Cardiac Amyloidosis: New Insights into Diagnosis and Management

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When amyloidosis affects the heart, a devastating and progressive process can lead to congestive heart failure, arrhythmias, conduction abnormalities, angina, and death. The signs and symptoms of cardiac amyloidosis are generally dominated by diastolic heart failure resulting from restrictive cardiomyopathy. Amyloid infiltration of the heart initially causes mild diastolic dysfunction, but late disease produces a thickened heart wall with a firm and rubbery consistency, which worsens cardiac relaxation and diastolic compliance. Patients usually complain of progressive dyspnea from congestive heart failure, chest discomfort secondary to microvascular involvement, and weight loss, which might be a manifestation of cardiac cachexia. Echocardiographic findings include nondilated ventricles with concentric left ventricular thickening, right ventricular thickening, prominent valves, dilated atria, and thickening of the interatrial septum. Recent advances in our understanding of the pathophysiology of amyloid have allowed the various types to be differentiated, which has led to targeted therapy for each unique pathophysiologic process.

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Key words: Amyloidosis • Dyspnea • Congestive heart failure • Hypotension • Diuretics

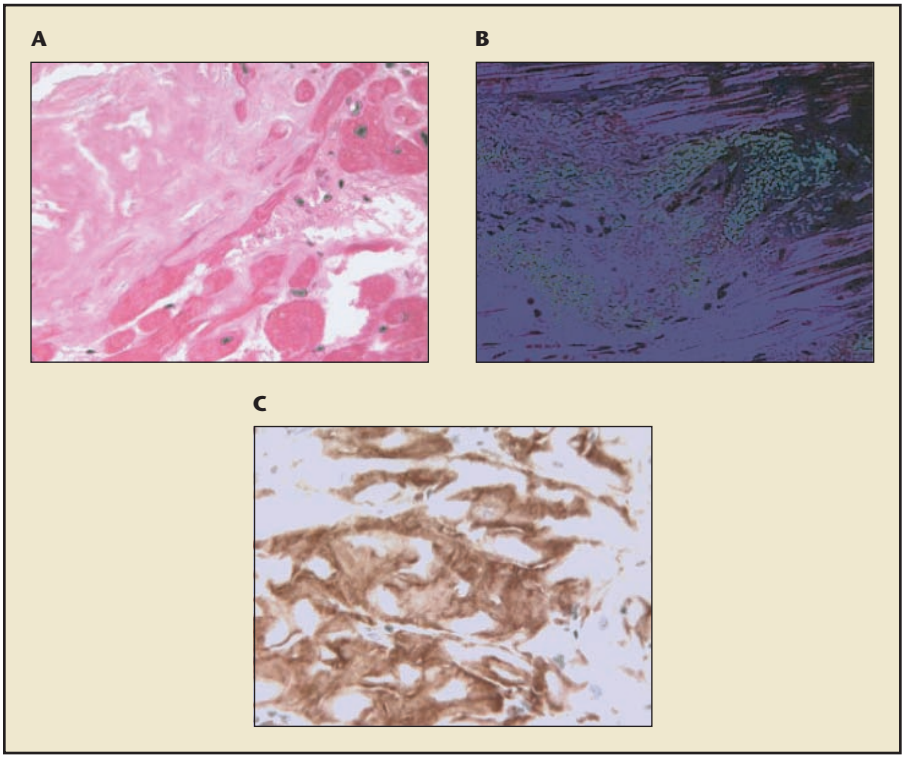
Amyloidosis constitutes a large group of diverse diseases that share the common feature of extracellular deposition of misfolded proteins in different organs. Cardiac amyloidosis, a manifestation of this process in the cardiovascular system, exhibits unique characteristics. This condition is underdiagnosed and often unrecognized, given the fact that there are several types of amyloid, each with distinctive features and treatment options.

In the 1830s, Matthias Schleiden, a German botanist, used the term *amyloid* to describe plant amylaceous material. In 1842, Rokitansky used the same term to describe the enlarged liver and spleen.[1] However, it was not until 1854 that Virchow first used iodine to examine amylacea under a microscope and compared its appearance to starch or cellulose.[2] To date, 24 heterogeneous proteins have been discovered that lead to amyloidosis. The misfolded proteins arise secondarily to genetic mutations or excess production, and form abnormal β-pleated sheets. These sheets form insoluble amyloid fibrils that resist proteolysis and cause mechanical disruption and local oxidative stress in various organs.[3] Regardless of which precursor protein causes disease, the deposits are virtually indistinguishable with light microscopy: when stained with Congo red, they demonstrate apple-green birefringence under polarized light (Figure 1).

