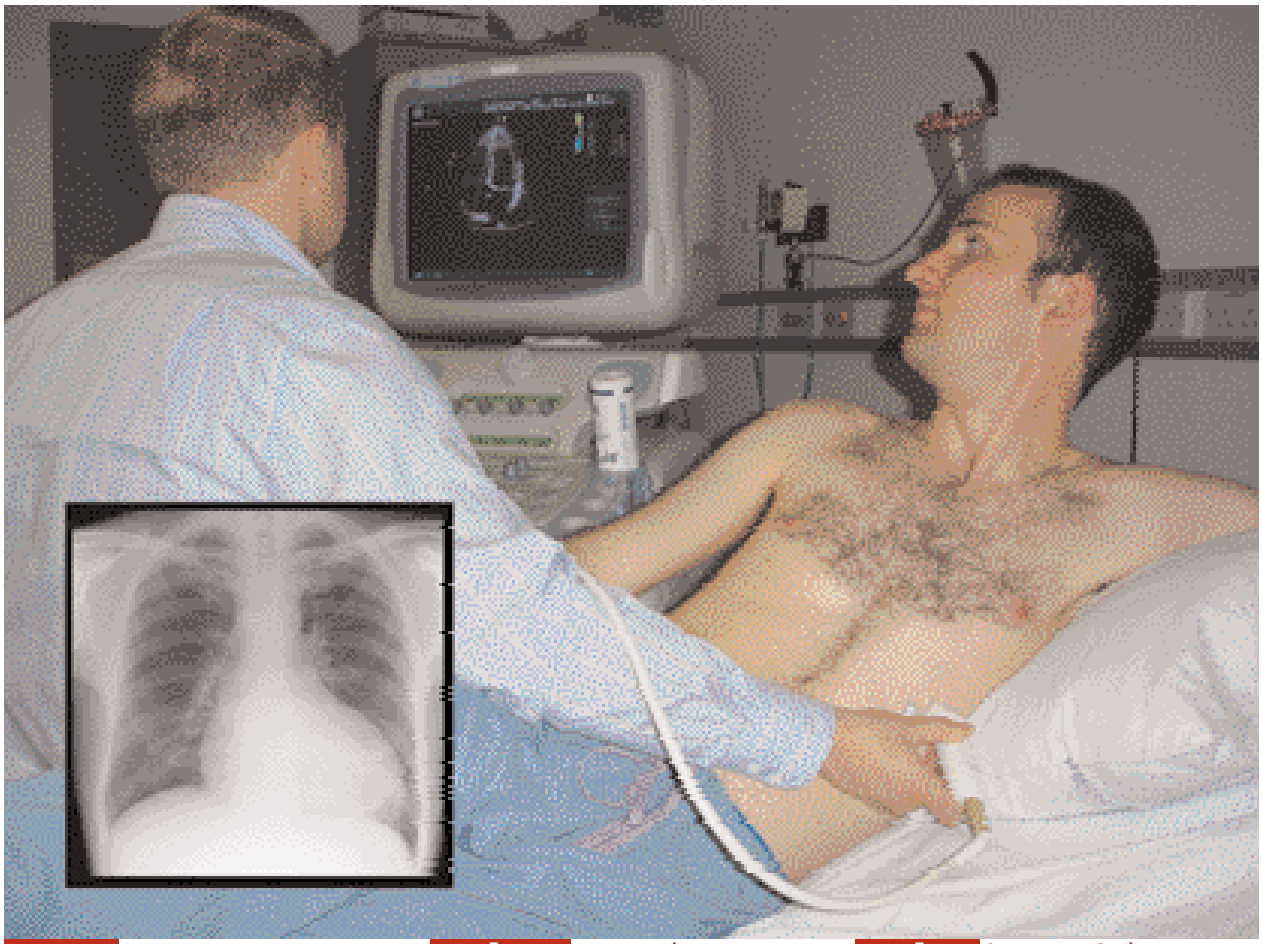
Preventing sudden death in patients with cardiomyopathies

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How are

What are the key presenting symptoms?

Who is at risk of sudden cardiac death?

