

# Amyloidosis and the Heart

## A Comprehensive Review

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**I**nfiltration of the heart from insoluble protein deposits in amyloidosis often results in restrictive cardiomyopathy that manifests late in its course with heart failure and conduction abnormalities. While the rare primary amyloidosis–related heart disease has been well characterized, senile amyloidosis occurring in the seventh decade of life most frequently affects the heart. Early diagnosis of cardiac amyloidosis may improve outcomes but requires heightened suspicion and a systematic clinical approach to evaluation. Demonstration of tissue infiltration of biopsy specimens using special stains, followed by immunohistochemical studies and genetic testing, is essential in defining the specific protein involved. The therapeutic strategy depends on the characterization of the type of amyloid protein and extent of disease and may include chemotherapy, stem cell transplantation, and liver transplantation. Heart transplantation is controversial and is generally performed only at isolated centers.

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Matthias Schleiden, a German botanist and co-creator of the cell theory, fashioned the word *amyloid* in 1834 to describe the waxy starch in plants. Today, amyloidosis describes the infiltration of multiple organs by insoluble deposits composed of fibrillar protein that arise from a diverse group of disease processes. To date, 24 heterogeneous proteins prone to misfolding have been discovered that comprise amyloid deposits.<sup>1</sup> The misfolded proteins arise secondary to genetic mutations or excess production and form a  $\beta$ -pleated sheet that aligns in an antiparallel manner. The sheets form insoluble amyloid fibrils that resist proteolysis and cause mechanical disruption and local oxidative stress in various organs.<sup>2</sup>

Regardless of which precursor protein causes disease, the deposits are virtually indistinguishable with light microscopy. The amorphous proteinaceous substance stains pink with Congo red staining, with apple-green birefringence under polarizing light microscopy. The spectrum of organ involvement can include the kid-

neys, heart, blood vessels, central and peripheral nervous systems, liver, intestines, lungs, eyes, skin, and bones.<sup>3</sup> Amyloid deposition in the heart is a devastating and progressive process that leads to congestive heart failure, angina, and arrhythmias. For patients with amyloidosis, infiltration of the heart confers the worst prognosis. In this systematic review, we discuss the clinical features of cardiac amyloidosis, present a diagnostic approach, and describe potential therapies.

### CLASSIFICATION

Cardiac amyloidosis is classified by the protein precursor as primary, secondary (reactive), senile systemic, hereditary, isolated atrial, and hemodialysis-associated amyloidosis. These distinct forms are differentiated by means of immunohistochemical and genetic testing, and prognosis and therapeutic strategies differ among these subtypes (**Table**).

#### Primary Amyloidosis

In primary amyloidosis (AL), a plasma cell defect produces amyloidogenic immuno-

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**Table. Classification of the Subtypes of Cardiac Amyloidosis**

Amyloidosis Type	Protein	Cardiac Involvement	Median Survival, mo	Extracardiac Manifestations	Diagnostic Testing
Primary (AL)	Light chain	22%-34%	13 (4 mo if heart failure present at diagnosis)	Renal failure, proteinuria, hepatomegaly, autonomic dysfunction, macroglossia, purpura, neuropathy, carpal tunnel syndrome	SPEP, UPEP, bone marrow biopsy tissue analysis revealing plasma cell dyscrasia, $\kappa$ and $\lambda$ light-chain antiserum staining
Hereditary (ATTR)	Mutant TTR	Variable	70	Severe neuropathy, autonomic dysfunction, renal failure, blindness	ATTR antiserum staining, serum TTR isoelectric focusing, restriction fragment length polymorphism analysis
Senile systemic (ATTR)	TTR	Common	75	Diffuse organ involvement	ATTR antiserum staining
Isolated atrial (AANF)	Atrial natriuretic factor	Limited to heart	...	None	Atrial natriuretic factor antiserum staining
Reactive (AA)	Amyloid A	<10%	24½	Renal failure, proteinuria, hepatomegaly associated with chronic inflammatory conditions	Target organ biopsy specimen analysis, AA antiserum staining
Dialysis-related ( $\beta_2$ -microglobulin)	$\beta_2$ -Microglobulin	Unknown, asymptomatic	...	Arthralgias, carpal tunnel syndrome, arthropathies, bone cysts, pathologic fractures	Synovial and bone biopsy specimen analysis, $\beta_2$ -microglobulin antiserum, serum $\beta_2$ -microglobulin concentration

