Clinical review

Aetiology, diagnosis, investigation, and management of the cardiomyopathies

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Cardiomyopathies are myocardial disorders that are not secondary to coronary disease or hypertension or to congenital, valvular, or pericardial abnormalities.¹

Classification is based on morphological and functional abnormalities, although overlap between groups is considerable. The four main types of cardiomyopathy are hypertrophic, dilated, restrictive, and arrhythmogenic right ventricular. Most heart muscle disorders affect mainly left ventricular structure and function, but the right ventricle is affected in arrhythmogenic right ventricular cardiomyopathy.

Methods

I performed a literature search of all papers published in English in 1996 using Medline and the keywords cardiomyopathy and heart muscle disease. I searched the sections on cardiomyopathies and inflammatory disorders in volumes 10 and 11 (1995 and 1996) of *Current Opinion in Cardiology* and the supplement on the cardiomyopathies of the *British Heart Journal* (December 1994). *Current Opinion in Cardiology* lists the world literature annually and reviews subjects in which knowledge has advanced during the previous year. Earlier publications have been assimilated into current knowledge, and comprehensive coverage can be found in textbooks such as *Diseases of the Heart*.²

I selected papers on the basis of quality, relevance, and interest. The recent literature is extensive and has concentrated on understanding the molecular biology and pathogenesis of the disease rather than its drug treatment.

Epidemiology and prevalence

Reliable data are scarce.³ Electrocardiographic and echocardiographic screening of defined populations showed that the prevalence of hypertrophic cardiomyopathy was between 1 in 500 and 1 in 5000 in the United States.⁴ Dilated cardiomyopathy accounts for between 1 in 50 and 1 in 25 cases of heart failure, most being secondary to coronary disease, hypertension, and valvular disease.

Hypertrophic cardiomyopathy

In 1960 the acronym HOCM (hypertrophic obstructive cardiomyopathy) seemed appropriate to describe a

Summary points

A molecular pathogenesis for dilated and hypertrophic cardiomyopathy is beginning to be elucidated

More than half of patients with hypertrophic cardiomyopathy and a quarter of patients with dilated cardiomyopathy have familial disease

Known genetic mutations occur in only about a half of families affected by hypertrophic cardiomyopathy, and considerable genetic diversity may give rise to similar phenotypes

Differences in phenotype expression within affected families may reflect other modifying genetic or environmental factors

Diagnosis of hypertrophic cardiomyopathy is based on the echocardiographic finding of unexplained thickening of part or all of the left ventricular wall with a normal or small sized cavity. Within affected families, however, electrocardiography is more sensitive than echocardiography in detecting the disorder.

Diagnosis of dilated cardiomyopathy is based on echocardiographic recognition of left ventricular dilatation and reduced contractile function after exclusion of valvular or coronary disease

new clinical entity that mimicked other better known conditions and included hypertrophy of the undilated left ventricle unrelated to pressure or volume overload (hokum or hocus-pocus is 1920s theatrical slang for trickery or shady dealings). Although known to pathologists in the past century, the disorder was rediscovered in 1958 by Teare, who described nine fatal cases, including two in a young brother and sister.⁵ This led him to suppose that the disorder might have a genetic origin. Clinical concentration at first focused on patients with murmurs caused by outflow tract gradients that mimicked aortic stenosis, but in most cases

Known loci of mutations associated with hypertrophic cardiomyopathy

Locus	Protein
Chromosome 14 q 11-q 12	β Myosin heavy chain gene
Chromosome 1 q 3	Troponin T
Chromosome 15 q 2	α Tropomyosin
Chromosome 11 p 13-q3	Cardiac myosin binding protein C
Chromosome 7 q 3*	

* Associated with Wolff-Parkinson-White syndrome.

gradients are present (or provokable) only for part of the clinical course.

Molecular genetics

Early studies suggested an autosomal dominant mode of inheritance but with some sporadic cases. In 1989 linkage was established to the gene for the β myosin heavy chain on chromosome 14, but this accounts for only about 30% of families and systematic testing has since found further loci (table). All the mutations so far affect proteins that regulate contraction.⁶

Family screening

Electrocardiography is more sensitive than echocardiography and may yield abnormal results in affected family members (those with detected mutations or who are obligate carriers) whose echocardiographic results are normal.⁷

Within families, affected members may have hearts varying from clinically normal to severely diseased. This phenotypic diversity implies the interplay of other modifying genetic or environmental factors which may determine or suppress expression of the disease (fig 1). The long term prognosis of apparently healthy adult carriers of mutations for hypertrophic cardiomyopathy is not yet known.

