How to Use Imaging

How to Image Cardiac Amyloidosis

Rodney H. Falk, MD; Candida C. Quarta, MD; Sharmila Dorbala, MD, MPH

Clinical Vignette

A 74-year-old man presented with decreasing exercise tolerance and mild ankle edema. He was previously fit but was now breathless on climbing 2 flights of stairs. He had no history of angina, orthopnea, or paroxysmal nocturnal dyspnea. His medical history included non–insulin-dependent diabetes mellitus treated for 10 years and mild hypertension. Six years earlier he had been diagnosed with a monoclonal gammopathy of unknown significance. At that time, a bone marrow biopsy showed 30% overall cellularity with 5% to 10% plasmacytosis (normal <4%) and immunoglobulin light-chain restriction. Approximately 3 years ago, he developed deep vein thrombosis and was treated with low-molecular-weight heparin. A year later, leg swelling occurred and was attributed to venous insufficiency. The following year, he developed progressive fatigue on exertion, and an abnormal ECG (Figure 1) led to a treadmill test that was considered normal. An echocardiogram showed concentric wall thickening (Movie 1 in the Data Supplement), and the possibility of cardiac amyloidosis was raised. A fat pad biopsy was negative for amyloid deposits. The bone marrow biopsy performed in 2005 (when his monoclonal gammopathy of unknown significance was diagnosed) was restained and was negative for amyloid. At that time, serum-free light chains were 108.9 mg/L (normal range, 5.7–26.3) with κ light chains of 13 mg/L (normal, 3.3–19) and an abnormal ratio of 0.12 (normal, 0.26–1.65). His brain natriuretic peptide measured 275 pg/mL. He was treated with oral diuretics, which improved leg swelling, but because of persistent symptoms, he sought medical care at our institution. On review of symptoms, he denied jaw claudication, symptoms of postural hypotension, easy bruising, or tongue swelling. He did give history suggestive of neuropathy with a leathery feeling in his feet but no numbness in his hands. Medications included metformin 500 mg twice a day, aspirin 80 mg daily, lisinopril 10 mg a day, glyburide 2.5 mg a day, atorvastatin 40 mg a day, and furosemide 40 mg a day for 3 to 4 days. He had no family history of heart failure. His father had died of a heart attack at the age of 69 years, and his mother had died at the age of 93 years. One sister had multiple myeloma and had died of pancreatic cancer. On physical examination, pulse was 80 bpm with a respiratory rate of 18 breaths per minute and blood pressure of 145/85 mm Hg seated and 130/60 mm Hg standing. The jugular venous pressure was elevated slightly with a prominent X and Y descent and a positive Kussmaul sign. Head and neck examination revealed submandibular swelling consistent with amyloid infiltration of the salivary glands. There was no macroglossia or periorbital bruising. Abdominal examination revealed a palpable smooth liver 2 to 3 fingerbreadths below the costal margin. Heart examination showed a nondisplaced apex without murmurs or additional sounds. There was bilateral dullness at the lung bases, suggesting effusions. He had mild right ankle edema with venous insufficiency. There was no hand wasting. Peripheral pulses were brisk.

This case represents a patient with a plasma cell dyscrasia, presenting with symptoms of progressive congestive heart failure and an echocardiogram suggestive of cardiac amyloidosis. The task is to confirm the suspected diagnosis and, if confirmed, to determine the type of amyloid because treatments and outcome differ among the different etiologic forms. The most common types of amyloid fibrils that affect the heart are derived from either light chains produced by a plasma cell dyscrasia (amyloid light-chain [AL] amyloidosis) or transthyretin (TTR), a protein mainly synthesized by the liver from either wild-type or mutant TTR-related amyloidosis. AL amyloidosis is in general characterized by a rapid and aggressive clinical course and systemic manifestations with cardiac involvement being associated with a worse prognosis. However, wild-type transthyretin-related amyloidosis (ATTR amyloidosis) is a slowly progressive disease that tends to affect the heart of elderly men almost invariably (the disease is commonly referred to as senile systemic amyloidosis). Mutant TTR amyloidosis is characterized by a high genotypic and phenotypic heterogeneity, with ≥100 etiologic mutations identified to date and with variable degrees of neurological, visceral, and cardiac involvement. If this patient does have cardiac amyloidosis, the coexisting plasma cell dyscrasia with elevated free light chains suggests AL amyloidosis. However, his age, the slowly progressive symptoms, and the disease limited to the heart are clinical features more consistent with wild-type ATTR amyloidosis.
Diagnosis of Cardiac Amyloidosis

