



## New insights into the pathology of inherited cardiomyopathy

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# NEW INSIGHTS INTO THE PATHOLOGY OF INHERITED CARDIOMYOPATHY

Siân E Hughes, William J McKenna

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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.<sup>1</sup> 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.<sup>w1</sup> 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 myofibrillary loss, imparting an empty or vacuolated appearance to myocytes.

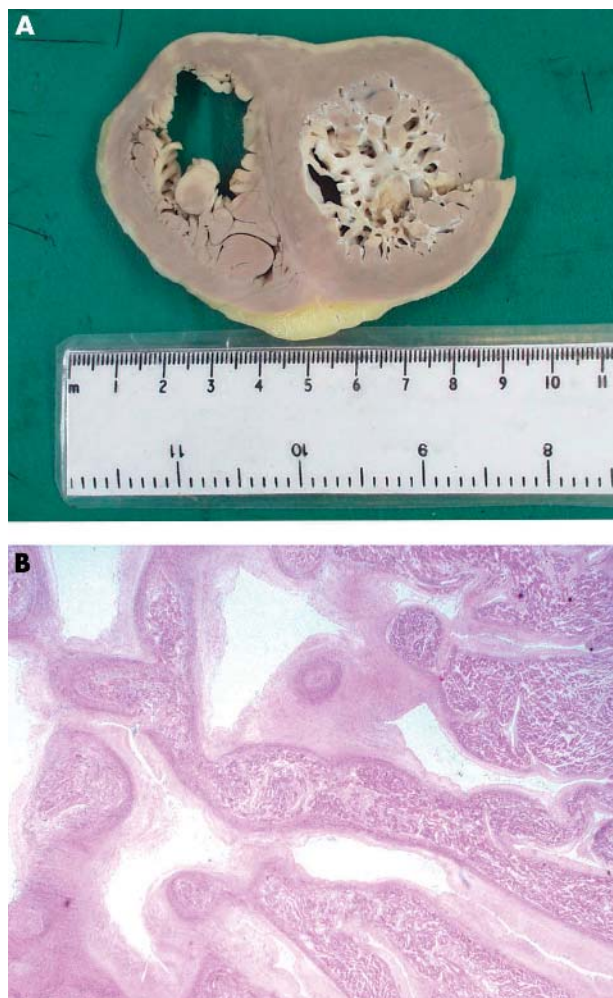
Although the aetiology of these cases is largely unknown, up to 35% of individuals with idiopathic DCM have familial disease.<sup>w2</sup> This has been shown by detailed pedigree analyses of relatives of index patients with DCM coupled with the identification of single gene mutations in structural proteins of the myocyte cytoskeleton or sarcolemma.<sup>2,3</sup> It has therefore been proposed that familial DCM is a form of "cytoskeletalopathy".<sup>3</sup> 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.<sup>2,4 w2</sup> 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,  $\delta$ -sarcoglycan,  $\beta$ -sarcoglycan, cardiac troponin T, and  $\alpha$ -tropomyosin.<sup>2</sup> 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.<sup>2,4</sup> 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.<sup>4</sup>

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.<sup>w3</sup> 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.<sup>w3</sup> Mutations of this gene are also responsible for

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**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.

Duchenne's and Becker's muscular dystrophies. Similarly, most individuals with these dystrophinopathies will develop DCM at some stage in their lives.<sup>w4</sup> The infantile form of X-linked DCM or Barth syndrome typically presents in male infants.<sup>w5</sup> It is characterised by neutropenia, 3-methylglutaconic aciduria, growth retardation, and mitochondrial dysfunction.<sup>w5</sup> 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.<sup>w6 w7</sup> 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.<sup>w7</sup> These include classical DCM, endocardial fibroelastosis, and left ventricular non-compaction (LVNC) with or without clinical features of Barth syndrome (isolated LVNC).<sup>2 w7</sup>

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.<sup>w8</sup> 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%.<sup>w9</sup> 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-compacted 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-compacted 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.<sup>5</sup> 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.<sup>w8</sup> 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.

