Evaluation of Cardiac Amyloidosis: A Pictorial Review of Echocardiographic, MRI and Nuclear Findings

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Learning objectives

The purpose of this poster is to
A) Review the clinical presentation and subtypes of cardiac amyloidosis

B) Illustrate the novel diagnostic and surveillance approaches to cardiac amyloidosis using strain-echocardiography, nuclear and magnetic resonance imaging (MRI)

Background

Amyloidosis is an infiltrative disorder characterized by deposition of misfolded amyloid fibrils in various organ systems. Cardiac involvement (cardiac amyloidosis) is common, and classically presents as a restrictive cardiomyopathy. Early detection of cardiac dysfunction is imperative for timely diagnosis and initiation of therapy. It is characterized by 4 subtypes that differ by their etiologies, severity of symptoms, prognosis and treatment (table 1). Primary or AL amyloidosis results from deposition of excess light chain immunoglobulins from overproduction of monoclonal plasma cells in the bone marrow. It is the most common subtype, and affects the heart in up to sixty percent cases [1]. It is also associated with a dismal prognosis, with a mean survival of four months if heart failure is present at diagnosis [1]. Approximately half of the patients with AL amyloidosis die from a cardiac etiology. In contrast, the familial (ATTR) subtype results from misfolding of hepatic transthyretin protein into amyloid protein due to genetic mutations. It is associated with a more favorable prognosis with a median survival of 2 years in absence of liver transplantation [1]. The senile subtype although present in up to 25% of patients older than 80 years, often does not manifest with any symptoms, and is often only identified on autopsy studies. Median survival is 75 months after diagnosis [1]. While treatment for the AL subtype is chemotherapy, treatment for senile amyloidosis is typically restricted to symptomatic relief and conventional therapy for heart failure. Although orthotropic liver transplant is an established treatment for patients with ATTR familial amyloidosis, several trials targeting amyloid fibril production and stabilization are underway. Novel drugs aimed at reducing the production of TTR protein through silencing the mRNA in the liver, and stabilizing the TTR tetramer precursor protein are currently in trials, and may potentially revolutionarize the treatment of TTR amyloidosis.

The diagnosis of cardiac amyloidosis requires a high index of suspicion as patients often present with non-specific symptoms such as pedal edema and poor appetite. In addition, many may remain asymptomatic until the late stages of disease. Endomyocardial biopsy continues to be the gold standard for diagnosis, but is an invasive procedure associated risks of ventricular wall perforation, cardiac tamponade, arrhythmia, pneumothorax and
bleeding. The role of cardiac imaging is widely growing and plays an important role in diagnosis, prognosis and management of patients with cardiac amyloidosis.

**Clinical Cardiac Manifestations**

Amyloid infiltration of the myocardium results in thickening of the left and right ventricular walls resulting in a restrictive physiology. Patients with cardiac amyloidosis, particularly of the AL subtype often present with signs of rapidly progressive diastolic heart failure. Dyspnea on exertion, hepatic congestion, ascites, pleural effusion and peripheral edema secondary to biventricular failure may be present. Amyloid deposition may also result in thickening of the interatrial septum. Infiltration of cardiac valves leads to diffuse thickening of the leaflets and may be accompanied by valvular regurgitation. Anginal chest pain may be present, and is a manifestation of intra-cardiac small vessel involvement. Infiltration of the electrical conduction system may lead to bundle branch, atrioventricular or sino-atrial node blocks. Syncope, if present, is associated with a poor prognosis due to inability to increase cardiac output in the setting of restrictive cardiomyopathy, arrhythmia, or autonomic dysfunction. Patients may rarely also present with sudden cardiac death as the first presenting symptom. Patients with senile amyloidosis typically have greater increase in mean left ventricular wall thickness and lower ejection fraction with normal ECG voltage compared to other amyloid subtypes.