The spectrum of organ involvement is fairly wide and can include the kidneys, heart, blood vessels, central and peripheral nervous systems, liver, intestines, lungs, eyes, skin, joints, and bones. When the heart is involved, a devastating and progressive process can lead to congestive heart failure, arrhythmias, conduction abnormalities, angina, and death.[4]

Recent advances in our understanding of the pathophysiology of amyloid have allowed the various types to be differentiated, which has led to targeted therapy for each unique pathophysiologic process. This article will review the classification, clinical manifestation, diagnosis, and potential therapeutic options for patients with cardiac amyloidosis.

Figure 1. *Endomyocardial biopsy.* **(A)** *Endomyocardial tissue fragments show deposits of amyloid material.* **(B)** *An apple-green birefringence is seen with Congo red stain viewed under polarized light.* **(C)** *An immunohistochemical study demonstrates reactivity of the amyloid deposits with antibodies against transthyretin in a case of TTR-amyloidosis. No reactivity was demonstrated with antibodies against kappa and lambda light chain, β-2-microglobulin, and amyloid A protein.* www.medreviews.com



Classification

Amyloidosis is classified into different forms based on the protein precursor: primary, secondary (reactive), senile, hereditary, isolated atrial, and hemodialysis-associated amyloidosis. They can each be distinctively differentiated by immunohistochemical and genetic testing, and prognosis and therapeutic options differ among the various subtypes (Table 1).

Primary Amyloidosis

The most common form of amyloidosis is the one associated with a plasma cell dyscrasia. In primary amyloidosis (also known as AL), a plasma cell defect produces amyloidogenic immunoglobulin light chain proteins. The most common plasma cell dyscrasia is multiple myeloma, and primary amyloidosis overlaps with it. However, only a minority of myeloma patients develop amyloidosis, and most patients with amyloidosis do not have multiple myeloma.

Primary amyloidosis is rare. It has an incidence of 9 per million, with 2000 to 3250 new cases per year in the United States. It affects more men than women (the ratio is 3:2), and usually occurs around the sixth decade of life.[5] The mean survival is 13.2 months, with 10-year survival of less than 5%. The heart is affected in 50% of patients, half of whom present with congestive heart failure.[6] Poor prognostic indicators include cardiac involvement with septal thickness greater than 15 mm, left ventricular ejection fracture of less than 40%, and presentation with congestive heart failure, in which case the median survival is less than

Table 1
Classification of Amyloidosis

Type of Amyloid	Amyloid Protein	Cardiac Involvement	Median Survival (Months)	Extracardiac Manifestations	Diagnostic Testing	Definitive Treatment
Primary (AL)	Immunoglobulin light chain	22% to 34%	13 (~ 6 if heart failure is present at diagnosis)	Renal failure, proteinuria, hepatomegaly, autonomic dysfunction, macroglossia, purpura, neuropathy, carpal tunnel syndrome	Serum and urine immunofixation, bone marrow biopsy, κ and λ light-chain testing	Chemotherapy Autologous stem-cell transplantation Heart transplantation
Hereditary (ATTR)	Mutant transthyretin protein	Variable	70	Severe neuropathy, autonomic dysfunction, renal failure, blindness	ATTR antiserum staining, serum TTR isoelectric focusing, polymerase chain reaction	Liver transplantation
Senile (ATTR)	Wild-type transthyretin	Common	75	Diffuse organ involvement	ATTR antiserum staining	Supportive
Isolated Atrial (AANF)	Atrial natriuretic peptide	Limited to heart	_	None	Atrial natriuretic factor antiserum staining	None
Reactive (AA)	Serum amyloid A protein	< 10%	24	Renal failure, proteinuria, hepatomegaly, association with chronic inflammatory conditions	AA antiserum staining	Treat underlying inflammatory condition Colchicine for familial Mediterranean fever
Dialysis-related (β2-microglobulin)	β2-microglobulin	Asymptomatic	_	Arthralgias, carpal tunnel syndrome, arthropathies, bone cyst, pathologic fractures	Synovial and bone biopsy specimen analysis, β2-microglobulin antiserum and serum concentrations	None

AL, primary amyloidosis; ATTR, amyloidosis transthyretin; AANF, atrial natriuretic factor amyloidosis; AA, secondary amyloidosis.

6 months. Death usually results from heart failure or arrhythmias.

