Review

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Diagnostic Modalities in the Detection of Cardiac Amyloidosis

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Abstract: Cardiac amyloidosis (CA) results mainly from infiltration of myocardium by either immunoglobulin light chain fibrils (AL) or transthyretin fibrils (ATTR), causing restrictive cardiomyopathy and eventually death if untreated (3). AL derives from monoclonal immunoglobulin light chain produced by plasma cell clone in the bone marrow, while ATTR is the misfolded form of hepatically-derived transthyretin (TTR) protein, and could be hereditary (hATTR) or wild-type (wtATTR). Over the last decade, improvement in diagnostic imaging and better clinical awareness has unleashed a notable presence of CA in the community, especially ATTR in the elderly population. These multimodality imaging modalities include echocardiography, cardiac magnetic resonance and radionuclide scintigraphy with bone-avid tracers. There has been remarkable progress in the therapeutic landscape as well, and there are disease-modifying therapies available now that can alter the course of the disease and improve survival if initiated at an early stage in the disease. There remains an unmet need for detecting this disease accurately and early, so that these patients could benefit the most from newly-emerging therapies.

Keywords: cardiac amyloidosis; transthyretin; echocardiography; cardiac magnetic resonance; Tc-pyrophosphate scintigraphy

Introduction

Amyloidosis constitutes a group of diseases in which misfolded proteins are deposited in various tissues, resulting in disruption of tissue architecture and dysfunction [1]. Cardiac involvement portends the worst prognosis [2]. Cardiac amyloidosis (CA) results mainly from infiltration of myocardium by either immunoglobulin light chain fibrils (AL) or transthyretin fibrils (ATTR), causing restrictive cardiomyopathy and eventually death if untreated [3]. AL derives from N-terminal fragment of a monoclonal immunoglobulin light chain produced by plasma cell clone in the bone marrow. ATTR is the misfolded form of hepatically-derived transthyretin (TTR) protein, a carrier of thyroxine and retinol binding protein in the human blood; this misfolding could be secondary to a genetic mutation (hATTR) or happen spontaneously (wtATTR).

CA shares many features with other cardiac diseases, including hypertrophic cardiomyopathy and aortic stenosis, and this phenotypic overlap commonly leads to misdiagnosis or underdiagnosis of CA. CA has been detected in about one-tenth of patients with hypertrophic cardiomyopathy as well as those with aortic stenosis, and has been diagnosed in ~13% of patients with heart failure with preserved ejection fraction [4–6]. Over the last few years, improvement in diagnostic imaging and better clinical awareness has uncovered a substantial presence of CA in the community, especially ATTR in the elderly population. There has been remarkable progress in the therapeutic landscape as well, and there are disease-modifying therapies available now that can alter the course of the disease and improve survival if initiated at an early stage in the disease. There remains an unmet need for

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detecting this disease accurately and early, so that these patients could benefit the most from newly-emerging therapies.

This review aims to discuss advancements and role of multimodality imaging in the diagnostic workup of CA. The features on echocardiography and cardiac magnetic resonance can raise suspicion for CA, and potentially pave the way for early disease detection, while nuclear scintigraphy serves to confirm the diagnosis of CA.

Echocardiography

Echocardiography emerges as a non-invasive, easily accessible, and highly reproducible imaging modality [7]. Given the common presentation of cardiac amyloidosis (CA) as heart failure, echocardiography is often the initial diagnostic tool for these patients [8]. It holds a Class 1B recommendation for diagnosing CA, as per the 2022 European Society of Cardiology Guidelines on cardio-oncology [9].

