Cardiomyopathies 1: classification, pathophysiology and symptoms

Cardiomyopathies are a mixed group of diseases of the myocardium (cardiac muscle) defined by structural or functional abnormalities that negatively affect the pump function of the heart. In some types, there is obstruction to the outflow of blood during the cardiac cycle (Jarvis and Saman, 2018). Advances in clinical and genomic medicine have led to better detection and understanding of cardiomyopathies (some of which have a strong genetic component). The understanding of cardiomyopathies has been enhanced by advances in the fields of medicine and genetics. This article – the first in a two-part series – describes the classification and pathophysiology of the main cardiomyopathies and their clinical presentation. The second article will cover diagnosis, management and the role of the multidisciplinary team in patient care.

Definition and classification

The American Heart Association describes cardiomyopathies as “a heterogeneous group of diseases of the myocardium associated with mechanical and/or electric dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation due to a variety of etiologies that are frequently genetic. Cardiomyopathies are either confined to the heart or part of generalised systemic disorders and often lead to cardiovascular death or progressive heart failure-related disability” (Maron et al, 2006).

Cardiomyopathies were previously divided into primary and secondary: a primary cardiomyopathy was confined to the cardiac muscle, while a secondary cardiomyopathy was part of a systemic disorder affecting multiple organs. Today, new and more-appropriate classifications are used.

The European Society of Cardiology orders cardiomyopathies according to morphological and functional phenotype (Elliott et al, 2008) (Fig 1). Cardiomyopathies can be further subdivided according to the underlying condition. According to Elliott et al (2008), the main types of cardiomyopathies are:

- Dilated cardiomyopathy (DCM);
- Hypertrophic cardiomyopathy (HCM);
- Restrictive cardiomyopathy (RCM);
- Arrhythmogenic cardiomyopathy (ACM);
- Unclassified cardiomyopathies.

Since the publication of Elliott et al’s (2008) classification system, another – the...
MOGE(S) tool – has been proposed (Arbustini et al, 2013). This allows health professionals to stage the disease by addressing five simple attributes of cardiomyopathic disorders (Box 1), although it may not be appropriate for all patients.

Table 1 shows the global prevalence of the main cardiomyopathies in children and adults. Patients with cardiomyopathies may be completely asymptomatic or experience a wide variety of signs and symptoms (Fig 2).

**Dilated cardiomyopathy**
The most common cause of heart failure (Weintraub et al, 2017), DCM is diagnosed on the basis that it cannot be explained by either abnormal loading conditions (increased blood pressure or volume) or coronary artery disease, where an ischaemic cardiomyopathy may occur (Elliott et al, 2008). DCM can develop at any age and is more common in males. In children, it accounts for around 60% of all cases of cardiomyopathy (Lipshultz et al, 2003).

The condition encompasses heterogeneous diseases characterised by inappropriate ventricular hypertrophy (thickening of the ventricle wall) or dilation of one or both ventricles (with thinning and enlargement). It occurs progressively (Weintraub et al, 2017) and can lead to decompensated heart failure. In the developed world, it is a common reason for needing a heart transplant (Maron et al, 2006).

DCM can be caused by an inherent problem in the myocardium. Approximately 20-48% of cases are genetic (Taylor et al, 2006), in which case the condition is called familial DCM. Gene defects affecting structural elements in the cardiac muscle cells (cardiomyocytes), ion channels, cytoskeleton and mitochondria have been identified (Braunwald, 2017; Sisakian, 2014).

DCM can also be secondary to systemic causes such as inflammation, malnutrition and infectious, autoimmune or endocrine diseases. In high-income countries, such as the UK, alcohol overuse contributes to 21-36% of cases (Weintraub et al, 2017). The risk of developing DCM as a result of alcohol misuse is influenced by various susceptibility factors, including those that are ethnic and genetic (Weintraub et al, 2017; Laonigro et al, 2009).

Table 2 outlines the causes of DCM. In many cases, no definitive cause is found (idiopathic DCM).

Approximately 80% of patients with DCM experience symptoms of heart failure such as dyspnoea, fatigue, chest pain, orthopnoea and paroxysmal nocturnal dyspnoea. They may also present with clinical features of an underlying systemic cause. To ascertain any underlying cause, it is important to take a detailed medical and family history, as well as enquiring about previous viral infections and drug and alcohol use.

