

and superior diastolic function assessment. Thus, while echocardiography is not sufficient by itself, to make the diagnosis of cardiac amyloidosis, it is an essential part of the diagnostic evaluation and ongoing management of patients with this disorder.

Cardiovascular magnetic resonance in cardiac amyloidosis provides structural and functional information that complements echocardiography.⁴² Cardiovascular magnetic resonance may have advantages when acoustic windows are poor, for characterization of the right ventricle, tissue characterization based on the contrast-enhanced patterns of myocardial infiltration, and precise quantification of cardiac chamber volumes and ventricular mass. However, CMR with late gadolinium enhancement (LGE) may be relatively contraindicated in patients with suspected cardiac amyloidosis and concomitant renal failure—a frequent occurrence. Moreover, in centers where CMR scanning in patients with pacemakers is not yet routine, echocardiography may be the only option for imaging cardiac structure and function. Although both the echocardiographic and CMR assessment of structure and function alone may be non-specific, some features provide more specificity, including biventricular long axis function impairment, apical sparing, reduced stroke volume index, pericardial effusion, marked biatrial enlargement, atrial appendage thrombus in sinus rhythm, sparkling texture of the myocardium, and/or disproportionate increase in left ventricular (LV) mass for electrocardiogram (ECG) voltages. Given the limitations of assessment of structure and function alone (by echo or CMR), tissue characterization by CMR adds high value, as discussed in subsequent sections.

Radionuclide imaging provides critical information on amyloid type that complements cardiac structural and functional characterization by echocardiography and CMR. It has long been appreciated that there is a unique myocardial uptake pattern in amyloid by scintigraphy with ^{99m}Tc-Technetium (Tc)-bisphosphonate derivatives (^{99m}Tc-pyrophosphate [PYP], ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), ^{99m}Tc hydroxymethylene- diphosphonate [^{99m}Tc-HMDP]). Many studies dating from the 1970s and 80s suggested ^{99m}Tc-PYP could assist in diagnosing amyloidosis.^{2,43-48} However, there was variable diagnostic accuracy, which limited early use of the technique, owing to the study of mixed patients populations with undifferentiated ATTR and AL subtypes. Subsequent studies comparing ^{99m}Tc-bisphosphonate scintigraphy to gold standard endomyocardial biopsy discovered that ATTR cardiac amyloidosis has avidity for bone radiotracers, whereas AL cardiac amyloidosis has minimal or no avidity for these tracers. Therefore, bone-avid radiotracers can definitively diagnose amyloid type when a plasma cell dyscrasia is excluded. Recognition of preferential ATTR binding to bone-avid ^{99m}Tc-bisphosphonate-based radiotracers resulted in renewed interest and greater clinical application of cardiac scintigraphy

with ^{99m}Tc-PYP, ^{99m}Tc-DPD, and ^{99m}Tc-HMDP. Although there is no direct comparison between these tracers, the information available suggests they can be used interchangeably. This is fortunate, given that there is limited access to ^{99m}Tc-DPD and ^{99m}Tc-HMDP in the United States and ^{99m}Tc-PYP in Europe.

EVIDENCE BASE FOR CARDIAC AMYLOIDOSIS IMAGING

Diagnosis

Cardiac amyloidosis is substantially underdiagnosed due to varied clinical manifestations, especially in the early stages of disease. An ideal non-invasive diagnostic method would identify cardiac involvement in amyloidosis and would also confirm the etiologic subtype. No existing diagnostic tools can provide this information individually, necessitating a multimodality cardiac imaging approach.

Echocardiography

Echocardiography plays a major role in the non-invasive diagnosis of cardiac amyloidosis due to its assessment of structure and function and its pervasive use in patients with concerning cardiac symptoms. The evaluation of cardiac amyloidosis using echocardiography focuses on morphological findings related to amyloid infiltration, in particular, thickened LV walls >1.2 cm in the absence of any other plausible causes of LV hypertrophy (Figure 2).²⁸ Although increased LV mass in the setting of low voltage ECG is suggestive of cardiac amyloidosis, a definitive distinction by echocardiography of amyloidosis from hypertrophic cardiomyopathy or other causes of LV hypertrophy is challenging.⁴⁹ Other echocardiographic findings that suggest infiltrative disease include normal to small LV cavity size; biatrial enlargement and dysfunction⁴¹; left atrial and left atrial appendage stasis and thrombi; thickened valves; right ventricular and interatrial septal thickening; pericardial effusion; and a restrictive transmitral Doppler filling pattern.⁵⁰⁻⁵⁴ Several of these features, including an overt restrictive mitral inflow pattern are uncommon until late in the disease process.^{34,51} However, reduced LV systolic thickening, filling pressures, cardiac output,³⁸ early diastolic dysfunction,^{39,40} and signs of raised filling pressures are commonly seen.^{34,52} A granular sparkling appearance of the myocardial walls may be appreciated, but it is not considered a highly specific finding and can be seen in other conditions, such as end-stage renal disease. The echocardiographic shift from fundamental to harmonic imaging has confounded this phenotype.

Tissue Doppler imaging (TDI) and speckle-tracking echocardiography (STE) refine the non-invasive recognition of cardiac amyloidosis by quantitating longitudinal systolic function.^{51,55,56} A pattern of reduced longitudinal shortening with preserved LV ejection fraction and radial shortening is characteristic of cardiac amyloidosis and