Cardiomyopathies are defined as diseases of the myocardium, which cause cardiac dysfunction with heart failure, arrhythmia, and sudden death. Cardiomyopathies represent a major cause of morbidity and mortality in both children and adults and are a frequent indication for cardiac transplantation. In 1995, the World Health Organization (WHO)/International Society and Federation of Cardiology (ISFC) task force recommended that the cardiomyopathies be classified into two main groups: specific cardiomyopathies, and primary cardiomyopathies. The specific cardiomyopathies include heart muscle disease associated with myocarditis, specific cardiac disease or general systemic disease. In contrast, the primary cardiomyopathies are diseases intrinsic to the myocardium itself and are classified pathophysiologically. This group includes dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and unclassified cardiomyopathy.

Dilated Cardiomyopathy and Isolated Left Ventricular Non-Compaction

Idiopathic dilated cardiomyopathy (DCM) is the most common cause of congestive heart failure in the young with an estimated prevalence of at least 36.5 per 100,000 persons in the USA. DCM is characterised by an increase in myocardial mass and a reduction in ventricular wall thickness. The heart assumes a globular shape and there is pronounced ventricular chamber dilatation, diffuse endocardial thickening, and atrial enlargement often with thrombi in the appendages. The histological changes associated with DCM are frequently non-specific and not all features may be present. These include the constellation of myocyte attenuation, interstitial fibrosis, myocyte nuclear hypertrophy, and pleomorphism. There is often an increase in interstitial T lymphocytes as well as focal accumulations of macrophages associated with individual myocyte death. Frequently there is extensive myofibrillar loss, imparting an empty or vacuolated appearance to myocytes.

Although the aetiology of these cases is largely unknown, up to 35% of individuals with idiopathic DCM have familial disease. This has been shown by detailed pedigree analyses of relatives of index patients with DCM coupled with the identification of single gene mutations in structural proteins of the myocyte cytoskeleton or sarcrolemma. It has therefore been proposed that familial DCM is a form of “cytoskeletalopathy”. Secondary causes of DCM include coronary artery disease, myocarditis, nutritional deficiency, systemic disease, cardiotoxins (for example, anthracycline), puerperium, alcohol, and skeletal muscle wasting diseases (that is, the muscular dystrophies).

The pattern of inheritance of familial DCM (FDCM) is variable and includes autosomal dominant, X-linked, autosomal recessive, and mitochondrial inheritance. The autosomal forms of FDCM are the most frequent and can be further grouped into either a pure DCM phenotype or DCM with cardiac conduction system disease. Major progress has been made in the identification of candidate disease loci and the genes responsible for FDCM. These include mutations in the genes encoding cardiac actin, desmin, δ-sarcoglycan, β-sarcoglycan, cardiac troponin T, and α-tropomyosin. Four candidate genetic loci have also been mapped for DCM with cardiac conduction system disease but to date there has been identification of only one gene, the lamin A/C gene. Mutations in the lamin A/C gene also cause autosomal dominant FDCM with mild skeletal myopathy as well as autosomal dominant Emery-Dreifuss muscular dystrophy.

The X-linked forms of DCM include X-linked dilated cardiomyopathy and Barth syndrome. X-linked dilated cardiomyopathy (XLCM) is a form of DCM occurring in males during adolescence or early adulthood with a rapidly progressive clinical course. Female carriers develop a mild form of DCM with onset in middle age. XLCM is associated with raised concentrations of creatine kinase (CK) but without clinical signs of skeletal myopathy and is caused by mutations in the dystrophin gene. Mutations of this gene are also responsible for...
Duchenne’s and Becker’s muscular dystrophies. Similarly, most individuals with these dystrophinopathies will develop DCM at some stage in their lives.\textsuperscript{w4} The infantile form of X-linked DCM or Barth syndrome typically presents in male infants.\textsuperscript{w5} It is characterised by neutropenia, 3-methylglutaconic aciduria, growth retardation, and mitochondrial dysfunction.\textsuperscript{w5} The cardiac manifestations include left ventricular dilatation, endocardial fibroelastosis, or a dilated hypertrophied left ventricle. Mutations in the gene G4.5, which encodes the protein tafazzin, cause Barth syndrome.\textsuperscript{w6} The function of the tafazzin protein is unknown, but mutations in the G4.5 gene appear to be responsible for a diverse spectrum of cardiac disease with unique clinical phenotypes.\textsuperscript{w7} These include classical DCM, endocardial fibroelastosis, and left ventricular non-compaction (LVNC) with or without clinical features of Barth syndrome (isolated LVNC).\textsuperscript{2} w7

