Oliver P. Guttmann and Perry Elliott 16.7.3 Specif

Oliver P. Guttmann and Perry Elliott 16.7.3 Specifific heart muscle disorders 3489

Oliver P. Guttmann and Perry Elliott

16.7.3 Specific heart muscle disorders 3489 Caforio AL, et al. (2013). Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology working group on myocardial and pericardial diseases. Eur Heart J, 34, 2636–48. Herman DS, et al. (2012). Truncations of titin causing dilated cardio- myopathy. N Engl J Med, 366, 619–28. Hershberger RE, Morales A, Siegfried JD (2010). Clinical and genetic issues in dilated cardiomyopathy: a review for genetics professionals. Genet Med, 12, 655–71. Jefferies JL, Towbin JA (2010). Dilated cardiomyopathy. Lancet, 375, 752–62. McNally EM, Mestroni L (2017). Dilated cardiomyopathy: genetic de- terminants and mechanisms. Circ Res, 121, 731–48. Pinto YM, et al. (2016). Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated 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. Sliwa K, et al. (2010). Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof-of-concept pilot study. Circulation, 121, 1465–73. Restrictive cardiomyopathy Muchtar E, Blauwet LA, Gertz MA (2017). Restrictive cardiomyop- athy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. Circ Res, 121, 819–37. Arrhythmogenic right ventricular cardiomyopathy Corrado D, et al. (2015). Treatment of arrhythmogenic right ven- tricular cardiomyopathy/dysplasia: an international task force con- sensus statement. Eur Heart J, 36,

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16.7.3 Specific heart muscle disorders Oliver P. Guttmann and Perry Elliott ESSENTIALS Systemic immune-mediated diseases Cardiovascular involvement is very common, but may be occult and often goes undetected. Any anatomical structure in the heart can be involved, hence patients may present with pericarditis, myocarditis, endocarditis, or coronary vasculitis. There is often no correlation between the extent of systemic disease and cardiac involvement. Systemic lupus erythematosus—more than 50% have cardiovascular involvement at some time; 30% have clinical pericarditis; myocarditis can occasionally present with heart failure or arrhythmias; marantic endocarditis can be identified in at least 30% at autopsy, but is rarely clinically significant; neonates born to mothers with systemic lupus erythematosus who have anti-Ro/anti-La antibodies frequently de- velop complete heart block; atherosclerosis is the leading cause of late death in systemic lupus erythematosus. Systemic sclerosis—symptomatic cardiac involvement is un- common (10%); pulmonary hypertension, usually secondary to lung involvement, has a very poor prognosis. Rheumatoid arthritis—10–15% have clinical cardiac involvement; echocardiography is abnormal in 60%, typically demonstrating pericarditis and/or pericardial effusion; vasculitis affecting epicar- dial arteries, nonspecific valvitis, and conduction disturbances are reported. Seronegative arthropathies—associated with pancarditis, proximal aortitis, aortic incompetence, and varying degrees of conduction abnormalities. Takayasu arteritis—proximal coronary arteries are involved in
15–20%; dilatation of the aortic root may cause aortic regurgitation; pulmonary artery aneurysms and stenoses are common; involve- ment of the renal arteries can cause malignant hypertension; aortic, coronary, pulmonary, and bronchial arterial fistulae are reported. Kawasaki disease—myocarditis is frequent (35%) in the acute stage, often in association with a pericardial effusion; coronary ar- tery involvement occurs in 20%, resulting in aneurysm formation and thrombotic occlusion, such that—in the longer term—patients can present with myocardial ischaemia. Other conditions Amyloidosis—in systemic AL (primary) amyloidosis up to 50% have cardiac involvement. The heart is frequently involved in familial amyloid polyneuropathy caused by mutations in the transthyretin gene in transthyretin and is the main organ involved in senile (wild-type) transthyretin amyloidosis. The typical clinical presentation mimics hypertrophic cardiomyopathy, with restrictive physiology. The ECG may show diminished voltages, loss of R waves in precor- dial leads with a pseudoinfarction pattern. Echocardiography may show a characteristic ‘sparkling’ appearance to the myocardium, thickening of the heart valves and the interatrial septum, and pericar- dial effusions. Symptomatic heart disease typically occurs late in the course of amyloidosis and carries a poor prognosis. Sarcoidosis—cardiac involvement is clinically apparent in less than 10% of cases, but sudden (presumed arrhythmic) death is not in- frequent among these. Isolated cardiac sarcoidosis can present with ventricular arrhythmia, AV block, or myocarditis. Endocrine disorders—diabetes is associated with an increased risk of developing heart failure; hyperthyroidism can cause a high-output state with heart failure with dilated cardiomyopathy and systolic dysfunction; hypothyroidism frequently causes pericardial effusion; phaeochromocytoma and acromegaly can cause cardiomyopathy. Neuromuscular disorders—myocardial dysfunction is common in the muscular dystrophies. In Duchenne and Becker muscular dys- trophy (dystrophin gene mutations) the commonest abnormality is dilated

cardiomyopathy; in laminopathies (lamin AC gene mu- tations) atrial arrhythmia, heart block, dilated cardiomyopathy, and sudden cardiac death are frequent.

section 16 Cardiovascular disorders 3490 Inherited metabolic disorders—hereditary haemochromatosis causes thickening of the ventricular walls, dilatation of the ven- tricular chambers, and heart failure; cardiac disease is par- ticularly important in lysosomal and glycogen storage diseases, including hypertrophic and dilated cardiomyopathy, arrhythmia, and valvular disease. Cardiomyopathy can also be caused by drugs, toxins, nutri- tional deficiency, and electrolyte disorders. Systemic immune-mediated diseases Systemic immune-mediated diseases are autoimmune and auto inflammatory diseases affecting at least two-organ systems, and can be classified as shown in Fig. 16.7.3.1. Autoinflammatory diseases are a family of conditions characterized by episodes of unprovoked inflammation in the absence of high autoantibody titres or auto re- active T lymphocytes, reflecting a primary dysfunction of the in- nate immune system. Autoimmune diseases are characterized by aberrant B, T, and dendritic cell responses with predominantly cell- mediated or autoantibody-mediated responses to self-antigens in genetically susceptible individuals. Cardiovascular involvement in systemic immune-mediated dis- eases may be occult and often goes undetected, but is associated with a poor prognosis. As any anatomical structure in the heart may be involved, patients can present with one or more features consistent with pericarditis, myocarditis, endocarditis, and vasculitis. There is often no correlation between the extent of systemic disease and cardiac involvement. For details of the cardiac manifestations of specific autoimmune rheumatic diseases and the vasculitides, see Tables 16.7.3.1 and 16.7.3.2. General approach to diagnosis of cardiac involvement The pattern of myocardial involvement varies in different systemic immune-mediated diseases, but there are some general consider- ations when assessing cardiac involvement. Symptoms suggesting myocarditis include dyspnoea, palpitations, chest pain, syncope, arrhythmia, and acute or chronic heart failure. As many systemic immune-mediated diseases are associated with accelerated coronary artery disease, myocardial ischaemia should also be ruled out when- ever there are cardiac symptoms. A strategy for diagnostic cardiac work up and management is shown in Fig. 16.7.3.2. An increase in serum cardiac troponin or NT-pro B-natriuretic peptide (BNP) supports a diagnosis of myocardial involvement, but myocarditis can occur in the absence of troponin release. Any unexplained abnormality on standard 12-lead electrocardiography (ECG) or 24-h-ECG Holter monitoring should raise suspicion of cardiac involvement. Standard echocardiography with Doppler and deformation imaging can detect subclinical myocardial, Rare monogenic autoimmune diseases Autoimmune Autoinflammatory Classic polygenic autoimmune diseases (organ nonspecific) Mixed pattern diseases with aquired component (MHC class 1 associations) and autoinflammatory components ALPS IPEX APECED Rheumatoid arthritis Coeliac disease Primary biliary cirrhosis Pemphigus, pemphigoid, Myasthenia gravis Dermatomyositis, polymyositis, Scleroderma Goodpasture syndrome ANCA associated vasculitis Sjogren syndrome Systemic lupus erythematosus Ankylosing spondylitis Reactive arthritis Psoriasis/psoriatic arthritis Behcet syndrome HLA-B.27 associated uveitis Crohn’s disease, ulcerative colitis AOSD and juvenile idiopathic arthritis (JIA) Gout/pseudogout/other crystal arthropathies Some categories of reactive arthritis and Psoriasis arthritis (no MHC associations) Nonantibody associated vasculitis including giant cell and Takayasu arteritis Idiopathic uveitis Acne and acneiform associated diseases Erythema nodosum associated disease, including sarcoidosis FMF, TRAPS, HIDS, PAPA DIRA DITRA FCAS NLRP 12 associated Autoinflammatory Disorders (NLRP12AD) PFAPA CANDLE Majeed syndrome Blau syndrome NOMID MAS CRMO FCAS 2 (Guadalupe type fever syndrome) Interferonopathies Mutant adenosine

