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Jay W. Mason and Heinz-Peter Schultheiss 16.7.2 The cardiomyopathies: Hypertrophic, dilated, restrictive, and right ventricular 3468 Oliver P. Guttmann and Perry Elliott

section 16 Cardiovascular disorders 3468 Wojinicz R, et al. (2001). Randomized, placebo-controlled study for immunosuppressive treatment of inflammatory dilated cardiomy- opathy: two-year follow-up results. Circulation, 104, 39–45. Yajima T, Knowlton KU (2009). Viral myocarditis from the perspective of the virus. Circulation, 119, 2615–24. 16.7.2 The cardiomyopathies: Hypertrophic, dilated, restrictive,
and right ventricular Oliver P. Guttmann and Perry Elliott ESSENTIALS The term cardiomyopathy is used to describe heart muscle disease unexplained by abnormal loading conditions (hypertension, valve disease, and others), congenital cardiac abnormalities, and ischaemic heart disease. The current classification is based on the predominant phenotype, that is, hypertrophic, dilated, arrhythmogenic right ven- tricular, restrictive, and unclassifiable (including left ventricular non-

compaction), and— where possible— incorporating inheritance and genotype. Cardiomyopathies associated with systemic diseases are described in Chapter 16.7.3. Hypertrophic cardiomyopathy The diagnosis of hypertrophic cardiomyopathy is based on the dem- onstration of unexplained myocardial hypertrophy, defined as a wall thickness measurement exceeding two standard deviations above normal for gender and age. In practice, in an adult of normal size, the presence of a left ventricular myocardial segment of 1.5 cm or greater in thickness is diagnostic. Less stringent criteria should be applied to first-degree relatives of an unequivocally affected individual. Ninety per cent of patients have familial disease, usually with autosomal dominant inheritance. Mutations in genes encoding proteins of the cardiac sarcomere are most common (60% of cases). Symptomatic presentation may be at any age, with breathlessness on exertion, chest pain, palpitation, syncope, or sudden death. In children and adolescents, the diagnosis is most often made during screening of siblings and offspring of affected family members. In most patients, the physical examination is unremarkable, but char- acteristic features include a rapid upstroke arterial pulse, a forceful left ventricular cardiac impulse with palpable atrial beat, an ejection systolic murmur, and a fourth heart sound. Investigation and diagnosis—the 12-lead ECG is the most sen- sitive diagnostic test, with ST-segment depression and T-wave changes being the most common abnormalities, usually associated with voltage changes of left ventricular hypertrophy and/or deep S waves in the anterior chest leads V1 to V3. Echocardiography reveals left ventricular hypertrophy that may be symmetric or asymmetric and localized to the septum or the free wall, but most commonly to both the septum and free wall with relative sparing of the posterior wall. Management—β-adrenoceptor blockers and calcium antagonists (verapamil, diltiazem) are the mainstay of symptomatic pharmaco- logical therapy. Surgery is considered for patients with left ventricular outflow tract obstruction (typically, resting left ventricular outflow tract gradient >50 mm Hg) and/or mitral valve abnormalities, the commonest operation being removal of a segment of the upper an- terior septum (myectomy) via a transaortic approach. Injection of alcohol into the septal artery that supplies the septal muscle is an alternative percutaneous technique that can be used in patients with suitable cardiac and coronary anatomy. Prognosis—overall annual cardiovascular mortality is 1–2%/ year, with sudden cardiac death (c.1%), heart failure (c.0.5%), and thromboembolism (c.0.1%) the main causes. The risk of death and other disease-related complications varies between individuals. Prevention of sudden death relies on risk factor stratification to identify high-risk individuals and targeted therapy with implantable cardioverter–defibrillators. Dilated cardiomyopathy Dilated cardiomyopathy is defined by dilatation and impaired sys- tolic function of the left or both ventricles not attributable to cor- onary artery disease, valvular abnormalities, or pericardial disease. Up to 50% of cases are familial, with many disease-causing gene mu- tations described. Initial presentation is usually with symptoms of cardiac failure, but other presentations include arrhythmia, systemic thromboembolism, or the incidental finding of an electrocardiographic or radiographic abnormality. Physical examination may reveal cardiac enlargement and signs of congestive heart failure. Investigation and diagnosis—on echocardiography, the presence of ventricular end-diastolic dimensions greater than two standard devi- ations above the mean and ejection fraction less than 50% is gener- ally sufficient to make the diagnosis. Management—symptomatic therapy involves the treatment of heart failure with diuretics, mineralocorticoid receptor antagon- ists, angiotensin-converting enzyme inhibitors, and β-blockers. Anticoagulation with warfarin is advised in patients in whom an intracardiac thrombus is identified echocardiographically, or those with a history of thromboembolism. Implantable cardioverter– defibrillators are warranted if sustained or symptomatic ventricular arrhythmias are documented and for primary prophylaxis in selected high-

risk patients. Cardiac resynchronization therapy can improve symptoms and prognosis in selected patients with broad QRS dur- ation, and cardiac transplantation may be appropriate for those with progressive deterioration. Restrictive cardiomyopathy Restrictive cardiomyopathies are defined by restrictive ventricular physiology in the presence of normal or reduced diastolic volumes of one or both ventricles, normal or reduced systolic volumes, and normal ventricular wall thickness. In developed countries amyloid- osis is the commonest cause; in the tropics it is endomyocardial fibrosis. Familial restrictive cardiomyopathy is usually caused by sarcomere protein gene mutations, with the full spectrum of re- strictive cardiomyopathy and hypertrophic cardiomyopathy some- times seen within individual families. Presentation is usually insidious. Left-sided disease may present with symptoms of pulmonary congestion and/or mitral regurgitation;

16.7.2 The cardiomyopathies: Hypertrophic, dilated, restrictive, and right ventricular 3469 right-sided disease presents with raised jugular venous pressure, hepatomegaly, ascites, and tricuspid regurgitation. Atrial fibrillation is common. Echocardiography confirms the diagnosis, typically showing that ventricular dimensions and wall thickness are normal, but the atria are grossly enlarged. Congestive symptoms from raised right atrial pressure can be im- proved with diuretics, though too great a reduction in ventricular filling pressure will lead to a reduction in cardiac output. Prognosis of advanced disease is poor. Arrhythmogenic right ventricular cardiomyopathy Arrhythmogenic right ventricular cardiomyopathy is a heart muscle disease characterized by progressive fibro-fatty replacement of right ventricular myocardium, associated with ventricular arrhythmia, heart failure, and sudden cardiac death. It is inherited and caused by mutations in desmosomal genes in at least 50% of cases. Symptomatic presentation is usually with palpitation and/or syn- cope from sustained ventricular arrhythmia, but the first presenta- tion of the disease may be with sudden cardiac death. There is no single diagnostic test, and the diagnosis is based on the presence of criteria encompassing structural, histological, electrocardiographic, arrhythmic, and genetic parameters. The most common electrocar- diographic abnormality is T-wave inversion in leads V1 to V3 in the absence of right bundle branch block. Typical echocardiographic findings include right ventricular dilatation, regional hypokinesia or dyskinesia, and aneurysms. Management—patients with symptomatic, non-life-threatening ventricular arrhythmias are treated empirically with β-blockers, amiodarone, or sotalol. Those with a history of sustained, haemo-dynamically compromising ventricular arrhythmia should be offered an implantable cardioverter–defibrillator. Introduction Cardiomyopathies are defined as heart muscle disorders unex- plained by abnormal loading conditions (hypertension, valve dis- ease, and others), congenital cardiac abnormalities, and ischaemic heart disease. The current classification is based on the predominant clinical phenotype and, when feasible, assessment of the familial and genetic basis. Heart muscle disease associated with systemic or extracardiac diseases are described in more detail in Chapter 16.7.3. Hypertrophic cardiomyopathy Definition Hypertrophic cardiomyopathy (HCM) is defined by the presence of increased myocardial thickness in the absence of loading con- ditions (hypertension, valve disease, and others) sufficient to cause the observed degree of hypertrophy. Historically, ventricular thick- ening caused by systemic diseases such as amyloidosis and glycogen storage disease has been excluded from the definition in order to separate conditions in which there is myocyte hypertrophy from those in which left ventricular mass and wall thickness are increased by interstitial infiltration or intracellular accumulation of metabolic substrates. In everyday clinical practice, however, it is frequently impossible to differentiate these two entities using noninvasive imaging, and hence metabolic and infiltrative disease should be con- sidered in the differential diagnosis of hypertrophic cardiomyopathy. Causes

Pedigree analysis reveals familial disease in 40–50% of patients, but when cardiovascular evaluation of first-degree relatives using elec- trocardiography (ECG) and echocardiography is performed, up to 90% of patients are found to have familial disease. In most cases, the inheritance is autosomal dominant. Approximately 60% of patients with familial hypertrophic car- diomyopathy have mutations in genes encoding proteins of the cardiac sarcomere: specifically, cardiac β-myosin heavy chain, car- diac myosin-binding protein C, essential and regulatory myosin light chain, α-tropomyosin, cardiac troponin T and I, cardiac actin, and α-myosin. Most mutations involve a single base-pair change in exons encoding highly conserved regions that result in amino acid substitutions. De novo mutations occur but appear to account for less than 10% of cases. Some 5–10% of patients carry multiple sarcomeric mutations, with compound heterozygotes presenting with more severe disease at an earlier age. Several genes related to the sarcomere Z-disc and calcium handling have been associated with hypertrophic cardiomyopathy, but are relatively uncommon. Variable clinical expression and incomplete penetrance is common, even within families bearing the same gene defect, but some phenotypes do seem to associate with particular mutations. β- Myosin heavy chain mutations that are fully penetrant are associated with worse prognosis (such as Arg403Glu or Arg453Cys), while dis- ease complications are uncommon in patients with mutations that cause mild or no clinical expression (such as Leu908Val). This con-trasts with troponin T disease, which although associated with mild hypertrophy and few symptoms can still cause premature sudden death. Mutations in myosin-binding protein C cause 20–30% of dis- ease; most are major deletions rather than single base-pair changes. Disease expression can occur later in life, sometimes associated with mild hypertension, but once disease expression occurs (abnormal ECG and/or echocardiogram), patients are at the same risk from symptoms and disease-related complications as patients with dis- ease onset in early life. The expression of disease in patients with troponin I mutations is variable and mutations in this gene may also cause restrictive cardiomyopathy. Many inborn errors of metabolism and congenital syndromes are associated with HCM. Most are inherited as autosomal reces- sive traits, but a few are X-linked. The most common metabolic dis- orders in adults with HCM are Anderson–Fabry disease (0.5–1% of patients older than 35–40 years), and disease caused by mutations in the gene encoding the γ2 subunit of the adenosine monophosphate activated protein kinase (PRKAG2) (1%). LAMP-2 mutations that cause Danon disease occur in 0.7% to 2.7%. Although still rare, metabolic disorders account for a greater proportion of disease in children and adolescents (Table 16.7.2.1). Pathology Hypertrophic cardiomyopathy may involve the left or both vent- ricles (Fig. 16.7.2.1). Hypertrophy in the left ventricle is usually asymmetric, involving the anterior and posterior septum and the free wall to a greater extent than the posterior wall. Right ven- tricular hypertrophy is seen in up to 30% of patients but isolated

 right ventricular hypertrophy (in the absence of pulmonary hyper- tension or right ventricular outflow obstruction) rarely if ever oc- curs. Many patients have structural abnormalities of the mitral valve, including increased leaflet area and length, and malposition or anomalous insertion of the papillary muscles. A common macroscopic finding is a patch of endocardial thickening just below the aortic valve, which results from contact of the septum with the anterior mitral leaflet in patients with dynamic left ventricular out- flow tract obstruction. The histological findings in hypertrophic cardiomyopathy are distinctive and provide the basis for the pathological diag- nosis. Affected myocardium shows interstitial fibrosis with gross disorganization of the muscle bundles resulting in a character- istic whorled pattern. The cell-to-cell orientation of muscle cells is lost (disarray) and there is disorganization of the myofibrillar