CARDIOMYOPATHIES REPRESENT A DIVERSE GROUP OF CONDITIONS WITH A COMMON final pathway of cardiac dysfunction. Estimates of the prevalence of nonischaemic cardiomyopathy in the community or hospital setting range from 2 to 15%.[1] In many cases a specific aetiology is not identified, and treatment frequently includes management for systolic heart failure.

In an average sized practice of 6,000 patients, GPs should expect 12 cases of hypertrophic cardiomyopathy, three cases of nonischaemic dilated cardiomyopathy and one case of arrhythmogenic right ventricular cardiomyopathy. Identification of these patients can be problematic, and suspicion should be raised in patients with:

- Severe, recurrent and exertional chest pain »

- Palpitations associated with dyspnoea, presyncope/syncope
- Exertional presyncope/syncope
- A family history of sudden cardiac death.

GPs should collaborate with coroners in cases of sudden cardiac death to identify inheritable causes and initiate screening of first-degree family members. First-line investigation should involve timely referral to a cardiologist, with a resting 12-lead ECG (abnormal repolarisation and prolonged QT-interval being the most discriminatory features), 24-hour Holter monitoring and a two-dimensional echocardiography.[2]

Management of cardiomyopathy is multidisciplinary and involves primary prevention of sudden cardiac death and symptom control. The cornerstones of management are:

- Restriction of competitive sports in those with a confirmed diagnosis.
- Awareness of drugs predisposing to prolonged QT interval
- Optimal heart failure management
- Aggressive treatment of traditional risk factors for ischaemic heart disease.

Cardiomyopathies can present at any age. The most common presenting complaint is symptoms of heart failure, however this only represents the tip of the iceberg. A significant proportion of individuals are asymptomatic until they present as cases of sudden cardiac death, usually caused by ventricular tachycardia or ventricular fibrillation. The annual incidence of sudden cardiac death in the general population in the UK is one per 1,000, and 15% of these deaths are attributable to cardiomyopathies.[2]

Currently population screening is not advocated in the UK to identify patients before the first arrhythmic episode, making early diagnosis challenging. However, screening is carried out in professional sportsmen and is recommended for competitive athletes.

‘Management is multidisciplinary and involves primary prevention of sudden cardiac death’

The traditional classification of cardiomyopathies as dilated, hypertrophic or restrictive has evolved following the identification of several new disease entities, particularly in the field of molecular genetics in cardiology.

A new definition has been proposed by the American Heart Association: ‘Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalised systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability.’[3]

Cardiomyopathies are divided into two major groups based on predominant organ involvement (see figure 1, p53):[1]

- Primary cardiomyopathies (genetic, mixed and acquired) are solely or predominately confined to heart muscle
- Secondary cardiomyopathies show pathological myocardial involvement as part of a large number and variety of generalised systemic (multi-organ) disorders.

In primary care, the most common cardiomyopathy encountered is hypertrophic cardiomyopathy, followed by nonischaemic dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is defined by the presence of myocardial hypertrophy in the absence of haemodynamic stress sufficient to cause that degree of hypertrophy. Its prevalence in the UK population is one per 500.[4] It is considered to be the most common cause of death during sporting activities, and has an annual cardiovascular mortality of approximately 1%.[4] Half of these deaths are caused by sudden cardiac death and the remainder by heart failure or stroke, predominantly in adult and elderly patients.

Most adults with hypertrophic cardiomyopathy have familial forms of the condition that demonstrate an autosomal dominant inheritance pattern with incomplete penetrance.

Mutations in 10 identified genes that encode for components of the cardiac sarcomere are responsible for 50-60% of cases. The most frequently identified mutations involve ß-myosin heavy chain (located on chromosome 14) and cardiac myosin binding protein C (located on chromosome 11). These mutations result in the classic histopathological description of myocyte disarray, in which individual cardiac myocytes vary in size and shape and have abnormal intercellular connections.

Diagnosis

Most patients with hypertrophic cardiomyopathy are asymptomatic and are diagnosed incidentally or when screening the family of sudden cardiac death cases. The most common symptoms are dyspnoea, related predominantly to diastolic dysfunction, and chest pain. Chest pain can be exertional or, more curiously, related to the consumption of large meals and alcohol. A combination of microvascular abnormalities and left ventricular outflow tract (LVOT) obstruction is thought to be involved. A day-to-day variation in the level of activity required to precipitate these symptoms is characteristic.