Abbreviations: SPEP, serum protein electrophoresis; TTR, transthyretin; UPEP, urine protein electrophoresis.

globulin light-chain proteins, resulting in an aggressive form of amyloidosis. Primary amyloidosis is rare, with an incidence of 8.9 per million population.<sup>4</sup> The mean survival has improved from 4.9 months in 1961 to 13.2 months in 1995.<sup>5,6</sup> Primary amyloidosis affects more men than women (3:2), usually around the sixth decade of life.<sup>7</sup>

Cardiac involvement in AL is common, and 60% of patients demonstrate electrocardiographic or echocardiographic abnormalities. Clinical manifestations of heart failure identify a more aggressive natural history (median survival, 4 months). Death is attributed to cardiac causes in at least half of the patients with primary amyloidosis, who die of either heart failure or an arrhythmia.<sup>6</sup>

Light-chain amyloidosis affects several organs, and extracardiac manifestations often lead to the initial diagnosis. Early in the disease, nonspecific systemic complaints including weakness, fatigue, and weight loss dominate. Hepatomegaly results from infiltration of the liver or from hepatic 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.<sup>6</sup>

Laboratory data reveal excess light-chain protein production. In one case series, 89% of patients with biopsy-confirmed primary amyloidosis had monoclonal light chains present at urine or serum protein immunofixation electrophoresis. The M protein type was primarily  $\lambda$  with a 2:1 predominance over  $\kappa$ . Bone marrow biopsy can reveal an increased fraction of plasma cells with proliferation of a clonal line and excessive  $\lambda$  and  $\kappa$  light-chain staining.<sup>6</sup>

### Secondary Amyloidosis

Secondary amyloidosis (AA) results from the accumulation of amyloid A fibrils formed from an acute-phase reactant, serum amyloid A protein. Secondary amyloidosis may be associated with rheumatoid arthritis, familial Mediterranean fever, chronic infections, and inflammatory bowel disease.

Secondary amyloidosis of the heart is typically clinically insignificant.<sup>8,9</sup> The primary pathologic findings involve the kidney, with development of proteinuria and renal failure. Treatment of the underlying process can reverse the disease.<sup>10</sup>

### Senile Systemic Amyloidosis

Senile systemic amyloidosis, an age-related disease, occurs in the aorta, heart tissue, brain, pancreas, lung, liver, kidney, and a number of other tissues.<sup>11</sup> Wild-type transthyretin (TTR), a transport protein synthesized in the liver and choroid plexus, forms the amyloid deposits.<sup>12</sup> Senile systemic amyloidosis affects men predominantly, usually after age 70 years, and affects the heart in 25% of persons older than 80 years.<sup>13</sup> The disease is often unrecognized; however, extensive amyloid deposition leads to clinically significant heart failure. The disease course is less aggressive than AL, with a median survival of 75 months.<sup>14</sup>

### Hereditary Amyloidosis

Hereditary (familial) amyloidosis is an autosomal dominant disease in which genetically mutated proteins form the amyloid fibrils. Mutations in both apolipoprotein I and TTR (ATTR) are known to lead to cardiac involvement, but our focus here is on TTR mutations, which are more prevalent.

Variant forms of TTR caused by more than 80 point mutations in the

DNA predispose the protein to misfolding and to amyloid formation.<sup>15</sup> The prominent feature is peripheral and autonomic neuropathy, a clinical entity referred to as familial amyloid polyneuropathy. Mutations causing significant cardiac disease are methionine-for-valine substitution at position 30, serine-for-isoleucine substitution at position 84, and alanine-for-threonine substitution at position 60.<sup>16</sup> While less aggressive than AL disease, ATTR-related cardiac amyloidosis also results in clinically significant heart failure.

