

CARDIOMYOPATHY

The cardiomyopathies: an overview

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The recent revision (table 1) of the definition of a cardiomyopathy by the World Health Organization¹ recognises that ventricular dysfunction can result from a failure to correct volume or pressure overload in valve disease or to control hypertension. Loss of myocardium caused by coronary artery disease also leads to severe ventricular dysfunction. All of these end stage conditions are categorised as specific cardiomyopathies. The second form of cardiomyopathy is caused by intrinsic disorders of the myocardium itself and is subdivided on the basis of the pathophysiology. Such a functional rather than an aetiological classification has drawbacks but reflects our current state of knowledge. The different functional abnormalities produce characteristic changes in ventricular shape easily recognised in short axis echocardiographic planes and by pathologists (fig 1).

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Table 1 The cardiomyopathies, as defined by the World Health Organization¹

Specific (secondary to external processes)	Intrinsic to myocardium
Hypertensive cardiomyopathy	Dilated cardiomyopathy (DCM)
Valvar cardiomyopathy	Hypertrophic cardiomyopathy (HCM)
Ischaemic cardiomyopathy	Arrhythmogenic right ventricular dysplasia (ARVD)
Cardiomyopathy secondary to systemic disease	Obliterative cardiomyopathy (OCM)
Inflammatory cardiomyopathy	

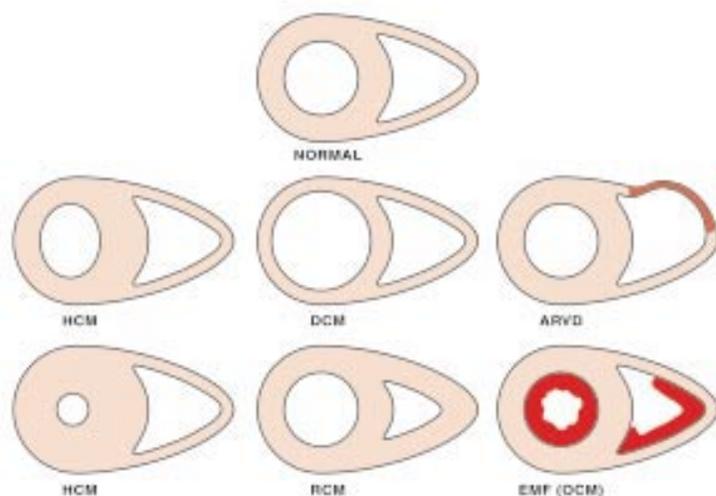


Figure 1: The morphological expression of the intrinsic cardiomyopathies as seen in short axis cuts across the right and left ventricle at mid septal level. Hypertrophic cardiomyopathy may be symmetric or asymmetric. HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; RCM, restrictive cardiomyopathy; ARVD, arrhythmogenic right ventricular dysplasia; EMF, endomyocardial fibrosis; OCM, obliterative cardiomyopathy.

Structural changes in dilated cardiomyopathy

- Increased left ventricular mass
- Normal or reduced left ventricular wall thickness
- Increased left ventricular cavity size
- Histology
 - myocyte nuclear size increase
 - myofibrillary loss within myocyte
 - focal myocyte death
 - increase in interstitial T lymphocytes/macrophages
 - interstitial fibrosis

Dilated cardiomyopathy

The pathophysiological entity dilated cardiomyopathy (DCM) is heterogeneous with regard both to its pathogenesis and its morphology. Common to the whole group is a poorly contracting dilated left ventricle with a normal or reduced left ventricular wall thickness. The lack of an increase in left ventricular wall thickness tends to mask a significant increase in left ventricular mass. In the terminal stages thrombus may develop in the apices of both ventricles. The histological changes within the myocardium are listed above. The individual myocytes are increased in length rather than in width and lose the normal number of intracellular contractile myofibrils, and thus appear empty and vacuolated on histology (fig 2). The degree of this histological change closely correlates with declining left ventricular function. The myocyte nuclei increase in size because of the synthesis of DNA and become polyploid. Death of individual myocytes occurs both by apoptosis and necrosis. Fibrosis characteristically is interstitial and begins to surround and isolate individual myocytes. The number of macrophages and T lymphocytes in the interstitial spaces is often increased compared with normal hearts. All of these histological changes vary widely in degree and type from case to case and give no information on causation.