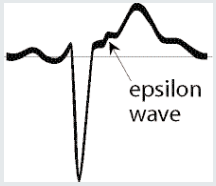
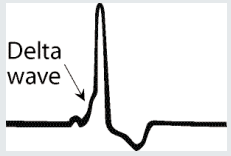
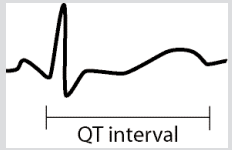
Diagnosis is by two-dimensional echocardiography demonstrating unexplained maximum left ventricular wall thickness >15mm in any myocardial segment (see figure 3, p56). However, any degree of wall thickness may be compatible with the diagnosis of hypertrophic cardiomyopathy because of the variability of gene expression.

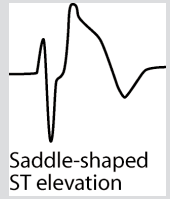
Approximately 25% of patients have dynamic LVOT obstruction caused by contact between the anterior mitral valve leaflet and the interventricular septum. This may produce pressure gradients across the obstruction significant enough to cause syncope. Further investigations are also performed in confirmed cases of hypertrophic cardiomyopathy to identify patients at high risk of sudden cardiac death (see table 1, pp50-51).

Management

The management of hypertrophic cardiomyopathy is complex and can change throughout the natural history of the disease. Strategies are mainly targeted at symptom relief and treatment of complications such as progressive heart failure and arrhythmias. Symptoms caused by progressive heart failure are treated in the conventional manner. However, »

Table 1. Summary of cardiomyopathies

		Presenting symptoms	Diagnostic aids	Management
Genetic	Structural	**Hypertrophic cardiomyopathy –** *Myocardial hypertrophy in the absence of haemodynamic stress sufficient to cause that degree of hypertrophy.* Most common cause of death during sports activities. Histology: myocyte hypertrophy and myofibrillar disarray. Seventy per cent autosomal dominant inheritance. Sudden cardiac death high-risk features: VF, VT, NSVT, family history of sudden cardiac death, syncope, extreme septal hypertrophy, hypotension on exercise stress testing and high-risk mutations.		
		● Common: chest pain and dyspnoea ● Chest pain precipitated by alcohol or large meals ● Day-to-day variation of exercise tolerance ● Exertional syncope ● Cardiac arrest	● ECG: LV hypertrophy with ST wave and T wave changes, deep Q waves in inferior and lateral leads (septal hypertrophy and fibrosis) ● Holter monitor: NSVT in 25% of adults with hypertrophic cardiomyopathy (asymptomatic) ● Echo: unexplained maximum LV wall thickness of >15mm	● Lifestyle modifications – restriction of activity ● LVOT obstruction: ß-blocker, disopyramide, verapamil ● Heart failure management ● Anti-arrhythmic agents: amiodarone ● Risk of sudden cardiac death: ICD ● Surgery – septal debulking procedures ● Genetic counselling
		Arrhythmogenic right ventricular cardiomyopathy – *Fibrofatty replacement of cardiac myocytes predominantly involving the right ventricle.* Prevalence approximately 1 per 5,000 patients. Thirty per cent autosomal dominant inheritance. Accounts for 3-4% of deaths in sports and 5% of sudden cardiac deaths in patients less than 65 years of age.		
		● Palpitations ● Syncope ● Atypical chest pain ● Dyspnoea	● ECG: T-wave inversion and preferentially prolonged QRS complex (V1-V3), epsilon waves, VT with LBBB ● Echo: Severe dilatation and reduction of RVEF with zero/mild LV impairment 	● Lifestyle modifications – restriction of activity ● Anti-arrhythmic medication: sotalol, amiodarone, ß-blocker ● ICD implantation
		Left ventricle noncompaction - *Congenital 'spongy' morphological appearance of myocardium with propensity to heart failure, arrhythmias and thromboembolic disease.*		
		● Dyspnoea ● Chest pain	● Echo: multiple trabeculations, intertrabecular recesses communicating with the ventricle ● ECG: marked biventricular hypertrophy	● Dependent upon functional abnormalities and comorbidities, including heart failure, systemic emboli and arrhythmias
		Conduction system disease - *Primary progressive development of cardiac conduction defects in His-Purkinje system.*		
		● Syncope ● Palpitations	● Lenègre disease: widened QRS complex, pauses, bradycardia ● WPW: delta wave and shortened PR interval 	● Anti-arrhythmic medication ● Devices: pacemaker insertion ● Radiofrequency ablation of accessory pathways
		Long QT syndrome - *Inherited prolongation of ventricular repolarisation – the most common ion channelopathy.*		
		● Syncope (particularly at young age) ● Palpitations ● Seizures ● Sudden cardiac death - exercise-induced events, for example swimming, diving - auditory and emotional triggers - sleep	● ECG: prolongation of corrected QT interval ● Repeated ECGs, exercise tests and Holter monitors may be required 	● Lifestyle modifications (avoid excessive exercise) ● Avoidance of drugs prolonging QT interval ● Drug therapy: ß-blockers, anti-arrhythmic medication, potassium ● Devices: pacemakers, ICD insertion ● Genetic screening