Early detection enables patients to be advised about lifestyle (to avoid athletic training and choose a

Fig 2 The massively hypertrophied heart of a 14 year old boy who died suddenly

future career). Appropriate treatment can also be started quickly in children deemed to be at high risk.

Clinical course

Hypertrophic cardiomyopathy is rarely detectable at birth but develops towards the end of the first decade with noticeable acceleration at puberty. Subsequently, evolution is often slow, with little apparent change over many decades,⁹ but in severe cases myocytes gradually reduce and are replaced increasingly by fibrous tissue, causing a gradual thinning of the ventricular wall and deterioration in systolic function. Stroke volume declines, and increasing diastolic indistensibility may lead to low output congestive failure with high filling pressures and considerable pulmonary hypertension.

Most papers on the clinical course of hypertrophic cardiomyopathy have come from major referral centres receiving the worst cases. Such reports have exaggerated the malignancy of the disorder, which often has a benign course and does not affect life expectancy.^{9 10}

Patients may be symptomless or have shortness of breath, chest pain, or syncope. The dyspnoea is caused by diastolic dysfunction, low cardiac output, and hyperventilation; the angina by ischaemia resulting from hypertrophy, microvascular changes, or coronary artery disease; and the syncope by arrhythmia, low left ventricular volume, or inappropriate vasodilatation. Sudden death is most common in adolescence and young adulthood (fig 2).¹⁰ People's fear of sudden death may manifest itself as avoidance of physical activity, a tendency to hyperventilate, and disability that is not strictly attributable to the disorder.

The main haemodynamic fault is a progressive impairment of diastolic filling of small ventricular

Fig 1 Hypertrophic cardiomyopathy and other hypertrophic heart disorders (based on Oakley et al⁶ and reproduced with permission)

Fig 3 Apical four chamber echocardiogram with colour flow Doppler in hypertrophic obstructive cardiomyopathy. Echocardiogram shows left ventricular outflow gradient and presence of mitral regurgitation, turbulent flow being shown by mosaic colour. LV=left ventricle, RV=right ventricle, LA=left atrium, RA=right atrium

cavities, so stroke volume is restricted despite a higher than normal ejection fraction. A systolic murmur is caused by a narrowed left ventricular outflow tract and often some mitral regurgitation (fig 3). The murmur is augmented by reduction in left ventricular size, as occurs on standing up from sitting, and is transiently abolished by squatting. Patients with concentric or apical hypertrophy usually do not have murmurs.

Senile pseudohypertrophic cardiomyopathy

Hypertrophic cardiomyopathy has increasingly been described in old age,¹¹ but age related echocardiographic changes may seem similar, particularly in systolic hypertension (hypertensive hypertrophic cardiomyopathy) (fig 1), and include diastolic indistensibility and a bent ventricular cavity. Protrusion of the ventricular septum may create turbulence in the outflow tract. Mitral regurgitation (associated with annular calcification) may also develop.

Investigation

Investigations other than electrocardiography, echocardiography, exercise testing, and ambulatory electrocardiography are not routinely required.

Electrocardiography

Electrocardiography almost always shows abnormalities except in children in their first decade. There is no typical pattern: an electrocardiogram may show an unusual axis, abnormal Q waves, deep S waves, and poor R wave progression in the chest leads or a short PR interval and a delta wave suggestive of pre-excitation. A pattern of left ventricular hypertrophy with no discernible cause is diagnostic. As the electrocardiographic abnormality rarely fits any other plausible clinical diagnosis it is thereby diagnostic and leads to echocardiography. The changes are thought to reflect the underlying myocardial disarray and focally slowed intraventricular conduction, whose extent and severity may determine the risk of sudden death.

Echocardiography

Echocardiography detects left ventricular wall thickening, which varies from localised thickening of the upper ventricular septum to global involvement.