Hepatomegaly can result from infiltration or passive congestion. Renal involvement causes profound proteinuria and nephrotic syndrome. Purpura and easy bruising, especially of the face and neck, occur from clotting factor deficiencies and fragile venules. Carpal tunnel syndrome, peripheral neuropathy, and macroglossia may also be present. Laboratory and bone marrow examinations reveal excess light chain protein production with λ predominance, with a λ:κ ratio of 3:1, whereas in myeloma the λ:κ ratio is 1:2.[7]

In addition, Comenzo and colleagues[8] described tropism of various light chains that are associated with certain involved organs and that may be dependent on the gene expression profile of the plasma cell clones. They concluded that patients with clones derived from the 6A Vλ germ line–gene were more likely to present with dominant renal involvement, whereas patients with clones derived from the 1C, 2A2, and 3R Vλ genes were more likely to present with dominant cardiac and multisystem disease.[8]

Hereditary Amyloidosis

In hereditary (familial) amyloidosis, genetically mutant proteins form amyloid fibrils. Most types are caused by deposition of mutant transthyretin (TTR) protein, previously known as *prealbumin*, a homotetrameric transport protein synthesized in the liver, choroids plexus, and retina that carries retinol and thyroxin in plasma and cerebrospinal fluid. Less commonly, other genetically mutant proteins such as apolipoprotein A-I, lysozyme, fibrinogen, and gelsolin can cause abnormal deposition as well.[9]

TTR contains 125 pairs of amino acids with more than 80 point mutations in the DNA that predispose the protein to misfolding and to amyloid formation, which are highly neurotoxic.[10] The specific site of the amino acid substitution determines the phenotype of the disease that is transmitted as autosomal dominant with high penetrance.

In hereditary amyloidosis, the predominant features are peripheral neuropathy, intracranial hemorrhage, and ocular deposition, without significant macroglossia. Cardiac involvement can occur, especially with certain mutations; mutations causing significant cardiac disease include methionine-for-valine substitution at position 30, serine-for-isoleucine substitution at position 84, and alanine-for-threonine substitution at position 60. The mutations usually present as conduction system abnormalities that most frequently manifest as sinus node dysfunction.[11]

An isoleucine 122 gene mutation of the TTR gene causes a familial amyloidosis primarily involving the heart. It presents without neurologic symptoms, and is unique among elderly African Americans. Approximately 4% of the African American population in the United States is heterozygous for this mutation, which leads to a greater than 7-fold risk of cardiac amyloidosis with predominant signs of right-sided congestive heart failure.[12,13]

Senile Systemic Amyloidosis

Senile systemic amyloidosis results from cardiac deposition of wild-type TTR, and usually presents as congestive heart failure and atrial fibrillation. It is almost exclusively a disorder of men. It is rare in individuals younger than 70 years and is present in 25% of all persons older than 80 years. However, unlike the poor prognosis with cardiac involvement in primary amyloidosis, the mean survival in senile systemic amyloidosis with cardiac involvement averages about 7.5 years from the onset of heart failure.[14]

Isolated Atrial Amyloidosis

Isolated atrial amyloidosis results from deposits of atrial natriuretic peptide, a protein secreted by atrial myocytes in response to increased wall stretch. The incidence of atrial amyloidosis increases with age—it is greater than 90% in the ninth decade of life. It occurs more often in women than in men. The disease also occurs in young patients with valvular disease and in patients with chronic atrial fibrillation. Its deposition is limited to underneath the endocardium, and it is a common finding at autopsy without any known clinical significance.[15]

Secondary Amyloidosis

Secondary amyloidosis (also known as AA) results from accumulation of amyloid A fibrils that are formed from an acute phase reactant, serum amyloid A protein. Its prevalence has decreased in the developed world due to the eradication of chronic infections. It is associated with juvenile and adult rheumatoid arthritis, familial Mediterranean fever, chronic infections such as tuberculosis or leprosy, and inflammatory bowel disease. Hepatic and renal amyloid deposition dominates the clinical picture. Secondary amyloidosis of the heart is typically insignificant. Treatment of the underlying process can reverse the disease.[16]

Hemodialysis-Associated Amyloidosis

This type of amyloidosis occurs in patients with chronic renal failure who are receiving dialysis and is due to accumulation of β2-microglobulin from long-standing uremia. The protein accumulates and deposits mainly in bones and joints. Renal transplantation normalizes the concentration and improves joint pain.[17]

Pathophysiology of Cardiac Amyloidosis

Amyloid infiltration of the heart initially causes mild diastolic dysfunction, but late disease produces a thickened heart wall with a firm and rubbery consistency, which worsens cardiac relaxation and diastolic compliance. The stiff heart wall elevates filling pressures, resulting in restrictive cardiomyopathy and signs and symptoms of pulmonary and/or systemic venous congestion. Increased diastolic filling pressures also lead to dilation of the atria. The less compliant left ventricle maintains its normal chamber diameter, with thickening of the free wall and the septum. As the disease progresses, myocyte necrosis and local interstitial fibrosis result in systolic ventricular dysfunction with a decline in the ejection fraction. The amyloid deposition into the atrial walls is often extensive, causing increased thickening of the intra-atrial septum. Amyloid deposits also lead to conduction abnormalities and arrhythmias, which predispose patients to bradyarrhythmias, atrial fibrillation, ventricular arrhythmias, and increased risk of sudden death. Small vessel occlusion from amyloid deposits can lead to angina and even myocardial necrosis.