Non - structural	**Short QT syndrome -** *QT interval <330 ms*			
	● Cardiac arrest secondary to VT or VF	● ECG: uncorrected QT interval <330 ms with heart rate close to 60 beats per minute, tall peaked T waves	● Drug therapy: limited data with use of flecainide ● ICD implantation	
	Brugada syndrome - *Rare condition associated with mutations in a sodium channel gene with characteristic ECG and risk of sudden cardiac death.*			
	● Syncope ● Palpitations ● Sudden death, usually while asleep ● Increased prevalence in young South-East Asian men	● ECG: distinctive pattern of RBBB and saddle-shaped ST-segment elevation in anterior precordial leads (V1-V3)  	● Sodium channel blockers to unmask ECG changes, if concealed ● ICD insertion ● Screening of family members	
	Catecholamine polymorphic ventricular tachycardia - *Syncope, sudden death, polymorphic VT triggered by vigorous exertion or acute emotional distress, normal resting ECG and absence of structural heart disease.*			
	● Young people including children ● Cardiac arrest on exertion or precipitated by acute emotional distress	● ECG: - sinus bradycardia and U waves during physical exertion or acute emotion ● alternating QRS axis demonstrating bidirectional ventricular tachycardia	● Lifestyle modifications (restriction on exercise) ● ß-blockers ● ICD insertion ● Genetic screening	
Mixed	**Dilated cardiomyopathy -** Dilated and impaired systolic function of one or both ventricles with normal coronary arteries. Incidence: 5-8 per 100,000 per year. Develops at any age. Predominant in men and Afro-Caribbeans. 20% familial and numerous aetiological factors known. Annual mortality 4%.			
	● Variable: asymptomatic, heart failure, thromboembolism and stroke, arrhythmia and sudden cardiac death	● Echo: marked dilation of LV cavity, normal or thin wall thickness, globally reduced systolic and impaired diastolic function ● Coronary angiography: normal vessels	● Medication: heart failure treatment (particularly ACE inhibitors), anti-arrhythmic medication and thromboembolism prevention ● Devices: biventricular pacing +/- ICD insertion	
	Restrictive cardiomyopathy - *Impaired diastolic filling of one or both ventricles with normal, or near normal, systolic function and bi-atrial enlargement.*			
	● Symptoms of heart failure ● Associated with haemochromatosis, amyloidosis, sarcoidosis and scleroderma	● ECG: nonspecific ● Echo: Normal to symmetrically thickened walls, rapid early diastolic filling, slow late diastolic filling and normal or slightly reduced ventricular volume and systolic function	● Heart failure treatment	
Acquired	**Puerperium -** *Dilated form associated with LV systolic dysfunction manifesting in third trimester of pregnancy.*			
	Myocarditis - *An acute or chronic inflammatory disease of the myocardium produced by a wide variety of infectious agents, toxins and drugs.*			
	Tachycardia-induced - *Reversible dilated cardiomyopathy with LV contractile dysfunction secondary to prolonged supraventricular or ventricular tachycardia.*			