#### The pathology of DCM and isolated LVNC: key points

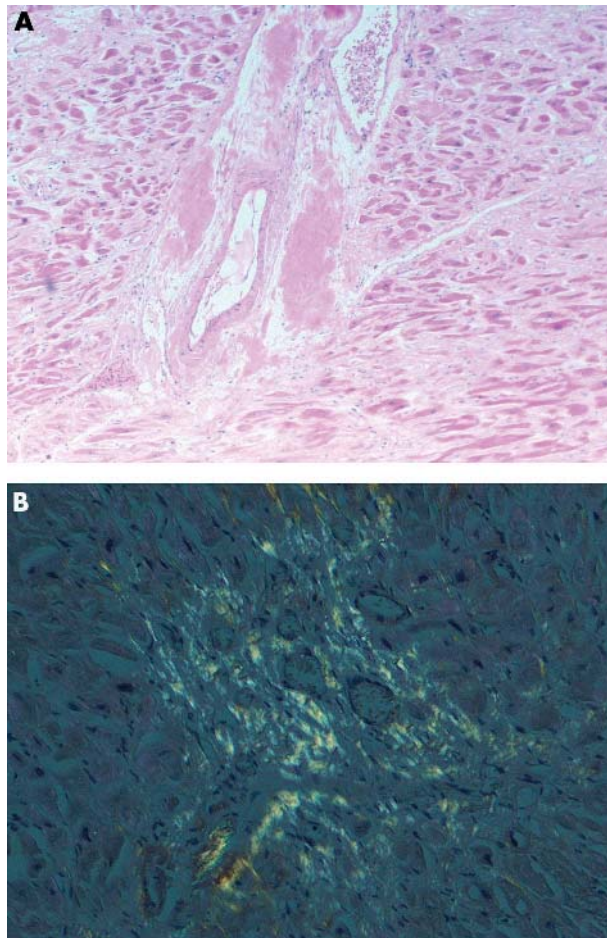
- ▶ Idiopathic DCM is the most common cause of congestive heart failure in the young
- ▶ The histological changes associated with DCM are often non-specific and not all features may be present
- ▶ Idiopathic DCM is often familial and is caused by mutations in structural proteins comprising the myocyte cytoskeleton or sarcolemma
- ▶ 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-compacted 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

## RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy (RCM) is the least common type of cardiomyopathy<sup>1</sup> 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.<sup>6</sup> RCM commonly results from myocardial or endomyocardial disease of diverse aetiologies, which “stiffen” the heart by infiltration or fibrosis.<sup>7</sup> 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.<sup>6,7</sup> 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.<sup>w10</sup> 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.<sup>7</sup>

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).<sup>8</sup> Hereditary systemic amyloidosis includes TTR-related amyloidosis (caused by the deposition of mutant TTR), apolipoprotein AI (ApoAI) amyloidosis,<sup>w11</sup> and apolipoprotein II (ApoAII) amyloidosis.<sup>w12</sup> Rarely reactive serum AA amyloidosis (caused by deposition of acute phase serum amyloid A protein) may involve the heart.<sup>9</sup>

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.<sup>9</sup>



**Figure 2** (A) Haematoxylin and eosin stained section of eosinophilic amyloid deposits within the myocardial interstitium and around blood vessels. (B) Congo red stained section of cardiac amyloidosis viewed under polarised light showing interstitial amyloid deposition with a perifibre distribution. The amyloid forms a “honeycomb” around individual myocytes and displays classical apple green birefringence.

Senile systemic amyloidosis is common and affects approximately 25% of the elderly population over the age of 80 years.<sup>8</sup> This disease tends to run a benign clinical course with deposits of unmutated (wild type) TTR in multiple

### The pathology of RCM: key points

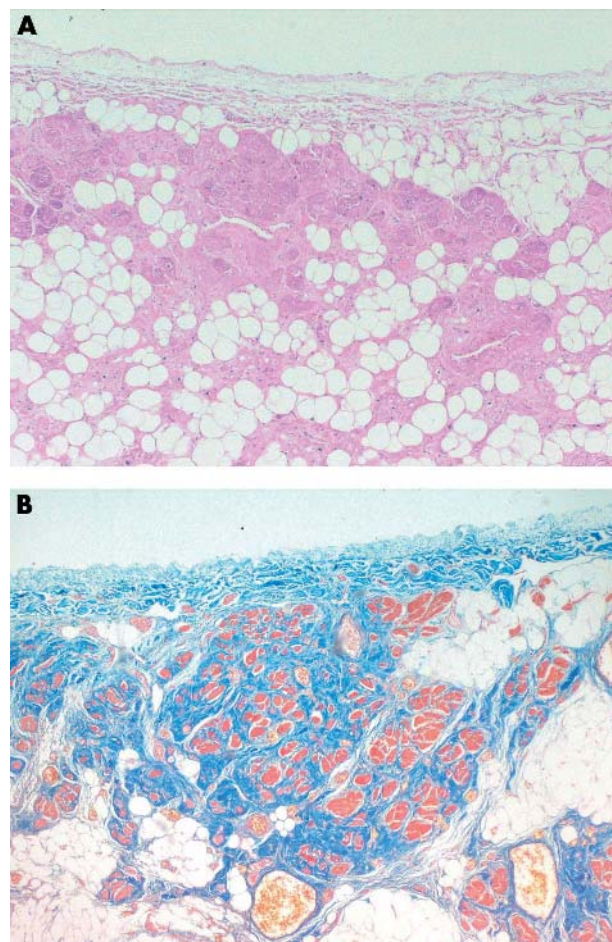
- ▶ RCM is the least common type of primary cardiomyopathy and may be classified as primary or secondary
- ▶ RCM is caused by myocardial or endomyocardial disease, which “stiffen” the heart by infiltration or fibrosis
- ▶ Cardiac amyloidosis is a secondary form of RCM caused by the deposition of insoluble 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

