Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies

A Scientific Statement From the American Heart Association

The intent of this American Heart Association (AHA) scientific statement is to summarize our current understanding of dilated cardiomyopathies. There is special emphasis on recent developments in diagnostic approaches and therapies for specific cardiomyopathies. Recommendations in this document are based on published studies, published practice guidelines from the American College of Cardiology (ACC)/AHA[1] and other organizations,[2,3] and the multidisciplinary expertise of the writing group. Existing evidence in epidemiology, classification, diagnosis, and management of specific cardiomyopathies is usually derived from nonrandomized observational studies, registries, case reports, or expert opinion based on clinical experience, not large-scale randomized clinical trials or systematic reviews. Therefore, in this document, rather than using the standard ACC/AHA classification schema of recommendations and level of evidence,[4] we have included key management strategies at the end of each section and categorized our recommendations according to the level of consensus. Although the format of our recommendations might resemble the ACC/AHA classification of recommendations used in the ACC/AHA practice guidelines, because of the preponderance of expert opinion or level of evidence C evidence in our document, we elected to use different terminology to provide a distinction from the practice guidelines, in which stronger levels and quality of evidence with randomized clinical trials or meta-analyses are usually present.[4] The levels of evidence follow the AHA and ACC methods of classifying the level of certainty of the treatment effect.[4]

DEFINITION OF DILATED CARDIOMYOPATHY

The term *dilated cardiomyopathy* (DCM) refers to a spectrum of heterogeneous myocardial disorders that are characterized by ventricular dilation and depressed myocardial performance in the absence of hypertension, valvular, congenital, or ischemic heart disease.[5]

In clinical practice, the pathogenesis of heart failure (HF) has often been placed into 2 categories: ischemic and nonischemic cardiomyopathy. The term *nonischemic cardiomyopathy* has been interchangeably used with DCM. Although this approach might be practical, it fails to recognize that nonischemic cardiomyopathy can include cardiomyopathies caused by volume or pressure overload (such as hypertension or valvular heart disease) that are not conventionally accepted under the definition of DCM.[1,5] Again, in general practice and clinical research trials, the term *ischemic cardiomyopathy* is defined as cardiomyopathy caused by ischemic heart disease. Current use of ischemic cardiomyopathy terminology implies ventricular dilation and depressed myocardial contractility caused by ischemia or infarction.

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CLASSIFICATION OF CARDIOMYOPATHIES

The first classification on this topic categorized cardiomyopathies as heart muscle diseases with dilated (DCM), hypertrophic, restrictive, arrhythmogenic right ventricular (ARVC), or nonclassifiable cardiomyopathy in 1980.[5] Subsequently, the World Health Organization/International Society and Federation of Cardiology classification in 1996 added inflammatory and viral cardiomyopathies as new and distinct entities.[5] With the development of molecular genetics, new classification schemes based on genomics such as the classification proposed by the AHA ensued,[6] which divided cardiomyopathies into 2 major groups based on predominant organ involvement. Primary cardiomyopathies (ie, genetic, nongenetic, and acquired) were defined as those solely or predominantly confined to heart muscle. Secondary cardiomyopathies had myocardial involvement as part of a large number and variety of generalized systemic (multiorgan) disorders, including systemic diseases such as amyloidosis, hemochromatosis, sarcoidosis, autoimmune/collagen vascular diseases, toxins, cancer therapy, and endocrine disorders such as diabetes mellitus.[6] The European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases took a different approach based on a clinically oriented classification in which heart muscle disorders were grouped into specific morphological and functional phenotypes, including hypertrophic cardiomyopathies, DCM, ARVC, restrictive cardiomyopathies, and unclassified cardiomyopathies. Each phenotype was then subclassified into familial and nonfamilial forms.[7] Most recently, the MOGE(S) nosology system was developed, which incorporates the morphofunctional phenotype (M), organ(s) involvement (O), genetic inheritance pattern (G), etiologic annotation (E) including genetic defect or underlying disease/substrate, and the functional status (S) of the disease using both the ACC/AHA HF stages and New York Heart Association (NYHA) functional class. This nomenclature is endorsed by the World Heart Federation, is supported by an Internet-assisted application, and assists in the description of cardiomyopathy in symptomatic or asymptomatic patients and family members in the context of genetic testing.[8,9]

Classifications of cardiomyopathies that mix anatomic designations (ie, hypertrophic and dilated) with functional ones (ie, restrictive) can be quite challenging and have failed to satisfy the purposes of all users.[1] Confusion can arise because the same disease could appear in 2 categories (ie, hypertrophic and restrictive); there could be heterogeneity of clinical expression in different phenotypes, and some diseases do not have a uniformly static expression but evolve as a consequence of remodeling from one category to another during their natural clinical course (eg, hypertrophic cardiomyopathy, amyloid, and other infiltrative conditions can progress from a nondilated, often hyperdynamic state to a dilated form). The most recent MOGE(S) classification provides flexibility for such potential transitions between morphofunctional types, involvement of different cardiac structures and organs, progression of symptomatology and functional status, and the addition of different causes such as genetic defects that might be discovered throughout the lifetime of a patient or affected families.[6,9] In this scientific statement, our aim is to target appropriate diagnostic and treatment strategies that prevent development and progression of HF in patients with specific cardiomyopathies, not necessarily to reexamine new classification strategies for cardiomyopathies.

EPIDEMIOLOGY AND NATURAL HISTORY OF DCM

Determining the incidence and prevalence of DCMs has been quite challenging because of geographic variations, patient selection, and changes in the diagnostic criteria. For example, the incidence of idiopathic DCM, which is defined as a cardiomyopathy when the exact cause remains initially unknown, doubled from 3.9 per 100 000 person-years between 1975 and 1979 to 7.9 per 100 000 person-years between1980 and 1984 in Olmsted County, MN.[10] Around the same time, the incidence of clinical and postmortem diagnosed cases remained 5 per 100 000 per year in Sweden, where the autopsy rates were 90%.[11] The prevalence of cardiomyopathy in underdeveloped and tropical countries is considerably higher than in developed countries. In the United States, the age-adjusted prevalence of DCM has been reported to be ≈36 cases per 100 000 population or 1:2500.[12,13] The prevalence of DCM in Japan is reportedly lower (17/100 000),[14] and in Africa[15] and Latin America, it is higher than that of the US population. As populations go through epidemiological and socioeconomic transitions and healthcare modifications, the prevalence of DCM could continue to change.

In most multicenter randomized trials in HF, ≈30% to 40% of the enrolled patients have nonischemic HF. According to ADHERE (Acute Decompensated Heart Failure National Registry), 47% of the patients admitted to the hospital with HF had nonischemic cardiomyopathy.[16] This number might not accurately reflect the true prevalence of nonischemic DCM, because a significant proportion of these patients will have HF caused by hypertension or valvular heart disease. With the inclusion of the pediatric population and the worldwide spectrum of causes of DCMs, the prevalence of nonischemic DCMs is thought to exceed that of ischemic DCMs.

DCM can occur at any age but most commonly occurs in the third or fourth decade of life. Advancing age is an independent risk factor for mortality in DCM.[17,18] Interestingly, with advances in pharmacological and device

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treatment, the prognosis of HF and DCM has improved significantly in the adult population,[19] even among the elderly.[20] The improvement in survival has been associated with the use of angiotensin-converting enzyme (ACE) inhibitors and β-blockers.[19] Compared with whites, blacks have almost a 3-fold increase in risk for developing DCM, which is not explained solely by the confounding variables of hypertension or social or economic factors.[21] Moreover, blacks have an ≈1.5- to 2-fold higher risk of dying of DCM compared with age-matched whites with DCM.[22] Regarding sex-related differences, the overall effect of female sex on the prognosis of HF, especially DCM, is not clear at this time and could be confounded by differing pathogeneses and an underrepresentation of women in clinical trials. In the Italian Multicenter Cardiomyopathy Registry, women with idiopathic DCM presented with more advanced HF and had a trend toward worse survival.[23] Analyses from MERIT-HR (Metoprolol Extended Release Randomized Intervention Trial in Heart Failure)[24] and CIBIS-II (Cardiac Insufficiency Bisoprolol Study)[25] suggested that female sex might be a significant independent predictor of survival in patients with HF, regardless of ischemic or nonischemic pathogenesis. Further studies will need to be conducted to provide more insight into the role of sex in the prognosis of DCM.

The natural history of DCM is not well established for 2 reasons. First, DCM represents a heterogeneous spectrum of myocardial disorders that can progress at different rates.[26] Second, the onset of the disease can be insidious, particularly in the case of familial or idiopathic DCMs, and could be missed for a significant period of time before the diagnosis. Approximately 25% of DCM patients with recent onset of symptoms of HF will have spontaneous improvement,[27] but patients with symptoms lasting >3 months who present with severe clinical decompensation generally have less chance of recovery.[27] Patients with idiopathic DCM have a better prognosis than those with other types of DCM.[28]

It should be recognized that many of the natural history studies of DCM were performed before ACE inhibitors and β-blockers were used routinely. Also, device therapies and cardiac transplantation were not commonly available.[17] More recent studies suggest that the prognosis for patients with DCM and mild left ventricular (LV) dilation might be more favorable, perhaps reflecting earlier diagnosis and better treatment. A number of variables imply a poor prognosis in patients with DCM, including LV and right ventricular (RV) enlargement, reduced LV and RV ejection fraction (EF), persistent S_3 gallop, right-sided HF, elevated LV filling pressures, moderate to severe mitral regurgitation, pulmonary hypertension, electrocardiographic findings of left bundle-branch block (LBBB), recurrent ventricular tachycardia, renal and hepatic dysfunction, elevated levels of brain natriuretic peptide (BNP), persistently elevated cardiac troponin levels, peak oxygen consumption <10 to 12 $mL \cdot kg^{-1} \cdot min^{-1}$, serum sodium <137 mmol/L, advanced NYHA functional class, age >64 years, and myocytolysis on endomyocardial biopsy (EMB).

In the United States, the cause of death appears to be pump failure in approximately two thirds and sudden cardiac death in approximately one third of all deaths of patients with DCM.[28–30] In existing clinical studies, patients with idiopathic DCM had a lower total mortality than patients with ischemic heart disease.[28]

DIAGNOSTIC STRATEGIES IN DCM

Evaluation of patients with DCM involves common diagnostic strategies recommended[1] for patients with HF or cardiomyopathy and requires a thorough understanding of the complex, diverse pathophysiology that must be individualized to the patient. The general approach of the writing committee is outlined in Figure 1.[1]

OVERALL MANAGEMENT STRATEGIES FOR DCM

The differential treatment benefit seen in DCM patients compared with patients with ischemic cardiomyopathy has been observed in several randomized clinical trials. Differential patient responsiveness to digoxin[31] or amiodarone[32] suggests that there could be response differences between ischemic and nonischemic HF; however, similar older reports of survival difference with β-blockers[33] and amlodipine[34] in patients with DCM but not ischemic cardiomyopathy were not reproduced in subsequent large-scale randomized trials. This has raised the question of whether there is truly a difference in response to treatment according to pathogenesis of HF. Currently, it is accepted that guideline-directed medical and device therapies, including implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) for HF, are beneficial in DCM.[1]

DIAGNOSTIC AND TREATMENT STRATEGIES FOR SPECIFIC CARDIOMYOPATHIES

In the following sections, diagnostic and treatment strategies for specific cardiomyopathies such as cardiac amyloidosis, cardiotoxins, peripartum cardiomyopathy, cardiac sarcoidosis, myocarditis, autoimmune cardiomyopathy, endocrine and metabolic cardiomyopathies, and genetic cardiomyopathies will be reviewed.

DIAGNOSTIC AND TREATMENT STRATEGIES FOR CARDIAC AMYLOIDOSIS

Definition, Pathogenesis, Epidemiology, and Prognosis

Cardiac amyloidosis usually starts as restrictive cardiomyopathy with mildly depressed LV systolic dysfunction

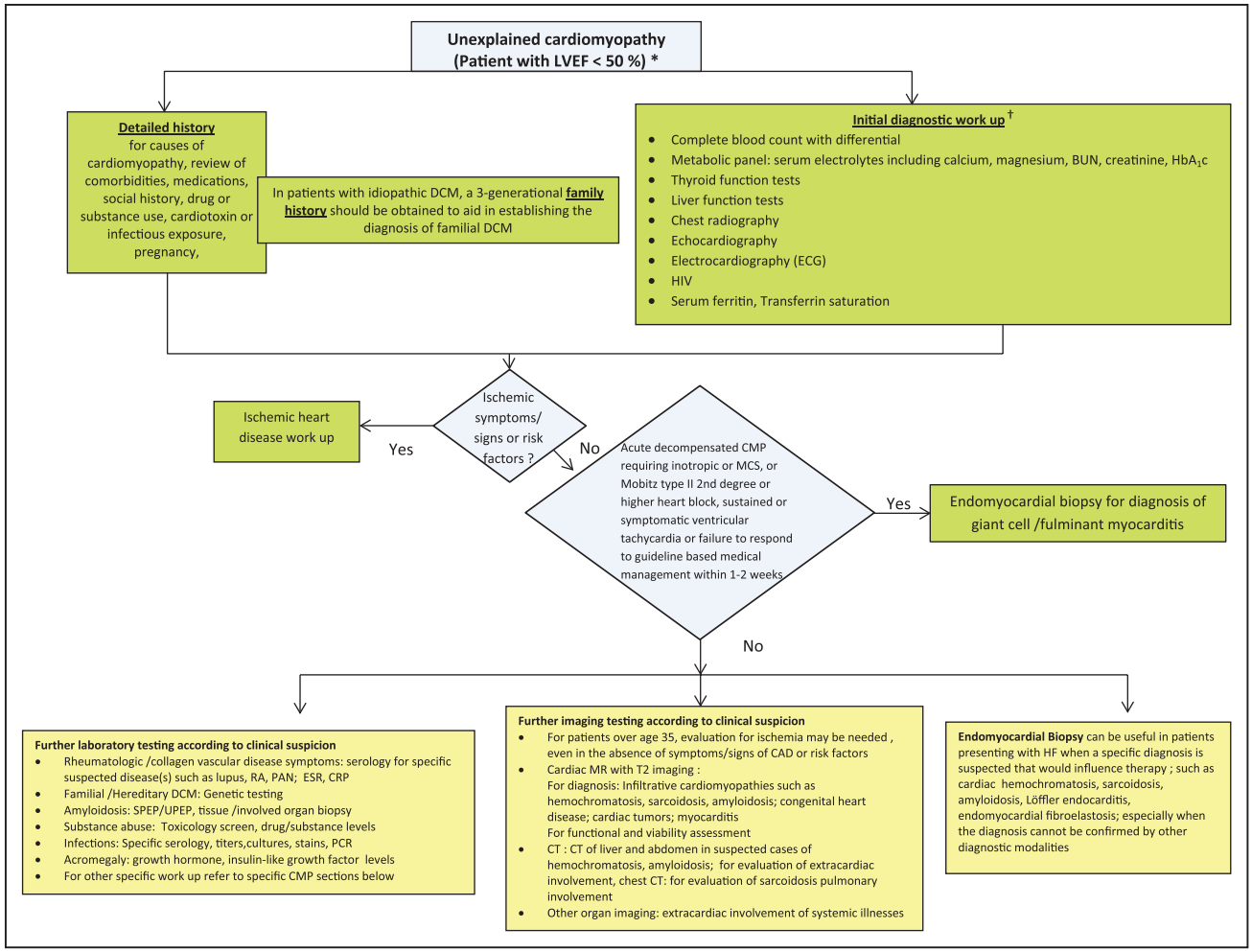

Figure 1. Diagnostic strategies in DCM.
BUN indicates blood urea nitrogen; CAD, coronary artery disease; CMP, cardiomyopathy; CRP, C-reactive protein; CT, computed tomography; DCM, dilated cardiomyopathy; ESR, erythrocyte sedimentation rate; HbA1c, hemoglobin A1c; HF, heart failure; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MR, magnetic resonance; PAN, polyarthritis nodosa; PCR, polymerase chain reaction; RA, rheumatoid arthritis; SPEP, serum protein electrophoresis; and UPEP, urine protein electrophoresis. *Current definition per 2013 guidelines[1]. Heart failure with reduced ejection fraction (HFrEF; ejection fraction <40%) or heart failure with borderline preserved ejection fraction (HFpEF; borderline ejection fraction 41%-49%). †These diagnostic tests are part of a routine workup of initial evaluation of a patient with heart failure.[1]

and significant diastolic HF and can progress to severe systolic dysfunction in advanced stages. Amyloidosis is a disease complex characterized by the deposition of protein fibrils in various organs, which leads to structural and functional derangement. There are various types of amyloidosis categorized on the basis of the type of protein fibrils deposited, as shown in Table 1. Amyloid deposition can occur in various organs, including the heart, kidney, liver, and nervous system. Cardiac involvement has been predominantly noted in amyloid light chain (AL) amyloidosis (also known as primary amyloidosis), hereditary, senile, and isolated atrial amyloidosis. The most common types of cardiac amyloidosis encountered in clinical practice are AL, senile, and certain hereditary/familial types.[35]

Once amyloid infiltration involves the heart, prognosis significantly worsens. Although senile and familial cardiac amyloidoses have a relatively mild course, with a median survival of 70 to 75 months, cardiac involvement in AL amyloidosis leads to rapid progression in cardiac symptoms and a significant reduction in survival. Median survival in AL amyloidosis is ≈13 months but decreases drastically to 4 months with the onset of HF symptoms.[36,37]

Pathophysiology and Clinical Presentation

Amyloid deposits in the myocardial interstitium disrupt myocyte function and can lead to diastolic and systolic dysfunction. Amyloid deposits can also directly cause myocyte necrosis by oxidative stress, and this can contribute further to systolic dysfunction. Moreover, deposits in the conduction tissue can affect electrical conduction. Amyloid deposition in the valves can lead

Table 1. Pathology, Organ Involvement, and Survival in Various Types of Amyloidosis

Amyloidosis Type	Protein	Cardiac Involvement	Median Survival (mo)	Extracardiac Manifestations
Primary or light-chain (AL)	Light chain	Up to 50%	13 (4 mo if heart failure present)	Kidney, liver, nervous system, skin, carpal tunnel syndrome
Hereditary	Mutant transthyretin	Variable	70	Kidney, nervous system, blindness
Senile	Transthyretin	Common	75	Diffuse organ involvement
Isolated atrial	Atrial natriuretic factor	Limited to heart	…	None
Reactive (AA)	Amyloid A	<10%	25	Kidney, liver
Dialysis related	β_2-microglobulin	Unknown	…	Joints, carpal tunnel syndrome, skeletal

AA indicates amyloid A (reactive amyloidosis); and AL, amyloid light chain.

to thickening but rarely to significant dysfunction. Furthermore, amyloid protein can deposit in the media and adventitia of coronary arteries and veins, and this can potentially result in cardiac ischemia. Amyloid deposits in the pericardium can result in the formation of pericardial effusion. In the early stages of cardiac amyloid deposition, there is an increase in myocardial stiffness leading to impaired diastolic function, which eventually leads to elevated filling pressures and diastolic HF with the restrictive cardiomyopathy phenotype. During these earlier stages, the heart is typically normal in size with normal systolic function. With disease progression, systolic dysfunction develops.[38]

Clinically, one of the main presentations encountered in patients with cardiac amyloidosis is with HF. Because of infiltration of the conduction system, abnormalities in the form of atrioventricular block are not uncommon. Atrial tachyarrhythmias can also occur because of amyloid deposition in the atrial wall and as a result of atrial dilation in the setting of elevated filling pressures. Some patients develop angina from amyloid deposition in the coronary arteries. Typically, intramyocardial coronary arteries are affected, and thus, examination of the epicardial arteries by coronary angiography might not show significant obstruction. Presyncope and syncope are not an uncommon presentation, likely multifactorial, and include infiltration of the autonomic nervous system and adrenal glands, hypovolemia caused by nephrotic syndrome, cardiac arrhythmias, and inability of a stiff heart to adequately respond to positional changes.[35,39,40]

Diagnosis

Diagnosis of amyloidosis not only involves the demonstration of amyloid protein in tissue specimens but also requires the identification of which organs are affected and the definition of the type of amyloidosis. Cardiac amyloidosis is usually suspected on echocardiography, typically performed because of HF symptoms or performed for screening purposes when the diagnosis of amyloidosis has been established in other organs.

Typical echocardiographic features of amyloidosis include thickened ventricular walls (right and left) in the setting of normal ventricular size, biatrial dilatation, presence of a pericardial effusion, and valvular thickening without significant dysfunction. Increased echogenicity of the myocardium, termed *granular, sparkling*, is not very sensitive or specific when evaluated in isolation but should raise suspicion when present in conjunction with other echocardiographic findings listed previously. Of note, the "granular, sparkling" finding has become less discernible because of newer echocardiographic techniques. An infiltrative disease process should be suspected if the ventricular walls are thickened in the absence of an obvious cause such as hypertension or aortic stenosis. Doppler studies typically demonstrate impaired LV relaxation and restrictive filling pattern. Initially, LV systolic function is preserved, but this gradually declines as the disease progresses.[41–43]

Reduced QRS voltage amplitude on ECG is noted in the limb leads in ≈50% of patients with cardiac amyloidosis despite the presence of ventricular wall thickening on cardiac imaging. Other electrocardiographic features include a pseudoinfarct pattern in the precordial leads, atrial fibrillation, and atrioventricular conduction abnormalities.[44]

Nuclear imaging with technetium pyrophosphate has been shown to be insensitive; however, if uptake is present, amyloid infiltration should be considered, depending on the clinical setting.[45] A small study showed that the radioactive tracer technetium Tc 99m dicarboxypropane diphosphonate can be useful in distinguishing between AL and transthyretin (TTR) amyloidosis.[46]

Late gadolinium enhancement in the subendocardium globally by cardiac magnetic resonance imaging (MRI) has been noted in patients thought to have cardiac amyloid involvement. The accuracy and utility of this imaging modality are still uncertain for the diagnosis of cardiac amyloidosis, but it could help identify the extent of cardiac involvement in patients with an established diagnosis of amyloidosis.[47,48]

BNP levels can be helpful in the diagnosis and follow-up of patients with cardiac amyloidosis. Elevations in BNP have been demonstrated even without evidence of clinical HF or increased wall stress, which suggests that it might be caused not only by elevated ventricular filling pressure but also by direct myocyte damage caused by extracellular deposits of amyloid. Increased natriuretic peptide levels suggest cardiac involvement with a sensitivity of 93% and specificity of 90%.[49,50] Elevated BNP levels have also been demonstrated to predict development of clinical cardiac involvement in the future.[51] Moreover, BNP levels have been shown to predict prognosis and mortality.[39,50] BNP levels decrease with chemotherapeutic treatment of AL amyloidosis, possibly suggesting organ response.[52]

The definitive diagnosis of amyloidosis is made histologically from biopsies of abdominal fat pad, gingiva, rectum, bone marrow, or other affected organs such as heart, liver, and kidney. Light microscopy shows amorphous pink deposits in the interstitium. With Congo red staining, amyloid fibrils produce apple-green birefringence under polarized microscopy. Other confirmative methods include electron microscopy and proteomic typing by mass spectrometry.[53,54] EMB that identifies amyloid protein in cardiac tissue provides the definitive diagnosis of cardiac amyloidosis. In patients with noncardiac tissue-proven systemic amyloidosis, echocardiographic or cardiac magnetic resonance (MR) findings suggestive of infiltrative cardiomyopathy (eg, wall thickness >12 mm) can support the diagnosis of cardiac amyloidosis without EMB.[55] The next step is to identify the type of amyloidosis, because this is instrumental in determining treatment strategy and prognosis. Immunohistochemistry can be performed on the tissue samples with antibodies against amyloid A, κ- and λ-light chains, and TTR amyloid.[41] If TTR amyloid is detected, DNA mutational analysis can help differentiate between senile and hereditary amyloidosis.[54] The presence of serum or urine monoclonal gammopathy suggests the presence of AL amyloidosis but does not establish the diagnosis. In reactive (AA) amyloidosis, the deposited protein is serum amyloid A protein, an acute-phase protein that is normally soluble and whose plasma concentration is highest during inflammation. AA amyloidosis is a complication of a number of inflammatory diseases and infections such as tuberculosis, chronic osteomyelitis, and autoimmune diseases. AA amyloid deposits are primarily in the liver, spleen, and kidney and rarely affect the heart.

Key Diagnostic Strategies for Cardiac Amyloidosis

Diagnostic Recommendations With Strong Level of Consensus for Cardiac Amyloidosis

1. In patients suspected of having cardiac and systemic amyloidosis, identification of amyloid protein in tissues such as abdominal fat pad, gingiva, or rectum or affected organs such as heart, liver, and kidney is recommended to diagnose amyloidosis *(Level of Evidence C)*.
2. If TTR amyloid is detected from a biopsy specimen, DNA mutational analysis should be used to differentiate between senile and hereditary amyloidosis *(Level of Evidence C)*.[54]
3. When the diagnosis of amyloidosis has been established, imaging and further laboratory studies or biopsies should be considered to identify the organs involved *(Level of Evidence C)*. The extent of organ involvement is critical in determining treatment strategies and prognosis.
4. Echocardiography should be performed in patients suspected of having cardiac amyloidosis or patients with systemic amyloidosis and HF *(Level of Evidence B)*.[41–43]

Recommendations With Moderate Level of Consensus for Cardiac Amyloidosis

1. Noncardiac tissue–proven amyloidosis along with echocardiographic or cardiac MRI findings suggestive of infiltrative cardiomyopathy and symptoms and signs of HF can be useful to diagnose cardiac amyloidosis without EMB *(Level of Evidence C)*.
2. In patients suspected of having cardiac amyloidosis, EMB is reasonable to identify amyloid protein in cardiac tissue, especially if there is no noncardiac tissue evidence of amyloidosis *(Level of Evidence C)*.
3. Natriuretic peptide (BNP or N-terminal proBNP) levels can be useful to detect early/preclinical cardiac involvement in patients with the diagnosis of amyloidosis and to predict future cardiac involvement and prognosis *(Level of Evidence B)*.[49–52]

Recommendations With Uncertainty for Cardiac Amyloidosis

1. The presence of serum or urine monoclonal gammopathy, which suggests the presence of AL amyloidosis, along with echocardiographic or cardiac MRI findings suggestive of infiltrative cardiomyopathy and symptoms and signs of HF may be considered to support the diagnosis of cardiac amyloidosis without EMB but does not establish the definitive diagnosis *(Level of Evidence C)*.[53–55]
2. Certain electrocardiographic features, such as presence of low QRS voltage in the presence of ventricular wall thickening, might be reasonable to suggest the presence of cardiac amyloidosis but do not confirm the diagnosis of cardiac amyloidosis *(Level of Evidence C)*.[44]
3. Use of nuclear imaging with technetium Tc 99m dicarboxypropane diphosphonate may be reasonable to distinguish between AL and TTR amyloidosis *(Level of Evidence B)*.[45,46]

Treatment

General HF Treatment

Treatment is for the most part supportive. It includes management of HF, arrhythmias, and conduction system problems. However, the use of the standard HF treatment regimen can be challenging in patients with cardiac amyloidosis. Diuretic and vasodilator agents should be used cautiously because of hypotension that can result from underfilling of a stiff heart. Also, caution should be exercised with the use of β-blockers, because cardiac output is heart rate dependent in the setting of severe restrictive physiology; β-blockers are usually avoided. Of note, digoxin binds to amyloid fibrils and thus can predispose to toxicity even in the setting of normal serum digoxin levels.[56] Similarly, calcium antagonists bind to amyloid fibrils, which can result in exaggerated hypotensive and negative inotropic responses.[57] Ultimately, judicious diuresis remains the mainstay of HF therapy in these patients. ACE inhibitors, or angiotensin receptor blockers (ARBs) if the patient is intolerant of ACE inhibitors, should be used with caution in patients with amyloidosis and probably should be avoided because of hypotension. β-Blockers can be used to increase diastolic filling time and control heart rate in the setting of atrial fibrillation, but they should be used cautiously if at all when cardiac output is low and there is severe restrictive physiology. They probably should be avoided in AL amyloidosis.

