Infiltrative Cardiomyopathies

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ABSTRACT: Infiltrative cardiomyopathies can result from a wide spectrum of both inherited and acquired conditions with varying systemic manifestations. They portend an adverse prognosis, with only a few exceptions (ie, glycogen storage disease), where early diagnosis can result in potentially curative treatment. The extent of cardiac abnormalities varies based on the degree of infiltration and results in increased ventricular wall thickness, chamber dilatation, and disruption of the conduction system. These changes often lead to the development of heart failure, atrioventricular (AV) block, and ventricular arrhythmia. Because these diseases are relatively rare, a high degree of clinical suspicion is important for diagnosis. Electrocardiography and echocardiography are helpful, but advanced techniques including cardiac magnetic resonance (CMR) and nuclear imaging are increasingly preferred. Treatment is dependent on the etiology and extent of the disease and involves medications, device therapy, and, in some cases, organ transplantation. Cardiac amyloid is the archetype of the infiltrative cardiomyopathies and is discussed in great detail in this review.

KEYWORDS: Infiltrative cardiomyopathy, amyloidosis, sarcoidosis, hemochromatosis

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Introduction

The infiltrative cardiomyopathies are a diverse group of cardiac diseases that are characterized by the deposition of abnormal substances within the heart tissue that causes the ventricular walls to develop either diastolic dysfunction or, less commonly and more of a late presentation of the disease, systolic dysfunction. A high degree of clinical suspicion is key to making the diagnosis, and confirmatory evidence is often obtained via endomyocardial biopsy, echocardiography, and cardiac magnetic resonance (CMR).

Herein, we provide a systematic review of the pathogenesis, clinical presentation, diagnosis, evaluation, and treatment of these diseases, focusing primarily on cardiac amyloidosis, sarcoidosis, and hemochromatosis. We then offer a brief overview of less common, although still important, etiologies such as Fabry disease, Dannon disease, and Friedreich's ataxia. Key clinical, epidemiologic, diagnostic, and therapeutic interventions are summarized in Table 1.

Cardiac Amyloidosis

Amyloidosis is a nonspecific term for a group of disorders characterized by the multisystem deposition of insoluble fibrillary proteins known as amyloid fibrils. Numerous forms exist, yet they all share a common molecular pathophysiology: culprit proteins misfold into β-pleated sheets stacked antiparallel to one another that are resistant to proteolysis and lead to local oxidative stress, mechanical disruption, and tissue damage.[1,2] The most common types of amyloidosis, defined by their precursor proteins, are primary Amyloid Light chain (AL), hereditary transthyretin-derived (ATTR), senile systemic (SSA), secondary (AA) amyloidosis. Cardiac involvement is common and is a major source of associated morbidity and mortality with amyloidosis.[3] In fact, numerous studies have shown that patients with elevated cardiac biomarkers such as troponin and brain natriuretic peptide levels have decreased survival as compared to patients without.[4,5]

AL amyloidosis is the most aggressive form and is caused by the deposition of immunoglobulin light chains secondary to an underlying plasma cell dyscrasia. Cardiac involvement occurs in about 50% of cases and has a major prognostic implication: whereas patients without cardiac involvement have a median survival upwards of 2 years, though with cardiac involvement have a median survival as low as 4 months.[4] ATTR amyloidosis, on the other hand, is an autosomal dominant condition that classically manifests in the sixth decade of life and is caused by more than 80 known pathogenic mutations in the sequence encoding the protein transthyretin (TTR).[6] In its mutant, destabilized state, hepatically synthetized TTR deposits in the peripheral nervous system and myocardium, causing neuropathy and cardiomyopathy. The most common cause of ATTR is the mutation Val122Ile (valine to isoleucine substitution at position 122). This mutation

Table 1. Common types of infiltrative cardiomyopathies.