Pathogenesis of dilated cardiomyopathy

In most cases of DCM no definite cause is identifiable. Some known causes, and some hypotheses, exist. The most prevalent toxic cause of DCM is alcohol. A wide range of structural abnormalities in the myocardium has been associated with high alcohol intake, and it is difficult to define the exact point at which these abnormalities can be called DCM. There is an excess of sudden death in alcoholics with large fatty livers even when the heart appears structurally normal. The spectrum continues through an isolated increase in left

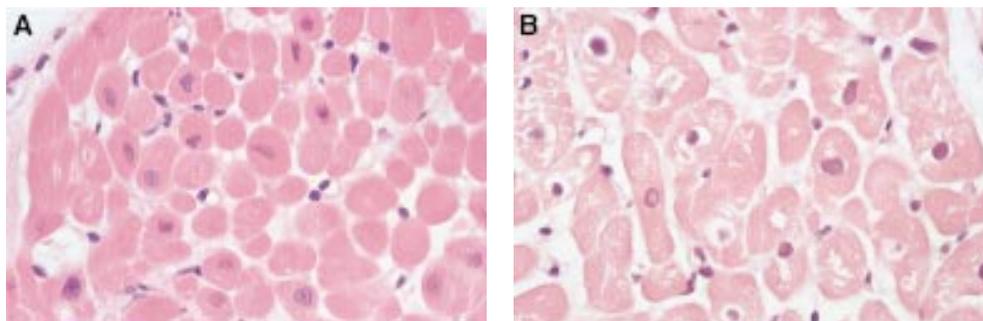


Figure 2: Dilated cardiomyopathy. (A) Normal cardiac biopsy, with the myocytes in cross section. Each myocyte has a uniform pink cytoplasm owing to the majority of the cell being filled by myofibrils. (B) Biopsy from a case of DCM. The myocytes have lost myofibrils and empty spaces have appeared within the cytoplasm.

ventricular mass, followed by left ventricular hypertrophy with interstitial fibrosis and fatty change or myofibrillary loss in myocytes, and culminating in fully developed DCM. There are no specific morphological features indicating alcohol as a cause of DCM; the best evidence may come from the results of totally withdrawing alcohol.

Single gene mutations in either the structural proteins of the myocyte, such as dystrophin, metavinculin, and lamin, or of mitochondrial DNA are recognised causes of DCM.² The majority of the skeletal muscle dystrophies, including the Duchene and Becker types, may have cardiac involvement. In some families cardiac involvement may be dominant and present first.³ Knowledge of the genes capable of causing DCM is far less well established than in hypertrophic cardiomyopathy (HCM), but the frequency of familial DCM is increasingly recognised as being far higher than initially realised. As many as 30% of index cases of DCM will have other family members with evidence of left ventricular dysfunction or enlargement on echocardiography.⁴

One view gaining ground is that DCM can be split into groups—one has histological evidence of chronic myocarditis while another group has evidence of viral persistence by polymerase chain reaction (PCR) analysis of myocardial tissue myocardium. Yet another group has neither myocarditis nor viral carriage. The definition of chronic myocarditis⁵ is based on an increase in the number of activated chronic inflammatory cells in the interstitial tissues. The cells have to be positively identified by immunohistochemistry as T cells or activated macrophages. More than 14 per square millimetre of myocardium is regarded as positive, particularly when associated with increased expression of class II major histocompatibility complex (MHC) antigens on endothelial and other cells. The hypothesis, as yet unproven by trials, is that each subgroup of DCM needs tailored treatment—that is, interferon, immunosuppression, etc—to improve prognosis. The differentiation of the four possible permutations—viral presence or absence, myocarditis presence or absence—takes sophisticated technology by the laboratory and would not be feasible to carry out in centres taking an occasional cardiac biopsy.

Hand in hand with the concept of chronic myocarditis is the idea that there is evidence of enhanced immune damage in some cases of DCM. Many cases show increased expression of class II antigens in the myocardium, and circulating autoantibodies to a wide range of components of the myocyte are present. Given that in DCM myocyte loss is occurring, the unanswered question is whether these antibodies are the cause of myocyte death or are nothing more than a secondary phenomenon.