In patients with amyloid cardiomyopathy, risk of intracardiac thrombus is high in the setting of atrial fibrillation and even in the setting of sinus rhythm. Thrombus formation in the atria has been demonstrated in patients with sinus rhythm when the atria develop mechanical "standstill" as a result of amyloid infiltration of the atrial walls. High left atrial pressures in the setting of HF also likely contribute to atrial dysfunction. The benefit of anticoagulation should be weighed against the potential increased risk of bleeding in patients with amyloid angiopathy. Anticoagulation is indicated in patients with atrial fibrillation and in those with a history of embolic stroke or transient ischemic attacks, and probably also in patients with demonstrable intracardiac thrombus. The value of screening for intracardiac thrombus in sinus rhythm is unknown.[58] Device-based therapy of cardiac rhythm abnormalities such as advanced-degree atrioventricular block should be performed in accordance with guideline recommendations.[59]

Patients with aggressive AL amyloidosis may have a very poor prognosis, and life expectancy will need to be taken into consideration in patients being considered for device therapy. Furthermore, it is not uncommon for terminal presentation to be with electromechanical dissociation rather than ventricular tachyarrhythmias.

Disease-Directed Therapy

In an attempt to eliminate plasma cell dyscrasia in AL amyloidosis, high-dose chemotherapy followed by autologous hematopoietic cell transplantation has been used. In AL amyloidosis without cardiac involvement, high-dose melphalan therapy with hematopoietic cell transplantation has been demonstrated to improve survival. Patients with important clinical cardiac involvement have been largely excluded from these studies. Because of significant hemodynamic fluctuations with hematopoietic cell transplantation, patients with cardiac involvement have increased morbidity and mortality. In a study of 312 patients with amyloidosis undergoing treatment with high-dose melphalan and hematopoietic cell transplantation, the median survival was 6.4 years in patients without cardiac involvement and 1.6 years in those with cardiac involvement. Notably, patients with LV ejection fraction (LVEF) ≤40% and decompensated HF were excluded. Treatment-related mortality was high (13% at 100 days), with 42% of deaths being cardiac deaths.[60]

In patients who are not candidates for hematopoietic cell transplantation, the following combination of chemotherapeutic agents has been shown to modestly improve survival in AL amyloidosis: melphalan and dexamethasone or cyclophosphamide, thalidomide and dexamethasone, or continuous oral melphalan.[61–64] In a study of 220 patients with AL amyloidosis (46 with cardiac involvement) randomized to colchicine versus melphalan, prednisone versus melphalan, and prednisone and colchicine, median survival was 8.5 months in the colchine group, 18 months in the melphalan and prednisone group, and 17 months in the melphalan, prednisone, and colchicine group ($P<0.001$).[65] Although ≈40% to 60% of patients experienced a hematologic response (partial or complete), only a small subset experienced a cardiac response defined by a decrease in wall thickness, improvement in LV function, and improvement in HF symptoms.[60,61,63]

In AL amyloidosis, cardiac transplantation is generally not recommended because of the high risk of recurrence in the transplanted heart. Moreover, prognosis is affected by progressive amyloid deposition in other organs.[66–68] Cardiac transplantation for amyloidosis has a bleak prognosis, with 5-year survival of only 20% to 30%.[69] In a small case series of 10 patients with cardiac amyloidosis who underwent cardiac transplantation, 4 patients developed amyloid deposition in the cardiac allograft, and late survival was dismal, with 39% alive at 48 months.[70] Survival appears to improve if cardiac transplantation is followed by bone marrow transplantation, reaching a 5-year survival rate of ≈35% to 55%.[68,71–76]

Post–cardiac transplantation survival for amyloidosis types other than AL appears to be better and similar to outcomes in cardiac transplantation performed for other conditions.[77] In the familial/hereditary form of amyloidosis caused by TTR genetic mutation, combined cardiac and liver transplantations have been performed successfully, with a 5-year survival rate of 50% to 80%.[78–80] In

these patients, liver transplantation cures the amyloidosis disease process, because the TTR protein is synthesized in the liver.

In AA amyloidosis, anti-inflammatory therapies, such as anti-tumor necrosis factor used for the treatment of rheumatoid arthritis (RA), have been shown to suppress serum amyloid A production. However, experience with cardiac involvement is unknown, because AA amyloidosis rarely affects the heart.[42]

Novel Therapeutic Agents

In recent studies, the proteasome inhibitor bortezomib has been demonstrated to successfully suppress clonal cell proliferation and result in significant hematologic and cardiac response in AL amyloidosis.[81–83] Currently, bortezomib is being evaluated in AL amyloidosis in phase II and III trials. ALN-TTR01, an RNA therapy that targets the TTR gene, is currently in phase I trials.[84] Diflunisal and tafamidis stabilize the TTR molecule, thereby preventing misfolding and inhibiting the formation of TTR amyloid fibrils.[85,86] Both agents are being investigated in the treatment of TTR amyloidoses. Tafamidis was shown to reduce disease progression in patients with TTR amyloidosis with early peripheral neuropathy. Epigallocatechin-3-gallate, a polyphenol found in green tea, has been shown to reduce amyloid fibril formation. In a small, nonrandomized study of patients with cardiac AL amyloidosis, regular green tea consumption was associated with a decrease in wall thickness and improvement in LV function and NYHA functional class.[87]

Key Management Strategies for Cardiac Amyloidosis

Recommendations With Strong Level of Consensus for Cardiac Amyloidosis

1. Warfarin therapy (with a goal international normalized ratio of 2 to 3) or direct thrombin inhibitors are indicated for patients with cardiac amyloidosis and paroxysmal or chronic atrial fibrillation or a history of embolic stroke/transient ischemic attack *(Level of Evidence A)*.[58]
2. Device-based therapy for patients with cardiac amyloidosis who have cardiac rhythm abnormalities should be performed with consideration for life expectancy *(Level of Evidence C)*.[59]

Recommendations With Moderate Level of Consensus for Cardiac Amyloidosis

1. Diuresis can be useful in patients with HF symptoms and congestion but should be used with caution against overdiuresis and volume contraction that can result in hypotension *(Level of Evidence C)*.
2. β-Blockers can be useful to increase diastolic filling time and control heart rate in the setting of atrial fibrillation, but β-blockers should be used cautiously because cardiac output is heart rate dependent in the setting of severe restrictive physiology or low-output HF *(Level of Evidence C)*.
3. Warfarin therapy (with a goal international normalized ratio of 2 to 3) is probably indicated for patients with imaging-proven intracardiac thrombus *(Level of Evidence C)*.
4. High-dose chemotherapy followed by autologous hematopoietic cell transplantation is reasonable in selected patients with AL amyloidosis who have cardiac involvement and LVEF ≥40% and compensated HF status *(Level of Evidence B)*.[60]
5. In patients who are not candidates for autologous hematopoietic cell transplantation, certain combinations of chemotherapeutic agents can be useful to improve survival in AL amyloidosis *(Level of Evidence B)*.[60–65]

Recommendations With Uncertainty for Cardiac Amyloidosis

1. Cardiac and liver transplantation for hereditary amyloidosis might be considered in selected patients with TTR-related amyloidosis *(Level of Evidence B)*.[78–80]
2. Cardiac transplantation followed by bone marrow transplantation in AL amyloidosis might be considered in very selected patients *(Level of Evidence B)*.[66–69,71–77]

Strategies to Avoid With Concern for Harm for Cardiac Amyloidosis

1. Digoxin should be avoided in patients with amyloidosis *(Level of Evidence C)*. Digoxin binds to amyloid fibrils and thus can predispose to toxicity even in the setting of normal serum digoxin levels.[56]
2. Calcium channel antagonists (nifedipine or verapamil) should not be administered, because they bind to amyloid fibrils and can result in exaggerated hypotensive and negative inotropic responses *(Level of Evidence C)*.[57]

CARDIOMYOPATHY RELATED TO CARDIOTOXINS

Alcoholic Cardiomyopathy

Epidemiology and Prognosis

Chronic alcoholism is one of the most important causes of DCM in the Western and developing world.[88] In the United States, in both sexes and in all races, long-term heavy alcohol consumption has been noted as one of the leading causes of nonischemic DCM.[88] The clinical diagnosis of alcoholic cardiomyopathy can be made when biventricular dysfunction and dilation are persistently observed in a person with a significant history of alcohol use, in the absence of other known causes of myocardial disease. Among patients with nonischemic

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cardiomyopathy, the prevalence of alcoholic cardiomyopathy is variable.[89] Alcoholic cardiomyopathy most commonly occurs in men 30 to 55 years of age who have been heavy consumers of alcohol for >10 years.[89] Women represent ≈14% of the alcoholic cardiomyopathy cases but might be more vulnerable, because alcoholic cardiomyopathy develops in women with a lower total lifetime exposure to alcohol than for men.[88] Death rates related to alcoholic cardiomyopathy are greater in men than women because of the higher prevalence of alcohol consumption in men, but alcohol intake is associated with a higher mortality risk in women than in men with DCM.[90] The risk of developing alcoholic cardiomyopathy appears to be related to mean daily alcohol intake, duration of drinking, and individual patient characteristics, including genetic susceptibility. In general, alcoholic patients consuming alcohol for >5 years are at risk for the development of alcoholic cardiomyopathy. Alcohol results in both acute and chronic depression of myocardial contractility even when ingested by young adults in quantities consumed during social drinking.[91] On the other hand, mild to moderate alcohol consumption has been reported to be protective against development of HF in the general population. According to the Framingham Heart Study, moderate alcohol consumption is not associated with an increased risk and in fact appears to be protective against the development of HF.[92] Similarly, in a prospective cohort study of elderly people, moderate alcohol consumption was associated with a decreasing risk of HF.[93] These findings raise the possibility that alcohol could be protective against HF in certain populations when used in moderation but detrimental in others, especially when used in excess. Genetic predisposition or the presence of synergistic cardiovascular factors such as hypertension, nutritional deficiencies, or arrhythmias could play a role.[94]

Treatment

The management of patients with alcohol cardiomyopathy should begin with total abstinence from alcohol in addition to the conventional management of HF. There are currently no studies of specific pharmacotherapies in patients with alcoholic cardiomyopathy other than the standard therapy for HF; however, numerous reports detail the reversibility of depressed LV function after the cessation of drinking.[95] Even if the depressed LV function does not normalize completely, the symptoms and signs of HF improve after abstinence. Unfortunately, the overall prognosis remains poor, with a mortality rate of 40% to 50% within 3 to 6 years if the patient is not abstinent. Survival is significantly lower for patients who continue to drink than for patients with idiopathic DCM or for patients with alcoholic cardiomyopathy who abstain from drinking. Because patients with chronic alcoholism could be prone to thiamine deficiency, which can result in or contribute to the development of cardiomyopathy, it is critical to supplement thiamine and folate in these patients.

Key Management Strategies for Alcoholic Cardiomyopathy

Recommendation With Strong Level of Consensus for Alcoholic Cardiomyopathy

1. In patients with alcoholic cardiomyopathy, total abstinence is recommended *(Level of Evidence C).*[88–91,94,95]

Cocaine-Related Cardiomyopathy

Definition, Epidemiology, and Prognosis

Although cocaine abuse has been associated with acute coronary events and regional myocardial injury, long-term cocaine use also has been associated with global DCM without the presence of coronary artery disease (CAD) or segmental infarct pattern. This has been termed *cocaine-related cardiomyopathy* and implies direct toxicity of cocaine on the myocardium. Depressed LV function has been reported in 4% to 18% of asymptomatic cocaine users without evidence of myocardial infarction (MI) or CAD.[96–98] Cocaine can produce LV dysfunction through its direct toxic effects on the myocardium, by provoking coronary arterial spasm and by causing increased reduced reuptake of catecholamines. These vasoactive effects of cocaine are further complicated with enhanced platelet aggregation, anti-cardiolipin antibody formation, and endothelial release of potent vasoconstrictors such as endothelin 1. Upregulation of tissue plasminogen activator inhibitors, increased platelet aggregation, and deceased fibrinolysis by cocaine predispose to coronary and microvascular disease.[97]

Treatment

Other than abstinence, very little is known about treatment of cocaine-induced cardiac dysfunction. Indeed, there are case reports of reversibility of cardiac function after cessation of drug use.[99] Early reports of cocaine-induced hypertension and myocardial ischemia caused by unopposed α-effects of β_1-adrenergic blocking agents in cocaine-related chest pain resulted in caution against the use of β-blockers in cocaine-related cardiac presentations. Therefore, the routine use of propranolol and subsequently all β_1-specific blockers was not recommended in the acute setting of cocaine-related acute coronary syndrome.[100] On the other hand, the safety and efficacy of β-blockers in patients with chronic HF or cardiomyopathy related to cocaine are unknown. β-Blockers with α-blocking properties such as carvedilol (an α_1-, β_1-, and β_2-receptor antagonist) might not have significant unopposed α-agonism with cocaine and might be beneficial in patients with cocaine-associated cardiomyopathy, especially after declaration of abstinence.

Key Management Strategies for Cocaine-Related Cardiomyopathy

Recommendations With Moderate Level of Consensus for Cocaine-Related Cardiomyopathy

1. It is reasonable to treat patients with cocaine-related cardiomyopathy who have demonstrated abstinence for >6 months with standard therapy for LV dysfunction, including β-blockers *(Level of Evidence C)*.
2. In patients at risk for relapse for cocaine abuse, nonselective β-blocker treatment with α_1-, β_1-, or β_2-receptor antagonism is reasonable because of potential protection against the unopposed α-agonism effects of cocaine with β_1-receptor antagonist treatment alone *(Level of Evidence C)*.

Cardiomyopathy Related to Methamphetamines and Other Stimulant Drugs

In the past decade, methamphetamine abuse has been associated with increasing numbers of reports of MI, pulmonary edema, aortic dissection, and DCM.[101] Especially among adult patients <45 years of age, crystal amphetamine has been implicated in a large number of cardiomyopathy cases. Methamphetamine users have an almost 4-fold increased risk of developing cardiomyopathy compared with nonusers.[102,103] Methamphetamine-associated cardiomyopathy could be reversible with appropriate medical therapy and cessation of use. By some reports, late gadolinium-enhancement cardiovascular MR has been helpful to identify the magnitude of fibrosis and likelihood of recovery in methamphetamine-associated cardiomyopathy cases.[104]

Other cardiostimulant drugs, such as ecstasy (3,4-methylenedioxy-*N*-methylamphetamine, or MDMA),[105] "bath salts" that contain synthetic cathinones with amphetamine/cocaine-like properties such as mephedrone methylenedioxypyrovalerone,[106] and khat chewing, which contains cathinone,[107] have cardiotoxic effects and have been implicated in cases of MI, arrhythmias, cardiac arrest, and cardiomyopathy. Although rare, misuse or overdose of drugs used for attention deficit and hyperactivity disorder, such as methylphenidate, dextroamphetamine, and dextroamphetamine-amphetamine, has been associated with MI, cardiomyopathy, and sudden death.[108]

Key Management Strategies for Cardiomyopathy Related to Methamphetamines and Other Stimulant Drugs

Recommendation With Strong Level of Consensus for Cardiomyopathy Related to Substance Abuse

1. In patients with cardiomyopathy related to substance abuse or overdose, total abstinence from cardiotoxic agents and drugs is recommended *(Level of Evidence C)*.

Cardiomyopathy Related to Chemotherapeutic Agents

Epidemiology and Prognosis

Myocardial damage from cytotoxic agents used in the treatment of cancer has been described for >40 years. By far the most commonly implicated direct cardiotoxins are the anthracycline-based therapeutic agents. These medications are still an integral part of the treatment for cancer, although their toxicity is known. There are many formulations of anthracycline-based treatment at the present time, including doxorubicin, daunorubicin, mitoxantrone, epirubicin, and liposomal versions.[109] There have been a host of studies that attempted to gain an understanding of whether dosing frequency, length of each infusion, total dose, and concomitant therapy (such as trastuzumab) are major determinants of the severity of cardiomyopathy.[110] What is clear from the totality of data is that the risk of toxicity is related in part to the total dose; however, there is evidence that cardiotoxicity can be seen at much lower doses than previously thought. The early detection of cardiotoxicity related to anthracyclines has improved significantly over the years, and this is the likely explanation for identification of cardiotoxicity at lower doses. In highly susceptible patients, even 1 dose could be enough. The probability of developing impaired myocardial function based on a combined index of signs, symptoms, and decline in LVEF is estimated to be ≈5%, 16%, and 26% for cumulative doxorubicin doses of 400, 500, and 550 mg/m^2, respectively. The cumulative anthracycline dose limit is 400 to 450 mg/m^2.[111] Some patients have been noted to exhibit morphological changes with a cumulative dose as low as 200 mg/m^2,[112] and cardiac troponin can be detectable in some patients even after 1 treatment. Thus, there is no safe cutoff dose for anthracycline cardiotoxicity. The detection of troponin leakage in the peripheral blood during or after anthracycline treatment correlates with cardiac event rate and can identify cardiotoxicity from anthracycline treatment.[113] There have been many potential mechanisms that have been reported.[114] Predominantly, anthracyclines create reactive oxygen species that result in a cascade of events that are potentially cytotoxic. Recently, alterations of the topoisomerase IIβ pathway and genetic predisposition have been noted to be important for development of cardiotoxicity.[115,116]

The most important factor regarding the treatment of anthracycline-related cardiotoxicity is certainly early identification and initiation of typical HF medical therapy. The historical dogma is that anthracycline toxicity is considered irreversible principally because the problem was identified much later, after therapy was given. With early

identification, the large majority of patients with LV dysfunction will improve with timely HF-based therapy.[117,118]

The prognosis of anthracycline-induced cardiomyopathy relates to the time course of treatment and preexisting additional risk factors for myocardial injury, such as radiation, coexisting CAD, and preexisting cardiac dysfunction. Prior radiotherapy to the heart/mediastinum also increases the risk of doxorubicin-induced cardiomyopathy. Other factors that influence LVEF in patients receiving anthracycline-containing regimens include fluid overload, sepsis, ischemic heart disease, and use of other chemotherapy drugs. Prevention of anthracycline-induced myocardial damage by use of free radical scavengers and antioxidants could reduce cardiotoxicity in some patients.

Other therapeutic agents known to result in cardiomyopathy include trastuzumab[119–121] and certain anti–vascular endothelial growth factor inhibitors,[122–124] and there is early evidence that potent proteasome inhibitors, such as bortezomib and carfilzomib, have molecular targets that are common to cancerous tissue and the vulnerable myocardium, resulting in cardiomyopathy.[125] Trastuzumab, a monoclonal antibody directed against the HER2 receptor, is widely used for the treatment of HER2-positive breast cancer and has a major impact on overall outcomes of those patients[121]; however, there is clearly a signal of cardiac dysfunction in susceptible patients. It is acknowledged that there are HER2 receptors on the cardiomyocyte, and inhibition of the HER2:HER4 signaling process in the myocardium is principally responsible for the cardiotoxicity seen with this agent.[126] The important distinction with anthracyclines is that this inhibition is not typically cytotoxic, and thus, cardiomyocyte death is not usually seen with trastuzumab. With this difference, it appears that reversal of cardiac dysfunction is very likely with appropriate HF therapy.[119] There are a few anti–vascular endothelial growth factor–based therapies that have been associated with cardiomyopathy, including sunitinib, bevacizumab, and sorafenib.[127] These agents have not been in use as long for the treatment of cancer, and the cancers being treated with them are not as common as those for which anthracyclines and trastuzumab are used. For these reasons, there is not as much reported experience with the treatment of cardiac dysfunction related to these therapies. Significant hypertension usually precedes the development of HF with anti–vascular endothelial growth factor medications; it is also generally acknowledged that if blood pressure is well controlled with antihypertensive drugs, the risk of HF is low with anti–vascular endothelial growth factor therapy. Several other newer classes of medications for the treatment of cancer are in development; at this time, there are not enough data to clearly implicate them as causing cardiomyopathy, but with expanded clinical use, there could be subsequent clinical signals of concern.

Diagnosis

Cardiotoxicity is historically defined as an LVEF decline of ≥5% to <55% with HF symptoms or an asymptomatic decrease of LVEF ≥10% to <55% during cancer therapy, although other LVEF cutoffs (<50% as a lower limit of normal, for example) have been proposed.[128,129] In general, if test results indicate deterioration in cardiac function associated with doxorubicin, the benefit of continued therapy should be evaluated carefully against the risk of producing irreversible cardiac damage.

Measurement of cardiac biomarkers during chemotherapy could be a useful diagnostic tool for identification, assessment, and monitoring of cardiotoxicity with cancer therapy. In particular, the role of troponin in identifying patients at risk for cardiotoxicity is clearly emerging as a new, possibly effective approach.[113,130]

The cardiac troponin release pattern after chemotherapy identifies patients at risk for future events. Although the value and duration of troponin elevation correlate closely with the degree of LV dysfunction, the optimal time or the cutoff points for troponin levels for diagnosis of cardiotoxicity are not well defined in all populations and will need to be individualized.[113] Cardiac troponin levels combined with longitudinal strain measured by echocardiography appear to provide better prediction for development of cardiotoxicity than other biomarkers or imaging alone.[131]

Anthracycline-induced cardiotoxicity can be manifested by early (or acute) or late (delayed) events. Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia or electrocardiographic abnormalities such as nonspecific ST-T–wave changes, reduction of the QRS voltage, or QRS prolongation, but the ECG is not a sensitive or specific method for monitoring anthracycline-related cardiotoxicity. EMB is recognized as the most sensitive diagnostic tool to detect anthracycline-induced cardiomyopathy; however, this invasive examination is not performed routinely.

Cardiomyopathy and clinical HF can be encountered several months or years after discontinuation of doxorubicin therapy. The risk of acute manifestations of doxorubicin cardiotoxicity in pediatric patients can be as great as or lower than in adults. Pediatric patients appear to be at particular risk for developing delayed cardiac toxicity. Doxorubicin-induced cardiomyopathy impairs myocardial growth as pediatric patients mature, subsequently leading to possible development of HF during early adulthood. As many as 40% of pediatric patients could have subclinical cardiac dysfunction, and 5% to 10% of pediatric patients could develop HF on long-term follow-up.

Monitoring Cardiac Function

Serial Imaging

Before a patient begins chemotherapy or radiation treatment, a baseline cardiac evaluation of LV assessment, including LVEF measurement, is recommended.[129] This is especially important in patients with risk factors for in-

creased cardiac toxicity. The risk of serious cardiotoxicity could be decreased through regular monitoring of cardiac function during the course of treatment, with prompt discontinuation of cardiotoxic chemotherapy at the first sign of impaired LVEF. The commonly used methods for assessment of cardiac function include echocardiography, multigated radionuclide angiography, and cardiac MRI.[132] Multigated radionuclide angiography is highly reproducible, but each scan delivers a dose of 800 mSv, and cumulative radiation exposure limits the suitability of this technique for frequently repeated monitoring. Echocardiograms are used regularly by cardiologists to monitor LVEF because they do not expose patients to ionizing radiation and can provide further information on diastolic function, hemodynamics, and pericardial disease, as well as valvular function. Newer echocardiographic modalities such as diastolic functional assessment strain imaging can manifest contractile abnormalities not easily discernable by measurement of LVEF alone. Stressing the myocardium by use of exercise or ionotropic agents can also yield earlier evidence of cardiotoxicity. Cardiac MRI is also very useful for LV function and structure assessment and has little between-test variability and good receiver operating characteristics.[132] Delayed-enhancement gadolinium imaging, degree of fibrosis, and increased myocardial signal intensity are being studied as subclinical signs of cardiotoxicity in pilot studies.[133,134]

It is important to remember that comparison of LV function should be performed using the same technique, because there could be differences in quantification of LVEF between different modalities, and the technique used for assessment should be consistent throughout follow-up unless new information is required by different imaging. Repeated determinations of LVEF should be performed, particularly with higher cumulative anthracycline doses, and the frequency of imaging might need to be individualized.[135] In patients with risk factors, particularly prior anthracycline use, the monitoring of cardiac function must be particularly strict, and the risks and benefits of continuing treatment with doxorubicin in patients with impaired cardiac function must be evaluated carefully.

Other imaging modalities such as radiolabeled metaiodobenzylguanidine or metaiodobenzylguanidine scintigraphy appear to detect doxorubicin-induced cardiomyopathy but have not been widely accepted. Radiolabeled anti-myosin antibodies have been shown to predict severe cardiotoxicity at low doxorubicin doses[136] and could be very sensitive, but they appear to lack the specificity to predict which patients should stop treatment.

Serial Laboratory Markers

The role of serial serum measurements of troponin (T and I isoforms) and atrial natriuretic peptide or BNP for cardiotoxicity is currently being investigated. Elevated troponin I after high-dose chemotherapy has been shown to predict LVEF decline,[137] and serial troponin I measurements can help stratify patients into different risk categories for future cardiac events.[113] On the other hand, in a prospective trial, elevated serum levels of atrial natriuretic peptide or BNP did not predict LVEF decline.[138] Proteomics have been shown to predict anthracycline-induced cardiotoxicity in animal models.[139] Surveillance for prediction and detection of cardiotoxicity using laboratory markers requires further validation before this strategy can be adopted for clinical use.

