Advances in ATTR-CM Imaging

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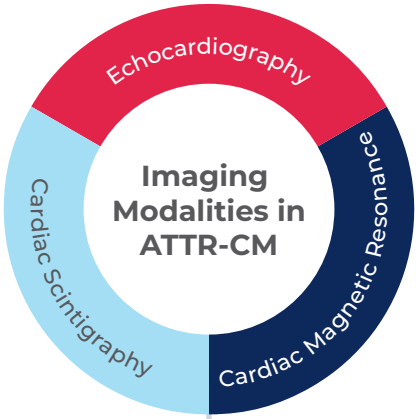
Introduction

Cardiac imaging is a reliable, noninvasive, and relatively inexpensive method that can be used alongside laboratory testing to diagnose transthyretin amyloid cardiomyopathy (ATTR-CM) and potentially monitor treatment response.[1–4] Prior to advances in cardiac imaging, an ATTR-CM diagnosis required an invasive endomyocardial biopsy that was not only technically challenging but also posed risks to the patient.[5] Now, multimodal imaging techniques can reveal cardiac manifestations of ATTR-CM without the need for invasive procedures, opening the door to timely interventions that can improve patient outcomes.[3,5–7]

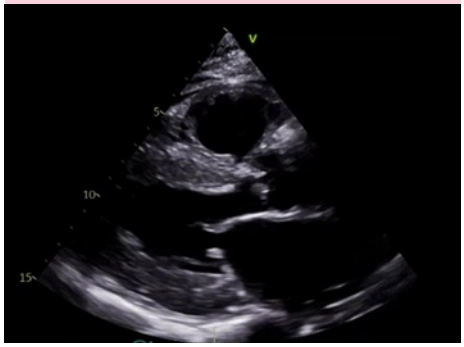
A Multimodal Approach

- Enables a comprehensive diagnostic assessment of the patient
- Can help determine ATTR-CM without invasive biopsy procedures
- Facilitates earlier diagnosis
- May reveal cardiac mechanisms influencing treatment response



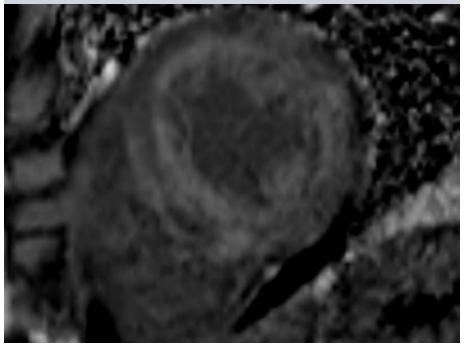
Echocardiography

- Assesses cardiac structure and function



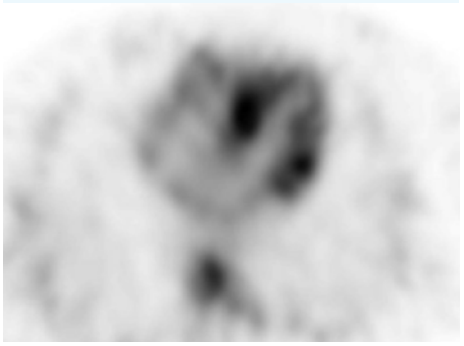
Cardiac Magnetic Resonance

- Assesses cardiac structure and function
- Characterizes myocardial tissue



Cardiac Scintigraphy with Bone-Avid Radiotracers

- Assesses cardiac amyloid deposits by measuring uptake of radiotracers



ATTR-CM, transthyretin amyloid cardiomyopathy.

All images were provided by Dr Cuddy.

