogenic right ventricular cardiomyopathy (ARVC) (Figure 6), was added to the classification, while myocardial disease causing restrictive physiology (RCM; Figure 7) and several unclassified cardiomyopathies were highlighted, including left ventricular noncompaction (LVNC; Figure 8) and endocardial fibroelastosis (Figure 9).

LVNC is frequently associated with monogenic, neuromuscular disorders or with chromosomal defects. As occurred in the past with mitral valve prolapse, LVNC may also be overdiagnosed, probably by including excessive, but normal ventricular trabeculation.

Myocarditis, mostly viral in origin, has also been included among secondary cardiomyopathies. The pathogenesis of myocardial damage in viral myocarditis evolving toward DCM can be related either to cytopathic effects or to triggering of autoimmunity. Both RNA (Coxsackie B) and DNA (Adeno) viruses attach to an identical receptor (Coxsackievirus-Adenovirus Receptor [CAR]) in the sarcolemma. Coxackie virus B encodes protease 2A which cleaves dystrophin, thus disrupting the cytoskeleton.

Since recognition that pathogenic mutations are frequently the cause of cardiomyopathies, it was proposed that these disorders could be classified according to the molecular genetic defect: sarcomeric cardiomyopathy, cell junction cardiomyopathy, ion channel cardiomyopathy, cytoskeletal cardiomyopathy, etc.

Subsequently, 2 distinct classifications were proposed to reflect the progress in understanding of the genetic basis of the cardiomyopathies (Figures 10 and 11). In 2006, a writing committee of the American Heart Association presented a classification which reflected the evolving genetic knowledge and also addressed inconsistencies in nomenclature of the previous classifications. In this Scientific Statement, the cardiomyopathies were considered to be primary when the disease is solely or predominantly of the heart muscle and secondary when myocardial involvement is associated with a multisystem disorder (eg, Anderson-Fabry disease, sarcoidosis, amyloidosis, etc) (Figures 12 through 14). The primary
cardiomyopathies were classified as genetic (HCM, ARVC), acquired (myocarditis), or mixed (both genetic and acquired DCM). Myocardial dysfunction in cardiomyopathies refers to predominant systolic dysfunction as in DCM and predominant diastolic dysfunction as in RCM.

Ion channel diseases with grossly normal hearts were included as cardiomyopathies because ion channel mutations are responsible for altering biophysical properties and protein structure, thereby creating abnormal ion channel interfaces and architecture with electrical dysfunction. Ion channel diseases with grossly normal hearts were included as cardiomyopathies because ion channel mutations are responsible for altering biophysical properties and protein structure, thereby creating abnormal ion channel interfaces and architecture with electrical dysfunction.17

The decision by the committee to consider arrhythmic disorders in hearts with normal systolic and diastolic function as cardiomyopathies was surprising to some, but was in keeping with the concept that channelopathies and related electrophysiological disturbances are disorders of the cardiomyocyte. The latter are a consequence of abnormal ion transport across the sarcolemmal or electromechanical coupling because of abnormalities of Ca++ release or uptake by the smooth sarcoplasmic reticulum. Thus, channelopathies and related disorders, such as long-QT (LQT) and short-QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia, were considered to be cardiomyopathies because they are diseases of the cardiomyocytes characterized by electrophysiological dysfunction that is arrhythmogenic. The authors of the American Heart Association Statement presented it as a living document that is amenable to new information.

Figure 2. Dilated cardiomyopathy. A, Schematic of dilated left ventricle, in the absence of valve disease. The blue area represents a normal left ventricle. The red area represents a dilated ventricle. B, Four-chamber view of a heart specimen with dilated ventricular cavities (first case of cardiac transplantation in Italy). C, Histology of the myocardium: myocytolysis with abnormal nuclei and no inflammatory infiltrates. Haematoxylin–Eosin stain.

Figure 3. Dilated cardiomyopathy (postinflammatory). A, Macroscopic view of the free wall of a dilated left ventricle: note diffuse postnecrotic scars of the free wall and papillary muscle, in the absence of coronary artery disease. B, Histology shows transmural myocardial fibrosis. Azan stain.

and future revision, particularly as the molecular biology of cardiomyopathies evolves. Also, genes encoding specific proteins may cause very different phenotypes. The fact that mutations in sarcomeric genes are associated with HCM and RCM, whereas DCM may be caused by genes encoding not only sarcomeric proteins, but also cytoskeletal and even ion channel and gap junction proteins, provides the challenge of discovering how these mutations are translated into such different phenotypes.

The goal of the 2008 European Society of Cardiology position statement was to update the classification system for cardiomyopathy to ensure its continued use in every day clinical practice. With this clinical focus, it grouped patients according to morphological and functional phenotypes. In this regard, it provided continuity with previous classifications but recognized that the original definitions of these conditions as idiopathic no longer applied because disease-causing genes had been identified. The European Society of Cardiology classification avoided the use of the terms primary and secondary cardiomyopathy because these distinctions may not be readily discernible. Furthermore, this classification did not include channelopathies and other inherited arrhythmias. However, it did acknowledge the importance of familial evaluation and genetic analysis to enable accurate diagnosis, leading hopefully to better management and outcomes.

For example, a young adult who complains of mild dyspnea on effort and is found to have a reduced ejection fraction with a dilated left ventricle exhibiting global impairment of left ventricular function may be classified as DCM initially. The finding on evaluation of relatives who have either died suddenly or required a pacemaker at a young age may suggest an arrhythmic form of DCM, in which genomic analysis reveals a mutation in lamin A/C. In such a patient, treatment should be focused on both the management of heart failure and the prevention and treatment of life-threatening arrhythmias.