Cardiac amyloidosis is often initially suspected in a patient presenting with unexplained heart failure symptoms and typical findings on ECG and 2-dimensional (2D) transthoracic echocardiography. Once suspected, advanced echocardiographic techniques, such as strain imaging, can be used, as can several other imaging modalities, although the diagnosis has to be eventually confirmed histologically, often requiring endomyocardial biopsy and special staining.

ECG findings in cardiac amyloidosis may include a low QRS voltage pattern (QRS amplitude, <1 mV in all the precordial leads or <0.05 mV in all the standard limb leads; 56%), pseudoinfarction patterns (60%), supraventricular arrhythmias (mainly atrial fibrillation), atrioventricular or intra- and interventricular conduction defects, and unusual axis deviations. The presence of a low-voltage ECG, despite increased left ventricular (LV) wall thickening on echocardiography, is highly suggestive of cardiac amyloidosis (particularly AL amyloidosis; Figure I in the Data Supplement), and a typical voltage:mass ratio has been described. Although the precise reasons for the low-voltage ECG are not known, myocyte atrophy and cardiac toxicity exerted by circulating light chains are possible contributing factors. Of note, the ECG may not demonstrate low-voltage complexes in individuals with ATTR

Table 1. Typical Echocardiographic Features of Cardiac Amyloidosis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Characteristic granular/sparkling appearance of the LV myocardium</td>
<td>Not specific. Need to differentiate from hypertrophic and other infiltrative diseases*</td>
</tr>
<tr>
<td>Increased LV wall thickness</td>
<td>Results from amyloid infiltration of interstitial space and may relate to amyloid burden</td>
</tr>
<tr>
<td>Decreased LV end-diastolic volumes</td>
<td>Leads to reduced stroke volume despite near-normal LVEF</td>
</tr>
<tr>
<td>Typically preserved or mildly reduced LVEF</td>
<td>LVEF may decrease in end-stage disease</td>
</tr>
<tr>
<td>High E/A ratio</td>
<td>Is seen because of restrictive pathophysiology, but a reduced amplitude A wave may suggest poor atrial function and higher risk of thrombus formation*</td>
</tr>
<tr>
<td>Shortened mitral E deceleration time (restrictive filling pattern), high E/e′ ratio</td>
<td>High E/e′ suggests increased left atrial pressures</td>
</tr>
<tr>
<td>Increased left and right atrial volumes and reduced atrial function</td>
<td>A common feature. Also imaged on CMR</td>
</tr>
<tr>
<td>LS in the left ventricle is impaired and worse at the base and mid-ventricular regions when compared with the apex</td>
<td>Atrial strain can be significantly reduced</td>
</tr>
<tr>
<td>RV thickening, reduced RV myocardial velocities on tissue Doppler imaging, and reduced RV LS</td>
<td>Specific patterns of LV LS may differentiate amyloid from aortic stenosis and hypertrophic cardiomyopathy*</td>
</tr>
<tr>
<td>Reduced tricuspid annular plane excursion despite normal RV end-diastolic dimension</td>
<td>TAPSE and RV LS are early indicators of cardiac involvement in patients with systemic AL amyloidosis16</td>
</tr>
<tr>
<td>Valve thickening</td>
<td>RV LS may be an independent predictor of cardiac death*</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Atrial septal thickening</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Dynamic LV outflow tract obstruction</td>
<td>A characteristic feature of cardiac amyloidosis</td>
</tr>
</tbody>
</table>

AL indicates amyloid light-chain; CMR, cardiac magnetic resonance; LS, longitudinal strain; LV, left ventricular; LVEF, LV ejection fraction; RV, right ventricular; and TAPSE, tricuspid annular plane excursion.