**ECG Manifestations**

Presence of low or normal voltage ECG in presence of increased wall thickness by cardiac imaging should raise suspicion for cardiac amyloidosis (figure 1). Other ECG features include presence of pseudoinfarct pattern (QS waves in precordial or inferior leads), intraventricular conduction delay (figure 2), bundle branch blocks, atrioventricular or sino-atrial node blocks. These changes represent infiltration of the myocardial conduction system with inactive amyloid protein. Rhythm disturbances especially atrial fibrillation is very common (figure 2) and may be secondary to amyloid deposition and restrictive cardiomyopathy. Decreased heart rate variability may also be present especially in the AL subtype.

**Images for this section:**
<table>
<thead>
<tr>
<th>Type</th>
<th>Composition</th>
<th>Etiology</th>
<th>Extra Cardiac Manifestations</th>
<th>Cardiac Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary AL</td>
<td>Immunoglobulin light chain fragments</td>
<td>Clonal bone marrow plasma cells. Underlying cell dyscrasia (multiple myeloma)</td>
<td>Hepatomegaly, renal failure, neuropathy, autonomic dysfunction, macroglossia, ecchymosis, carpal tunnel syndrome</td>
<td>Clinical cardiac involvement in up to 34% cases. Presents with HFPEF, arrhythmia, syncope, ischemic heart disease</td>
</tr>
<tr>
<td>Familial ATTR</td>
<td>Mutant transthyretin protein</td>
<td>Misfolding of hepatic transthyretin protein into amyloid protein due to genetic mutations</td>
<td>Neuropathy, hepatic failure, renal failure, autonomic dysfunction</td>
<td>Commonly results in cardiac involvement</td>
</tr>
<tr>
<td>Senile ATTR</td>
<td>Wild-type transthyretin protein</td>
<td>Age related protein deposition (rarely occurs in people ≤ 70 years)</td>
<td>Predominantly cardiac involvement</td>
<td>Few clinical symptoms, often diagnosed at autopsy</td>
</tr>
<tr>
<td>Secondary/ Reactive AA</td>
<td>Amyloid associated protein (acute phase reactant)</td>
<td>Chronic inflammatory conditions (rheumatoid arthritis, crohns disease, osteomyelitis)</td>
<td>Renal failure proteinuria</td>
<td>Cardiac involvement in only 2% cases.</td>
</tr>
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</table>

**Table 1:** Table 1: Overview of the Amyloid Subtypes
Fig. 1: ECG of a patient with primary AL amyloidosis. Low voltage, and QS waves in septal leads is noted. Echocardiography demonstrated thickened left ventricular walls.
Fig. 2: ECG of a patient with AL amyloidosis. Atrial fibrillation, non-specific intraventricular conduction delay, and pseudoinfarct pattern with QS waves in anteroseptal and inferior leads is seen.
Findings and procedure details

Echocardiography

Echocardiography remains the first line imaging modality for evaluation of patients with cardiac amyloidosis given the ease of image acquisition, low cost, unparallel diastolic assessment, no need for any nephrotoxic contrast and ease of serial assessment. A constellation of findings are classically seen and include symmetric left ventricular wall thickening with a speckled appearance to the myocardium, small left ventricular chamber volume, preserved ejection fraction, thickening of the right ventricular wall, interatrial septum and valve leaflets, and biatrial enlargement (figures 3-8). Pericardial and pleural effusions are commonly present. Severely enlarged atria with atrial thrombi may also be seen.

Patients with amyloidosis have reduced diastolic function with a restrictive filling pattern. Doppler echocardiography may demonstrate early deceleration of transmitral filling velocity (E wave), diminished late diastolic flow velocity (A wave), and a reduced ratio of E to A wave (figure 9).