organs including the heart. However, in some elderly male individuals there may be massive deposition of amyloid in the heart causing congestive cardiac failure and eventual death.<sup>8</sup>

Hereditary systemic amyloidosis is uncommon but its recognition has important implications for patient management and genetic counselling. The principal mode of inheritance of TTR-related amyloidosis is autosomal dominant, while some cases appear to occur sporadically.<sup>w13</sup> The clinical phenotype of hereditary TTR-related amyloidosis varies according to the type of TTR mutation. For example, polyneuropathy and autonomic dysfunction predominate in many types of TTR-related amyloidosis, which is designated as familial amyloid polyneuropathy (FAP). This form of hereditary amyloidosis is frequently caused by TTR Met30 mutations.<sup>8 w13</sup> Conversely, TTR Thr45, TTR Met111, and TTR Lys92 mutations are associated mainly with cardiac disease.<sup>w13</sup>

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.<sup>6</sup> Similarly, early diagnosis of patients with FAP caused by mutant TTR may benefit from liver transplantation.<sup>w14</sup>

EMF is a restrictive obliterative 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.<sup>10</sup> 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 Uganda and is termed tropical EMF or Davies' disease. Tropical EMF has a worldwide distribution but is most prevalent in tropical and subtropical countries in Africa, Asia, and South America. Histologically, in the acute phase there is eosinophilic infiltration amounting to myocarditis, and in established disease there is extensive fibrosis of the endocardium and inner half of the myocardium (endomyocardium). Irrespective of the geographical origin eosinophils are central to the pathogenesis of EMF, whereby endocardial damage occurs because of enzyme release from degranulated eosinophils in the circulation.<sup>10</sup> Compared with its temperate zone counterpart, the more chronic course of tropical EMF may be related to the less pronounced eosinophilia observed with



**Figure 3** (A) Haematoxylin and eosin stained section of the "fibrofatty" or "cardiomyopathic" variant of ARVC. The fibroadipose replacement advances from the epicardium to the endocardium. There is associated myocardial atrophy and progressive myocyte loss. (B) Modified Masson's stain demonstrating that strands and islands of residual myocytes are surrounded by fibrous tissue.

parasitic infections.<sup>10</sup> 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.<sup>10</sup>

### 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.<sup>11 12</sup> Sudden death is more common in adolescents and young adults and may be precipitated by exertion.<sup>12</sup> Two pathological variants have been described in the literature and include a predominantly "fatty" variant and a "fibrofatty" variant.<sup>11 13</sup> The "fatty" variant is characterised by transmural infiltration of adipose tissue with sparing of the septum and left ventricle and without

wall thinning.<sup>11–13</sup> In contrast, the “fibrofatty” or “cardiomyopathic” variant is characterised by extensive replacement-type fibrosis. Islands or strands of surviving myocytes exhibit a combination of degenerative change with myocyte vacuolisation and are frequently associated with focal mononuclear inflammatory cell infiltrates.<sup>11 13 14</sup>