Some forms of cardiomyopathy which are difficult to classify may also belong in the DCM group. Patients may present with very mild symptoms and a left ventricle which is dilated. These cases may be early forms of DCM and their frequency is increased in asymptomatic family members of index DCM cases. Myocardial fibrosis may occur without any clear cause, such as coronary disease, and be associated with ventricular arrhythmias rather than left ventricular dilatation and heart failure. Such cases have been equated in the past with healed myocarditis but are increasingly being recognised as familial, although the genes are not identified.

Hypertrophic cardiomyopathy

The heart of a patient with archetypal HCM has an asymmetric or a symmetric increase in left ventricular wall thickness (fig 1) with a left ventricular cavity which is reduced in size. A high proportion of cases are now recognised to be caused by mutations in genes coding for myofibrillary proteins. At least nine individual genes coding for different myofibrillary proteins have been identified.⁶ Affected individuals are heterozygous and produce a mixture of the normal (known by geneticists as the wild form) protein and abnormal (mutant) protein. The abnormal protein interferes with the organisation or function of the myofibrils within the myocyte producing the histological feature of myocyte disarray (fig 3). The unexplained feature is that while some cases appear to have the whole of the left ventricle involved, in others it is confined to a specific region, the most common being anteroseptal close to the left ventricular outflow tract. Other distributions include the posteroseptal region, lateral region,

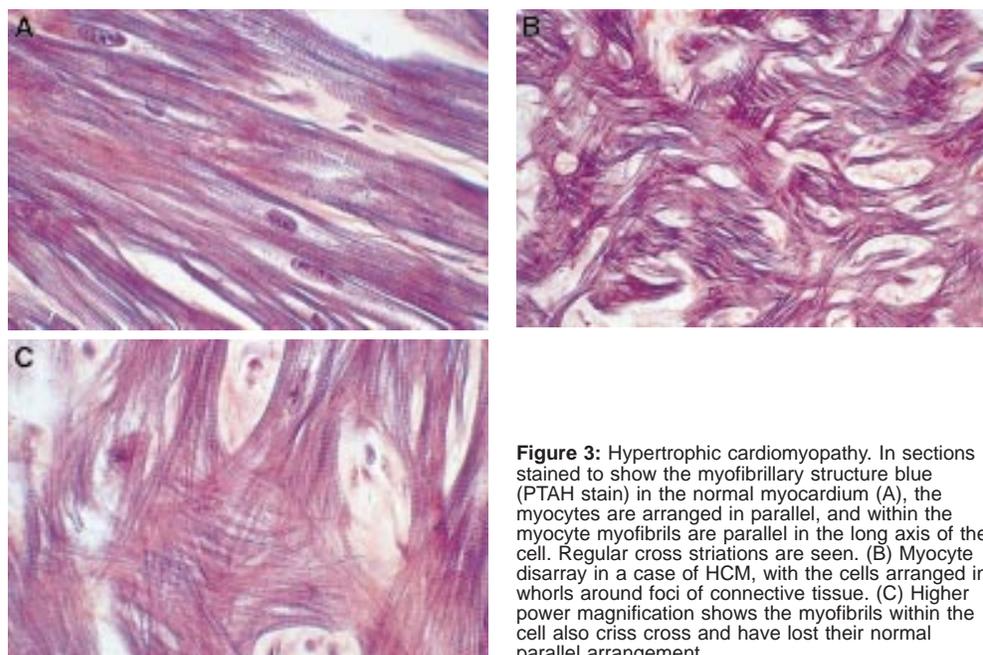


Figure 3: Hypertrophic cardiomyopathy. In sections stained to show the myofibrillary structure blue (PTAH stain) in the normal myocardium (A), the myocytes are arranged in parallel, and within the myocyte myofibrils are parallel in the long axis of the cell. Regular cross striations are seen. (B) Myocyte disarray in a case of HCM, with the cells arranged in whorls around foci of connective tissue. (C) Higher power magnification shows the myofibrils within the cell also criss cross and have lost their normal parallel arrangement.

and the apex of the left ventricle. Right ventricular involvement is present in at least a third of cases.

