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REVIEW

Multi-modality imaging in transthyretin amyloid cardiomyopathy

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Abstract

Transthyretin amyloid (TTR) cardiomyopathy is a disease of insidious onset, which is often accompanied by debilitating neurological and/or cardiac complications. The true prevalence is not fully known due to its elusive presentation, being often under-recognized and usually diagnosed only late in its natural history and in older patients. Because of this, effective treatment options are usually precluded by multiple comorbidities and frailty associated with such patients. Therefore, high clinical suspicion with earlier and better detection of this disease is needed. In this review, the novel applications of multimodality imaging in the diagnostic pathway of TTR cardiomyopathy are explored. These include the complimentary roles of transthoracic echocardiography, cardiac magnetic resonance, nuclear scintigraphy and positron emission tomography in quantifying cardiac dysfunction, diagnosis and risk stratification. Recent advances in novel therapeutic options for TTR have further enhanced the importance of a timely and accurate diagnosis of this disease.

Key words: Multimodality imaging; Cardiac amyloidosis; Transthyretin; Echocardiography; Cardiac magnetic resonance; Nuclear imaging

Core tip: Non-invasive diagnosis of transthyretin amyloid (TTR) cardiomyopathy is improving with significant developments in multiple imaging modalities available to date. A greater appreciation of the various strengths and limitations of these imaging modalities is vital, as is high clinical suspicion and timely investigation for the disease, which remains insidious and elusive. This is of particular relevance in light of emerging novel effective therapeutic options. This focused review aims to highlight the role of multimodality imaging in the diagnosis and risk stratification of patients with TTR

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INTRODUCTION

Transthyretin amyloid (TTR) cardiomyopathy is a disease characterized by extracellular accumulation of abnormal amyloid protein fibrils due to autosomal dominant hereditary mutation transmission or from a wild type (acquired) form, previously referred to as senile amyloidosis. Transthyretin is a protein primarily synthesized in the liver and can dissociate, subsequently aggregating to produce amyloid. Distinctively, TTR cardiomyopathy lies in one part of the spectrum of amyloid cardiomyopathy compared to primary systemic amyloidosis or light-chain amyloid (AL) cardiomyopathy, often due to plasma cell dyscrasia.

However, amyloid cardiomyopathy, particularly the TTR subtype, is often under-diagnosed, as patients are often asymptomatic or present with nonspecific symptoms early in the trajectory of the disease. Although certain electrocardiographic markers (*i.e.*, low voltage QRS) may suggest the presence of amyloid cardiomyopathy, these markers are not specific, particularly for TTR[1]. Left ventricular (LV) hypertrophy criteria on electrocardiography has only been observed in 25% of TTR cardiomyopathy[2]. While biomarkers such as natriuretic peptides and troponin may be elevated in TTR cardiomyopathy, inferring worse prognosis, their utility in diagnosis of the disease is limited[3,4]. The diagnostic yield is further challenged by the utility of the gold standard of endomyocardial biopsy, which may be limited by sampling errors in early disease and false positive/negative rates of approximately 10%[5].

Therefore, the true prevalence of TTR cardiomyopathy is not fully known as it is usually diagnosed late in its natural history when the disease is well established. Previous reports using imaging and histological evidence have estimated TTR cardiomyopathy prevalence to be between 0.36% to 25% in different cohorts of elderly patients, including those with aortic stenosis and heart failure with preserved ejection fraction. These have been associated with worse outcomes[6-12]. With that, these observations support the need for higher clinical suspicion and earlier screening and diagnosis of TTR cardiomyopathy with non-invasive imaging modalities.

Indeed, the timely detection of TTR cardiomyopathy may allow earlier implementation of disease-modifying therapy, improving survival. Conventionally, orthotopic liver and/or heart transplantation has been offered to these patients as possible curative treatments, as the misfolded TTR protein is synthesized in the liver[13]. Advanced age at liver transplantation and duration of disease have been associated with increased mortality[13]. Patients are also more likely to be suitable surgical candidates at earlier stages of the disease. Furthermore, recent studies have demonstrated beneficial outcomes in patients with TTR treated with novel medical therapies[14,15]. Published data from the ATTR-ACT trial has shown significant reductions in all-cause mortality in TTR-diagnosed patients treated with Tafamidis, a novel agent with TTR stabilizing properties, along with improvements in cardiovascular-related hospitalizations and quality of life measurements[14]. The authors of this study speculate that treatment with this agent early in the disease course will convey greater benefit, similar to its effect in TTR familial amyloid neuropathy[16]. In a subpopulation of the APOLLO study, the RNA inhibitor, Patisiran, has shown statistically significant improvements in certain exploratory endpoints measuring cardiac function, including natriuretic peptide levels, LV wall thickness and global longitudinal strain[15]. These therapeutic options offer promising solutions and support the need for a timely diagnosis. Otherwise, TTR cardiomyopathy is commonly associated with long-term debilitating neurological and cardiac complications such as arrhythmias and heart failure[17].