A spectrum of morphological abnormalities is found in ARVC. In some cases there is diffuse dilatation of the entire right ventricle, but usually the pathological changes are frequently focal, manifest as localised aneurysms or areas of thinning.<sup>w15</sup> The latter may be difficult to detect macroscopically at necropsy in cases of sudden death. ARVC has a predilection for certain sites within the right ventricle and wall aneurysms tend to be located in the apical, inflow, and infundibular regions of the right ventricle—the so called “triangle of dysplasia”.<sup>w15</sup> With disease progression there is also involvement of the left ventricle with subepicardial posterior wall fibrosis and fibro-adipose infiltration.<sup>12 13 15</sup> This may eventually lead to biventricular cardiomyopathy and heart failure and simulate DCM. Although ARVC is usually regarded as a selective disorder of the right ventricle, an unusual phenotype of ARVC characterised by isolated subepicardial and midmural fibrofatty replacement of the left ventricular myocardium has been observed (personal observation), which may present with sudden unexpected death in young individuals. It is likely that this phenotype is part of the ARVC spectrum since left ventricular subepicardial myocardial lesions are rare in other cardiac diseases but common in ARVC. In agreement with Gallo and colleagues, in view of the isolated left ventricular or biventricular involvement of this disease, this cardiomyopathy should be termed “arrhythmogenic cardiomyopathy”.<sup>15</sup>

The morphological spectrum of ARVC remains to be fully defined. Indeed, there is controversy in the literature surrounding the “fatty” variant<sup>11 13</sup> and whether this type of ARVC is in fact part of the normal spectrum of adipose infiltration of the right ventricle. This can be very prominent in the subepicardial and mediomural layers of the hearts of elderly females and obese individuals.<sup>14 16</sup> The amount of subepicardial fat increases with increasing body weight and adipose tissue in the heart may constitute up to 52% of the heart weight at necropsy.<sup>14</sup> Furthermore, the site of sampling of the right ventricle is paramount. For example, significant fatty infiltration of the heart may be observed in the anteroapical region of the right ventricle of normal hearts, but a 15% fat replacement is abnormal when observed in the right ventricular outflow tract.<sup>14</sup> It is likely that future genetic studies will resolve the controversy surrounding the different morphological variants of ARVC.

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.

There are several current concepts surrounding the pathogenesis of ARVC. These include the progressive loss of myocytes by programmed cell death (apoptosis) as a consequence of myocardial injury.<sup>w16</sup> In some cases of ARVC, myocarditis has been implicated and both enteroviruses and adenoviruses have been identified as potential aetiological agents in some<sup>w17</sup> but not all studies.<sup>w18</sup> Indeed, focal inflammatory cell infiltrates comprised of T lymphocytes in association with necrotic myocytes are a common finding in the hearts of individuals with ARVC, but whether myocarditis is a primary event or secondary to myocyte necrosis remains speculative.<sup>11</sup> The strongly familial (about 30–50% of cases) occurrence of ARVC suggests that a genetically determined loss of myocytes may account for many cases of this disease.<sup>12</sup>

The exact incidence and prevalence of ARVC in the general population is still unknown but it may be the second most common cause of sudden unexpected cardiac death in previously healthy young individuals. Familial ARVC shows a predominantly autosomal dominant mode of inheritance and incomplete penetrance.<sup>12</sup> An autosomal recessive form of ARVC associated with palmoplantar keratoderma and woolly hair (Naxos disease) has also been reported.<sup>w19</sup> This form of ARVC is caused by mutations in the plakoglobin gene, the product of which is an integral component of desmosomes and adherens junctions.<sup>w19</sup> The search for the genes responsible for autosomal dominant ARVC is underway and gene linkage analysis of large pedigrees has revealed multiple chromosomal loci.<sup>17 w20</sup> The recent identification of mutations in the desmoplakin gene (ARVD8) and the cardiac ryanodine receptor gene (ARVC type 2 or ARVD2), which encodes a protein (RYR2) involved in intracellular calcium homeostasis and excitation–contraction coupling, will undoubtedly provide further insights into the pathogenesis of this disease.<sup>w19–21</sup> The current working hypothesis to further determine the genetic basis and understand pathogenesis is that ARVC is a disease of cell adhesion.