Clinical Manifestation of Cardiac Amyloidosis

The signs and symptoms of cardiac amyloidosis are generally dominated by diastolic heart failure resulting from restrictive cardiomyopathy. Patients usually complain of progressive dyspnea from congestive heart failure, chest discomfort secondary to microvascular involvement, and weight loss, which might be a manifestation of cardiac cachexia. Syncope or light-headedness may result from orthostatic hypotension due to autonomic neuropathy or cardiac conduction and rhythm disturbances. Findings of right-sided heart failure tend to predominate, with elevated jugular venous pressure, hepatomegaly, ascites, and bilateral lower extremity edema.

Hypertension is unusual, and in fact most patients have low pressure. In patients with a history of hypertension, there may be "spontaneous" resolution of hypertension resulting from cardiac involvement. Other manifestations include valvular regurgitation, atrial and ventricular arrhythmias, conduction abnormalities, or sudden death. On rare occasions, electromechanical dissociation or pulseless electrical activity may also result from cardiac amyloidosis.

Noncardiac findings may include easy bruising, periorbital ecchymoses (the so-called "raccoon eyes" that are specific for primary amyloidosis), edema, macroglossia, tooth indentation, dysphonia, hoarseness, nail dystrophy, and alopecia. Soft tissue amyloid deposition may manifest as submandibular swelling and "shoulder-pad sign," carpal tunnel syndrome, and peripheral neuropathy.

Electrocardiogram Abnormalities

Abnormalities seen on an electrocardiogram include low QRS voltage (< 10 mV in all pericordial leads or < 5 mV in all limb leads), Q waves resembling myocardial infarction (pseudoinfarction pattern), arrhythmias, and conduction abnormalities. The low QRS voltage in association with increased left ventricular wall thickness on echocardiography results from displacement of viable myocardium with amyloid deposits. Thus, the "voltage-thickness paradox" should suggest the diagnosis of cardiac amyloidosis (Figure 2).

Cardiac Biomarkers

Serum markers of cardiac injury or stress can be persistently elevated in amyloidosis. Troponin may be elevated due to myocyte necrosis from

Figure 2. *An electrocardiogram in a patient with cardiac amyloidosis shows sinus rhythm with an isolated premature ventricular contraction, a left atrial abnormality, diffuse-low voltage QRS, intraventricular conduction abnormality, and a pseudoinfarct pattern in the precordial leads.*
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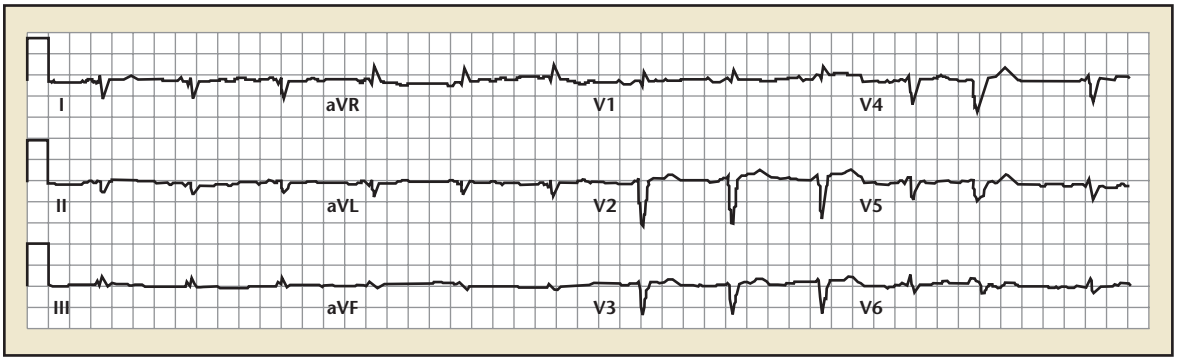

amyloid deposits and ischemia related to intramural vessel obstruction.[18] Natriuretic peptide levels are also elevated secondary to elevated filling pressures.[19] In addition, elevations in both troponin and natriuretic peptide levels signify a poor prognosis.[20,21]

Echocardiographic Features

The echocardiographic features are an essential part of the diagnosis of cardiac amyloidosis. Echocardiographic findings include nondilated ventricles with concentric left ventricular thickening, right ventricular thickening, prominent valves, dilated atria, and thickening of the interatrial septum (Figure 3). The myocardial texture visible on an echocardiogram often shows a granular or sparkling pattern; however, this finding is not specific to amyloidosis.[22] Increasing wall thickness is inversely correlated with survival.[23]

Although ventricular septal thickening can sometimes mimic hypertrophic cardiomyopathy, increased interatrial septal wall thickening is more likely in cardiac amyloidosis than in hypertrophic cardiomyopathy.[24] The left ventricular ejection fraction is usually nearly normal until late in the course of the disease, when systolic function declines with a fall in ejection fraction.