Prevention

Despite efforts to identify risk factors, develop less toxic derivatives, and detect subclinical toxicity earlier, there is no consensus on the best approach to prevent anthracycline-induced cardiotoxicity. Primary prevention strategies include reducing cardiotoxicity by administering anthracyclines via continuous infusion, which results in lower peak blood concentrations than bolus infusion; using liposome encapsulation; using less cardiotoxic derivatives (eg, epirubicin or idarubicin); or using cardioprotective agents such as dexrazoxane in conjunction with treatment. Other investigated agents include use of β-blockers, ACE inhibitors, and ARBs even before development of cardiomyopathy. Various anthracycline schedules were evaluated in early clinical trials, including a single bolus dose every 3 weeks, 3 divided doses every week, or 3 divided doses given on 3 consecutive days every 3 weeks. Divided doses appear to cause significantly less damage than bolus doses.[140] Another strategy to reduce cardiotoxicity is to use liposomal encapsulation, which modifies pharmacokinetics and tissue distribution, restricting anthracyclines to inside the vessel wall of organs with tight capillary junctions (such as the heart), where it can more readily penetrate through tumor vasculature without compromising antitumor efficacy.[141,142] Dexrazoxane is the only cardioprotective agent for anthracycline-induced cardiotoxicity that has been approved by the US Food and Drug Administration.[143–145] Although the primary mechanism of cardioprotection against dexrazoxane was thought to be through iron chelation, with recognition that other iron chelators do not perform similarly, its mechanism of protection is now thought to be through its interference with topoisomerase 2β, which conceals DNA double-strand breaks.[146]

In several small clinical trials, β-blockers (carvedilol, metoprolol, nebivolol) or ACE-inhibitor therapy (enalapril) prevented declines in LVEF compared with control groups given anthracycline therapy.[147–150] These studies were small, with relatively short-term follow-up (5 to 6 months), did not demonstrate any differences according to cardiac troponin levels or cardiac MRI findings, and were not powered to address clinical outcomes. Treatment with β-blockers, ACE inhibitors, or ARBs preemptively to prevent cardiac toxicity of chemotherapy has not been widely adopted, although high-risk patients did

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appear to benefit from the combination of carvedilol and enalapril in a randomized prospective trial.[142,147]

Treatment

In patients who have evidence of cardiotoxicity detected by cardiac biomarkers such as troponin, the natriuretic peptides, or imaging with the latest technology (such as strain imaging), it is best to initiate treatment with HF medications. Several studies examined treatment with β-blockers or ACE inhibitors[117,151,152] for secondary prevention in high-risk patients after anthracycline treatment. Most found that LVEF recovery was more likely with early initiation of an ACE inhibitor and β-blocker. Systolic HF should be treated with guideline-directed medical therapy according to current guidelines.[1] If LVEF improves on subsequent reassessments, treatment can be restarted after multidisciplinary assessment, with risk of recurrent cardiac injury taken into consideration.

Key Management Strategies for Cardiomyopathy Related to Chemotherapeutic Agents

Treatment Recommendations With Strong Level of Consensus for Cardiomyopathy Related to Chemotherapeutic Agents

1. Patients treated with cardiotoxic chemotherapeutic agents should have cardiac functional assessment with LVEF measurement at baseline, after completing treatment, and while on treatment at regular intervals, or sooner if HF symptoms develop *(Level of Evidence B)*.[128]
2. If test results indicate deterioration in cardiac function associated with cardiotoxic chemotherapy, the benefit of continued therapy should be carefully evaluated against the risk of producing irreversible cardiac damage *(Level of Evidence C)*.
3. Cancer patients with systolic HF should be treated with guideline-directed medical therapy *(Level of Evidence B)*.[1,151]

Recommendations With Moderate Level of Consensus for Cardiomyopathy Related to Chemotherapeutic Agents

1. Measurement of cardiac troponin is reasonable to identify patients at risk of cardiotoxicity with cancer therapy *(Level of Evidence B)*.[113,137]
2. In patients at high risk for cardiac toxicity, strategies such as administration of divided continuous infusions, liposome encapsulation, use of less cardiotoxic derivatives, or use of cardioprotective agents such as dexrazoxane in conjunction with treatment can be useful to reduce cardiotoxicity of doxorubicin chemotherapy *(Level of Evidence B)*.[140–145]

Recommendations With Uncertainty for Cardiomyopathy Related to Chemotherapeutic Agents

1. The usefulness of serial/repeated measurements of cardiac biomarkers for monitoring cardiotoxicity with cancer therapy is uncertain *(Level of Evidence C)*.[138]
2. Usefulness of β-blockers, ACE inhibitors, or ARBs for primary prevention of cardiac toxicity of chemotherapy is uncertain at this time *(Level of Evidence B)*.[147–150]

Other Myocardial Toxins

In addition to the classic toxins described above, there are a number of other potentially toxic agents that can lead to LV dysfunction and HF, including phenothiazines, antidepressant drugs, carbon monoxide, lead, lithium, methysergide, pseudoephedrine, ephedrine, cobalt, anabolic steroids, hydroxychloroquine, clozapine, and catecholamines.[153] One such agent, ephedra, which has been used for the purposes of athletic performance enhancement and weight loss, has been linked to a high rate of serious adverse outcomes, including LV systolic dysfunction, development of HF,[154–156] and cardiac deaths. This resulted in a ban of this agent by the US Food and Drug Administration, and ephedra is included in the list of prohibited substances in sport by the World Antidoping Agency. High doses of decongestants such as pseudoephedrine or ephedrine have also been implicated in cardiotoxicity,[157] and overuse should be avoided.

PERIPARTUM CARDIOMYOPATHY

Epidemiology

Initially described in 1849, peripartum cardiomyopathy (PPCM) is defined as HF caused by idiopathic systolic dysfunction presenting during the last month of pregnancy or in the first 5 months postpartum. Over the past decade, investigators have recommended a broader definition of *pregnancy-associated cardiomyopathy*, which includes cardiomyopathy presenting earlier in pregnancy.[158,159] PPCM is considered to be a rare cause of HF, yet the incidence appears to be increasing, possibly because of increased recognition. Other factors that could account for the higher incidence of PPCM include increasing maternal age and the rise in multifetal pregnancies.[160] The true incidence of PPCM is difficult to discern because of variations in study methods, definitions, and population studied. Most studies have been conducted in limited populations in the United States, South Africa, and Haiti. When these limitations are taken into account, the incidence of PPCM has been described as 1 in 1149 to 1 in 4350 live births in the United States, 1 in 1000 in South Africa, and 1 in 300 in Haiti.[161–165] In a population study using the National Hospital Discharge Survey to evaluate incidence of PPCM in the United States in >51 million live births, there was a trend toward increased incidence of PPCM from 1990 to 2002. Between 1990 and 1993, the incidence of PPCM was 1 in 4350 live births and increased to 1 in 2229 live births between 2000 and 2002. The mean incidence of PPCM in this study was 1 in 3189 births.[161]

Ethnicity

PPCM has a higher incidence among women of African descent, although socioeconomic factors may confound this association.[161,162] The Peripartum Cardiomyopathy Research Study, a population study of >240 000 deliveries designed to evaluate PPCM incidence, outcomes, and predictors in an ethnically diverse southern California population, demonstrated a much higher incidence of PPCM in black women, 1 in 1421 deliveries, than in Hispanics, Asians, and whites. Hispanic women had the lowest incidence of PPCM, 1 in 9861 deliveries. PPCM occurred in 1 in 2675 deliveries in Asians and in 1 in 4075 deliveries in whites.[162] A similar study conducted in Augusta, GA, and Memphis, TN, found that black women had a 15.7-fold risk of PPCM compared with nonblack women.[166] Black women remained at significant risk even after adjustment for other risk factors such as income, hypertension, diabetes mellitus, alcohol use, tobacco, age, and number of pregnancies.

Pathogenesis

The pathogenesis of PPCM remains unknown; however, it is suspected that there are both inflammatory and genetic components. The timing of the most common presentation in the early postpartum period suggests an autoimmune component, most likely related to the cessation of the need for fetal tolerance and the resetting of maternal cellular immunity.[167] Viral causes and nutritional deficiency could play a significant role, particularly in areas of the world such as those with very high incidence.[163] Genetic predisposition and familial syndromes have been recognized in women with PPCM, with a similar rate to that seen in other forms of primary nonischemic DCM.[168,169] A genome-wide association analysis discovered and replicated a novel genomic locus linked to an increased risk of PPCM at chromosome 12p11.22,[170] providing further supporting evidence of a genetic pathogenesis for PPCM.

Prognosis

Although prognosis appears to vary somewhat by geographic region and perhaps ethnicity, overall prognosis appears to be improving either as a result of better medical management of HF, earlier recognition, or both.[159,171,172] Heart transplantation is performed in 6% to 11% of patients with PPCM.* The mortality of PPCM has been reported to be lower than that of other forms of cardiomyopathies.[26] In the United States, the mortality after diagnosis of PPCM has ranged from 0% to <10% in contemporary analyses.[26,160–162,175] Amos and colleagues[173] reported no mortality in a US population at a mean follow-up of 43 months in 55 patients with PPCM who were followed up between 1990 and 2003. In that study, 62% of patients improved, and of those, 75% had a subsequent LVEF >45%. Most studies in the United States have consisted of predominantly white populations, which may have favorably skewed the prognosis. A US study that targeted an indigent population of mostly black women demonstrated a mortality rate of 15.9% at 2 years, similar to the mortality seen in Haiti and South Africa.[171] Blacks appear to have a 6.4-fold increased risk of death compared with whites.[176]

In South Africa and Haiti, mortality related to PPCM appears to be higher than that in the general population in the United States. In South Africa, the mortality rate is 10% to 15% at 6 months and 28% at 2 years, although it was higher in earlier reports.[158,172,177] In Haiti, mortality has been reported to be up to 15% at 2.2 years.[163] Cause of death is usually sudden cardiac death or progressive HF.[174,176]

Cardiomegaly that persists for >4 to 6 months after diagnosis indicates a poor prognosis, with a 50% mortality rate at 6 years. Recovery of LV function is seen in approximately two thirds of patients, and recovery of LV function is higher in women with baseline LVEF ≥30% than in those with LVEF <30%.[174] Early recovery in patients with PPCM appears to be significantly related to the degree of myocardial insult at the time of diagnosis. Baseline LVEF, however, has a limited sensitivity for prediction of failure to improve in individual patients.

Recovery of LV Function

Recovery of LV function (EF ≥50%) has been reported in 45% to 78% of women with PPCM among US patients.[173,174,178] Most recovery appears to occur during the first 6 months after diagnosis, although late recovery can occur.[159] Ventricular dilatation has been reported to be a poor prognostic sign for recovery, with 1 study suggesting that an initial LV end-diastolic dimension >5.6 cm was associated with less recovery.[164] Other potential predictors of recovery include higher initial EF, presence of gestational hypertension, breastfeeding, postpartum diagnosis, lack of troponin elevation, lower BNP, absence of LV thrombus, and nonblack ethnicity.[173,174,178–181] In a small study of 7 women, the presence of contractile reserve was associated with recovery of LV function.[182] Of note, withdrawal of HF therapy did not appear to be associated with clinical deterioration over a follow-up period of 29 months in a single-center study.[173]

Subsequent Pregnancy

Subsequent pregnancy in women with PPCM has been associated with a substantial rate of recurrence, notably a reduction in LVEF and recurrence of HF.[183] In a cohort described by Elkayam et al,[184] 21% of women with re-

*References 26, 161, 162, 164, 171, 173, 174.

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covered LV function and 44% of those with persistent LV dysfunction had a 20% reduction in EF with subsequent pregnancy. Although none of the patients with recovered LV function died, 19% of those with persistent LV dysfunction died. Contractile reserve by stress echocardiography has been suggested to assist in risk stratification in women with recovered LVEF.[184] Women with seemingly recovered LV function may have abnormal contractile reserve, which suggests an impaired ability to handle hemodynamic stress,[185] whereas the presence of normal contractile reserve can identify women with recovered LV function who may be at low risk of relapse.[186] In summary, in women with a history of PPCM and persistent LV dysfunction, subsequent pregnancy carries a significant mortality risk and is clearly contraindicated. Even women who have completely recovered LV function before the subsequent pregnancy could experience a significant reduction in LV function and should be counseled on the risk of subsequent pregnancy.

Clinical Presentation

The most common clinical presentation of PPCM consists of symptoms consistent with LV dysfunction and congestive HF. Symptoms may mimic those encountered in a normal pregnancy and in other cardiopulmonary diseases such as pulmonary embolus or CAD, which could contribute to delayed or missed diagnosis. Physical examination may reveal tachycardia, hypertension, mitral regurgitation murmur, ascites, splenomegaly, S_3 gallop, and jugular venous distention, and postural hypotension can be present in the later stages.[165,179,187] LV thrombus, with embolic complications including MI caused by coronary emboli, has been reported.[188] LV hypertrophy and nonspecific ST-T–wave changes are among the most common electrocardiographic findings; however, sinus tachycardia and normal or low-voltage QRS complexes with inverted T waves can also be present.[179]

Diagnosis

To confirm the diagnosis of PPCM, a full history, physical examination, and diagnostic testing should be completed to exclude a previous history of heart disease and other causes of cardiomyopathy. For the classic definition of PPCM, the history should confirm that the onset of HF began in the last months of pregnancy or the months after delivery, and cardiac evaluation should confirm the presence of LV dysfunction.[158,189] Usual HF symptoms should prompt an evaluation of PPCM when seen in women during the puerperium period.[190,191] Symptoms can mimic those encountered in a normal pregnancy and in other cardiopulmonary diseases such as pulmonary embolus or CAD, which can contribute to delayed or missed diagnosis impacting outcomes.[174] Pregnancy-induced hypertension or preeclampsia has been found in up to 68% of patients presenting with PPCM.[159,171,179,192] Noncardiac conditions such as pneumonia or other acute lung injury, pulmonary embolus, amniotic fluid embolus, or renal failure with volume overload should be considered in the differential diagnosis. Timely diagnosis of PPCM should occur to prevent delay of treatment and potential related complications.[173] Multidisciplinary care for patients with PPCM should include cardiologists, high-risk obstetrics and perinatologists, cardiac anesthesiologists, cardiac intensivists, and pediatricians.[158,193] Genetic predisposition can play a role in development of PPCM; therefore, in patients in whom PPCM is suspected who have a familial pattern and history, genetic testing and genetic counseling could be helpful.

The usual laboratory assessment for suspected cardiomyopathies should be completed. A chest radiograph should be performed to rule out other causes of dyspnea and to assess for cardiomegaly, pleural effusions, and other evidence of congestion.[191,193] An ECG should be performed in patients presenting with presumed PPCM to assess for atrial and ventricular arrhythmias and other electrocardiographic abnormalities (LV hypertrophy, sinus tachycardia, and nonspecific ST-T–wave abnormalities) that are often present in patients presenting with PPCM.[174,191,193]

Natriuretic peptide levels (BNP or N-terminal proBNP) are usually elevated in patients with PPCM.[180] Measurement of cardiac troponin at the time of diagnosis can be considered, because it has moderate predictive ability for ventricular recovery, and levels correlate inversely with LV function recovery at follow-up.[181] Markers of inflammation such as C-reactive protein, high-sensitivity C-reactive protein, oxidatively modified low-density lipoprotein, interferon-γ, and Fas/apolipoprotein 1 are usually elevated in patients with PPCM,[172,180] but their role in diagnosis or prognosis is uncertain at this time.

Cardiac Assessment Imaging

Cardiac imaging should be performed to assess the presence and extent of LV dysfunction and to assess the degree of dilation, because both have relevant prognostic implications. Such imaging will further assess the presence of an intracardiac thrombus.[158,189] Echocardiography is most commonly used to evaluate suspected PPCM and can demonstrate moderate to severe LV systolic dysfunction, LV dilatation, 4-chamber enlargement, mitral and tricuspid regurgitation, biatrial enlargement, elevated pulmonary pressures, and RV enlargement.[160,164,175] Hibbard and colleagues[194] proposed strict echocardiographic parameters as part of the definition of PPCM, which included EF <45% or fractional shortening <30% and increased LV end-diastolic dimension >2.7 cm/m^2. However, although evidence of systolic dysfunction is necessary for the generally accepted diagnosis of PPCM, LV enlargement is not required.

Cardiac MRI has been evaluated in several small studies and case reports and is a reasonable choice as the imaging modality for patients suspected of having PPCM.[195–198] The use of gadolinium during a cardiac MRI is not recommended during pregnancy.[199] Although MRI can be useful in evaluating chamber size and function and determining the presence of LV thrombus, the role of cardiac MR in predicting recovery potential remains uncertain, and data are limited. In a study of 8 women with PPCM, none exhibited late gadolinium enhancement, and there was no difference in the patterns between those who experienced LV recovery and those who did not.[197]

Assessment for Ischemia

Left-sided heart catheterization or noninvasive testing for ischemia can be considered in some patients presenting with PPCM to assess the suspected presence of CAD, particularly those women at higher risk for CAD. LV thrombus, with embolic complications including MI caused by coronary emboli, has been reported in patients with PPCM.[188] Thus, assessment for ischemia is important, particularly in those women at higher risk for coronary events.

Endomyocardial Biopsy

The role of EMB in the evaluation of PPCM remains limited, and in general, EMB does not assist in therapy or the determination of recovery potential. An EMB can be considered for selected women suspected of having PPCM, yet its role remains controversial.[200,201] There are several older reports of lymphocytic infiltrate and myocarditis in patients with PPCM.[202–204] In a population of 18 women with PPCM, Bhakta et al[201] and Midei and colleagues[202] found myocarditis in 78% as early as 7 days after presentation and as late as 6.5 months. However, the incidence of lymphocytic myocarditis varies widely in published series and closely parallels the incidence found in biopsy series of other forms of recent-onset cardiomyopathy.

In summary, high suspicion for PPCM based on a complete medical history and physical examination should prompt further evaluation, because missed or delayed diagnosis can result in significant morbidity and mortality.

Key Diagnostic Strategies for PPCM

Recommendations With Strong Level of Consensus for PPCM

1. Timely diagnosis of PPCM should occur to prevent delay of treatment and potential related complications[174] *(Level of Evidence C).*
2. Criteria for the diagnosis of PPCM should include a history confirming the onset of HF began in the last months of pregnancy or the months after delivery, the presence of LV dysfunction, and the exclusion of other reasons for cardiomyopathy *(Level of Evidence B).*
3. Cardiac imaging should be performed to assess the presence and extent of LV dysfunction, the degree of dilation, and the presence of an intracardiac thrombus at the presentation of PPCM[158,189] *(Level of Evidence B).*
4. PPCM patients should be managed by a multidisciplinary team, which should include cardiologists, high-risk obstetricians, and perinatologists, and also may include cardiac anesthesiologists, cardiac intensivists, and pediatricians[158] *(Level of Evidence C).*

Recommendations With Uncertainty for PPCM

1. The use of cardiac biomarkers such as cardiac troponin or natriuretic peptides is of uncertain benefit for diagnosis, prognosis, or prediction of recovery of patients with PPCM[180,181] *(Level of Evidence B).*
2. The usefulness of cardiac imaging, including echocardiography or cardiac MR, in predicting recovery from PPCM remains uncertain[160,164,174,175,197] *(Level of Evidence B).*

Treatment

Guideline-directed medical therapy known to have benefit in treating LV dysfunction and HF should be considered,[1] but it is important to take into account both pregnancy and breastfeeding status, because certain classes of medications are not safe (Table 2[205–208]). Management of acute decompensated HF in the setting of PPCM should mirror that of acute HF of other causes.[1,191]

Mechanical circulatory support (MCS), either as temporary or bridge to transplantation, and heart transplantation have been used successfully in patients with PPCM for whom medical therapy has failed and who require continuous inotropic therapy.[1,158,209–211] Given the hypercoagulable state known to exist during pregnancy, anticoagulation can be considered in patients with PPCM with severe LV dysfunction (LVEF <30%) to prevent thrombus formation,[158,174,193,212] but warfarin should not be used during pregnancy.

Special Consideration for Therapy During Pregnancy

Pregnant women with PPCM should be referred to a center with experience with this condition for multidisciplinary care with close monitoring before, during, and after delivery. Diuretic agents should be used when appropriate to treat volume overload, yet they should be used sparingly to avoid reductions in fetal blood flow.[211,212] ACE inhibitors or ARBs are contraindicated during pregnancy because of significant fetal risks.[213] As an alternative to ACE inhibitors or ARBs, hydralazine can be considered for the management of hypertension in pregnant women with PPCM, with or without intravenous nitroglycerine or long-acting nitrates.[214] Use of β-blockers during pregnancy can af-

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Table 2. Safety of Cardiac Medications During Pregnancy

Medication	Pregnancy Safety*[205]	Lactation Safety[205–207]	Considerations
ACEI/ARB	Category D	Not for use in nursing	Benazepril, captopril, or enalapril may be considered during breastfeeding[205,207]†
			Candesartan and losartan: risk during breastfeeding cannot be ruled out†
β-Blockers			β_1-selective preferred
Metoprolol succinate	Category C	Caution	May cause fetal bradycardia, growth retardation, hypoglycemia[205,207]
Carvedilol	Category C	Not for use in nursing	Metoprolol: compatible with breastfeeding‡
			Carvedilol: risk during breastfeeding cannot be ruled out†
Aldosterone antagonist			Potential fetal androgenic effects
Spironolactone	Category C	Not for use in nursing	Spironolactone: compatible with breastfeeding‡
Eplerenone	Category B		Eplerenone: risk during breastfeeding cannot be ruled out†
Diuretic agents	Category C	Caution	May cause reduced fetal blood flow[207]
			Furosemide: risk during breastfeeding cannot be ruled out†
Digoxin	Category C	Caution	Compatible with breastfeeding†
Hydralazine	Category C	Caution	Compatible with breastfeeding†
Warfarin	Category X	Caution	Category D during pregnancy if mechanic heart valve present[205]
			Compatible with breastfeeding†
Heparin (intravenous)	Category C	Caution	Compatible with breastfeeding†
Enoxaparin	Category B	Not for use in nursing	Risk during breastfeeding cannot be ruled out†
Nitroglycerin	Category C	Caution	Risk during breastfeeding cannot be ruled out†
Nitroprusside	Category C	Not for use in nursing	Risk during breastfeeding cannot be ruled out†
			Risk of cyanide toxicity
Nesiritide	Category C	Caution	Risk during breastfeeding cannot be ruled out†
Milrinone	Category C	Caution	Risk during breastfeeding cannot be ruled out†
Dobutamine	Category B	Not for use in nursing	Risk during breastfeeding cannot be ruled out†
Dopamine	Category C	Caution	May alter milk production/composition†
Epinephrine	Category C	Caution	Risk during breastfeeding cannot be ruled out†

ACEI indicates angiotensin-converting enzyme inhibitor; and ARB, angiotensin receptor blocker.

*US Food and Drug Administration pregnancy category: A, controlled studies show no risk to fetus; B, either animal studies show no risk and there are no controlled trials in humans, or animal studies have shown risk but controlled trials in humans showed no risk; C, no evidence of risk in humans, but animal studies show increased risk to fetus; D, positive evidence of risk in humans; and X, positive fetal risk.

†According to information available from Micromedex Solutions.[208]

‡From Committee on Drugs, American Academy of Pediatrics.[207]

fect the growing fetus by slowing fetal heart rate and lowering fetal blood sugar level and blood pressure. Animal studies have revealed evidence of fetotoxicity and teratogenicity at high human doses, and most β-blockers have been assigned to pregnancy category C by the US Food and Drug Administration.[207] However, there are no controlled data in human pregnancy. For patients with PPCM, β-blockers can be used, although with caution, with monitoring of fetal heart rate and growth. β-Blockers have long been used in pregnant women with hypertension without any known adverse effects on the fetus, and it is usually believed that if the benefit outweighs the risk, patients who have been taking these agents before diagnosis can continue to use them.

Prompt delivery is recommended for patients with PPCM who are unstable.[215,216] Vaginal delivery is preferred for patients with PPCM. Delivery through cesarean section should be reserved for patients with PPCM who are critically ill or for other obstetric indications.[215,217] Earlier delivery may not be required if the mother and fetus are stable.

Breastfeeding

Breastfeeding in women with PPCM is controversial, and conflicting data exist. A retrospective study has suggested better outcomes among women who breastfeed[178]; however, other investigators have suggested that prolactin subfragments will have negative effects on myocardial recovery and are specifically involved in the pathogenesis of PPCM. In general, ACE inhibitors are not recommended for women who are breastfeeding infants, particularly during the infant's first month of life,[218] because of concerns about the potential for neonatal hypotension. However, given very low levels in breast milk for several ACE inhibitors studied, including captopril, enalapril, benazepril, and quinapril, the likelihood of significant levels of these drugs in a breastfed infant is small.[219] Although in general, breastfeeding is not recommended for women with decompensated HF who require significant medical therapy, the risk and benefits of breastfeeding for mother and child need to be balanced carefully.

Device Therapy

It may be reasonable to allow for ≥6 months of optimal medical therapy in patients with PPCM to allow for possible myocardial recovery when considering the timing of placement of a cardiac device such as an ICD with or without CRT using current guideline selection requirements.[1,158,173,174,220,221] Wearable defibrillator life vests for high-risk patients with LVEF <35% can be considered while waiting for a response to medical therapy in the absence of a clear indication for an ICD.[176,222]

Continuing Medical Therapy and Follow-up

The duration of standard HF treatments should be indefinite, specifically when ventricular function fails to normalize.[191] HF medications are sometimes discontinued in the setting of normalized ventricular function after 12 months of treatment,[191] but this is very controversial and is not supported by trial data. Close clinical follow-up with annual assessment of LVEF should be performed for a minimum of several years after recovery, particularly if subsequent pregnancy is still being considered.[220]

Family Planning

Discussions about future family planning should occur with patients with PPCM and their partners. Patients with PPCM whose ventricular function does not normalize should be counseled against a subsequent pregnancy because it carries a significant risk of morbidity and mortality.[184] Even in the setting of normalized ventricular function,[183,184,193] women with a history of PPCM should be counseled that a subsequent pregnancy carries a 20% risk of recurrent HF and LV dysfunction. Dobutamine stress testing has been recommended in women with apparent recovery of LV function who are considering a pregnancy to assess contractile reserve and further risk stratify the potential for recurrence, but this has not been validated prospectively.[184]

Experimental Therapies

Bromocriptine has been suggested as adjunctive treatment for PPCM to decrease prolactin on the basis of its proposed mechanistic role in this syndrome. Bromocriptine as therapy for PPCM has been investigated in animal models and in a small 20-patient study in South Africa[223]; however, its efficacy has not been established, and a European randomized trial is now under way. Further study is needed before recommendations on its use can be issued. Pentoxifylline, a nonselective phosphodiesterase inhibitor that increases intracellular adenosine 3′,5′-cyclic phosphate, inhibits tumor necrosis factor synthesis, and reduces inflammation, has also been studied in a limited PPCM population and was associated with improvements in ventricular function, NYHA functional class, and survival; however, this result has not been replicated, and its safety is not well established. Its widespread use will require further study.[224] In a small series of women with PPCM treated with immunoglobulin,[225] improvements in ventricular function were reported, but this was not confirmed in a larger randomized trial in subjects with recent-onset cardiomyopathy.[226] In a similar fashion, immunosuppressive therapy was used previously in patients with PPCM on the basis of the occasional finding of lymphocytic myocarditis; however, in the absence of proven benefit for subjects with lymphocytic myocarditis in the Myocarditis Treatment Trial,[227] immunosuppression is not recommended for patients with PPCM, particularly given the expense and potential adverse effects of this therapy.