Deaminase 2 (organ nonspecific) Polygenic autoinflammatory diseases Rare monogenic autoinflammatory diseases Fig. 16.7.3.1 Classification of systemic inflammatory diseases. ALPS, autoimmune lymphoproliferative syndrome; AOSD, adult-onset Still's disease; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CMRO, chronic multifocal recurrent osteomyelitis; DIRA, deficiency of interleukin-1 receptor antagonist; DITRA, deficiency of the interleukin-36-receptor antagonist; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinaemia D with periodic fever syndrome; HLA, human leukocyte antigen; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; MAS, macrophage activation syndrome; MHC, major histocompatibility complex; NOMID (also known as CINCA), neonatal onset multisystem inflammatory disease; PAPA, pyogenic arthritis, pyoderma gangrenosum, and severe cystic acne; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and adenitis; TRAPS, tumour necrosis factor receptor-associated periodic fever syndrome. From Caforio ALP, et al. (2017). Diagnosis and management of myocardial involvement in systemic immune-mediated diseases: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Disease. Eur Heart J, 38(35), 2649–62, by permission of Oxford University Press.

16.7.3 Specific heart muscle disorders 3491 pericardial, and valvular involvement. Tricuspid and pulmonary Doppler are important methods of assessment for the noninvasive diagnosis of pulmonary hypertension. Cardiac magnetic resonance imaging with tissue characterization sequences provide supportive evidence for cardiac involvement. Specifically, a subepicardial or mid-myocardial late gadolinium enhancement pattern correlates with disease activity in rheumatoid arthritis and systemic scler- osis, and such imaging can also identify early disease in these con- ditions. Computed tomography (CT) is used for the diagnosis of aortic disease, coronary atheroma, and pericardial disease. Positron emission tomography (PET) is useful for detection of myocardial inflammation in sarcoidosis. Autoimmune rheumatic disorders Systemic lupus erythematosus Systemic lupus erythematosus (SLE) is a multisystem immune dis- order characterized by the formation of autoantibodies to various cell antigens. The pathogenesis of SLE myocarditis is thought to be immune-complex mediated. Immunoglobulin deposits and granular complement are evident at autopsy and on endomyocardial biopsy. The prevalence of cardiovascular involvement at some point in the illness is more than 50%. The pericardium is most commonly affected, with as many as 30% of patients having clinical pericarditis at some stage, and up to 80% affected at autopsy. Progression to con- strictive pericarditis or tamponade is extremely rare. Clinically evident myocardial involvement occurs less fre- quently, but is reported in 40–50% of patients at autopsy: signs and symptoms are uncommon, but patients may occasionally pre- sent with heart failure or arrhythmias. Unexplained increases in troponin I and/or NT-pro BNP, global or segmental hypokinesis on transthoracic echocardiography, and a nonischaemic pat- tern of myocardial late gadolinium enhancement and/or oedema on cardiac magnetic resonance imaging, support the diagnosis of myocarditis. SLE myocarditis may be associated with muta- tions in the gene encoding the 3′-5′ DNA exonuclease TREX1. Other factors that may contribute to ventricular dysfunction in Table 16.7.3.1 Cardiac manifestations of systemic immune- mediated diseases and the vasculitides Disease Cardiac manifestation Systemic lupus erythematosus Accelerated atherosclerosis Noninfective endocarditis (Libman–Sacks) Myocarditis Pericarditis Rheumatoid arthritis Coronary arteritis Aortic and mitral regurgitation Seronegative arthropathies— ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, ulcerative colitis,

Crohn’s disease Pancarditis Proximal aortitis Conduction disease Systemic sclerosis Myocarditis Pericarditis Arrhythmias Granulomatosis with polyangiitis (GPA; formerly Wegener’s granulomatosis) Constrictive pericarditis Atrioventricular block Eosinophilic granulomatosis with polyangiitis (EGPA; also known as Churg–Strauss syndrome) Congestive cardiac failure Pericarditis Coronary arteritis/myocardial infarction Arrhythmias Polyarteritis nodosa Hypertension Congestive heart failure Partial or complete coronary artery occlusion Pericarditis Arrhythmias Takayasu’s syndrome Pericarditis Aortic arch vasculitis Heart failure Table 16.7.3.2 Cardiac involvement in the more common autoimmune rheumatic disorders Pericardial involvement Myocardial involvement Valvular involvement Coronary/arteritis Conduction system involvement Rheumatoid arthritis 16–40% at autopsy 10–15% clinical pericarditis 4–20% at autopsy Symptomatic in <5%

> “ 50% valvulitis at autopsy Symptoms rare 11–20% involvement of coronary vessels at autopsy Vasculitis affecting the aorta rare Any part of conduction system involved Varying degrees of heart block in 0.1% SLE 45–66% at autopsy 20–30% clinical pericarditis 30% at autopsy Symptomatic in <10% Libman–Sacks lesions in 30% at autopsy Coronary vessels involved in <10% Vasculitis affecting the aorta rare Any part of conduction system involved Varying degrees of heart block in <1% Systemic sclerosis and variants 70% at autopsy 7–15% clinical pericarditis Up to 60% at autopsy Symptoms rare Rare, AR, and MVP described Symptoms in <10% Reversible perfusion defects in up to 40% Vasculitis demonstrated rarely Any part of conduction system involved; Abnormal ECG in 50% Polymyositis/ dermatomyositis Clinical involvement rare (usually in children with dermatomyositis) Up to 25% at autopsy Symptoms in 13–26% MVP common Other lesions rare Any part of conduction system involved Symptoms extremely rare Seronegative spondyloarthropathies <1% incidence of pericarditis in AS and Reiter’s Myocardial involvement/ dysfunction common on echo in AS Symptoms rare Aortic incompetence most common: 1–10% in AS, 1–15% in Reiter’s MR very rare Aortitis: 1–10% in AS, 1–15% in Reiter’s Heart block: 8% in AS, 8% in Reiter’s, rare in other forms of spondyloarthropathy AR, aortic regurgitation; AS, ankylosing spondylitis; MR, mitral regurgitation; MVP, mitral valve prolapse; SLE, systemic lupus erythematosus.

section 16 Cardiovascular disorders 3492 SLE include atherosclerosis, hypertension, and drug therapy, in particular chloroquine. The latter can be distinguished using endomyocardial biopsy. As many as one-third of patients with SLE have systolic murmurs, which are usually caused by hyperdynamic flow. The classic verru- cous vegetations adherent to the endocardium described by Libman and Sacks in 1924 (marantic endocarditis) can be identified in 30% or more at autopsy. These lesions most commonly affect the mitral valve but are rarely clinically significant. Neonates born to mothers with SLE who have anti-Ro/anti- La antibodies frequently develop complete heart block (see Chapter 14.14). Various degrees of heart block and bundle branch block can be seen in adults, but complete heart block is rare. Arrhythmias such as atrial fibrillation and flutter may also occur, particularly in association with pericarditis. Myocardial infarction is uncommon in patients with SLE, but ac- celerated or premature atherosclerosis is the leading cause of late death in SLE.