Doppler echocardiography provides useful information characterizing the progression of cardiac dysfunction. Early amyloid deposition impairs isovolumetric relaxation, resulting in decreased early diastolic flow velocity across the mitral valve (E) and increased dependence on atrial contraction for ventricular filling, leading to increased late diastolic filling velocities (A).[25] The decreased E:A ratio of flow velocities is an early sign of amyloid involvement. As compliance declines further, left atrial pressure increases—as does early diastolic filling across the mitral valve—thus pseudonormalizing the E:A ratio.[26]

Pulsed tissue Doppler imaging can demonstrate the presence of diastolic dysfunction more accurately and can provide evidence of systolic impairment.[27] Strain and strain rate imaging provide even greater sensitivity, demonstrating long-axis dysfunction in early cardiac amyloidosis and showing disproportionate impairment of longitudinal contraction despite apparently preserved fractional shortening.[28]

Cardiac Catheterization

Although patients can present with symptoms of typical angina, due to involvement of small vessels, a coronary angiogram usually reveals normal epicardial coronary arteries. However, in older patients, concomitant atherosclerotic coronary artery decrease may be an incidental finding. Intracardiac filling pressures are elevated, and left ventricular and right ventricular pressure tracings may demonstrate early diastolic dip and mid-to-late diastolic plateau, the "square root sign," and equalization of left and right ventricular filling pressures.[29] These findings may simulate those of constrictive pericarditis (Figure 4).

Noninvasive Imaging

Early studies suggested that diffuse myocardial uptake of radiolabeled technetium pyrophosphate may be a good diagnostic marker of cardiac amyloidosis; however, subsequent studies pointed out the relatively low sensitivity of this test for detection of cardiac amyloid, thus limiting its diagnostic utility for detection of cardiac amyloidosis.[30] A more recent study, however, suggested that a different tracer, technetium Tc 99m–3,3,-diphosphono-1,2-propanodicarboxylic acid, may be capable of differentiating TTR-associated amyloidosis from primary amyloidosis.[31]

Recent studies have also demonstrated that ^{123}I-labeled serum amyloid P scintigraphy, which identifies a nonfibrillar glycoprotein contained in amyloid deposits, serves as a sensitive test for diagnosing amyloidosis in patients with primary and secondary amyloidosis. Nevertheless, this test had poor sensitivity for amyloidosis TTR.[32]