Familial amyloid polyneuropathy is generally classified by ancestral affiliation.<sup>17</sup> Over years, patients develop progressive peripheral and autonomic neuropathy. Hyperesthesia to pain and temperature, motor weakness, and a diminished deep tendon reflex ascend from the lower extremities, and patients often become wheelchair dependent. Inactivity masks exertional symptoms from the underlying cardiomyopathy. Autonomic dysfunction includes impotence, decreased bowel motility, incontinence, and orthostatic hypotension.<sup>16</sup>

An isoleucine 122 gene mutation of the TTR DNA causes a familial amyloidosis primarily involving the heart without neurologic symptoms and is unique to elderly black persons. It is estimated that 1.3 million black persons are heterozygous for isoleucine 122.<sup>18</sup> Presentation of the phenotype is variable, and the penetrance of the disease has yet to be defined.<sup>19</sup>

If tissue sampling confirms the presence of TTR in the amyloid deposits, isoelectric focusing of the patient's serum can differentiate mutant from normal TTR.<sup>20</sup> Genetic testing by restriction fragment length polymorphism analysis can identify the type of mutation.

### Isolated Atrial Amyloidosis

Isolated atrial amyloidosis (AANF) is composed of atrial natriuretic peptide, a protein secreted by atrial myocytes in response to increased wall stretch.<sup>21-23</sup> The incidence of AANF increases with age (>90% in the ninth decade of life) and in females.<sup>24</sup> The disease also occurs in young patients with valvular dis-

ease and in patients with chronic atrial fibrillation.<sup>25-27</sup> AANF is limited to the heart as thin, linear deposits along and underneath the endocardium. It is unclear whether the disease process has any clinical significance.<sup>28</sup>

### Hemodialysis-Related Amyloidosis

Patients receiving long-term dialysis can develop cardiac amyloidosis with accumulation of  $\beta_2$ -microglobulin from long-standing uremia.<sup>29,30</sup> The protein accumulates with declining renal function and is ineffectively cleared with hemodialysis. The clinical effect of deposits occurring in the myocardium, pericardium, and cardiac valves is minimal, and the predominant symptoms are from joint involvement.<sup>31,32</sup> Renal transplantation normalizes  $\beta_2$ -microglobulin concentrations and improves joint pain.<sup>33</sup>

### PATHOPHYSIOLOGY

While several types of amyloid infiltrate the heart, only senile, hereditary, and primary amyloidosis commonly cause clinically significant disease. Amyloid infiltration of the heart interrupts contractile function and electrical conduction and influences coronary flow. Amyloid penetrates the myocardial interstitium in the form of nodular deposits and branching filaments interlacing individual myocytes. Early mild diastolic dysfunction can be noted at echocardiography, but late disease produces a thickened heart wall with a firm and rubbery consistency, worsening cardiac relaxation and compliance. The stiff heart wall elevates filling pressures, resulting in restrictive cardiomyopathy.<sup>34,35</sup> Increased diastolic filling pressures lead to dilation of the atrial chambers. The less compliant left ventricle remains of normal chamber diameter with thickening of the free wall and septum.<sup>36,37</sup> With progression, myocyte necrosis and local interstitial fibrosis result in systolic ventricular dysfunction. The deposition into the atrial walls is extensive and in rare cases can cause mechanical failure and conduction standstill.<sup>38,39</sup> Endocardial deposi-

tion may cause valvular insufficiency and worsen congestive heart failure. In rare cases, pericardial involvement occurs with high-grade disease and can lead to constrictive physiologic findings.<sup>36</sup> There are reports of pulmonary amyloid infiltration resulting in pulmonary hypertension and cor pulmonale.<sup>40</sup>

In addition to mechanical disruption, amyloid deposits induce oxidant stress that depresses myocyte contractile function.<sup>41</sup> Amyloid also modulates interstitial matrix composition and tissue remodeling by disabling the balance of matrix metalloproteinases and their inhibitors.<sup>42</sup>

Myocardial ischemia results from microvasculature disease. Amyloid deposits spare the epicardial vessels, while involvement of the intramural vasculature is present in 90% of patients with AL amyloidosis.<sup>36,43</sup> Although severe obstruction is rare, diffuse involvement leads to numerous endocardial foci of ischemia, microinfarction, and eventual fibrosis, contributing to further myocardial dysfunction.<sup>44</sup>