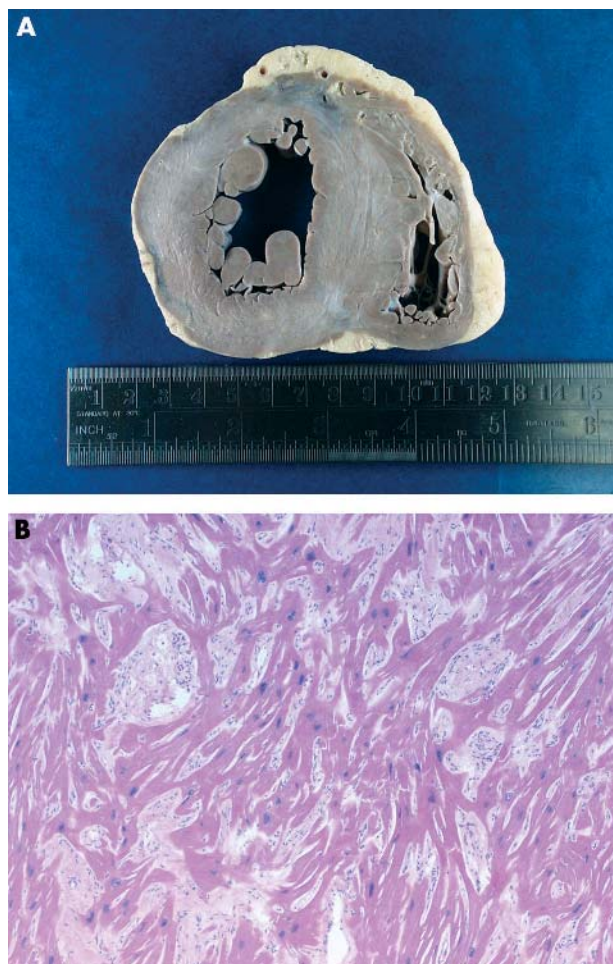
## HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a common autosomal dominant genetic disorder affecting 1:500 of the population.<sup>17</sup> This condition was described in 1958 by a pathologist, Donald Teare, who classified the unique asymmetrical thickening of the left ventricular wall in a series of young adults as a benign muscular hamartoma of the heart.<sup>18</sup>

HCM is characterised macroscopically by left ventricular hypertrophy, which may be asymmetrical (fig 4A) or symmetrical.<sup>w22</sup> The symmetrical form of HCM accounts for over one third of cases and is characterised by concentric thickening of the left ventricle with a small ventricular cavity dimension.<sup>w22</sup> The classical anatomical form of HCM, described by Teare in 1958, involves thickening of the basal anterior septum which bulges beneath the aortic valve and causes narrowing of the left ventricular outflow tract.<sup>18</sup> This is accompanied by anterior displacement of the papillary muscles and the mitral leaflets with coaptation occurring in the body of the leaflets rather than at their tips. As a consequence, endocardial fibrosis occurs over the septum immediately beneath the aortic valve leading to the formation of a sub-aortic mitral impact lesion. This lesion is a mirror image of the anterior cusp of the mitral valve and chordae tendineae and in the past has been regarded as

### 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
- ▶ The morphological spectrum of ARVC is not fully defined
- ▶ Identification of mutations in the plakoglobin and desmoplakin gene indicate that ARVC is a genetic disease of cell adhesion



**Figure 4** (A) Photograph of a necropsy heart at mid septal level from an individual with familial HCM. The hypertrophy involves both the free and septal walls of the left ventricle. There is disproportionate thickening of the interventricular septum, which is consistent with the asymmetrical variant of HCM. (B) Haematoxylin and eosin stained section of myocyte disarray in HCM. Disarray is characterised by hypertrophied myocytes arranged obliquely and perpendicularly around foci of interstitial collagen in a pinwheel pattern. Myocyte disarray is also accompanied by internal disorganisation of the myofibrillary architecture and nuclear changes. The latter includes hypertrophy, pleomorphism, and hyperchromasia.

pathognomonic of HCM,<sup>w22</sup> but may be observed in hypertrophied hearts with diverse aetiologies.<sup>19</sup>

HCM may affect any portion of the left ventricle and several unusual and rare morphological variants of HCM have been described. These include HCM with either mid ventricular cavity obstruction or apical hypertrophy. The latter was first recognised in Japan in the 1970s but has become increasingly recognised in western populations.<sup>w23</sup> HCM may also progress to a dilated or “burnt out” phase in approximately 10% of patients and resemble DCM.<sup>17</sup>

Histology is vital for the diagnosis of HCM. The main pathological hallmarks are the triad of myocyte hypertrophy, disarray, and interstitial fibrosis (fig 4B).<sup>19</sup> <sup>w22</sup> 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.<sup>w22</sup> 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.<sup>19</sup> Thus, extensive myocyte disarray serves as both a highly sensitive and specific marker for the diagnosis of HCM.