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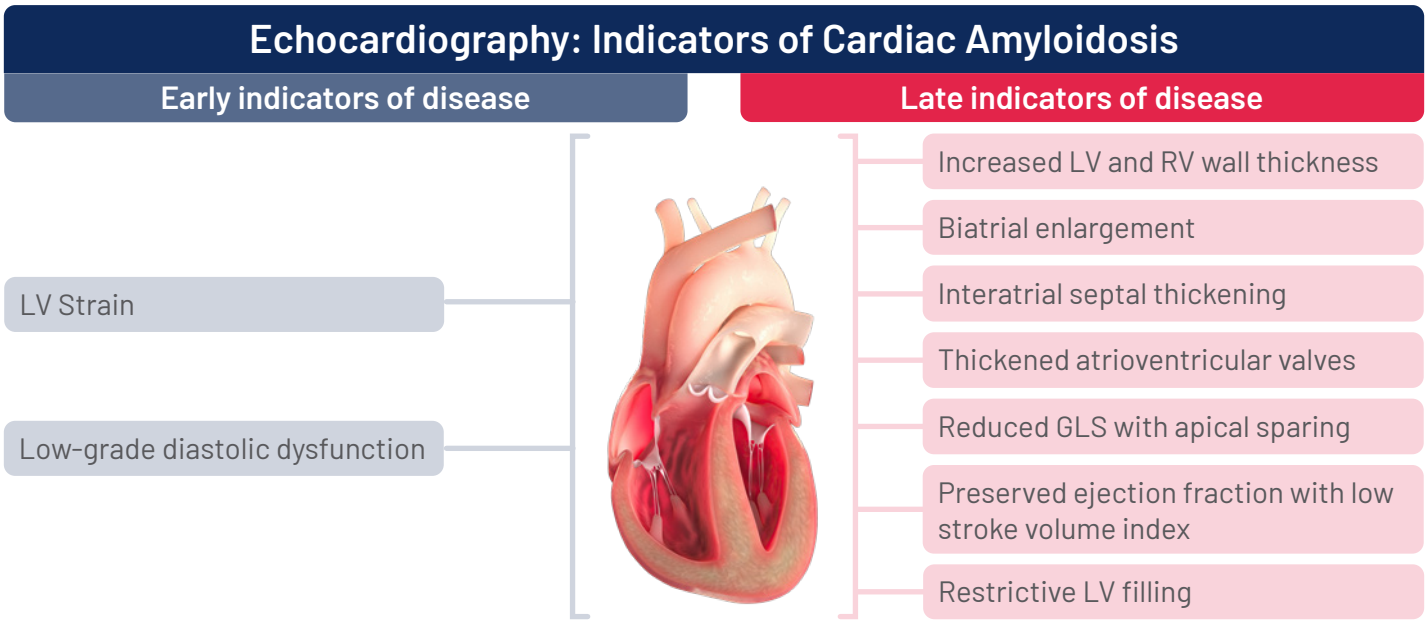
Diagnostic Imaging Modalities for ATTR-CM

Echocardiography

Echocardiography is a first-line imaging modality to assess cardiac function and structure in cardiac disease.[2,3] It is a noninvasive, widely available, low-cost option to quickly evaluate cardiac parameters.[3] Structural and functional features may raise suspicion of cardiac amyloidosis (CA) and can guide further testing for ATTR-CM.[2,7] Echocardiographic features of CA include increased left ventricular (LV) and right ventricular wall thickness, biatrial enlargement, preserved ejection fraction with low stroke volume index, restrictive LV filling, reduced global longitudinal strain with apical sparing, thickened atrioventricular valves, and pericardial effusion.[7,8] These features can vary by disease stage. Early features of amyloid infiltration include abnormal LV strain and grade I or II diastolic dysfunction, whereas advanced disease features include decreased ejection fraction and more marked ventricular wall thickening and atrial enlargement.[8,9]



ATTR-CM, transthyretin amyloid cardiomyopathy; GLS, global longitudinal strain; LV, left ventricular; RV, right ventricular.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMR) enables the characterization of myocardial tissues and assessment of cardiac function and structure; it is the best noninvasive imaging modality for differentiating CA from other causes of LV wall thickening or heart failure.[2,3,7] Through administration of a gadolinium-based contrast agent and T1 mapping, CMR enables visualization of the increase in extracellular volume (ECV) that results from amyloid fibril deposition.[3,9] Diagnostic indicators include increased ECV fraction, longer myocardial longitudinal relaxation time (T1), and late gadolinium enhancement with a diffuse, subendocardial, and/or transmural distribution.[2,3] Similar to echocardiography, CMR raises suspicion but does not enable differential diagnosis of ATTR-CM from other causes of CA, such as light chain (AL) amyloidosis.[7,10] CMR is becoming more widely available but is considerably more expensive than other imaging modalities.[3,10]

Cardiac scintigraphy with bone-avid radiotracers

Cardiac scintigraphy with bone-avid radiotracers can confirm the diagnosis of ATTR-CM when the criteria within the 2023 ACC Expert Consensus Algorithm are met.[5,11,12] This includes serum and urine testing to exclude light-chain cardiac amyloidosis (AL-CA).[7,11] The positive predictive value and specificity for ATTR-CM are close to 100% when these criteria are met.[12–14] It is relatively inexpensive, falling between echocardiography and CMR, and is highly accurate in detecting ATTR-CM when AL-CA has been excluded.[3] Through the use of different technetium-^{99m}–labeled radiotracers (eg, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD], ^{99m}Tc-pyrophosphate [PYP], or ^{99m}Tc-hydroxymethlene-diphosphate [HMD]), amyloid deposits are revealed by radiotracer uptake in the myocardium with the use of planar or single photon emission computed tomography imaging (SPECT).[2,7] However, the American Society of Nuclear Cardiology strongly recommends against using planar imaging alone, and emphasizes the use of SPECT or SPECT/CT for image interpretation.[2,7,15] Image interpretation for diagnostic purposes relies on comparing myocardial uptake to rib uptake. Other quantitative methods can be used, such as heart to contralateral ratio, but a positive scan is considered to be myocardial uptake equal to grade 2 or greater than grade 3 rib uptake.[5,16]

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Guideline Recommendations for the Use of Imaging in ATTR-CM Diagnosis