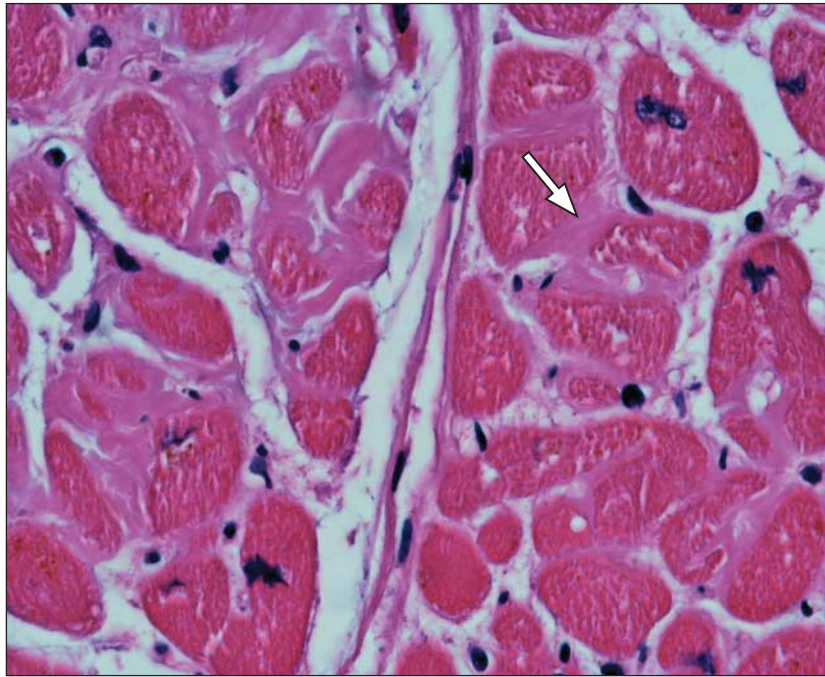
Direct invasion of the conduction system is rare. However, perivascular fibrosis secondary to microvascular ischemia commonly involves the sinus node and bundle of His.<sup>45,46</sup>

### CLINICAL CHARACTERISTICS

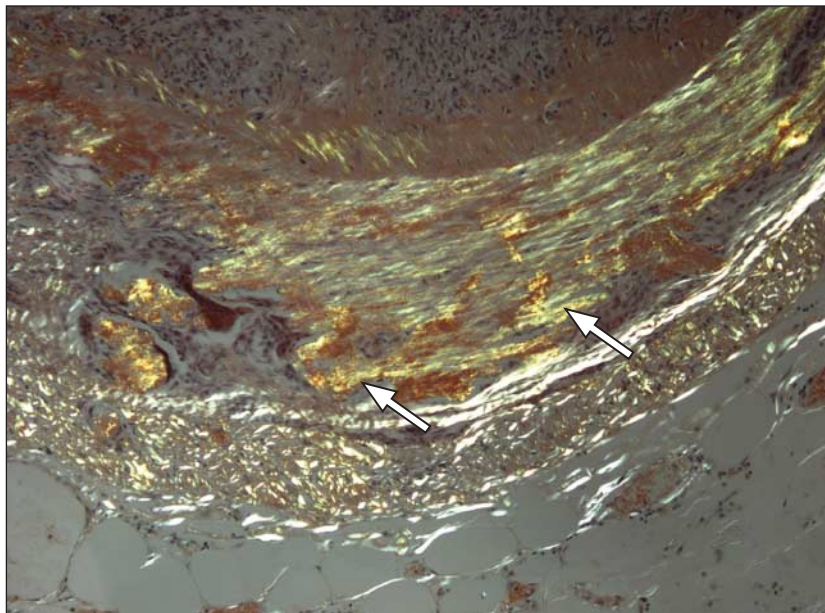
While systemic symptoms of amyloidosis are variable, cardiac findings are dominated by diastolic heart failure resulting from restrictive cardiomyopathy. Findings of right-sided heart failure predominate, including lower extremity edema, hepatomegaly, ascites, and elevated jugular pressure.<sup>7</sup> A murmur may be present from valvular insufficiency, and atrial fibrillation is common.