Its cause is unknown, but suggested contributory fac- tors include chronic inflammation, immune complex deposition, antiphospholipid antibodies, hypertension, dyslipidaemia, and hyperglycaemia (caused by chronic steroid administration). Death from the cardiac complications of lupus is rare. Mild peri- cardial disease may respond to nonsteroidal anti-inflammatory drugs, heart failure is treated conventionally, and conduction defects may require pacing. Coronary vasculitis and/or lupus myocarditis are usually treated with steroids and other immunosuppressants such as azathioprine, cyclophosphamide, or intravenous immuno- globulin (IVIg), but there are no trials to guide therapeutic decision- making in these rare conditions. Antiphospholipid syndrome The antiphospholipid syndrome is recognized both in patients without SLE (primary) and with SLE. It is a thrombophilic dis- order characterized by arterial and venous occlusions, recurrent fetal loss, thrombocytopenia, and increased maternal compli- cations of pregnancy, and is associated with persistently raised titres of anticardiolipin antibodies. Anticoagulation is indicated in patients with thrombotic symptoms and prevents miscar- riage in pregnant women. In refractory cases plasmapheresis can be used. Systemic sclerosis Systemic sclerosis is characterized by abnormal collagen deposition in various organ systems and cardiac involvement may be primary or secondary to concomitant kidney and/or pulmonary vascular/ interstitial disease. Symptomatic heart disease is uncommon (10%), but cardiac involvement is frequently detected at autopsy (60%), when the most common features are chronic pericarditis (70%) and myocardial fibrosis (37%). Clinically these cause heart failure, ventricular arrhythmia, and conduction disease. A high arrhythmic burden has been reported, with a 5% sudden death rate in patients with both skeletal and cardiac muscle disease. Rare cases of cardiac tamponade have been described. Valve involvement is uncommon, except for tricuspid regurgitation, which occurs in 40% of patients and is usually associated with pulmonary hypertension. Pulmonary hypertension is present in 47% of patients, usually secondary to lung involvement, and is associated with a 1-year survival of only 50%. Involvement of the large epicardial blood vessels is not a feature Cardiac red flags (one or more) in a patient with known SIDs: unexplained dyspnoea, palpitations, chest pain with or without troponin increase, syncope, arrhythmia, acute or chronic heart failure, aborted sudden cardiac death, fulminant unexplained cardiogenic shock Cardiological evaluation History, Examination, ECG, Echo, Troponin, BNP/pro-BNP, CMR, PET, CT, complete heart catheterisation; if available, serum cardiac autoantibodies Exclude: pericardial, valvular and coronary artery disease, extra-cardiac causes (e.g. pulmonary embolism) Specific work-up tailored to the individual case and clinically oriented No coronary artery disease, no known causes for cardiac red flags Clinically suspected myocardial involvement in SIDs (e.g. myocarditis) Consider EMB (histology, immunohistology, special stains, search for infectious agents

- Multidisciplinary management at baseline and follow-up including a cardiologist
- Disease-specific therapies: personalised and targeted to lowest level of disease activity, e.g. treat-to-target strategy Fig. 16.7.3.2 Myocardial involvement in systemic immune-mediated diseases: diagnostic workup and management. CMR, cardiac magnetic resonance; CT, computed tomography; EMB, endomyocardial biopsy; SIDs, systemic immune-mediated diseases. From Caforio ALP, et al. (2017). Diagnosis and management of myocardial involvement in systemic immune-mediated diseases: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Disease. Eur Heart J, 38(35), 2649–62, by permission of Oxford University Press.

16.7.3 Specific heart muscle disorders 3493 of systemic sclerosis, but microvascular dysfunction is common and may contribute to myocardial ischaemia and patchy myocar- dial fibrosis. In the limited form of systemic sclerosis (formerly known as CREST syndrome) the overall prognosis is more favour- able: pulmonary hypertension without severe lung disease occurs in 10–15%, and subclinical left ventricular dysfunction is reported. Autoimmune myocarditis should be managed by immunosuppres- sive treatment. Rheumatoid arthritis Cardiac involvement is found in up to 60% of patients on echo- cardiography, but in only 10–15% clinically. The presence of car- diac disease correlates with the severity of joint disease and the presence of rheumatoid nodules, male gender, age, high titres of rheumatoid factor, and other systemic markers of disease activity. Histological changes consist of a nonspecific inflammatory infil- trate, myocyte necrosis, and fibrosis affecting any part of the heart. Focal lymphocytic, diffuse necrotizing or granulomatous myocar- ditis may cause cardiomyopathy in 3–30% of patients. Rheumatoid nodules may accompany this, and the heart may be affected rarely 5% by secondary amyloidosis. Myocarditis is reported in up to 40% at autopsy, but symptoms are uncommon. Pericarditis oc- curs more frequently, and up to 40% of patients have an effusion on echocardiography, but progression to constrictive pericarditis or tamponade is rare. Acute vasculitis involving the larger epi- cardial arteries has been reported but is uncommon. Accelerated atherosclerosis is considered a complication, resulting from com- bination of chronic systemic inflammation and oxidative stress in addition to classic cardiovascular risk factors. Nonspecific valvitis may affect the mitral and particularly the aortic valve: this may eventually lead to scarred, hyalinized, and even incompetent valves. Rheumatoid nodules may occasionally deform the mitral valve and lead to valvular incompetence. Conduction disturb- ances may be secondary to infiltration by rheumatoid nodules: the commonest ECG abnormality is first-degree heart block, but left bundle branch block and complete heart block are also described. Although pericarditis is usually responsive to steroids, it is unclear whether steroids or disease-modifying drugs alter the other car- diac manifestations. Seronegative arthropathies This group of disorders is characterized by the absence of rheuma- toid factor and includes ankylosing spondylitis, Reiter’s syndrome, and psoriatic and gastrointestinal arthropathies. These may all be associated with cardiac involvement, in particular pancarditis, prox- imal aortitis, aortic incompetence, and varying degrees of conduc- tion abnormalities. They may also result in amyloid deposition. On occasion cardiac disease may present before joint disease. Treatment is empirical and based on symptomatology. Polymyositis and dermatomyositis Cardiac symptoms in polymyositis or dermatomyositis are rare, but post-mortem and clinical studies suggest that left ventricular diastolic dysfunction and conduction disturbances are present in 40–50% of cases. When cardiac symptoms are present they are as- sociated with a poor prognosis. Rare cases of cardiac tamponade are reported. Interstitial lung disease, found in 5–30% of cases, may lead to right heart failure. Treatment is symptomatic. Vasculitides Takayasu’s arteritis Takayasu’s arteritis is a rare inflammatory arteritis that predomin- antly affects the thoracic aorta and the proximal portions of its major branches, the pulmonary arteries, and the coronary vessels. Asians are thought to be affected more than other ethnic groups with a 10:1 female to male ratio. The disease typically evolves from an early in- flammatory stage to a fibrotic obliterative phase with arterial aneur- ysms, stenoses, and occlusions. The proximal coronary arteries are involved in 15–20% of cases. Dilatation of the aortic root may cause aortic regurgitation. Pulmonary artery aneurysms and stenoses are common and can cause pulmonary hypertension, right heart failure, and pulmonary haemorrhage. Involvement of the renal arteries can cause malignant hypertension. Compared with healthy controls, higher rates of hypertension, low birth rate, and increased perinatal mortality occur in women with a diagnosis of Takayasu’s arteritis. Aortic, coronary,