However many of these features may be absent in early stages of the disease and mild left ventricular wall thickening may mimic hypertrophic cardiomyopathy, end stage renal disease, or hypertensive heart disease. Presence of left ventricular wall thickening with effusions, right ventricular wall thickening and interatrial septal thickening is highly suggestive of an infiltrative disorder. Combining left ventricular wall thickness and mass with ECG findings can also improve the diagnostic ability of echocardiography. Increased left ventricular wall thickness, worsening diastolic function, reduced left ventricular ejection fraction and reduced right ventricular longitudinal function are all inversely correlated with survival [2]. However, 2D- echocardiography is unable to readily distinguish between the amyloid subtypes.

Strain echocardiography

Speckle-tracking strain echocardiography is more sensitive for diagnosis of cardiac amyloidosis, and may suggest the diagnosis even in the absence of 2D- and Doppler findings. The strain polar map may demonstrate significantly reduced mid and basal longitudinal strain with relative sparing of the longitudinal function at the apex (figure 10-11). Abnormal left and right ventricular longitudinal strain are independent predictors of survival in patients with AL amyloidosis even after adjusting for clinical variables and serologic markers [3]. Longitudinal strain in the basal antero-septal left ventricular segment greater than -7.5 was associated with increased risk of death [4]. However similar to 2D echocardiography, strain imaging is also currently unable to differentiate between amyloid subtypes.
Figures 4-11 represent transthoracic echocardiography images from a 55 year old female with AL amyloidosis with cardiac involvement. Note the increased wall thickness of the left and right ventricular walls, interatrial septum and valve leaflets secondary to amyloid deposition. The myocardial walls have a speckled appearance characteristic of amyloidosis. Systolic contractile function is preserved with an ejection fraction of 55%. A restrictive filling pattern is noted. Small circumferential pericardial effusion and severe biatrial enlargement are also seen. The left ventricular longitudinal function is markedly decreased. There is severe global reduction in longitudinal strain, with worst function in the base and relative preservation of the apex.

**Cardiac Magnetic Resonance Imaging**

Compared with echocardiography, cardiac MRI offers superior myocardial border delineation and more accurate assessment of the left ventricular chamber size and ejection fraction as it is not limited to an acoustic window, and can image in any 3 dimensional plane. Compared with echo, the principal advantage of cardiac MRI is its ability to visualize extracellular infiltration of amyloid deposits. However patients with cardiac amyloidosis often have renal failure, and in such cases use of gadolinium should be avoided due to the risk of nephrogenic systemic fibrosis.

Patients with cardiac amyloidosis often have permanent pacemakers or defibrillators that may preclude MRI acquisition or result in artifacts. Additionally although diastolic parameters such as mitral inflow peak velocity, deceleration times and E/A ratio can now be reliably measured by cardiac MRI, echocardiography continues to be superior in its ability to characterize diastolic function. Figures 12-14 demonstrate classic findings of cardiac amyloidosis seen on MRI including left and ventricular wall thickening, interatrial septal thickening, pericardial effusion, and biatrial enlargement.

Gadolinium is an extracellular contrast agent and in the normal myocardium is not retained in the heart. Amyloid deposition results in expansion of the extracellular space and retention of contrast in the myocardium. This results in shortening of the myocardial T1 times that approaches the blood pool resulting in abnormal gadolinium kinetics. Often it is difficult to obtain an adequate T1 time to null the myocardium and on late gadolinium enhanced sequence the myocardium and blood pool are often indistinguishable. The abnormal gadolinium kinetics seen in amyloidosis, may lead to nulling of the myocardium before the blood pool (figure 15).

Patients often present with global subendocardial or transmural late gadolinium enhancement (LGE). Such LGE may be seen early in disease course in absence of increased left ventricular wall thickness and correlates with disease severity [5]. Figure 16 demonstrates late gadolinium enhancement of the ventricular walls and interatrial septum. The extent of LGE has been found to be the strongest independent predictor
of B-type natriuretic peptide (BNP), but did not correlate with survival [5]. Limited data suggest T1 and T2 mapping in patients with amyloidosis are abnormal and hold promise as useful diagnostic sequences, but more research is needed.