CONDITION	EPIDEMIOLOGY	PATHOLOGY	ECG	ECHOCARDIOGRAM	CMR	TREATMENT
Cardiac amyloidosis	6th or 7th decade acquired (AL, SSA) or inherited (ATTR)	Extracellular amyloid fibrils	Low-voltage QRS; pseudoinfarction; AV block	LV and RV hypertrophy; granular speckled myocardium; restricted basal longitudinal strain	Global LGE (Also consider radionuclide scanning)	AL: chemotherapy (CyBordD); TTR: diflunisal/tafamidis; ± heart-liver transplant
Cardiac Sarcoidosis	3rd or 4th decade; African Americans, northern Europeans, Japanese; female>male	Noncaseating granulomas surrounded by fibrosis	High-grade AV block	Septal thinning/ thickening; noncoronary segmental wall motion abnormalities	Pathy LGE, predominantly LV free wall and basal septum (Also consider FDG-PET)	Corticosteroids, PPM/ICD; ± cardiac transplant
Hemochromatosis/IOC	4th or 5th decade; inherited (*primary, HFE* mutation) or acquired (secondary)	Intracellular iron	Nonspecific repolarization abnormalities	Diastolic disease ⁄ global systolic dysfunction	Shortened T2* time	Phlebotomy; chelation
Fabry Disease	2nd through 5th decade X1 linked error of glycosphingolipid metabolism	Perinuclear vacuoles and myocardial fibrosis	Increased voltage QRS	Concentric LV hypertrophy	LGE of the basal segments of the anterolateral and inferolateral walls	Enzyme replacement
Danon Disease	2nd or 3rd decade; inherited (LAMP2 deficiency)	Myocyte hypertrophy with vacuolization	Increased voltage QRS; short PR with delta wave	Massive LV hypertrophy with possible outflow tract obstruction	Sunbendocardial LGE sparing the septum	Supportive
Friedreich's Ataxia	2nd and 3rd decade; inherited (*frataxin* mutation)	Nonspecific myocyte hypertrophy and fibrosis	Nonspecific repolarization abnormalities	Increased septal thickness	Not used	Supportive

Abbreviations: CMR, cardiac magnetic resonance; ECG, electrocardiography; IOC, iron overload cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricle; RV, right ventricle.

is present in 3–4% of African-Americans though its true prevalence is underestimated given its frequent misdiagnosis as hypertensive cardiomyopathy.[7] Conversely, SSA amyloidosis or wt-ATTR is mainly an age-related disorder, although it can occur at a younger age, which results from the deposition of the wild-type TTR protein that forms amyloid fibrils. The pathogenesis is poorly understood and is thought to involve posttranslational alterations in normally transcribed TTR or its chaperone proteins.[8] Similar to Val122Ile-ATTR, SSA manifests mainly beyond the sixth decade of life and has a more indolent course than AL amyloidosis, with a median survival of 4–6 years following diagnosis.[2,9] Cardiac involvement in secondary (or AA) amyloidosis, typically a result of chronic inflammatory conditions, is rare and occurs in less than 5% of cases.[10]

Pathogenesis. The extracellular deposition of amyloid fibrils within the heart leads to abnormalities in three processes vital to normal cardiac function: contractility, conduction, and coronary blood flow. Amyloid accumulation causes the myocardial wall to thicken and become firm, rubbery, and noncompliant.[11] As a result, intracardiac pressures rise and progressive biventricular diastolic dysfunction ensues.[12,13] As the disease progresses, cumulative myocyte damage and local fibrosis can give rise to systolic dysfunction, though this is typically seen in very advanced disease. Involvement of the sinoatrial node, atrioventricular (AV) node, and bundle branches can manifest as various degrees of heart block and complex ventricular arrhythmias can also be seen.[14] Involvement of the distal coronary microvasculature can result in diffuse pockets of myocardial ischemia that further contribute to myocardial dysfunction.[15] While rare, obstructive intramural coronary amyloidosis can even result in acute myocardial infarction.[16]

Clinical presentation. Amyloidosis has varied extracardiac manifestations affecting multiple organ systems, including the gastrointestinal tract, kidneys, liver, and neurological system.