Key Treatment Strategies for PPCM

Treatment Recommendations With Strong Level of Consensus for PPCM

1. Guideline-directed medical therapy known to benefit patients with LV dysfunction (ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists) and HF should be considered,[1] taking into account both pregnancy and breastfeeding status because certain classes of medications may not be safe during pregnancy or lactation *(Level of Evidence B)*.
2. The duration of standard HF medications in patients with PPCM should be indefinite when LV function fails to normalize[1] *(Level of Evidence C)*.
3. Patients with PPCM whose ventricular function does not normalize after pregnancy should be counseled against a subsequent pregnancy, because it carries a significant risk of morbidity and mortality[174,183,184] *(Level of Evidence B)*.
4. Cardiac device therapy with an ICD, CRT, or both should be considered for patients with PPCM whose

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ventricular function does not normalize after pregnancy according to current guidelines[1,221] *(Level of Evidence B)*.

5. Patients with PPCM for whom medical therapy has failed and who require continuous inotropic therapy should be considered for temporary or bridge MCS or for heart transplantation[1,158,209–211] *(Level of Evidence B)*.
6. Prompt delivery is recommended for pregnant women with PPCM whose condition is unstable or who have maternal extremis[215–217] *(Level of Evidence B)*.
7. Close clinical follow-up with annual assessment of LVEF should be performed for a minimum of several years after recovery, particularly if subsequent pregnancy is still being considered[174,220] *(Level of Evidence B)*.
8. Pregnant women with PPCM should be referred to a center with experience with this condition for multidisciplinary care, with close monitoring before, during, and after delivery *(Level of Evidence C)*.

Treatment Recommendations With Moderate Level of Consensus for PPCM

1. Anticoagulation is reasonable in patients with PPCM and severe LV dysfunction to prevent thrombus formation given the risk of hypercoagulable state during pregnancy[158,174,193,212] *(Level of Evidence C)*.
2. It is reasonable to allow for ≥6 months of standard medical therapy in patients with PPCM to allow for possible myocardial recovery when considering the timing of placement of a cardiac device such as an ICD, with or without CRT[158,173,174,220] *(Level of Evidence B)*.

Treatment Recommendations With Uncertainty for PPCM

1. The efficacy and safety of experimental therapies such as bromocriptine or pentoxifylline for treatment of PPCM are uncertain at this time[223,224] *(Level of Evidence B)*.
2. Wearable defibrillator life vests for high-risk patients with LVEF <35% may be considered while waiting for a response to medical therapy in the absence of a clear indication for an ICD[174,222] *(Level of Evidence B)*.

Strategies to Avoid With Concern for Harm for PPCM

1. In women with a history of PPCM and persistent LV dysfunction, subsequent pregnancy carries a significant mortality risk and is contraindicated *(Level of Evidence C)*.
2. The use of gadolinium during a cardiac MRI is potentially harmful to the fetus during pregnancy[199] *(Level of Evidence B)*.
3. Use of ACE inhibitors, warfarin, or ARBs is potentially harmful during pregnancy because of significant fetal risks[213] *(Level of Evidence B)*.

CARDIAC SARCOIDOSIS

Definition and Pathophysiology

Sarcoidosis is a multisystem inflammatory disease of unknown origin characterized by noncaseating granuloma formation in multiple organ systems.[228–231] After an early stage of granulomatous inflammation, sarcoidosis can resolve or progress to end-organ fibrosis. Autopsy series suggest that 20% to 50% of patients with sarcoidosis have some degree of cardiac involvement[228,232,233]; however, only a fraction of these patients have clinically recognized cardiac sarcoidosis. At early stages of the disease, the majority of cardiac sarcoidosis cases are clinically silent. The incidence of progressive HF, conduction abnormalities, malignant arrhythmias, and sudden cardiac death increases markedly as cardiac sarcoidosis becomes clinically recognizable.[230,231] Cardiac sarcoidosis most commonly affects the myocardium but can also affect the pericardium and endocardium.[234] Myocardial infiltration may be associated with conduction disease, ventricular tachycardia, aneurysm formation, or global reductions in LVEF. It is estimated that ≈5% of patients will have cardiac-predominant disease, but present without characteristic pulmonary, dermatologic, or ocular features.[228] Cardiac disease is one of the more common causes of death in sarcoidosis.[229–231] This mortality risk may be preventable with the use of appropriate therapies.

Diagnosis

The diagnosis of cardiac sarcoidosis can be challenging.[229] The noncaseating granuloma is the characteristic pathological lesion of sarcoidosis; however, these granulomas are not specific to sarcoidosis and can be the result of various infectious and noninfectious causes.[228–231] Diagnostic criteria for cardiac sarcoidosis have been proposed that rely on pathological demonstration of cardiac granulomas or noninvasive evidence of cardiac involvement in a patient with pathologically proven extracardiac sarcoidosis.[234]

The evaluation includes a detailed history and physical examination, ECG, and chest radiograph. Abnormal electrocardiographic findings include bundle-branch block, new atrioventricular block, frequent premature ventricular complexes, ventricular tachycardia, pathologic Q waves, and ST-T changes. First-degree heart block caused by disease of the conduction system is common and can progress to complete heart block.[228,229] In patients with clinically evident cardiac sarcoidosis, complete heart block is a common finding. Complete heart block occurs at a younger age in patients with sarcoidosis than in patients with complete heart block attributable to other causes.[230] Any of these electrocardiographic findings should prompt further investigation.[234] Patients with cardiac symptoms, an abnormal ECG, or

cardiomegaly on chest radiograph should be evaluated with transthoracic echocardiogram, Holter monitoring, and subsequent advanced imaging.[228,229,231]

Echocardiography is an essential component of the diagnostic workup of patients with suspected cardiac sarcoidosis.[229,230,235] Abnormalities in ventricular systolic and diastolic dysfunction, wall-motion abnormalities, abnormal septal thickness, and abnormal Doppler filling patterns are the most frequent findings suggestive of cardiac sarcoidosis. Holter monitoring also plays an important part in the diagnostic workup.[230] More than 100 ventricular ectopic beats in 24 hours has been proposed as an evaluation criteria.[230]

Because the myocardial lesions in cardiac sarcoidosis are patchy, and many involve only the LV, an RV EMB provides diagnostic evidence of cardiac sarcoidosis in only 25% to 50% of autopsy-confirmed cases.[232] Cardiac MRI with late gadolinium enhancement has emerged as a valuable imaging tool for the diagnosis of cardiac involvement in sarcoidosis.[229,235,236] Early enhancement of sarcoid granulomas in T2-weighted gadolinium images suggests the presence of inflammation and edema.[235–237] Late enhancement in T2-weighted gadolinium images suggests fibrotic changes and scarring.[235,236] The most common areas of distribution of lesions are usually midmyocardial, with preferential involvement of the basal segments of the septum and lateral walls.[235,236] On the basis of current evidence, cardiac MRI, if available, is considered the imaging study of choice in patients suspected of having cardiac sarcoidosis.[235,236] Positron emission tomography imaging with fluorodeoxyglucose can also identify inflammation and has better diagnostic accuracy than older techniques.[235–237] It has also been reported that positron emission tomography imaging can predict adverse clinical events.[237]

The prognosis of patients with symptomatic cardiac sarcoidosis has not been well characterized. In an autopsy series that included 113 patients, survival in most patients was limited to ≈2 years after the development of cardiac signs and symptoms.[232] More recent reports suggest substantially better outcomes: 44% of 250 patients survived for >5 years after the diagnosis of cardiac sarcoidosis, and 75% of 75 steroid-treated patients survived for 5 years.[238] Yet the majority of patients in these series ultimately died of cardiac complications of sarcoidosis. Survival was reported to be 89% for patients with an EF ≥50%.[239] Important predictors of mortality include LV end-diastolic diameter, NHYA functional class, and sustained ventricular tachycardia.[239]

Treatment

Corticosteroids are the mainstay of therapy for sarcoidosis.[228,229,231] Corticosteroids are used to suppress inflammation and granuloma formation. Although there are no randomized controlled trials that have established the efficacy of corticosteroids in cardiac sarcoidosis, retrospective studies suggest benefit particularly in the stabilization or improvement of LV function.[228,231] Although these studies support the use of corticosteroids for cardiac sarcoidosis, the optimal dose, when to begin treatment, and the duration of treatment all have not been well established.[231] On the basis of observational studies, steroid therapy in patients with established cardiac sarcoidosis and active inflammation should be initiated before LV systolic function declines. Although corticosteroid treatment of symptomatic patients with cardiac sarcoidosis is common practice, the treatment of asymptomatic or minimally symptomatic patients is more controversial.[231] Corticosteroids are commonly initiated at a high dose (prednisone 40–60 mg daily) and tapered off slowly over a period of months if clinical and imaging features remain stable or improve. Patients should be followed up closely for relapse after discontinuation of corticosteroid treatment. Other immunosuppressive therapies such as methotrexate, azathioprine, cyclophosphamide, pentoxifylline, and thalidomide have also been used in the treatment of cardiac sarcoidosis.[231] These agents may be considered in patients who cannot tolerate corticosteroids and in patients who continue to worsen clinically despite corticosteroid treatment.[231]

Patients with cardiac sarcoidosis and reduced LVEF or symptomatic HF should also be treated with standard HF therapy.[1] However, because fatal arrhythmias account for 25% to 65% of deaths caused by cardiac sarcoidosis, particular attention is needed to identify patients who would benefit from placement of a permanent pacemaker with an ICD.[228,229,231] Although limited, current evidence suggests that ICDs could prevent death caused by dangerous arrhythmias or sudden cardiac death in patients with reduced LVEF, as well as those with relatively preserved LVEF.[2,231] In support of this recommendation, the 2012 American College of Cardiology Foundation (ACCF)/AHA/Heart Rhythm Society guidelines for device-based therapy listed cardiac sarcoidosis as a reasonable indication for ICD implantation, with a Class IIa recommendation.[240,241] In a retrospective study, patients with isolated cardiac sarcoidosis had very high rates of appropriate ICD therapy.[242] Whether patients with cardiac sarcoidosis without functional cardiac myocardial impairment and without spontaneous significant arrhythmias should be considered for ICD therapy or at least some risk-stratification strategy is more controversial.[231]

Cardiac transplantation has been used with success in patients with cardiac sarcoidosis. Sarcoidosis can occasionally recur in the transplanted heart as early as 24 weeks after transplantation; however, these recurrences usually respond to treatment with steroids. Zaidi et al[243] reviewed 65 patients with cardiac sarcoidosis and reported that patients with sarcoidosis undergoing orthotopic heart transplantation have better mean short- and intermediate-term survival than patients undergoing

transplantation for other reasons. Thus, patients with end-stage HF or intractable arrhythmias should be considered for transplantation. Other surgical interventions have been reported with variable success in cardiac sarcoidosis, such as aneurysm resection and ventricular exclusion of affected myocardium.[231]

Key Diagnostic and Management Strategies for Cardiac Sarcoidosis

Recommendations With Strong Level of Consensus for Cardiac Sarcoidosis

1. An echocardiogram should be performed in patients with signs and symptoms of HF to assess LVEF *(Level of Evidence C)*.
2. Referral for cardiac transplantation or MCS should be made for patients with advanced HF in the absence of significant extracardiac burden of sarcoid disease *(Level of Evidence C)*.
3. Corticosteroids are recommended to treat patients with cardiac sarcoidosis[228,229,231] *(Level of Evidence B)*.
4. Standard guideline-directed medical therapy for HF is recommended to treat HF with reduced EF in patients with cardiac sarcoidosis[1] *(Level of Evidence B)*.

Recommendations With Moderate Level of Consensus for Cardiac Sarcoidosis

1. Cardiac MRI or positron emission tomography imaging with fluorodeoxyglucose imaging can be useful to diagnose cardiac sarcoidosis or follow response to therapy[235–237] *(Level of Evidence B)*.
2. EMB can be useful to confirm cardiac sarcoidosis when pathology yields evidence of noncaseating granulomas, but absence does not rule out the possibility of cardiac sarcoidosis *(Level of Evidence C)*.
3. Other immunosuppressive therapies (eg, methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, pentoxifylline, and thalidomide) are reasonable in patients who cannot tolerate corticosteroids and in patients who continue to worsen clinically despite treatment with corticosteroids[244] *(Level of Evidence C)*.
4. In collaboration with a pulmonologist or rheumatologist, immune-modulating therapy can be useful to treat sarcoidosis *(Level of Evidence C)*.
5. ICD implantation is reasonable for patients with cardiac sarcoidosis *(Level of Evidence C)*.

MYOCARDITIS

Definition and Classification

Myocarditis in the broadest sense refers to any inflammatory disease of the myocardium and can be classified by pathogenesis, clinical presentation, or histology.[245,246] Myocarditis requires histological or immunohistological confirmation by EMB, surgical heart specimens, or an autopsy.[247] However, myocarditis is often suspected clinically but infrequently confirmed by biopsy in clinical practice. In many case series, the diagnosis of myocarditis rests on a compatible clinical scenario associated with noninvasive biomarker and imaging features rather than a pathological diagnosis (Table 3[248]). Nevertheless, many cases of clinical myocarditis are probably not true myocarditis, as evidenced by the Clinical Trial of Immunosuppressive Therapy for Myocarditis.[227]

When myocarditis is suspected and EMB is infeasible or not clearly indicated, noninvasive diagnostic criteria can be used to diagnose suspected or probable acute myocarditis. A recent definition of probable acute myocarditis is one of several clinical syndromes, including HF of <3 months' duration, associated with an otherwise unexplained elevation in troponin or electrocardiographic features of cardiac injury.[249] New wall motion abnormalities, a pericardial effusion on echocardiography, or characteristic tissue features on MRI strengthen the diagnosis.[250]

Causes of Myocarditis

The causes of myocarditis are diverse and vary regionally. In North America and Western Europe, viral infections are the most commonly identified causes of DCM caused by myocarditis.[251] Chagas disease, poststreptococcal rheumatic heart disease, and HIV are important causes of DCM in specific world regions. Case series of myocarditis caused by diphtheria have been reported from Afghanistan and India.[251] Myocarditis caused by typhoid fever, rubella, and even scorpion bite has been reported from other regions of Asia. Thus, a careful travel and exposure history is essential for the evaluation of unexplained cardiomyopathy.

Although almost 2 dozen viruses have been linked to myocarditis, the most frequent in Western Europe are parvovirus B19 and human herpes virus 6. Coxsackie B and other enteroviruses remain important pathogens in acute and fulminant myocarditis. Fulminant myocarditis is associated with higher cardiac troponin levels than acute myocarditis, and higher cardiac troponin levels are associated with lower LVEF in children.[252]

Coinfection with ≥2 viruses occurs in a substantial minority of cases. Viral persistence after the acute disease can be detected from heart biopsy samples in the setting of chronic DCM. Clinical trials are under way to determine whether treatment with antiviral agents of myocarditis at various phases of the clinical illness can impact clinical outcomes.

Noninfectious causes are collectively less common than infectious causes but contribute meaningfully in specific demographic groups because immunomodulatory therapy can impact outcomes. Kawasaki disease–

Table 3. Diagnostic Criteria for Clinically Suspected Myocarditis

Clinical presentations*
Acute chest pain, pericarditic, or pseudoischemic
New onset (days up to 3 mo) or worsening of dyspnea at rest or exercise, and/or fatigue, with or without signs of left- and/or right-sided heart failure
Subacute/chronic (>3 mo) or worsening of dyspnea at rest or exercise, and or fatigue with or without left- and/or right-sided heart failure
Palpitation and/or unexplained arrhythmia symptoms and/or syncope and/or aborted sudden cardiac death
Unexplained cardiogenic shock
Diagnostic criteria
I. ECG/Holter/stress test features New abnormal 12-lead ECG and/or Holter stress testing, any of the following: first- to third-degree atrioventricular block or bundle-branch block; ST/T-wave changes; sinus arrest; ventricular tachycardia or fibrillation and asystole; atrial fibrillation; reduced R-wave height; intraventricular conduction delay (widened QRS complex); abnormal Q waves; low-voltage, frequent premature beats; supraventricular tachycardia
II. Myocardiocytolysis markers Elevated TnT/TnI
III. Functional and structural abnormalities on cardiac imaging (echocardiogram/angiography/CMR) New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi
IV. Tissue characterization by CMR Edema and/or LGE of classic myocarditic pattern (see Role of Cardiac MRI in Suspected Myocarditis)

Clinically suspected myocarditis if ≥1 clinical presentation and ≥1 diagnostic criteria from different categories in the absence of (1) angiographically detectable coronary artery disease (coronary stenosis ≥50%) or (2) known preexisting cardiovascular disease or extracardiac causes that could explain the syndrome (eg, valve disease, congenital heart disease, hyperthyroidism). Suspicion is higher with higher number of fulfilled criteria. CMR indicates cardiac magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricular; RV, right ventricular; TnI, troponin I; and TnT, troponin T.

*If the patient is asymptomatic, ≥2 diagnostic criteria should be met.

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related myocarditis can affect children in association with coronary vasculitis.[253] Lupus erythematosus can affect the myocardium with or without pericarditis.[254] In the setting of new DCM with an elevated eosinophil count, a hypersensitivity reaction to a drug or vaccine or an idiopathic hypereosinophilic syndrome should be considered.[255] Cardiac sarcoidosis often affects the heart without clinical evidence of extracardiac disease.[231] A minority of subacute or early chronic DCM cases can have active inflammation and improve with immunosuppression.[256,257] Finally, giant cell myocarditis is an aggressive, noninfectious autoimmune disorder that is rapidly fatal without advanced HF treatment and multidrug immunosuppression.[258]

Pathogenesis of Myocarditis

The pathogenesis of myocarditis is largely based on small animal models of enteroviral and autoimmune myocarditis.[259] From these experimental data, human myocarditis is conceptualized as a 3-phase model consisting of acute injury, a host innate and acquired immunologic response, and finally, recovery or a transition to fibrosis and DCM over several weeks to months.[260] A clear distinction of these phases in human disease is rare, but the peak of inflammation often follows a clinical viral illness by a few days to weeks. The initial injury can cause an acute DCM with contractile impairment mediated by cytokines and direct viral myocyte injury. After several months, the same dilated ventricle can result from diffuse scar with little or no inflammation. The transition from acute myocarditis to chronic fibrotic DCM probably occurs over months, with substantial individual variability, which creates a window for personalized therapies.

Recent advances in the understanding of T-cell plasticity have influenced this model and are now under investigation in human disease. For example, an interleukin 17–producing CD4+ T-cell subtype appears to mediate fibrosis after myocarditis in murine models.[261] T-regulatory cells can suppress Th17 cell function and are decreased in myocarditis and DCM.[262] Therapies such as immunoadsorption of anti-heart antibodies can increase T-regulatory and decrease T-effector cell levels.[263] If confirmed in larger trials, therapies to alter the balance between regulatory T cells and T-effector cells could attenuate the development of chronic DCM. Measurement of multiple viral titers in the blood is expensive and has not proven to be very useful over the years.

Clinical Features and Diagnostic Evaluation of Suspected Myocarditis

Myocarditis most commonly presents in young adults with a chest pain syndrome resembling acute MI with normal coronary arteries or pericarditis with elevated troponin values.[264] Sudden death of myocarditis is an uncommon but important cause of death in children and young athletes. The focus of this section will be on the management of myocarditis that presents as an initially unexplained, usually dilated, cardiomyopathy.

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There are no clinically available and specific blood tests to confirm the diagnosis of myocarditis. Nonspecific serum markers of inflammation such as an erythrocyte sedimentation rate and C-reactive protein can be elevated in myocarditis. Biomarkers of cardiac injury can be elevated, particularly in patients with acute and clinically severe disease that requires hospitalization. However, troponin I was elevated in only 34% of the US Myocarditis Treatment Trial subjects with histologically acute myocarditis and an average of 1 month of symptoms.[265] Current troponin assays with higher sensitivity might prove more useful, as might soluble ST2, a clinically available serum biomarker that in part reflects inflammation. The ESC working group position statement recommends that a troponin be obtained in the clinical setting of suspected myocarditis.[248] Natriuretic peptides and other biomarkers should be assessed in accordance with the 2013 ACCF/AHA HF management guidelines.[1] The ESC working group position statement recommends that an ECG be performed in the setting of suspected myocarditis to look for features that predict outcomes.[248] A QRS width of >120 ms predicts a higher risk of death or transplantation.[265] PR-segment depression and diffuse ST-segment elevation suggest an associated pericarditis. Low voltage, especially in the presence of thickened LV walls by echocardiography in the absence of an infiltrative disorder such as amyloidosis, suggests myocardial edema.

Role of Cardiac MRI in Suspected Myocarditis

Cardiac MR can differentiate ischemic from nonischemic cardiomyopathy by the pattern of myocardial damage on T1-weighted, post–gadolinium contrast sequences (DGE).[250] In ischemic cardiomyopathy, DGE usually shows heightened endocardial signal intensity in a coronary distribution. The pattern of DGE signal in myocarditis is usually epicardial or in the midwall. Non–contrast-enhanced T2-weighted sequences and early postgadolinium T1-weighted sequences have been used separately and in combination with DGE to diagnose myocarditis.[250] T1 and T2 mapping can increase sensitivity and reduce artifacts, respectively.[266,267] The presence of DGE in biopsy-proven viral myocarditis might predict subsequent risk of ventricular arrhythmias and cardiovascular death.[268] The diagnostic cardiac MR features of acute myocarditis evolve from a focal to a more diffuse pattern and can resolve.[269]

When to Perform an EMB

Confirmation of myocarditis requires histological or immunohistological analysis, but the 2013 ACCF/AHA guideline on the management of HF[1] and the 2013 ESC working group position article disagree regarding the indications for EMB.[248] The ESC position article supports the broad use of EMB for the diagnosis and management of myocarditis based on the presence or absence of viral genomes and inflammation. The 2007 AHA/ACCF/ESC consensus scientific statement on the role of EMB for the management of cardiovascular disease identified 13 scenarios in which EMB might be considered.[200] Only 2 of these scenarios had a Class I recommendation. These scenarios described settings in which giant cell myocarditis was likely or in which lymphocytic myocarditis was suspected in the setting of fulminant HF. In 2013, a study from Johns Hopkins confirmed that EMB changed management in 20% to 25% of patients who fit these scenarios.[268] In addition, EMB results changed prognosis or management in 20% to 25% of subjects with unexplained restrictive cardiomyopathy or chronic DCM complicated by high-grade heart block or ventricular arrhythmias. In general, EMB should be performed in settings in which histological information will uniquely impact prognosis or guide treatment.[200] On the basis of these data, a reasonable algorithm for the use of EMB that balances probable clinical impact with safety is illustrated in Figure 2.

The tissue obtained by RV EMB should be sectioned and stained for standard histology. Isolated RV EMB with only standard histology has a low sensitivity of 10% to 22% compared with a clinical "gold standard."[270] The sensitivity of EMB increases if immunoperoxidase stains (eg, anti-CD3, anti-CD68, anti-HLA antigens) are used or if LV EMB is performed for isolated LV disease.[246,271,272] The sensitivity of EMB for acute giant cell myocarditis is higher, between 80% and 85%.[273] The role of viral genome analysis of EMB tissue to guide management remains uncertain.

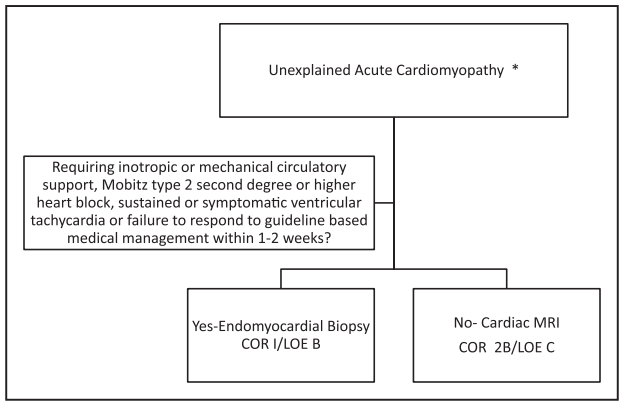

Figure 2. Algorithm for the evaluation of suspected myocarditis in the setting of unexplained acute cardiomyopathy.

COR indicates Class of Recommendation; LOE, Level of Evidence; and MRI, magnetic resonance imaging.

*Usually a dilated cardiomyopathy. Fulminant myocarditis may have normal end-diastolic diameter with mildly thickened walls. Exclude ischemic, hemodynamic (valvular, hypertensive), metabolic, and toxic causes of cardiomyopathy as indicated clinically.

Treatment of Myocarditis

Myocarditis that presents as DCM should be treated per current guidelines for systolic HF.[1,3] Individual trials and a meta-analysis suggest that immunosuppression is generally not indicated for the management of acute lymphocytic myocarditis in adults. In cases of giant cell myocarditis, cardiac sarcoidosis, or eosinophilic myocarditis, treatments directed at modifying the immune response should be considered.[231,258] Sustained aerobic exercise during acute viral myocarditis leads to increased mortality in animal models and can lead to sudden death. Competitive sport participation should be avoided for 3 to 6 months after the diagnosis of myocarditis. Reassessment with clinical evaluation and functional testing is indicated before competitive sport participation is resumed.[248,274,275] Nonsteroidal anti-inflammatory drugs should be avoided because of the risk of increased inflammation and mortality. Acute arrhythmia management is supportive, because arrhythmias often resolve with resolution of acute inflammation. In patients with drug-refractory ventricular arrhythmias after myocarditis, endocardial and epicardial radiofrequency catheter ablation can be effective.[34]

MCS might be required in patients with myocarditis who develop cardiogenic shock despite optimal medical management. Some patients with myocarditis can be bridged to recovery. The role of immunosuppression in patients requiring MCS has not been investigated systematically and remains uncertain.