pulmonary, and bronchial arterial fistulae are reported. Subclinical myocardial involvement, in the absence of cor- onary lesions, is reported in up to 50% of patients. Pericarditis is rare. Assessment of disease activity in Takayasu arteritis is challen- ging as there are no gold standard clinical signs or laboratory measures. Computerized tomography and magnetic resonance angiography show vascular stenosis, occlusions, and aneurysms. Fluorodeoxyglucose positron emission tomography-computerized tomography (FDG-PET/CT) often shows vascular inflammation before any structural changes. There are no randomized controlled trials of immunosuppressive therapy, but corticosteroids with adjunctive immunosuppressive agents are standard care. Biological agents such as antitumour ne- crosis factor (TNF) agents, tocilizumab, and rituximab have been used in refractory cases. Patients with ischaemic vascular lesions are treated with endovascular intervention or vascular surgery, but re- currence is frequent. Polyarteritis nodosa Classic polyarteritis nodosa (PAN) is a rare, ANCA-negative, non- granulomatous, necrotizing arteritis of small and medium-sized vessels without microscopic angiitis or glomerulonephritis. The most typical cardiovascular complication is malignant hypertension caused by renal artery vasculitis. Coronary vasculitis causing an- eurysms, myocardial infarction, and cardiomyopathy are reported, but they are rare. Pericarditis and clinically important conduction system involvement is uncommon. Valve disease is not seen. Giant cell (temporal) arteritis Giant cell arteritis is a granulomatous arteritis of the aorta and its major branches, in particular the carotid artery. It usually affects people older than 50 years of age. Around 5–10% of patients have cardiac involvement, the most common lesions being thoracic aortic aneurysms and aortic regurgitation. 18F-FDG-PET scan may show tracer uptake in the aorta and large arteries in the absence of clinical activity and may be associated with aortic dilatation. Coronary ar- terial involvement is rare. Kawasaki’s disease Kawasaki’s disease (or mucocutaneous lymph node syndrome) is an acute vasculitis of small and medium-sized vessels that typically

 presents in children aged less than 5 years, with a peak at 1 year and a small male predominance (1.5:1). Diagnosis is based on the presence of persistent fever in combination with a polymorphous exanthema, cervical lymphadenopathy, nonpurulent conjunctival injection, changes of the lips and oral cavity (strawberry tongue, cracked lips, redness of the mucosae), and changes in extremities (swelling, redness, and desquamation of the palms). desquamation in the subacute phase). In the acute stage, myocarditis is frequent (35%), often in associ- ation with pericardial effusions, treatment being with aspirin and high-dose γ-globulin. Coronary artery involvement occurs in 20%, resulting in aneurysm formation and thrombotic occlusion, such that in the longer-term patients can present with acute coronary syndromes and myocardial ischaemia, which are managed conven- tionally. See Chapter 19.11.12 for further discussion. Antineutrophil cytoplasm antibody (ANCA)-associated vasculitides Antineutrophil cytoplasm antibody (ANCA)-associated vasculit- ides are small-vessel vasculitides that include granulomatosis with polyangiitis (GPA; formerly Wegener’s granulomatosis), micro- scopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA; also known as Churg–Strauss syndrome). ANCA-associated vasculitides affect both genders equally and the average age at diagnosis is in the fifth decade. Microscopic polyangiitis Microscopic polyangiitis is a necrotizing vasculitis of capillaries, venules, and arterioles with occasional involvement of medium-sized vessels. Cardiac involvement is rare, but described in the forms of pericarditis, heart failure, and myocardial infarction. Granulomatosis with polyangiitis (formerly Wegener’s granulomatosis) Granulomatosis with polyangiitis is a necrotizing vasculitis of me- dium and small vessels associated with granulomatous lesions in the upper and lower respiratory tract, but any other

organ can be affected. Pericarditis (35% of cases), coronary arteritis (12%), and cardiomyopathy (30%) are the most frequently reported cardiac ab- normalities. Valvulitis and arrhythmias have also been described, but their frequency varies substantially between series. Coronary arteritis is relatively common at post-mortem, but rarely causes myocardial infarction. Myocarditis and complete heart block are rare (2%). Treatment is with combinations of immunosuppressant drugs, including biologic agents such as rituximab. Eosinophilic granulomatosis with polyangiitis (formerly Churg– Strauss syndrome) and other hypereosinophilic syndromes Hypereosinophilic syndromes are defined by a persistent blood eo- sinophilia (>1.5 × 109/litre) lasting for more than six consecutive months, associated with evidence of eosinophil-induced organ damage in the absence of other causes of hypereosinophilia, such as allergy, parasitic infection, or malignancy. Hypereosinophilia is a fea- ture of some vasculitides, in particular eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome). Some cases of hypereosinophilia are caused by stem cell mutations that lead to expression of fusion genes (mainly FIP1L1-PDGFRA) with constitutive tyrosine kinase activity that cause overproduction of interleukin-5 by activated T-cell subsets. Clinically, hypereosinophilia syndromes can be classified into chronic eosinophilic leukaemia, lymphocytic hypereosinophilic syndrome, myeloproliferative hypereosinophilic syndrome, and idiopathic hypereosinophilic syndrome. The term organ-restricted eosinophilic disease is used when disease is confined to a specific organ or tissue. Löeffler’s fibroplastic endocarditis with eosinophilia refers to cardiac disease caused by direct toxicity of circulating eosinophils. Hypereosinophilic heart disease includes endomyocarditis, endo myocardial fibrosis, or cardiomyopathy. It is characterized by endocar- dial thickening and apical obliteration caused by large mural thrombi. A restrictive left ventricular filling pattern is typical. Gadolinium delayed-enhanced cardiac magnetic resonance imaging identifies regions of myocardial fibrosis and thrombosis. Diffuse myocardial involvement may lead to heart failure, ventricular remodelling, and dilated cardiomyopathy. Involvement of the atrioventricular valves can lead to severe mitral and tricuspid regurgitation. General therapy includes anticoagulation and heart failure therapy. Patients with the FIP1L1-PDGFRA fusion gene chromo- somal rearrangement are treated with the tyrosine kinase inhibitor imatinib, often following pretreatment with corticosteroids. For patients without the FIP1L1-PDGFRA fusion gene, corticosteroids are the usual first-line therapy; steroid-sparing and second-line drugs include hydroxycarbamide, interferon alfa, cyclophospha- mide, and imatinib. The prognosis is generally poor, even if the hypereosinophilia is resolved, due to high mortality from heart failure, sudden death, or thromboembolism, depending on the underlying cause and end-organ damage. Behçet’s disease Behçet’s disease is a relapsing inflammatory disorder character- ized by oral and genital ulceration, uveitis, and arterial and venous thrombosis. The disease is common in the eastern Mediterranean and eastern Asia. Cardiac disease, including myocarditis, atrio- ventricular block, pericarditis, and valve disease, is present in less than 5% of patients. Coronary artery disease is very rare (<1%) but poses challenges for revascularization because of tissue fragility and pseudoaneurysm formation. Aneurysms may also be seen in the pul- monary (Hugues–Stovin syndrome), coronary, and other arteries. Amyloidosis Amyloidosis describes a group of diverse diseases (see Chapter 12.12.3) that is characterized by extracellular insoluble fi- brils derived from the aggregation of various misfolded proteins that deposit with a range of chaperone proteins in organs such as the heart, kidneys, liver, gastrointestinal tract, lungs, and soft tis- sues. There are more than 30 proteins that can form amyloid fi- brils, five of which frequently infiltrate the heart and cause cardiac amyloidosis: immunoglobulin light chain (AL or primary amyloid- osis), immunoglobulin heavy chain (AH), transthyretin (ATTR), serum amyloid A (AA), and apolipoprotein A I (AApoA1). The overwhelming majority of patients with cardiac

amyloidosis are af- fected by either AL or ATTR amyloidosis.