architecture within cells. Myocardial cells are broad, short, and often bizarre in shape. Foci of disorganized cells are often interspersed among areas of hypertrophied muscle cells that are otherwise normal in appearance. Such changes are not com- pletely specific: small amounts of myofibre disarray may be seen in congenitally abnormal hearts and in secondary left ventricular hypertrophy; disarray is also present at the junction of the septum with the anterior and posterior walls of the left ventricle in normal subjects. However, the extent of myocyte disarray in normal subjects rarely exceeds 5%, while in hypertrophic cardiomyop- athy up to 40% of the myocardium may be involved. As well as contributing to diastolic and systolic dysfunction, the disorgan- ized myocardial architecture provides a substrate for electrical instability. Pathophysiology Diastolic dysfunction Diastolic abnormalities caused by myocardial hypertrophy, myo- cardial ischaemia, myocyte disarray, and fibrosis are common but variable in severity. Typically, left ventricular end-diastolic pressure and atrial pressures are elevated as a consequence of ab- normal left ventricular diastolic filling and reduced compliance. The isovolumic relaxation time is prolonged, left ventricular filling is slow, and the proportion of filling volume that results from atrial systolic contraction (while still preserved) may be increased. Occasionally, there is rapid early filling with restrictive physiology similar to that seen in constrictive pericarditis or endocardial fi- brosis (see Chapter 16.8). Systolic function and dynamic outflow tract obstruction Most patients with hypertrophic cardiomyopathy have rapid and near-complete ventricular emptying resulting in a high ejection frac- tion but the stroke volume, particularly during exercise is frequently reduced. ‘End-stage’ hypertrophic cardiomyopathy—characterized by severe impairment of contractile performance, restrictive left ventricular physiology, and heart failure symptoms—is uncommon (>5%), but can develop at any age including childhood and adoles- cence. In most, the time from onset of symptoms to diagnosis of severe systolic impairment is long (a mean of 14 years). Approximately 30% of patients have a gradient between the body and outflow tract of the left ventricle at rest; an additional 20–25% have latent gradients that develop following manoeuvres that in- crease myocardial contractility or that reduce ventricular afterload or venous return. The presence and magnitude of a gradient is de- termined by the size and geometry of the left ventricular outflow tract, which are in turn a function of the severity of septal hyper- trophy, mitral leaflet morphology, and papillary muscle size and position. The conventionally accepted mechanism of the gradient is that Venturi forces from increased ejection velocity in the nar- rowed outflow tract draw the anterior and/or posterior mitral leaf- lets towards the septum, but other data suggest that the abnormally positioned mitral valve leaflets are ‘driven’ rather than sucked into the septum. By convention, left ventricular outflow tract obstruc- tion is defined as an instantaneous peak Doppler LV outflow tract pressure gradient of 30 mm Hg or more at rest, or during physio- logical provocation such as Valsalva manoeuvre, standing, and ex- ercise. A gradient of 50 mm Hg or more is usually considered to be the threshold at which LV outflow tract obstruction is haemo- dynamically important. Table 16.7.2.1 Nonsarcomeric causes of left ventricular hypertrophy, including mitochondrial cardiomyopathies, neuromuscular diseases, and malformation syndromes Metabolic Glycogen storage disease (GSD): Pompe disease (GSD II), Forbes’ disease (GSD III), Danon Total lipodystrophy Hurler’s syndrome Carnitine disorders AMP kinase (PRKAG2) Lysosomal storage disease: Anderson–Fabry disease Infant of a diabetic mother Hypertrophic cardiomyopathy with associated syndromes Noonan’s syndrome LEOPARD syndrome Beckwith–Wiedemann syndrome Mitochondrial myopathy MELAS MERFF NADH–coenzyme Q reductase deficiency Neuromuscular diseases Cytochrome b deficiency Friedreich’s ataxia, FHL1 Amyloidosis Familial ATTR Wild type ATTR (senile) AL amyloidosis Drug-induced Tacrolimus Hydroxychloroquine Steroids Miscellaneous causes Hypertension In utero ritodrine HCl exposure Swyer’s syndrome (46,

XY pure gonadal dysgenesis) AL, amyloid light chain; ATTR, amyloid transthyretin; FHL1, four and a half LIM domains 1; GSD, glycogen storage disorder; MELAS, myopathy, encephalopathy, lactic acidosis, stroke-like episodes; MERFF, myoclonic epilepsy and ragged red fibres.

16.7.2 The cardiomyopathies: Hypertrophic, dilated, restrictive, and right ventricular 3471 Myocardial ischaemia Patients with hypertrophic cardiomyopathy have reduced coronary flow reserve and evidence for myocardial ischaemia during rapid atrial pacing and pharmacological stress. Myocardial ischaemia is almost certainly a major cause of exertional symptoms and may be a trigger for ventricular arrhythmia. However, detection of ischaemia in everyday clinical practice is challenging because conventional markers of ischaemia such as ST-segment change and reversible per- fusion abnormalities on single photon emission computed tomog- raphy (SPECT) imaging correlate poorly with objective biochemical markers of ischaemia. Diagnosis Left ventricular hypertrophy in the absence of moderate to severe hypertension and valve disease occurs in about 1 in 500 adults. The prevalence of HCM in children is unknown, but population-based studies report an annual incidence of 0.3–0.5 per 100 000 (range 0.005–0.07%). The diagnosis of HCM is based on the demonstra- tion of unexplained myocardial hypertrophy, defined as a wall thick- ness measurement exceeding two standard deviations for gender and age. In practice, in an adult of normal size the presence of a left ventricular myocardial segment of 1.5 cm or greater in thickness is diagnostic. Less stringent criteria should be applied to first-degree relatives of an unequivocally affected individual, where the prob- ability of carrying the disease gene is 1 in 2 (Table 16.7.2.2). Problems in diagnosis may arise in patients with moderate to se- vere hypertension. The determinants of the hypertrophic response in a patient with hypertension are unknown, but are partly influ- enced by racial origin, with a greater increase in left ventricular mass in African-Caribbean individuals. In general, however, hyper- trophic cardiomyopathy should be suspected in any individual with hypertension and a wall thickness in excess of 1.5 cm, particularly if the ECG shows widespread repolarization abnormalities or there is evidence of good blood pressure control. The physiological changes of athletic training can rarely mimic hypertrophic cardiomyopathy. Athletes who participate in events that combine both isometric and isotonic activities (e.g. rowing and cycling) have the greatest increases in left ventricular wall thick- ness. Pure strength training is associated with an increase in left ventricular mass and wall thickness relative to the left ventricular cavity size, but is rarely associated with an increase in absolute wall thickness (unless the athlete also uses anabolic steroids). A diag- nosis of hypertrophic cardiomyopathy in an elite athlete is likely when left ventricular wall thickness exceeds 1.6 cm in males and 1.4 cm in females and when they are symptomatic or have a family history of HCM. In athletes, the ECG frequently displays voltage criteria for left ventricular hypertrophy, sinus bradycardia, and sinus arrhythmia. Abnormal Q waves or marked repolarization ab- normalities are rare in elite athletes and should raise suspicion of myocardial disease. Echocardiographic features favouring hyper- trophic cardiomyopathy include small left ventricular cavity di- mensions, left atrial enlargement, left ventricular outflow gradients, and diastolic impairment. The absence of fibrosis on cardiac MRI may be helpful in differentiating HCM from physiological adapta- tion in athletes. Fig. 16.7.2.1 Transverse short-axis section through the ventricles from patients with cardiomyopathy. Upper left shows symmetrical left ventricular hypertrophy in hypertrophic cardiomyopathy. Upper right shows dense white fibrous tissue obliterating the apex of both ventricles in endomyocardial fibrosis. Lower left shows a globular, dilated left ventricle in a child with dilated cardiomyopathy. Lower right shows a grossly dilated right ventricle with adipose infiltration of the right ventricular free wall in arrhythmogenic right ventricular dysplasia. Reproduced from Davies MJ, 1986, Colour Atlas of

Cardiovascular Pathology, with permission from Oxford University Press.

section 16 Cardiovascular disorders 3472 Clinical features History Symptomatic presentation may be at any age with breathlessness on exertion, chest pain, palpitation, syncope, or sudden cardiac death. HCM is occasionally found at autopsy in a stillborn baby or pre- sents during infancy with cardiac failure, which is usually fatal. In children and adolescents, the diagnosis is most often made during screening of siblings and offspring of affected family members. Paroxysmal symptoms or mild impairment of exercise tolerance are often present, but in the absence of a murmur, may not prompt car- diac evaluation. About 50% of adults present with symptoms; in the remainder the diagnosis is made during family screening or following the de- tection of an unsuspected abnormality on physical, electrocardio- graphic, or echocardiographic examination. Dyspnoea is common (>50%) as a consequence of elevated left atrial and pulmonary ca- pillary wedge pressures resulting from impaired left ventricular re- laxation and filling, and about 50% complain of chest pain, which is exertional, atypical, or both in similar proportions of patients. Atypical pain may have no obvious precipitant; more commonly it follows exercise-or anxiety-related tachycardia, when it persists for up to several hours after the stress has been removed without en- zymatic evidence of myocardial damage. Syncopal episodes occur in 15 to 25%, but in only a few are there findings suggestive of an ar- rhythmia or evidence of overt conduction disease: in most patients, the mechanism cannot be determined. Patients rarely present with paroxysmal nocturnal dyspnoea, ascites, or peripheral oedema. Physical examination In most patients with hypertrophic cardiomyopathy the physical examination is unremarkable. There may be a rapid upstroke ar- terial pulse reflecting dynamic left ventricular emptying. In about one-third, the jugular venous pulse may demonstrate a prominent ‘a’ wave, reflecting diminished right ventricular compliance secondary to right ventricular hypertrophy. Many patients have a forceful left ventricular cardiac impulse, best appreciated on full-held expiration in the left lateral position, when there may be a palpable atrial beat reflecting forceful atrial systolic contraction that may or may not be associated with significant forward flow of blood. The first and second heart sounds are usually normal, and—unless the patient is in atrial fibrillation—there is likely to be a loud fourth heart sound, reflecting increased atrial systolic flow into a non- compliant ventricle. However, in those patients (20–30%) who have a resting left ventricular outflow tract gradient, the most obvious physical sign is an ejection systolic murmur. This murmur starts well after the first heart sound and ends before the second. It is best heard at the left sternal border, radiating towards the aortic and mi- tral areas, but not into the neck or the axilla. The intensity varies with changes in ventricular volume; it can be increased by physiological and pharmacological manoeuvres that decrease afterload or venous return (amyl nitrate, standing, Valsalva, and others), and decreased by manoeuvres that increase afterload and venous return (squatting, phenylephrine, and others). Occasionally there is an ejection sound at the onset of the systolic murmur. Most patients with a left ventricular outflow tract gradient also have mitral regurgitation. Doppler examination reveals that mitral regurgitation usually begins just before (30–40 ms) the onset of the gradient and continues for the duration of systole. Radiation of the systolic murmur to the axilla is often the best auscultatory clue to the presence of coexistent mitral regurgitation, which may be mod- erate to severe, either alone or in association with a left ventricular outflow tract gradient. A mid-diastolic rumble may sometimes re- sult from increased transmitral flow in patients with severe mitral regurgitation. Early diastolic murmurs of aortic incompetence may develop fol- lowing surgical myectomy or infective endocarditis involving the aortic valve. Although such murmurs are rare in the absence of such complications, they appear to occur more commonly than would be expected by chance and may

reflect traction on the noncoronary Table 16.7.2.2 Major and minor criteria for the diagnosis of hypertrophic cardiomyopathy in adult members of affected families. Criteria are fulfilled if (1) one major echocardiographic, or (2) two minor echocardiographic, or (3) one minor echocardiographic plus two minor electrocardiographic abnormalities are seen Major criteria Minor criteria Echocardiography Left ventricular wall thickness ≥13 mm in the anterior septum or posterior wall
or ≥15 mm in the posterior septum or free wall Left ventricular wall thickness of 12 mm in the anterior septum or posterior wall or of 14 mm in the posterior septum or free wall Severe SAM (septal–leaflet contact) Moderate SAM (no septal–leaflet contact) Redundant mitral valve leaflets Electrocardiography Left ventricular hypertrophy + repolarization changes (Romhilt and Estes) Complete bundle branch block or (minor) interventricular conduction defect (in LV leads) T-wave inversion in leads I and aVL (≥3 mm) (with QRS–T-wave axis difference ≥30°),
V3–V6 (≥3 mm), or II and III and aVF (≥5 mm) Minor repolarization changes in LV leads Abnormal Q (>40 ms or >25% R wave) in at least two leads from II, III, aVF (in absence
of left anterior hemiblock), V1–V4; or I, aVL, V5–V6 Deep S in V2 (>25 mm) Clinical There are no clinical major criteria Unexplained chest pain, dyspnoea, or syncope LV, left ventricular; SAM, systolic anterior motion of the mitral valve. Reproduced from Heart, McKenna WJ, et al., 77, 130–2. Copyright 1997 with permission from the BMJ Publishing Group Ltd.