The overall rate of survival after cardiac transplantation for adult patients with myocarditis is similar to that for other causes of cardiac failure. However, recent data suggest a higher posttransplantation risk in children if active myocarditis is present in the explanted heart.[276–278]

Key Diagnostic and Management Strategies for Myocarditis

Recommendations With Strong Level of Consensus for Myocarditis

1. Cardiac troponin levels are useful for diagnosis and should be obtained in patients with clinically suspected myocarditis *(Level of Evidence C)*.
2. A 12-lead ECG should be performed in all patients with clinically suspected myocarditis *(Level of Evidence C)*.
3. A standard transthoracic echocardiogram should be performed in all patients with clinically suspected myocarditis *(Level of Evidence C)*.
4. EMB should be performed in those patients with clinically suspected unexplained acute myocarditis who require inotropic support or MCS and those with Mobitz type 2 second-degree or higher heart block, sustained or symptomatic ventricular tachycardia, or failure to respond to guideline-based medical management within 1 to 2 weeks *(Level of Evidence C)*.
5. Patients with HF caused by clinically suspected or confirmed myocarditis should be managed medically according to the current HF guidelines[1] *(Level of Evidence C)*.
6. Patients with HF caused by clinically suspected or confirmed myocarditis should refrain from competitive athletics for a minimum of 3 to 6 months *(Level of Evidence C)*.
7. Patients with HF caused by clinically suspected or confirmed myocarditis should be considered for advanced cardiac support, including MCS and heart transplantation, according to the current guidelines[1,277,278] *(Level of Evidence C)*.
8. Immunosuppressive therapy that includes calcineurin inhibitors and corticosteroids is indicated for the treatment of acute DCM caused by giant cell myocarditis *(Level of Evidence B)*.[258]

Recommendations With Moderate Level of Consensus for Myocarditis

1. Cardiovascular MR is reasonable for the diagnosis of myocarditis in clinically stable patients with clinically suspected myocarditis *(Level of Evidence C)*.

Recommendations With Uncertainty for Myocarditis

1. EMB may be considered in those patients with clinically suspected myocarditis who meet the criteria listed in Table 3[248] *(Level of Evidence C)*.

Strategies to Avoid With Concern for No Benefit for Myocarditis

1. In the absence of ventricular arrhythmias or syncope, an ICD is not indicated acutely for patients with recent-onset DCM and LVEF <30% caused by clinically suspected or confirmed myocarditis *(Level of Evidence C)*.

OTHER INFECTIOUS CAUSES OF DCM

Acquired Immunodeficiency Syndrome

Several investigators have reported that there is an association between HIV syndrome and DCM. Studies published before the introduction of highly active antiretroviral therapy regimens correlated the incidence and course of HIV infection in relation to DCM in both children and adults. In a long-term echocardiographic follow-up in the pre–highly active antiretroviral therapy era, 40% of initially asymptomatic HIV-positive patients were diagnosed with DCM with significantly depressed LVEF during the 5-year follow-up.[279] The incidence of DCM was higher among patients with AIDS or low CD4 counts.[279] Patients should be screened for other potential causes of cardiomyopathy, including ischemic heart disease, because highly active antiretroviral therapy has been associated

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with an increased incidence of cardiovascular events such as MI, hypertension, and substance abuse.

Current hypotheses concerning the pathogenesis of cardiomyopathy associated with HIV include infection of myocardial cells with HIV type 1 or coinfection with other viruses, postviral cardiac autoimmunity, autonomic dysfunction, cardiotoxicity from illicit drugs and pharmacological agents, nutritional deficiencies, and prolonged immunosuppression.[280,281] It has been demonstrated that targeted myocardial expression of HIV transactivator in transgenic mice results in cardiomyopathy and mitochondrial damage, which supports the hypothesis that the HIV infection of the heart causes AIDS cardiomyopathy.[282] However, how HIV type 1 infection of the heart results in DCM in HIV has not been characterized. Although human myocardial cells are not known to express CD4 cells, autopsy series of people who died of AIDS-related illnesses have demonstrated histological evidence of myocarditis in ≈50% of the patients.[283] Using in situ hybridization techniques, HIV nucleic acid sequences were detected in cardiac tissue sections in approximately one third of the patients who died of AIDS.[284] Symptomatic HF is seen in approximately one half of these patients with myocardial involvement. Other than treatment for HIV, the treatment of HF in patients with symptomatic HIV cardiomyopathy is the same as the conventional treatment for patients with DCM. The prognosis of HIV cardiomyopathy when untreated remains poor, with a >50% mortality rate in 2 to 3 years, especially among patients in sub-Saharan Africa.[284]

Key Diagnostic and Management Strategies for HIV DCM

Recommendations With Strong Level of Consensus for HIV DCM

1. Patients with DCM and risk factors for HIV should be screened for HIV as a possible cause of DCM *(Level of Evidence C)*.
2. Treatment of HIV with antiretroviral therapy is useful in prevention and treatment of DCM related to HIV *(Level of Evidence C)*.
3. Patients with HIV cardiomyopathy should be treated with standard guideline-directed medical and device therapies for patients with systolic HF[1] *(Level of Evidence C)*.

Chagas Disease

Although Chagas disease is a relatively uncommon cause of DCM in other parts of the world, it remains a leading cause of death in many areas of Central and South America. Indeed, 50 000 people die of Chagas disease each year.[285] *Trypanosoma cruzi*, the causative organism for Chagas disease, primarily infects wild and domestic mammals and insects. Humans become involved when infected vectors infest the simple houses that are common in Latin America. It is estimated that 16 to 18 million people have chronic *T cruzi* infection.[286] Chagas control programs in certain South American countries have demonstrated a significant decline in seropositive subjects from 47.8% to 17.1%, which suggests a reduction in transmission of the disease.[285]

There are 3 different clinical and pathophysiological phases of the disease: the acute, indeterminate, and chronic phases. Sudden cardiac death can occur during each phase; however, DCM is a late manifestation of the disease and is generally seen during the chronic phase. Acute Chagas disease is usually a mild illness with a low case-fatality rate. The systemic spread of the parasites from the site of entry and their initial multiplication can be accompanied by fever, malaise, and edema of the face and lower extremities, as well as generalized lymphadenopathy and hepatosplenomegaly. Muscles, including the heart, are often heavily parasitized, and severe myocarditis develops in a small proportion of patients. The acute illness resolves spontaneously over a period of 1 to 2 months in most patients, who then enter the indeterminate phase of *T cruzi* infection. In this phase, there are no symptoms, but there are lifelong, low-grade parasitemias in association with antibodies. Many people in this phase have subtle signs of cardiac or gastrointestinal involvement long before the disease becomes symptomatic. Most infected people remain in the indeterminate phase for life; however, this carrier state can be a major cause of transfusion-associated transmission of the parasite. Symptomatic chronic Chagas disease develops in ≈10% to 30% of infected people, years or even decades after the *T cruzi* infection is acquired. The heart is most commonly affected, and the pathological changes usually include biventricular enlargement, thinning of ventricular walls, apical aneurysms, and mural thrombi. Widespread lymphocytic infiltration is often seen in stained specimens of cardiac tissue, as well as diffuse interstitial fibrosis and atrophy of myocardial cells. The conduction system is often affected, typically resulting in right bundle-branch block, left anterior fascicular block, or complete atrioventricular block. There may be dysrhythmias, cardiomyopathy, and thromboembolism over time. Death usually results from rhythm disturbances or progressive HF. The overall prognosis for patients with Chagas cardiomyopathy and HF is poor, with 50% of patients dying within a period of 4 years. The presence of complete heart block, atrial fibrillation, LBBB, and complex ventricular ectopy suggests poor prognosis.[287]

The leading hypothesis with respect to the pathogenesis of Chagas cardiomyopathy is that patients develop progressive myocardial damage caused by parasite persistence and autoimmune responses.[285] The neurogenic hypothesis of Chagas cardiomyopathy suggests that the

cardiac parasympathetic neurons are irreversibly damaged by the parasite during the acute phase of the disease. As a consequence, the cardiac sympathetic nervous system is unopposed, and the cardiotoxic effects of a permanent and excessive sympathetic activation are responsible for the relentless progression of myocardial damage.[288] Myocardial ischemia and coronary microcirculation abnormalities have also been demonstrated in animal models and in humans with Chagas disease.

The pharmacological treatment for *T cruzi* infection remains unsatisfactory. Extensive clinical experience with 2 drugs, benznidazole and nifurtimox, suggests that although they can shorten the acute phase of *T cruzi* infection and decrease mortality, they achieve parasitologic cures in only ≈50% of treated patients; moreover, these drugs cause substantial toxicity.[285] Other than treatment of the infection, treatment of cardiomyopathy is the same as the conventional treatment of patients with DCM.

Key Diagnostic and Management Strategies for Chagas Disease

Recommendations With Strong Level of Consensus for Chagas Disease

1. Patients with DCM and epidemiological risk factors for Chagas disease, such as origin from Central or South America or exposure to infected vectors, should be screened for Chagas disease *(Level of Evidence C)*.

AUTOIMMUNE CARDIOMYOPATHY

Autoimmune diseases have long been established as rare causes of cardiomyopathy and HF. There are several proposed mechanisms, including immune-mediated myocarditis, progressive fibrosis, and apoptosis with resultant restrictive and dilated phenotypes, progressive atherosclerosis with subsequent ischemic cardiomyopathy, and HF as a result of therapies used for the primary rheumatologic disorder.[289] The more well-described associations between autoimmune/rheumatologic disorders and HF include systemic lupus erythematosus (SLE), scleroderma, RA, dermatomyositis, and polyarteritis nodosa (PAN). Sporadic case reports have also associated HF with ankylosing spondylitis, psoriatic arthritis, celiac sprue, vasculitis, and inclusion body myositis through a variety of mechanisms. Given the increased attention to diagnosis of atherosclerosis and use of biomarkers, patients with these conditions are increasingly prevalent.

Systemic Lupus Erythematosus

Epidemiology and Prognosis

Overall, cardiovascular risk remains a concern for patients with SLE, with cardiovascular disease typically occurring 4 to 20 years after diagnosis. Despite improvements in background therapy for these patients, cardiovascular mortality persists.[290,291] Although a number of cardiac abnormalities have been reported in patients with SLE, the development of DCM is not a prominent manifestation of this disease process. Global LV dysfunction has been reported in 5%, segmental LV wall-motion abnormalities in 4%, and RV enlargement in 4% of patients with SLE. In general, the abnormalities in cardiac function correlate with disease activity.[254] Patients with SLE were 1 to 3 times more likely to be hospitalized with newly diagnosed HF than healthy cohorts in a large hospital discharge database, with the highest risk difference occurring among women <45 years of age.[292] There are 3 main mechanisms for SLE-induced HF, which include atherosclerosis, myocarditis/inflammation, and drug-induced impairments from underlying treatment. Relative risks of MI and progressive atherosclerosis in SLE patients range from 2- to 10-fold higher than for age-matched control subjects, with greater risk among younger patients.[291] Among 1249 newly diagnosed SLE patients followed up for 8 years, confirmed HF occurred in only 2%, with ≈20% of those with HF having atherosclerosis as the primary cause.[293] Concomitant presence of antiphospholipid antibodies can further increase the risk of thrombosis-mediated MI and thus HF. Myocarditis is often unrecognized in SLE; it frequently is found at autopsy or at EMB and is less easily detected clinically.[294,295] Myocarditis has been described in up to 9% of SLE patients and historically in >50% of postmortem examinations, although the rate of the autopsy evidence of myocarditis has diminished in the setting of corticosteroid use.[296] The clinical presentation is often indistinguishable from other forms of myocarditis. Hydroxychloroquine is a common therapy for patients with SLE, and many case reports have linked this drug to cardiomyopathy with treatment durations ranging from 1 to 27 years and variable impact on mortality.[297] Animal studies have linked hydroxychloroquine to decreased EF and cardiac fibrosis.[298] Classic findings of chloroquine- or hydroxychloroquine-mediated heart disease include progressive bundle-branch block and atrioventricular heart block, biventricular hypertrophy, and classic findings on EMB (membrane-bound concentric lamellar bodies or myelin figures, vacuolization in the absence of CAD, and large secondary lysosomes and curvilinear bodies).[299,300]

Diagnosis

Diagnostic strategies for SLE-mediated HF include standard echocardiography, ECGs, and coronary angiography. These strategies do not help to delineate SLE as the primary cause. EMB can be helpful in specific causes detailed above, but results are generally nonspecific, with myocardial lesions characterized by an increase in interstitial connective tissue and myocardial scarring and with limited sensitivity and specificity. Some stud-

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ies suggest that depolarization abnormalities on signal-averaged ECG accompanied by echocardiographic evidence of abnormal LV filling could reflect the presence of myocardial fibrosis and could be a marker of subclinical myocardial involvement in SLE patients.[301] Cardiac involvement can manifest itself by conduction system abnormalities such as complete atrioventricular heart block. Cardiac MR and myocardial strain and strain rate can identify patients with early manifestation of SLE-induced cardiomyopathy.[302,303] Thus, the diagnosis is often based on strong clinical suspicion.

Treatment

Treatment of SLE-HF is dependent on the underlying cause. Myocarditis associated with SLE should be treated with intravenous methylprednisolone 1000 mg/d initially, followed by high-dose oral prednisone at 1 to 2 $mg \cdot kg^{-1} \cdot d^{-1}$ for 1 to 2 weeks.[304] Small reports of use of intravenous immunoglobulin, azathioprine, and cyclophosphamide for SLE-related myocarditis have been published.[296,305–307] Thrombosis and atherosclerosis should be treated with standard percutaneous and pharmacological interventions, as detailed in other guidelines for acute MI, and chronic CAD and chronic HF should be treated according to ACCF/AHA guidelines.[1] Comorbid illnesses, including hypertension (which is common), should also be treated.

Rheumatoid Arthritis

Epidemiology and Prognosis

Cardiac involvement in RA generally results from the development of myocarditis or pericarditis. HF can result from drug treatment of RA, myocarditis, vasculitis, valvular involvement, progressive atherosclerosis/MI, and amyloidosis[308]; however, the development of DCM is rare in these patients. In a retrospective study of 172 patients with juvenile RA, symptomatic cardiac involvement occurred in 7.6% of patients and included pericarditis, perimyocarditis, and myocarditis.[309] In a population study in Rochester, MN, of 575 patients with RA with a mean of 46 years of follow-up, the presence of RA was associated with a 2-fold increased risk of HF compared with a non-RA population; this was in the absence of traditional risk factors, with a greater risk for women than men.[310] Both myocarditis and pericarditis are regarded as poor prognostic factors in RA.[309] Myocardial involvement in RA is thought to be secondary to disturbances in the microcirculation with microvasculitis and occurs in the absence of any clinical symptoms of electrocardiographic changes. Although chronic inflammation is thought to play an integral role in HF development in patients with RA, the direct mechanisms have not been elucidated. Elevated C-reactive protein, interleukin 6, and tumor necrosis factor-α have been linked to development of HF and mortality after HF development.[311] The presence of persistently elevated erythrocyte sedimentation rate levels, RA vasculitis, or RA lung disease was independently associated with worse mortality in patients with RA and HF.[312] In the National Databank for Rheumatic Disease, patients with RA had a higher risk of HF development than osteoarthritis, occurring at a rate of 3.9% over 2 years[313]; however, in the absence of traditional HF risk factors, the rate of HF development was rare at 0.4%. Patients with rheumatoid factor seropositivity had a higher risk of HF than seronegative RA patients (hazard ratio 2.59). Excess risk for mortality and HF occurs early after diagnosis, based on an inception cohort.[314] Limited data suggest that treatment of the RA with steroids can increase the risk of HF,[315] whereas in a large, nested case-control study,[316] treatment with methotrexate and other disease-modifying antirheumatic drugs reduced the risk of incident HF. However, etanercept and infliximab should probably not be used in patients with established HF, because prior trials found that these drugs can enhance the development of HF.

Diagnosis

Diagnostic strategies for RA-mediated HF include the use of biomarkers such as BNP, echocardiography, and angiography to exclude atherosclerosis as an intermediate cause. Cardiac involvement in RA patients can manifest itself by pericardial effusions, diastolic dysfunction, and evidence of inflammation on nuclear scans and cardiac MR. There is no pathognomonic diagnostic test for RA-induced HF, and the diagnosis is typically based on strong clinical suspicion. Biopsy can reveal a diffuse, necrotizing, or granulomatous pattern, which is nonspecific.[317]

Treatment

Treatment of RA-HF is dependent on the underlying cause. Chronic HF should be treated according to ACCF/AHA guidelines.[1] If patients have asymptomatic LV dysfunction, ACE inhibitors and β-blockers should be used in accordance with stage B HF management guidelines. Comorbid illnesses, including hypertension (which is common), should also be treated.[1]

Scleroderma

Epidemiology and Prognosis

Traditionally, the development of DCM is rare in patients with scleroderma. Pulmonary hypertension and restrictive physiology are more common.[318] An echocardiographic study showed that although there was no difference in LV dimensions or fractional shortening in patients with scleroderma, there was indication of systolic impairment in the majority of patients.[319] In the EULAR (the European League Against Rheumatism) Scleroderma Trials and Research (EUSTAR) cohort, 26% of fatal scleroderma cases were attributable to HF.[320] A distinctive focal myocardial lesion, ranging

from contraction band necrosis to replacement fibrosis without morphological abnormalities of the coronary arteries, is noted in approximately half of all patients with scleroderma. This is postulated to be attributable to intermittent vascular spasm with intramyocardial Raynaud's phenomenon. Thus, progressive systemic sclerosis can lead to conduction abnormalities, arrhythmias, HF, angina pectoris with normal coronary arteries, myocardial fibrosis, pericarditis, and sudden death. Late contrast enhancement with gadolinium can be used to characterize patchy fibrosis and myocardial edema interspersed with normal myocardium in scleroderma.[321] Cardiac involvement in systemic sclerosis portends an ominous prognosis and is probably most directly related to the extent of myocardial fibrosis.

Diagnosis

Diagnosis is often based on a high clinical suspicion. An ECG may demonstrate first-degree atrioventricular block and sinus node disease, and Holter monitoring may demonstrate ventricular arrhythmias and atrial fibrillation. Speckle tracking imaging to assess longitudinal strain may demonstrate early manifestation of scleroderma-mediated HF, and cardiac MR may also demonstrate patchy fibrosis.[322] Scleroderma patients with evidence of skeletal myopathy were 2.5 times more likely to have HF or arrhythmias than scleroderma patients without myopathy, and they also more frequently had autoantibodies, including anti-PM/Scl antibodies and anti-ribonucleoprotein antibody.[323] An EMB can be useful if there is suspicion of acute myocarditis, given reports of favorable response to intravenous methylprednisolone.[324]

Treatment

No specific treatments are available for scleroderma-induced HF. Careful use of vasodilator therapy should be considered, although relative hypotension might prevent aggressive up-titration of traditional HF medicines. Autologous stem cell transplantation was performed in 90 patients with systemic scleroderma, but HF was considered a contraindication, and 1 of the deaths occurred in a scleroderma patient with undiagnosed HF.[325] Routine treatment with steroids could worsen the disease. Treatment of concomitant pulmonary arterial hypertension might be an approach to relieve symptoms. Cardiac transplantation can be considered if the systemic burden of scleroderma is low.[326]

Dermatomyositis

Epidemiology and Prognosis

The overall epidemiology of DCM in dermatomyositis is not well established; however, the most common cardiac manifestation of polymyositis or dermatomyositis is HF, ranging from 32% to 77% of total cardiovascular events in a recent meta-analysis of 1530 patients.[327] An autopsy study at Johns Hopkins revealed active myocarditis in 25% of cases and focal fibrosis in 25%; skeletal muscle involvement was present in all cases of HF.[328] Another autopsy study of 20 patients with polymyositis revealed 9 patients with prior HF and 13 with abnormal ECGs.[329] Myocarditis was confirmed in 6 of 20 patients, and small-vessel disease was prevalent.

Diagnosis

A creatine kinase isoenzyme and cardiac troponin can be used as markers of overall disease severity but are not specific, because these markers can be elevated in the absence of cardiac manifestation of dermatomyositis.[330] HF can occur even in the absence of systemic inflammation. DCM could be caused by direct mononuclear inflammatory cell infiltrates and result in degeneration of myocytes, or it can be caused by progressive atherosclerosis or vasculitis that results in necrosis.[331] EMB demonstrates inflammation, necrosis, and degenerative changes similar to those seen in skeletal muscles; however, given the nonspecific nature of the biopsy, EMB is used infrequently. Electrocardiographic abnormalities are common.

Treatment

Treatment of patients is often focused on traditional background therapy for HF. In a small study of 4 patients with cardiac MR evidence of early cardiac manifestations of dermatomyositis, there was some improvement with intravenous methylprednisolone.[332] Heart transplantation can be used only rarely in patients without significant systemic involvement of dermatomyositis.

Polyarteritis Nodosa

DCM in PAN is quite rare. PAN is a systemic necrotizing vasculitis that preferentially targets medium-sized arteries and can lead to myocardial dysfunction as a result of coronary angiitis, MI, and hypertension.[333,334] Epidemiology of PAN-induced DCM is not well established given the sporadic nature of cases, although an estimated 5% to 20% of patients will have some cardiac involvement.[335] A published series of 348 patients with PAN demonstrated incidences of severe hypertension in 6.9% and cardiomyopathy in 7.5%, with a higher risk among patients with PAN related to hepatitis B.[336] Myocarditis is a rare cause of HF in PAN. The development of HF portends a poor prognosis.[334] Diagnosis is usually dependent on a high level of clinical suspicion. In the setting of biopsy-proven PAN, there should be a high clinical suspicion with progressive angina and deterioration of LV function. Angiography can be helpful for diagnosis. The typical treatment is aggressive immunosuppression with steroids and selective revascularization with possible treatment of concomitant active hepatitis B.[337,338] A case study of a patient with PAN reported that the pa-

tient responded to treatment with steroids and relapsed after a rapid taper.[339]

Key Diagnostic and Management Strategies for Autoimmune Cardiomyopathy

Recommendations With Strong Level of Consensus for Autoimmune Cardiomyopathy

1. In patients with DCM and autoimmune disease, coronary angiography is useful to exclude atherosclerosis *(Level of Evidence C)*.[293]
2. Hypertension control should be optimized in patients with autoimmune-mediated HF *(Level of Evidence C)*.
3. In collaboration with a rheumatologist, immune-modulating therapy without cardiac toxicity should be used to treat the underlying autoimmune condition in patients with HF *(Level of Evidence C)*.
4. Echocardiogram should be performed in patients with signs and symptoms of HF to assess cardiac function and structure *(Level of Evidence C)*.
5. Patients with systolic HF should be treated with guideline-directed medical and device therapies according to current guidelines[1] *(Level of Evidence C)*.
6. Patients with progressive signs and symptoms of HF should be evaluated by a cardiologist *(Level of Evidence C)*.

Recommendations With Moderate Level of Consensus for Autoimmune Cardiomyopathy

1. EMB can be useful to confirm hydroxychloroquine-mediated HF *(Level of Evidence C)*.[296]
2. Cardiac biomarkers such as natriuretic peptides (BNP, N-terminal proBNP) and cardiac troponin can be useful in identifying patients with autoimmune disease who have HF or are at risk for HF *(Level of Evidence B)*.
3. Cardiac MR or fluorodeoxyglucose positon emission tomography imaging can be useful to identify patients at risk for HF and to identify the degree of fibrosis *(Level of Evidence B)*.[302,303,321]
4. Intravenous steroids, systemic immunosuppressants, or immunomodulatory agents can be useful for biopsy-proven myocarditis believed to be caused by SLE, RA, and PAN *(Level of Evidence B)*.[296,305–307,316,332]
5. Referral for cardiac transplantation or MCS is reasonable for patients with advanced HF in the absence of significant extracardiac burden of autoimmune disease *(Level of Evidence B)*.[326]

Strategies to Avoid Because of Potential Harm or No Benefit for Autoimmune Cardiomyopathy

1. Routine use of EMB is not recommended in patients with cardiomyopathy caused by suspected autoimmune, rheumatologic, or collagen vascular disease *(Level of Evidence C)*.