*Hypertrophic cardiomyopathy, hypertensive heart disease with or without renal failure, Anderson Fabry’s disease, mucopolysaccharidosis, Friedreich ataxia.
amyloidosis, particularly in patients with underlying hypertensive heart disease.

Echocardiography is the cornerstone for the diagnosis and management of patients with known or suspected cardiac amyloidosis. Typical echocardiographic features (Table 1) may lead us to consider cardiac amyloidosis in patients with unexplained increased LV wall thickness. Echocardiography also provides valuable information about amyloid burden, LV filling pressures, and other hemodynamic features that are vital for the initial evaluation, management, and follow-up of these patients.

Increased LV wall thickness on echocardiography, often with a restrictive filling pattern, is a classic feature, but it indicates advanced cardiac amyloidosis. The clinical manifestations of cardiac amyloidosis are manifold, and misdiagnosis as true LV hypertrophy is frequent; hence, it is important to be vigilant for the typical echocardiographic findings that suggest amyloidosis. Coexisting right ventricular free wall or atrial septal thickening strongly suggests an infiltrative cardiomyopathy because these are rarely seen in association with true LV hypertrophy. Also, transthyretin amyloidosis caused by mutant TTR (variant V122I, valine to isoleucine substitution at position 122) is common among blacks (3%–4%) and usually manifests with heart failure symptoms in the sixth or seventh decades; unexplained LV thickening in these individuals should be carefully evaluated, including genetic testing, before labeling as hypertensive heart disease. Patients with ATTR amyloidosis tend to demonstrate greater degrees of LV thickening when compared with those with AL amyloidosis (Figure II in the Data Supplement). However, there is an overlap, and the echocardiographic features AL and ATTR amyloidosis are indistinguishable despite a much better prognosis in the latter.

When compared with conventional mitral inflow spectral Doppler velocities (E wave and A wave), left4 and right5 ventricular tissue Doppler imaging (early diastolic parameters of e' and a'; Figure 2), tricuspid annular plane excursion6 (Figure 3), and strain imaging of the right5,6 and left ventricles (longitudinal 2D strain; Figure 4) are more insightful and sensitive for the early identification of cardiac amyloidosis. A specific pattern of longitudinal strain characterized by worse longitudinal strain in the mid and basal ventricle with relative sparing of the apex4 may help distinguish LV infiltration because of amyloid from true ventricular hypertrophy of hypertensive heart disease or hypertrophic cardiomyopathy.7,8 In a recent study,9 although there was an overlap, an apex:base ratio of longitudinal systolic strain of >2.1 distinguished cardiac amyloidosis from other causes of LV hypertrophy, such as hypertension, Fabry disease, Friedreich ataxia with a sensitivity 88%, specificity 85%, positive predictive value 67%, and negative predictive value 96%. Furthermore, abnormal longitudinal strain predicted

Figure 2. The value of tissue Doppler imaging in early diagnosis of cardiac amyloidosis. Images from a patient with light-chain amyloidosis demonstrate relatively normal mitral inflow parameters (E and A waves with normal deceleration time), but abnormal pulmonary venous Doppler flow (diastolic predominance) and abnormal tissue Doppler images showing a reversed e’ and a’ ratio, suggesting pseudonormalization of transmitral flow. E/e’ is elevated consistent with elevated left ventricular filling pressure. HR indicates heart rate.
worse survival in patients with AL amyloidosis. Koyama and Falk demonstrated that, in 119 patients with systemic AL amyloidosis (70 with cardiac amyloidosis), abnormal basal segment longitudinal strain was an independent predictor of survival. In a subsequent study of 206 patients with systemic AL amyloidosis, a 2D LV global longitudinal strain of <11.78% was shown to be an independent predictor of survival.