Echocardiography plays a pivotal role in quantifying key parameters, such as myocardial wall and valve thickness, myocardial mass, and cardiac chamber size, which are commonly affected in CA [10,11]. Notably, the left ventricular ejection fraction (LVEF) is usually preserved until advanced stages of the disease. Consequently, prevalent echocardiographic findings resemble those seen in diastolic heart failure, characterized by elevated filling pressure, increased wall thickness, and reduced chamber size [7]. Nonetheless, certain echocardiographic features are more commonly seen in CA which help to differentiate it from other etiologies of hypertrophic cardiomyopathy. These features, when considered alongside clinical and demographic characteristics, contribute to a comprehensive diagnostic evaluation.

In CA, diastolic parameters evolve from low E-wave and high A-wave velocity, decreased E/A ratio, and normal deceleration time in early disease to normal E-wave, small A-wave, high E/A ratio, and rapid deceleration time in late stages of the disease [11] Additionally, a small S-wave on tissue Doppler is indicative of advanced disease [7]. Tissue Doppler commonly reveals markedly reduced mitral and tricuspid e′ velocities and a high E/e′ ratio, suggesting elevated filling pressures even in the absence of overt increase in left ventricular wall thickness-consistent with features of a restrictive myocardial pattern [11,12] A restrictive pattern on tissue Doppler imaging of the mitral annulus of e′, a′, and s′ less than 5 cm/s along with pericardial effusion can be highly suggestive of CA [7]. Notably, AL-CA typically exhibits a restrictive pattern early in the disease compared to ATTR-CA [12].

Left ventricular hypertrophy (LVH) is the predominant echocardiographic finding in CA, presenting usually as symmetrical in AL-CA compared to asymmetrical in ATTR-CA [13]. The amyloid deposition imparts a distinctive speckled or granular appearance to the myocardium on echocardiography [10,14]. In addition, LV wall thickness exceeding 12 mm, and diastolic dysfunction of grade 2 or above in the absence of aortic valve disease or severe uncontrolled hypertension raise suspicion of CA [15]. Moreover, the electrocardiogram (EKG) features of CA helps to differentiates it from other etiologies of LVH. These include low voltage EKG in limb leads, poor R wave progression in the right chest leads, significantly reduced R-wave voltage in V5 and V6 leads, and pseudo infarct pattern in the anterior chest leads [11]. Although these EKG features are not diagnostic, they heighten suspicion when considered alongside echocardiographic findings [16].

Speckle tracking echocardiography (STE) reveals significantly impaired left ventricular global longitudinal strain (LVGLS) despite preserved ejection fraction, which is a marker for poor prognosis [11]. LVGLS is particularly worse in the basal and mid LV segments, with relative sparing of the apical segment, creating a distinctive “cherry on top” appearance on bull’s eye plot [17]. A relative regional strain ratio of >1 demonstrates high sensitivity and specificity for CA [14]. Among CA subtypes, AL-CA exhibits worse LVGLS than ATTR-CA at a given wall thickness [18]. A prior study identified LVEF/GLS >4.95 as a better screening tool, with sensitivity and specificity of 75% and 66%, respectively [19]. Moreover, three-dimensional (3-D) STE, incorporating additional parameters such as global area strain and global circumferential strain, has enhanced sensitivity in identifying features consistent with CA and also prognosticating the disease [10].

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Amyloid deposition in the atrial myocardium causes thickening of the atrial septum, and values exceeding 6mm have demonstrated a specificity of 100% for diagnosing CA [10]. Another common feature is the biatrial enlargement that is driven by elevated filling pressures and serves as an imaging marker for early subclinical changes in ATTR-CA [20]. Due to the impairment of left atrial (LA) structure and function by the deposition of amyloid fibrils, there is a higher prevalence of thromboembolic events in CA patients, even among those in sinus rhythm [21]. This phenomenon is attributed to atrial cardiopathy due to reduced LA reservoir and contractile strain that can be detected by STE prior to impairment of traditional echocardiographic parameters, such as elevated left atrial volume index and left atrial enlargement [22].