Cardiac magnetic resonance imaging enables high-resolution imaging

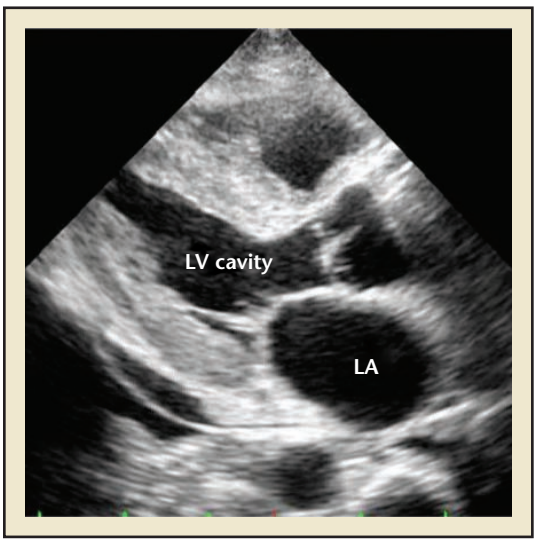

Figure 3. *Echocardiography in a parasternal, long-axis view shows thickened left ventricular (LV) walls, normal LV cavity size, and an enlarged left atrium (LA) in a patient with cardiac amyloidosis.*
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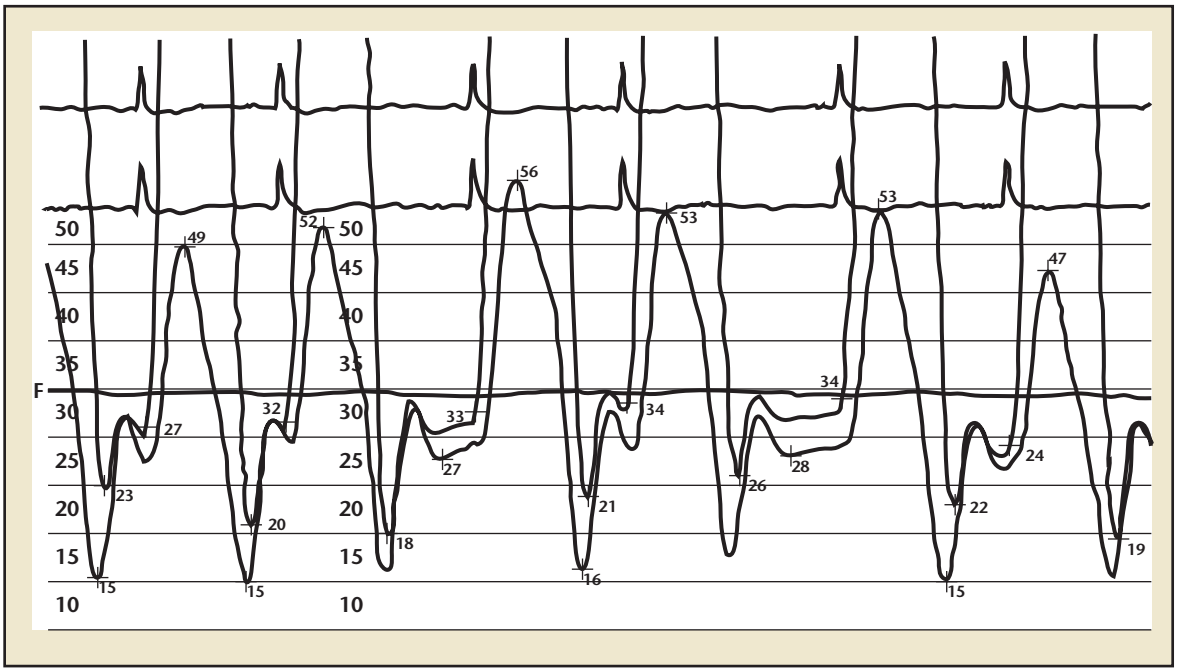


Figure 4. *Simultaneous left ventricular (LV) and right ventricular (RV) pressure tracings demonstrating elevated LV and RV diastolic pressures with a diastolic dip-plateau pattern (square-root sign) in a patient with restrictive cardiomyopathy resulting from cardiac amyloidosis. The square-root sign is prominent during long R-R intervals in this patient, who also had atrial fibrillation. Similar hemodynamic findings may also occur in patients with constrictive pericarditis.* www.medreviews.com

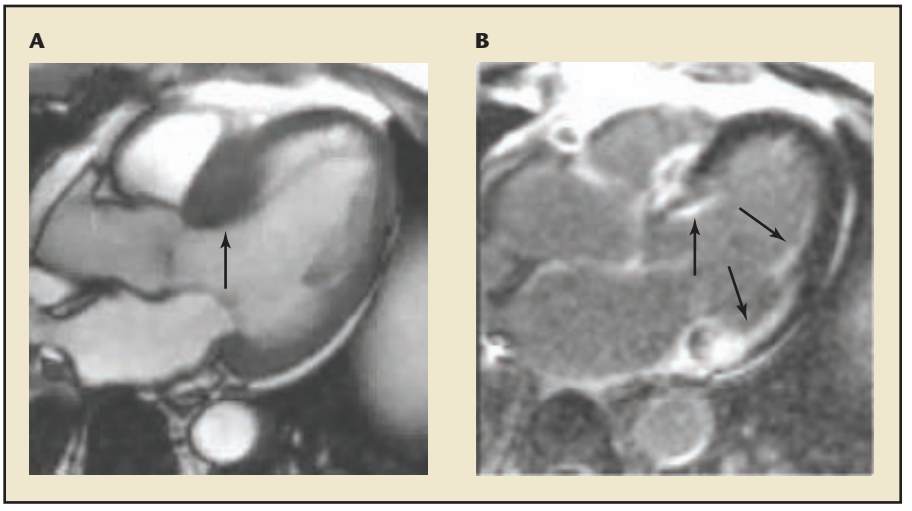
of the myocardium and evaluation of chamber dimensions, wall thickness, and regional wall motion.[33] In addition, decreased tissue signal intensity along with late subendocardium tissue enhancement by gadolinium are a result of myocardial amyloid deposits and may differentiate cardiac amyloidosis from other causes of cardiomyopathy (Figure 5).[34,35]

Tissue Diagnosis

The diagnosis of amyloidosis often requires a tissue biopsy and histological analysis. Congo red staining identifies amyloid as amorphous pink deposits; however, when Congo red–stained tissue is examined under polarized light, apple-green birefringence is noted as a characteristic feature of amyloid deposits.

Fine-needle aspiration of the abdominal fat is a simple procedure that is positive for amyloid deposits in more than 80% of patients with primary amyloidosis.[36,37] The rectal submucosa can also be utilized, with a sensitivity of 75% to 85%.[38] If the disease is limited to the heart, or biopsy from other sites are nondiagnostic, an endomyocardial biopsy specimen may be the only method of diagnosing cardiac amyloidosis.