Where the upper interventricular septum is involved encroachment of myocardial muscle on the left ventricular outflow tract occurs; this, combined with systolic anterior movement of the mitral valve, leads to contact between the septal endocardium and the anterior cusp. Endocardial thickening develops on the septum as a mirror image of the anterior cusp. This band of severe endocardial thickening, which may be up to 1 cm thick, is removed in subaortic surgical resections. The anterior cusp of the mitral valve develops fibrosis caused by mechanical trauma and incurs a risk of bacterial endocarditis. The genes which cause HCM can be associated with dysplastic changes in the small intramyocardial arteries, significantly reducing the lumen size. These changes may play a role in causing angina and are associated with increasing fibrosis which, over the years, may alter the ventricular shape from HCM to become more like DCM.

An unexplained feature of HCM is the variation in the appearances of the heart (phenotype), even within a family in which all the members have the same gene mutation. The exact mutation does cause some variation in the phenotype. Of the genes so far identified as being responsible for HCM, left ventricular outflow obstruction is a feature of β heavy chain myosin gene mutations while symmetric, rather modest left ventricular wall thickening is found in troponin T mutations. Onset in late adult life is characteristic of myosin binding protein C mutations. The rapid expansion of knowledge concerning the phenotype of the myofibrillary genes creates semantic problems. In troponin T families the left ventricular mass may not be raised and the left ventricular wall thickness may be normal, yet there is myocyte disarray and a risk of sudden death. Thus there is HCM without hypertrophy.



Figure 4: The range of natural histories encountered in subjects with HCM caused by myofibrillary gene mutations. CCF, chronic cardiac failure; LV, left ventricular.

The potential natural history (fig 4) of HCM caused by the myofibrillary genes is well known, but it is not easy to predict which path an individual will follow or indeed the frequency of each path in the general community.

HCM is compatible with long life but there is a constant risk of sudden death. Sudden deaths in HCM can occur at any age, from childhood to over 90 years, in subjects who have been asymptomatic all their life. The characteristic morphological changes in ventricular shape in HCM do not develop until early adolescence, making it impossible to identify gene carriers with certainty by echocardiography alone in children.

It is now recognised that cases exist in which there is an increase in left ventricular mass, with striking symmetric or asymmetric left ventricular wall thickening, yet disarray is absent and mutations in the myofibrillary genes are not found. These cases indicate that other genes outside the sarcomeric complex can produce thick walled left ventricles. Mitochondrial gene disorders, glycogen storage disease, and Fabry's disease are among the known causes of the phenomenon.

Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM), in which the left ventricle is nearly normal in shape but there is a failure of the myocardium to relax in diastole, is one form of cardiomyopathy where cardiac biopsy may help. The most common form is myocardial amyloid. It is usually easy to recognise amyloid on histology by its characteristic green colour under polarised light after staining with Sirius red dye. Amyloid is not, however, evenly distributed in the ventricle and false negatives occur. Some cases develop a florid myocardial fibrotic response masking the amyloid. For these reasons electron microscopy studies of the biopsy may improve the sensitivity. Other causes of restriction include diffuse perimyocyte fibrosis. This pattern of fibrosis is seen to a degree in many cases of DCM, but when in a uniform distribution it appears to cause predominant restriction. The pathogenesis of this form is unknown. Another form of RCM is familial and associated with myocyte disarray on biopsy, but without other clinical or morphological features of HCM. The gene(s) responsible have not yet been identified.

Arrhythmogenic right ventricular dysplasia

First recognised in young subjects with normal exercise tolerance who died suddenly, arrhythmogenic right ventricular dysplasia (ARVD) is characterised by areas in the right ventricle where there is transmural replacement of the myocytes largely by adipose tissue, but with some fibrosis leading to focal areas of aneurysmal dilatation. The first cases recognised were at the extreme end of the spectrum, but family studies⁷ and wider clinical studies using magnetic resonance imaging in subjects with unexplained ventricular tachycardia revealed that the areas of abnormality may be small—no more than 1–2 cm across. About a third of cases have concomitant left ventricular involvement with fibrofatty replacement of myocytes, often subpericardial and maximal on the posterior wall. In most but not all cases the myocardial involvement, while acting as a substrate for arrhythmias, does not significantly reduce right or left ventricular contractile function.