On examination, the cardiac apex beat may be displaced due to ventricular dilation and there may be signs of congestive heart failure, such as swollen legs from peripheral and/or sacral oedema, crackles from pulmonary congestion and distended neck veins from raised internal jugular

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**Box 1. MOGE(S) tool**

**M** = morphological phenotype of the cardiomyopathy (for example, dilated or restrictive)

**O** = organ involvement

**G** = genetic or familial inheritance (for example, autosomal dominant)

**E** = etiological annotation, with details of genetic defect or underlying disease or cause

**S** = stage of disease

Source: Arbustini et al (2013)

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**Table 1. Cardiomyopathies: prevalence in children and adults**

<table>
<thead>
<tr>
<th>Type of cardiomyopathy</th>
<th>Childhood (1yr-puberty)</th>
<th>Adults (19-64yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated cardiomyopathy</td>
<td>Uncommon*</td>
<td>1250-500’</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Uncommon</td>
<td>1250-500’</td>
</tr>
<tr>
<td>Restrictive cardiomyopathy</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy*</td>
<td>Uncommon</td>
<td>12,000-5,000</td>
</tr>
</tbody>
</table>

*Presentation in the first year of life is 14 times more common than later in childhood and in adolescence. **Now called arrhythmogenic cardiomyopathy. 

Estimate generated from HCM/DCM incidence data (Hershberger et al, 2013).

Source: Adapted from McKenna et al (2017)
venous pressure. Auscultation may reveal a 'gallop rhythm' caused by an extra heart sound (S3) that occurs as part of congestive heart failure, or there may be features of mitral regurgitation occurring as a result of a dilated left ventricle.

**Hypertrophic cardiomyopathy**

First identified in 1957 at St George's Hospital in London in eight patients who presented with asymmetrical cardiac septal thickening (hypertrophy) of the left ventricle, HCM has since been recognised globally, with a prevalence of 0.2% in the general population (Houston and Stevens, 2015). Patients may present with sudden cardiac death. Mortality is estimated at 1% a year (Houston and Stevens, 2015; Elliott et al, 2014).

HCM is a heterogeneous disorder characterised by left ventricular hypertrophy and, in some cases, left ventricular outflow tract obstruction (Houston and Stevens, 2015). In around 60% of adults and adolescents, the condition is caused by familial disease (Marian and Braunwald, 2017). A large number of genetic mutations in HCM have been described including those affecting proteins important for sarcomere function (β-myosin heavy chain gene, myosin-binding protein C and troponin T account for 70-80% of all cases of inherited HCM (Marian and Braunwald, 2017; Sisakian, 2014). Some patients inherit more than one gene defect resulting in mitral valve regurgitation. Another type of murmur may be present, caused by turbulent flow through the outflow tract, which is mid-systolic with a crescendo-decrescendo sound.

**Restrictive cardiomyopathy**

Characterised by ventricular stiffness leading to reduced ventricular filling and diastolic volume during the cardiac cycle, RCM is suspected when patients have near-normal systolic function but diastolic dysfunction on echocardiography. Unlike the other cardiomyopathies, which are defined by morphological changes in the ventricles, RCM is defined based on the resulting haemodynamic problems (Sisakian, 2014). It is the least common cardiomyopathy and makes up 5% of paediatric cardiomyopathies (Muchtar et al, 2017).

There are several causes of RCM but in 50% no cause is identified (Muchtar et al, 2017). Certain types of RCM affect certain ethnic groups more than others; for instance, endomyocardial fibrosis is a cause of RCM that is most prevalent in tropical countries and sub-Saharan African countries, such as Cameroon (Muchtar et al, 2017; Chelo et al, 2015). In other regions, RMC more commonly occurs because of amyloidosis, sarcoidosis and haemochromatosis (Muchtar et al, 2017).

RCM can develop from a primary cause; for example, endomyocardial fibrosis. It can also be secondary to:
- Other systemic conditions that cause infiltration of the myocardium; for example, amyloidosis, sarcoidosis and radiation effects;
- Conditions that cause abnormal loading within the myocardial cells; for example, haemochromatosis (a state of iron overload), glycogen storage disorders or...
**Arrhythmogenic cardiomyopathy**

This genetic cardiomyopathy was first identified in 1700 in a family that had a specific dilation of the right ventricle (Braunwald, 2017). Since then, there have been several reports of patients with the condition, characterised by ventricle muscle that has been replaced with fibrofatty tissue.

Until recently, ACM was called arrhythmogenic right ventricular cardiomyopathy (Corrado et al, 2017), but it has become apparent that the left ventricle can be affected in up to 75% of patients (Sisakian, 2014; Falase and Ogah, 2012). The condition shows characteristic features on echocardiography, including a hyperdynamic left ventricular segment and abnormal shape in systole resembling an octopus trap (called takotsubo in Japanese). Thus the apex of the heart may balloon but it is not strictly considered as a DCM as it has different clinical features of presentation. An electrocardiogram may show left ventricular contractile dysfunction and associated ST elevation. Many patients will need an angiogram to assess the coronary vasculature and rule out myocardial infarction. In stress-induced cardiomyopathy, the functional and structural changes to the myocardium are reversible. They may resolve within days or weeks with treatment strategies that use diuretics and nitrates and are aimed at reducing life-threatening complications (Kato et al, 2017).