VF: ventricular fibrillation, VT: ventricular tachycardia, NSVT: non-sustained ventricular tachycardia, LVOT: left ventricular outflow tract obstruction, LV: left ventricle, ICD: implantable cardioverter defibrillator, LBBB: left bundle branch block, RBBB: right bundle branch block, EF: ejection fraction, WPW: Wolf Parkinson White syndrome, RVEF: right ventricular ejection fraction

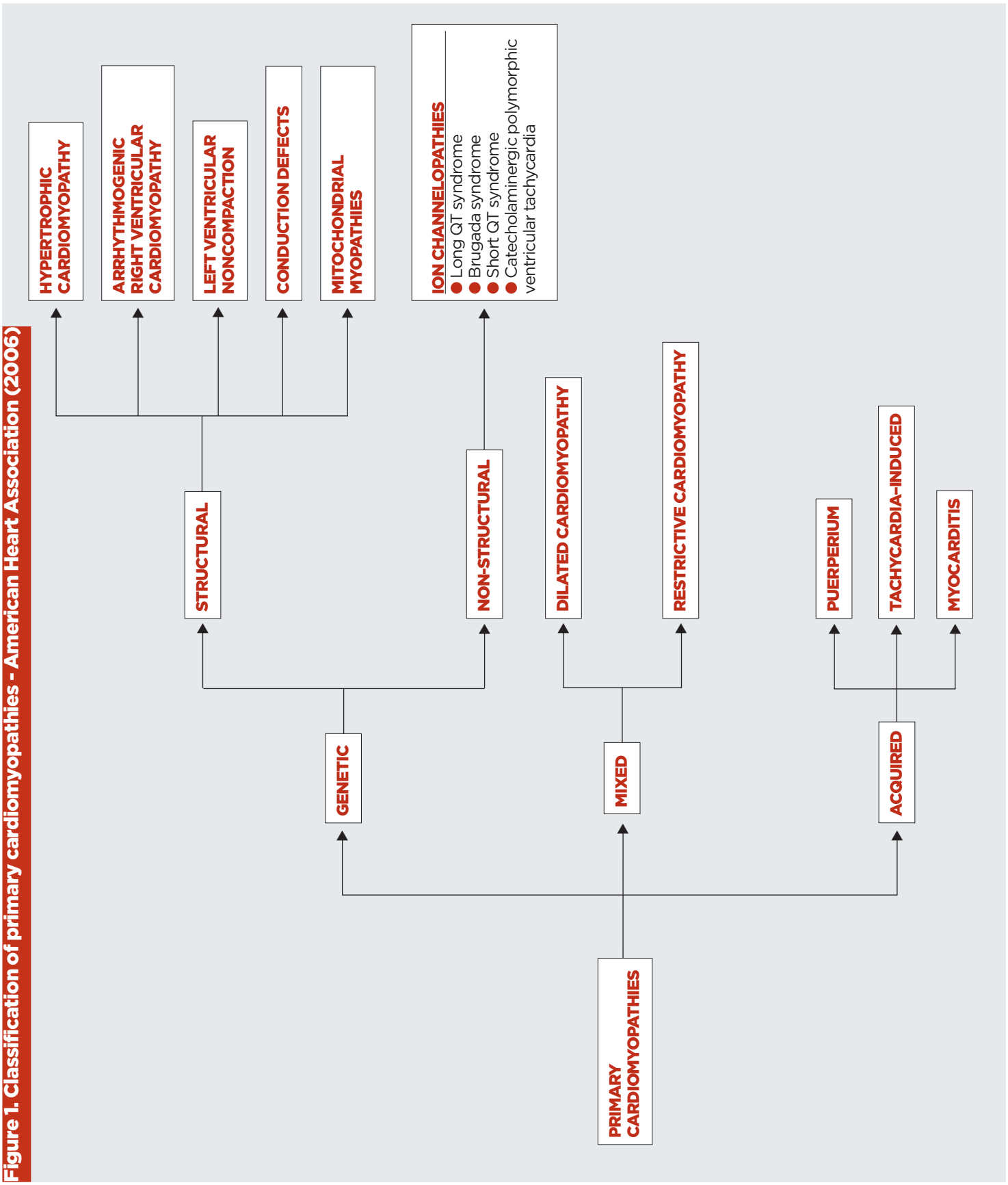


Figure 1. Classification of primary cardiomyopathies – American Heart Association (2006)