In patients with a known family history or with clear ECG and echocardiographic changes suggesting ARVD, cardiac biopsy is a useful confirmatory investigation but is rarely diagnostic in its own right. The focal nature of the disease means false negatives are common, while simple adipose infiltration into the right ventricular myocardium without replacement of myocytes or fibrosis is a common finding in normal subjects, particular women. Biopsy findings of fat in the right ventricular wall can be overinterpreted and lead to false positives. The diagnosis of ARVD has to be based on the concordance of clinical and pathological features.

ARVD is genetic and several sites of candidate genes have been identified on different chromosomes. At present what these genes control or produce is unknown. The histological changes are different from those in DCM because although myocytes are being lost in both conditions, in ARVD there is a predominant replacement by adipose tissue. One suggestion is that in ARVD myocytes are being lost by apoptosis which does not invoke replacement fibrosis. In many cases of ARVD there is an inflammatory cell infiltrate in the abnormal areas of myocardium. This has been interpreted as a myocarditic component but could be a secondary rather than a primary change. Once the candidate genes are identified it may become clear how the phenotype is produced.

The frequency of ARVD is impossible to establish accurately at present because the less striking cases are underdiagnosed both in life and after death. It appears to be a major cause of sudden death in young people in northern Italy, while in the UK HCM remains numerically more important as a cause of sudden death.

Obliterative cardiomyopathy

In this condition thrombus develops on the endocardium of the apex and inflow segments of one or both ventricles. The ventricular cavity begins to be obliterated and the tricuspid and mitral valves are involved. The thrombus undergoes conversion to fibrous tissue as the disease progresses. The ultimate expression is of a small ventricular cavity with massive endocardial thickening by fibrosis leading to the condition known as endomyocardial fibrosis. In temperate climates the disease is caused by endocardial damage resulting from the release of cationic proteins from activated eosinophils in the circulation.⁸ In many cases the thrombus is infiltrated by eosinophils but this is not a prerequisite for the condition. Any cause of systemic hypereosinophilia, including eosinophilic leukaemia, Churg Strauss syndrome, Bechet's syndrome, and idiopathic hypereosinophilia, can cause endomyocardial fibrosis. While hypereosinophilia persists and degranulated eosinophils are present in the circulation the deposition of thrombus continues. Cases in which the eosinophilia occurred in a single episode in the past may present at the end stage of the disease, with massive endocardial fibrosis restricting both ventricular contraction and cavity volume. Recognition of the cause can only be made by a history of previous disease likely to be associated with increased eosinophil activation. Decortication of the thick layer of fibrous tissue, with replacement of the mitral or tricuspid valves, may be needed. In tropical countries in Asia, Africa, and South America an identical end stage cardiac disease occurs, but the link to previous hypereosinophilia is less well established, and other factors such as nutritional deficiency or ingestion of unknown toxins are widely debated as causes.

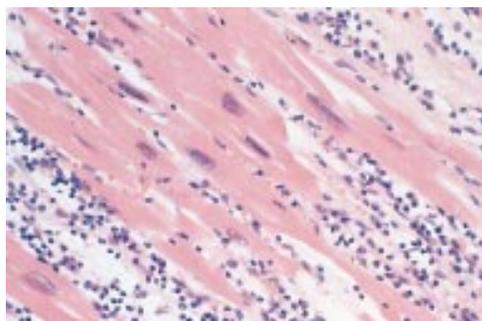


Figure 5: Acute myocarditis. There is a heavy but focal increase of lymphocytic cells in the interstitial tissues of the myocardium.