16.7.2 The cardiomyopathies: Hypertrophic, dilated, restrictive, and right ventricular 3473 cusp of the aortic valve by the septum. An ejection systolic murmur in the pulmonary area, reflecting right ventricular outflow tract ob- struction, is also rare; when present, it is usually associated with severe biventricular hypertrophy in the young or in those with co- existent Noonan’s syndrome and a dysplastic pulmonary valve (see Chapter 16.12). Prognosis Patients with hypertrophic cardiomyopathy experience slow pro- gression of symptoms and gradual deterioration of left ventricular function, and are at risk of sudden cardiac death throughout life. Annual mortality rates are in the range of 1–2%, but the risk of death and other disease-related complications varies between individuals and within individuals during the course of the disease. Severe heart failure symptoms may develop in association with progressive myocardial wall thinning caused by myocardial fibrosis and severe reduction in left ventricular systolic performance and/ or diastolic filling. The development of systolic failure is associated with a poor prognosis, with rapid progression from onset to death or transplantation, and an overall mortality rate of up to 11% per year. Left atrial size provides important prognostic information on the risk of sudden cardiac death and atrial fibrillation/flutter. Atrial arrhythmias are important in the clinical course, leading to a risk of acute deterioration and thromboembolic stroke. Onset of atrial fibrillation is part of the evolution of patients with diastolic dys- function, and with appropriate management need not represent a major cause of morbidity or mortality. A few patients who experi- ence such deterioration present with a clinical picture resembling restrictive cardiomyopathy, with grossly enlarged atria, signs of right heart failure, and relative preservation of left ventricular systolic performance. Left ventricular hypertrophy develops during childhood and ado- lescence, but is rarely progressive in adults. The trigger and other de- terminants of disease expression in late-onset disease are uncertain. Investigations Cardiological evaluation of patients with hypertrophic cardiomyop- athy is performed to confirm the diagnosis, to guide symptomatic therapy, and to assess the risk of complications, particularly that of sudden death. Electrocardiography The 12-lead ECG is the most sensitive diagnostic test, although oc- casionally normal (c.5%), particularly in the young. At the time of diagnosis, 5–10% of patients are in atrial fibrillation. Many have an

intraventricular conduction delay and 20% have left-axis devi- ation, but complete right bundle or left bundle branch block is un- common (c.5%). The latter may develop following surgery and is occasionally seen in elderly patients. ST-segment depression and T-wave changes are the most common abnormalities and are usu- ally associated with voltage changes of left ventricular hypertrophy and/or deep S waves in the anterior chest leads V1 to V3. Isolated repolarization changes or giant negative T waves are occasionally seen. Voltage criteria for left ventricular hypertrophy are rare in the absence of repolarization changes. About 20% of patients have ab- normal Q waves, either inferiorly (II, III, and aVF), or less com- monly in leads V1 to V3. P-wave abnormalities of left and/or right atrial overload are common. The distribution of the PR interval is similar to that in the normal population, but occasionally a short PR interval may be associated with a slurred upstroke to the QRS com- plex. This is not usually associated with evidence of pre- excitation, although patients with hypertrophic cardiomyopathy and acces- sory pathways have been described. Despite the many electrocar- diographic abnormalities, there is no ECG that is typical of HCM; a useful rule is to consider the diagnosis whenever the ECG is bizarre, particularly in younger patients. The incidence of arrhythmias during 48-h ambulatory elec- trocardiographic monitoring increases with age. Nonsustained ventricular tachycardia is detected in 20–25% of adults and, al- though usually asymptomatic, is associated with an increased risk of sudden cardiac death. Supraventricular arrhythmias are also common in adults and can be poorly tolerated if sustained (>30 s) unless the ventricular response is controlled. Atrial fibrillation or flutter carry an increased risk of thromboembolism. By con- trast, most children and adolescents are in sinus rhythm, and ar- rhythmias during ambulatory electrocardiographic monitoring are uncommon. The increased incidence of supraventricular ar- rhythmias with age is related to increased left atrial dimensions and increased left ventricular diastolic pressure. The aetiology of ven- tricular arrhythmias is not known, but may relate to myocyte loss and myocardial fibrosis. Documented sustained ventricular tachy- cardia is uncommon, but is a recognized complication in patients with an apical aneurysm, which may develop as a consequence of midventricular obstruction. Chest radiography The chest radiograph may be normal or show evidence of left and/or right atrial or left ventricular enlargement; if left atrial pressure has been chronically elevated, there may be evidence of redistribution of blood flow to upper lung zones. Mitral valve annular calcification is seen, particularly in elderly patients. Echocardiography Left ventricular hypertrophy may be symmetric or asymmetric and localized to the septum or the free wall, but most commonly to both the septum and free wall with relative sparing of the posterior wall (Fig. 16.7.2.2). Isolated apical hypertrophic cardiomyopathy oc- curs in about 10% of patients. Approximately one-third of patients also have hypertrophy of the right ventricular free wall, the pres- ence and severity of which is strongly related to the severity of left ventricular hypertrophy. Typically, left ventricular end-systolic and end-diastolic dimensions are reduced, and the left atrial dimension is increased. Indices of systolic function such as ejection fraction may be increased, but systolic function is often impaired, which may be best appreciated by measurement of long-axis rather than short- axis function. Colour Doppler provides a sensitive method of detecting left ventricular outflow tract turbulence (Fig. 16.7.2.3), and when combined with continuous wave Doppler the peak velocity (Vmax) of left ventricular blood flow can be measured and left ventricular outflow tract gradients calculated. Doppler gradients (pressure gradient (mm Hg) = 4 Vmax2) are seen in 20–30% of patients and correlate well with those measured invasively. Systolic anterior motion of the mitral valve is usually present when the calculated outflow tract gradient is more than 30 mm Hg, and early closure or fluttering of the aortic valve leaflets is often seen in association

section 16 Cardiovascular disorders 3474 with such motion. A posteriorly directed mitral regurgitant jet is seen in association with and related to the magnitude of the out- flow tract gradient (Fig. 16.7.2.3). An anterior regurgitant jet or mitral regurgitation in the absence of obstruction suggests the coexistence of structural mitral valve abnormalities. Other imaging techniques Good-quality echocardiography suffices for diagnostic and thera- peutic purposes in most patients with hypertrophic cardiomy- opathy, but cardiac MRI is useful in selected cases to assess right ventricular, apical, and lateral left ventricular involvement. Gadolinium-enhanced cardiac MRI permits detection of myo- cardial fibrosis, the extent of which may predict evolution to the burnt-out phase. Cardiac catheterization Two-dimensional echo/Doppler evaluation has replaced invasive haemodynamic measurements and angiography as the method of assessing left ventricular structure and function in hypertrophic car- diomyopathy. Cardiac catheterization is not necessary for diagnosis and is rarely indicated unless symptoms are refractory and direct measurement of cardiac pressures is potentially informative, particu- larly in assessing the severity of mitral regurgitation. Coronary ar- teriography may be necessary to exclude coexistent coronary artery disease in older patients who have significant angina or ST-segment changes during exercise. The left coronary arteries are usually large in calibre. The left anterior descending and septal perforator ar- teries may demonstrate narrowing during systole in the absence of fixed obstructive lesions, but such changes do not appear to relate to symptoms. Left ventricular angiography is rarely indicated, but rec- ognition of the abnormally shaped ventricle, which typically ejects at least 75% of its contents in association with mild mitral regurgi- tation, may provide a valuable diagnostic clue when hypertrophic cardiomyopathy was not suspected before catheterization. Exercise testing Maximal exercise testing in association with respiratory gas analysis provides useful functional and prognostic information, which can be monitored serially. Oxygen consumption at peak exercise (peak Vo2) is usually moderately reduced, even in patients who do not complain of exertional symptoms. Continuous measurement of the blood pres- sure during upright treadmill or bicycle exercise reveals that about one- third of younger patients (<40 years) have an abnormal blood pressure response, with either a drop of more than 10 mm Hg from peak record- ings or a failure to rise by 20 mm Hg or more despite an appropriate increase in cardiac output. Such changes are usually asymptomatic but are associated with an increased risk of sudden death. The mechanism of the hypotensive response during exercise in hypertrophic cardio- myopathy varies, but may relate to myocardial mechanoreceptor ac- tivation and altered baroreflex control causing inappropriate drops in systemic vasculature resistance, to a poor cardiac output response, or to exercise-induced left ventricular outflow tract obstruction. ST-segment depression of up to 2 mm from baseline is documented in 25% of patients, but appears not to be of prognostic significance. Electrophysiological studies Electrophysiological studies may occasionally be necessary in pa- tients with sustained, rapid palpitation to identify associated ac- cessory pathways or aid management of sustained monomorphic ventricular tachycardia. Conventional, programmed ventricular stimulation does not aid the identification of high-risk patients (see ‘Risk stratification’). Tests for specific causes of hypertrophic cardiomyopathy Several clinical features that suggest particular causes of hypertrophic cardiomyopathy are listed in Table 16.7.2.3; the presence of such clues should trigger appropriate biochemical and genetic testing. Management Pharmacological The goal of therapy is to improve symptoms and prevent com- plications, in particular sudden cardiac death. β-Adrenoreceptor Fig. 16.7.2.2 An echocardiogram (parasternal long-axis view) of a patient with hypertrophic obstructive cardiomyopathy demonstrating hypertrophy of the interventricular septum (IVS), enlargement of the left atrium (LA), and systolic anterior motion of the mitral valve, bringing it into contact with the septum (arrow). Fig. 16.7.2.3

Colour-flow Doppler image (parasternal long-axis view) of the same patient as shown in Fig. 16.7.2.2, demonstrating left ventricular outflow tract (LVOT) turbulence and mitral regurgitation (MR) with a posteriorly directed jet.

16.7.2 The cardiomyopathies: Hypertrophic, dilated, restrictive, and right ventricular 3475 blockers and calcium antagonists, especially verapamil, are the mainstay of symptomatic pharmacological therapy. Both drugs have several potentially beneficial actions, including a decrease in myocardial oxygen consumption and blunting of the heart rate response during exercise, thereby increasing time for filling. Both agents exert a negative inotropic effect, thereby reducing hyperdynamic systolic function and left ventricular gradients, and they may improve dia- stolic function, verapamil by improving relaxation and β-blockers by increasing compliance. The side effects of propranolol are rarely serious, but the suppressant effect of verapamil on atrioventricular nodal conduction may cause problems in patients with unsuspected pre-existing conduction disease, and its vasodilatory and negative inotropic effects can result in acute pulmonary oedema and death in symptomatic patients with severe obstruction and pulmonary hypertension. Disopyramide may be added if β-adrenoreceptor blockers and cal- cium antagonists are ineffective in patients with LV outflow tract obstruction. This Class IA antiarrhythmic drug can abolish LV outflow pressure gradients and improve exercise tolerance and func- tional capacity without proarrhythmic effects. Anticholinergic side effects including dry eyes and mouth, urinary hesitancy or reten- tion, and constipation are dose-limiting. Endocarditis is a rare complication of hypertrophic cardiomy- opathy, occurring predominantly in patients with left ventricular outflow tract turbulence and/or mitral regurgitation. Current guide- lines no longer support the previous recommendation of antibiotic prophylaxis in patients with outflow tract obstruction or intrinsic valve disease. Surgical Surgery is a therapeutic option in patients with LV outflow tract obstruction. The conventional indication for surgery is a resting left ventricular outflow tract gradient of more than 50 mm Hg in patients refractory to medical therapy, and the commonest operation is the removal of a segment of the upper anterior septum (myectomy) via a transaortic approach. Transventricular approaches have been used, but these are associated with a higher incidence of late complica- tions, particularly of cardiac failure. Mitral valve repair and papillary muscle remodelling may be required, and mitral valve replacement has also been advocated; excellent results can be achieved in patients with severe mitral regurgitation, but operative mortality and mor- bidity are higher. Specialist hypertrophic cardiomyopathy centres re- port perioperative mortality of 1% or less for septal myectomy, with 70–80% success in abolishing gradients and improving symptoms. Alcohol septal ablation Injection of alcohol into the septal artery that supplies the septal muscle has been developed as a percutaneous approach to gra- dient reduction. Most experienced centres have reported symp- tomatic improvement in 70% of patients. As for surgery and dual-chamber (DDD) pacing (see next), patient selection—in par- ticular, regarding the mechanism of the gradient—and technical considerations are important determinants of outcome. The major complication has been the need for a pacemaker in up to 20%. At present, alcohol septal ablation offers a therapeutic option that is especially used in older patients with suitable anatomy who are refractory to drugs. Pacing Alteration of the ventricular activation sequence by pacing the right ventricular apex may result in reduction of gradients and filling pressures and improved symptoms in selected patients. The role of atrioventricular synchronous pacing (DDD pacing) in symptom- atic management of obstruction has been evaluated in two random- ized multicentre trials, demonstrating symptomatic improvement and gradient reduction (50%), but no change in exercise capacity. Table 16.7.2.3 Clinical features suggesting the aetiology of hypertrophic