Table 2

Summary of heart failure management

Functional Status	Medical therapy to be considered	Device therapy
Asymptomatic NYHA* class I	● ACE inhibitor (if intolerant, substitute with angiotensin-II receptor antagonist or hydralazine/isosorbide dinitrate combination) ● ß-blocker ● Diuretic	ICD† implantation if: ● Ventricular arrhythmia and haemodynamic instability ● Successful cardiac resuscitation
Symptoms with moderate activity NYHA* class II	As above plus: ● Digoxin if symptomatic ● Amlodipine if further vasodilation required	As above plus: ● Ejection fraction 35%
Symptoms with mild activity NYHA* class III	As above plus: ● Aldosterone antagonist (spironolactone) ● Digoxin ● If Afro-Carribbean, hydralazine/isosorbide dinitrate combination	As above plus: ● If interventricular conduction delay or dyssynchrony, consider cardiac resynchronisation therapy
Symptoms at rest NYHA* class IV	As above plus: ● Consider inotrope infusion, ventricular assist device, cardiac transplantation	As above

*NYHA: New York Heart Association
†ICD: implantable cardioverter defibrillator

ACE inhibitors must be used with caution as they may worsen the LVOT gradient (see table 2, above). Symptoms associated with significant LVOT obstruction are treated with negatively inotropic agents, including ß-blockers, disopyramide and verapamil.

In patients with LVOT obstruction refractory to pharmacological management, surgery may be considered to de-bulk the interventricular septum. This may be carried out by septal myotomy-myomectomy in open surgery, or by the more recently developed percutaneous transcoronary septal myocardial ablation. In this approach alcohol is injected into septal perforating vessels to produce localised myocardial necrosis.

‘Patients at high risk of sudden cardiac death are candidates for ICD insertion’

Atrial fibrillation (AF) is poorly tolerated in patients with hypertrophic cardiomyopathy and may cause severe deterioration in symptoms. If normal sinus rhythm cannot be sustained, control of the ventricular response with ß-blockers and calcium channel blockers is almost as effective. In those with paroxysmal AF, amiodarone is the most effective treatment to maintain sinus rhythm. Patients at high risk of sudden cardiac death, or who have experienced aborted sudden cardiac death or sustained ventricular tachycardia, are candidates for implantable cardioverter defibrillator (ICD) insertion.[4]

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy is characterised by dilatation and impaired systolic function of one or both ventricles, with normal coronary arteries. Five to eight people per 100,000 develop this disorder each year.[5] It can develop at any age and is more common in men and Afro-Caribbean patients.

Dilated cardiomyopathy conveys a 50% risk of mortality within two years of symptom onset. The risk is 4% per year thereafter.[6] It is the most common indication for cardiac transplant. Sudden cardiac death resulting from malignant arrhythmias is the most common cause of death in dilated cardiomyopathy.

Around 50% of cases of nonischaemic dilated cardiomyopathy are idiopathic. Data suggest that at least 20% of cases of dilated cardiomyopathy are familial, and multiple patterns of inheritance have been identified. In the autosomal dominant form several genes have been implicated. These include actin, laminin and desmin, which code for cytoskeletal proteins.

Infectious causes of myocarditis, which account for 9% of dilated cardiomyopathy, include viral (such as enteroviruses and HIV), bacterial and parasitic infections, such as Chagas disease. Dilated cardiomyopathy can also result from toxins (for example alcohol or chemotherapeutic agents), pregnancy, infiltrative disorders, nutritional deficiencies, connective tissue diseases and chronic endocrine disorders (such as thyroid dysfunction or phaeochromocytomas). »

Mechanism

Damaged myocardium is replaced by fibrous scar tissue, with compensatory hypertrophy of the remainder of the myocardium until this mechanism is exceeded and overt dilated cardiomyopathy and heart failure develop.

Functional mitral and tricuspid regurgitation with atrial and ventricular dilatation predispose the patient to arrhythmias and thromboembolic disease.

There may be a preceding flu-like illness indicating myocarditis before the onset of heart failure, of which exertional dyspnoea is the most common presenting symptom. Tachycardia develops and blood pressure may become low. Peripheral oedema, ascites and pulmonary oedema may develop.