Of note, echocardiography can reveal the presence of left atrial dysfunction despite sinus rhythm, increasing the risk of stasis and thrombus formation; anticoagulation should be considered in individuals with amyloidosis who are in sinus rhythm but demonstrate impaired atrial function. Impairment of left atrial function may be identified by small late diastolic mitral inflow velocity (small A wave; Figure 5; Movie II in the Data Supplement), reduced atrial ejection fraction, or reduced atrial strain (Figure 6). Modesto et al demonstrated abnormal septal left atrial strain in 60% of subjects with cardiac amyloidosis. Left atrial systolic strain was significantly lower in cardiac amyloid subjects when compared with that in control subjects (peak lateral strain, 5.5±4% versus 19±4%; P<0.0001).

Cardiac MRI (CMR) provides high spatial resolution and high signal:noise ratio images without the limitation of poor echocardiographic windows. Increased myocardial mass, atrial structure, as well as atrial and ventricular function and other typical morphological features of restrictive cardiomyopathy can be imaged (Table 1; Figure 7; Movie III in the Data Supplement). Additional findings of amyloidosis on CMR rely on tissue characterization: late gadolinium enhancement (LGE), abnormally prolonged T1 times (before or after contrast), and an expansion of the extracellular volume.

Gadolinium kinetics are abnormal in cardiac amyloidosis, with a faster washout of gadolinium from myocardium and blood pool when compared with that in nonamyloid control subjects. LGE images are typically obtained ≈5 minutes after infusion of 0.1 to 0.2 mmol/kg of gadolinium injection using a previously validated inversion recovery pulse sequence. Characteristic LGE patterns are observed in the left ventricle and the atria and permit an earlier diagnosis of cardiac amyloidosis (Table 2). LGE on CMR identified cardiac involvement in 47% of patients with known systemic amyloidosis and normal wall thickness on echocardiogram. In contrast, among patients with documented cardiac amyloidosis based on echocardiography or endomyocardial biopsy, LV LGE was universal in patients with both AL and ATTR; right ventricular LGE was present in all patients with ATTR and in 72% of patients with AL. Diffuse LGE in the atrial wall may be a characteristic feature of cardiac amyloidosis.

Subendocardial T1 is shortened in cardiac amyloidosis, and T1 mapping may identify cardiac involvement at an earlier stage when compared with overt LGE images. Indeed, on T1 mapping, if the myocardium crosses the null point (becomes black) at a T1 time point before the blood pool, it indicates the presence of diffuse global hyperenhancement and is characteristic of cardiac amyloidosis. In a recent study, rapid visual T1 assessment was performed ≥1 to 2 minutes ≈5 to 10 minutes after gadolinium administration. In this study, among subjects with cardiac amyloidosis and LGE, a pattern of diffuse LGE was noted in 81%; both diffuse LGE (hazard ratio, 6.0; 95% confidence interval, 3.01–12.1; P<0.0001) and any LGE (hazard ratio, 6.5; 95% confidence interval, 3.0–14.2; P<0.0001) were independently predictive of mortality.

Native (precontrast) T1 mapping techniques have been studied in AL and ATTR cardiac amyloidosis, using a shortened modified look-locker inversion recovery sequence. Although there was an overlap, the native T1 times in patients with AL cardiac amyloidosis (1130±68 ms) and ATTR cardiac amyloidosis (1097±43 ms) were significantly prolonged when compared with hypertrophic cardiomyopathy (1026±64 ms; P<0.0001) and normal subjects (967±34 ms; P<0.0001). Native T1 mapping techniques may be particularly helpful in
patients with renal dysfunction (because of risk of gadolinium toxicity and nephrogenic systemic fibrosis).

Direct quantification of the volume of distribution of gadolinium (myocardial extracellular volume [ECV]) by CMR is determined by pre- and postcontrast R1 (1/T1) for the blood and myocardium taking into account serum hematocrit. Serial R1 measurements after contrast injection can improve the accuracy of ECV measurement. The expansion of ECV is demonstrated even in myocardial segments without apparent LGE, suggesting incremental diagnostic value. In patients with AL amyloid, ECV correlated directly with LV mass, tissue Doppler imaging S wave, brain natriuretic peptide, and troponin levels, suggesting that ECV may represent a marker of amyloid burden in the heart. T2-weighted sequences show hypointense signal in cardiac amyloidosis, and a lower T2 ratio was independently associated with shortened survival.