Anginal chest pain secondary to microvascular involvement with amyloid can also occur. Rare cases of amyloid manifesting as chest pain from intramural obstruction without evidence of myocardial deposition have been reported.<sup>47-51</sup>

Patients often have syncope and light-headedness resulting from autonomic dysfunction or arrhythmia in the setting of poor cardiac reserve. Amyloid deposition leads to obliteration of adrenergic input into the heart and alters baseline and



**Figure 1.** View of myocardium at microscopy. The amorphous extracellular amyloid deposits (arrow) stain pink, and they disrupt the organization of the heart muscle (hematoxylin-eosin, original magnification  $\times 400$ ).



**Figure 2.** View of myocardium under polarizing microscopy. Amyloid infiltration of the myocardium (arrows) forms an apple-green birefringence under polarizing microscopy owing to the  $\beta$ -pleated fibrillar structure (Congo red stain, original magnification  $\times 100$ ).

compensatory neurohormonal cardiac stimulation.<sup>52</sup> Often, autocorrection of hypertension is observed as relative hypotension develops.<sup>7</sup>

### DIAGNOSIS

Diagnosis of amyloidosis must be established by histologic analysis of tissue. Congo red staining identi-

fies amorphous pink deposits at light microscopy, which exhibit apple-green birefringence at examination under polarized microscopy (**Figures 1, 2, and 3**). If disease is limited to the heart, as in isoleucine 122 hereditary amyloidosis, examination of endomyocardial biopsy tissue is the only method of diagnosing the disease. Four en-

domyocardial biopsy samples ensure near 100% sensitivity for detecting disease.<sup>53</sup> Less invasive tissue sampling methods are available for diagnosing systemic amyloid disease. The rectal submucosa has been the traditional biopsy site, with a reported sensitivity of 75% to 85%, but can be complicated by bleeding or perforation.<sup>54,55</sup> Abdominal fat aspiration is without serious complications and is more sensitive (84%-88%) for diagnosing systemic amyloidosis.<sup>56-58</sup> Endomyocardial biopsy specimens should be analyzed if less invasive methods fail to enable diagnosis of amyloidosis.

Cardiac nonamyloidotic immunoglobulin deposition disease describes the nonfibrillary deposition of monoclonal immunoglobulin light chain in the setting of a plasma cell dyscrasia that mimics cardiac amyloidosis. Unlike amyloidosis, the biopsy specimen appears normal at microscopy with negative Congo red staining, and the disease usually improves with resolution of the blood disorder.<sup>59</sup>

### CARDIAC BIOMARKERS

Serum markers of cardiac injury or stress are often elevated in cardiac amyloidosis. Cardiac-specific troponin serum concentrations may rise because of myocyte necrosis from amyloid deposits and ischemia related to intramural vessel obstruction.<sup>60</sup> Natriuretic peptide levels are also elevated secondary to elevated filling pressures and possibly myocyte necrosis.<sup>61,62</sup> Elevations in the troponin and natriuretic peptide levels portend a poor prognosis; however, their usefulness in monitoring disease progression is unknown.<sup>63,64</sup>

### ELECTROCARDIOGRAPHY

Low-voltage QRS amplitudes in the precordial leads ( $\leq 10$  mV in all leads) or limb leads ( $\leq 5$  mV in all leads), a pseudoinfarction pattern (QS waves in consecutive leads), and conduction delays are common. The low-voltage amplitudes in relation to wall thickness result from the displacement of viable myocardium with amyloid deposits; however, they also occur in other condi-

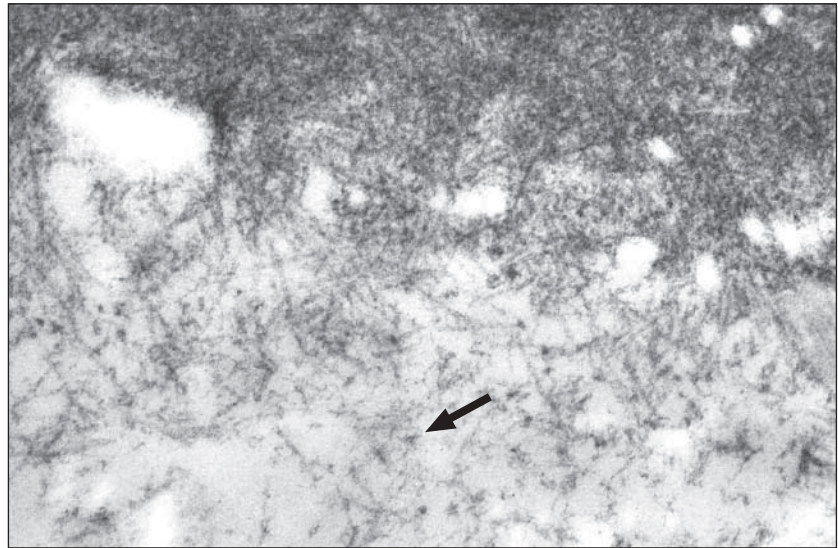
tions, including obesity, emphysema, hypothyroidism, effusion, myocardial fibrosis, and adrenal insufficiency.