Diagnosis

Diagnosis is aided by a two-dimensional echocardiography revealing dilatation of the cardiac chambers, particularly the left ventricle and/or right ventricle, with reduced wall thickness and poor global contraction (see figure 4, right).

Cardiac MRI may be used, but if the diagnosis remains in doubt cardiac catheterisation, the gold standard investigation, will provide additional information about the function of the heart and confirm diagnosis. The pressures within each chamber can be measured and a myocardial biopsy can be taken for histological examination.

Management

Management should target the underlying cause in individual cases. However, optimal pharmacological treatment of heart failure is key.

Interventricular conduction delay occurs in up to 30% of patients, leading to asynchronous ventricular contraction and worsening mitral regurgitation.

Cardiac resynchronisation therapy with biventricular pacemaker insertion improves quality of life, cardiac function and survival.[7] Recent trials also advocate insertion of ICDs for the primary prevention of sudden cardiac death in patients with a left ventricular ejection fraction 35%.[8]

For refractory end-stage heart failure, surgical options include valve annuloplasty, mechanical cardiac assist devices and cardiac transplantation.[3]

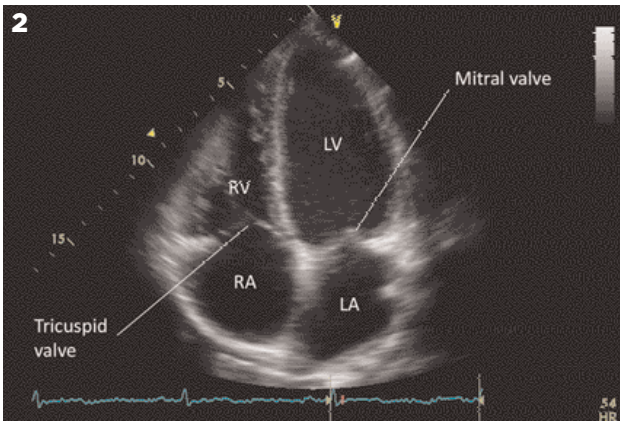


FIGURE 2 Apical four chamber view of a normal heart

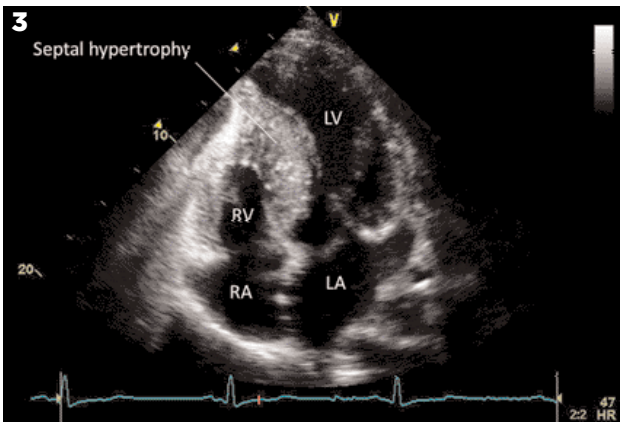


FIGURE 3 Apical four chamber view of hypertrophic cardiomyopathy

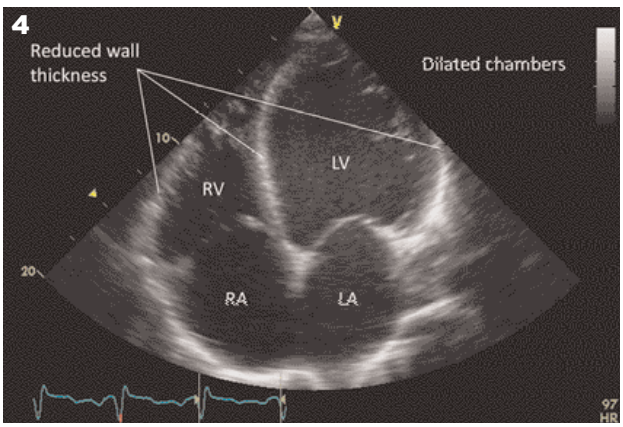


FIGURE 4 Apical four chamber view of dilated cardiomyopathy

key points

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Cardiomyopathies can be defined as:
'...a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalised systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability.'