**Nuclear Imaging**

Several SPECT radiotracers have been evaluated targeting different components altered in cardiac amyloidosis - sympathetic innervation, amyloid deposition and perfusion (table 2).

**Sympathetic Tracers**

$^{123}$I-MIBG (meta iodo benzyl guanidine), a norepinephrine analog, has recently been FDA approved in United States for assessment of myocardial sympathetic innervation in patients with heart failure and ejection fraction < 35%. Patients with familial cardiac amyloidosis were shown to have extensive myocardial adrenergic denervation as assessed by MIBG scintigraphy, in absence of perfusion, clinical or echocardiographic parameters [6]. This study suggests that MIBG imaging can detect early familial cardiac amyloidosis characterized by autonomic nervous system disorder, before signs on echocardiography. Additionally, Noordzif et al demonstrated that in 61 patients with early amyloidosis (39 primary AL, 11 secondary AA and 11 familial) MIBG uptake in the heart was lower with a higher wash out rate in patients with cardiac amyloidosis regardless of the subtype compared to normal controls[6].

**Amyloid Deposition by Technetium-based Radiotracers**

The $^{99m}$Tc-phosphate derived radiotracers were initially developed for bone imaging, but were shown to accumulate in hearts of patients with cardiac amyloidosis. Although the exact mechanism is not well characterized, it is postulated that these phosphate based radiotracers bind the high calcium content in transthyretin amyloid fibrils, compared to AL subtype. The technetium-based radiotracers hold most promise and maybe able to distinguish the ATTR from AL subtype non-invasively.

$^{99m}$Tc-DPD (technetium-3,3-diphosphono-1,2-propanodicarboxylic acid) is used in Europe and Asia, but not FDA approved in the United States. High cardiac uptake of $^{99m}$Tc-DPD has been shown to be present in patients with TTR amyloidosis, compared to low-no uptake in patients with AL amyloidosis [7]. Using a 4-point visual scoring (0= no uptake and 3= strong uptake) a cut off # 2 had a 100% negative predictive value for excluding AL amyloid and a 88% positive predictive value for presence of TTR amyloid. Increased uptake of $^{99m}$Tc-DPD may also be seen in senile amyloidosis [8]. It may also hold promise to identify cardiac involvement in patients with early stages of
disease with normal 2D-echocardiography. Furthermore, uptake of $^{99m}$Tc-DPD tracer in the myocardium has been shown to correlate with disease severity and survival [9,10].

$^{99m}$Tc-DPD, is however, not FDA approved in the United States. Another similar SPECT tracer $^{99m}$Tc-PYP (technetium pyrophosphate) is FDA approved in the United States, and may be capable of differentiating TTR from AL amyloidosis (figure 17 and 18). In one study, using 45 patients with amyloidosis (12 AL, 16 ATTR wild type and 17 ATTR familial) Bokhari and colleagues reported some radiotracer uptake in myocardium of patients with AL subtype amyloidosis [11]. However using a quantitative score by drawing a region of interest over the heart and correcting for contralateral counts the authors were able to differentiate ATTR from AL subtype with 97% sensitivity and 100% specificity for detecting ATTR subtype. In the study, cardiac $^{99m}$Tc-PYP retention correlated with left ventricular thickness and mass, but not with ejection fraction as determined by echocardiography [11]. Additional studies are underway particularly to evaluate if negative PYP scan can reliably differentiate between cardiac AL amyloid and a patient with no cardiac amyloidosis. Prognostic data using the $^{99m}$Tc-PYP tracer is currently unavailable.

**Perfusion**

Perfusion tracers (technetium SPECT and N-13 ammonia PET) have only a limited role in evaluation of patients with cardiac amyloidosis and essentially demonstrate normal perfusion without ischemia.