Isolated LVNC was first described over a decade ago and is now gaining increased recognition as an important cause of heart failure and its complications.\textsuperscript{w8} It is a rare congenital myocardial disorder but important in the differential diagnosis of adult patients presenting with cardiac failure. In the largest published series of isolated LVNC, this cardiomyopathy was diagnosed in 17 of 37,555 adult echocardiograms, a prevalence of 0.05%.\textsuperscript{w9} Isolated LVNC is not well characterised or widely recognised and currently falls into the category of unclassified cardiomyopathy by the WHO. Isolated LVNC tends to affect the left ventricle with or without right ventricular involvement and results in systolic and diastolic ventricular dysfunction. Pathologically the non-compact ed endocardial layer of the myocardium is comprised of excessively numerous and prominent trabeculations with deep intertrabecular recesses extending into the compacted myocardial layer (fig 1A). Most commonly the apical and mid ventricular segments of both the inferior and lateral wall of the left ventricle are affected. Histologically the non-compact ed layer is comprised of numerous “finger-like” trabeculations with prominent fibrosis (fig 1B).

Isolated LVNC occurs because of postnatal persistence of the embryonic pattern of myoarchitecture. During the first six weeks of fetal life, before the development of the coronary circulation, the human left ventricular endocardium consists of a spongy meshwork of abundant fine trabeculae with deep intertrabecular recesses, which serve to increase myocardial oxygenation. At 12 weeks, when ventricular septation is complete, the trabeculae start to solidify at their basal area contributing to added thickness of the compacted myocardial layer. The large spaces within the trabecular meshwork flatten or disappear. Compaction of the ventricle is completed in the early fetal period and progresses from the epicardium to the endocardium and from the base of the heart to its apex.\textsuperscript{3} However, in isolated LVNC this process appears to be arrested at some point during development. Although non-compaction of the ventricular myocardium is a congenital myocardial disorder, the onset of symptoms is frequently delayed until adulthood.\textsuperscript{w8} Undoubtedly, increased awareness of the pathology of isolated LVNC will improve the diagnosis of this rare cardiomyopathy and facilitate its recognition as a distinct entity.

![Figure 1](A) Photograph of an explanted heart at mid septal level showing the gross morphological features of non-compaction in isolated LVNC. The non-compacted endocardial layer of the myocardium is comprised of excessively numerous and prominent trabeculations with deep intertrabecular recesses extending into the compacted myocardial layer imparting a distinctive “spongy” appearance. (B) Haematoxylin and eosin stained section of isolated LVNC. The non-compacted myocardial layer is comprised of prominent and elongated “finger-like” trabeculations. Within individual trabeculations there is fibrosis, which is most pronounced on the endocardial surface.

The pathology of DCM and isolated LVNC: key points

- Idiopathic DCM is the most common cause of congestive heart failure in the young
- The histological changes associated with DCM are often non-specific and not all features may be present
- Idiopathic DCM is often familial and is caused by mutations in structural proteins comprising the myocyte cytoskeleton or sarclemma
- Isolated LVNC currently falls into the category of unclassified cardiomyopathy by WHO
- Isolated LVNC occurs because of postnatal persistence of the embryonic pattern of myoarchitecture and is characterised by a lack of compaction of the endocardium
- The non-compact ed endocardial layer is comprised of numerous “finger-like” trabeculations
- Isolated LVNC is caused by mutations in the gene G4.5, which encodes the novel protein tafazzin

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RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy (RCM) is the least common type of cardiomyopathy and is characterised by restrictive filling and reduced diastolic volume of either or both ventricles with normal or near normal systolic function and wall thickness. Clinically and haemodynamically RCM simulates constrictive pericarditis and may lead to diagnostic uncertainty. RCM commonly results from myocardial or endomyocardial disease of diverse aetiologies, which “stiffen” the heart by infiltration or fibrosis. RCM may be classified as primary or secondary. The primary restrictive cardiomyopathies include endomyocardial fibrosis (EMF), Loeffler’s endocarditis, and idiopathic RCM. The latter is non-infiltrative and the only detectable histological abnormality is interstitial fibrosis of the myocardium. Idiopathic RCM is often characterised by skeletal myopathy and autosomal dominant transmission. Similarly, a subset of patients with familial HCM caused by troponin I mutations can also present primarily with restrictive physiology and may resemble RCM. The secondary forms of RCM are more common and include the specific heart muscle diseases in which the heart is affected as part of a multisystem disorder. These can be subclassified as non-infiltrative (for example, carcinoid heart disease, anthracycline toxicity), infiltrative (for example, amyloidosis, sarcoidosis) or as storage disorders (for example, haemochromatosis, glycogen storage disease, Fabry’s disease). In interstitial disease, the infiltrates localise between myocytes, whereas in storage disorders the deposits occur within the cell.