Gastrointestinal disease in amyloidosis results from either mucosal infiltration or neuromuscular infiltration. In addition, an extrinsic autonomic neuropathy may also affect gut function. The distribution of clinically apparent gastrointestinal involvement varies with the type of amyloidosis. Patients usually present with one of the four syndromes: malabsorption, gastrointestinal bleeding, chronic gastrointestinal dysmotility, and protein losing enteropathy.[17] Renal involvement most often presents as nephrotic syndrome or asymptomatic proteinuria. However, primary deposition can be limited to the blood vessels or tubules; such patients present with renal failure with little or no proteinuria.[18] End-stage renal disease is the cause of death in a minority of patients. Neurologic involvements are quite common and may affect peripheral and autonomic nervous system or central nervous system. Symptoms of numbness, paresthesia, and pain are often presenting complaints. Compression of peripheral nerves, especially the median nerve within the carpal tunnel, can cause more localized sensory changes. Bowel and bladder dysfunction can be because of autonomic nervous system involvement. Occasionally, amyloid deposits in the brain can lead to dementia with sporadic or familial Alzheimer disease as well as cerebral amyloid angiopathy resulting in cortical and subcortical intracranial bleeding.[19]

The principal manifestation of amyloid cardiomyopathy is clinical heart failure that may or may not be concomitant with other symptoms of systemic amyloidosis. While dyspnea and exercise intolerance occur, pulmonary edema is rare and symptoms of right-sided heart failure predominate, including lower extremity edema, hepatomegaly, and ascites.[20] Patients may present with an acute coronary syndrome-like picture with angina and elevated troponin levels despite the absence of obstructive coronary disease on coronary angiography.[11,21,22] Syncope and presyncope can also occur and are multifactorial in origin, arising from autonomic dysfunction, increased sensitivity to intravascular fluid depletion in the setting of restrictive physiology, and rarely ventricular arrhythmias.[23] Other possible advanced manifestations include high-grade conduction disease requiring pacemaker implantation,[24] cardiac tamponade from pericardial involvement,[25] and systemic thromboembolism from atrial thrombi both in the presence or absence of atrial fibrillation (to which patients with cardiac amyloidosis are predisposed).[26]

Diagnosis and evaluation. The workup and diagnosis of amyloid cardiomyopathy can be challenging and can involve numerous healthcare professionals from different specialties.

Electrocardiography. The typical electrocardiographic findings in cardiac amyloidosis reflect displacement of myocardium with amyloid deposits and direct involvement of the electrical conduction system. Low-voltage QRS is seen in 50% of cases of AL amyloidosis, and the combination of low-voltage QRS and left ventricular (LV) hypertrophy on echocardiogram is suggestive of cardiac amyloid.[27] A pseudoinfarct pattern (poor R-wave progression or QS waves) in the precordial leads is also present in about 50% of cases.[27] Less common findings include first-degree AV block (21%), nonspecific intraventricular conduction delay (16%), second- or third-degree AV block (3%), atrial fibrillation or flutter (20%), and ventricular tachycardia (5%).[27]

Echocardiography. The classic two-dimensional echocardiographic findings of amyloid cardiomyopathy include increased LV and right ventricular (RV) wall thickness, normal or small LV cavity size with preserved ejection fraction, and biatrial enlargement.[28] The absence of ventricular wall thickness does not exclude the disorder, however, as up to one-third of cases can present with normal LV wall size.[29] Concomitant valvular and papillary muscle thickening and small-to-moderate pericardial effusions are also common. While nonspecific, a granular, speckled appearance of the ventricular myocardium in the presence of other typical findings is suggestive of cardiac amyloidosis.[30] Progressively worsening diastolic dysfunction toward a restrictive pattern as measured

by Doppler echocardiography is a hallmark of the disease and can be used to monitor disease progression.[13] More novel echocardiographic parameters that detect early signs of systolic dysfunction, such as regional strain and strain rate imaging, have been recently studied in patients with AL amyloid and have been associated with outcomes. It has been shown that restricted basal longitudinal strain using tissue Doppler analysis is a helpful diagnostic echocardiographic finding that, when present, is associated with poor suvival.[31,32]

Cardiac magnetic resonance. CMR can prove useful in the evaluation of amyloid cardiomyopathy, particularly in the early stages of the disease when myocardial thickening is absent or when echocardiography cannot distinguish from hypertensive cardiomyopathy. The classic finding on CMR is a unique pattern of global transmural or subendocardial late gadolinium enhancement (LGE).[33]

Radionuclide imaging. Recent studies have shown that the radiotracer ^{99m}Tc-DPD very sensitively localizes to TTR cardiac amyloid deposits and can readily distinguish between the AL and TTR forms of the disease.[34] While ^{99m}Tc-DPD is not currently available in the US, similar findings have been reported using the FDA-approved radiotracer ^{99m}Tc-PYP using Single photon emission computed tomography (SPECT) imaging.[35] With further studies, nuclear scintigraphy may prove to be a vital part of the diagnostic algorithm for cardiac amyloidosis.

