Emerging role of echocardiography, cardiac magnetic resonance imaging and ^{99m}Tc -labeled bone tracer scintigraphy for the diagnosis of cardiac amyloidosis

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Cardiac amyloidosis (CA) is an uncommon form of infiltrative cardiomyopathy that presents with progressive heart failure (HF) and has a poor prognosis. The disease process is characterized by the extracellular deposition of amyloid fibril deposits which typically are either monoclonal light chain (AL) or transthyretin (ATTR) proteins¹. Progressive increases in wall thickness are associated with greater impairment of left ventricular function² and can be identified with echocardiography or cardiac magnetic resonance imaging (CMRI). However, the clinical diagnosis may be missed due to the lack of specificity of these structural changes or delayed pending confirmatory tissue biopsy. Clinical presentation usually includes symptoms of heart failure but may include angina which has been attributed to small vessel disease.^{3,4}

New therapies are being developed for ATTR amyloidosis and include micro-RNA inhibitors that interrupt the production of amyloid proteins⁵ and molecular stabilizers of the transthyretin tetramer such as tafamidis.⁶ Although imaging with ^{99m}Tc -labeled bone tracers has been described for imaging CA for many years, recent studies have demonstrated high diagnostic accuracy for ATTR CA. Early and accurate

diagnosis has increasing clinical importance with the possibility of these new and specific treatments.

ECHOCARDIOGRAPHY

Echocardiography is a first line screening tool for CA in patients with cardiac hypertrophy. Conventional echocardiographic features of CA are thickened left ventricular walls with normal to small left ventricular cavity size, biatrial enlargement, diastolic dysfunction, pericardial effusion, thickened valves, thickening of the interatrial septum, and subsequent reduced fractional shortening.⁷ These echocardiographic features are not specific and are variably present especially in the early stages of the disease.

Tissue Doppler is a more advanced technique and further improves diagnostic accuracy for CA. Myocardial strain (a measure of tissue deformation) and strain rate (the temporal derivative of strain) by tissue Doppler are important tools for assessing systolic and diastolic function.⁸ In normal hearts, longitudinal velocities in the lateral wall are higher than in the septum and there is also a base-to-apex gradient, with higher velocities at the base and lower at the apex.⁹ Longitudinal left ventricular mechanics are sensitive for early detection of myocardial disease. Diastolic dysfunction is the earliest echocardiographic abnormality in CA and may occur before HF symptoms develop.¹⁰ Peak systolic SR can detect abnormal lower basal and mid left ventricular values after wall thickening is present and before the onset of HF. Systolic abnormalities are even more prominent after the development of HF.¹⁰

Severely impaired longitudinal shortening with preserved apical values has been described in CA^{11,12} and is an important feature that increases specificity in the differentiation between the different etiologies of

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wall thickening. Longitudinal strain is often severely affected by CA because the majority of the longitudinal fibers are subendocardial, the most vulnerable area, and the first to be affected by amyloid deposition. Altered microvascular function may also play a role in longitudinal impairment.⁴ The much greater restriction of basal compared to apical wall motion may be related to the regions of preferential deposition of amyloid and greater mechanical effects between regions. Others have speculated that the basal-to-apical longitudinal strain gradient in CA involves higher wall stress and tendency for remodeling and apoptosis in the basal segments as a result of turbulent flow in the LV outflow tract.^{13,14} The relatively increased amyloid deposition in the basal segments can be explained by the high mechanical displacement of cardiac myocytes in these segments. These patterns are similar in patients with CA due to different types of protein deposition, and echocardiography cannot differentiate between different CA subtypes. Abnormal strain dynamics have been reported as predictors of death in cardiac amyloidosis.¹⁵

CARDIAC MAGNETIC RESONANCE IMAGING

CMRI is a valued tool for the diagnosis, follow-up, and assessing prognosis in CA. Late gadolinium enhancement (LGE) is the hallmark for the diagnosis of CA and has a distinct distribution in the subendocardial region that can progress into all myocardial layers as the disease progresses. LGE is attributed to the expansion of the extracellular matrix^{16–18} due to the infiltration of amyloid. MRI LGE has a good sensitivity (80%) and excellent specificity (94%) for detection of cardiac amyloidosis in comparison to the gold standard of endomyocardial biopsy.¹⁷

Longitudinal strain by feature tracking correlates with myocardial amyloid burden. Furthermore, there is a strong negative correlation between the amyloid burden measured by histopathology and segmental longitudinal strain in all major types of amyloidosis. Similar to the echocardiographic pattern, amyloid deposits in CMRI also are found to be more prominent in the basal and mid-cavity sections of affected hearts although later in the course of the disease it is diffuse. These same regions of prominent amyloid deposition have longitudinal strain impairment, indicating regional contractile dysfunction.^{16,18}