16.7.3 Specific heart muscle disorders 3495 AL cardiac amyloidosis is a rare condition with an estimated preva- lence of 8 to 12 per million. The population prevalence of TTR- cardiac amyloidosis is less certain, but recent data suggest that is relatively common in older people with heart failure with preserved ejection fraction, low-flow aortic stenosis, and atrial fibrillation. AL amyloidosis occurs equally between the genders and as many as 50% of patients have cardiac involvement, which will mani- fest clinically in up to one-half of these. Multiorgan involvement causing neuropathy and nephropathy is typical. Some ‘benign’ gammopathies are implicated in the pathogenesis, but any B-cell dyscrasia can be the cause. The heart is frequently involved in familial amyloid polyneurop- athy. This is the most common type of hereditary amyloidosis and is caused by one of more than 70 mutations in the transthyretin (TTR) gene. Senile TTR amyloidosis caused by deposition of wild-type TTR is extremely common; indeed, almost all individuals over the age of 80 years will have scattered deposits of amyloid, particularly affecting the aorta: clinical involvement is variable, depending on the extent of deposition. In patients with severe cardiac involve- ment, there is a large male predominance, and the condition is al- most exclusive to individuals older than 65 years of age. The disease is slowly progressive with a median survival of about 75 months. The extracellular deposition of amyloid results in a firm, thick- ened, noncompliant myocardium. Deposition occurs throughout the atrial and ventricular muscle and in the specialized conduction tissue: fibrosis of these structures may occur. Valvular function is rarely affected, although thickening of cardiac valves is common. Intramural coronary arteries and veins frequently contain deposits, which can occasionally compromise the lumina of these vessels. Amyloid heart disease most frequently mimics hypertrophic car- diomyopathy with restrictive physiology. The reduced compliance of the myocardium produces the characteristic diastolic dip and plateau (square root sign) in the ventricular pressure waveform. An impaired rate of early diastolic filling is characteristic and systolic dysfunction may also occur, leading to congestive heart failure. Arrhythmias are common, in particular ventricular premature beats and atrial fibrillation. Complex ventricular arrhythmias may be harbingers of sudden death. Progressive atrioventricular con- duction delay is common and infiltration of the autonomic nervous system results in orthostatic hypotension in 10% of cases. The chest radiograph may show cardiomegaly in patients with systolic dysfunction but is often normal in those with restrictive cardiomyopathy, although pulmonary congestion may be prom- inent. Electrocardiography (CG) shows diminished voltages in about 50% of patients, and loss of R waves in precordial leads; the presence of Q waves in the inferior leads may simulate myocar- dial infarction. Echocardiography reveals an increased thickness of the ventricular walls with small ventricular chambers, dilated atria, intra-atrial septal thickening, left ventricular dysfunction, and a characteristic ‘sparkling’ appearance to the myocardium. The pattern of hypertrophy is usually concentric but may be asymmet- rical septal. 99mTc-phosphate derivatives (99mTc-PYP and 99mTc- 3,3-diphosphono-1,2-propanodicarboxylic (DPD)) are useful in diagnosing ATTR-cardiac amyloidosis, which is particularly avid for bone tracers, and radionuclide imaging with these ligands may better estimate amyloid load than cardiac magnetic resonance imaging. Serum amyloid protein scintigraphy is useful to assess extracardiac but not cardiac involvement in AL amyloidosis. Cardiac magnetic resonance imaging with gadolinium contrast agents has a charac- teristic pattern of late enhancement once there is left ventricular hypertrophy and/or systolic impairment. Myocardial T1 mapping by cardiac magnetic resonance is also useful in the diagnosis of car- diac amyloidosis. In AL cardiac amyloidosis, troponin T, and BNP plasma concentrations are usually elevated and relate to

prognosis. Diagnosis can be confirmed histologically from rectal, salivary gland, subcutaneous fat, or (if necessary) cardiac biopsy; all forms of amyloid show an amorphous proteinaceous substance that demon- strates apple green birefringence under polarized light when stained with Congo Red. Genetic testing can be used to confirm hereditary TTR amyloidosis. Symptomatic heart disease typically presents late in the course of amyloidosis and the presence of clinical signs is an ominous feature, with mortality approaching 100% at 2 years for AL amyl- oidosis. Treatment is supportive in combination with measures to suppress the underlying amyloidogenic condition. Chemotherapy or peripheral autologous stem cell therapy may be appropriate in some cases of AL amyloidosis. Orthotopic liver transplantation or combined heart and liver transplantation have shown promising results, particularly in selected cases of TTR-related familial amyl- oidosis. Anticoagulation is important in patients with atrial ar- rhythmia due to the high incidence of thromboembolism. Digoxin and calcium channel antagonists should be avoided as they select- ively bind to amyloid fibrils, enhancing their effect. Patients with symptomatic conduction system disease require a pacemaker. Diuretics and vasodilators should be used cautiously as they may aggravate hypotension. Cardiac transplantation is feasible in selected cases, but is a palliative procedure without treatment of the underlying process. Sarcoidosis Sarcoid is a multisystem granulomatous disorder of unknown aeti- ology. The overall prevalence is about 20 per 100 000 population. Myocardial involvement is seen in 20–30% of patients at autopsy but is clinically apparent in less than 10% of cases. Primary cardiac in- volvement is extremely rare. Noncaseating granulomas may involve any region of the heart, although the left ventricular free wall and interventricular septum are the most commonly affected sites. The granulomas can be lo- calized or widespread, and healing may result in the formation of scars. The ventricular muscle eventually becomes increasingly non- compliant, leading to defects in contractile function as well as wall motion. Replacement of large portions of the ventricle by sarcoid tissue may lead to aneurysm formation. Granulomas and fibrosis may also extend to involve nodal or conducting tissue. Isolated peri- cardial involvement is rare, although pericardial effusions are com- monly seen on echo. Valvular dysfunction occurs in less than 5% of patients and may be the result of infiltration of papillary muscles or direct valvular involvement, which is less common. Clinical manifestations of myocardial sarcoidosis are shown in Table 16.7.3.3. Chest pain has been described in up to 28% of pa- tients, and since about one-half of these will have abnormal thallium

 perfusion scans despite arteriographically normal coronary arteries, this is thought to be secondary to microvascular dysfunction. Sudden death secondary to ventricular tachycardia and fibrilla- tion occurs in some cases. The presence of a ventricular aneurysm may be associated with resistant ventricular arrhythmias and neces- sitate its resection. Conduction disturbances such as complete heart block are a frequent occurrence, particularly in the acute phase of the disease. The electrocardiogram is frequently abnormal, with T-wave abnormalities and varying degrees of intraventricular or atrioventricular block. Pathological Q waves may simulate myo- cardial infarction when myocardial involvement becomes exten- sive. Echocardiography shows features which may mimic dilated, restrictive or arrhythmogenic cardiomyopathy with systolic and/or diastolic dysfunction, regional wall motion abnormalities, and an- eurysms. Gallium or fluorodeoxyglucose (FDG) PET, single photon emission computed tomography (SPECT), and magnetic resonance imaging with gadolinium late enhancement have all been used to detect affected areas of myocardium. Endomyocardial biopsy can be diagnostic, but may be negative due to the patchy nature of the disease. Steroids can improve symptoms as well as electrocardiographic and echocardiographic features and myocardial perfusion de- fects, but