cardiomyopathy Clinical feature Examples Symptoms Acroparaesthesiae, tinnitus, deafness (Anderson–Fabry disease) Skeletal muscle weakness (desminopathy, mitochondrial cytopathy, and others) Physical examination Retinitis pigmentosa (mitochondrial, Danon disease, and others) Postural hypotension (amyloidosis) Cutaneous angiokeratoma (Anderson–Fabry disease) Lentigines (LEOPARD syndrome) Facial morphology (Noonan, Anderson–Fabry disease, and others) Electrocardiogram Glycogen storage disease: short PR interval, left ventricular hypertrophy Anderson–Fabry disease: short PR interval, left ventricular hypertrophy, repolarization abnormalities, bundle branch block, AV conduction delay Amyloidosis: low voltage QRS, pseudoinfarct pattern, atrial arrhythmias Mitochondrial disease: conduction defects, accessory pathways Danon: pre-excitation, left ventricular hypertrophy AMP kinase: pre-excitation/premature conduction disease Echocardiography Concentric/biventricular hypertrophy (infiltrative and storage disorders and others) Valve thickening (Anderson–Fabry disease, amyloidosis, and others) Family history X-linked inheritance (Anderson–Fabry disease, Danon, and others) Diabetes, epilepsy, and deafness (mitochondrial) Biochemistry Creatine kinase (glycogen storage disease, mitochondrial, and others) Lactate (mitochondrial) Renal dysfunction (Anderson–Fabry disease, mitochondrial, and others) Paraproteinaemia (amyloid) Exercise testing Severe premature acidosis (mitochondrial)

section 16 Cardiovascular disorders 3476 However, the placebo effect of the procedure was considerable. Nevertheless, pacing offers a therapeutic option in patients with obstruction that is refractory to drug treatment, and in whom sur- gery is either not acceptable or inappropriate. It appears that elderly patients with localized septal hypertrophy and without significant free wall involvement or mitral regurgitation may be the most likely to respond. Clinical approach to individual symptoms Dyspnoea Dyspnoea most often occurs in patients who also experience chest pain or discomfort. Treatment depends on the predominant mechanism. In patients with dyspnoea who have slow filling that continues throughout diastole, β-blockers and verapamil are appro- priate. Conversely, those with rapid, early filling may benefit from a relative tachycardia and do better without negative chronotropic agents. When dyspnoea is associated with significant obstruction, β-blockers, disopyramide, and (failing these) myectomy or the other nonpharmacological options may be beneficial. Disopyramide should be used in the maximum tolerated dose (anticholinergic side effects may limit higher doses) in conjunction with a conven- tional β-blocker. Occasionally, dyspnoea is associated with severe mitral regurgitation and responds well to mitral valve repair or replacement. Chest pain Exertional chest pain often responds to therapy with β-adrenoreceptor blockers and calcium antagonists, and when refractory can respond to very high doses of these agents (propranolol 480 mg daily, bisoprolol 10 mg daily, and verapamil 480 mg daily). Short-acting nitrates, di- uretics, and high-dose verapamil may be useful in selected patients, perhaps by reducing filling pressures and improving coronary flow to subendocardial layers. Atypical chest pain may persist long after the initial stimulus has been removed. Arrhythmia Arrhythmias are a common complication of hypertrophic cardio- myopathy. The overall prevalence and annual incidence of atrial fibrillation are around 23% and 3%, respectively. Treatment with anticoagulants and verapamil or β-blockers is appropriate once atrial fibrillation is established, the aims being to control the ven- tricular response and prevent emboli. Most patients who develop atrial fibrillation during electrocardiographic monitoring are un- aware of changes from sinus rhythm to atrial fibrillation as long as the ventricular response is well controlled. However, in a few cases the loss of atrial systolic contribution to filling volume is important, when electrical cardioversion can be facilitated by prior therapy (4–6 weeks) with amiodarone (300 mg daily) if pharmacological cardioversion does not occur first. Sustained (>30 s)

episodes of paroxysmal atrial fibrillation or supraventricular tachycardia can cause haemodynamic collapse and systemic emboli. Low-dose amiodarone (1000–1400 mg weekly) is effective in suppressing such episodes and also provides control of the ventricular response should breakthrough occur. All patients with atrial fibrillation or flutter should be considered for anticoagulation (unless contraindicated) as embolic complications are common, even when atrial dimensions are only moderately increased. Nonsustained episodes of supraventricular arrhythmia are common, and although often asymptomatic, they are a marker (al- beit of low positive predictive accuracy) for the subsequent devel- opment of established atrial fibrillation. The threshold to introduce amiodarone or β-adrenoreceptor blockers and calcium antagonists, with or without anticoagulation, should be low if they occur in the presence of atrial enlargement. Episodes of nonsustained ventricular tachycardia are common but are rarely symptomatic: therapy is war- ranted only if it can be shown to improve prognosis (see prevention of sudden cardiac death). Prevention of sudden cardiac death Sudden cardiac death is a consequence of multiple interacting mech- anisms. The histological abnormalities—particularly myocyte dis- array, small-vessel disease, and replacement scarring—contribute to the underlying anatomical substrate. Events may be triggered by haemodynamic alterations, myocardial ischaemia, and arrhythmias, including ventricular tachycardia, atrial fibrillation, atrioventricular block, and rapid conduction of a supraventricular arrhythmia via an accessory pathway. Intense physical exertion may also contribute to the aforementioned triggers. The interaction of triggers and sub- strate may be modified by inappropriate peripheral vascular re- sponses and the development of myocardial ischaemia. Risk stratification Prevention of sudden death relies on risk factor stratification to identify a high-risk cohort who will benefit from an implantable cardioverter–defibrillator (ICD). Several adverse features that can be elicited from the clinical history and noninvasive evaluation have been identified (Box 16.7.2.1). Their relative importance varies with age; for example, the finding of nonsustained ventricular tachy- cardia on 24-h electrocardiographic monitoring in children and adolescents is uncommon (<5%), but is associated with an eightfold increased risk of sudden death, whereas in adults this arrhythmia is common (20–25%), but in isolation confers only a twofold increased risk. In young people (<25 years) the finding of nonsustained ven- tricular tachycardia, severe and extensive left ventricular hyper- trophy, unexplained syncope (particularly if recurrent or exertional), or a family history where a high proportion of affected individuals experienced premature (<40 years) sudden death warrants prophy- lactic treatment. Such patients usually also exhibit abnormal blood pressure responses to exercise; indeed, the finding of a normal ex- ercise blood pressure response appears to identify the low-risk younger (<40 years) patient (negative predictive accuracy 97%), al- lowing appropriate reassurance that is also clinically important. In Box 16.7.2.1 Risk factors for sudden death • Family history of sudden death (≥1 premature (<40 years) sudden death) • Unexplained syncope within previous year • Abnormal exercise blood pressure • Nonsustained ventricular tachycardia (≥3 beats at ≥120 beats/min) • Severe left ventricular hypertrophy (>3 cm) • Severe left ventricular outflow tract obstruction (>90 mm Hg) • Cardiac arrest (or sustained ventricular tachycardia)

16.7.2 The cardiomyopathies: Hypertrophic, dilated, restrictive, and right ventricular 3477 adults aged 25 to 60 years, the positive predictive accuracy for each of the risk factors is much lower (15–20%): conventionally, prophy- lactic treatment was advised for those with two or more risk factors who would have a predicted risk of sudden death of at least 3% per year. Those with a single risk factor have an annual sudden death risk of 1%, but the confidence limits range from 0.2 to 2%, indicating that some but not all single risk factor patients may benefit from an ICD. Recently,

a large multicentre longitudinal cohort study of 3675 patients (HCM-RISK SCD) developed and validated a statistical sudden cardiac death risk prediction model, which provides indi- vidualized risk estimates. This model uses left atrial diameter, peak left ventricular outflow tract gradient, and patient age, together with the same major risk factors recommended in previous guidelines (with the exception of abnormal blood pressure response) to esti- mate the risk of sudden cardiac death at 5 years. It is important to consider risk in all patients, even those who are asymptomatic or who have mild echocardiographic features of hypertrophic cardio- myopathy. Although children and adolescents with severe congestive symptoms may be at greater risk, the data reveals that the severity of chest pain, dyspnoea, and exercise limitation are not reliable pre- dictors of the risk of sudden death in adults. In addition, it is recog- nized that most patients who die suddenly have mild (1.5–2.0 cm) or moderate (2.0–2.5 cm) left ventricular hypertrophy, while some genetic defects (e.g. cardiac troponin T) may cause sudden death in the absence of symptoms or hypertrophy. The presence of a left ventricular outflow tract gradient is also as- sociated with sudden death. The management of symptomatic pa- tients should be focused on gradient reduction; in asymptomatic patients, severe left ventricular outflow tract obstruction should be considered in the overall risk profile of the patient. Diastolic impair- ment with abnormal Doppler filling patterns associated with symp- tomatic limitation and poor prognosis, and atrial enlargement is associated with premature sudden cardiac death. Some investigators have suggested that the induction of sus- tained ventricular arrhythmias during programmed electrophysio- logical stimulation is associated with a higher risk of sudden death. However, the predictive accuracy is low, and as most high-risk patients can be identified using noninvasive clinical markers, the inherent risks and inconvenience associated with programmed stimulation dictate that it should not be used routinely to assess risk in hypertrophic cardiomyopathy. Dilated cardiomyopathy Definition Dilated cardiomyopathy (DCM) is a heart muscle disorder defined by dilatation and impaired systolic function of the left ventricle or both ventricles in the absence of coronary artery disease, valvular abnor- malities, or pericardial disease. Systolic dysfunction is defined by an abnormal LV ejection fraction, preferably demonstrated by echocar- diography or MR imaging. LV dilatation is defined by LV end-diastolic volumes or diameters greater than 2SD from normal according to standard nomograms. Many different cardiac and systemic diseases are associated with left ventricular dilatation and impaired contract- ility (see Chapter 16.7.3). When no identifiable cause is found, the condition is referred to as idiopathic dilated cardiomyopathy. Dilated cardiomyopathy has been described in Western, African, and Asian populations, affecting both genders and all ages. In North America and Europe, symptomatic dilated cardiomyopathy has an incidence and prevalence of 20 and 38 per 100 000, respectively, and is the commonest indication for cardiac transplantation. A recent position statement from the European Society of Cardiology (ESC) working group on myocardial and pericardial diseases proposed a revised definition of DCM (Fig. 16.7.2.4) to Preclinical or early phase (Relative of patients with DCM or hypokinetic non dilated CM) DCM clinical spectrum No cardiac expression Isolated ventricular dilation Arrhythmic CM Hypokinetic nondilated CM Dilated CM Clinical phase (Mutation carrier and/or AHA positive) (Dilation/no hypokinesia)* ∧ (Arrhythmias or conduction defect) (Hypokinesia/no dilation) Progressive expression of the phenotype *Shown by two independent imaging modalities, ∧mutation carrier or not, anti-heart autoantibody (AHA) positive or negative (LV dilation + hypokinesia) (HNDC or DCMND-H) (DCMD-H) (DCMD-NH, with or without Mut+AHA+) (DCMND-NH-A/CD, with or without Mut+AHA+) (DCMND-NH-Mut+AHA+) ∧ ∧ (no LV abn, no arrhythmia) Fig. 16.7.2.4 Description of the clinical spectrum of DCM. LV abn, left ventricle abnormality. DCM can be further classified as ND or D

(nondilation/dilation) or NH or H (nonhypokinetic/hypokinetic) or mut + (mutation carrier) or AHA + (antiheart autoantibody positive) or
A/CD (arrhythmia/conduction defect). Reprinted from Pinto YM, et al. (2016). Proposal for a revised definition of dilated cardiomyopathy, hypokinetic nondilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. Eur Heart J, 37(23), 1850–8, by permission of Oxford University Press.