LGE, T1 prolongation, and ECV expansion may be observed in amyloidosis, other infiltrative diseases, inflammation, and fibrosis. Therefore, although certain LGE patterns, T1 times (native or postcontrast), and ECV values are sensitive to diagnose amyloidosis, they are not specific and cannot exclusively obviate the need for a definitive histological diagnosis. Notably, a difficulty in nulling of myocardial signal on the LGE images, despite the use of a T1 scout, may suggest underlying amyloid (especially if the blood pool images are unusually dark indicating rapid contrast sequestration) rather than suboptimal image quality. CMR is contraindicated in certain patients with cardiac devices (pacemakers and implantable cardioverter defibrillators) and claustrophobia. Atrial fibrillation may limit image quality of gated sequences. Patient cooperation is required for brief periods of breath holds and for ≈45-minute scanning. Whether a contrast-enhanced gated cardiac computed tomographic scan may provide at least some of the information as a CMR scan with short scan time, especially in patients with intracardiac devices, needs to be further evaluated.

Radionuclide imaging of cardiac amyloidosis can be performed using single-photon emission computed tomography— or positron emission tomography—based radiotracers. Among single-photon

Figure 4. Left ventricular strain imaging in cardiac amyloidosis. Apical 4-chamber peak systolic strain image illustrating a classic strain pattern of relatively well-preserved apical strain (green and blue lines) with significant basal impairment (red and yellow lines). This is seen in the series of curves and the bull’s-eye color-coded strain image. FR indicates frame heart; and HR, heart rate. Reprinted from Lubberink et al with permission of the publisher. Copyright ©2013, the Society of Nuclear Medicine and Molecular Imaging, Inc.

Figure 5. Loss of atrial function in cardiac amyloidosis. A transmural Doppler image (A) showing a normal deceleration time but a small A wave in a patient with transthyretin amyloidosis in sinus rhythm who presented with stroke because of thrombus formation related to left atrial dysfunction. The pulmonary venous flow in a patient with transthyretin amyloidosis (B) demonstrating almost exclusive diastolic flow because of restrictive filling—the atrium functions as a conduit with loss of contractile and reservoir function. This patient also had spontaneous echo contrast in the left ventricle (Movie II in the Data Supplement). HR indicates heart rate.
emission computed tomographic tracers, direct amyloid imaging agents (I-123–labeled serum amyloid P component), bone imaging agents (Tc-99m pyrophosphate or Tc-99m 3,3-diphosphono-1,2-propanodicarboxylic acid [DPD]), and agents to image cardiac sympathetic innervation (I-123 metaiodobenzylguanidine) are available for use. Metaiodobenzylguanidine is a norepinephrine analog, which is actively taken up by sympathetic nerve terminals and not further metabolized, enabling us to image cardiac sympathetic innervation. I-123–labeled serum amyloid P component scans have been used in systemic amyloidosis to image noncardiac organs, but the technique is not of proven value for imaging cardiac amyloidosis because of limited signal:noise ratio in the heart. Radionuclide scans (Figure 8A) may be helpful to diagnose cardiac amyloidosis in patients who cannot undergo a CMR study for any reason.