Dubrey et al<sup>7</sup> reported that electrocardiograms for 75% of patients with cardiac amyloidosis demonstrated a pseudoinfarction pattern, and more than 70% exhibited low-voltage amplitudes. In another series, Murtagh et al<sup>65</sup> challenged these findings and found that only 47% of electrocardiograms demonstrated a pseudoinfarction pattern and that 46% exhibited low-voltage amplitudes. Numerous arrhythmias have been described, including atrial fibrillation, atrial flutter, ventricular tachycardia, atrioventricular block, prolonged QT interval, and junctional rhythm.<sup>7</sup>

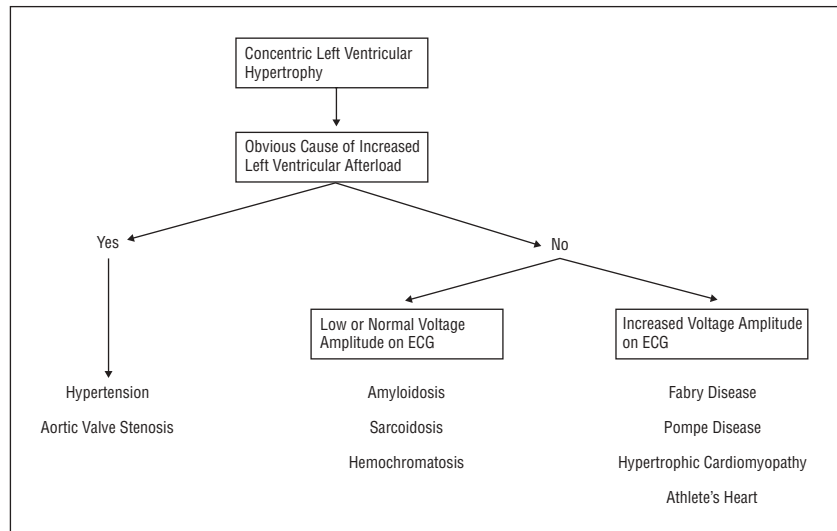
### ECHOCARDIOGRAPHY

Echocardiography offers a noninvasive diagnostic approach for monitoring progression of disease. To our knowledge, Siqueira-Filho et al<sup>66</sup> first described the “granular sparkling” refractile myocardium pathognomonic for the disease. Similar studies in patients with symptomatic disease revealed increased ventricular mass with thickening of the ventricular septal and free walls. Increasing wall thickness is inversely correlated with survival.<sup>67</sup> Septal thickening can often imitate hypertrophic obstructive cardiomyopathy.<sup>68,69</sup> Increased atrial septal wall thickening and granular sparkling myocardium are highly specific for differentiating cardiac amyloidosis from other causes of left ventricular hypertrophy.<sup>70</sup> Both atria are typically dilated and the ventricular chamber dimensions are normal. Systolic function can be depressed with extensive disease.<sup>66</sup>

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).<sup>71</sup> The decreased E:A ratio of flow velocities is an earlier sign of amyloid involve-



**Figure 3.** View of cardiac amyloidosis at electron microscopy. Note fibril mesh (arrow) within the myocardium (original magnification  $\times 7500$ ).