Estimates of the prevalence of nonischaemic cardiomyopathy in the community or hospital setting range from 2 to 15%.In many cases a specific aetiology is not identified and treatment frequently includes management for systolic heart failure.

Cardiomyopathies can present at any age. The most common presenting complaint is symptoms of heart failure. A significant proportion of individuals are asymptomatic until they present as cases of sudden cardiac death. Screening is carried out in professional sportsmen and is recommended for competitive athletes.

In primary care, the most common cardiomyopathy encountered is hypertrophic cardiomyopathy, followed by nonischaemic dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy.

Hypertrophic cardiomyopathy is considered to be the most common cause of death during sporting activities, and has an annual cardiovascular mortality of approximately 1%. Most patients with hypertrophic cardiomyopathy are asymptomatic and are diagnosed incidentally, or when screening the family of sudden cardiac death cases. The most common symptoms are dyspnoea and chest pain. Chest pain can be exertional or related to the consumption of large meals and alcohol. Diagnosis is by two-dimensional echocardiography.

Dilated cardiomyopathy is characterised by dilatation and impaired systolic function of one or both ventricles, with normal coronary arteries. It can develop at any age and is more common in men and Afro-Caribbean patients. Sudden cardiac death resulting from malignant arrhythmias is the most common cause of death in dilated cardiomyopathy.

Arrythmogenic right ventricular cardiomyopathy most commonly presents with symptomatic ventricular arrhythmias, originating from the right ventricle, associated with dyspnoea, palpitations and presyncope/ syncope. These characteristically occur during exercise.

Cardiomyopathy should be suspected in patients with:
- Severe, recurrent and exertional chest pain
- Palpitations associated with dyspnoea, presyncope/syncope
- Exertional presyncope/syncope
- A family history of sudden cardiac death.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy is characterised pathologically by fibrofatty replacement of myocytes, with a propensity to cause malignant ventricular arrhythmias. The prevalence is one per 5,000 in the general population and it is responsible for 20% of cases of sudden cardiac death in patients under 30 years, with an annual mortality of 3% in untreated cases in the US.[9]

'Management of dilated cardiomyopathy should target the underlying cause'

Around 50% of cases demonstrate an autosomal dominant mode of inheritance, with variable penetrance and expression. Four genes have been identified on chromosome 8 that are individually responsible: the cardiac ryanodine receptor; desmoplakin; plakophillin-2 and transforming growth factor-ß.

Arrythmogenic right ventricular cardiomyopathy most commonly presents with symptomatic ventricular arrhythmias, originating from the right ventricle and associated with dyspnoea, palpitations and presyncope/syncope. These characteristically occur during exercise, indicating an adrenergic trigger.

Symptoms of heart failure predominate late in the natural history of the disease.

Diagnosis

Definitive diagnosis requires confirmation of characteristic histological findings at biopsy or postmortem, thus clinical diagnosis remains problematic.

In 1994 an expert consensus group proposed criteria for diagnosis.[10] These are divided into major and minor criteria and involve structural and functional changes on imaging, ECG changes, identification of ventricular arrhythmias and family history.

More than half of patients with arrhythmogenic right ventricular cardiomyopathy demonstrate repolarisation abnormalities on ECG. T wave inversion in leads V1-V3 in the absence of a complete right bundle branch block is a minor criterion, but is useful in raising suspicion. Delayed right ventricle activation is a major criterion and manifests as epsilon waves (small amplitude potentials that occur at the end of the QRS complex in 30% of cases) and preferential widening of the QRS in V1-V3 compared with V6.

Although echocardiography is the first-line imaging modality, the gold standard for diagnosis is right ventricle angiography identifying severe dilatation and/or functional loss of the right ventricle.

Management

In addition to restriction of activities, current evidence suggests that either sotalol alone, or amiodarone alone or in combination with ß-blockers, are most effective at reducing symptoms of, and suppressing, ventricular arrhythmias.

ICD implantation is advocated in those at high risk of sudden cardiac death, as judged by an aborted cardiac arrest or threatening arrhythmias not suppressed by drug therapy, and as primary prevention in those with extensive disease, family history of sudden cardiac death or unexplained syncope.[9]

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