Bone imaging agents, such as Tc-99m pyrophosphate or Tc-99m DPD, are probably taken up via a calcium-mediated mechanism and seem to be helpful to identify (both mutant and wild type) ATTR amyloidosis. In 1 study, Tc-99m DPD was able to differentiate between AL and ATTR amyloidosis noninvasively, with patients with all ATTR showing DPD uptake and none of the patients with AL showing DPD uptake (Figure III in the Data Supplement). It has been subsequently documented that DPD is taken up in the heart of some patients with AL amyloidosis (for reasons that remain unclear), but patients with ATTR amyloid undoubtedly show a more intense uptake than those with AL disease. DPD is not available in the United States, but Tc-99m is, and it is avidly taken up by the heart in ATTR amyloid cardiomyopathy. Bokhari et al showed that a heart:contralateral lung ratio of 1.5 on Tc-99m pyrophosphate imaging distinguished ATTR amyloidosis (≥1.5) from AL amyloidosis (<1.5). The combination of increased wall thickness and high heart to whole-body Tc-99m DPD uptake is also a significant independent predictor of major adverse cardiovascular events. Therefore, when ATTR amyloidosis of the heart is suspected based on the clinical presentation, Tc-99m pyrophosphate/DPD scan may be preferable to a CMR study, recognizing that while a positive Tc-99m pyrophosphate/DPD scan suggests ATTR amyloidosis, a negative Tc-99m pyrophosphate/DPD scan does not rule out AL cardiac amyloid. Also, because bone imaging agents are not taken up by normal myocardium, blood pool activity may be noted in negative scans, and this must be distinguished from active myocardial uptake in amyloidosis (Figure 8B).

I-123 metaiodobenzylguanidine scintigraphy is used to image cardiac sympathetic denervation (not amyloidosis). Myocardial sympathetic denervation may be an early feature of cardiac involvement particularly in individuals with transthyretin familial amyloid polyneuropathy. Familial amyloid polyneuropathy is an autosomal dominant disease with single point mutations to the transthyretin gene presenting with neuropathy (sensorimotor and autonomic neuropathy, V30M) with or without cardiac involvement or isolated cardiac involvement (V122I). Also, in 1 recent study of 142 individuals with familial amyloid neuropathy V30M variant, a heart:mediastinal ratio of <1.6 when compared with ≥1.6 on
I-123 metaiodobenzylguanidine scintigraphy identified individuals with a high mortality risk (hazard ratio, 7.9; 95% confidence interval, 3.38–15.2).

Direct imaging of amyloid fibrils, using positron emission tomographic tracers of C-11 Pittsburgh B compound\(^3\) (Figure IV in the Data Supplement) and F-18 florbetapir (Figure 9), seems promising and is currently under investigation. These direct amyloid imaging agents offer the potential quantitation of amyloid burden and identification of early cardiac involvement before overt cardiac structural changes.

**Table 2. Typical CMR Features of Cardiac Amyloidosis**

<table>
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<tr>
<th>Parameters</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Characteristic morphological features of cardiac amyloidosis/restrictive cardiomyopathy as listed in Table 1</td>
<td>Better resolution images than echocardiography</td>
</tr>
<tr>
<td>LV LGE</td>
<td>No limitation of difficult echo windows</td>
</tr>
<tr>
<td></td>
<td>Diffuse and subendocardial LGE of the LV myocardium is more common than patchy focal delayed enhancement</td>
</tr>
<tr>
<td></td>
<td>May be an early feature of cardiac involvement when compared with increased wall thickness</td>
</tr>
<tr>
<td>Atrial LGE and function</td>
<td>A characteristic feature of cardiac amyloidosis</td>
</tr>
<tr>
<td></td>
<td>Atrial function can be studied well with CMR</td>
</tr>
<tr>
<td>T1 mapping</td>
<td>Subendocardial T1 relaxation time may be shortened in cardiac amyloidosis</td>
</tr>
<tr>
<td></td>
<td>This is an early feature of cardiac amyloid involvement</td>
</tr>
<tr>
<td>Extracellular volume estimation based on T1 mapping and hematocrit measures</td>
<td>Extracellular volume expansion may permit an early diagnosis of cardiac amyloid even before overt LV LGE</td>
</tr>
</tbody>
</table>

CMR indicates cardiac magnetic resonance; LGE, late gadolinium enhancement; and LV, left ventricular.
Is There a Gold Standard for the Noninvasive Diagnosis of Cardiac Amyloidosis?