Figure 5. *Magnetic resonance image (MRI) of a patient with cardiac amyloidosis.* **(A)** *Pre-contrast cine MRI of the left ventricular outflow tract revealing hypertrophy (arrow) of the ventricular septum.* **(B)** *Delayed enhancement MRI revealing mid-myocardial hyperenhancement in the septal wall as well as the lateral wall (arrows).* www.medreviews.com



Once the tissue diagnosis has been established, further work-up to identify the type of amyloidosis is often necessary. This work-up includes specific immunostains of the tissue to identify the nature and type of amyloid pattern. Serum and urine immunofixation and bone marrow biopsy can establish diagnosis of primary amyloidosis. Even more sensitive is testing with the free light-chain assay, which can detect circulating free light chains with more than 10-fold sensitivity than immunofixation.[39] Other features of amyloidosis may require genetic analyses.

Management

The treatment of cardiac amyloidosis involves the management of both congestive heart failure and other cardiac manifestations as well as of the underlying basis for amyloidosis. The initial goal of medical therapy is the relief of symptoms. This goal is best reached with cautious use of diuretics for relief of symptoms and signs of fluid overload. Given the hypotension associated with amyloidosis, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are often poorly tolerated but may be helpful when used in small doses and with careful monitoring. The tendency for orthostatic hypotension from autonomic neuropathy may preclude the use of vasodilators and negative inotropic agents, such as β-blockers and calcium channel blockers.[40,41]

Digoxin should be used with caution if at all because the risk of digoxin toxicity is increased (perhaps due to binding of digoxin to amyloid fibrils, which thereby elevates myocardial digoxin levels even in the setting of therapeutic serum digoxin levels).[42] The presence of atrial fibrillation in amyloidosis is associated with a very high rate of thromboembolic events. With atrial infiltration and dysfunction, atrial thrombi may be present, even during sinus rhythm.[43] Anticoagulant therapy may be needed to reduce the risk of intracardiac thrombus formation and thromboembolic events, especially in patients with atrial fibrillation; however, the benefit of routine anticoagulation in sinus rhythm remains undefined.

Although cardiac pacing improves symptoms, it has not been shown to improve survival, and is indicated only in patients with significant bradyarrhythmias. No data are available on the benefits of biventricular pacing or automatic implantable cardioverter-defibrillators in this population.[44]

The definitive treatment of cardiac amyloidosis is dependent on the specific etiology of amyloidosis. In the case of primary amyloidosis, a combination of high-dose chemotherapy as well as autologous stem cell transplantation is necessary to halt the production of the paraprotein responsible for amyloidosis.[45] The regimen of melphalan and prednisone given as a "pulsed" dose seems to have little benefit in patients with cardiac amyloidosis.[46]

Stem cell transplantation has shown promising results for the treatment of primary amyloidosis. Compared with other hematologic malignancies, transplant-related mortality is increased 5-fold in amyloidosis.[47] The increased mortality has been attributed to extensive and diffuse systemic end-organ damage from amyloid deposits: patients with 2 involved organs have a 20% mortality, and patients with 3 or more involved organs have a 70% mortality.[48]

In selected cases, cardiac transplantation may be considered for primary amyloidosis. Short-term mortality does not differ from that of other transplant recipients,[49] although increased long-term mortality has been shown; most likely, it is secondary to the progression of the disease in the heart as well as the other organs.[50,51] However, with the combination of high-dose chemotherapy and stem cell transplantation, it is now possible to transplant the heart and use chemotherapy 6 to 12 months later to abolish amyloid production. In the Mayo Clinic experience, 22 patients have recently undergone cardiac transplantation, with survival anywhere from 1 to 106 months post-transplantation.[52]

In hereditary or familial TTR cardiac amyloidosis, in which the liver is responsible for the production of abnormal proteins, definitive therapy includes liver transplantation, which removes the source of abnormal TTR production.[53] Patients with significant cardiomyopathy have undergone successful combined liver and heart transplantation.[54]

Stem cell transplantation has shown promising results for the treatment of primary amyloidosis.