**Left ventricular non-compaction**

Left ventricular non-compaction (or spongy myocardium) is a rare congenital cardiomyopathy (Nunez-Gil and Feltes-Guzmán, 2012). It typically affects the apex of the heart and is defined by an altered myocardial wall with prominent trabeculae (irregular muscular columns projecting from the inner surface of the heart) and deep intratrabecular recesses, which results in a thickened myocardium with two layers (one non-compacted layer and one thin compacted layer).

There is continuity between the left ventricular cavity and deep intratrabecular recesses, which fill with blood from the ventricular cavity without evidence of communication with the epicardial coronary artery system (Attenhofer-Jost and Connolly, 2019). Complications include heart failure, arrhythmias and embolic events (Nunez-Gil and Feltes-Guzmán, 2012).

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**Table 2: Causes of dilated cardiomyopathy**

<table>
<thead>
<tr>
<th>Generic cause</th>
<th>Examples or causative factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Cardiac genetic defects: titin, lamin A/C, beta-myosin heavy chain, troponin T, myosin-binding protein C, myopalladin, sodium channel alpha unit, phospholamban</td>
</tr>
<tr>
<td></td>
<td>Neuromuscular genetic defects: Duchenne muscular dystrophy, Becker muscular dystrophy</td>
</tr>
<tr>
<td></td>
<td>Syndromes: mitochondrial diseases, Barth syndrome</td>
</tr>
<tr>
<td>Infective</td>
<td>Viral (for example, coxsackievirus), fungal, parasitic, rickettsial and protozoal diseases</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Giant-cell myocarditis, non-infectious myocarditis, polymyositis and dermatomyositis, Churg-Strauss syndrome, granulomatosis with polyangiitis, systemic lupus erythematosus, sarcoidosis</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Alcohol, cocaine, amphetamines or iron overload</td>
</tr>
<tr>
<td>Nutritional deficiencies</td>
<td>Selenium, thiamine, zinc and/or copper</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Antineoplastic drugs (paclitaxel, anthracyclines, alkylating agents), psychiatric drugs (clozapine, olanzapine, risperidone), others (chloroquine, tretinoin)</td>
</tr>
<tr>
<td>Endocrine and/or pregnancy related</td>
<td>Hypo- and hyperthyroidism, Cushing’s disease, Addison’s disease, phaeochromocytoma, acromegaly, diabetes, peripartum cardiomyopathy</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td>Fatty acid oxidation, carnitine deficiency, glycogen storage diseases, mucopolysaccharidosis, disorders of oxidative phosphorylation, organic acidurias</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
<td>Hypocalcaemia, hypophosphataemia</td>
</tr>
</tbody>
</table>

Source: Adapted from Weintraub et al (2017)
Histiocytoid cardiomyopathy

Histiocytoid cardiomyopathy (or Purkinje cell hamartoma) is a rare cardiomyopathy that presents between birth and the age of four years and is more common in females. It is associated with arrhythmias and sudden cardiac death as well as congenital heart defects. It may occur in conjunction with extra-cardiac features, including abnormalities of the nervous system and the eyes.

Histiocytoid cardiomyopathy is thought to be caused by a developmental defect of the Purkinje cells (part of the conducting system of the heart), but findings of excessive numbers of abnormally shaped mitochondria in cardiac tissue suggest that mitochondrial dysfunction may play a role (Shehata et al, 2015).

Conclusion

Patients with cardiomyopathies may experience a range of signs and symptoms, or none. It is important to take a careful clinical history of their presenting symptoms, along with relevant details of their medical history, medication use, family history and alcohol use.

Part 2 in this series will describe diagnosis and management, as well as the role of the multidisciplinary team in the care of patients with cardiomyopathies.

Table 3. Causes of restrictive cardiomyopathy

<table>
<thead>
<tr>
<th>Generic cause</th>
<th>Examples or causative factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrative diseases</td>
<td>Amyloidosis, sarcoidosis, primary hyperoxaluria</td>
</tr>
<tr>
<td>Storage diseases</td>
<td>Gaucher disease, haemachromatosis, glycogen storage diseases, Fabry disease, mucopolysaccharidosis type I and II, Niemann-Pick disease</td>
</tr>
<tr>
<td>Non-infiltrative</td>
<td>Idiopathic diabetic cardiomyopathy, systemic sclerosis, myofibrillar myopathies, pseudoxanthoma elasticum, sarcocermic protein disorders, Werner’s syndrome</td>
</tr>
<tr>
<td>Endomyocardial</td>
<td>Carcinoid heart disease, endomyocardial fibrosis (idiopathic hypeerosinophilic syndrome, chronic eosinophilic leukaemia)</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Serotonin, methysergide, ergotamines, busulfan, antineoplastic drugs and treatments (hydroxychloroquine, anthracyclines, radiation)</td>
</tr>
<tr>
<td>Other</td>
<td>Secondary to other types of cardiomyopathies</td>
</tr>
</tbody>
</table>

References