ENDOCRINE/METABOLIC CAUSES

Obesity Cardiomyopathy

Epidemiology and Pathophysiology

Obesity has reached epidemic proportions in the United States, with more than two thirds of adults being either overweight or obese.[340] Obesity is linked to the development of several conditions that increase the risk of HF, including atherosclerosis, hypertension, and diabetes mellitus.[341] In addition, obesity has been shown to be independently associated with the development of HF.[342,343] In a study of 5881 participants in the Framingham Heart Study, the risk of HF per unit of body mass index (BMI) increase was 5% for men and 7% for women, even after adjustment for demographics and known risk factors of MI, diabetes mellitus, hypertension, and cholesterol.[342] Overweight and obesity are also exceedingly prevalent in HF. Although the prevalence can vary depending on the population studied, recent studies have shown that 29% to 40% of HF patients are overweight, and 30% to 49% are obese. A significantly higher prevalence of obesity exists in patients with HF and preserved EF than in patients with HF and reduced EF.[342,344–346]

Obesity can produce a range of hemodynamic changes that can predispose to changes in cardiac morphology and ventricular function, including LV dilation, eccentric or concentric LV hypertrophy, LV systolic and diastolic dysfunction, and RV dysfunction (Figure 3[346a]). These changes occur in all classes of obesity but are most pronounced in the severely obese.[347,348] In most studies, noninvasive ejection indices such as LV fractional shortening and LVEF have been reported for assessment of LV function in obesity.[348–354] Even in studies in which LV systolic function was lower in obese than in lean patients, LV ejection phase indices usually remained within the normal range or were mildly impaired in the majority of those with depressed values.[347–350] In contrast, some studies also found supranormal LV systolic function in obese subjects.[347,348] Although the concept of a cardiomyopathy related to obesity has been described previously,[355–357] severe LV systolic dysfunction occurs uncommonly because of obesity alone, and the presence of LV systolic dysfunction should trigger an investigation for other contributory factors before it is attributed to obesity alone.[347]

As with LV diastolic filling, adverse loading conditions correlate negatively with LV systolic function, particularly those that produce increased afterload.[349] Similarly, longer durations of obesity are associated with greater decrements in LV systolic function.[350] Severity of obesity is inversely related to LV ejection phase index

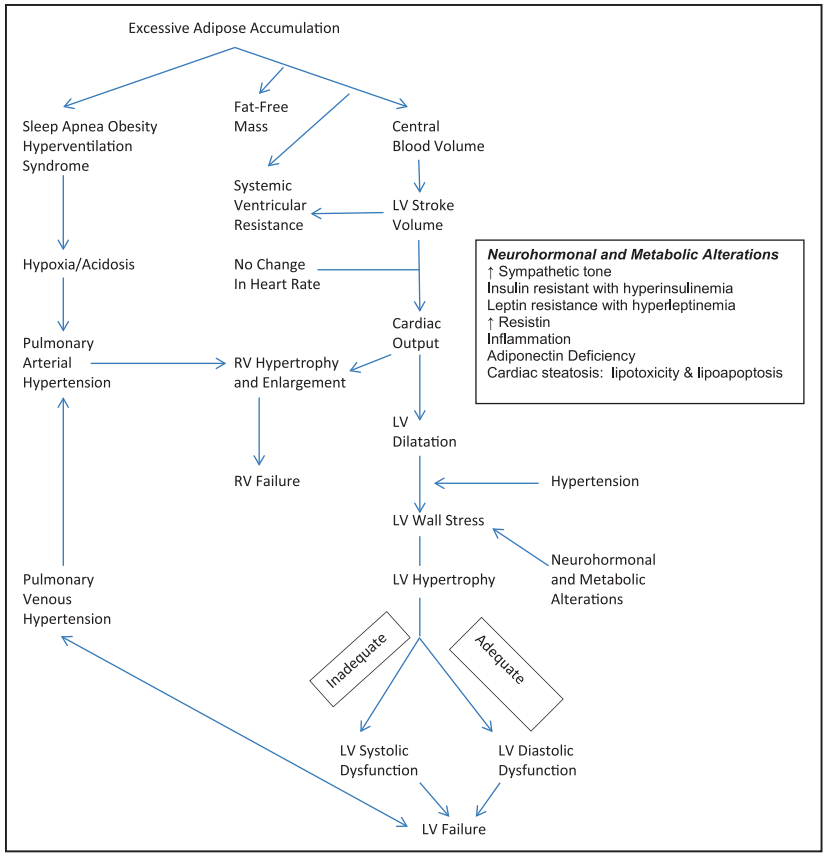

Figure 3. Pathophysiology of obesity cardiomyopathy.
LV indicates left ventricular; RV, right ventricular. Modified from Alpert et al[346a,347] with permission from Elsevier and Springer. © Springer Science+Business Media New York 2014.

values. Newer noninvasive modalities, such as tissue Doppler imaging and speckle track imaging,[347,348,351,352] have demonstrated significantly lower mitral systolic annular velocities in obese patients than in nonobese patients, with a progressive decrease as severity of obesity increases, as well as abnormal myocardial systolic deformation and abnormal longitudinal strain and strain rate, often with a compensatory increase in radial strain. Abnormalities detected by these newer modalities of tissue Doppler imaging and speckle track imaging are frequently present in the absence of clinical HF and with normal LV ejection phase indices, which suggests that subclinical LV systolic dysfunction is common in obesity.[347,348,351,352] As noted above, frank systolic dysfunction as manifested by obesity-related DCM, with or without clinical HF, is uncommon and usually associated with severe or morbid obesity.

Diagnosis

There are no specific diagnostic criteria for obesity-related DCM. The diagnosis is usually a diagnosis of exclusion after other causes of DCM have been ruled out. Patients who have HF either exclusively or predominantly as a result of their obesity are considered to have obesity cardiomyopathy, usually with a BMI >40 kg/m^2.[358] Obese HF patients have lower levels of BNP and N-terminal proBNP than lower-weight HF patients, and levels are lower as the severity of obesity increases. The lower levels of BNP are observed in both the acute and chronic states of HF. This makes levels of natriuretic peptide less helpful in the diagnosis of HF in obese patients, because patients can have normal or minimally elevated levels of BNP, even in the setting of acute decompensated HF and elevated filling pressures.[359,360] Because signs and symptoms of dyspnea and edema are not specific for HF in obese patients, and jugular venous pressure can be difficult to estimate accurately because of body habitus, hemodynamic confirmation may be needed more often in obese than in lean patients to confirm the clinical diagnosis of HF.

Treatment

The mainstays of treatment for obesity-related DCM and HF include treatment for LV systolic dysfunction and symptomatic HF as outlined in the "2013 ACCF/AHA Guideline for the Management of Heart Failure."[1] In addition, patients may benefit from focused management of comorbidities such as diabetes mellitus, hypertension, and metabolic syndrome. The role of exercise in obese patients with HF, with respect to both weight loss and safety, is an important one. The largest study of exercise intervention in HF, HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training), demonstrated that aerobic exercise training in patients with systolic HF (n=2331) was associated with a nonsignificant trend toward a reduction in mortality or

hospitalization and a substantial improvement in health status.[361,362] In a post hoc analysis of HF-ACTION, obese patients (BMI >30 kg/m^2) had a slightly greater degree of weight loss with exercise intervention than the control groups, although the changes in weight were minimal, with median weight change <1 kg. In addition, nonsignificant reductions in the composite end point of all-cause mortality/hospitalization were seen across the broad range of BMI categories.[344] Improvement in quality of life was also seen in all the BMI ranges, as was safety of the exercise. Therefore, physical activity as part of an exercise program is safe in obese patients with HF and can improve quality of life, although it was not effective at inducing weight loss.

Although obesity is an independent risk factor for the development of HF, once HF develops, obesity has been found in numerous studies to be associated with improved survival compared with normal BMI.[348,363,364] This is termed the *obesity paradox*. Most data suggest that the best survival is seen in patients with class I obesity (ie, BMI <30–35 kg/m^2), with a J-shaped curve for greater degrees of obesity. Various theories have been put forth to explain the obesity paradox.[348] In view of this finding, recommendations for intentional weight loss in obese HF patients have been controversial; however, obese HF patients could benefit from weight loss for a variety of reasons, including but not limited to improving their quality of life, improving other medical conditions such as diabetes mellitus or sleep apnea, or in those with advanced disease, improving their candidacy for aggressive therapies such as heart transplantation or ventricular assist device placement. The long-term effect of intentional weight loss in obese HF patients has not been well studied prospectively. A few notable, small, short-term studies of interventions to achieve weight loss, including dietary intervention, physical activity, pharmacotherapy, and surgery, have been performed in populations of obese patients with HF.[344,364,365] Weight loss as a result of bariatric surgery or diet has been shown to be associated with reversal of several hemodynamic and structural abnormalities caused by obesity.[346a,365,367] As expected, weight loss and its impact are much more substantial after bariatric surgery than with diet alone.

Structural changes observed after bariatric surgery–induced weight loss include reduction in LV internal dimension, reversal of eccentric and concentric hypertrophy and remodeling, improvement in LV shortening fraction, and improvement in LVEF.[349,357,363,364] For example, a small retrospective study evaluated effects after symptomatic HF patients (NYHA functional class 2.9±0.7) with severe obesity (BMI 53±7 kg/m^2) and DCM (LVEF 22±7%) underwent bariatric surgery, with matched control subjects. At 1-year follow-up, hospital readmission in patients who underwent bariatric surgery was significantly lower than in control subjects, and LVEF improved significantly in the surgical group but not in control subjects. NYHA functional class also improved in the surgical group but deteriorated in control subjects. Furthermore, in the surgical arm, 1 patient underwent successful transplantation, and another was listed for transplantation.[364] However, randomized controlled trials are needed to assess the definitive efficacy and safety of bariatric surgery and related weight loss in outcomes for patients with obesity and HF, and specifically in patients with obesity cardiomyopathy.

Key Diagnostic and Management Strategies for Obesity Cardiomyopathy

Recommendations With Strong Level of Consensus for Obesity Cardiomyopathy

1. Standard guideline-directed workup is recommended for assessment of the pathogenesis and prognosis in obese patients with HF *(Level of Evidence C)*.
2. Standard guideline-directed medical therapy for HF is recommended to treat obese patients with HF[1] *(Level of Evidence B)*.
3. Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status, including those who are obese *(Level of Evidence B)*.[344,361,362]

Recommendations With Uncertainty for Obesity Cardiomyopathy

1. Purposeful weight loss via healthy dietary intervention, physical activity, or weight loss drugs such as orlistat for the purposes of improving health-related quality of life or managing comorbidities such as diabetes mellitus, hypertension, or sleep apnea may be reasonable in obese patients with HF *(Level of Evidence C)*.
2. Purposeful weight reduction, including with bariatric surgery, dietary intervention, or weight loss drugs such as orlistat, is of uncertain benefit to reduce morbidity or mortality in HF *(Level of Evidence B)*.[346a,349,357,363–365,367]

Thyroid Disorders and Cardiomyopathy

Epidemiology and Pathophysiology

The systolic and diastolic functions of the heart are influenced by thyroid hormones. Ventricular contractile function is also influenced by changes in hemodynamic conditions secondary to effects that the thyroid hormones have on the peripheral vascular tone. Triiodothyronine (T3) generally increases the force and speed of systolic contraction and the speed of diastolic relaxation, through its effects on myosin isoforms and calcium-handling proteins.[368–370] In addition, T3 decreases vascular resistance, including coronary vascular tone,

and increases coronary arteriolar angiogenesis. Thyroid hormones can also promote both physiological and pathological myocardial hypertrophies.[371] Hypothyroidism promotes myocardial fibrosis by stimulating fibroblasts, whereas the reverse is seen in hyperthyroidism.[372] Chronic hypothyroidism in adult rats leads to loss of coronary arterioles, impaired blood flow, and a maladaptive change in myocyte shape. Hyperthyroidism and hypothyroidism can both lead to cardiovascular injury, including HF. However, a DCM related only to the thyroid disorder is present only in a small proportion of these patients.

The hemodynamic effects of hyperthyroidism include decreased systemic vascular resistance, increased resting heart rate and LV contractility, and enhanced isovolumic ventricular relaxation.[373] Decreased systemic vascular resistance stimulates renin release with activation of the angiotensin-aldosterone axis, which results in renal sodium reabsorption and increased blood volume. Increased release of erythropoietin caused by hyperthyroidism adds to the circulating blood volume, which can increase up to 25%. Hyperthyroidism thus results in an increased preload, a decreased afterload, and a cardiac output that is increased by up to 300% from a euthyroid state.[374]

In contrast to a fall in mean systemic arterial pressure, pulmonary artery hypertension is increasingly being recognized in hyperthyroidism.[375] This finding could be the result of an increased pulmonary blood flow unaccompanied by the same decrease in pulmonary vascular resistance that occurs in the systemic circulation. Pulmonary artery hypertension may in turn result in an increased load on the RV, leading to RV dilatation and a rise in right atrial and central venous pressures.[376]

Presentation and Diagnosis

Patients with hyperthyroidism may occasionally have exertional dyspnea or other symptoms and signs of HF.[368] In view of the increased cardiac contractile function of patients with hyperthyroidism, the development of HF is unexpected, raising the possibility of hyperthyroid cardiomyopathy. As noted above, in most patients with hyperthyroidism, the cardiac output is high, and the subnormal response to exercise might be the result of an inability to increase heart rate maximally or to lower vascular resistance further, as normally occurs with exercise.[377,378] Abnormal LV function may be observed during exercise in hyperthyroidism, which suggests that there may be a reversible functional cardiomyopathy, independent of β-adrenoceptor activation, that is presumably a direct effect of an excess in circulating thyroid hormones.[377] The term *high-output failure*, often used in hyperthyroidism, is not really appropriate, because the ability of the heart to maintain increased cardiac output at rest and with exercise is preserved in most cases. However, occasionally patients with severe, long-standing hyperthyroidism have poor cardiac contractility, low cardiac output, and symptoms and signs of HF. Most often, these findings are noted in conjunction with persistent sinus tachycardia or rapid ventricular rates from atrial fibrillation or atrial flutter, with the HF being a result of a rate-related or tachycardia-induced cardiomyopathy (See the Tachycardia-Induced Cardiomyopathy section). Furthermore, the presence of hyperthyroidism does not exclude other common causes of HF; in older patients with underlying ischemic, hypertensive, or valvular heart disease, the increased workload that results from hyperthyroidism can further impair cardiac function and precipitate HF. Prompt recognition and effective management of cardiac and other organ-system manifestations in patients >50 years of age are important, because cardiovascular complications are the chief cause of death after treatment of hyperthyroidism.

The hemodynamic changes typical of hypothyroidism are opposite to those of hyperthyroidism, but they are accompanied by fewer symptoms and signs. The most common signs are bradycardia, mild hypertension (often diastolic), and a narrowed pulse pressure. Pericardial effusions and nonpitting edema (myxedema) can occur in patients with severe, long-standing hypothyroidism, but DCM is not a characteristic feature.[368,379] There are, however, case reports of patients with hypothyroidism and DCM in whom the cardiomyopathy improved with thyroid hormonal replacement.[380] The low cardiac output in hypothyroidism is caused by bradycardia, a decrease in ventricular filling, and a decrease in cardiac contractility.[381] Systemic vascular resistance can increase by as much as 50%,[381] and diastolic relaxation and filling are slowed. However, clinical HF is rare, because the cardiac output is usually sufficient to meet the lowered systemic demands in hypothyroidism.[379]

In summary, although hypothyroidism and hyperthyroidism are rarely the primary cause of DCM and HF, they more often coexist in patients with HF of various causes. Because of the relative ease of diagnosing these conditions by thyroid function testing and the availability of definitive treatments of these conditions, thyroid function tests are recommended in all patients presenting with HF.

Treatment

Hyperthyroidism

The initial treatment of patients with the entire spectrum of cardiac-related symptoms and signs of hyperthyroidism, from sinus tachycardia and exertional dyspnea to HF, should include a β-blocker. The goal of therapy is to lower the heart rate to nearly normal.[368] This will cause the tachycardia-mediated component of ventricular dysfunction to improve, whereas the direct inotropic effects of thyroid hormone will persist.[377,382] β-Blockers are associated with rapid improvement in the cardiac, neuro-

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muscular, and psychological manifestations of hyperthyroidism. Definitive therapy for hyperthyroidism can then be pursued with iodine 131 alone or in combination with an antithyroid drug, as appropriate. Clinical HF is otherwise treated based on guideline-recommended therapies for HF.

Hypothyroidism

Thyroxine therapy is thought to reverse the cardiovascular changes associated with hypothyroidism.[381,383] Older patients or those with known or suspected ischemic heart disease or cardiac dysfunction should initially be given ≈25% to 50% of the anticipated replacement dose, and the dose should then be increased in stepwise fashion at 6- to 8-week intervals.[368,384] Although cautious replacement is advised, in a large study of patients with hypothyroidism who were evaluated for clinical evidence of ischemic heart disease after the initiation of thyroid hormone therapy, new or worsening angina or acute MI was rare, and more patients had improvement in anginal symptoms, which reinforces the important and potentially beneficial effects of thyroid hormone in improving the efficiency of myocardial oxygen consumption and simultaneously lowering systemic vascular resistance. Whether patients with subclinical hypothyroidism should be treated is controversial, but from a cardiac perspective, treatment appears to offer benefit with minimal risk.[383] In addition, there are case reports of patients with hypothyroidism and DCM in whom the cardiomyopathy improved with thyroid hormonal replacement.

Of note, thyroid hormone metabolism has been seen to be altered in many patients with acute and chronic cardiac disease, including HF. Patients with HF may have low levels of free T3 (FT3) in the background of normal levels of thyroid-stimulating hormone and free T4 (FT4). The decrease in levels of FT3 may be proportional to the severity of HF.[368,370] Although some small clinical trials have shown improvement in cardiac function with short-term treatment using T3 replacement therapy, trials evaluating clinical outcomes in HF patients are not available.[370]

Key Diagnostic and Management Strategies for Thyroid Disorders and Cardiomyopathy

Recommendations With Strong Level of Consensus for Thyroid Disorders and Cardiomyopathy

1. It is recommended that all patients with DCM have thyroid function tests as part of their initial workup *(Level of Evidence C)*.
2. Hypothyroidism and hyperthyroidism should be treated in patients with DCM *(Level of Evidence C)*.

Recommendations With Moderate Level of Consensus for Thyroid Disorders and Cardiomyopathy

1. Use of β-blockers is reasonable in patients with cardiac-related symptoms and signs of hyperthyroidism *(Level of Evidence C)*.

Growth Hormone Disorders

Growth Hormone

Growth hormone (GH) and insulin-like growth factor (IGF)-1 appear to be physiological modulators of myocardial structure and function.[385,386] GH activates cardiac cell growth without altering the collagen content of the myocardium or the capillary density.[387,388] It also induces physiological ventricular remodeling, in which the growth response is associated with enhanced contractile performance.[387,388] It has been suggested that by reducing the energy cost, GH could improve the thermodynamic efficiency of the contractile apparatus.[389] Moreover, experimental studies suggest that GH and IGF-1 have stimulatory effects on myocardial contractility, possibly mediated by changes in intracellular calcium handling. Furthermore, impairment of cardiac growth and function occurs in patients with GH deficiency.[390,391] The administration of GH to patients with GH deficiency is associated with an increase in wall thickness and normalization of cardiac performance.[391,392] On the other hand, acromegaly is associated with cardiac hypertrophy and a hyperkinetic syndrome, with increased cardiac output and reduced vascular resistance.[393,394]

Acromegaly

Chronic excess of GH and IGF-1 secretion affects cardiac morphology and performance, which results in a specific acromegalic cardiomyopathy[395] characterized by biventricular concentric hypertrophy[396] caused by the relative increase of cardiac myocyte width for the parallel apposition of new sarcomeres.[397] However, cardiac histological abnormalities noted in acromegaly have also included interstitial fibrosis, increased extracellular collagen deposition, myofibrillar derangement, and areas of monocyte necrosis and lymphomononuclear infiltration.[398] The natural history of acromegalic cardiomyopathy is thought to progress through 3 stages. The first stage, typical of young patients with a short disease duration, is characterized by biventricular cardiac hypertrophy with increased contractility and systolic output, the hyperkinetic stage.[372,399] The second stage consists of more significant hypertrophy associated with diastolic filling abnormalities at rest and impaired cardiac performance during exercise. The end stage of untreated acromegaly, usually late in the disease course, is characterized by impaired systolic and diastolic performance with low cardiac output and overt HF.[400] In late stages, it can be difficult to differentiate DCM secondary to acromegaly from idiopathic DCM, because at this stage, the morphological or histological features might not be diagnostic of acromegalic cardiomyopathy. The prevalence of LV hypertrophy may be greater in patients >50 years of age than in younger patients, which suggests that aging and long duration of exposure to elevated GH and IGF-1 levels are important determinants of cardiac abnormalities.[372,401] Therefore, cardiac involvement can

be considered as an early event in acromegaly, which worsens in proportion to the duration of disease activity. Although cardiac hypertrophy typically occurs even in the absence of other cardiovascular risk factors, coexistence of cardiovascular risk factors, including hypertension, diabetes mellitus, and dyslipidemia, accelerates the onset and progression of cardiac complications.[402]

The specificity of heart disease in acromegaly is also supported by the evidence that pharmacological suppression of GH production leads to significant regression of hypertrophy and improvement of cardiac dysfunction.[385,403,404] Several studies have demonstrated that LV hypertrophy can be reversed by suppression of GH and IGF-1 levels with surgical treatment for acromegaly or with administration of octreotide.[385,403,404] The increased prevalence of LV hypertrophy in patients with hypertension and glucose tolerance abnormalities emphasizes the need for optimal control of blood pressure and hyperglycemia together with efficacious suppression of GH and IGF-1 levels.[401] Although a case report of severe congestive HF from acromegalic cardiomyopathy suggests that cardiac function could be recovered significantly and that LV mass could be decreased with transsphenoidal surgery and administration of octreotide,[405] other reports suggest that these beneficial effects appear earlier in young patients with short disease duration than in elderly patients.[401] Some reports indicate that the treatment of acromegaly might improve cardiac function in the short term, but the long-term prognosis is questionable.[406] Reduction of the LV mass, which led to a consequent improvement of diastolic filling, was obtained after short- and long-term treatment with octreotide.[399] In contrast, systolic function might improve only in patients who achieve biochemical control of the disease.[407]

GH Deficiency

GH-deficient adults without GH replacement therapy have reduced LV mass with impairment of myocardial contractility indices and cardiac output[391,408] and decreased exercise capacity.[385] Although some studies suggest that cardiac dysfunction might be more severe in GH-deficient patients with childhood-onset disease than in patients with adult-onset disease caused by the lack of GH/IGF-1 during growth and development of the heart,[391] this has not been seen consistently across other studies.[409] Short-term placebo-controlled studies have shown that GH replacement therapy in adult GH-deficient patients has an anabolic effect on cardiac structure, which results in an improvement in both diastolic and systolic function.[391,410,411] A few open-label studies have determined the long-term effects of GH replacement therapy on cardiac function. Studies thus far suggest that low-dose individualized GH replacement therapy improves cardiac function with less risk of developing cardiac hypertrophy. Combined with the increased muscle strength, this could explain the improved exercise capacity in GH-deficient adults observed after GH replacement. However, if an inappropriately high dose of GH is given, there is a risk of an unwanted increment in LV mass, particularly in elderly GH-deficient patients during long-term treatment.[412,413]

In addition, between one third and two thirds of HF patients are also affected by GH or IGF-1 deficiency.[414,415] Smaller, mostly short-term trials of GH administration to patients with systolic HF have demonstrated improvement in various parameters of cardiac structure, LVEF, functional status, and exercise performance.[416,417] However, larger longer-term randomized placebo-controlled trials are needed to confirm these results and to evaluate the beneficial effects of GH administration on clinical outcomes in patients with systolic HF.

Key Diagnostic and Management Strategies for GH Cardiomyopathy

Recommendations With Strong Level of Consensus for GH Cardiomyopathy

1. Testing for acromegaly or for GH deficiency is indicated in patients with DCM who have other signs and symptoms of those clinical disorders *(Level of Evidence C)*.
2. Appropriate therapy of the primary disorder of excess or deficiency of GH should be performed in all patients with coexisting DCM *(Level of Evidence C)*.

STRESS-INDUCED CARDIOMYOPATHY OR APICAL BALLOONING SYNDROME

Definition and Pathophysiology

Stress-induced cardiomyopathy, also referred to as Tako-tsubo cardiomyopathy, is characterized by acute transient LV dysfunction triggered by a profound emotional or physical stressor. It has been referred to as Tako-tsubo because of its distinctive pattern of apical ballooning, similar to octopus catching pots used in Japan. Stress-induced cardiomyopathy has a predilection for postmenopausal women, with a mean age of 65 years and with 96% of women being ≥50 years of age in 1 series.[418] The incidence of stress-induced cardiomyopathy is not known.

The mechanisms underlying stress-induced cardiomyopathy are not well understood, but evidence supports an adrenergically mediated process. Catecholamine surges are an evolutionary response to stress and danger, and supraphysiological elevations of plasma catecholamines have been demonstrated in stress cardiomyopathy.[419] Although the ventricular apex has relatively sparse sympathetic innervation, there is evidence that it is more responsive to sympathetic stimuli because of increased β_2-adrenergic receptor density.[420] Other theories include microvascular vasospasm,[421] impaired fatty

acid metabolism,[422] transient LV outflow tract obstruction,[423] and catecholamine-mediated myocardial stunning caused by direct myocyte injury.[419] High levels of circulating epinephrine can trigger a switch in intracellular signal trafficking in ventricular cardiomyocytes, from Gs protein to Gi protein signaling, via the β_2-adrenergic receptor, which is protective against the proapoptotic effects of intense activation of β_1-adrenoceptors but is also negatively inotropic. This effect can be greatest at the apical myocardium, where the β-adrenergic receptor density is greatest.[424] Regional differences in myocardial blood flow caused by base-to-apex perfusion gradient have also been postulated.[425]

Clinical Presentation and Prognosis

Clinical presentation typically mimics that of acute ST-segment–elevation MI, but CAD is typically not present. A usual scenario is that of an older woman without prior cardiac history presenting with chest pain minutes to hours after experiencing a psychological or physical stress. ST-segment elevation is typically seen in the precordial leads but can also occur in the inferior and lateral leads.[421] Although this finding is common, it is also variable and can occur in 46% to 100% of patients.[426] Modest elevation of troponins, typically within 24 hours, is also common.[418,426] Although LV dysfunction may be seen on echocardiogram, echocardiography might not adequately characterize the apex, and diagnosis is usually made by cardiac catheterization and left ventriculogram. Angiograms are often performed because of suspicion of acute coronary syndrome, but the absence of coronary artery stenosis and the presence of apical ballooning suggests stress-induced cardiomyopathy. Perhaps an underappreciated finding is that RV involvement can occur in 30% of patients with stress cardiomyopathy.[427,428] Diagnostic criteria have been proposed for apical ballooning syndrome[429,430] that usually require the following: (1) Transient hypokinesis, akinesis, or dyskinesis of the LV midsegments, with or without apical involvement, is present. The regional wall motion abnormalities extend beyond a single epicardial vascular distribution. A stressful trigger is often but not always present. (2) There is no obstructive coronary disease or angiographic evidence of acute plaque rupture. (3) New electrocardiographic abnormalities (ST-segment elevation or T-wave inversion) or modest elevation in cardiac troponin is present. (4) There is no pheochromocytoma or myocarditis.

The prognosis is generally favorable, with the majority of patients surviving in most series, although hemodynamic compromise can occur[418] and in-hospital mortality has been reported to be as high as 4.5%.[431] Resolution of LV dysfunction occurs usually within 6±3 days.[418] Congestive HF has been reported in up to 20% of patients,[427,432] typically occurring in the setting of RV involvement.[427,428,432] LV rupture and mitral regurgitation have also been reported.[433,434]

Several cases of stress-induced cardiomyopathy have been reported in association with pheochromocytoma, even in the absence of other classic symptoms of pheochromocytoma.[435–437] Therefore, it has been suggested that the evaluation of pheochromocytoma should be considered in patients with stress-induced cardiomyopathy. For this reason, the absence of pheochromocytoma is usually required for the diagnosis of transient LV apical ballooning syndrome.[430]

Treatment

The management of stress-induced cardiomyopathy is supportive and centers on managing HF symptoms and treating hypotension and cardiogenic shock with the appropriate therapies. Although the mechanism of stress cardiomyopathy is neurohormonally mediated, the role of neurohormonal agents is as yet unknown. A catecholamine-mediated process could have implications for management (eg, agents such as dobutamine theoretically could worsen stress-induced cardiomyopathy); however, this has not been reported or studied clinically. Some β-blockers can also cause stimulus trafficking of β_2-adrenergic receptors to Gi protein coupling, resulting in negative inotropy.[438] Thus, intra-aortic balloon pump and calcium-sensitizing agents have been suggested as first- and second-line therapies.[424] The relatively infrequent occurrence of stress-induced cardiomyopathy and the study of only small series have limited the capacity to develop standardized treatment strategies for stress-induced cardiomyopathy.