Inflammatory cardiomyopathy (myocarditis)

The clinical picture of acute myocarditis is characterised by the rapid onset of cardiac failure or arrhythmias, or both, with fever, malaise, myalgia, and sometimes pericarditis; it has a morphological counterpart (Dallas criteria)⁹ of myocyte necrosis, usually in a multifocal but sometimes regional distribution, with a heavy interstitial infiltrate of T lymphocytes (fig 5). In practice the characteristic morphology occurs only in fatal and severe cases, and biopsy of the myocardium often shows no evidence of the typical tissue changes despite a confident clinical diagnosis of acute myocarditis. The reported positivity rate varies from centre to centre but is usually no more than 10%. In biopsy positive cases of myocarditis there is no clear evidence that immunosuppression is beneficial with regard to outcome. The biopsy negative but clinically positive cases create a diagnostic challenge and are likely to be heterogeneous in origin. Some may be genuine cases of myocarditis, but the biopsy is taken after the T lymphocyte infiltrate has cleared. Other cases may reflect the limitations of cardiac biopsy because with a focal disease the sample taken may come from an area of normal myocardium.

A significant number of cases of clinically suspected myocarditis prove to have interstitial fibrosis and therefore represent longstanding disease. A factor such as viral infection may have precipitated non-specifically the onset of symptoms as the first presentation of DCM. In the absence of any current evidence that treatment other than supportive therapy for cardiac failure will improve prognosis, it is not clear whether myocardial biopsy will give any data of value for treating individual subjects. Centres carrying out large numbers of cardiac biopsies to elucidate the mechanisms of cardiac disease for the future have more justification for biopsy.

Viral infection and acute myocarditis

The major cause of acute myocarditis is perceived to be viral, involving in particular the coxsackie group of viruses. This is based on very well established links between viruses and

acute myocarditis in animals such as mice (coxsackie) and dogs (parvovirus). What occurs in other animals is likely to occur in man. Coxsackie genomic material is found in about a third of human cases of acute myocarditis using PCR technology on myocardial tissue. The younger the subject the more likely is virus to be found. One facet of viral myocarditis in experimental animals is that viral replication ceases before the myocyte damage occurs. It is therefore rarely possible to culture replicating virus from the heart. The same is true of human acute myocarditis, and diagnosis has to be based on PCR on cardiac tissue and rising titres in sequential serology.

It is probable that human myocarditis can be caused by viruses other than those from the coxsackie group, and the adeno group is beginning to be seen as potentially cardiotoxic. A very wide range of viruses such as those responsible for chicken pox, measles, rubella, and mumps often cause a minor degree of what is taken to be myocarditis based on ECG changes. A small subgroup of myocarditis may be caused by non-viral organisms, such as the spirochaete *Borrelia burgdorferi* in Lyme disease, toxoplasma, and leptospira, while in South America *Trypanosoma cruzi* is by far the most common cause of the acute myocarditis of Chagas' disease.

Patients with biopsy positive or negative myocarditis may die in the acute phase or recover. Recovery is usually complete although there are a few reported cases of slow progression into DCM. Trials are underway to investigate the possibility that cases in which virus can be detected by PCR on biopsy tissue have a different pattern of behaviour and prognosis, and should be treated with interferon.

The Dallas criteria for acute myocarditis on cardiac biopsy defined the need for severe myocyte damage plus a T lymphocyte interstitial inflammatory cell infiltrate. A form of myocarditis occurs in which myocyte damage is mild or absent but there is a florid interstitial inflammatory cell infiltrate of a more pleomorphic type containing plasma cells and eosinophils. This form of chronic myocarditis may be associated with ventricular arrhythmias rather than cardiac failure. Its pathogenesis is unknown but drug hypersensitivity has been implicated in some cases.

Giant cell myocarditis

Myocardial involvement by sarcoid has a range of patterns.¹⁰ There may be a diffuse distribution of giant cell granulomas or a single regional mass of sarcoid tissue which is initially expanded in volume, but as fibrosis develops the mass shrinks and may develop into a ventricular aneurysm. Cardiac biopsy to diagnose myocardial sarcoid in a subject with chronic arrhythmias can give a specific positive diagnosis but the false negative rate is high.

A different form of idiopathic giant cell myocarditis¹¹ occurs as an acute onset disease with very severe cardiac failure leading to death

within a week unless cardiac transplantation is available. There are irregular areas of myocardial necrosis, at the margins of which are large giant cells but no organised granulomas such as occur in sarcoid. No virus has been implicated. The only known association is with autoimmune disease and thymomas, although the majority of cases occur suddenly in subjects who have no other pre-existing disease. Recurrence of the giant cell myocarditis in donor hearts can occur.

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