section 16 Cardiovascular disorders 3478 encompass both preclinical or early phase and the clinical phase of the disease. The DCM clinical spectrum includes isolated ven- tricular dilatation or arrhythmic DCM in the preclinical or early phase, hypokinetic nondilated cardiomyopathy, and dilated cardio- myopathy. The definition of hypokinetic nondilated cardiomyop- athy requires LV ejection fraction less than 45% that is not explained by abnormal loading conditions or coronary artery disease. Causes Syndromic diseases (e.g. mitochondrial diseases), drug toxicity, toxins, nutritional deficiency, electrolyte disturbances, endocrine abnormalities, infection, and auto- immune disease are important causes of DCM and need to be considered in the differential diag- nosis (see Chapter 16.7.3). Pedigree analysis of patients with ‘idiopathic’ DCM reveals fa- milial disease in at least 25% of cases; a further 20–30% of relatives have mild abnormalities of left ventricular performance that evolve into dilated cardiomyopathy in about one-third. Inheritance is usu- ally autosomal dominant with incomplete penetrance, with a smaller number of families having X-linked transmission. Penetrance is age dependent and has been estimated to be 10% in those aged less than 20 years, 34% in young adults aged 20 to 30 years, 60% in adults aged 30 to 40 years, and 90% in those over 40 years. Guidelines for the diagnosis of familial disease based on the iden- tification of major and minor criteria are shown in Box 16.7.2.2 and Fig. 16.7.2.5. If a relative satisfies the criteria for DCM or hypokinetic nondilated cardiomyopathy just described, then they have definite disease. They have probable disease if they have one major plus at least one minor criterion, or have one major criterion and are carrying the proband’s causative mutation. They have possible disease if they have two minor criteria, one minor criterion, and are carrying the proband’s causative mutation, or have one major criterion but without any minor criterion and without genetic information from the family. Disease-causing mutations are reported in numerous genes, most of which are important in maintaining cardiomyocyte cytoskeletal integrity, including dystrophin, metavinculin, cardiac actin (auto- somal dominant), lamin A/C (associated with premature conduc- tion disease and sudden death), desmin, myosin-binding protein C, troponin T and C, β-myosin heavy chain, and Z-line associated pro- tein (ZASP). Lamin A/C mutations also cause Emery–Dreifuss and limb-girdle muscular dystrophy and familial partial lipodystrophy; desmin may cause conduction disease with restrictive cardiomyop- athy; dystrophin mutations cause childhood (Duchenne) and adult (Becker) forms of muscular dystrophy. Myotonic dystrophy—type I (DM1) due to mutations in DMPK and type II (DM2) due to mu- tations in CNBP—can be associated with AV block. A further gene mutation implicated in the development of dilated cardiomyopathy (DCM) is titin (TTN), which is a connectin linking the Z-line to the M-line in the sarcomere. The frequency of TTN mutations is high in subjects with dilated cardiomyopathy (27%), but they are also found in some normal individuals. Other genes implicated include RNA-binding Motif-20 (RBM 20), myopalladin (MYPN), sodium channel α-unit (SCN5A), BaCl2-associated athanogene 3 (BAG3), and phospholamban (PLN). Different patterns of disease expression are recognized. Disease progression appears to be slow (over decades) in most cases, and conduction disturbance is a late complication related to disease se- verity. However, in some families (<10%), particularly those with mutations in the lamin A/C gene, the early stages are character- ized by

progressive conduction disease, and left ventricular dilata- tion and impairment are later manifestations, in the fourth to sixth decade. Sudden death in the absence of severe left ventricular im- pairment is seen in disease caused by mutations in lamin A/C or desmosomal genes. Pathology and pathophysiology Macroscopic examination of hearts with dilated cardiomyopathy re- veals dilated cardiac chambers (see Fig. 16.7.2.1), mural thrombi, and platelet aggregates with normal extra-and intramural coronary Index case

- DCM (dilated LV & reduced EF)
- Familial
- Nonfamilial yes yes yes Probable disease Definitive disease (DCM/HNDC) Possible disease Possible disease No disease +≥1 minor criterion? OR mutation carrier? ≥2 minor without mutation carrier? OR 1 minor criterion + mutation carrier? yes no no no no Relative Criteria as for index cases? Major criteria for relatives? (dilated LV OR LV EF 45–50%)
- HNDC (EF <45% & no dilation) Fig. 16.7.2.5 Diagnostic criteria for DCM in probands (index cases) and relatives. Reprinted from Pinto YM, et al. (2016). Proposal for a revised definition of dilated cardiomyopathy, hypokinetic nondilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. Eur Heart J, 37(23), 1850–8, by permission of Oxford University Press. Box 16.7.2.2 Diagnostic criteria for relatives of an index case of dilated cardiomyopathy Major criteria • Unexplained decrease of LV ejection fraction to <50% (but >45%) • Unexplained LV end-diastolic dilatation (>2SD + 5%) according to standard nomograms Minor criteria • ECG showing complete left bundle branch block or atrioventricular block • Unexplained ventricular arrhythmia • Left ventricular segmental wall motion abnormalities in the absence of intraventricular conduction defect • Late enhancement of nonischaemic origin on cardiac MR imaging • Evidence of nonischaemic myocardial abnormalities (inflammation, necrosis and/or fibrosis) on endomyocardial biopsies • Presence of serum organ-specific and disease-specific antiheart anti- bodies by one or more autoantibody tests Adapted from Pinto YM, et al. (2016). Proposal for a revised definition of di- lated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its im- plications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. Eur Heart J, 37(23),1850–8.

16.7.2 The cardiomyopathies: Hypertrophic, dilated, restrictive, and right ventricular 3479 arteries. Myocardial mass is increased, but ventricular wall thick- ness is normal or reduced. Histology is nonspecific with patchy perimyocyte and interstitial fibrosis, various stages of myocyte death, as well as myocyte hypertrophy and often extensive myofibrillary loss, resulting in a vacuolated appearance of the myocytes. An inter- stitial T-lymphocyte infiltrate and focal accumulations of macro- phages associated with individual myocyte death are common. The identification of disease-causing mutations in genes encoding various components of the cardiac myocyte cytoskeletal and sarcomeric contractile apparatus shows that the pathogenesis of di- lated cardiomyopathy is heterogeneous. Two models have been pro- posed to explain ventricular remodelling in dilated cardiomyopathy. In the ‘final common pathway’ hypothesis, dilated cardiomyopathy reflects a nonspecific degenerative state, which may result from a variety of stimuli, including genetic mutations, viral infections, toxins, and volume overload. The alternative hypothesis suggests that several distinct, independent pathways can remodel the heart and cause dilated cardiomyopathy—in other words, the different causes of dilated cardiomyopathy share a

common histopathology, but their molecular biology is distinct. The final common pathways resulting in dilated cardiomyopathy include altered myocyte ener- getics and calcium handling. Clinical features History Initial presentation is usually with symptoms of cardiac failure (fa- tigue, breathlessness, decreased exercise tolerance, and others), but arrhythmia (atrial fibrillation, ventricular tachycardia, atrioven- tricular block), systemic embolism, or the incidental finding of an ECG or radiographic abnormality during routine screening may prompt earlier diagnosis. Physical examination Physical examination may be entirely normal or may reveal evi- dence of myocardial dysfunction with cardiac enlargement and signs of congestive heart failure. Systolic blood pressure is often low, with a narrow pulse pressure and a low-volume arterial pulse. Pulsus alternans may be present in patients with severe left ven- tricular failure, and the jugular veins may be distended, with a prom- inent V wave reflecting tricuspid regurgitation. In such patients, the liver may be engorged and pulsatile, and there is usually peripheral oedema and ascites. The precordium often reveals a diffuse and dyskinetic left (and occasionally right) ventricular impulse. The apex is usually displaced laterally, reflecting ventricular dilatation. The second heart sound is usually normally split, but paradoxical split- ting may be present when there is left bundle branch block, which occurs in about 15% of patients. With severe disease and the de- velopment of pulmonary hypertension, the pulmonary component of the second heart sound may be accentuated. Characteristically, a presystolic gallop or fourth heart sound is present before the de- velopment of overt cardiac failure. However, once cardiac decom- pensation has occurred, ventricular gallop or third heart sound is often present. When there is significant ventricular dilatation, sys- tolic murmurs are common, reflecting mitral and (less commonly) tricuspid regurgitation. The development of unexplained cardiac failure in the last month of pregnancy or 5 months post-partum is termed peripartum cardiomyopathy. There is sometimes uncertainty whether the car- diac failure is acute or chronic and exacerbated by the haemo- dynamic stress of pregnancy and labour. When the heart failure is acute and there is persistence of left ventricular chamber dilatation or impaired systolic performance, the diagnosis of peripartum car- diomyopathy can legitimately be made. An abnormally cleaved pro- lactin producing a raised 16 kDa prolactin level (normal prolactin is 23 kDa) has been identified in some patients with peripartum cardiomyopathy and, in a pilot study, treatment with the prolactin inhibitor bromocriptine improved left ventricular function and outcome. The diagnostic utility of urinary 16 kDa prolactin, its potential genetic basis, and the spectrum of therapeutic utility of bromocriptine remain to be determined. Genetic predisposition to peripartum cardiomyopathy includes mutations in titin (TTN) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which alters oxidative stress and has been reported to be involved in the pathogenesis. For further discussion of cardiac disease in preg- nancy, see Chapter 14.6. Prognosis The natural history of dilated cardiomyopathy is uncertain because the diagnosis is usually not made until clinical features, which are late manifestations of the disease, become obvious. Follow-up of asymptomatic first-degree relatives suggests that disease progres- sion is insidious over decades. An upper respiratory tract infection or a salt or fluid load can precipitate clinical presentation. Symptoms develop when filling pressures rise or when stroke volume dimin- ishes sufficiently to cause salt and water retention and oedema. Once clinical symptoms and signs of impaired ventricular performance are apparent, prognosis is related to the degree of left ventricular dilatation and impaired contractile performance, but survival has been substantially improved by modern management with angio- tensin converting enzyme (ACE) inhibitors, β-blockade, mineralo- corticoid antagonists, aggressive treatment of arrhythmias, and cardiac transplantation. Arrhythmia Atrial arrhythmias, particularly atrial fibrillation, are common and associated with the severity of symptoms, left ventricular dys- function, and poor prognosis,

but atrial fibrillation is not an inde- pendent predictor of disease progression or sudden cardiac death. Occasionally, however, persistent atrial tachycardia or atrial fibril- lation may cause gradual deterioration in left ventricular function, resembling dilated cardiomyopathy (‘tachycardia induced cardio- myopathy’). In this situation, systolic function usually returns to normal with control of the arrhythmia. Ventricular arrhythmias are common and like supraventricular arrhythmias are markers of disease severity. Nonsustained ven- tricular tachycardia during ECG monitoring is seen in about 20% of asymptomatic or mildly symptomatic patients and in up to 70% of those who are severely symptomatic. The prognostic sig- nificance of this arrhythmia is controversial: its presence early in the course of disease, when left ventricular function is relatively preserved, is probably an independent marker of sudden death risk, whereas in general markers of haemodynamic severity (such as ejection fraction, left ventricular end-diastolic dimension, or filling pressures) are more predictive of disease-related mortality

section 16 Cardiovascular disorders 3480 and sudden death. Risk of sudden death in patients with severe disease (New York Heart Association, NYHA class III or IV) in- creases approximately threefold when syncope is present. Investigation Electrocardiography The electrocardiographic features of dilated cardiomyopathy are nonspecific and highly variable. Sinus tachycardia is common (particularly in children and infants); nonspecific ST-segment and T-wave changes may be seen, most commonly in the inferior and lateral leads; and pathological Q waves may be present in the septal leads in patients with extensive left ventricular fibrosis. Atrial en- largement is common, and in advanced disease may be associated with bundle branch block. All degrees of atrioventricular block may also be seen and should raise the possibility of mutations in specific genes such as lamin A/C and DES (which encodes desmin) if associ- ated with relatively mild impairment of left ventricular function, or when present in a young patient. Chest radiography The chest radiograph is usually abnormal in patients with dilated cardiomyopathy, except in a rare subset of patients with acute viral myocarditis associated with left ventricular systolic impairment and preserved cavity dimensions. An increased cardiothoracic ratio (>0.5) is typically seen, reflecting left ventricular and left atrial dila- tation. Increased pulmonary vascular markings and pleural effu- sions may be present in patients with elevated left ventricular filling pressures. Echocardiography Echocardiography is used to identify the presence of left ventricular cavity dilatation and systolic impairment, which are the typical fea- tures of the condition. In general, the presence of ventricular end- diastolic dimensions more than two standard deviations above body surface area-corrected mean values and fractional shortening less than 25% are sufficient to make the diagnosis (Fig. 16.7.2.6). Two-dimensional echocardiography is also used to determine whether intracavitary thrombus is present in the ventricles. Colour-flow Doppler may be used to determine the presence and quantify the severity of functional mitral and tricuspid regurgitation (Fig. 16.7.2.7). Pulsed wave and-continuous wave Doppler can be used to estimate pulmonary artery pressures. Patients with dilated cardiomyopathy usually have abnormalities of diastolic left ven- tricular function in addition to systolic impairment: these can be assessed using mitral inflow, pulmonary vein, and tissue Doppler parameters. Cardiac biomarkers Serum creatine kinase should be measured in all patients with di- lated cardiomyopathy because this simple test may provide an important clue to the aetiology of the condition (e.g. muscular dys- trophy, lamin A/C defect, and others). Other cardiac biomarkers (e.g. troponin I and troponin T), may also be elevated in dilated cardiomyopathy, particularly in association with an inflammatory cause. Plasma natriuretic peptide levels are elevated in chronic heart failure and predict mortality. Many of the systemic diseases that are associated with heart muscle disorders have typical clinical, immunological, and

biochemical features (see Chapter 16.7.3), and in the absence of clinical clues to (a) (b) Fig. 16.7.2.6 Echocardiographic appearances of two patients with familial dilated cardiomyopathy. (a) Parasternal long-axis view showing significant left atrial (LA) and biventricular dilatation with a thin intraventricular septum (IVS). (b) Apical four-chamber view demonstrating a globular dilated left ventricle. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. Fig. 16.7.2.7 Colour-flow Doppler image of the same patient as shown in Fig. 16.7.2.6a demonstrating a regurgitant tricuspid jet (TR).