In reactive amyloidosis (secondary amyloidosis) that is caused by chronic infections, antimicrobial therapy can halt progression. In inflammatory arthritides, chlorambucil and tumor necrosis factor show promise.[16,55] Finally, colchicine has been successful in the treatment of familial Mediterranean fever.[56]

Evolving New Therapies for Amyloidosis

There is currently ongoing investigation into the development of drugs that will stabilize TTR and prevent formation of TTR-amyloid.[57] One

such compound, genistein, the major isoflavone natural product in soy, works in this manner and is an excellent inhibitor of TTR tetramer dissociation and TTR-amyloidogenesis.[58] Another investigational approach uses small molecules that directly affect amyloid deposits, targeting the common fibrillar architecture, and common protective elements. These molecules work by clearing serum amyloid P component from amyloid deposits[59] or inhibiting their interaction with glycosaminoglycans[60] (Figure 6). Recently, eprodisate, which binds to glycosaminoglycan binding sites on amyloid fibrils and is thought to destabilize them, was studied in patients with primary amyloidosis. The study demonstrated a decline in the risk of worsening renal function and the rate of decline in creatinine clearance, although there was no effect on the progression to endstage renal disease or death.[61]

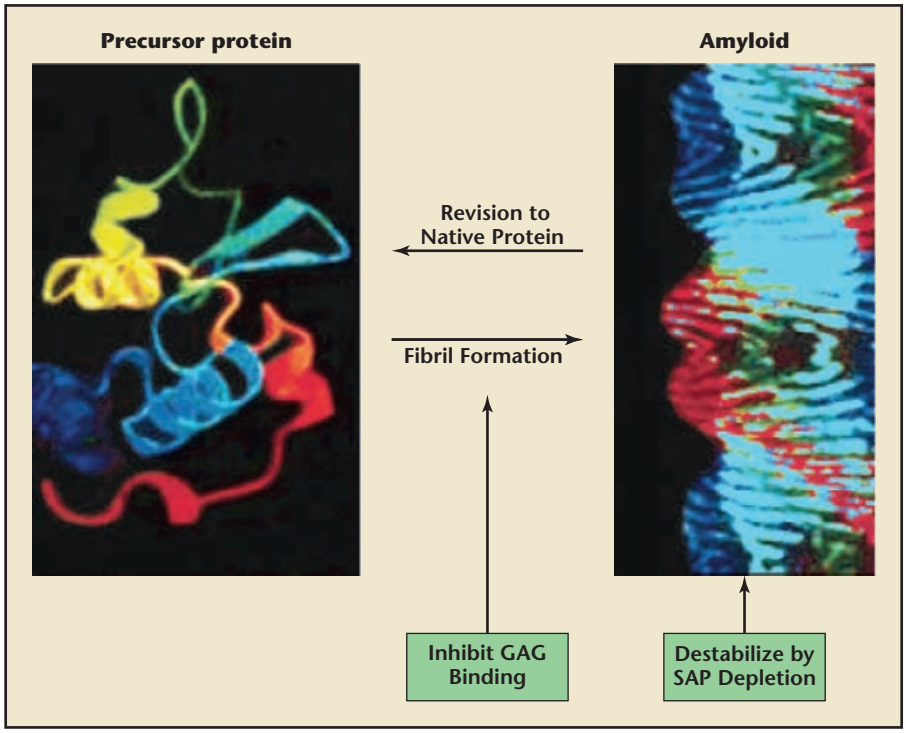


Figure 6. *A schematic illustrating the various novel targets for inhibition of amyloidosis. Amyloid deposits require the production of amyloidogenic proteins, their subsequent interaction with extracellular matrix components such as glycosaminoglycans (GAG), and their stabilization by interaction with serum amyloid P (SAP). Pharmacological inhibition of amyloidosis can be achieved through inhibition of amyloidogenicity of precursor proteins, inhibition of binding with GAG, and destabilization of the amyloid through depletion of SAP. These strategies are under intense investigation.* www.medreviews.com

Conclusion

Cardiac amyloidosis presents with distinctive clinical features and findings on electrocardiography and echocardiography that require heightened awareness of the disease pathophysiology and molecular genetics. It is important to recognize that several forms of amyloidosis may cause cardiac abnormalities, and that the underlying molecular physiology alters the disease progression, treatment, and survival. Therefore, considerable attention should be placed on differentiating the types. Medical therapy is limited to symptom management. However, chemotherapy, stem cell transplantation, and

Main Points

- In primary amyloidosis, the heart is affected in 50% of patients, half of whom present with congestive heart failure.
- Cardiac involvement can occur with hereditary amyloidosis, especially with certain mutations.
- Senile systemic amyloidosis results from cardiac deposition of wild-type transthyretin, and usually presents as congestive heart failure and atrial fibrillation.
- Amyloid infiltration of the heart initially causes mild diastolic dysfunction, but late disease produces a thickened heart wall with a firm and rubbery consistency, which worsens cardiac relaxation and diastolic compliance.
- The signs and symptoms of cardiac amyloidosis are generally dominated by diastolic heart failure resulting from restrictive cardiomyopathy.
- The initial goal of medical therapy is the relief of symptoms. This goal is best reached with cautious use of diuretics for relief of symptoms and signs of fluid overload.

solid organ transplantation offer increased survival advantage in selected cases. In addition, novel insights into molecular mechanisms of the disease have yielded optimism toward the development of new therapies directly targeting amyloid deposits. ■

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