To diagnose ATTR-CM, the American College of Cardiology guidelines recommend first identifying CA using echocardiography or CMR and then ruling out AL-CA with laboratory testing.[11] If laboratory tests are negative for AL-CA, cardiac scintigraphy with bone-avid radiotracers should be conducted as soon as possible after clinical suspicion of CA to confirm diagnosis of ATTR-CM and prevent treatment delays.[11] Similarly, guidelines from the American Heart Association and other organizations recommend confirming an ATTR-CM diagnosis through positive cardiac scintigraphy combined with a negative laboratory test for AL-CA and consistent echocardiography or CMR findings.[13,14] Echocardiography is recommended for screening and monitoring at all stages of ATTR-CM, while cardiac scintigraphy is considered appropriate to screen for CA in patients with heart failure and red flags for ATTR-CM.[13,14]

Comparison of ATTR-CM Imaging Modalities

	Cardiac scintigraphy	CMR	Echocardiography
Availability	Limited to specialist centers	Becoming more widely available	Widely available
Relative cost	Low	High	Low
Time required	1–3 hour wait between radiotracer injection and image acquisition	30–60 minutes	30–60 minutes
Safety considerations	Radioactive tracer	Challenging with arrhythmia, contraindicated with some cardiac devices	Generally safe
Diagnostic use	Confirms ATTR-CM in the absence of light chain abnormality	Distinguishes CA from other forms of cardiomyopathy	Features raise suspicion of CA
Use in monitoring	Limited data	Evidence emerging that ECV may be an appropriate measure of amyloid burden and progression	Established use in monitoring left ventricular function as disease progresses

ATTR-CM, transthyretin amyloid cardiomyopathy; CA, cardiac amyloidosis; CMR, cardiac magnetic resonance imaging; ECV, extracellular.

Role of Imaging in ATTR-CM Management

With the evolving ATTR-CM treatment landscape, there is an increasing need to monitor disease progression and treatment response.[2,7] Echocardiography is currently the most frequently used modality used to monitor disease progression and assess worsening cardiac symptoms.[2,9] Expert consensus from the European Society of Cardiology recommends measuring LV wall thickness and mass, systolic function, and diastolic dysfunction by echocardiogram every 6–12 months to quantify disease progression.[9] While CMR and cardiac scintigraphy play a role in identifying ATTR-CM, serial data are more limited for these modalities in disease progression.[2,7]

Cardiac scintigraphy with bone-avid radiotracers is not recommended for response monitoring due to conflicting evidence.[5] For example, in a case of hereditary ATTR-CM, initial cardiac scintigraphy showed elevated ^{99m}Tc-PYP uptake, and the patient started treatment with diflunisal and later switched to vutrisiran. A follow-up scan after 17 months showed minimal uptake, whereas a PET/CT scan using a radiolabeled amyloid-reactive peptide demonstrated diffuse cardiac uptake.[17] Other studies have shown improvement in cardiac scintigraphy (eg, reductions in tracer uptake over time),[18] but with other imaging metrics showing no improvement.[19] Investigations into quantitative cardiac scintigraphy and newer positron emission tomography tracers have shown initial promising results, but require further study before entering clinical use.[2,5,20] There are some data that indicate ECV measured by CMR may be a useful tool for response monitoring, but whether this measure correlates with long-term clinical outcomes remains unknown.[2] Additional studies are needed to validate and establish a universally reliable imaging metric for ATTR-CM management.[9]

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Future Directions in ATTR-CM Imaging

Utilizing multimodal imaging with echocardiography, CMR, and cardiac scintigraphy enables a comprehensive diagnostic assessment and can help identify ATTR-CM without the need for an invasive biopsy in the majority of patients.[3] This approach not only facilitates earlier diagnosis, but also provides important prognostic information on disease burden and impact on cardiac function.[7]

Additionally, artificial intelligence (AI) may soon enable prediction of ATTR-CM through analysis of imaging data, electronic health records (EHRs), and electrocardiograms.[2,21] Emerging evidence indicates improved diagnostic efficiency and accuracy through AI machine learning and deep learning algorithms across various imaging modalities.[2] A recent study utilizing a machine learning pipeline with echocardiographic images successfully automated the identification of cardiac views, segmentation of chambers, quantification of structures and functions, and detection of disease.[22] When used with EHRs, a different machine learning algorithm accurately identified patients with ATTR-CM, and deep learning algorithms have successfully classified CA subtypes and Perugini grades from CMR and cardiac scintigraphy images, respectively.[2]

Conclusions

Increasing awareness and appropriate use of imaging techniques have contributed to earlier ATTR-CM diagnosis over the last decade, reducing the need for invasive procedures such as endomyocardial biopsy.[2, 23] Moreover, the application of AI is enhancing the efficiency and accuracy of image interpretation, promising further improvements in disease prediction and treatment monitoring.[2,21,22] As research continues to evolve, multimodal imaging approaches and AI-driven technologies hold significant potential to optimize patient diagnosis, care, and outcomes in ATTR-CM.

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