Cardiac amyloidosis is caused by the deposition of insoluble amyloid protein fibrils in the interstitium or vessel walls of the myocardium and each type has different clinicopathological features. The principal forms of amyloidosis which affect the heart include AL amyloidosis, senile systemic amyloidosis, and hereditary amyloidosis. AL amyloidosis is known as primary systemic amyloidosis and is caused by the deposition of immunoglobulin light chains. Senile systemic amyloidosis occurs because of the deposition of unmutated or wild type transthyretin (TTR). Hereditary systemic amyloidosis includes TTR-related amyloidosis (caused by the deposition of mutant TTR), apolipoprotein AI (ApoAI) amyloidosis, and apolipoprotein II (ApoAII) amyloidosis. Rarely reactive serum AA amyloidosis (caused by deposition of acute phase serum amyloid A protein) may involve the heart.

Cardiac amyloidosis is characterised macroscopically by atrial dilatation and the ventricles are of normal or near normal size. In some cases mild to moderate left ventricular hypertrophy and/or right ventricular hypertrophy may be evident and some cases may simulate HCM clinically. The myocardium has a waxy appearance and a rubbery non-compliant texture. Microscopically there are deposits of eosinophilic material within the myocardial interstitium, cardiac valves, and within the media of intramyocardial coronary arteries (fig 2A). The deposits stain red with Congo red and display classical apple green birefringence when viewed under polarised light (fig 2B). The pattern of amyloid deposition in the heart can be classified as nodular, perifibre, or mixed type with or without vascular involvement. Similarly, the extent of amyloid deposition can be graded as 1 through to 4, corresponding with less than 10%, 10–25%, 26–50%, and more than 50% histological involvement of the myocardium, respectively.

The pathology of RCM: key points

- RCM is the least common type of primary cardiomyopathy and may be classified as primary or secondary
- RCM is caused by myocardial or endomyocardial disease, which “stiffen” the heart by infiltration or fibrosis
- Cardiac amyloidosis is a secondary form of RCM caused by the deposition of insoluble amyloid protein fibrils
- The principal types of amyloidosis which affect the heart include AL amyloidosis, senile systemic amyloidosis, and hereditary amyloidosis
- Hereditary amyloidosis is uncommon but its recognition has major implications for patient management and genetic counselling
- Endomyocardial biopsy is valuable for the diagnosis of cardiac amyloidosis
- Amyloid deposits stain red with Congo red and display apple green birefringence when viewed under polarised light
Disease.w13 TTR Lys92 mutations are associated mainly with cardiac death.8 Similarly, early diagnosis of patients with FAP caused by MSN mutations.8 w13 Conversely, TTR Thr45, TTR Met111, and TTR Lys92 mutations are associated mainly with cardiac disease.w13

Endomyocardial biopsy is valuable for the diagnosis of cardiac amyloidosis, whereby amyloid protein deposits surround individual myocytes and form a characteristic “honeycomb” pattern. Endomyocardial biopsy can thus facilitate the identification of a subset of patients with specific forms of RCM. This avoids some patients undergoing unnecessary thoracotomy with constrictive/restrictive physiology, where the differentiation of RCM from constrictive pericarditis can be difficult. Furthermore, it is possible to perform immunohistochemical studies on endomyocardial biopsy specimens to identify the amyloid fibril type. In the UK, this service is provided by the National Amyloidosis Centre, which is based at the Royal Free Hospital in London. Typing is of relevance because in order to be able to offer appropriate treatment it is essential to classify the subtype of amyloidosis. For example, RCM caused by light chain deposition may be reversible after response to treatment and remission of the underlying plasma cell dyscrasia." Similarly, early diagnosis of patients with FAP caused by mutant TTR may benefit from liver transplantation.w13