The global subendocardial pattern of LGE in earlier stages of the disease may extend later in the course of the disease and become transmural with abnormal myocardial and blood-pool gadolinium kinetics¹⁵ leading to the homogeneous pattern of enhancement with faster washout of gadolinium from myocardium and blood pool when compared to normal hearts. Diffuse

LGE in the atrial wall may be a characteristic feature of cardiac amyloidosis.¹⁹

Subendocardial T1 is shortened in cardiac amyloidosis, and T1 mapping may identify cardiac involvement earlier than the presence of LGE. On T1 mapping, diffuse global hyperenhancement is present if the myocardium nulls or becomes black at a T1 time point before the blood pool and is characteristic of cardiac amyloidosis.²⁰

CMRI can differentiate to some extent between the different types of CA. More extensive LGE may be found in ATTR versus AL amyloidosis and RV free wall LGE is more prevalent in patients with ATTR amyloidosis. These patterns may overlap when ATTR amyloidosis is in early stages or the AL type is in late stages and reduce CMRI ability to differentiate between types.

^{99m}Tc-Labeled Bone Tracer Scintigraphy

Cardiac uptake of ^{99m}Tc-labeled bone tracers has been found useful for the early diagnosis of CA and earlier than can be detected by echocardiography and CMRI.^{21–23} Scintigraphic myocardial retention can quantify amyloid deposition with correlation to echocardiographic impaired longitudinal function and interventricular septum thickening^{22,24} and can also distinguish between the different types of CA such as ATTR which is characterized by higher uptake than AL type.

The exact mechanism of bone-seeking tracers binding to amyloid is still not completely clear. High concentration of calcium in amyloid tissue may contribute.²⁵ The higher uptake in ATTR CA may be due to different composition of amyloid fibrils, different affinities of diphosphonate for amyloid proteins, and differences in tissue involvement.²²

Increased calcium concentration in the tissue affected by amyloid deposition also is influenced by the development of abnormality in calcium flux and cardiac function that is impaired in CA.²⁶ In diastolic dysfunction, there may be an increase in sarcomere Ca²⁺ sensitivity and a decrease in the rate of Ca²⁺ reuptake, leading to Ca²⁺ overload. Expansion of interstitial volume is also a cause for soft tissue localization of bone-seeking radiopharmaceuticals.

In the current study by Van Der Gucht et al.²⁷ the regional distribution of early-phase uptake ^{99m}Tc-Hydroxymethylene diphosphonate (^{99m}Tc-HMDP) was determined in 61 ATTR patients (29 wild-type and 32 hereditary). Patients underwent whole-body planar imaging 10 minutes after radiotracer injection followed by chest SPECT/CT. Segmental uptake was quantitated as % of maximal uptake and was significantly lower in the apical segments consistent with a base-to-apex gradient similar to previous echocardiographic and

Table 1. Relative comparisons between imaging modalities for the diagnosis of CA

	Echocardiography	CMRI	Scintigraphy
Availability	+++	+	+++
Cost	+++	+	+++
Lack of radiation	+++	+++	+
Contraindications	+++	+	+++
Early diagnosis	+	+	+++
Sensitivity	++	++	+++
Specificity	+	+++	+++

+ = Less favorable, ++ = neutral, +++ = most favorable

CMRI findings. This pattern of apical sparing is emerging as a classic finding for the diagnosis of CA with all 3 noninvasive imaging modalities. This phenomenon is shown as lack of LGE on CMRI, less uptake of radiopharmaceutical on scintigraphy, and preserved longitudinal strain and strain rate on echocardiography or CMRI. The imaging finding is consistent with the pathologic pattern of amyloid deposition and the mechanical stress gradient. Demonstrating apical sparing and the base-to-apex gradient may add to the specificity of these diagnostic tools.

IMPORTANT DIAGNOSTIC ROLE FOR SCINTIGRAPHY WITH BONE TRACERS

Noninvasive methods for the early diagnosis of CA are crucial in the management of these patients. Echocardiography can suggest the diagnosis but lacks specificity. Strain measurements may be helpful but these sophisticated measurements are not widely available. CMRI patterns may suggest CA but are not consistently diagnostic. Radionuclide techniques with bone tracers bind specifically and with varying affinities to different types of amyloid proteins. Table 1 shows a comparison between the noninvasive imaging modalities. Scintigraphy is widely available, has low cost, and few contraindications, offers early diagnosis with high diagnostic accuracy and has low patient radiation dose. Thus, scintigraphy appears to have an important and unique clinical role for the early diagnosis of patients with suspected CA. Furthermore, quantification of disease extent with scintigraphy may be also useful in the subsequent management of CA patients, particularly with assessing response to new therapies.

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