Tissue diagnosis. Endomyocardial biopsy remains the gold standard for the diagnosis of cardiac amyloidosis with a sensitivity of virtually 100%.[36,37] If typical cardiac features are seen on noninvastive tests (ie, ECG, echocardiogram, and CMR), however, a noncardiac tissue sample staining positive for amyloid is sufficient to infer the diagnosis of amyloid cardiomyopathy.[38] Fine-needle aspiration of the abdominal fat pad is the safest method for obtaining tissue diagnosis and is positive for amyloid deposition in over 70% of patients with AL amyloidosis.[39] Less common sites include the rectum and kidney. If AL amyloidosis is suspected, a bone marrow biopsy should be performed to evaluate the underlying plasma cell dyscrasia, as should tests for serum and urine protein electrophoresis with immunofixation and serum free light chains.

Treatment. The treatment of cardiac amyloidosis involves the management of heart failure that results from restrictive cardiomyopathy and therapy that targets the underlying protein disorder. Euvolemia is attained via the use of loop diuretics, with caution against overdiuresis as this can lead to hypotension and azotemia in the setting of increased preload dependence. Unlike in systolic heart failure, beta-blockers and ACE inhibitors are typically avoided, the former because cardiac output tends to be more dependent on heart rate in the setting of a fixed stroke volume, and the latter because neurohormonal blockade can result in profound hypotension in the setting of the underlying autonomic neuropathy.[40,41] Calcium channel blockers and digitalis may selectively bind amyloid fibrils and are thus relatively contraindicated given an increased risk of toxicity.[42,43] The role of implantable cardioverter-defibrillators (ICDs) in the primary prevention of sudden cardiac death (SCD) remains unclear. While SCD in cardiac amyloid patients is typically attributed to electromechanical dissociation rather than sustained ventricular arrhythmia,[42] newer observational evidence points to a potential beneficial role of ICDs for primary prevention of SCD in these patients.[44]

Until recently, the treatment of AL amyloidosis resulting from a clonal proliferation of plasma cells involved the use of a melphalan-based cytotoxic chemotherapy regimen with or without autologous stem cell transplantation.[45] However, more recent studies have demonstrated high rates of near complete clonal responses with bortezomib-based regimens (ie, CyBorD) that are now considered to be the preferred treatment option.[46] Cardiac transplantation is a rare but viable option in patients with AL amyloidosis with isolated cardiac disease that makes them poor candidates for neoadjuvant chemotherapy. When cardiac transplantation is followed by adjuvant chemotherapy and stem cell transplantation, these patients can have sustained cardiac and hematologic responses.[47]

In ATTR amyloidosis, hepatically synthesized mutant TTR misfolds into pathogenic amyloid fibrils. Accordingly, liver transplantation is potentially curative in this condition, though only if performed on patients without existing cardiac involvement. This is because a proportion of patients with existing amyloid cardiomyopathy at the time of liver transplantation will continue to show progressive restrictive cardiomyopathy because of wild-type TTR deposition similar to that seen in SSA amyloidosis.[48] In selected patients, combined heart and liver transplantation is possible though is rarely performed.[49,50]

A number of pharmacotherapies designed to reduce, stabilize, or silence TTR activity or production have been discovered or are under active investigation. The nonsteroidal anti-inflammatory drugs (NSAIDs) diflunisal and its non-NSAID analog tafamidis have garnered the most attention. By tightening TTR tetramer associations, these agents inhibit the monomeration of TTR that is necessary for amyloid formation. Both agents have been shown in phase III trials of patients with ATTR amyloidosis to reduce the rate of progression of neurologic endpoints,[51,52] though trials specifically assessing their efficacy in amyloid cardiomyopathy are still pending. Other novel agents, such as small interfering RNAs,[53] antisense oligonucleotides,[54] and green tea extracts,[55] aimed at reducing TTR production are also under active investigation.