Moreover, unexplained thickening of the right ventricular (RV) wall with values >5 mm and reduced function raises suspicion of CA [10]. STE and traditional echocardiography have both shown impaired right ventricular free wall longitudinal strain with apical sparing and TAPSE, respectively [15]. Among CA subtypes, AL-CA exhibit greater apical sparing compared to ATTR-CA. The RV apical/(basal+middle) ratio >0.8 is reported to have a sensitivity, specificity, and accuracy of 97.8%, 90.0%, and 94.7%, respectively, to distinguish AL-CA from ATTR-CA [23].

While traditional echocardiography and STE are not considered the gold standard for diagnosing CA, they can identify features that assist clinicians in maintaining a high suspicion for CA and proceeding to the next steps in the diagnostic algorithm for this disease.

Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) imaging serves as a critical tool in distinguishing myocardial hypertrophy attributable to cardiac amyloidosis (CA) from other causes. Offering advanced three-dimensional structural and functional imaging with superior spatial resolution compared to echocardiography, CMR enables precise tissue characterization. While it may not definitively discriminate between amyloid transthyretin (ATTR) and amyloid light-chain (AL) CA, CMR effectively captures anomalous gadolinium kinetics, visible on post-gadolinium T1 inversion recovery imaging, where both gadolinium and blood exhibit null signals simultaneously. Amyloid infiltration leads to an expansion of the extracellular space, accurately depicted with gadolinium-based contrast agents. These agents passively distribute within the enlarged extracellular space created by amyloid fibrils, producing a distinctive pattern of diffuse, subendocardial, and/or transmural late gadolinium enhancement (LGE) on CMR—highly indicative of CA [24]. The LGE pattern also serves as a prognostic indicator, with transmural enhancement signifying advanced cardiac amyloidosis and correlating with a poorer prognosis [25]. It is noteworthy that the administration of gadolinium-based contrast agents carries potential risks, such as the development of nephrogenic systemic fibrosis in patients with a glomerular filtration rate below 30 mL/min/1.73 m2 [26].

T1 mapping offers deeper insights into myocardial response to CA pathology by precisely quantifying longitudinal relaxation times on a pixel-by-pixel basis. Native T1, measured before contrast administration, demonstrates elevation in early CA stages, preceding ventricular thickening or detectable late gadolinium enhancement (LGE) [27]. Apart from aiding in CA diagnosis, native T1 mapping proves invaluable for monitoring disease progression. Adverse prognosis is associated with pre-contrast T1 times exceeding 1044 ms for AL and 1077 ms for ATTR [28,29]. Additionally, T1 mapping estimates myocardial extracellular volume (ECV) fraction, serving as a surrogate for quantifying amyloid burden and correlating with disease severity in AL and ATTR. ECV measurement can effectively track treatment response in AL patients [30,31]. Furthermore, T2 mapping complements T1, LGE, and ECV findings by visualizing and quantifying myocardial edema. Although elevated in both ATTR and AL, untreated AL patients exhibit higher T2 values compared to treated AL and ATTR patients, rendering T2 mapping pertinent for AL prognostication [32].

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Nuclear Scintigraphy with Bone-Seeking Tracers