TACHYCARDIA-INDUCED CARDIOMYOPATHY

Definition and Pathophysiology

Tachycardia-induced cardiomyopathy is a reversible cause of HF characterized by LV myocardial dysfunction caused by increased ventricular rate. First described in 1913, tachycardia-induced cardiomyopathy is a reversible form of systolic dysfunction resulting from chronic supraventricular and ventricular arrhythmias.[439] The degree of dysfunction correlates with the duration and rate of the tachyarrhythmia. Reversibility of the cardiomyopathy with treatment of the arrhythmia is the rule, although this may not be complete in all cases. Virtually any supraventricular tachycardia with a rapid ventricular response can induce cardiomyopathy. Ventricular arrhythmias, including frequent premature ventricular complexes, can also induce cardiomyopathy. Experimental models have illustrated the detrimental cardiac effects of chronic atrial and ventricular pacing in dogs and pigs.[440] In these models, persistent tachycardia results in systolic HF that is hemodynamically and neurohormonally similar to that

in humans. Chronic and rapid atrial and ventricular pacing results in neurohormonal activation characterized by reduction in serum sodium, activation of the renin-angiotensin system, and an increase in plasma atrial natriuretic peptide, aldosterone, norepinephrine, and epinephrine.[441] Abnormal myocardial and cellular remodeling occurs, which results in biventricular dilatation, decreased contractility, and elevated filling pressures. Proposed mechanisms include myocardial energy depletion and decreased energy utilization, myocardial ischemia, and abnormal calcium handling. Maintenance of sinus rhythm or control of ventricular rate is critical to the treatment of patients with tachycardia-induced cardiomyopathy.[442] Ventricular pacing at high rates can also cause cardiomyopathy. Additionally, RV pacing alone can exacerbate HF symptoms, increase hospitalization for HF, and increase mortality.[443] Use of CRT in patients with a conduction delay caused by pacing can result in improved LV function and functional capacity.

In humans, tachycardia as the causative factor of cardiomyopathy is implied by tachyarrhythmia in the presence of and preceding LV dysfunction and restoration of hemodynamic and myocardial derangements after elimination of the tachyarrhythmia. Tachycardia-mediated cardiomyopathy is characterized by LV dilatation without hypertrophy; however, during the recovery phase, hypertrophy and persistent diastolic dysfunction occur, which suggests irreversible structural changes despite apparent recovery.[444] Tachycardia-mediated cardiomyopathy can occur at any age and has been described in a fetus. Atrial fibrillation is the most common cause of tachycardia-mediated cardiomyopathy, but a broad range of both ventricular and supraventricular arrhythmias, including inappropriate sinus tachycardia, has been described as causing tachycardia-mediated cardiomyopathy. Genetic factors also have been implicated. Patients who are homozygous for a deletion polymorphism in the *ACE* gene (DD) might have a greater tendency to develop cardiomyopathy in the setting of tachycardia. Although the initial insult with tachycardia-induced cardiomyopathy can develop over 1 month to years, recurrence of arrhythmia can result in a rapid decline in LV function. In one series, tachycardia was present for a mean of 8 years before the discovery of LV dysfunction and HF; however, with recurrent tachycardia, HF developed within 6 months. The prognosis of tachycardia-induced cardiomyopathy is unclear, and sudden death has been described in small series even after elimination or control of the tachyarrhythmia and near normalization of the EF, which suggests persistent ultrastructural changes despite rhythm and rate management.[445]

Treatment

Treatment of tachycardia-induced cardiomyopathy is focused on aggressive attempts at eliminating or controlling the tachycardia. Catheter ablation might be required and is often curative. Standard HF therapy should be used to attenuate adverse remodeling. Although tachycardia-induced cardiomyopathy is an increasingly recognized mechanism for HF, data regarding its pathogenesis and management remain sparse. Although there are data suggesting that a heart rate >100 beats per minute can lead to cardiomyopathy, the heart rate at which tachycardia-induced cardiomyopathy occurs is not defined. In addition, the contribution of the duration of the arrhythmia, type, persistence, and irregularity remain to be defined. The role of ICDs is not known. Although improvement of EF can suggest that an ICD is not indicated, the extent to which ultrastructural changes persist is not known.

Key Diagnostic and Management Strategies for Tachycardia-Induced Cardiomyopathy

Recommendations With Strong Level of Consensus for Tachycardia-Induced Cardiomyopathy

1. Maintenance of sinus rhythm or control of ventricular rate is indicated in treating patients with tachycardia-induced cardiomyopathy *(Level of Evidence B)*.[442,444]

LBBB-INDUCED CARDIOMYOPATHY

Pathophysiology and Epidemiology

It is estimated that LBBB occurs in 25% of patients with HF.[446] Although it is clear that remodeling of the LV can result in conduction system abnormalities, it has become increasingly recognized that LBBB could be causative in the development of HF.[447] The Framingham study demonstrated that 28% of subjects who were free of cardiovascular disease and who developed LBBB, developed HF coincident with the development of LBBB or shortly thereafter at a mean of 3.3 years.[448] In animals, asynchronous activation of the myocardium can contribute to myocardial remodeling.[449,450]

Management

CRT[451] can be useful in patients in whom LBBB-induced cardiomyopathy is suspected. Abnormal strain patterns have been demonstrated in HF patients with LBBB and can be reversed by CRT.[452] Vaillant et al[453] reported 6 cases of patients with HF and LBBB in whom EF improved substantially and in 4 cases normalized with CRT. In patients with HF, LBBB is a predictor of super-response to CRT and favorable outcome with CRT. Thus, there is supporting evidence of the existence of a cardiomyopathy that can be induced by LBBB and that is reversible with resynchronization of the activation sequence. Identifying this entity is difficult, but it may be suggested by the pro-

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longed presence of LBBB in patients with HF or the subsequent development of HF in a patient with LBBB. Patients who have LBBB and HF might meet the criteria for CRT; however, for those patients with LBBB and lesser degrees of LV dysfunction, there are no data to guide therapy or to prevent subsequent development of cardiomyopathy.

Key Diagnostic and Management Strategies for LBBB-Induced Cardiomyopathy

Recommendations With Uncertainty for LBBB-Induced Cardiomyopathy

1. CRT may be considered for suspected cardiomyopathy caused by LBBB *(Level of Evidence B)*.[447,452,453]

PREMATURE VENTRICULAR CONTRACTIONS AND CARDIOMYOPATHY

Pathophysiology and Epidemiology

Improvement or resolution of cardiomyopathy has been reported after elimination or suppression of premature ventricular contractions (PVCs), which raises the question of a possible PVC-induced cardiomyopathy.[454–457] The proposed mechanisms underlying PVC-induced cardiomyopathy include ventricular dyssynchrony and increased myocardial oxygen demand.[458] This is supported by evidence that LBBB creates dyssynchrony that can impair diastolic function and worsen mitral regurgitation.[459,460] PVC burden is related to cardiomyopathy; the minimum PVC burden that appears to result in cardiomyopathy is 10%.[461] PVC burden ≥24% is independently associated with cardiomyopathy.[461] Although the prevalence and incidence are unknown, in a referral HF population, tachycardia-induced cardiomyopathy was found in 6.8% of patients. Among 60 patients with idiopathic, frequent PVCs (>10/h), 22% had LV dysfunction.[462] Patients with LV dysfunction had a greater burden of PVCs. Radiofrequency ablation resulted in normalization of EF in 82% of the patients with LV dysfunction within 6 months. The RV outflow tract was the most common origin of PVCs (52% of cases). Those patients who did not respond to radiofrequency ablation had progression of cardiomyopathy, and there was no improvement in EF among a control group who had a similar burden of PVCs and did not receive radiofrequency ablation.[462]

A direct link between PVCs and cardiomyopathy has been demonstrated in an animal model.[458] In humans, PVC-induced cardiomyopathy is inferred from the improvement of EF with treatment of the PVCs or from the presence of PVCs in a structurally normal heart and subsequent LV dysfunction. Frequently, patients present after the onset of ventricular dysfunction; thus, it can be challenging to determine whether PVCs are causative or a result of the cardiomyopathy. Some clues that PVCs are the cause of cardiomyopathy include the following: The patient is young and otherwise healthy, asymptomatic, and typically male; has no prior cardiac history or family history of relevance; has >10 000 to >20 000 PVCs per 24 hours; has the presence of outflow tract or fascicular morphology; has an improvement of LV function with PVC suppression; and has recovery of LV function with ablation.[463] A PVC burden >16% can distinguish PVC-associated cardiomyopathy with a sensitivity of 100% and specificity of 87%. Of note, male predominance is reported at 65%.[463]

Management

Radiofrequency ablation is reportedly successful in reducing PVC burden in patients with LV dysfunction, improving ventricular function in both structurally normal and abnormal hearts.[462–466] PVC radiofrequency ablation in patients with LV dysfunction improves LV dilatation, mitral regurgitation, and EF.[464,465] PVC suppression with antiarrhythmic drugs typically has been associated with increased mortality; however, in PVC-induced cardiomyopathy, antiarrhythmic drugs, including β-blockers, have been reported to be successful.[455] Typically, PVCs are not suppressed unless they are symptomatic; however, because improvement in EF can be seen in those with PVC-induced cardiomyopathy, consideration can be given to those with cardiomyopathy of unknown cause and a high burden of PVCs, although this has not been studied prospectively.

Key Diagnostic and Management Strategies for PVC-Induced Cardiomyopathy

Recommendations With Moderate Level of Consensus for PVC-Induced Cardiomyopathy

1. Radiofrequency ablation can be effective in PVC-induced cardiomyopathy *(Level of Evidence B)*.[462,464,466]

GENETIC CAUSES OF DCM

Our understanding of the genetic causes of cardiomyopathy has expanded significantly over the past decade. In many cases, the genetic and mechanistic causes of these disorders follow a disturbance in a particular, disease-specific "final common pathway."[467] For instance, hypertrophic cardiomyopathy is now viewed as predominantly an inherited abnormality of contractile protein function (disease of the sarcomere) with an occasional infiltrative cause.[468] Progress in understanding the genetics of familial DCM has been complicated by its heterogeneous causes, but a genetic cause is thought to occur in ≈50% of subjects (higher in children).[469] Some people who inherit the altered gene never develop the

phenotypic features of familial DCM, known as reduced penetrance.

The genes identified to date as causative appear to disturb the functional link between the cytoskeleton and sarcomere most commonly.[470,471] Multiple genes have been identified for ARVC, most of which result in disturbed desmosome/intercalated disk function.[472] Although the genetic basis for the development of restrictive cardiomyopathy and LV noncompaction cardiomyopathy (LVNC) has been more elusive, genes for both have been identified and appear to include sarcomere dysfunction as critical factors.[473] There could be heterogeneity of clinical expression of genetic cardiomyopathies in different phenotypes. Some diseases do not have a uniformly static expression but evolve as a consequence of remodeling from one category to another during their natural clinical course and can progress from a nondilated state to a dilated form. Although phenotypically different from DCM, some patients with ARVC, hypertrophic cardiomyopathy, and LVNC subsequently develop dilated ventricles. Therefore, in this section, we will review the current genetic knowledge of each DCM. We will also review other cardiomyopathies such as ARVC and LVNC, which are not considered predominantly as DCM and have other distinct phenotypic characteristics but which can develop DCM features.

Clinical genetic testing is relatively new, and the methodology has varied over time; however, the importance of genetic testing is gaining wider recognition as panels of genetic testing are being incorporated into clinical laboratory panels.[474] A significant proportion of idiopathic DCM cases could have genetic causes and could benefit from genetic screening, especially in familial or suspected cases; however, randomized clinical trials that demonstrate an association of genetic testing for specific disorders with disease-specific gene panels and improvement in clinical outcomes are not available, and this awaits future studies.

Clinical Genetics of DCM

DCM was initially believed to be inherited in a small percentage of cases until Michels et al[475] showed that ≈20% of patients had family members with echocardiographic evidence of DCM when family screening was performed. More recently, inherited familial DCM has been shown to occur in 30% to 50% of cases, with autosomal dominant inheritance being the predominant pattern of transmission; X-linked, autosomal recessive, and mitochondrial inheritance patterns are less common but occur.[476]

Molecular Genetics of DCM

Over the past 20 years, substantial progress has been made in the understanding of the genetic causes of familial DCM.[477] Progress in gene identification was made in the early 1990s, initially in families with X-linked forms of DCM, with genes for the autosomal dominant forms of DCM identified subsequently. In the case of X-linked forms of DCM, 3 disorders have been well characterized: X-linked cardiomyopathy (XLCM), which presents in adolescents and young adults[478]; Barth syndrome, which is most frequently identified in infancy[479]; and Danon disease, which most commonly presents with hypertrophic cardiomyopathy in boys, which later becomes DCM and affects female carriers with late-onset DCM.[480] All develop HF.

X-Linked DCM

First described in 1987 by Berko and Swift[478] as DCM that occurs in males in the teen years and early 20s, with rapid progression from congestive HF to death caused by ventricular tachycardia/ventricular fibrillation or transplantation, these patients are distinguished by elevated serum creatine kinase muscle isoforms. Female carriers tend to develop mild to moderate DCM in the fifth decade, and the disease is slowly progressive. Towbin and colleagues[481] were the first to identify the disease-causing gene and to characterize the functional defect. In their report, the dystrophin gene was shown to be responsible for the clinical abnormalities, and protein analysis demonstrated severe reduction or absence of dystrophin protein in the hearts of these patients. These findings were later confirmed by Muntoni et al,[482] and a muscle promoter–exon 1 dystrophin deletion was identified in another family with XLCM. Subsequently, multiple mutations were identified in dystrophin in patients with XLCM.[483,484]

Dystrophin is a cytoskeletal protein that provides structural support to the myocyte by creating a lattice-like network to the sarcolemma.[483] In addition, dystrophin plays a major role in linking the sarcomeric contractile apparatus to the sarcolemma and extracellular matrix.[483] Furthermore, dystrophin is involved in cell signaling, particularly through its interactions with nitric oxide synthase.[483] The dystrophin gene is responsible for Duchenne and Becker muscular dystrophy when mutated as well.[483] These skeletal myopathies present early in life (Duchenne muscular dystrophy is diagnosed before 12 years of age, whereas Becker muscular dystrophy is seen in teenage males >16 years of age), and the vast majority of patients develop DCM before their 20th birthday. In most patients, serum creatine kinase muscle isoforms are elevated, similar to what is seen in XLCM; in addition, manifesting female carriers develop disease late in life, similar to XLCM. Also, immunohistochemical analysis has demonstrated reduced levels (or absence) of dystrophin, similar to what is seen in the hearts of patients with XLCM.

In addition to the dysfunction of dystrophin, mutations in dystrophin secondarily affect proteins that interact with dystrophin. At the amino-terminus (N-terminus), dystrophin binds to the sarcomeric protein actin, a member of the thin filament of the contractile apparatus. At the carboxy-terminus (C-terminus), dystrophin interacts with α-dystroglycan,

a dystrophin-associated membrane-bound protein that is involved in the function of the dystrophin-associated protein complex, which includes β-dystroglycan, the sarcoglycan subcomplex (α-, β-, γ-, δ-, and ε-sarcoglycan), syntrophins, and dystrobrevins.[483,485] In turn, this complex interacts with α_2-laminin and the extracellular matrix. Like dystrophin, mutations in these genes lead to muscular dystrophies with or without cardiomyopathy, which supports the contention that this group of proteins is important to the normal function of the myocytes of the heart and skeletal muscles. In both cases, mechanical stress[486] appears to play a significant role in the age-onset–dependent dysfunction of these muscles.

Another X-linked gene causing DCM is tafazzin, the gene that causes Barth syndrome.[479,487] Initially described as X-linked cardioskeletal myopathy with abnormal mitochondria and neutropenia, this disorder typically presents in male infants as HF associated with neutropenia (cyclic), 3-methylglutaconic aciduria, and cardiolipin deficiency.[479,487] Mitochondrial dysfunction is noted on electron microscopy and electron transport chain biochemical analysis. These infants typically have LV dysfunction and dilatation, endocardial fibroelastosis, or a dilated and hypertrophic LV with trabeculations (LV noncompaction). In some cases, these infants succumb to HF, sudden death, or sepsis attributable to leukocyte dysfunction. Tafazzin encodes the tafazzin protein, the gene product of which is an acyltransferase, which results in cardiolipin abnormalities.[488]

Autosomal Dominant DCM

The most common form of inherited DCM is the autosomal dominant form of disease.[474,475] Patients with this form of the disease present as classic "pure" DCM or DCM associated with conduction system disease.[489] Patients usually present in the third decade of life with mild conduction system disease that can progress to complete heart block over decades. DCM usually presents late in the course but is out of proportion to the degree of conduction system disease.[489] The echocardiographic and histological findings in both subgroups are classic for DCM, although the conduction system may be fibrotic in patients with conduction system disease. Furthermore, there may be other forms of DCM associated with arrhythmia. For example, mutations in the *LMNA* gene, which encodes A-type nuclear lamins, have been implicated in familial cardiomyopathies inherited in an autosomal dominant manner, characterized by LV enlargement and reduced systolic function preceded or accompanied by significant conduction system disease or arrhythmias. LMNA-DCM usually presents in early to mid-adulthood with symptomatic conduction system disease or arrhythmias or with symptomatic DCM including HF or embolus from an LV mural thrombus. Sudden cardiac death can occur and in some instances is the presenting manifestation; sudden cardiac death also can occur with little systolic dysfunction.[490]

Genetic heterogeneity exists for autosomal dominant DCM or conduction system disease.[476,491] The genes identified to date primarily include genes encoding cytoskeletal and sarcomeric proteins, although some ion channel genes and others have also been identified. These include the cytoskeletal and Z-disk–encoding genes δ-sarcoglycan, β-sarcoglycan, desmin, lamin A/C, metavinculin, muscle LIM protein, titin, α-actinin-2, nebulette, myopalladin, and ZO-2–associated speckle protein; the sarcomere-encoding genes actin, troponin T, β-myosin heavy chain, myosin-binding protein C, and α-tropomyosin; and the ion homeostasis genes phospholamban and SCN5A.[491–494] Of note, the truncating mutations of the gene encoding titin, TTN, are a common cause of DCM, occurring in ≈25% of familial cases of idiopathic DCM and in 18% of sporadic cases, and constitute probably the most commonly known genetic cause of DCM.[495]

Mechanistically, cytoskeletal proteins (desmin, δ-sarcoglycan, metavinculin, and muscle LIM protein) are thought to cause defects of force transmission that result in the DCM phenotype, whereas defects of force generation have been speculated to cause sarcomeric protein–induced DCM.[494] Purevjav et al[496] have shown that a mutation in a Z-disk gene can disrupt its protein binding partner's function, and depending on this interaction, differential phenotypes and severity occur. This is likely to have broad applicability with other genetic causes of cardiomyopathies.

Genetic testing in DCM is fair at present, with ≈30% to 40% of patients having a genetic diagnosis identified when the test is performed.[473,474,477] Sequencing panels including but not limited to these genes are offered by several laboratories in the United States and worldwide.[497,498]

Clinical Genetics of Noncompaction Cardiomyopathy

The genetic pathogenesis of LVNC is heterogeneous. Mutations, familial inheritance, and chromosomal abnormalities have been implicated. In a majority of the adult patients with isolated LVNC, it is an autosomal dominant disorder. The familial, X-linked disorders, autosomal recessive, and mitochondrial (maternal) inheritance have also been described.[499–501] In X-linked LVNC, usually caused by Barth syndrome, males almost exclusively develop the disease, although a female with cardiomyopathy has been described.[502] When LVNC is associated with congenital heart disease (CHD), the congenital cardiac defect may be heterogeneous in families, but this form of LVNC is transmitted as an autosomal dominant trait along with the congenital heart abnormality.[500,503] In some families with autosomal dominant LVNC associated with CHD, affected members may have very minor forms of CHD (eg, small ventricular septal defects, atrial septal defects, and patent ductus arteriosus) that may have normalized spontaneously, whereas other family members may have severe forms of CHD (eg, hypoplastic left heart syndrome, Ebstein anomaly).[504] Penetrance may be reduced in some

families. Ichida et al[502] reported that 44% of LVNC patients in their study had inherited LVNC, with 70% having autosomal dominant and 30% having X-linked inheritance.

Molecular Genetics of Noncompaction Cardiomyopathy

The first genetic cause of isolated LVNC was initially described by Bleyl et al[503] when they identified mutations in the X-linked tafazzin gene, the gene also responsible for Barth syndrome, in patients and carrier females. Multiple genes that cause autosomal dominant LVNC have been identified, including mutations in genes that cause CHD with LVNC. In patients with hypoplastic left heart syndrome and LVNC, α-dystrobrevin was identified, whereas mutations in Nkx-2.5 in children with LVNC and atrial septal defect and β-myosin heavy chain (MYH7) in patients with LVNC and Ebstein anomaly have also been reported.[501,502,505] In LVNC without CHD, mutations in the Z-line protein–encoding ZASP/LDB3 gene and the sarcomere-encoding genes[506,507] (β-myosin heavy chain [MYH7], α-cardiac actin [ACTC], cardiac troponin T [TNNT2], cardiac myosin–binding protein C [MYBPC3], α-tropomyosin [TMP1], and cardiac troponin I [TNNI3]) appear to account for ≥20% of LVNC.[500,508,509] Hoedemaekers et al[507] additionally demonstrated an association of LVNC with genetic variants in 2 calcium-handling genes, as well as TAZ, and lamin A/C (LMNA), whereas Probst et al[508] further showed that sarcomere gene mutations are important in LVNC, showing a prevalence of 29%, with MYH7 and MYBPC3 most frequently mutated (13% and 8%, respectively). Dellefave et al[509] also identified sarcomere mutations in LVNC, including those with presentation of HF in infancy.

In addition to sarcomere-encoding genes and the cytoskeleton, mutations in the sodium channel gene, *SCN5A*, were shown by Shan et al[510] to cause LVNC and rhythm disturbance. Another cytoskeletal protein associated with LVNC is dystrophin in boys with Duchenne and Becker muscular dystrophies.[511] Homozygous 2-bp deletion (5208_5209delAG) in an alternatively spliced region of desmoplakin has also been reported in LVNC.[512] This caused Carvajal syndrome with LVNC and severe early-onset HF, woolly hair, and an acantholytic form of palmoplantar keratoderma.[512] Mitochondrial genome mutations have also been identified.[513] As noted, chromosomal abnormalities and syndromic patients have also been identified with LVNC.[506,514,515] LVNC has also been associated with chromosome 8p23.1 deletion.[516] LVNC can be associated with other syndromes with genetic mutations such as Coffin-Lowry syndrome, Sotos syndrome, Hunter-McAlpine syndrome,[517–519] and Charcot-Marie-Tooth disease.[520] Genetic testing in patients with LVNC appears to detect clinically significant variants in 35% to 40% of people, with most-common sarcomere-encoding genes.[492,507,508]

Clinical Genetics of Arrhythmogenic Cardiomyopathy

The pathological condition known initially as arrhythmogenic RV dysplasia and more recently called ARVC or arrhythmogenic ventricular cardiomyopathy is characterized by fibrofatty replacement of the myocardium, most typically in the RV free wall but also affecting the LV.[521] In addition, the pathological features usually include inflammatory infiltrate; fibrosis is essentially always seen, but the fatty infiltrate is variable and in many cases not noted at all. A spectrum of RV or LV involvement occurs, from no functional impairment in some patients to severe impairment in others.[521] Classically, patients with ARVC present with syncope or palpitations secondary to ventricular tachycardia of LBBB morphology, originating from the areas of fibrofatty replacement, although HF can occur. Those with only LV involvement present with arrhythmias and HF. Using a defined referral population, Peters et al[522] estimated the prevalence of ARVC to be 1 per 1000 population; other estimates range from 1 per 1667 to 1 per 5000 population. Familial occurrence is now widely recognized, with autosomal dominant inheritance predominating. Autosomal recessive forms, usually in the form of a cardiocutaneous disorder, also occur. Naxos disease, an autosomal recessive disorder, is characterized by ARVC associated with palmoplantar keratoderma and wooly hair; Carvajal syndrome is similar, but in this case, the LV is usually affected.[523]

Molecular Genetics of Arrhythmogenic Cardiomyopathy

The final common pathway of arrhythmogenic ventricular cardiomyopathy appears to be a disturbance of desmosomes and the intercalated disk. The majority of genes identified to date encode proteins of the desmosome or desmosome-interacting proteins.[523–526] These include the desmosome-encoding genes desmoplakin (*DSP*), junctional plakoglobin (*JUP*), plakophillin-2 (*PKP2*), plakophillin-4 (*PKP4*), desmocollin-2 (*DSC2*), and desmoglein-2 (*DSG2*) and the desmosome-interacting genes desmin, titin, αT-catenin (*CTNNA3),* lamin A/C, transforming growth factor-β3 (*TGF β3*), and transmembrane protein 43 (*TMTM43*), with *PKP2* and *DSP* appearing to be the most common.[525,527–530] Mutations in these genes reportedly occur in ≈50% to 65% of probands.[531] The presence of multiple mutations in desmosomal genes has been reported in a significant proportion of cases.[531,532] In addition, a founder mutation in phospholamban (PLN R14del), a regulator of the sarcoplasmic reticulum Ca^{2+}- (SERCA2a) pump in cardiac muscle and thus important for maintaining Ca^{2+} homeostasis, has also been reported.[533]

Genetic testing in arrhythmogenic ventricular cardiomyopathy is good, with ≈50% of patients having a genetic diagnosis identified when the test is performed.[534]

Key Diagnostic Strategies for Familial Cardiomyopathy

Recommendations With Strong Level of Consensus for Familial Cardiomyopathy

1. In patients with idiopathic DCM, a 3-generational family history should be obtained to aid in establishing the diagnosis of familial DCM *(Level of Evidence C).*

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2. First-degree relatives of patients with familial cardiomyopathy should undergo periodic serial echocardiographic screening with assessment of LV function and size *(Level of Evidence C)*.
3. Mutation-specific genetic testing is recommended for family members and appropriate relatives after the identification of a DCM-causative mutation in the index case *(Level of Evidence B)*.

Recommendations With Moderate Level of Consensus for Familial Cardiomyopathy

1. In patients with familial or idiopathic cardiomyopathy, genetic testing can be useful in conjunction with genetic counseling *(Level of Evidence B)*.[467,473,474,492]
2. Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to facilitate cascade screening within the family, and to help with family planning *(Level of Evidence A)*.†

Recommendations With Uncertainty for Familial Cardiomyopathy

1. It may be reasonable for first-degree relatives of patients with idiopathic cardiomyopathy to undergo periodic serial echocardiographic screening with assessment of LV function and size *(Level of Evidence C)*.