Hypertrophy is occasionally limited to the lateral or posterior wall or more often to the apex and septum. In the benign Japanese form the abnormality is confined to the apical region and is characteristically accompanied by giant T wave inversion in the left ventricular leads of the electrocardiogram that simulates non Q wave infarction.

Although echocardiographic results confirm the diagnosis, they may also give a false diagnosis if the moderator band, elements of the tricuspid valve, or ventricular strings are included in the measurement of the ventricular septum. Other types of hypertrophied hearts may cause difficulty in differentiation (fig 1).

Exercise testing

Exercise testing is important in assessing symptoms and functional capacity. A fall in blood pressure or failure of blood pressure to rise may indicate risk of syncope and sudden death.

Ambulatory electrocardiography

Bursts of ventricular tachycardia may be ominous, but in children at high risk such arrhythmias are notably absent. Atrial arrhythmias usually cause symptomatic deterioration.

Treatment

Shortness of breath and angina are usually alleviated by a β blocker. Children may respond well to verapamil, but this drug may precipitate pulmonary oedema or bradycardia in older patients. Left ventricular outflow tract gradients are poorly correlated with either symptoms or prognosis, but in a few patients disopyramide may reduce both gradient and disability.¹² Atrial fibrillation causes deterioration and risk of thromboembolism. Amiodarone helps to preserve sinus rhythm, but long term anticoagulant treatment is needed. Repeated DC cardioversion is worth while. Sequential pacing may encourage preservation of sinus rhythm, but when atrial function becomes irretrievably lost atrioventricular nodal ablation and pacing may bring considerable improvement. Antibiotic prophylaxis is needed to prevent infective endocarditis in patients with outflow gradients or mitral regurgitation, or both.

Amiodarone may also reduce the risk of sudden death, but patients who have survived cardiac arrest outside hospital need to be fitted with an internal cardioverter defibrillator.

Sequential (DDD) pacing is being tried instead of surgical myectomy¹³ to relieve outflow tract gradients.^{14 15} Per-catheter infarction of part of the outflow ventricular septum by selectively occluding a septal branch of the left anterior descending coronary artery reduces the outflow tract gradient,¹⁶ but unlike pacing it is irreversible. Mitral valve replacement with a low profile valve may relieve pulmonary congestion in patients with mitral regurgitation. Transplantation may be needed occasionally in patients who develop congestive heart failure.

Dilated cardiomyopathy

Dilated cardiomyopathy is characterised by a dilated hypokinetic left ventricle. Although cases were originally thought to be mainly sporadic, about a

Fig 4 Development of dilated cardiomyopathy from myocarditis

quarter of symptom-free relatives have abnormal echocardiograms and may later develop clinical disease.¹⁷ A genetic susceptibility to mount a reaction to myocardial infection or toxicity would explain a dominant inheritance in some families (fig 4).^{18–20}

Other dilated hearts

The worst cases of peripartum cardiomyopathy develop heart failure in the first few days post partum. Endomyocardial biopsy usually shows myocarditis.²¹ If the disease is not rapidly fatal patients may show sustained improvement.

In alcoholic cardiomyopathy improvement may follow abstinence. Sometimes, X linked cardiomyopathies with reduced or absent myocardial dystrophin may masquerade as idiopathic in the absence of a family history of skeletal myopathy.^{22–23} Numerous endocrine, metabolic, and autoimmune diseases may all give rise to heart failure. They are important but numerically rare.

Clinical features

Shortness of breath is usually the first complaint; less often patients present with atypical chest pain, embolism, or arrhythmia. Any age and either sex may be affected. The first symptoms are often erroneously ascribed to a chest infection.

Abnormal physical signs are often subtle but may include a prominent left ventricle, gallop rhythm, or mitral pansystolic murmur and basal crackles.

An electrocardiogram may show only sinus tachycardia or an intraventricular conduction delay, left bundle branch block, or non-specific changes in ST and T waves. Chest radiography may show pulmonary venous congestion and cardiac enlargement but is an insensitive tool in detecting left ventricular dilatation.

Echocardiography reveals left ventricular dilatation but cannot exclude a coronary origin, and coronary arteriography is needed as well as a viral, autoimmune, and biochemical screen. Endomyocardial biopsy may identify a specific pathology or a viral or an

autoimmune aetiology. It is the only way to confirm acute myocarditis (fig 5).²¹

Treatment

Diuretics and angiotensin converting enzyme inhibitors are the lynch pins of treatment.²⁴ Digoxin is helpful in advanced cases or if atrial fibrillation develops,²⁵ and anticoagulant treatment is important.