Nuclear scintigraphy with the ^{99m}Tc-labeled bone-seeking tracers including ^{99m}Tc-pyrophosphate, 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), and ^{99m}Tc-hydroxymethylene diphosphonate have revolutionized the field of CA. By circumventing the need for endomyocardial biopsy for diagnostic purposes, this noninvasive testing has enabled widespread recognition of this disease in the general population. A multicentered study of 1217 patients with suspected cardiac amyloidosis revealed a high sensitivity and specificity of ^{99m}Tc-labeled bone-seeking tracers in detecting ATTR in the absence of paraproteinemia [33]. A metaanalysis of six studies comprising of 529 patients showed a high diagnostic accuracy of bone scintigraphy using technetium-labelled radiotracers with a sensitivity 92.2% (95% CI 89-95%), specificity 95.4% (95% CI 77-99%), LR+ 7.02 (95% CI 3.42-14.4), LR- 0.09 (95% CI 0.06-0.14), and DOR 81.6 (95% CI 44-153) [34]. Importantly, bone scintigraphy is only useful in detecting ATTR, whereas histological confirmation is need to establish the diagnosis of AL. The tropism of the bone-seeking tracers for ATTR, but not AL, amyloidosis is probably attributable to calcium binding [35]. It has been shown that microcalcifications contribute to bone scintigraphy's selectivity for ATTR, with higher microcalcification density in ATTR compared to AL (mean=16.8 vs. 6.5 per 200× field, P=.008), irrespective of age, cardiac function, and serum calcium and creatinine levels [35]. In the United States, the 99mTc-pyrophosphate (99mTc-PYP) tracer is available, while in Europe, 99mTc-hydroxymethylene diphosphonate (99mTc-HMDP) and 99mTc-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) are employed; these tracers exhibit comparable diagnostic efficacy.

Nuclear scintigraphy interpretation employs a semiquantitative approach, visually grading tracer uptake. Myocardial tracer uptake is contrasted with bone uptake in the rib cage, graded as follows: 0 for no myocardial uptake, 1 for mild uptake (less than in bone), 2 for equal uptake to bone, and 3 for substantial uptake (greater than in bone) [36]. A multicentered study, encompassing a sizable cohort of biopsy-proven ATTR patients, affirmed 100% specificity and positive predictive value for ATTR when grade 2 or 3 uptake was observed without paraproteinemia [37].

Quantitative assessment involves drawing circular regions of interest over the heart and mirrored on the contralateral chest wall. Radiotracer uptake is quantified using the heart-to-contralateral lung (H/CL) ratio, with a ratio exceeding 1.5 indicative of ATTR diagnosis, and a ratio ≥1.6 associated with poor survival [38,39].

It is crucial to highlight that nuclear scintigraphy, particularly with a visual grade of 2 or 3 indicating myocardial uptake, demonstrates high sensitivity (>99%) for ATTR but a comparatively lower specificity of 82–86%. This is because patients with AL can also exhibit a grade of 1 or 2 [38,40]. Therefore, as bone scintigraphy alone cannot definitively establish an ATTR diagnosis and exclude AL, the standard practice involves conducting urine and serum immunofixation electrophoresis, along with obtaining serum free light chains and kappa/lambda ratio for AL disease. When urine and serum tests yield negative results for AL, the specificity of nuclear scintigraphy increases to 100%. Consequently, a confident diagnosis of ATTR can be made, even without histological confirmation, in a patient displaying a typical clinical phenotype (such as a history of bilateral carpal tunnel surgery), consistent echocardiographic and/or CMR features of CA, grade 2 or 3 tracer uptake in the heart on ^{99m}Tc-PYP scintigraphy, and undetectable monoclonal gammopathy in the blood and urine.

Knowledge Gaps and Directions for Future

The emergence of innovated imaging techniques has helped significantly in non-invasive diagnosis of CA. There still remain knowledge gaps that need to be addressed. There is a need for a risk calculator, using imaging markers, to accurately assess disease burden, progression and prognosis. Most of the current tools are based on laboratory markers, and hence with the advancements in multimodality imaging there remains a need for imaging-based risk assessment tools. There are certain ATTR mutations that cannot be detected using nuclear scintigraphy, and it is an unexplored area in CA.

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Conclusions

The emergence of sophisticated imaging modalities has revolutionized the field of CA, and has helped in the timely detection of the disease. Echocardiography is often the first test that raises suspicion for CA. CMR can easily distinguish CA from other etiologies of hypertrophic cardiomyopathy, and can also help to monitor disease progression as well as predict prognosis. Nuclear scintigraphy with bone tracers establishes the diagnosis of ATTR in the absence of paraproteinemia, circumventing the need for endomyocardial biopsy.

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