Cardiac Sarcoidosis

Sarcoidosis is an idiopathic disease characterized by the presence of noncaseating granulomas that can affect any organ in the body. The majority of affected persons are of age 25–45 years and the highest incidence occurs in northern Northern European, Japanese, and in African-Americans.[56] Pulmonary disease is most common and occurs in 90% of cases, whereas the prevalence of cardiac involvement is estimated to be

25–30% based on postmortem studies performed in US.[57] Despite this, cardiac involvement is often clinically silent and is recognized in only 5% of cases of systemic sarcoidosis. When present, however, cardiac sarcoidosis can be severe and lead to progressive heart failure or SCD. Therefore, meticulous screening using modern cardiac imaging techniques should be done in the appropriate cohort of patients.

Pathogenesis. The major pathologic feature of sarcoidosis is granulomatous infiltration that disrupts normal organ function. The disease is characterized by three successive stages: edema, granuloma formation, and fibrosis leading to scar formation.[58] Sarcoid can involve any part of the heart, including the pericardium, myocardium, and endocardium, though most typically involves the LV free wall and the basal aspect of the interventricular septum.[59] In the initial stages of the disease when more tissue edema is present, the myocardium thickens and diastolic dysfunction predominates. In the later stages of the disease where granulomatous inflammation gives way to fibrosis, the ventricles dilate, global or segmental hypokinesia ensues, and systolic dysfunction predominates. The patchy nature of myocardial involvement can result in uneven wall motion abnormalities that do not conform to any particular coronary distribution.[57] Given the predilection for involvement of the basal interventricular septum, conduction system disease is particularly common and can manifest as bundle branch block or high-grade AV block. Scar formation can also result in reentrant ventricular arrhythmias.[60]

Clinical presentation. The clinical manifestations of cardiac sarcoidosis correlate with the location, and the extent of granulomatous infiltration and initial presentations include asymptomatic electrocardiographic findings, heart failure, and SCD. Conduction abnormalities are common and can be an incidental finding or discovered in the workup of syncope. Complete heart block (CHB) is the most frequently encountered abnormality in patients with clinically active cardiac sarcoidosis and can occur in 25–30% of cases.[61] First- and second-degree AV block and bundle branch block are also common. Nonsustained or sustained ventricular tachycardia can occur in as many as 23% of cases and manifest as palpitations, syncope, or SCD. In fact, SCD because of ventricular tachyarrhythmias or CHB may account for 25–65% of deaths and may be the initial presentation in as many as 40% of patients with previously undiagnosed cardiac sarcoidosis.[62] Progressive left-sided heart failure, which can be either diastolic or systolic in etiology depending on the stage of the disease, is also frequently encountered and is a major cause of mortality in 25% of patients with cardiac sarcoid, second only to SCD.[58,63]

Diagnosis and evaluation. There are no current internationally accepted guidelines for the diagnosis of cardiac sarcoidosis, yet two have been proposed.[64,65] Moreover, in patients with known systemic sarcoidosis, there is no established screening protocol to assess the development of cardiac involvement. While endomyocardial biopsy remains the gold standard for diagnosis, it has relatively low sensitivity given the patchy nature of myocardial involvement and its tendency to involve the less accessible LV.[66] As such, a noncardiac biopsy consistent with sarcoidosis coupled with typical cardiac clinical features is regarded as diagnostically sufficient.[65]

Electrocardiography. Electrocardiographic findings are common in patients with cardiac sarcoidosis and, as such, an ECG should be performed in every patient with systemic sarcoidosis in whom the presence of typical conduction abnormalities (see Clinical Presentation section), while nonspecific, may signify cardiac disease.

Echocardiography. Suspected cases, particularly in those with ECG abnormalities, should undergo echocardiographic assessment. Echocardiography is relatively insensitive in early disease, as focal myocardial involvement may be too small to result in detectable abnormalities.[67] As the degree of involvement increases, however, typical findings include septal thinning (or thickening), LV dilatation with systolic dysfunction, and segmental wall motion abnormalities in a noncoronary distribution. Other abnormalities include ventricular aneurysms, papillary muscle thickening, valvular abnormalities, and pericardial effusions.[67]