If β blockers are used they should be introduced tentatively in very small doses because some patients' condition may deteriorate before they benefit, and improvement may be delayed. Patients with a resting tachycardia are both more likely to benefit and more likely to be made worse if the β blocker is introduced too rapidly.²⁶

The use of growth hormone as a possible inotrope for the treatment of dilated cardiomyopathy is under investigation.²⁷

Ventricular ectopic beats are frequent and ventricular tachycardia may occur. Atrial fibrillation if sustained may precipitate "tachycardia failure" even in a normal heart and in dilated cardiomyopathy may lead to end stage failure which is reversed on slowing the heart.

Sudden death is common, and patients resuscitated from cardiac arrest should be considered for an internal cardioverter defibrillator, as should most patients with ventricular tachycardia which is not prevented by drug treatment. Some patients do not die of ventricular fibrillation but of asystole or electromechanical dissociation, which may be precipitated by certain antiarrhythmic drugs.²⁸

Patients with only mild left ventricular dysfunction often live for years without detectable change. Although angiotensin converting enzyme inhibitors and β blockers have considerably improved prognosis,^{24–29} patients who have continually severe symptoms, have heart failure, or require increasing drug treatment still do badly, as do most patients with ventricular arrhythmias. No study has shown reduction in mortality with antiarrhythmic drug treatment, apart from amiodarone.²⁸ It is important to ensure normokalaemia and that the patient is not deficient in

Fig 5 Fresh postmortem heart from 42 year old woman with cardiac amyloidosis showing thickened left ventricular walls with a small cavity, features that superficially resemble symmetrical hypertrophy in hypertrophic cardiomyopathy both on echocardiography and at necropsy

magnesium. All inotropic agents apart from digoxin may worsen prognosis. Digoxin does not increase overall mortality and reduces the number of hospital admissions for recurrent heart failure.

The role of cytokines in determining progressive myocardial damage has gradually emerged.³⁰ Patients with congestive heart failure express increased plasma concentrations of tumour necrosis factor.^{31 32} Cytokines generated by activated immune cells cause an increase in nitric oxide through induction of nitric oxide synthase in myocardial cells with a direct depressant effect on myocardial contraction.^{31 32} These cytokines may also activate cytotoxic T cells, causing further inflammatory myocardial injury.

Dilated cardiomyopathy remains the most common indication for cardiac transplantation, which has excellent functional results and survival rates of 80% at one year and 70% at five years,³³ but its application is limited by shortage of donor organs. This has led to reassessment of so called myoplasty, in which the heart is wrapped with skeletal muscle and then paced, and to trials of ventricular reduction (to reduce wall tension and improve left ventricular geometry).

Mechanical devices to entrain the failing heart and maintain an adequate stroke volume are starting to be developed.

Restrictive cardiomyopathy

In restrictive cardiomyopathy, diastolic dysfunction predominates in the absence of systolic dilatation. Increased stiffness leads to an excessive rise in ventricular diastolic pressure for each increment in volume.

Amyloid infiltration causes a restrictive syndrome with progressive wall thickening. Most patients are elderly and have immunological amyloid, although they may not have myeloma or macroglobulinaemia. Patients tend to be hypotensive, with a low voltage electrocardiogram and echocardiographic features of thick ventricular walls, small cavities, and thickened valves and atrial septum (fig 5). The prognosis is poor: usually patients die less than a year after diagnosis. Transplantation is indicated for patients who do not have aggressive myeloma.³⁴

Arrhythmogenic right ventricular cardiomyopathy

Familial and progressive with a predominance in young males, arrhythmogenic right ventricular cardiomyopathy is characterised by progressive fibroadipose replacement of segments of the free wall of the right ventricle.³⁵ It should be suspected in patients with multiple ectopic beats or tachycardia of right ventricular origin and is a cause of sudden death in previously symptom-free young people, often during strenuous exercise.

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Endpiece

Alternative definitions

Prejudice: A vagrant opinion without visible means of support.

Ambrose Bierce, *The Devil's Dictionary* (1911)