EMF is a restrictive obliteratorative cardiomyopathy and is characterised by a fibrotic thickened endocardium and mural thrombi in the apices of both ventricles with partial cavity obliteration and involvement of both atrioventricular valves. Two forms of EMF occur and the cardiac pathologies of both are similar.10 The first type of EMF known as Loeffler’s endocarditis is an uncommon, rapidly progressive disease and occurs in temperate climates where it is related to hypereosinophilic states (for example, idiopathic hypereosinophilic syndrome, eosinophilic leukaemia, Churg-Strauss syndrome). The second type of EMF is of unknown aetiology and was originally encountered and described in the subtype. 11 13 The “fatty” variant is considered to be the less pronounced eosinophilia observed with parasitic infections.10 Both disorders share similar cardiac pathologies and are likely to represent a continuum, whereby Loeffler’s endocarditis and tropical EMF represent the same disease process but at different stages.10

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a disease predominantly of the right ventricular myocardium characterised by the progressive loss of myocytes. This is caused by either massive or partial replacement of myocardium by fatty or fibro-fatty tissue advancing from the epicardium to the endocardium and sparing the trabeculae (fig 3A,B). Residual islands or strands of myocytes are surrounded by fat or fibrous tissue providing a substrate for electrical instability leading to sustained ventricular arrhythmias and sudden death.11 12 Sudden death is more common in adolescents and young adults and may be precipitated by exertion.12 Two pathological variants have been described in the literature and include a predominantly “fatty” variant and a “fibrofatty” variant.11 13 The “fatty” variant is characterised by transmural infiltration of adipose tissue with sparing of the septum and left ventricle and without
The pathology of ARVC: key points

- ARVC is characterised by massive or partial replacement of myocardium by fibroadipose tissue
- ARVC may involve the left ventricle
- Identification of mutations in the plakoglobin and desmoplakin gene indicate that ARVC is a genetic disease of cell adhesion
- The morphological spectrum of ARVC is not fully defined
- Endomyocardial biopsy has a limited role for the diagnosis of ARVC, since the interventricular septum is rarely involved and biopsy of the thinned right ventricle is potentially hazardous because of the high risk of perforation and cardiac tamponade.
Hypertrophied hearts with diverse aetiologies. The pathological hallmarks are the triad of myocyte hypertrophy, disarray, and interstitial fibrosis (fig 4B). Myocyte disarray is characterised by architectural disorganisation of the myocardium, whereby adjacent myocytes are aligned perpendicularly or obliquely to each other in or around collagen (fig 4B) in either a pinwheel or herringbone pattern. The myocyte nuclei also exhibit distinct changes including nuclear hypertrophy, pleomorphism, and hyperchromasia. Within the myocyte itself there is disorganisation of the myofibrillary architecture with loss of the usual parallel alignment of myofibrils. Unfortunately, myocyte disarray per se is not pathognomonic of HCM and has been observed in the hearts of individuals with congenital heart disease and in the normal adult heart, but in these settings is usually mild in extent. Thus, extensive myocyte disarray serves as both a highly sensitive and specific marker for the diagnosis of HCM.

Small vessel disease or arterial dysplasia is another pathological feature of HCM. Arterial dysplasia is characterised by narrowing of the small intramural coronary arteries due to wall thickening by smooth muscle cell hyperplasia. Furthermore, small vessel disease in individuals with HCM may lead to replacement fibrosis and the development of the dilated phase of HCM. HCM is a disease of the cardiac sarcomere and is caused by mutations in the genes encoding β-myosin heavy chain, cardiac regulatory and essential myosin light chains, myosin binding protein C, α-cardiac actin, cardiac troponin T, cardiac troponin I, α-tropomyosin, titin, and troponin C. Most mutations are single point missense mutations or small deletions or insertions. The most frequent causes of HCM are due to mutations in cardiac β-myosin heavy chain, cardiac troponin T, cardiac troponin I, and myosin binding protein C genes.

For each gene several different mutations have been identified and specific mutations are associated with different disease severity and prognosis. For example, mutations in troponin T cause only mild or subclinical hypertrophy yet are associated with a poor prognosis and a high risk of sudden death. In contrast, mutations in myosin binding protein C are associated with mild disease and onset in middle age or late adult life. Similarly, genotype–phenotype correlation studies have led to the discovery of “malignant” mutations in the cardiac β-myosin heavy chain gene, which cause a severe form of HCM with early onset, complete penetrance, and increased risk of sudden cardiac death. Conversely, other mutations are associated with an intermediate or a benign clinical course. HCM also exhibits intrafamilial phenotypic variation, whereby affected individuals from the same family with an identical genetic mutation display distinct clinical
and morphological manifestations. This suggests that lifestyle factors or modifier genes are likely to influence the hypertrophic response.29