Cardiac magnetic resonance and fluorodeoxyglucose (FDG)-positron emission tomography (PET). CMR is currently the technique of choice in the evaluation of suspected cases of cardiac sarcoidosis at many centers. Findings on CMR vary with the stage of the disease: in the early inflammatory stage, abnormalities include myocardial thickening and increased T2 signal, whereas in the later fibrotic stage, classic findings include focal areas of myocardial thinning with LGE.[68,69] The presence of LGE on CMR appears to be of prognostic value, as LGE is associated with an increased risk of adverse events, including death.[70] The inflammatory nature of sarcoidosis also renders positron emission tomography (PET) useful in its diagnosis, as 18F-FDG accumulates in inflammatory cells in the heart of involved patients. Unlike in CMR, there is no distinct pattern of FDG uptake that is pathognomonic for cardiac sarcoidosis, though focal or focal on diffuse uptake is suggestive of the disorder.[69] At present, FDG-PET appears to be more sensitive but less specific than CMR,[71] and its use seems most appropriate in patients who have contraindications to CMR or where CMR is not available. Both tests can be used to monitor response to therapy.

Treatment. Glucocorticoids are the mainstay in medical management of cardiac sarcoidosis and should be initiated promptly after the diagnosis is made. Current strategies are based on small observational studies as there are no randomized controlled trials confirming their efficacy.[72,73] A typical regimen consists of high-dose prednisone for 8–12 weeks followed by gradual tapering over the next year. Prior studies in which patients were stratified by the degree of LV dysfunction (on the basis of LV ejection fraction) indicate that greater benefit is seen when steroids are started early in the disease course before LV systolic function declines.[73,74] The ultimate length of treatment is based on clinical response and can be guided

by monitoring the improvement in LGE on CMR.[75] While steroids can be discontinued if disease becomes dormant, any evidence of relapse should trigger the clinician to reinitiate therapy at starting doses. In patients who are either steroid resistant or steroid intolerant, alternative immunosuppressive agents have been used with reported success, including methotrexate, azathioprine, antimalarial agents, cyclophosphamide, infliximab, and thalidomide.[76]

The high incidence of SCD in cardiac sarcoidosis warrants careful consideration of the use of pacemakers and ICDs, as these interventions are potentially acutely lifesaving. The presence of CHB or high-grade AV block is an indication of permanent pacemaker implantation, even if the AV block reverses transiently.[60] ICD implantation at the time of pacemaker implantation for AV block is a relative indication according to expert consensus, even in the absence of sustained ventricular tachycardia.[60] Strict indications for ICD implantation include sustained ventricular arrhythmia and/or Left ventricular ejection fraction (LVEF) <35% despite optimal medical management (including immunosuppression); relative indications include unexplained syncope or presyncope and inducible ventricular arrhythmias during EP study with LVEF <50% despite optimal medical therapy.

Cardiac transplantation remains an option for young patients with end-stage, New York Heart Association (NYHA) Class IV heart failure despite optimal medical therapy and for those with intractable ventricular arrhythmias. While sarcoid can recur in the transplanted allograft, 1-year posttransplant survival is equal to if not better in sarcoid patients as compared to non-sarcoid patients,[77] and the results of the long-term studies are also promising.[78]

Hemochromatosis and Iron Overload Cardiomyopathy (IOC)

Hemochromatosis is a syndrome characterized by the excess deposition of iron. Primary or hereditary hemochromatosis (HH) is an autosomal recessive disorder associated with a mutation of the *HFE* gene located on chromosome 6. An estimated 10% of Caucasians in the United States are heterozygous for this trait, but it is the 0.3–1% that are homozygous that comprise the population at risk for developing end-organ damage because of the disease.[79,80] The exact mechanism by which *HFE* is involved in iron homeostasis is unknown, although it appears to play a role in sensing the signals that stimulate intestinal cells to increase iron absorption.[81] Patients with HH are often asymptomatic through middle age, at which point, iron levels finally exceed the storage capacity of cells and tissue damage occurs, primarily in the liver, joints, thyroid, pancreas, and heart.[82] Secondary hemochromatosis, on the other hand, occurs secondary to iron overload because of another condition, such as certain types of anemia, repeated blood transfusions, long-term hemodialysis, or chronic liver disease. The degree of cardiac involvement varies depending on the specific etiology. For example, heart disease is a significant cause of morbidity and mortality in thalassemia patients, accounting for an estimated 71% of deaths.[83] Yet sickle cell patients appear to be relatively protected from myocardial iron deposition and cardiac dysfunction, perhaps as a result of the intermittent nature of transfusions.[84] IOC is the term used to describe the cardiac dysfunction that results from the accumulation of iron in the heart whether from primary or secondary hemochromatosis.[85]