MYOCARDIAL STORAGE–RELATED CARDIOMYOPATHY

Iron-Overload Cardiomyopathy

Definition/Pathogenesis/Epidemiology/Prognosis

Iron overload of the cardiac myocyte occurs in the setting of abnormal iron absorption, such as hereditary hemochromatosis (HH), or as a result of high-volume blood or parenteral iron infusions. HH is common among people with northern European ancestry and is the most identified genetic disorder among whites.[535] In America, the incidence is 1 case per 500 people.[536] Cardiac involvement occurs as much as 35% of the time.[536] Clinical diagnosis is important, because cardiomyopathy in the setting of iron overload predicts a poor prognosis. Survival with cardiac HH is only 44% at 1 year and <25% at 5 years. A common cause of iron-loading anemia is β thalassemia major, which is present in ≈60 000 births annually.[537] Patients with β thalassemia major with cardiac iron overload develop rapidly advancing HF, and cardiomyopathy accounts for 71% of deaths in these patients. Symptoms typically present by the sixth month of life and lead to a poor prognosis in which average survival is 35 years.[537] Thought potentially to present an evolutionary advantage in malaria, β thalassemia major is most commonly seen in people of Mediterranean descent.

†References 467, 473, 477, 478, 483, 492–495, 500, 507.

Pathophysiology/Clinical Presentation

Iron hemostasis is tightly regulated, as excess iron generates reactive oxygen species, which leads to cellular oxidation and fibrosis.[538] Under normal conditions, adequate cellular ferritin leads to downregulation of transferrin receptor. Organs that have high transferrin receptor density relative to other tissues (eg, heart liver, thyroid, gonads, and pancreatic islets) demonstrate dysfunction related to iron overload.[535]

Diagnosis/Treatment

Upon clinical suspicion, the diagnosis of iron overload begins with serological testing and includes investigation for end-organ involvement. Serum transferrin saturation (serum iron/total iron binding capacity of >45% and elevated serum ferritin >200 μg/L in men or >150 μg/L in women) supports the diagnosis. If HH is suspected, especially with a known family history of HH, testing for the HH genotype should be performed.[535] Cardiomyopathy develops late in the disease process, often when treatment is no longer possible. In addition, serum iron studies poorly correlate with disease severity. Early identification of cardiac involvement in populations known to be susceptible is imperative. Diagnosis of cardiac iron overload is possible with cardiac MRI, in which a decreased T2 signal correlates with myocardial iron infiltration and depressed LV function. This noninvasive modality is useful in identifying when therapy is indicated, and serial imaging can measure response to medical therapy.[539] The established treatment for HH is phlebotomy, and in secondary iron overload, there is a role for chelation therapy; clinical therapy recommendations are well outlined in the American Association for the Study of Liver Diseases hemochromatosis practice guideline.[535]

Key Diagnostic Strategies for Iron-Overload Cardiomyopathy

Recommendations With Strong Level of Consensus for Iron-Overload Cardiomyopathy

1. When evaluating a new cardiomyopathy, screening for iron overload should include serum ferritin and transferrin saturation *(Level of Evidence B)*.[535]
2. In the setting of transferrin saturation >45% or ferritin >250 μg/L (males) or >200 μg/L (females), cardiac MRI should be performed *(Level of Evidence B)*.[539]

Metabolic Cardiomyopathies: Fabry Disease, Pompe Disease, and Niemann-Pick Disease

Definition/Pathogenesis/Epidemiology/Prognosis

Lysosomal storage disorders are characterized by a specific enzyme deficiency that leads to cellular dysfunction as a result of pathogenic lysosomal accumulation. Two lysosomal storage disorders, Pompe disease

(glycogen storage disease type II) and Anderson-Fabry disease, are known to cause cardiomyopathy.[540–543] Pompe disease is a rare autosomal recessive disease that is caused by deficiency in lysosomal enzyme α-1-4-glucosidase. It affects 1 in 40 000 births, with a higher incidence in blacks, southern Chinese, and Taiwanese.[542] Typically, Pompe disease presents in infants, in whom cardiac involvement leads to death within the first year. Presentation later in life follows a slower and variable course in which the primary manifestation may be skeletal disease.

Anderson-Fabry disease is an X-linked disorder characterized by a deficiency in the lysosomal hydrolase α-galactosidase A. The incidence is reported to be 1 in 40 000 to 117 000 live births.[543] The average age of onset is 9 years in males and 13 years in females. Cardiac manifestations present at a mean age of 32 years in males and 40 years in females.[543]

Pathophysiology/Clinical Presentation

Glycogen synthesis in the fed state allows for sustained glucose supply during fasting. Glycogen stores are primarily in the liver; however, glycogen within the myocyte provides an immediate reserve in times of high metabolic demand. In the setting of Pompe disease, overload of glycogen within the lysosome leads to cellular dysfunction and myofibril loss.

In Fabry disease, deficiency in α-galactosidase A promotes lysosomal accumulation of globotriaosylceramide. The result is endothelial dysfunction that leads to ischemia and infarction in the microcirculation[541] and results in myocardial hypertrophy and fibrosis. Lysosomal inclusions and lamellar bodies are characteristically seen by electron microscopy.

Diagnosis/Treatment

In Pompe disease, echocardiography is used to assess myocardial function; however, cardiac MRI is reported to be feasible, providing quantification of LV mass, function, and the presence of myocardial fibrosis.[544] This disorder is often misdiagnosed by echocardiography as hypertrophic cardiomyopathy, because they can have similar echocardiographic features. Before 2006, the prognosis for Pompe disease was poor, especially in the infant population. Since that time, enzyme replacement therapy in the form of recombinant human α-glucosidase (alglucosidase alfa) has changed the course of Pompe disease.[542,545,546] Chronic enzyme replacement therapy allows reversal of cardiac dysfunction and improvement in prognosis and quality of life.[545,546] It has been shown that when treatment is initiated before 5 months of life, regression of LV hypertrophy and decreased B-type natriuretic enzymes can be seen within 6 months of therapy.[546] The natural progression of disease in the era of enzyme replacement therapy is not yet known; however, assessment of cardiac function will play a key role in longitudinal management.

The diagnosis in Fabry disease is often made after patients present with end-organ dysfunction such as renal failure, cerebrovascular disease, and cardiomyopathy. Echocardiography is useful in evaluating cardiac function, but myocardial biopsy is diagnostic.[543]

Enzyme replacement therapy with agalsidase-α and agalsidase-β leads to tissue clearance of globotriaosylceramide, and is effective in decreasing LV mass, improving EF, and restoring normal diastolic function.[547] This treatment is less effective when initiated after irreversible damage to the microcirculation has occurred.

Key Management Strategies for Metabolic Cardiomyopathies

Treatment Recommendations With Strong Level of Consensus for Metabolic Cardiomyopathies

1. Enzyme replacement therapy is recommended for patients with Pompe and Fabry lysosomal storage disorders *(Level of Evidence B)*.[542,545–547]

ENDOMYOCARDIAL FIBROSIS AND HYPEREOSINOPHILIC SYNDROME (LÖEFFLER ENDOCARDITIS)

Definition/Pathogenesis/Epidemiology/Prognosis

Eosinophilic myocarditis occurs when overproduction of eosinophils leads to myocardial damage through infiltration and release of inflammatory cytokines. The pathogenesis may be because of hypereosinophilic syndrome or a number of secondary causes, such as allergy (particularly drug or vaccination), neoplastic process, or parasitic infection. Löeffler endocarditis is characterized by eosinophilia, myocardial fibrosis, systemic thromboembolism, and acute HF and likely represents late stages of eosinophilic myocarditis.

Pathophysiology/Clinical Presentation

Endomyocardial fibrosis primarily presents as restrictive cardiomyopathy and is most common in tropical and subtropical regions, where it is understood to be related to parasitic infection or nutritional deficiency.[548–550] Multiple organ systems are involved, including cutaneous (69%), pulmonary (44%), gastrointestinal (38%), and cardiac (20%).[549] Eosinophilic myocarditis is the primary manifestation of the disease only 5% of the time but remains the number one cause of morbidity and mortality because of its often dramatic presentation and rapidly progressive course.[549,551] Eosinophilic myocarditis progresses in 3 stages (necrotic, thrombotic, and fibrotic). The initial necrotic stage is characterized by myocardial necrosis and is often subclinical but can present as fulminant myocarditis.[551] In the next stage, thrombus formation along the damaged myocardium leads to a high risk

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of thromboembolism.[549,552] In the final stage, fibrosis and unfavorable myocardial remodeling leads to restrictive cardiomyopathy.

Diagnosis/Treatment

The diagnosis of hypereosinophilic syndrome is made in the presence of eosinophils >1500/μL.[549,553] Historically, a 6-month duration of eosinophilia was required for diagnosis, but now greater importance is placed on a constellation of symptoms.[549] Echocardiography and MRI can be helpful in the diagnosis of eosinophilic myocarditis; however, myocardial biopsy remains the gold standard. After diagnosis, evaluation for secondary causes is essential, followed by treatment of the offending agent. If hypereosinophilic syndrome is suspected, a hematology consultation is warranted for specific analysis that can guide treatment. Corticosteroid therapy is generally considered primary therapy for eosinophilic myocarditis, but its efficacy is not well supported.[552]

Key Diagnostic Strategies for Hypereosinophilic Syndrome

Recommendations With Moderate Level of Consensus for Hypereosinophilic Syndrome

1. If eosinophilic myocarditis is suspected, EMB is reasonable *(Level of Evidence C)*.

PEDIATRIC DCM

Presentation, Pathophysiology, and Epidemiology

DCM is the most common form of cardiomyopathy[554] and a major cause of morbidity and mortality in children. DCM represents 55% of all cardiomyopathies in children; however, survival has not improved dramatically in the past 3 decades, despite advances in treatment and in determining pathogenesis. Large multicenter registries such as the Pediatric Cardiomyopathy Registry have determined the epidemiology and the outcomes of pediatric cardiomyopathies. The incidence is 0.53 cases per 100 000 children, which is one-tenth the incidence of adult DCM. Because only symptomatic patients are identified, the true incidence could be underrepresented.[554] A similar incidence was confirmed in an Australian study of pediatric DCM.[555] A DCM phenotype can accompany a viral pathogenesis, mutations in myocardial proteins and inborn errors of metabolism, and myocardial toxins. However, two thirds of cases are idiopathic within the Pediatric Cardiomyopathy Registry. Familial cardiomyopathy occurs in 30% of cases[554]; thus, routine screening of first-degree relatives should be undertaken.[556,557]

Some pediatric DCM cases have a mixed phenotype that includes LV hypertrophy with reduced systolic function, and others have LV noncompaction. Multiple genes have been identified that cause DCM. These genes appear to encode cytoskeletal or sarcomeric proteins. Children presenting with a newly encountered DCM phenotype need a thorough evaluation, which should exclude secondary cardiomyopathies from toxins (eg, anthracyclines), nutritional disorders (eg, rickets), and inborn errors of metabolism. Electrolyte abnormalities, anomalous left coronary artery from the pulmonary artery, and other coronary abnormalities associated with ischemia must be ruled out. Primary arrhythmias (eg, atrial tachycardias and permanent junctional reciprocating tachycardia) can manifest with the DCM phenotype and are treatable with radiofrequency ablation or medication.

Myocarditis is a frequent cause of a new-onset DCM phenotype in children. Myocarditis is an acquired inflammatory disorder of the heart and presents with systolic dysfunction, arrhythmias, and low cardiac output syndrome. The most common causes of myocarditis are viral, including enteroviruses, adenoviruses, and parvovirus B19.[558] Foerster and colleagues[559] reported superior survival in children with viral cardiomyopathy compared with idiopathic DCM in a multicenter Pediatric Cardiomyopathy Registry study; time to death, transplantation, and echocardiographic normalization 3 years after presentation in the biopsy-confirmed myocarditis and probable myocarditis groups were significantly better than in patients with idiopathic DCM.[559]

If myocarditis is suspected, evaluation of nasal swab and stool for viruses, as well as blood polymerase chain reaction tests, can aid in the diagnosis. In addition, acquired cardiac dysfunction from rheumatic heart disease and Kawasaki syndrome can have DCM features. Toxins and some medications (eg, antimicrobial agents) can lead to a hypersensitivity reaction similar to clinical myocarditis, as well as collagen vascular disorders such as SLE. Expert opinion varies on the utility of EMB for the diagnosis of new-onset DCM. A biopsy could diagnose myocarditis or point to metabolic cardiomyopathies if electron microscopy proves abnormal. In children with DCM phenotype and musculoskeletal abnormalities, skeletal muscle biopsy can aid in the diagnosis; genetic testing for specific mutations involving mitochondria are clinically available and should be performed in these patients.

Prognosis and Outcomes

DCM has one of the highest mortalities among heart diseases in children, with death or transplant occurring in nearly half the patients within the first 2 years of diagnosis.[554] In a report from Pahl et al from the Pediatric Cardiomyopathy Registry,[560] the incidence of sudden

death in 1803 children with DCM was 3% by 5 years after diagnosis, which is lower than in adults with DCM. In children with DCM, deaths of advanced HF are more common than sudden death, and indications for ICD use are controversial for primary prevention in this cohort. A risk stratification rule (86% sensitivity) included age at diagnosis younger than 14.3 years, LV dilation, and LV posterior wall thinning as markers for higher risk of sudden cardiac death.[560] In another study, factors that offered a better prognosis in DCM phenotype were younger age (especially <2 years), higher EF at presentation, and the presence of myocarditis.[561] Biomarkers are being used more frequently to monitor adults with HF. In pediatric patients, a BNP level >300 pg/mL was a strong predictor of death, transplantation, or HF hospitalization.[562] Two separate National Institutes of Health–sponsored multicenter studies from centers in the Pediatric Cardiomyopathy Registry are planned to assess genotype/phenotype correlations in all types of cardiomyopathy and to assess the utility of biomarkers to monitor these patients.

DCM in children remains a challenging problem, with a high rate of transplantation or death within 2 years of diagnosis. Efforts to identify a cause and target therapies will potentially improve outcomes in the future.

Treatment

In 2004, the International Society for Heart and Lung Transplantation published practice guidelines for the management of HF in children.[563] A follow-up monograph from the International Society for Heart and Lung Transplantation concerning HF in children was published in 2014, with specific chapters that included sections on pediatric cardiomyopathy.[564] An adaptation of the adult HF stages was proposed for the pediatric patient as a framework for treatment. These guidelines are based on expert consensus opinions because multicenter studies in the pediatric HF population are rare. Standard HF treatment in children includes digoxin, diuretic agents, and inotropes, as well as the use of ACE inhibitors and, more recently, β-blockers. The multicenter randomized, placebo-controlled trial of carvedilol in children did not prove a benefit for patients with DCM, although the study had only 161 total patients and the population was quite young, where the rate of spontaneous recovery is high.[565] The use of immunosuppressive therapy for children with myocarditis is controversial and varies among heart centers. A small series reported use of intravenous immunoglobulin in 21 children.[566] Compared with historical controls, LV function and survival tended to be higher at 1 year; however, the number of patients in the study was small.[566] Similarly, use of steroids for myocarditis has not been studied in large series of children, but anecdotal and single-center studies suggest there could be benefit.

The utility of ICDs, biventricular pacing, and pacemakers has not been studied in large series of children; however, ICDs are believed to be beneficial in selected patients. Mechanical assist devices, including extracorporeal membrane oxygenation and biventricular assist devices, are offered in the most extreme cases of DCM with severe LV dysfunction and provide good success rates as a bridge to heart transplantation.[567,568] Heart transplantation offers excellent results for children with intractable HF and DCM. In a multicenter study of 1098 patients with DCM from the Pediatric Heart Transplant Study, waitlist mortality was fairly low (11%), except in patients on ventilators or mechanical support or who had arrhythmias.[569] Survival at 10 years after heart transplantation was 72%, with a higher risk of death associated with black race, older age, mechanical ventilation, extracorporeal membrane oxygenation, longer ischemic time, and earlier era of transplantation.[569]

Key Diagnostic and Management Strategies for Pediatric DCM

Recommendations With Strong Level of Consensus for Pediatric DCM

1. In pediatric patients with cardiomyopathy phenotype, underlying causes such as primary arrhythmias, cardiotoxins, CHD, or other structural defects such as anomalous left coronary artery from the pulmonary artery should be ruled out before making the diagnosis of idiopathic DCM *(Level of Evidence B)*.[554]
2. Comprehensive or targeted DCM genetic testing (LMNA and SCN5A) is recommended for patients with DCM and significant cardiac conduction disease (ie, first-, second-, or third-degree heart block) or a family history of premature unexpected sudden death *(Level of Evidence A)*.[556,557]
3. Mutation-specific genetic testing is recommended for family members and appropriate relatives after the identification of a DCM-causative mutation in the index case *(Level of Evidence B)*.[556,557]
4. In severe acute HF from DCM, mechanical assist devices and extracorporeal membrane oxygenation are beneficial as a bridge to heart transplantation *(Level of Evidence B)*.[567,568]
5. Heart transplantation is recommended for children with severe end-stage HF from DCM refractory to treatment *(Level of Evidence B)*.[567]
6. In children with DCM, guideline-directed medical therapy for adult HF patients should be followed, using diuretic agents, β-blockers, ACE inhibitors, and other medications as appropriate, because the evidence in the pediatric population is limited *(Level of Evidence C)*.

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Recommendations With Moderate Level of Consensus for Pediatric DCM

1. Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, facilitate cascade screening within the family, and help with family planning *(Level of Evidence A)*.[556,557]
2. In first-degree relatives of children with DCM phenotype, ECG and echocardiographic screening for cardiomyopathy can be beneficial *(Level of Evidence C)*.
3. ICDs can be useful in high-risk patients with DCM to prevent sudden death *(Level of Evidence C)*.

Recommendations With Uncertainty for Pediatric DCM

1. If myocarditis is suspected, it might be reasonable to evaluate nasal swab and stool for viruses, as well as blood polymerase chain reaction *(Level of Evidence C)*.
2. In young patients with clinical signs of myocarditis who do not recover, an EMB may be considered to guide further therapy *(Level of Evidence C)*.
3. In young patients with clinical or biopsy-proven myocarditis, treatment with intravenous immunoglobulin may be considered; however, the evidence in the pediatric literature is limited *(Level of Evidence C)*.
4. In pediatric patients with DCM phenotype, and musculoskeletal symptoms such as hypotonia, a skeletal muscle biopsy may aid in the diagnosis, and genetic testing may be considered *(Level of Evidence C)*.
5. In pediatric patients with DCM phenotype, it may be reasonable to measure serum natriuretic peptide levels to follow clinical course *(Level of Evidence C)*.

Strategies to Avoid With Concern for No Benefit for Pediatric DCM

1. In pediatric patients with clinical signs of myocarditis, anti-inflammatory therapy with steroids is not beneficial in the pediatric literature *(Level of Evidence C)*.

CARE COORDINATION IN DCM

Coordination of care has gained importance, given the emphasis on patient safety and reducing complications associated with chronic and complex illnesses such as cardiomyopathies. Coordination of care requires maximizing communication across providers, facilitating transitions, creating a plan of care, monitoring and adjusting the plan as changes present, ensuring medication reconciliation, supporting self-management, and linking patients to community resources.[1,570] Important benefits of coordinated care include improvements in clinical outcomes and cost/healthcare utilization outcomes (eg, enhanced disease management, patient satisfaction, quality of life–decreased readmissions, urgent/emergent care visits, and hospital days).[570]

A joint position statement by the Heart Failure Society of America and the American Association of Heart Failure Nurses[571] endorses nurses to practice at their full potential and to become partners in redesigning HF care, which would be applicable to management of cardiomyopathies. Healthcare delivery is at its best when coordination of care for HF patients and their families occurs across the care continuum, as well as within and between specialists involved with patient care. This approach is highly relevant in cardiomyopathies, because these diseases can involve systems other than the cardiovascular system and can require input from different specialists. The basis of the coordination of care for HF patients between cardiovascular specialists, primary care, and others (eg, home care, cardiac rehabilitation) has been described in HF guidelines.[1] Key aspects of the coordination of care are translatable to patients with cardiomyopathies. Care coordination is of considerable importance for patients with any form of cardiomyopathy, and vulnerable patients with the highest risk stand to benefit the most from coordinated care. Given the vast differences in the many types of DCMs, a one-size-fits-all approach to coordinating care is impossible. Table 4 serves as a guide for coordination of care for patients with specific types of cardiomyopathy.

For example, pediatric cardiomyopathy is often treated with cardiac transplantation, with the majority of children living longer and surviving into adulthood.[572] Yet given the lack of evidence to guide the overall management of pediatric cardiomyopathies, models from care of adults with HF that use multidisciplinary teams should be considered. Coordination of care is necessary between pediatric cardiologists, primary care pediatricians, medical geneticists, and genetic counselors and often should include specialists in the areas of nutrition and exercise rehabilitation. Similarly, patients with heritable cardiomyopathies require surveillance monitoring, prevention of secondary complications, and often genetic screening. Collaboration with experts in cardiovascular genetics is recommended, as well as with physicians, nurses, pharmacists, and genetic counselors. Another example of a cardiomyopathy that requires care coordination is chemotherapy-induced cardiomyopathy. It is important for oncologists to collaborate with cardiologists to evaluate cardiac function, prevent induced cardiomyopathy, monitor the patient during treatment, and treat HF if it develops.[573] Similarly, rheumatologic or infiltrative cardiomyopathies can involve more than one system; for that reason, coordination of care among subspecialties such as rheumatology, internal medicine, or other relevant subspecialties is imperative. For management of women with peripartum cardiomyopathy, perinatologists and high-risk obstetricians should coordinate care with HF

Table 4. Examples of DCM Requiring Unique Considerations in Coordinating Care

Type of Cardiomyopathy	Specialists to Involve When Coordinating Care*	Unique Considerations
Cardiac amyloidosis	Hematologists	Coordination of care with other specialties when systemic disease is present (nephrology, hepatology, neurology, immunologists)
		Genetic testing
Anthracycline-induced cardiomyopathy	Oncologists, stem cell and bone marrow transplant teams (for hematologic malignancies)	Requires preliminary and multidisciplinary discussion about which treatments have the best efficacy with limited cardiotoxic effects; if such agents are used, monitoring with cardiology for cardiomyopathy should occur
		Collaborate with cardiologists/heart failure specialists for treatment
Peripartum cardiomyopathy	High-risk obstetricians, intensivists, cardiac and obstetric anesthesiologists, family planning counselors, neonatologists	Need for various specialists is determined based on active pregnancy, clinical condition, and desire for future pregnancies
Genetic cardiomyopathies	Genetic counselors, DNA storage experts, perinatologist	Provide genetic risk assessment to patients and families
		Incorporate new gene discoveries into clinical genetic laboratories
		Begin early and maintain longitudinal screening for first-degree relatives
		Fetal DNA analysis or preimplantation genetic testing
Pediatric cardiomyopathies	Pediatricians, congenital heart disease cardiologists, adult heart failure centers (for transition after childhood)	Genetic testing
		Evaluation of extracardiac disease and/or metabolic derangements
		Primary care pediatricians
		Local and national support groups
Obesity cardiomyopathy	Bariatric centers	
Autoimmune cardiomyopathies	Rheumatologist	
Infectious cardiomyopathies	Infectious disease specialists	

ACEI indicates angiotensin-converting enzyme inhibitor; BB, β-blocker; DCM, dilated cardiomyopathy; and LVD, left ventricular dysfunction.

*In addition to the usual care by heart failure cardiologists, heart failure nursing specialists, general and interventional cardiologists, pathologists, cardiac imaging specialists, cardiac surgeons, cardiac anesthesiologists, electrophysiologists and the full multidisciplinary team (social worker, pharmacists, nutritionists, financial coordinators, care managers, cardiac rehabilitation, homecare and hospice).

cardiologists, intensive care specialists, and cardiac and obstetric anesthesiologists to optimize outcomes for the mother and fetus.

SUMMARY

DCM is an important cause of HF. Characterized by the common phenotype of ventricular dilation and depressed myocardial performance, its pathogenesis varies significantly, ranging from metabolic, endocrine, autoimmune, rheumatologic, infiltrative, genetic, and infectious causes to cardiotoxins. The rapidly expanding field of molecular genetics and diagnostic and biomarker strategies will likely allow us to capture an even better understanding of how cardiomyopathies develop. Demographics and treatment also vary significantly according to the cause. Treatment should be individualized and should target the underlying cause, in addition to the standard systolic HF therapies. In certain cases, with elimination of the cause and the appropriate treatment, reversal of myocardial remodeling and recovery of cardiac dysfunction can occur. Although current clinical research strategies usually target systolic HF as a group, future studies targeting specific cardiomyopathies will be critical for detection and treatment of specific cardiomyopathies.

FOOTNOTES

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies: A Scientific Statement From the American Heart Association

Biykem Bozkurt, Monica Colvin, Jennifer Cook, Leslie T. Cooper, Anita Deswal, Gregg C. Fonarow, Gary S. Francis, Daniel Lenihan, Eldrin F. Lewis, Dennis M. McNamara, Elfriede Pahl, Ramachandran S. Vasan, Kumudha Ramasubbu, Kismet Rasmusson, Jeffrey A. Towbin and Clyde Yancy

On behalf of the American Heart Association Committee on Heart Failure and Transplantation of the Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; and Council on Quality of Care and Outcomes Research

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Correction to: Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies: A Scientific Statement From the American Heart Association

In the article by Bozkurt et al, "Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies: A Scientific Statement From the American Heart Association," which published ahead of print November 3, 2016, and appeared in the December 6, 2016, issue of the journal (*Circulation.* 2016;134:e579–e646. doi: 10.1161/CIR.0000000000000455), several corrections were needed.

1. On page e579, in the author byline, "Vasan S. Ramachandran, MD, FAHA" has been updated to "Ramachandran S. Vasan, MD, FAHA."
2. On page e608, Figure 3, the figure legend read, "Figure 3. Pathophysiology of obesity cardiomyopathy. LV indicates left ventricular; RV, right ventricular. Modified from Alpert et al[346a] with permission from Elsevier. © 2014, Elsevier Inc." It has been updated to read, "Figure 3. Pathophysiology of obesity cardiomyopathy. LV indicates left ventricular; RV, right ventricular. Modified from Alpert et al[346a,347] with permission from Elsevier and Springer. © Springer Science+Business Media New York 2014."
3. On page e625, in the left column, the second paragraph, the first sentence, "Ramachandran VS" has been updated to "Vasan RS."
4. On page e626, in the Writing Group Disclosures table, "Vasan S. Ramachandran" has been updated to "Ramachandran S. Vasan."

These corrections have been made to the current online version of the article, which is available at http://circ.ahajournals.org/lookup/doi/10.1161/CIR.0000000000000455.

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