**Images for this section:**
Fig. 3: Echocardiography in patient with AL amyloidosis. Parasternal long axis (top left), short axis (top right) and 4-chamber views (bottom) are illustrated demonstrating increased left ventricular wall thickness, pleural effusion (*) and biatrial enlargement. Speckled appearance to the myocardium characteristic of amyloidosis is also seen.
Fig. 4: Echocardiography in patient with AL amyloidosis. Video of a 4-chamber view demonstrating borderline increased left ventricular wall thickness, preserved ejection fraction, bialtrial enlargement, thickened inter-atrial septum and thickened mitral and tricuspid leaflets secondary to amyloid deposition. The right ventricle is on the right and left ventricle on the left.
Fig. 5: Echocardiography in patient with AL amyloidosis. Zoomed in view of the parasternal long axis illustrating the classic granular speckled myocardial appearance, thickened valvular leaflets, thickened biventricular walls, and small pericardial effusion—all of which are consistent with cardiac amyloidosis.
Fig. 6: Echocardiography in patient with AL amyloidosis. Short axis view at the base illustrating the classic granular speckled myocardial appearance, thickened mitral valve leaflets, thickened biventricular walls, and small circumferential pericardial effusion- all of which are consist with cardiac amyloidosis.
Fig. 7: Echocardiography in patient with AL amyloidosis. Short axis view at the mid ventricle illustrating the classic granular speckled myocardial appearance, thickened left and right ventricular walls, and small circumferential pericardial effusion- all of which are consist with cardiac amyloidosis.
Fig. 8: Echocardiography in patient with AL amyloidosis. Short axis view at the apex illustrating the classic granular speckled myocardial appearance, thickened left and more prominently the right ventricular walls.
Fig. 9: Transthoracic echocardiography with doppler imaging in AL amyloidosis. Restrictive transmitral doppler pattern (top) and reduced tissue doppler velocities (bottom) and reduced longitudinal systolic shortening are seen, consistent with grade 3-4 diastolic dysfunction in a patient with advanced cardiac AL amyloidosis.
**Fig. 10:** Transthoracic echocardiogram with speckle tracking in AL amyloidosis. The red and yellow lines represent longitudinal motion in the basal segments, while the green and pink lines represent apical motion. The graph demonstrates loss of longitudinal left ventricular function at the base, with near preservation of the apex.
Fig. 11: Global longitudinal strain: Bull’s Eye Map in AL amyloidosis. Global longitudinal strain with Bull’s eye map on a patient with AL amyloidosis, with increased left ventricular wall thickness, EF 65%, and grade 3 (restrictive) diastolic function. The apical sparing of longitudinal strain with worsened basal function is classic for cardiac amyloidosis.
Fig. 12: Cardiac MRI in patient with AL amyloidosis. Steady state free precession images in short axis at the base (top left), mid (top middle) and apex (top right) demonstrate thickened biventricular walls, with circumferential pericardial effusion of increased signal intensity. 4-chamber view (bottom) also demonstrates the pericardial effusion, and mildly thickened atrial walls and interatrial septum. Gadolinium was not given due to presence of renal failure.
Fig. 13: Short-axis steady state free precession cine sequence of cardiac MRI (apex to base) demonstrating thickened left and right ventricular wall secondary to amyloid deposition. The systolic function is moderately reduced with ejection fraction of 40%, and restrictive filling is noted. Tiny pericardial effusion is also present.
Fig. 14: Cardiac MRI of familial TTR amyloid. 4-chamber view steady state free precession sequence of cardiac MRI image demonstrating thickened left and right ventricular wall, and thickened interatrial septum secondary to amyloid deposition. Mild bi-atrial enlargement is present. Small pericardial effusion is also seen.
Fig. 15: Sequential post gadolinium images from a cardiac MRI T1 scout sequence. As inversion time increases myocardium nulls first (red arrow), followed by the blood stream (yellow arrow). This is due to increased gadolinium retention in the myocardium that shortens the inversion time.
Fig. 16: Late gadolinium enhancement on cardiac MRI in cardiac amyloidosis. Short axis (left) and 4-chamber view (right) images demonstrating global subendocardial late gadolinium enhancement in the left ventricle, right ventricle, atrial septum, and atrial free walls, classic for cardiac amyloidosis.
### Table 2: Nuclear tracers used in evaluation of cardiac amyloidosis