The definitive diagnosis of amyloidosis is generally accepted as requiring a biopsy with the typical appearance of amyloid deposits, staining with amyloid-specific stains (classically Congo red, with apple-green birefringence under polarized light). A positive myocardial biopsy is indicative of amyloid in the heart but with the caveat that elderly patients have a high prevalence of cardiac amyloid deposits, which may be infrequent and patchy and of no clinical significance. Once there is enough amyloid in the heart to cause ventricular wall thickening, endomyocardial biopsy almost always contains a significant amount of amyloid. However, in unskilled hands, with inadequate staining, false-negative reports may occur. Thus, if noninvasive imaging is strongly suggestive of amyloidosis, particularly in the setting of a typical clinical picture, a negative cardiac biopsy should not be viewed as ruling out the diagnosis, and an expert second-opinion review should be sought, with consideration of rebiopsy in selected cases. A typical noninvasive abnormality on cardiac imaging, whether echocardiography, magnetic resonance imaging, or possibly technetium pyrophosphate imaging in transthyretin amyloidosis, is specific enough in the setting of a positive noncardiac biopsy, such as a fat pad biopsy or renal biopsy, to conclude that cardiac amyloid is definitely present in clinically significant amounts. Similarly, it is almost certain that a strongly positive Tc-99m pyrophosphate scan in a patient who tests positive for a variant transthyretin known to be amyloidogenic will have ATTR cardiac amyloidosis.

We do not, however, think that there is a single noninvasive test that can be considered either the ultimate gold standard...
for the diagnosis or even a gold standard when considered against other noninvasive testing modalities. Most commonly, the noninvasive diagnosis of cardiac involvement in patients with systemic amyloidosis is suspected initially by echocardiography based on increased wall thickness and a restrictive LV filling pattern. Typical LV longitudinal strain abnormalities with preserved apical strain when compared with basal strain may strengthen the likelihood that increased LV mass is because of amyloid infiltration, yet there may be overlap with other LV diseases associated with true hypertrophy. Characteristic patterns of LGE on CMR, increase in ECV fraction, and prolongation of the T1 times may suggest cardiac amyloidosis even before overt LV wall thickening, but by themselves they are also not pathognomonic for this diagnosis. Radionuclide techniques with specific binding to components of amyloid can identify systemic amyloid deposits. However, the amyloid-specific radiotracer used (I-123 serum amyloid P component) is not available in North America nor is it useful for imaging cardiac amyloidosis because of blood pool activity. The diagnostic accuracy of amyloid-specific positron emission tomography radiotracers, F-18 florbetapir and C-1 Pittsburgh B compound, is still currently under investigation. Although bone imaging radiotracers (Tc-99m DPD and Tc-99m pyrophosphate) are excellent for imaging ATTR cardiac amyloidosis, to the extent that they may identify early cardiac involvement in asymptomatic familial ATTR disease when other imaging techniques are negative, they are poorly, or not at all, taken up by the myocardium in individuals with AL cardiac amyloidosis. Thus, rather than seeking a gold standard for diagnosing this disease, the clinician and imaging specialist is better served by taking a broader approach, using where appropriate multiple modalities while considering the clinical picture and the appropriate timing of cardiac biopsy. A diagnostic algorithm to evaluate patients with suspected cardiac amyloidosis is shown in Figure 10.