there is a lack of randomized trial data. Steroid-sparing agents such as methotrexate and azathioprine may be used in re- lapsing or refractory disease. Amiodarone may be of benefit in re- sistant arrhythmia, and the insertion of an implantable defibrillator (ICD) may protect against sudden death in susceptible patients. Transplantation may improve prognosis and quality of life in pa- tients who remain symptomatic despite these measures, although recurrence in the graft has been documented. Cardiac disease in endocrine disorders Diabetes A man with diabetes has a relative risk of developing heart failure that is 2.4 times higher than that of a man without diabetes, and the equivalent relative risk for a woman is 5:1. The risk has been shown to be independent of age, systolic blood pressure, serum cholesterol, and weight. People with diabetes have elevated end- diastolic pressures, reduced ejection fractions, left ventricular dila- tation, and hypertrophy, even in the absence of coronary artery disease. Diastolic dysfunction as well as a diffuse hypokinesis of the myocardium has also been demonstrated. Implicated mechanisms include small-vessel disease and autonomic neuropathy. The most prominent histopathological finding is myocardial fi- brosis. Occasionally a picture resembling restrictive heart disease is seen, with a small left ventricular chamber and reduced compliance of the left ventricle. The treatment of heart failure is the same as in patients without diabetes, although β-blockers with intrinsic sympathomimetic ac- tivity are preferred. Preload and afterload reducing agents should be used cautiously because of autonomic dysfunction. It is unclear whether tight glucose control affects the progression of diabetic car- diomyopathy, but it is clearly prudent for other reasons to optimize control as well as to reduce obesity and control hypertension. Hyperthyroidism In general, excess thyroid hormone results in a high-output state with tachycardia, increased cardiac contractility, and peripheral vasodilatation. In the long term this can result in ventricular hyper- trophy and an increase in ejection fraction. However, some patients may develop a low-output state with symptoms of heart failure and echocardiographic demonstration of dilated cardiomyopathy and systolic dysfunction. These changes may be a result of long-standing tachycardia and increased cardiac work, but thyroxine (T4) itself may directly alter the expression of cardiac proteins involved in cardiac function, and there is also some evidence that direct auto- immune myocardial damage may occur in Graves' disease. Typical cardiac symptoms of hyperthyroidism include angina-like chest pain, fatigue, palpitations, and exertional dyspnoea. Cardiac findings include sinus tachycardia and atrial flutter or fibrillation in 17–20%. These may be complicated by thromboembolism in up to 40%; also by congestive heart failure. Mitral valve prolapse has been reported in patients with Graves' disease. Control of the ventricular rate in atrial fibrillation should be achieved with digoxin, β-blockers, or calcium channel antagonists. The increased metabolic clearance of digoxin may necessitate a higher maintenance dose. Attempts at cardioversion should gener- ally be deferred until the patient is euthyroid, at which time they may have spontaneously reverted to sinus rhythm. The presence of an al- ready dilated vascular bed means that diuretics should be used with caution and vasodilators are generally contraindicated. Hypothyroidism Patients suffering from hypothyroidism, whether in its mild form or myxoedema, present a wide variety of symptoms. Complaints of fa- tigue, lethargy, mental slowness, and cold intolerance usually dom- inate. Less frequently, symptoms suggestive of cardiac dysfunction such as dyspnoea on exertion, syncope, or angina-like chest pain may be prominent. The most common cardiac abnormality is pericardial effusion, which is usually asymptomatic but reported in at least 30% of untreated patients. Heart failure generally represents exacerbation of pre-existing cardiac disease by the superimposed haemodynamic consequences of thyroid deficiency—bradycardia, diminished myo- cardial contractility, and increased peripheral vascular resistance. Rarely, hypothyroidism alone can closely resemble cardiomyopathy and be severe enough to cause heart failure.

Echocardiographic evi- dence of asymmetric thickening of the interventricular septum as well as reduced dimensions of the left ventricular outflow tract has Table 16.7.3.3 Clinical manifestations in myocardial sarcoidosis Abnormality Reported percentage
of patients affected Atrioventricular block 41–52 Ventricular ectopics 31–47 Congestive heart failure 12–19 Sudden death 21–38 Bundle branch block 26–34 Supraventricular tachycardia 11–25 Ventricular tachycardia 12–23 Simulating myocardial infarction on ECG 14–18 Pericarditis/pulmonary embolism 4–8

 been reported. The characteristic ECG findings are sinus brady- cardia, prolongation of the QT interval, and a reduction in voltages if there is an associated pericardial effusion. The management of heart failure involves the identification of any coexisting cardiac disease and thyroid hormone replacement. Levothyroxine significantly enhances myocardial performance within 1 week but in patients with known or suspected coronary ar- tery disease it should be initiated at a lower dose than usual, typically 25 micrograms/day, and increased slowly at 4-to 6-week intervals until the thyroid-stimulating hormone is within the normal range. Tri-iodothyronine (T3) may be preferable in severe cases as clinical improvement occurs sooner. β-blockade can be used prophylac- tically or added if treatment with thyroxine exacerbates ischaemic heart disease. Adrenal disorders An acute takotsubo-like (see later) catecholamine cardiomyopathy has been described in 3–11% of cases in large series of patients with phaeochromocytoma or paraganglioma. Cardiac function improves following effective treatment of the tumour. Acromegaly In a large series of patients presenting with acromegaly, 10% had overt high-output heart failure with a dilated left ventricle, increased ventricular mass, and modest decline in ejection fraction. Effective treatment of the acromegaly, with control of growth hormone secre- tion, can produce stabilization or improvement in cardiac function, but prognosis is poor if this cannot be achieved. Cardiac disease in neuromuscular disorders Myocardial dysfunction is particularly common in the muscular dystrophies, a group of disorders characterized by progressive skel- etal and cardiac muscle involvement (Table 16.7.3.4). Dystrophic effects on skeletal muscle result in fibre necrosis, followed by fi- brosis and fatty replacement. These structural and functional changes, which occur in the ventricles, can lead to the development of cardiomyopathy, in particular dilated cardiomyopathy and heart failure. The effect on the specialized conducting tissue may lead to bradyarrhythmias, conduction defects, malignant arrhythmias, and sudden death. Duchenne and Becker muscular dystrophy are progressive dis- orders arising from abnormalities (deletion, duplication, or point mutation) in the genes coding for the extrasarcomeric cytoskeletal protein dystrophin. In addition to defects in dystrophin, other de- fects that cause muscular dystrophy and dilated cardiomyopathy in- clude those affecting the genes for the intracellular proteins emerin (a transmembrane protein that is embedded in the inner nuclear cell membrane) and lamin A/C (filament-like proteins that form a proteinaceous mesh underlying and attached to the inner nuclear membrane). Mutations in desmin, a type III intermediate filament protein, cause dilated cardiomyopathy, restrictive cardiomyopathy, and progressive distal myopathy. By the age of 13 years more than 50% of boys with Duchenne mus- cular dystrophy have an abnormal echocardiogram (hypertrophic or dilated cardiomyopathy). ECG abnormalities (poor R wave ampli- tude, axis deviation, and Q waves) are found in more than 90% from an early age. There is some evidence that angiotensin-converting enzyme (ACE) inhibitors delay progression of dilated cardiomyop- athies in Duchenne muscular dystrophy. Cardiac death occurs in up to 50% of patients with Becker mus- cular dystrophy. ECG and echocardiography are abnormal in most patients, and it is noteworthy that the severity of cardiomyopathy is not related

to the degree of skeletal muscle involvement. Autosomal dominant Emery–Dreifuss muscular dystrophy and limb girdle muscular dystrophy type 1B are caused by mutation in lamin A/C. Heart block is common and patients require pacing at a mean age of 32 years. About 35% of patients will have early-onset di- lated cardiomyopathy (age 19–55 years). ICD implantation is often indicated as pacemakers do not prevent sudden cardiac death. Myotonic dystrophy type I is an autosomal dominant disease caused by expanding CTG repeats in the DMPK gene. Cardiomyopathy is rare, but cardiac involvement in the form of distal atrioventricular conduction disturbance is very common (90%). Bradycardia, PR interval prolongation, atrioventricular block, bundle branch block, and atrial arrhythmias are described. Sudden cardiac death occurs in 10–33% of patients. An electrophysiology study should be con- sidered in patients with first-degree atrioventricular block or with evidence of arrhythmia and syncope/near syncope. Implantation of a permanent pacemaker is indicated if the HV interval is greater than 70 ms. Therapy with ICD can be considered in patients with symptomatic ventricular arrhythmia. Myotonic dystrophy type II is similar to type I, but less severe, with cardiac involvement in about 20% of patients. Cardiac disease in inherited metabolic disorders Haemochromatosis Hereditary haemochromatosis is the most common single-gene dis- order in people of northern European origin, where approximately 3 to 5 persons per 1000 are homozygous for the condition. It results in excessive and inappropriate mucosal absorption of iron, which is then deposited predominantly in the heart, liver, gonads, and pan- creas. Clinical involvement of the heart is uncommon, but thickening of the ventricular walls together with dilatation of the ventricular chambers and heart failure is described. Histopathologically, myo- cardial degeneration and fibrosis occur over time and may extend to involve the conducting system of the heart. The ECG most commonly reveals changes in ST and T waves. Supraventricular arrhythmias are characteristic, with atrioven- tricular conduction defects and ventricular arrhythmias being less common. Echocardiography typically shows a mixed dilated and restrictive cardiomyopathy with thickened ventricular walls, ven- tricular chamber enlargement, systolic and/or diastolic dysfunction. Endomyocardial biopsy may be useful to confirm the diagnosis. Treatment involves repeated phlebotomy and/or iron chelators. Lysosomal diseases Cardiac disease is particularly important in lysosomal storage disorders. They are categorized into mucopolysaccharidoses, mucolipidoses, glycoproteinoses, and glycosphingolipidoses (Anderson–Fabry disease). The prevalence of lysosomal storage dis- orders is about 1 in 7000. With the exception of Anderson–Fabry,