16.7.2 The cardiomyopathies: Hypertrophic, dilated, restrictive, and right ventricular 3481 suggest a systemic disease an exhaustive ‘routine screen’ is probably not cost-effective. There are, however, several potential reversible secondary causes of heart muscle disorder that may simulate dilated cardiomyopathy, and basic screening tests should include serum phosphorus (hypophosphataemia), serum calcium (hypocalcaemia), serum creatinine and urea (uraemia), thyroid function tests (hyper- thyroidism), and serum iron and ferritin (haemochromatosis). Exercise testing Symptom-limited exercise testing (treadmill or bicycle) combined with respiratory gas analysis is a useful technique to assess func- tional limitation in patients with dilated cardiomyopathy and pro- vides a means of objectively evaluating disease progression. The detection of respiratory markers of severe lactic acidaemia during metabolic exercise testing may suggest a mitochondrial or other metabolic cause for dilated cardiomyopathy. Assessment of exercise capacity is essential in the assessment of patients prior to cardiac transplantation. Cardiac catheterization Cardiac catheterization is performed to exclude coronary artery disease as a cause of impaired systolic function. Haemodynamic assessment of left ventricular end-diastolic and pulmonary ar- tery pressures is performed as part of cardiac transplant work-up. Endomyocardial biopsy may be diagnostic and is recommended in patients with clinically suspected myocarditis (i.e. acute chest pain in the absence of coronary artery disease), new-onset (days up to 3 months) or worsening of dyspnoea at rest or exercise with or without left and/or right heart failure signs, unexplained arrhythmia and/or aborted sudden cardiac death or unexplained cardiogenic shock, in the presence of biochemical markers of cardiac damage or compatible cardiac imaging features. See Chapter 16.7.1 for fur- ther discussion. Endomyocardial biopsy should also be considered when there is a clinical suspicion of storage or metabolic disease that cannot be confirmed by other means. Cardiac MRI Cardiac MRI may be a useful alternative imaging technique in patients with poor echocardiographic windows. In addition, the detection of fibrosis with gadolinium contrast enhancement may provide additional prognostic and diagnostic information. Cardiac MRI is also helpful in suspected myocarditis. In ischaemic car- diomyopathy, cardiac MRI shows segmental wall motion abnor malities or wall thinning in a particular coronary territory in addition to subendocardial or transmural late gadolinium en- hancement, whereas in nonischaemic cardiomyopathy this en- hancement is located mostly in the mid-wall to subepicardial layer. A nontransmural, patchy or epi/mid-myocardial distribution may therefore help exclude myocardial infarction as the cause of left ventricular dysfunction. Inflammatory cell injury leads to in- creased cell permeability and tissue oedema, which cardiac MRI can detect by T2-weighted imaging. Electrophysiological testing Programmed electrical stimulation is of limited clinical value in the identification of high-risk patients. Polymorphic ventricular tachy- cardia is inducible in up to 30% of cases, but this is a nonspecific finding. Approximately 10% of patients have inducible sustained monomorphic ventricular tachycardia; about one-third of these die suddenly, but most (75%) who die in this way do not have indu- cible ventricular tachycardia during programmed stimulation. In some patients, ventricular tachycardia arises as the consequence of bundle branch re-entry. This

tachycardia is typically rapid (mean cycle length 280 ms) and uses a macro re-entrant circuit that in- volves the His–Purkinje system, usually with right bundle branch anterograde conduction and left bundle branch retrograde con- duction. Differentiation from myocardial ventricular tachycardia is confirmed by the presence of a His or right bundle branch potential preceding each QRS: diagnosis is important since catheter ablation of either the left or right bundle branch is usually curative. Management Management in dilated cardiomyopathy aims to improve symptoms, to attenuate disease progression, and prevent arrhythmia, stroke, and sudden death. Pharmacological treatment Symptomatic therapy is the treatment of heart failure with reliance on diuretics, ACE inhibitors, and β-blockers (see Chapters 16.5.2 and 16.5.3). Diuretics Loop and/or thiazide diuretics should be used in all patients with fluid retention to achieve a euvolaemic state, but they should never be used as monotherapy as they exacerbate neurohormonal activa- tion, thereby worsening disease progression. The aldosterone antag- onist, spironolactone, reduces the overall risk of death by 30% in adults with severe heart failure (NYHA class IV and ejection frac- tion <35%): side effects include hyperkalaemia (infrequent in the presence of normal renal function) and painful gynaecomastia. Eplerenone is similar to spironolactone but more selective for the mineralocorticoid receptor, thus avoiding oestrogenic problems such as gynaecomastia. ACE inhibitors and angiotensin receptor blockers Activation of the renin–angiotensin–aldosterone system is central to the pathophysiology of heart failure, regardless of the underlying aetiology, and ACE inhibitors should be considered in all patients with dilated cardiomyopathy. Many clinical trials have shown that ACE inhibitors improve symptoms, reduce hospitalizations, and reduce cardiovascular mortality in adults with symptomatic heart failure, and reduce the rate of disease progression in asymptomatic patients. ACE inhibitors are usually well tolerated, the most common side effects being cough and symptomatic hypotension. The angiotensin receptor blockers (ARBs) have similar haemo- dynamic effects to ACE inhibitors. Clinical trials in adults with heart failure have shown similar efficacy, and safety to ACE inhibitors, such that ARBs are currently recommended in adults who are in- tolerant of ACE inhibitors. Combination treatment with ACE in- hibitors and ARBs may be more beneficial at preventing ventricular remodelling than either drug alone, but with little additional benefit on overall survival. Combination therapy of sacubitril (a neprilysin inhibitor) and valsartan (ARB) has shown significant symptomatic and prog- nostic benefit in patients treated for heart failure. Neprilysin is a neutral endopeptidase that degrades vasoactive peptides including

 natriuretic peptides, hence its inhibition leads to vasodilatation and reduction of extracellular fluid volume via increased sodium excretion. β-Blockers Excess sympathetic activity contributes to heart failure and nu- merous multicentre placebo-controlled trials—using carvedilol, metoprolol, and bisoprolol—have shown substantial reductions in mortality (both sudden death and death from progressive heart failure) in adults with NYHA class II and III heart failure symp- toms. β-Blockers are usually well tolerated, but side effects include bradycardia, hypotension, and fluid retention, and they are generally contraindicated in asthma. β-Blockers should be started at low doses and slowly up-titrated; they should not be started in patients with decompensated heart failure. Digoxin Digoxin improves symptoms in patients with heart failure, but no survival benefit has been demonstrated in large study cohorts. High serum digoxin levels may be associated with increased mortality in some patients. Digoxin should be used only in patients who remain symptomatic in spite of treatment with diuretics, ACE inhibitors, and β-blockers, or to control heart rate in patients with permanent atrial fibrillation. Anticoagulation The prevalence of intramural thrombi and systemic thrombo- embolism ranges

between 3% and 50%, with an incidence between 1.5% and 3.5% per year. Anticoagulation with warfarin or novel oral anticoagulants is therefore advised in patients in whom an intracardiac thrombus is identified echocardiographically, or those with a history of thromboembolism. There are no trial data to guide prophylactic anticoagulation in dilated cardiomyopathy, but pa- tients with severe ventricular dilatation and moderate to severe sys- tolic impairment may also benefit from anticoagulation. Treatment of arrhythmia in dilated cardiomyopathy If sustained or symptomatic arrhythmias are documented during 24-h ECG monitoring or exercise testing, conventional treat- ment is warranted (see Chapter 16.4). Many commonly prescribed antiarrhythmic agents should be avoided or used with caution be- cause of their negative inotropic and proarrhythmic effects. Data on amiodarone are contradictory, but the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) showed that amiodarone had no beneficial effect on survival when compared with implantable cardioverter–defibrillators. It can, however, be used safely to prevent or treat atrial arrhythmias. Nonpharmacological treatment Permanent pacing can correct two important intracardiac con- duction abnormalities. First, a small subset of patients who have marked PR interval prolongation (>220 ms), usually secondary to atrioventricular nodal disease, experience deleterious effects on left ventricular haemodynamics with reduction in diastolic ventricular filling time and the development of end-diastolic tricuspid and mi- tral regurgitation. Correction of PR interval prolongation with short atrioventricular delay dual-chamber pacing may increase stroke volume and blood pressure, thus decreasing mitral regurgitation with dramatic clinical improvement. Second, patients with marked intraventricular conduction delay (left bundle branch block >150 ms) have dyssynchronous contraction of the left ventricular free wall and interventricular septum (which may decrease ejection fraction) and late activation of the anterolateral papillary muscle (which may increase functional mitral regurgitation). Biventricular or left ven- tricular pacing with specialized leads via the coronary sinus can cor- rect both problems and has been shown to improve symptoms and prognosis in randomized trials. In addition, the resultant increase in blood pressure and pacemaker maintenance of the desired min- imum heart rate permits use of higher doses of β-blockade and ACE inhibition with potential secondary benefit. Implantation of an implantable cardioverter–defibrillator (ICD) is recommended for patients with heart failure and reduced ejec- tion fraction. Evidence for this on prognostic grounds is strong for heart failure due to coronary artery disease. Subgroup analyses have primarily been used as evidence for patients with systolic heart failure that is not due to coronary artery disease. A large prospective study (DANISH trial) did not show a significant prognostic benefit of prophylactic ICD implantation in patients with nonischaemic cardiomyopathy. Cardiac transplantation may be appropriate in patients with pro- gressive deterioration. In addition, improvements in left ventricular assist devices and artificial heart technology provide alternatives that are now reasonably seen as viable future treatment options. These issues are discussed in Chapter 16.5.5. Restrictive cardiomyopathy Definition Restrictive left ventricular physiology is characterized by a pattern of ventricular filling in which increased stiffness of the myocardium causes ventricular pressure to rise precipitously with only small in- creases in volume. The definition of restrictive cardiomyopathy has been confusing because this pattern can occur with a wide range of different pathologies. For the purposes of this chapter, restrictive cardiomyopathies are defined by restrictive ventricular physiology in the presence of normal or reduced diastolic volumes of one or both ventricles, normal or reduced systolic volumes, and normal ventricular wall thickness. Historically, systolic function was said to be preserved in restrictive cardiomyopathy, but it is rare for con- tractility to be truly normal. Causes Though restrictive physiology is often seen in hypertrophic cardio- myopathy and dilated cardiomyopathy, restrictive cardiomyopathy, as defined

earlier, is uncommon. There are many causes including infiltrative and storage disorders, and endomyocardial disease including Loeffler's endocarditis with hypereosinophilia. In the Western world amyloidosis is the commonest cause in adults, with some familial cases caused by mutations in the transthyretin gene. In the tropics, endomyocardial fibrosis is the commonest cause in adults, and probably also in children. Rare reports of familial restrictive cardiomyopathy associated with autosomal dominant skeletal myopathy, autosomal recessive musculoskeletal abnormalities, and Noonan's syndrome have been described in children. Mutations in the gene encoding desmin (an intermediate filament protein) cause restrictive cardiomyopathy as- sociated with skeletal myopathy and, in some cases, abnormalities of