**Epidemiology and Burden**

Reliable epidemiology of the cardiomyopathies is available predominantly from developed countries where accurate prevalence data that rely on application of established diagnostic evaluations and criteria are gathered. The diagnosis
of DCM has been difficult to standardize given the influence of body size, athletic training, and biological heterogeneity on measurements of left ventricular volume and contractile function. Prevalence data also vary when disease expression is related to age (HCM), age and sex (Brugada syndrome), or is present at birth (LQT). In addition, founder effects may influence prevalence and perceptions of disease severity (ARVC).

Table 1 presents a summary of disease prevalence in children and adults for HCM, DCM, ARVC, RCM, and channelopathies. A disease prevalence of 1:250 to 500 for HCM in adults seems to be similar in all races, and disease expression usually occurs in adolescents and young adults, whereas...
it is uncommon in children. Robust data on the epidemiology of DCM are lacking, but estimates suggest incidence and prevalence figures of approximately twice those seen in HCM. Incidence in children is greatest in the first year of life (4.58/100,000) and much less common from age 1 to 18 years (0.34/100,000). The prevalence of ARVC has not been systematically studied, but is estimated at 1/2000 to 5000; robust epidemiological data are lacking in part because of the multiple clinical evaluations required for diagnosis. ARVC in childhood is rare, and, like in HCM, disease expression usually occurs during adolescence and early adulthood, but may develop at any age, in keeping with the concept of genetically determined cardiomyopathy.

For LQT syndrome, a prevalence of 1:2000 has been established in neonates, and data suggest that this is similar for all ages and races, although event rates differ for LQT1, LQT2, and LQT3 with respect to age and sex.

Criteria for the diagnosis of Brugada syndrome include a type 1 ECG pattern (coved ST-segment elevation with J point amplitude $\geq 0.2$ mV followed by negative T wave) with at least 1 additional feature suggestive of arrhythmia (eg, unexplained sudden cardiac death aged <45 years in a relative).

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**Figure 10. American Heart Association Classification of Cardiomyopathies.** Primary cardiomyopathies in which the clinically relevant disease processes solely or predominantly involve the myocardium. The conditions have been segregated according to their genetic or nongenetic causes. *Predominantly nongenetic; familial disease with a genetic origin has been reported in a minority of cases. ARVC/D indicates arrhythmogenic right ventricular cardiomyopathy/dysplasia; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LQTS, long-QT syndrome; LVNC, left ventricular noncompaction; SQTS, short-QT syndrome; and SUND, sudden unexpected nocturnal death syndrome. Reproduced from Maron et al with permission of the publisher. Copyright ©2006, American Heart Association, Inc.

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**Figure 11. European Society of Cardiology Classification of Cardiomyopathies.** Summary of proposed classification system. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; and RCM, restrictive cardiomyopathy. From Elliott et al with permission of the publisher. Copyright ©2007, Oxford University Press.

Figure 13. Secondary dilated cardiomyopathy caused by sarcoidosis. A, Gross specimen from cardiac transplantation with dilated cardiomyopathy and posterior aneurysm of the left ventricle. B, At histology, noncaseous giant cells granuloma within the myocardium. Haematoxylin–Eosin stain.

Figure 14. Secondary restrictive cardiomyopathy caused by cardiac amyloidosis. A, Macroscopic specimen sectioned to reveal the left atrium and left ventricle. The walls are stiff, the mitral valve normal, and the left atrium dilated. B, Congo Red histochemical staining reveals amyloid interstitial deposits. C, The same as (B) at polarized light, revealing green apple–colored deposits.
Table 1. Prevalence of the Most Common Inherited Cardiac Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Children (1–puberty)</th>
<th>Adults (19–64 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM</td>
<td>Uncommon</td>
<td>1:250/500*</td>
</tr>
<tr>
<td>DCM</td>
<td>Uncommon†</td>
<td>1:250/500‡</td>
</tr>
<tr>
<td>ARVC</td>
<td>Uncommon</td>
<td>1:2000</td>
</tr>
<tr>
<td>RCM</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>LQT</td>
<td>1:2000</td>
<td>1:2000</td>
</tr>
<tr>
<td>Brugada (type 1 ECG)</td>
<td>Uncommon</td>
<td>1:2000/5000$</td>
</tr>
<tr>
<td>CPVT</td>
<td>1:5000/10000</td>
<td>1:5000/10000</td>
</tr>
</tbody>
</table>

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LQT, long QT; and RCM, restrictive cardiomyopathy.

*General population including gene carriers.20,24
†Presentation in first year of life 14× more common than during childhood and adolescence.25
‡Estimate generated from HCM/DCM incidence data.32
§Prevalence of 1:1000 from Japan in adults aged 40–64 y.30

Perspectives

The prevalence of catecholaminergic polymorphic ventricular tachycardia is unknown, and reported figures of 1:5000/10000 may be an underestimate of this condition which typically presents with exercise-related syncope and sudden death in children and adolescents despite normal ECG and 2-dimensional echocardiographic studies.20

Overall, cardiomyopathy is an important problem. In 1 center, a cardiomyopathy was present in more than half of patients <35 years dying suddenly (Table 2) or requiring cardiac transplantation (Table 3).

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Table 2. Cardiomyopathy in 712 Sudden Cardiac Death Cases in the Young Studied at the University of Padua (1980–2016)22

<table>
<thead>
<tr>
<th>Condition</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocarditis</td>
<td>14</td>
</tr>
<tr>
<td>HCM</td>
<td>10</td>
</tr>
<tr>
<td>ARVC</td>
<td>10</td>
</tr>
<tr>
<td>Normal heart (Channelopathies?)</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
</tr>
</tbody>
</table>

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; and HCM, hypertrophic cardiomyopathy.

References


Classification, Epidemiology, and Global Burden of Cardiomyopathies
William J. McKenna, Barry J. Maron and Gaetano Thiene

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