 Danon’s, and Hunter’s syndrome, which are X-linked, all are auto- somal recessively inherited. Cardiac involvement is character- ized by substrate accumulation within the myocardium and heart valves. This results in structural abnormalities and arrhythmias. Management requires a multidisciplinary approach in view of the chronic and progressive nature of these diseases. Treatment options (depending on the particular disorder) include substrate inhib- ition therapy, surgical intervention, bone marrow transplantation

Table 16.7.3.4 Cardiovascular abnormalities in neuromuscular disorders

Condition	Inheritance	Cardiac disease	Noncardiac manifestations	Genetic defects
Duchenne	X-linked 1:3500 male births	HCM and DCM reported	Symptoms uncommon	Begins in first decade, 62% have ECG changes by age 10 years: short PQ, prolonged QT, tall R in V1
Conduction system anomalies/dependency by age 12	Death in adolescence	Severe muscle weakness, proximal- girdle distribution at 2–5 years in males	Calf pseudohypertrophy, mild cognitive impairment, high CPK	Wheelchair	Xp21; dystrophin gene mutations
Becker	X-linked 1:15 000 male births	High incidence of clinical cardiac involvement, heart failure is the most common cause of death	DCM seen	ECG usually

abnormal: reduced R wave or prominent Q in 1, AVL, and V6 Arrhythmias and heart block in <10% Mild to moderate muscle weakness, proximal-girdle distribution from childhood, and ambulation preserved at least until late teens Calf pseudohypertrophy, high CPK Lifespan usually dependent on severity of cardiac involvement Xp21; dystrophin gene mutations X-linked dilated cardiomyopathy X-linked (rare) 2nd or 3rd decade onset of CM and heart failure, rapid cardiac progression Milder variants possible Heart block not reported, arrhythmias in <10% No muscular weakness. Muscle cramps, myalgias CPK usually elevated Xp21; altered or selective loss of cardiac dystrophin Limb girdle AD Variable degrees of AV block, AF, with high degree block, bradycardia, palpitations, and syncope Mild to moderate muscle weakness, proximal limb girdle distribution. CPK elevated Lamin A/C gene, 1q11–21 1B AD DCM in 35% 19–55 yrs, 90% conduction anomalies by 30 yrs, SCD in 50% (despite pacing) Childhood onset of contractures, mild muscle weakness in humeroperoneal distribution Lower extremities affected first CPK elevated moderately May be little evidence of skeletal myopathy Allelic to AD-EDMD and isolated cardiomyopathy with conduction system disease mapped to 1q 2A AR Cardiac involvement rare Muscle weakness, proximal-girdle distribution CPK elevated 15q15 Calpain-3 (calcium activated neutral protease) With sarcoglycan deficiency AR DCM reported Arrhythmias uncommon Proximal-girdle distribution of muscle weakness Calf pseudohypertrophy. CPK elevated Severity varies from Duchenne to Becker-like α-Sarcoglycan, 17q12 β-Sarcoglycan, 4q12 γ-Sarcoglycan, 13q12 δ-Sarcoglycan, 5q3 Myotonic (1:8000) AD Conduction defects and arrhythmias common yet most remain asymptomatic ECG changes in 23–80%: prolonged PR and QRS intervals Left and right bundle branch block, AF, a flutter, and bradycardias MVP common DCM and HCM detected rarely Muscle weakness, may be associated with frontal balding, cataracts, hypogonadism, and myotonia 19q13.3 Myotonin-protein kinase gene mutations (unstable CTG trinucleotide repeats) Emery–Dreifuss X-linked AV block is the most common feature, high incidence of sudden death (pacemaker advised) Sinus node disease as well as tachyarrhythmias are common DCM is rare Childhood onset of contractures, mild muscle weakness in humeroperoneal distribution Lower extremities affected first CPK elevated moderately No calf pseudohypertrophy Xq28 defect of nuclear transmembrane protein emerin Desminopathies AD (actually more common than X-linked) AD, AR DCM associated with conduction system disease commonly seen Ventricular fibrillation reported despite pacing Restrictive cardiomyopathy Cardiac conduction blocks Arrhythmias Echo/MRI changes of DCM Same as X-linked form May be little evidence of skeletal myopathy Progressive distal myopathy CPK elevated 1.q11–21 Lamin A/C mutation (allelic to LGMD1B) DES 2q35 AD, autosomal dominant; AR, autosomal recessive; AF, atrial fibrillation; AV, atrioventricular; CM, cardiomyopathy; CPK, creatinine phosphokinase; DCM, dilated cardiomyopathy; EDMD, Emery–Dreifuss muscular dystrophy; HCM, hypertrophic cardiomyopathy; MVP, mitral valve prolapse. Adapted from Cox GF, Kunkel LM (1997). Dystrophies and heart disease. Current Opinion in Cardiology, 12, 329–42.

16.7.3 Specific heart muscle disorders 3499 to replace enzyme deficiencies, and enzyme replacement therapy (available at very considerable cost for mucopolysaccharidoses I, II, and VI, Pompe’s, Gaucher’s, and Anderson–Fabry disease). Mucopolysaccharidoses Mucopolysaccharidosis type I (Hurler’s syndrome, Hurler–Scheie syndrome, and Scheie’s syndrome) is a progressive childhood disorder with skeletal and cardiopulmonary involvement. Cardiac involvement consists of systolic and diastolic dysfunction and progressive aortic and mitral valve disease. Mucopolysaccharidosis type II (Hunter’s syndrome) is characterized by later onset, similar cardiomyopathy and valvular involvement as in mucopolysaccharidosis type I. Sudden cardiac death due to atrioventricular block has been described. Anderson–Fabry disease (angiokeratoma