**Figure 4.** Approach to diagnosis of left ventricular hypertrophy. ECG indicates electrocardiogram.

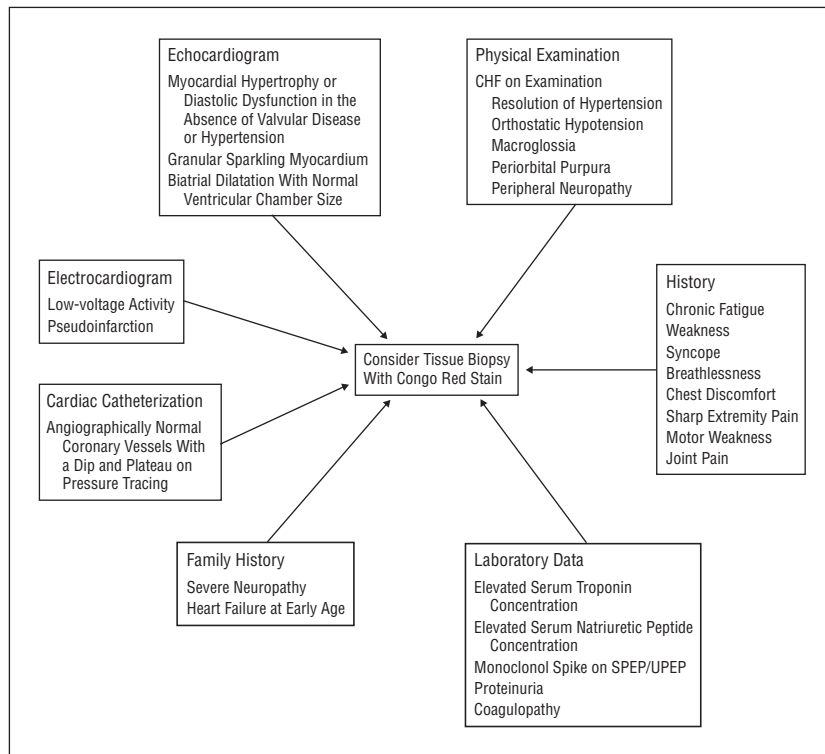
ment. As the heart wall becomes less compliant, left atrial pressures increase, as does early diastolic filling across the mitral valve, thus pseudo-normalizing the E:A ratio.<sup>72</sup>

The echocardiographic findings of cardiac amyloidosis mimic other causes of left ventricular hypertrophy; thus, it is helpful to combine diagnostic methods to identify cardiac amyloidosis.<sup>70</sup> Specifically, comparing the voltage on the electrocardiogram with the wall thickness on the echocardiogram can identify patients with infiltrative cardiomyopathy (**Figure 4**). Recent advances in echocardiography, including strain and strain rate Doppler imaging, may further improve

the sensitivity of detecting cardiac amyloidosis.<sup>73</sup>

### CARDIAC CATHETERIZATION

The coronary angiogram is usually normal because only in rare cases does amyloid involve the epicardial vessels. Right-sided heart catheterization enables measurement of intracardiac pressures for diagnosis of restrictive cardiomyopathy. Characteristic findings on the hemodynamic profile of extensive amyloid deposition in the myocardium are indistinguishable from other causes of restrictive cardiomyopathy. Diastolic pressure is elevated in both ventricles and right-sided



**Figure 5.** Constellation of symptoms and signs and objective data suggestive of cardiac amyloidosis. CHF indicates congestive heart failure; SPEP, serum protein electrophoresis; and UPEP, urine protein electrophoresis.

pressure tracings reveal a dip and plateau or square root sign.

### NUCLEAR SCINTIGRAPHY

Scintigraphic evaluation of the heart for uptake of radiolabeled phosphonates by amyloid was first explored more than 20 years ago.<sup>74,75</sup> Sensitivity for diagnosis has been variable; thus, the test has not been incorporated into the routine workup for cardiac amyloidosis.<sup>76</sup> A recent study, however, indicates that technetium Tc 99m-3,3,-diphosphono-1,2-propionic acid may be capable of differentiating TTR-associated amyloidosis from AL amyloidosis.<sup>77</sup>

### CARDIAC MAGNETIC RESONANCE IMAGING

Cardiac magnetic resonance imaging enables high-resolution 3-dimensional imaging of the myocardium and evaluation of chamber diameters, wall thickness and consistency, and regional wall motion.<sup>78</sup> In addition, decreased tissue signal intensity along with late subendocardium tissue enhancement by gadolinium are a result of myocardial

amyloid deposits and can help differentiate cardiac amyloidosis from other causes of cardiomyopathy.<sup>79,80</sup>