The diagnosis of HCM is complicated by the recognition of other diseases, which echocardiographically simulate HCM with symmetrical or asymmetrical left ventricular hypertrophy, yet disarray and mutations in the sarcomeric genes are absent. These include glycogen storage disease, mutations in cardiac mitochondrial respiratory enzymes or mitochondrial DNA, and Fabry’s disease.23-24

Fabry’s disease is an X-linked autosomal recessive metabolic storage disorder, caused by deficiency of the enzyme lysosomal α-galactosidase A. This leads to the widespread accumulation of neutral glycosphingolipid in multiple organs. Recently, an atypical variant of Fabry’s disease has been described, which predominantly affects the heart. The prevalence of cardiac Fabry’s was found to be between 4–6% of all male patients attending a tertiary referral centre for evaluation of HCM.25 In endomyocardial biopsies, the presence of myocyte sarcoplasmic vacuolisation in haematoxylin and cosin stained sections (fig 5A) raises the possibility of a myocardial metabolic storage disease. The diagnosis of Fabry’s disease can be confirmed by electron microscopy, which reveals the presence of numerous concentric lamellar bodies or myelin figures within the myocyte sarcoplasm (fig 5B). The increased recognition of cardiac Fabry’s disease underscores the value of performing routine electron microscopic studies for the diagnosis of some types of cardiomyopathy.

CONCLUSION

Advances in molecular genetics have heralded the identification of single gene defects and candidate disease loci responsible for DCM, HCM, RCM, and ARVC as well as cardiomyopathies of unknown cause, such as isolated LVNC. These advances, coupled with phenotype–genotype correlation analyses, have shown that the pathology of several types of cardiomyopathy encompasses a much broader morphological spectrum than previously realised. Pathological studies have facilitated the recognition of isolated LVNC as a distinct cardiomyopathy with unique morphological and histological features.

The value of endomyocardial biopsy for the diagnosis of some types of cardiomyopathy remains controversial. However, endomyocardial biopsy combined with routine electron microscopy has emerged as a useful tool in the diagnostic armoury for distinguishing a subset of individuals with cardiac Fabry’s disease, which clinically simulates HCM.

Undoubtedly, in the future, the enormous impact of scientific progress in unravelling the genetic basis and aetiology of primary myocardial disease will broaden current concepts surrounding the pathology of the primary cardiomyopathies.

REFERENCES


3 An excellent up-to-date review of the identification of the genes responsible for cardiomyopathies providing further insights into the pathogenesis of these disorders.


6 A comprehensive review of the molecular genetic basis of DCM.


8 An excellent review article with stunning electron micrographs explaining developmental patterning of the myocardium. This article provides a unique insight into the pathology of isolated LVNC.


10 A helpful review article providing an overview of the pathogenesis, natural history, and diagnostic evaluation of the restrictive cardiomyopathies.


8 A comprehensive review of the restrictive cardiomyopathies.

9 An excellent review article discussing the genetics of HCM.

10 A study reviewing necropsy material from 33 patients with senile systemic amyloidosis and providing fresh insights into the clinicopathological features and pathogenesis of this disease.


12 A necropsy study describing the gross and microscopic pathology of cardiac amyloidosis and comparing the extent and pattern of amyloid deposits in primary amyloidosis and senile amyloidosis.

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► An excellent review of the aetiology and pathology of tropical and temperate EMF.
► This landmark study describes and explains the clinicopathological profile and natural history of ARVC.
► This article provides a comprehensive review of the major progress over the last decade in our understanding of the aetiopathogenesis, morbid anatomy, and clinical presentation of ARVC.
► This article describes the different pathological patterns encountered in ARVC.
► This article examines the relation between ARVC and adipose infiltration of the right ventricle. The study concludes that adipose infiltration per se should not be considered synonymous with ARVC.
► This article addresses the contribution of cardiac adipose tissue to heart weight, which may constitute up to 50% of the cardiac mass.
► An up-to-date review article providing a comprehensive systematic analysis of the HCM literature.
► The classical article by Donald Teare describing the necropsy findings in a series of young adults, which prompted recognition of HCM.
► An excellent review article describing and explaining the molecular genetics and pathogenesis of HCM.

Additional references appear on the Heart website—http://www.heartjnl.com/supplemental
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