Pathogenesis. In IOC, deposition of excess iron begins in the epicardium and then progresses into the myocardium and endocardium.[86] As the storage capacity of cardiac cells is exceeded, excess iron becomes released intracellularly as hemosiderin and free iron. This results in the formation of reactive oxygen species, which in turn initiates the processes of lipid peroxidation, membrane permeability alteration, and myocyte death.[87] The association between HH and cardiac abnormalities is well described. Early in the disease process, excess iron is preferentially deposited in the ventricles. This manifests as progressive diastolic dysfunction consistent with restrictive physiology.[88] As the disease progresses and maladaptive remodeling occurs, the LV dilates and systolic dysfunction develops.

Clinical presentation. Systemic involvement of multisystem iron deposition typically results in classic symptoms of skin hyperpigmentation, diabetes mellitus, and liver disease. Clinically, the manifestations of cardiac iron deposition can be varied. Biventricular failure may lead to classic symptoms of heart failure, while involvement of the conduction system can precipitate supraventricular arrhythmias or AV block. As in other infiltrative cardiomyopathies, the extent of cardiac dysfunction, as well as the severity of symptoms, is determined primarily by the quantity of myocardial iron deposition.[89]

Diagnosis and evaluation. *Electrocardiography.* ECG is often nondiagnostic in early disease, but may allow for the detection of conduction system abnormalities.[90] Advanced disease is associated with low-voltage QRS and repolarization abnormalities, such as nonspecific ST- and T-wave changes.[91]

Echocardiography. Echocardiography is one of the most widely used tools in the screening of patients with IOC. Early findings typically include impaired diastolic LV function with a restrictive filling pattern.[86,92] Disease progression is characterized by either development of a dilated cardiomyopathy (with decreased LV ventricular ejection fraction) or continuation of the restrictive phenotype. While it does not allow for accurate quantification of myocardial iron content, echocardiography is useful in screening at-risk patients and in monitoring disease progression or response to treatment.[85]

Cardiac magnetic resonance. The benefit of CMR is that it allows for the qualitative assessment of myocardial iron load. And as such is the preferred imaging technique for the assessment of IOC. Iron exerts a nonhomogenous paramagnetic effect that shortens the MR relaxation parameter T2*; as tissue iron increases, T2* decreases.[93–95] Myocardial T2* is inversely correlated with LV ejection fraction and directly associated

with the development of heart failure, arrhythmias, and the need for treatment.[96]

Tissue diagnosis. Because the hepatic uptake of iron occurs significantly faster than myocardial iron deposition, cardiac involvement typically develops later in the disease process.[97] Accordingly, liver biopsy frequently precedes and precludes the necessity for endomyocardial biopsy in patients with suspected IOC. Myocardial biopsy may be indicated if patients primarily present with cardiac symptoms or if findings on liver biopsy are equivocal.[37,98]

Treatment. Early diagnosis and treatment of iron overload is critical in preventing or even reversing cardiac dysfunction. For non-anemic patients with IOC, phlebotomy is the first-line treatment. Phlebotomy mobilizes the excess iron stored in cells, decreasing myocardial iron content and improving LV function.[99] For patients with IOC with anemia, malignancy, or hemodynamic instability, iron chelation therapy is the treatment of choice.[100] Chelating agents, including deferoxamine, deferasirox, and deferiprone, bind to excess iron and facilitate iron excretion in the bile or urine. Research shows that deferoxamine reduces the amount of iron in myocardial cells and can improve LV ejection fraction.[101] Finally, cardiac transplantation is a potential treatment option for patients with severe congestive heart failure that's resistant to conventional medical management. One case series reported a 10-year survival of 41% in patients with IOC who had undergone cardiac transplantation.[102] Combined heart–liver transplantation may be offered to patients with both IOC and cirrhosis, though experience is limited.[49,103] For all patients, transplantation must be done in conjunction with aggressive phlebotomy or chelation therapy in order to prevent hemochromatosis of the transplanted heart.[100]