corporis diffusum universale) Anderson–Fabry disease is an X-linked condition with a population prevalence of 1 in 40 000–117 000 live births. It is caused by mutations in the gene encoding the lysosomal enzyme α-galactosidase A, which leads to intralysosomal accumulation of neutral glycosphingolipids, mainly globotriaosylceramide (Gb3), in various organ systems. The disease is characterized by progressive clinical manifestations and pre- mature death from renal disease, stroke, and cardiac disease. The ECG often shows left ventricular hypertrophy, a short PR interval, conduction defects, and arrhythmias. Echocardiography usually demonstrates in- creased thickness of the left ventricle, which may simulate hypertrophic cardiomyopathy. Differentiation from other hypertrophic or restrictive processes may require magnetic resonance imaging or endomyocardial biopsy. A low leucocyte α-galactosidase activity is diagnostic in males. Enzyme replacement therapy is available for these patients. Gaucher's disease Gaucher's disease is the most common sphingolipidosis, caused by a deficiency in β-glucocerebrosidase that leads to lysosomal accumu- lation of glucocerebroside within macrophages. Lipid-laden macro- phages (Gaucher cells) accumulate within the reticuloendothelial system resulting in hepatosplenomegaly, bone marrow replacement, anaemia, and thrombocytopenia. Valvular and aortic calcification, heart failure, and pericarditis are reported, but the heart is not in- volved in most patients. Pulmonary hypertension occurs in up to 30% of untreated patients, with enzyme replacement treatment re- ducing the prevalence to 7.4%. Glycogen storage diseases Glycogen storage diseases affect the storage, synthesis, and break- down of glycogen. Glycogen storage disease types II (Pompe's dis- ease), IIb (Danon's disease), III, IV, and VI, IX, and 0 affect the heart, causing left ventricular hypertrophy, restrictive cardiomyopathy, di- lated cardiomyopathy, and conduction disease. Pompe's disease presents in neonates and infants with short PR interval, QT dispersion, and extreme left ventricular hypertrophy on ECG. On echocardiography severe concentric biventricular hyper- trophy, small left ventricular cavity, left ventricular outflow tract obstruction, and diastolic dysfunction are evident. The adult-onset form presents with few cardiac features. Conduction abnormalities are common. Danon's disease presents in boys with hypertrophic cardiomyop- athy, conduction disease, and skeletal muscle weakness; female car- riers present later in adulthood with dilated cardiomyopathy. Disease caused by mutations in the PRKAG2 (AMP kinase) gene is characterized by biventricular hypertrophy, impaired systolic function, high-grade atrioventricular conduction system disease, and ventricular pre-excitation. Mitochondrial diseases Defects affecting mitochondrial DNA are maternally inherited. Prevalence studies suggest that mitochondrial DNA defects affect 9.2 in 100 000 adults aged less than 65 years. Neurological sequelae usually present before cardiac manifestations. Conduction defects (Kearns–Sayre syndrome), left ventricular hypertrophy, and dilated cardiomyopathy are presenting features. Ocular myopathy with large mitochondrial DNA deletions can be associated with ECG abnormalities. Arrhythmias, in particular ventricular tachycardia, may occur in about 10% of patients. Second-or third-degree atrioventricular block necessitates cardiac pacing, and sudden death can occur. The serum creatine kinase may be mildly elevated and the blood lactate high. Management consists of supportive care and surveillance in addition to genetic counselling and pharmacological therapies for mitochondrial disease. Takotsubo (stress-induced) cardiomyopathy Transient left ventricular apical ballooning syndrome, takotsubo cardiomyopathy, is a cardiac syndrome characterized by transient left ventricular dysfunction. It is associated with ECG changes that can mimic acute myocardial infarction. The left ventricular angio- gram usually reveals a hyperkinetic base and a hypokinetic apex, mimicking the shape of a round-bottomed, narrow-necked pot used to catch octopus in Japan (tako-tsubo). Coronary spasm, microvascular dysfunction, or cardiotoxicity due to catecholamines have been postulated as causes. Most cases (up to 88%) occur in postmenopausal women (mean

age 58–77 years). The onset of symptoms is frequently preceded by physical or emotional stress. The most common presentation is with chest pain and dyspnoea, but cardiogenic shock and ventricular ar- rhythmias are reported in 4.2% and 1.5% of patients, respectively. Between 21% and 49% of patients will have ST-segment eleva- tion at the time of presentation, typically in the precordial leads. Reciprocal inferior ST depression is less likely when compared to patients with anterior ST elevation myocardial infarction. Most patients recover fully, and the left ventricular impairment usually improves swiftly in a period of days to weeks. The prognosis is gen- erally very good, with a recurrence in few patients (3–5%) and a mortality of about 1%. There are no randomized controlled studies on therapy of takotsubo cardiomyopathy. Empirical supportive treatment is ad- vised with use of diuretics and vasodilators. In view of the potential role of catecholamines and sympathetic activation, β-blockers have been recommended as well. Patients with haemodynamic instability may require mechanical support. Other conditions Other conditions that can cause DCM are shown in Table 16.7.3.5.

section 16 Cardiovascular disorders 3500 FURTHER READING Bargout R (2004). Sarcoid heart disease: clinical course and treatment. Int J Cardiol, 97, 173–82. Benson MD, Dasgupta NR (2016). Amyloid cardiomyopathy. J Am Coll Cardiol, 68, 25–8. Caforio ALP, et al. (2017). Diagnosis and management of myocar- dial involvement in systemic immune-mediated diseases: a pos- ition statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Disease. Eur Heart J, 38, 2649–62. Dawson DK (2017). Acute stress-induced (takotsubo) cardiomyop- athy. Heart, 104, 96–102. Dubrey SW, Falk RH (2010). Diagnosis and management of cardiac sarcoidosis. Prog Cardiovasc Dis, 52, 336–46. Dubrey SW, Comenzo RL (2012). Amyloid diseases of the heart: cur- rent and future therapies. Q J Med, 105, 617–31. Gianni M (2006). Apical ballooning syndrome or takotsubo cardiomy- opathy: a systematic review. Eur Heart J, 27, 1523–9. Gotlib J (2014). World Health Organization-defined eosinophilic dis- orders: 2014 update on diagnosis, risk stratification, and manage- ment. Am J Hematol, 89, 325–37. Guertl B, Noehammer C, Hoefler G (2000). Metabolic cardiomyop- athies. Int J Exp Pathol, 81, 349–72. Hermans MC, et al. (2010). Hereditary muscular dystrophies and the heart. Neuromusc Disord, 20, 479–92. Jabbar A, et al. (2017). Thyroid hormones and cardiovascular disease. Nat Rev Cardiol, 14, 39–55. Lofiego C (2005). Ventricular remodeling in Löeffler endocarditis: im- plications for therapeutic decision making. Eur J Heart Fail, 7, 1023–6. McGeoch L (2015). Vasculitis Clinical Research Consortium. Cardiac involvement in granulomatosis with polyangiitis. J Rheumatol, 42, 1209–12. Pinto YM, et al. (2016). Proposal for a revised definition of dilated cardio- myopathy, hypokinetic non-dilated cardiomyopathy, and its implica- tions for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. Eur Heart J, 37(23), 1850–8. Shabina H, Isenberg DA (1999). Autoimmune rheumatic diseases and the heart. Hospl Med, 60, 95–9. Wicks E, Elliott P (2012). Genetics and metabolic cardiomyopathies. Herz, 37, 598–610. Zhang R, Gupta D, Albert SG (2017). Phaeochromocytoma as a revers- ible cause of cardiomyopathy: analysis and review of the literature. Int J Cardiol, 249, 319–23. Zipes DP, et al. (eds) (2018). Braunwald’s heart disease: a textbook of cardiovascular medicine, 11th edition, pp. 1580–616. W. B. Saunders, Philadelphia, PA.

Table 16.7.3.5 Miscellaneous conditions that can cause dilated cardiomyopathy

Transient	Cause	Example	Comments
	Drugs	Antineoplastic drugs	Anthracyclines, cyclophosphamide, trastuzumab
		Psychiatric drugs	Clozapine, phenothiazines
		Other drugs	Chloroquine, antiretroviral agents (zidovudine, didanosine, zalcitabine), methysergide
	Toxic	Ethanol	Risk related to mean daily intake and duration of alcohol intake; good response to withdrawal
		Cocaine, amphetamines, ecstasy	Chronic users
		Other toxic	Cobalt (Quebec beer drinkers’ cardiomyopathy; possible following degeneration of metal-on- metal hip replacements), lead, lithium, mercury, beryllium,

anabolic/androgenic steroids Nutritional deficiency Thiamine (Beri-Beri) High-output cardiac failure associated with malnutrition and alcohol abuse Selenium Affects children and women of childbearing age in some areas of China where local diets contain almost no selenium (Keshan disease) Zinc and copper Possible causes of DCM Carnitine Inherited cases in children; possible role in cardiomyopathy of dialysis patients Electrolyte disturbance Hypocalcaemia Chronic severe vitamin D deficiency in adults; rickets in children Hypophosphataemia Uraemia

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Revision #1
Created 2026-01-22 16:39:44 UTC by Omar Ayman
Updated 2026-01-22 16:39:44 UTC by Omar Ayman