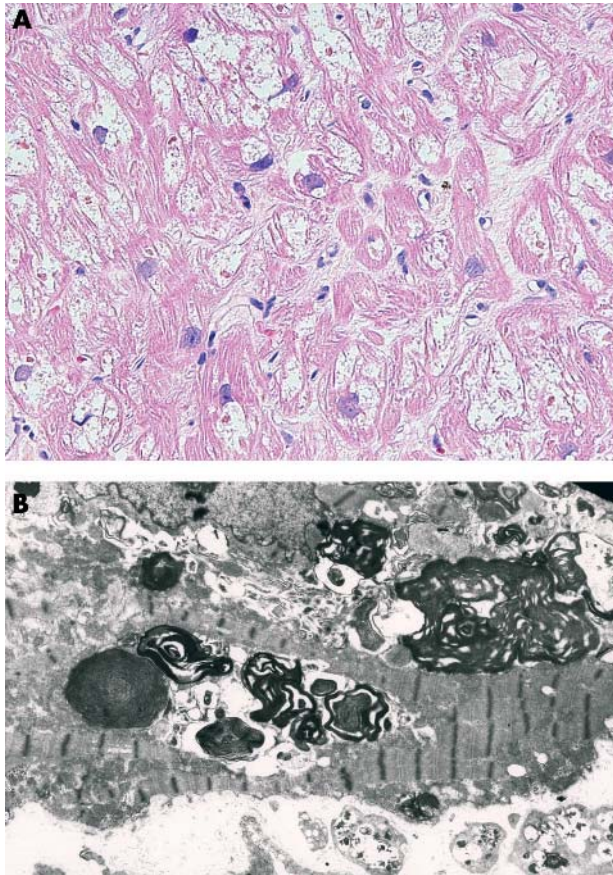
Small vessel disease or arterial dysplasia is another pathological feature of HCM.<sup>17</sup> Arterial dysplasia is characterised by narrowing of the small intramural coronary arteries due to wall thickening by smooth muscle cell hyperplasia.<sup>17</sup> Furthermore, small vessel disease in individuals with HCM may lead to replacement fibrosis and the development of the dilated phase of HCM.<sup>17</sup>

HCM is a disease of the cardiac sarcomere and is caused by mutations in the genes encoding  $\beta$ -myosin heavy chain, cardiac regulatory and essential myosin light chains, myosin binding protein C,  $\alpha$ -cardiac actin, cardiac troponin T, cardiac troponin I,  $\alpha$ -tropomyosin, titin, and troponin C.<sup>2</sup> <sup>20</sup> Most mutations are single point missense mutations or small deletions or insertions. The most frequent causes of HCM are due to mutations in cardiac  $\beta$ -myosin heavy chain, cardiac troponin T, cardiac troponin I, and myosin binding protein C genes.<sup>20</sup>

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  $\beta$ -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

#### The pathology of HCM: key points

- ▶ HCM is a common autosomal dominant genetic disease of the cardiac sarcomere with a prevalence of 1:500
- ▶ The asymmetrical variant of HCM may be associated with a subaortic mitral impact lesion but this is not pathognomonic of HCM
- ▶ The principal histological hallmarks of HCM are myocyte disarray, hypertrophy, and interstitial fibrosis
- ▶ Myocyte disarray occurs in the normal heart but when extensive it serves as a sensitive and specific marker for the diagnosis of HCM
- ▶ Fabry’s disease is an X-linked autosomal recessive metabolic storage disorder, which echocardiographically may simulate HCM
- ▶ The diagnosis of Fabry’s disease can be confirmed by the identification of numerous concentric lamellar inclusions in the myocyte sarcoplasm by electron microscopy



**Figure 5** (A) Endomyocardial biopsy specimen from a patient with a clinical diagnosis of HCM. The myocytes show irregular hypertrophy and prominent sarcoplasmic vacuolisation suggestive of a myocardial metabolic storage disease. (B) Electron microscopy confirmed the presence of numerous electron dense concentric lamellar inclusions in the myocyte sarcoplasm consistent with the cardiac variant of Fabry's disease. The diagnosis was subsequently confirmed by genotyping.

and morphological manifestations. This suggests that lifestyle factors or modifier genes are likely to influence the hypertrophic response.<sup>20</sup>

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.<sup>w24</sup>

Fabry's disease is an X-linked autosomal recessive metabolic storage disorder, caused by deficiency of the enzyme lysosomal  $\alpha$ -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.<sup>w25</sup> In endomyocardial biopsies, the presence of myocyte sarcoplasmic vacuolisation in haematoxylin and eosin 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.

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