**Approach to the Patient Described Above**

The echocardiogram was repeated and showed an echogenic granular myocardium with moderate concentric LV thickening (14 mm), ejection fraction of 60%, a restrictive filling pattern, with an early diastolic mitral tissue Doppler velocity ($e'$) of 0.06 cm/s (Movie I in the Data Supplement). There was no aortic stenosis. Both atria were enlarged, and there was moderate mitral valve regurgitation. Longitudinal strain imaging
by speckle tracking revealed a typical pattern of apical sparing, with severe basal longitudinal dysfunction and depressed global longitudinal strain (Figure 4). A bone marrow biopsy was repeated, and it showed a moderately hypocellular marrow (80% fat), with ≈10% plasma cells. Immunoperoxidase staining revealed monotypic CD138-positive plasma cells positive for immunoglobulin λ light chains and IgG heavy chain. There was a corresponding IgG λ paraprotein in the serum detected by immunofixation. Although this hematologic picture strongly suggested a diagnosis of AL amyloidosis, the clinical picture of isolated cardiac amyloidosis in an older man was more akin to the presentation of wild-type ATTR amyloidosis. Hence, a Tc-99m pyrophosphate scintigraphy was performed and strongly positive (Figure 8A), suggesting a diagnosis of ATTR amyloidosis. Endomyocardial biopsy was then performed and documented an extensive amyloid deposition along with moderate myocyte hypertrophy. Immunofluorescence staining of the amyloid deposits, performed on a fresh sample of myocardium, was strongly positive for transthyretin and negative for IgG, IgM, IgA, κ light chain, λ light chain, and protein A. Because of the unusual clinical picture, proteomics analysis was performed on the biopsy samples, which confirmed transthyretin-derived amyloidosis. ATTR genotyping showed no evidence of a mutant protein, thereby confirming a diagnosis of senile systemic amyloidosis.

In summary, the plasma cell dyscrasia in this patient, although usually highly suggestive of AL amyloidosis when associated with a positive biopsy for amyloid and an abnormal free light-chain ratio, was an unrelated phenomenon. It represents either a monoclonal gammopathy of unknown significance, which is found in approximately 5% of the elderly population, or a borderline smouldering multiple myeloma. The impression that the disease was clinically more like senile systemic amyloidosis led to performance of the Tc-99m PYP, which by strengthening the clinical impression in the face of conflicting hematologic data led to the ultimate performance of definitive molecular analysis of biopsy tissue, confirming ATTR and thereby sparing the patients inappropriate chemotherapy.

Acknowledgments

We are grateful to Dr Raymond Y. Kwong for his review and comments on the cardiac magnetic resonance imaging.

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References

Key Words: amyloidosis • cardiac imaging techniques • echocardiography • multimodal imaging • radionuclide imaging
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Supplemental Figure Legends

**Supplemental Figure 1.** Low voltage QRS complexes in a patient with AL amyloidosis.

**Supplemental Figure 2 A and 2B.** 2A: A transesophageal echocardiogram image (bicaval view) from a patient with ATTR amyloidosis, showing interatrial septal thickening from amyloid deposition. 2B: A transaxial prospectively gated contrast enhanced multidetector cardiac CT image from a patient with familial TTR cardiac amyloidosis showing interatrial septal thickening. Note that the Hounsfield unit measurements from the interatrial septum (48 HU) are significantly higher than epicardial fat (-21 HU) suggesting amyloid deposits.

**Supplemental Figure 3. Tc-99m DPD imaging in cardiac amyloidosis.** Tc-99m DPD\(^1\)(3A) images in cardiac amyloidosis. Reprinted from Perugini et al\(^1\) with permission of the publisher. Copyright © 2005, Elsevier. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

**Supplemental Figure 4. Radionuclide imaging in cardiac amyloidosis.** C-11 PiB (Pittsburgh B compound) images\(^2\) in cardiac amyloidosis. C-11 PiB images are shown in the top row and myocardial perfusion images in the bottom row. Reprinted from Antoni et al\(^2\) with permission of the publisher. Copyright © 2013, Society of Nuclear Medicine and Molecular Imaging, Inc. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
Supplemental Video Legends

**Supplemental Video 1.** Apical 4 - chamber view of echocardiogram demonstrating biatrial enlargement, increased thickness of the left and right ventricles with normal ejection fraction.

**Supplemental Video 2.** Spontaneous echo contrast. This apical 4-chamber view echocardiogram shows spontaneous echo-contrast in the left ventricle during diastole from impaired atrial contraction and poor ventricular relaxation.

**Supplemental Video 3.** A 4 chamber view gated cardiac MRI study demonstrates the typical morphological features of increased left ventricular wall thickness, atrial enlargement and pleural and pericardial effusions.