16.7.2 The cardiomyopathies: Hypertrophic, dilated, restrictive, and right ventricular 3483 the cardiac conduction system. Familial restrictive cardiomyopathy is increasingly recognized as a specific phenotype within the spec- trum of hypertrophic cardiomyopathy caused by sarcomere muta- tions, particularly troponin I and β-myosin heavy chain. Families are described in which restrictive cardiomyopathy and asymmetric hypertrophy are seen alone and in combination in carriers of affected genes. Pathology Restrictive cardiomyopathy is best regarded as a heterogeneous group of conditions with different aetiologies rather than a single disease entity. Macroscopically, restrictive cardiomyopathy is char- acterized by marked biatrial dilatation in the presence of normal heart weight, a small ventricular cavity, and no left ventricular hypertrophy. The histological features of idiopathic restrictive car- diomyopathy are usually nonspecific, with patchy interstitial fibrosis that may range in extent from very mild to severe. There may also be fibrosis of the sinoatrial and atrioventricular nodes. Myocyte dis- array is not uncommon in patients with pure restrictive cardiomy- opathy, even in the absence of macroscopic ventricular hypertrophy, consistent with restrictive cardiomyopathy being a clinically unrec- ognized manifestation of hypertrophic cardiomyopathy caused by sarcomere protein gene mutations. When restrictive cardiomyopathy is caused by endomyocardial fi- brosis the cardiac pathology is distinctive, with endocardial fibrosis and overlying thrombosis involving the inflow tracts and the apices, but sparing the outflow tracts of one or both ventricles. Necrotic, thrombotic, and fibrotic stages have been defined in patients with endomyocardial fibrosis and hypereosinophilia. In the necrotic stage, there is an acute inflammatory reaction characterized by eo- sinophilic abscesses in the myocardium, with associated necrosis and arteritis. The endocardium is often thickened and mural thrombi may develop. The thrombotic stage is characterized by endocardial thrombus formation that may be severe, with massive intracavitary thrombosis causing restriction to ventricular filling and a low- output state with high filling pressures. There is a risk of systemic emboli. During the necrotic and thrombotic stages the disease may mimic a hyperacute rheumatic carditis (see Chapter 16.9.1). If the patient survives, healing by fibrosis with hyaline fibrous tissue oc- curs. There is no further evidence of inflammation and the impact of the disease is caused by the effect of the dense fibrous tissue on ven- tricular filling volume and atrioventricular valve function. Clinical features and investigation Disease onset is usually insidious. Left-sided disease may present with symptoms of pulmonary congestion and/or mitral regurgita- tion; right-sided disease with raised jugular venous pressure, hep- atomegaly, ascites, and tricuspid regurgitation. Radiographic and electrocardiographic appearances are nonspecific, showing evi- dence of raised left and/or right atrial pressure and cardiomegaly with left ventricular hypertrophy. Pulmonary infiltrates, non- specific repolarization changes, and fascicular blocks may be seen. Two-dimensional echocardiography confirms the diagnosis, al- lowing visualization of the structural abnormalities involving the endocardium and atrioventricular valves as well as demonstration of

the abnormal physiology with restriction to filling (Fig. 16.7.2.8). There may be intracavitary thrombus with apical cavity obliteration, or bright echoes from the endocardium of the right or left ventricle with tethering of the chordae and reduced excursion of the posterior mitral valve leaflet. Typically, ventricular dimensions and wall thick- ness are normal, whereas the atria are grossly enlarged. Left ven- tricular filling terminates early and is followed by a plateau phase coincident with the third heart sound. Diagnosis and management Idiopathic restrictive cardiomyopathy Demonstration of diagnostic features requires detailed imaging and may involve haemodynamic measurements at cardiac catheteriza- tion. Endomyocardial biopsy may be required to exclude storage and infiltrative diseases. It is particularly important to differentiate idiopathic restrictive cardiomyopathy from constrictive pericarditis, where surgical therapy may be curative (see Chapter 16.8). The clin- ical course of idiopathic restrictive cardiomyopathy is protracted (one to two decades), but once congestive symptoms develop, time to transplant or death is typically less than 5 years. Endomyocardial fibrosis The principal haemodynamic consequence of endomyocardial scarring is a restriction to normal filling. Early diastolic pressures are normal, but there is a rapid mid-diastolic rise which plateaus (square root sign) and is not associated with impairment of systolic performance. A similar functional haemodynamic abnormality is seen in pericardial constriction (see Chapter 16.8), but in the latter condition end-diastolic pressures are usually similar within the two ventricles, whereas in endomyocardial fibrosis there is usually in- equality of the end-diastolic pressures. Mitral and tricuspid regurgi- tation may be severe and both ventricles appear abnormal in shape on angiography due to obliteration of the apices. This may be par- ticularly marked in the right ventricle in which the infundibulum is hypertrophied and hypocontractile. In addition, the fibrotic process results in smoothing of the internal architecture of the ventricle with loss of the normal trabeculae. The presence of intracavitary thrombi in the left ventricle may give rise to the erroneous diagnosis of a car- diac tumour. The structural and physiological abnormalities that can be dem- onstrated with two-dimensional echocardiography or during car- diac catheterization result from the thrombotic and fibrotic stages of the disease. Diagnosis may be difficult during the early acute phase, RA LA Fig. 16.7.2.8 Two-dimensional echocardiogram (apical four-chamber view) showing normal-sized ventricles with massive dilatation of left (LA) and right (RA) atria.

 when the appearances of the left and right ventricle are far less ab- normal, and may require confirmation by endomyocardial biopsy. In later stages, however, the diagnosis should be readily apparent, and the risk of biopsy is excessive. There is no good medical treatment for advanced disease and the prognosis is poor, with 35–50% 2-year mortality. Congestive symp- toms from raised right atrial pressure can be improved with diuretics, though too great a reduction in ventricular filling pressure will lead to a reduction in cardiac output. Arrhythmias are common, but their prognostic significance is uncertain, and they should not be treated un- less they are sustained or associated with symptoms. Antiarrhythmic drugs that significantly slow the heart rate may be deleterious because of the small stroke volume. Digoxin may be helpful to control the ventricular response in atrial fibrillation, but cannot be expected to improve congestive symptoms as systolic function is usually well pre- served. Anticoagulants may help to prevent venous thrombosis and systemic emboli; both warfarin and antiplatelet drugs are advised. Surgery with either mitral and/or tricuspid valve replacement, with or without decortication of the endocardium, has been carried out in some patients with endomyocardial fibrosis. Good long-term results have been obtained, but there is significant perioperative mortality (15–20%). Arrhythmogenic right ventricular cardiomyopathy Definition Arrhythmogenic right

ventricular cardiomyopathy (ARVC, which replaces the older term ‘arrhythmogenic right ventricular dysplasia’) is a heart muscle disease characterized by progressive fibro-fatty re- placement of right ventricular myocardium, initially with regional and later with global right and left ventricular involvement, associated with ventricular arrhythmia, heart failure, and sudden cardiac death, with as many as 20% of such deaths in young individuals and athletes attributable to the condition. Arrhythmogenic right ventricular car- diomyopathy occurs worldwide in all ethnic groups. The prevalence is unknown, but is conservatively estimated to be between 1 in 1000 and 1 in 5000. Causes Systematic family studies have shown that arrhythmogenic right ventricular cardiomyopathy is inherited in at least 50% of cases. The mode of transmission is usually autosomal dominant with variable penetrance, but rare autosomal recessive forms provided the first in- sights into the genetic basis of the condition. Two autosomal reces- sive syndromes characterized by arrhythmogenic right ventricular cardiomyopathy, woolly hair, and palmoplantar keratoderma (Naxos disease, Carvajal–Huerta syndrome) are caused by muta- tions in the genes encoding plakoglobin and desmoplakin, respect- ively. These proteins are important components of the desmosome, with key roles in cell-to-cell adhesion and transduction of mech- anical stress. Analysis of these and similar proteins in families with the more common autosomal dominant form of disease have re- vealed mutations in desmoplakin, plakophilin, desmoglein, and desmocollin. There are isolated reports of nondesmosomal gene mutations in arrhythmogenic right ventricular cardiomyopathy involving the ryanodine-2 receptor (more typically associated with catecholaminergic polymorphic ventricular tachycardia) trans- forming growth factor β, and lamin AC. Overlap with dilated cardiomyopathy While right ventricular disease defines ARVC, there are several characteristics that can overlap with DCM. Specifically, involvement of the left ventricle ranging from scars on cardiac MR imaging to severe LV dilation and systolic impairment is reported in many pa- tients. There is also overlap in the cause of disease (e.g. desmosomal gene mutations are common in patients with a clinical diagnosis of DCM). Even though the degree to which both DCM and ARVC coexist within families is poorly characterized, the presence of right ventricular abnormalities such as dilatation and ventricular ectopy of right ventricular origin in relatives of patients with DCM may be a diagnostic red flag for the presence of familial disease. Likewise, the presence of LV dysfunction in a relative of a patient with un- equivocal ARVC does not necessarily imply a different disease. Pathology and pathophysiology Segmental disease is usual in arrhythmogenic right ventricular car- diomyopathy, with involvement of the diaphragmatic, apical, and infundibular regions of the right ventricular free wall (the ‘triangle of dysplasia’). Evolution to more diffuse right ventricular involve- ment and left ventricular abnormalities with heart failure is more common than previously suspected. Macroscopic examination of the heart may show diffuse thinning of the right ventricular wall, with aneurysms present in up to 50% of cases. The fibro-fatty re- placement of the myocardium may be focal or widespread, usually involves the subepicardial layer of the right ventricular free wall and, when severe, may appear transmural. Isolated and predominantly left ventricular disease caused by desmosomal mutations is not un- common. Histologically, arrhythmogenic right ventricular cardio- myopathy is characterized by replacement myocardial fibrosis with thinning and discrete bulges of the ventricular apices and of the right ventricular free wall, often in association with lymphocytic infil- trates surrounding degenerating or necrotic myocytes. Suggested arrhythmic mechanisms include re-entry circuits arising from fibro-fatty myocardial replacement and heterogeneous conduction resulting from destabilization of cell adhesion com- plexes and gap junctions. Clinical features Symptomatic presentation is usually with palpitation and/or syn- cope from sustained ventricular arrhythmia, but the first presen- tation of the disease—especially in young people—may be with sudden cardiac death in an individual who

was previously asymp- tomatic. Occasionally, the victim will have experienced syncope in the months preceding their death (particularly during exercise). Other symptoms are presyncope and chest pain. Features of right and later biventricular failure may be present, including dyspnoea on exertion, as the disease progresses. ‘Hot phases’ are recognized, during which previously stable patients may suffer repeated epi- sodes of ventricular arrhythmia and be prone to sudden death. Investigation There is no single diagnostic test for arrhythmogenic right ventricular cardiomyopathy, and the diagnosis is based on the presence of major and minor criteria encompassing structural, histological, electro- cardiographic, arrhythmic, and genetic factors (Table 16.7.2.4).