Other Infiltrative Cardiomyopathies

Fabry disease. Fabry disease is a lysosomal storage disease caused by a deficiency of the enzyme alpha-galactosidase A, which leads to the accumulation of glycosphingolipid in various tissues.[104] Although it is an X-linked condition, female carriers can also be affected.[105] Commonly involved organs include the kidneys, heart, peripheral nerves, and skin.[105] About 60% of patients with Fabry disease develop cardiac manifestations as the disease progresses, including dyspnea, angina, palpitations, or syncope.[106] These complications result from conduction disturbances, valvular abnormalities, or restrictive cardiomyopathy because of glycosphingolipid infiltration into the myocardium.[105,107] There is also a variant of the disease that affects cardiac tissue exclusively, typically presenting as unexplained LV hypertrophy in middle-aged adults. One of the earliest signs of Fabry disease on electrocardiography is a significantly shortened PR interval,[108] which can be followed by signs of LV hypertrophy. Echocardiography shows concentric LV hypertrophy with a preserved ejection fraction. CMR can be used to identify myocardial fibrosis, characteristically seen as a pattern of delayed enhancement in the basal inferolateral LV wall.[109] Enzyme replacement is the mainstay of treatment and should be initiated before the development of tissue injury and fibrosis.[110]

Danon disease. Danon disease is a rare X-linked disorder characterized by a deficiency in lysosome-associated membrane protein 2 (LAMP2).[111] Disease typically manifests in the teenage years as skeletal myopathy, mental retardation, and heart failure.[111] Cardiomyopathy is nearly universal and is the leading cause of mortality in patients with the disorder. Pathologic examination reveals massive cardiac hypertrophy with myocyte disarray, enlargement, and vacuolization.[112] A preexcitation pattern with short PR interval and delta wave is commonly seen on ECG, which explains the predisposition to ventricular tachycardia with this disorder. Echocardiographic abnormalities include marked LV hypertrophy, which can be accompanied by outflow tract obstruction.[112] Subendocardial LGE with septal sparing is the most typical pattern on CMR, though experience with this modality is limited in this disorder.[113] While cardiac transplantation has been performed,[114] most patients die of the disease early in life.

Friedreich's ataxia. Friedreich's ataxia is an autosomal recessive neurodegenerative disorder with an estimated prevalence of one in 50,000 in the Caucasian population.[115] The disease is caused by a mutation of the frataxin gene, located on chromosome 9. Symptoms generally present by age 25 and include ataxia in all four limbs, cardiomyopathy, and diabetes mellitus.[116] Almost all patients with Friedreich's ataxia develop cardiac abnormalities, with phenotypes that include both LV hypertrophy and LV outflow obstruction.[116,117] Microscopic examination reveals myocyte hypertrophy and increased fibrosis.[118] The primary clinical manifestations are heart failure and arrhythmias that may lead to SCD. Electrocardiogram is generally abnormal and may feature T-wave inversion, left axis deviation, and repolarization abnormalities.[116] About 65% of patients with Friedreich's ataxia have increased interventricular septal thickness on echocardiography, but as the disease progresses, cardiac wall thickness decreases and dilated cardiomyopathy can develop.[119,120] Cardiac MRI is not routinely used in the assessment of Friedreich's ataxia but can help determine the extent of cardiac involvement.[121] Treatment is largely supportive and limited to conventional heart failure medications, antiarrhythmics, and device implantation.[121]

Conclusion

Despite varied genetic or acquired etiologies, the infiltration of the heart by abnormal substances is the hallmark pathophysiologic process of the infiltrative cardiomyopathies. Disease occurs in a wide variety of age groups, and extra-cardiac manifestations are common given the systemic nature of the underlying disease. Conduction abnormalities and diastolic heart failure with restrictive physiology predominate in the

early stages, yet ventricular arrhythmias are not infrequent and adverse remodeling results in systolic dysfunction in advanced cases. While tissue is essential to the diagnosis, an extracardiac sample is usually sufficient when classic findings are seen on advanced cardiac imaging. Depending on the etiology and extent of involvement, medications, device therapy, and transplantation can be effective, though treatment is largely supportive in many cases.

Author Contributions

Wrote the first draft of the manuscript: DB. Contributed to the writing of the manuscript: DB, MY, PC. Agreed with manuscript results and conclusions: DB, MY, PC, FL. Jointly developed the structure and arguments for the paper: DB, MY, PC. Made critical revisions and approved the final version: MY, FL. All authors reviewed and approved the final manuscript.

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