**Figure 5** shows the clinical and diagnostic findings that should raise suspicion for cardiac amyloidosis.

## TREATMENT

### Medical Therapy

The primary goal of medical therapy is relief of symptoms, and decongestion is achieved by cautious diuresis. Orthostatic hypotension and obliteration of sympathetic input preclude use of negative inotropic agents. Reports describe clinical deterioration when cardiac amyloidosis is treated with calcium channel blockers.<sup>81,82</sup> Similar reasoning extends to  $\beta$ -adrenergic receptor blockers, but this has not been demonstrated in the available literature. Digoxin binds to amyloid fibrils in vivo, and digoxin toxic effects have been reported.<sup>83,84</sup> The binding properties of digoxin to amyloid deposits may disrupt safe administration of the medication. Patients should be instructed to monitor their weight and their fluid and salt intake daily.

### Use of Devices

Permanent pacemaker implantation is indicated in patients meeting guidelines for device placement.<sup>85</sup> While cardiac pacing improves symptoms, it has not been shown to improve survival.<sup>86</sup> No data are available on biventricular pacing or automatic implantable cardioverter-defibrillators in this population.

### Chemotherapy and Stem Cell Transplantation

Treatment for AL includes oral chemotherapy (melphalan and prednisone) or high-dose chemotherapy with autologous stem cell transplantation. The benefit of oral chemotherapy is inadequate, and the greatest survival benefits are limited to patients without cardiac involvement.<sup>87,88</sup>

Stem cell transplantation has shown promising results for the treatment of primary amyloidosis.<sup>89,90</sup> Compared with other hematologic malignancies, transplant-related mortality is increased 5-fold in amyloidosis. The increased mortality has been attributed to extensive and diffuse systemic end-organ damage from amyloid deposits, and patients with extensive cardiac disease are not optimal candidates for therapy.<sup>89,91</sup>

### Solid Organ Transplantation

Heart transplantation is not generally accepted as a viable treatment for cardiac amyloidosis because limited case series have suggested poor long-term survival as a result of disease recurrence in the allograft; however, extracardiac amyloid disease and sepsis are common modes of death.<sup>92,93</sup> Adjuvant chemotherapy with transplantation has not been shown to improve mortality, but only limited data are available for modern regimens.<sup>94,95</sup> Newer mechanical circulatory support ventricular assist devices may offer an alternative palliative therapy in end-stage heart failure as destination therapy, but no specific use of such devices in amyloidosis has been reported.<sup>96</sup>

Liver transplantation removes the source of mutant TTR and is the only

known curative treatment for hereditary amyloidosis. More than 500 patients with hereditary amyloidosis have undergone transplantation surgery.<sup>97,98</sup> Five-year survival is reportedly 60% to 77%, with substantial improvement in neuropathy.<sup>99-102</sup> If extensive cardiac infiltration is also present, combined heart and liver transplantation has been successfully performed in selected patients.<sup>103</sup> Early identification of candidates for transplantation is critical because those with less severe manifestations of disease burden tolerate surgery better.<sup>104</sup>

## SUMMARY

Cardiac amyloidosis is a rare disorder that poses a diagnostic challenge because its clinical characteristics overlap with common causes of cardiac disease. Heightened clinical suspicion coupled with classic findings, including low-voltage amplitudes on electrocardiograms and hyperrefractile myocardium on echocardiograms, typically help in the diagnosis of late-stage disease. While successful therapeutic interventions are limited, early diagnosis portends a better response to current therapy and prolonged survival. Thus, awareness and understanding of amyloidosis is important for cardiologists and general practitioners alike.

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#### Correction

**Error in Table.** In the Original Investigation by Stewart et al titled "Effect of Exercise on Blood Pressure in Older Persons: A Randomized Controlled Trial," published in the April 11, 2005, issue of the ARCHIVES (2005;165: 756-762), there was an error in Table 4. The side headings "Abdominal total fat" and "Abdominal visceral fat" should be exchanged, keeping the values where they are.