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Table 16.7.2.4 Revised Task Force criteria I. Global or regional dysfunction and structural alterationsa Major By 2D echo: Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): • PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m2) • PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m2) • or fractional area change ≤33% By MRI: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: • Ratio of RV end-diastolic volume to BSA ≥110 ml/m2 (male) or ≥100 ml/m2 (female) • or RV ejection fraction ≤40% By RV angiography: • Regional RV akinesia, dyskinesia, or aneurysm Minor By 2D echo: Regional RV akinesia or dyskinesia and 1 of the following (end diastole): • PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m2) • PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m2)v • or fractional area change >33% to ≤40% By MRI: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: • Ratio of RV end-diastolic volume to BSA ≥100 to <110 ml/m2 (male) or ≥90 to <100 ml/m2 (female) • or RV ejection fraction >40% to ≤45% II. Tissue characterization of wall Major Residual myocytes<60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy Minor Residual myocytes 60–75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy III. Repolarization abnormalities Major Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS ≥120 ms) Minor Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete RBBB) or in V4, V5, or V6 Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete RBBB IV. Depolarization/conduction abnormalities Major Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T-wave) in the right precordial leads (V1–V3) Minor Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG Filtered QRS duration (fQRS) ≥114 ms Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms Root-mean-square voltage of terminal 40 ms ≤20 μV Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V1, V2, or V3, in the absence of complete RBBB V. Arrhythmias Major Nonsustained or sustained ventricular tachycardia of left bundle branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL) Minor Nonsustained or sustained ventricular tachycardia of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis

500 ventricular extrasystoles per 24 h (Holter) VI. Family history Major ARVC confirmed in a first-degree relative who meets current Task Force criteria ARVC confirmed pathologically at autopsy or surgery in a first-degree relative Identification of a pathogenic mutationb categorized as associated or probably associated with ARVC in the patient under evaluation Minor History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative ARVC confirmed pathologically or by current Task Force criteria in second-degree relative a VF, augmented voltage unipolar left foot lead; aVL, augmented voltage unipolar left arm lead; BSA, body surface area; LBBB, left bundle branch block; PLAX, parasternal long-axis view; PSAX, parasternal short-axis view; RBBB, right bundle branch block; RVOT, RV outflow tract. Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria, or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories. b A pathogenic mutation is a DNA alteration associated with ARVC that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree. From Marcus FI, et al. (2010). Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. Eur Heart J, 31, 806–14.

section 16 Cardiovascular disorders 3486 The diagnosis of arrhythmogenic right ventricular cardiomyopathy is fulfilled in the presence of two major criteria, or one major plus two minor criteria, or four minor criteria from different categories. The recently revised criteria reflect family studies which (1) show that at least 30% of patients have left ventricular involvement in the form of regional or global left ventricular dysfunction, and many have subclinical left ventricular fibrosis (evident on magnetic resonance) affecting particularly the posterolateral segments, and (2) show that first-degree relatives of affected individuals may have minor car- diac abnormalities, which—although not fulfilling these diagnostic criteria—are likely to represent disease expression in the context of an autosomal dominant disease. Electrocardiography The most common electrocardiographic abnormality is T-wave in- version in leads V1 to V3 in the absence of right bundle branch block (but note that this is a normal finding in children and there- fore cannot be used as a diagnostic criterion) (Fig. 16.7.2.9). Other electrocardiographic features include QRS dispersion (localized prolongation of the QRS complex in the right ventricular leads, with a difference in QRS duration of at least 40 ms between right and left precordial leads), right intraventricular conduction delay (progressing to right bundle branch block in some patients) and the presence of an epsilon wave (a terminal notch in the QRS com- plex), typically seen in lead V1. Ventricular tachycardia is of left bundle branch block morphology, suggesting a right ventricular origin. The signal-averaged ECG is used to detect late potentials which predict susceptibility to ventricular arrhythmia and disease progression. Exercise testing The role of exercise testing in

arrhythmogenic right ventricular car- diomyopathy is primarily to detect ventricular arrhythmias induced by physical activity. Ventricular ectopy and nonsustained ven- tricular tachycardia of right ventricular origin have been described in young patients. Cardiopulmonary exercise testing may be useful as an objective measure of functional capacity in patients with ad- vanced disease. Echocardiography Echocardiography is used to confirm the diagnosis and to ex- clude congenital heart disease, which may present as a differential diagnosis for arrhythmogenic right ventricular cardiomyopathy. Typical echocardiographic findings include right ventricular dilatation, regional hypokinesia or dyskinesia, free wall aneur- ysms, increased echogenicity of the moderator band, and right ventricular apical hypertrabeculation. Left ventricular involve- ment with posterior wall hypokinesia or ventricular dilatation may be seen in up to 30% of cases. In patients in whom the right ventricle is difficult to visualize adequately using standard two- dimensional echocardiography, injection of echocardiographic contrast may provide improved definition of the right ventricular endocardial border. Cardiac MRI Assessment of the right ventricle using echocardiography is chal- lenging, even in experienced hands. Cardiovascular MRI has the advantage that it is a three-dimensional technique with no limi- tations imposed by acoustic windows (Fig. 16.7.2.10). When per- formed with a dedicated protocol by experienced operators, in both children and adults, the technique has a high sensitivity for detecting right ventricular abnormalities in individuals who fulfil conventional diagnostic criteria. Assessment of right ventricular fat, gadolinium late enhancement, and wall thinning on MRI are not considered to be adequately robust measures for inclusion in the revised diagnostic criteria. Left ventricular late enhancement, which often involves the epi-and mid-myocardial segments of the posterolateral wall, may provide the earliest nonelectrical mani- festation of desmosomal disease and be observed with otherwise normal left ventricular structure and function. Fig. 16.7.2.9 A 12-lead ECG from a young woman showing the most common electrocardiographic abnormalities found in arrhythmogenic right ventricular cardiomyopathy with low voltage and T-wave inversion in the precordial leads V1–V4.

Endomyocardial biopsy Although a histological diagnosis of arrhythmogenic right ven- tricular cardiomyopathy may be definitive, the sensitivity of endomyocardial biopsies is low because (1) the disease is segmental in nature; (2) the amount of tissue usually obtained is insufficient to differentiate fibro-fatty replacement from islands of adipose tissue that are not infrequently seen between myocytes in the right ven- tricle of normal subjects; and (3) samples are usually taken from the septum, a region that is less frequently involved. The complication rate—which includes cardiac perforation and tamponade because of thinning of the right ventricular wall—is also relatively high, hence endomyocardial biopsies are no longer considered part of the rou- tine diagnostic work-up for the condition. Management Treatment in arrhythmogenic right ventricular cardiomyopathy is individualized according to the presence of symptoms, arrhythmia, and perceived risk of sudden death. Patients with symptomatic, non-life-threatening ventricular arrhythmias are treated empirically with β-adrenoreceptor blockers, amiodarone, or sotalol. β-blockers are particularly effective at treating symptoms related to exercise- induced arrhythmia, and sotalol suppresses ventricular arrhythmia in most patients. Those with a history of sustained, haemodynam- ically compromising ventricular arrhythmia should be offered an implantable cardioverter–defibrillator (ICD). Studies in such pa- tients have shown a high rate of appropriate device discharges, ran- ging from 15% to 22% per year. More problematic is the prevention of sudden death in patients without such a history. Some markers of increased risk have been

proposed, including unexplained syncope, symptomatic ventricular tachycardia, family history of sudden death, young age, left ventricular involvement, and diffuse right ven- tricular dilatation. However, population-based survival studies are needed to evaluate the significance of these and other factors (such as asymptomatic nonsustained ventricular tachycardia). Patients with severe right ventricular or biventricular involve- ment should be treated according to current heart failure treat- ment guidelines, including the use of diuretics, ACE inhibitors, and anticoagulation. Patients with advanced disease are candidates for cardiac transplantation (see Chapter 16.5.5). Evaluation, genetic testing, and follow-up of asymptomatic patients with cardiomyopathy It is now possible to offer genetic testing to individuals with un- equivocal cardiomyopathy, particularly with highly penetrant dis- ease in large families and in families affected by a sudden cardiac death. If a disease-causing mutation is identified, relatives can be offered predictive genetic testing, but this should only be done after appropriate genetic counselling and informed consent obtained by a trained healthcare professional working within a multidisciplinary team. This is to ensure understanding of the psychological, social, professional, ethical, and legal implications of a genetic disease. In children and adolescents with a sarcomeric protein gene mu- tation, ECG and echocardiographic manifestations of myocar- dial hypertrophy often develop during growth. For this reason, young people should be assessed annually during adolescence. The earliest clinical manifestations of hypertrophic cardiomyopathy Fig. 16.7.2.10 Arrhythmogenic right ventricular cardiomyopathy. On the cine images (top) the right ventricle (RV) is globally dilated with multiple RV wall motion abnormalities. There are two areas of LV involvement with wall thinning (free wall, apex). On T1-weighted imaging, fat can be seen in the septum and RV trabeculae (arrows). After contrast, late enhancement representing fibrosis is also seen (arrows).

 are electrocardiographic, while diastolic dysfunction and altered biomarkers of collagen synthesis may precede the development of left ventricular hypertrophy and also provide early markers of dis- ease. In adults, de novo development of unexplained left ventricular hypertrophy is uncommon, but it does occur, particularly in patients with myosin-binding protein C gene mutations. In dilated cardio- myopathy follow-up of asymptomatic first-degree relatives suggests that disease progression is slow (over decades). The same applies to arrhythmogenic right ventricular cardiomyopathy. Asymptomatic normal adults with a family history of cardiomy- opathy but no identifiable mutation should be offered rescreening every 5 years, or sooner should they develop symptoms. This includes a clinical evaluation with ECG and echocardiography. Rescreening should be guided by the age of onset and severity of cardiomyopathy within the family. Individuals with nondiagnostic clinical features that could represent early disease should be seen more frequently. Athletes, sports, and cardiomyopathy Differentiation between pathological changes of HCM and physio- logical hypertrophy in athletes is required by many governing bodies prior to participation in competitive exercise. Careful assess- ment is needed and often a detraining period of 3 months is recom- mended. Presence of a family history of HCM or sudden cardiac death, symptoms (palpitations, syncope), and ECG changes such as Q waves, ST depression, deep T-wave inversions in inferolateral leads, all favour a diagnosis of HCM rather than athlete’s heart. Other important clues to a diagnosis of HCM include low aerobic capacity, a maximal wall thickness of more than 13 mm, and dia- stolic dysfunction (Box 16.7.2.3). The upper limits of left ventricular wall thickness used to discrim- inate physiological left ventricular hypertrophy from HCM are es- tablished in white athletes. Left ventricular hypertrophy with a wall thickness of more than 15 mm can be physiological in black athletes. The most extreme increase in left ventricular wall thickness have been observed in isotonic or endurance exercise such as rowing, cycling, or swimming. Female

athletes have smaller left ventricular diastolic cavity dimension and smaller wall thickness than males. International guidelines advise against competitive exercise in HCM in view of a potential increased risk of sudden cardiac death. Some evidence implicates physical exercise in increased disease progression and risk of sudden death in arrhythmogenic right ven- tricular cardiomyopathy. Data on exercise in dilated cardiomyop- athy is very limited and controversial.

FURTHER READING Hypertrophic cardiomyopathy Davies MJ, McKenna WJ (1995). Hypertrophic cardiomyopathy: path- ology and pathogenesis. Histopathology, 26, 493–500. Elliott P, McKenna WJ (2004). Hypertrophic cardiomyopathy. Lancet, 363, 1881–91. Elliott P, et al. (2008). Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on myocardial and pericardial diseases. Eur Heart J, 29, 270–6. Elliott P, et al. (2014). ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J, 35, 2733–79. Jacoby D, McKenna WJ (2012). Genetics of cardiomyopathy. Eur Heart J, 33, 296–304. Maron BJ (2002). Hypertrophic cardiomyopathy. A systematic review. JAMA, 287, 1308–20. Maron BJ, et al. (2003). American College of Cardiology Foundation Task Force on clinical expert consensus documents; European Society of Cardiology Committee for practice guidelines. American College of Cardiology/European Society of Cardiology clinical expert con- sensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the European Society of Cardiology Committee for practice guidelines. Eur Heart J, 24, 1965–91. O'Mahony C, et al. (2014). A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk- SCD). Eur Heart J, 35, 2010–20. Priori SG, et al. (2015). ESC guidelines for the management of pa- tients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC). Eur Heart J, 36, 2793–867. Rapezzi C, et al. (2013). Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on myocardial and pericardial diseases. Eur Heart J, 34, 1448–58. Richard P, et al. (2003). Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a mo- lecular diagnosis strategy. Circulation, 107, 2227–32. Wang L, Seidman JG, Seidman CE (2010). Narrative review: harnessing molecular genetics for the diagnosis and management of hyper- trophic cardiomyopathy. Ann Intern Med, 152, 513–20, W181. Dilated cardiomyopathy Caforio AL, et al. (2007). Prospective familial assessment in dilated cardiomyopathy: cardiac autoantibodies predict disease develop- ment in asymptomatic relatives. Circulation, 115, 76–83. Box 16.7.2.3 Features favouring a diagnosis of pathological versus physiological hypertrophy in athletes with mild left ventricular hypertrophy (≥12 mm) • Family history of HCM or sudden cardiac death in first-degree relative(s) ≤40 years • Female gender • Palpitations, syncope • ECG: Abnormal Q waves in at least two leads, ST depression, deep T-wave inversion in inferolateral leads • Peak VO2 <100% of predicted • MWT ≥14 mm • Small left ventricle cavity size (left ventricular end-diastolic diameter <45 mm) • Diastolic dysfunction • Reduced longitudinal left ventricular function • No response to detraining for 3 months • Left atrial enlargement >50 mm • Myocardial fibrosis on cardiac MRI Adapted from Elliott PM, Lambiase PD, Kumar D (2011). Inherited cardiac disease. Oxford University Press, Oxford.

Revision #1
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Updated 2026-01-22 16:39:42 UTC by Omar Ayman