<table>
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<tr>
<th>Nuclear Tracer</th>
<th>Mechanism of Action</th>
<th>Characteristics</th>
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<tr>
<td><strong>SPECT Tracers</strong></td>
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<tr>
<td>$^{123}$I-MIBG</td>
<td>Cardiac sympathetic innervation</td>
<td>Decreased uptake in heart and increased wash out rate reflecting cardiac sympathetic denervation. May detect early cardiac involvement.</td>
</tr>
<tr>
<td>$^{99m}$Tc-DPD</td>
<td>Amyloid deposition (calcium seeking tracer)</td>
<td>Increased uptake in ATTR amyloidosis. Mild to no uptake in AL amyloidosis. Not available in US. Has prognostic value.</td>
</tr>
<tr>
<td>$^{99m}$Tc-PYP</td>
<td>Amyloid deposition (calcium seeking tracer)</td>
<td>May differentiate ATTR from AL subtype. Limited studies, but FDA approved in US.</td>
</tr>
<tr>
<td>$^{201}$TI-redistribution</td>
<td>Perfusion</td>
<td>High wash out rate in amyloidosis</td>
</tr>
<tr>
<td><strong>PET Tracers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{11}$C-PIB</td>
<td>Binds amyloid fibrils</td>
<td>Increased uptake in both ATTR and AL amyloidosis, and no uptake in normal volunteers. Currently experimental. Short half-life and needs on-site cyclotron.</td>
</tr>
<tr>
<td>$^{18}$F florbetapir</td>
<td>Binds amyloid fibrils</td>
<td>FDA approved for amyloid imaging in brain in Alzheimer’s patients. Role in cardiac studies is not well established.</td>
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*Table 2*: Table 2: Nuclear tracers used in evaluation of cardiac amyloidosis
**Fig. 17:** 99mTC-PYP imaging in TTR cardiac amyloidosis. Non contrast CT heart (top left) is included. A positive 99mTc-PYP SPECT-only (bottom left), fused SPECT/CT (top right) and maximal intensity projection image (bottom right) are illustrated demonstrating increased cardiac uptake in a patient with familial TTR cardiac amyloidosis.
Fig. 18: 99mTC-PYP imaging in AL cardiac amyloidosis. Non contrast CT heart (top left) is included, and demonstrates presence of a pacemaker lead in the right ventricle. A negative 99mTc-PYP SPECT-only (bottom left), fused SPECT/CT (top right) and maximal intensity projection image (bottom right) are illustrated demonstrating no myocardial tracer uptake in a patient with biopsy proven AL-amyloidosis.
Conclusion

Cardiac amyloidosis is a rare disorder that requires heightened suspicion and a systematic approach to diagnosis. Presence of thickened myocardial walls on echocardiography or MRI with low-normal voltage on electrocardiogram is suggestive of the diagnosis. Clinical management of TTR differs substantially from AL amyloidosis and other forms of heart failure, and thus early disease recognition has important diagnostic, therapeutic and prognostic implications. Although endomyocardial biopsy remains the gold standard for detection of cardiac involvement in amyloidosis, advancements in cardiac imaging have improved the ability to non-invasively detect presence and type of amyloid deposition in the heart. LGE-MRI and strain echocardiography are sensitive to detect cardiac involvement in early stages of the disease. Bone seeking radiotracers $^{99m}$Tc-DPD and $^{99m}$Tc-PYP may differentiate TTR from AL amyloidosis. Additional SPECT and PET radiotracers for improved diagnosis and assessment of cardiac amyloidosis are currently under investigation.

Personal information

No conflicts of interest.

References


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