With that, this focused review aims to highlight the role of multimodality imaging in the diagnosis and risk stratification of patients with TTR cardiomyopathy.

TRANSTHORACIC ECHOCARDIOGRAPHY

Echocardiography is the primary initial imaging modality performed in the investigation of amyloid cardiomyopathy when clinically suspected. While it is a widely available and inexpensive imaging modality, its ability to differentiate between amyloid cardiomyopathy subtypes is limited and when amyloid cardiomyopathy is suspected based on echocardiography, further investigations are necessary to confirm TTR cardiomyopathy.

Increased LV wall thickness, particularly in the absence of high electrocardiographic voltages, and diastolic dysfunction are among the common early echocardiographic features seen which can raise suspicion of amyloid cardiomyopathy, although the differentials for such features are wide[18,19]. In the later stages of the disease, a restrictive filling pattern and biatrial dilatation may be accompanied by pleural and/or pericardial effusions[19-21]. Although not highly specific, LV wall thickness tends to increase to a greater degree in TTR compared to AL cardiomyopathy[18].

Using myocardial strain analysis, the presence of relative apical sparing of longitudinal strain is very characteristic of amyloid cardiomyopathy and has been demonstrated as a reproducible method of accurately differentiating amyloid cardiomyopathy from other causes of LV hypertrophy. In a study comparing 55 patients with amyloid cardiomyopathy to 30 patients with LV hypertrophy due to due to either hypertrophic cardiomyopathy or aortic stenosis, the presence of relative apical longitudinal strain was 93% sensitive and 82% specific in identifying amyloid cardiomyopathy[22].

This apical sparing pattern of global circumferential strain is usually observed unless severe diastolic dysfunction is present[23]. Furthermore, this imaging technique may better aid the identification of amyloid cardiomyopathy in challenging patient subgroups with mild LV wall thickening and preserved ejection fraction[24]. Despite that, there is limited data on echocardiographic features specific to TTR cardiomyopathy. In a study of biopsy-proven TTR patients using speckle-tracking echocardiography, acquired TTR was characterized by lower LV ejection fraction, as well as lower basal and mid LV radial strain compared to inherited TTR[25].

In addition, only few echocardiographic markers have demonstrated prognostic value specific to TTR cardiomyopathy. Among these, impairment of left atrial function, using conventional and strain-derived speckle-tracking parameters, has been demonstrated in amyloid cardiomyopathy and closely correlates to LV deformation. Acquired TTR was associated with worse left atrial function when compared to inherited TTR or AL[26]. In terms of strain imaging, 4-chamber longitudinal strain was significantly associated with major adverse cardiovascular events in amyloid cardiomyopathy, superior to traditional parameters[27]. Relative apical sparing pattern of global longitudinal strain may indicate worse prognosis, particularly when combined with low LV ejection fraction[28]. In assessing the right ventricle, TAPSE can independently predict major adverse events in amyloid cardiomyopathy patients[29]. Right ventricular dilatation has also been associated with more severe cases of amyloid cardiomyopathy and infers very poor prognosis[30].

BONE SCINTIGRAPHY

In 1975, ^{99m}Tc -methylene diphosphonate accumulation in amyloid cardiomyopathy was reported for the first time[31]. Since then, multiple bone scintigraphy tracers have been tested, although their cellular binding mechanisms are not fully known. Several of these tracers have been predominantly utilized and are described below. Scintigraphy tracer uptake in TTR cardiomyopathy has been suggested as possibly due to the increased number of small microcalcifications seen in the myocardium in TTR[32]. The presence of cardiac tracer uptake confirms amyloid cardiomyopathy but has not been able to exclusively differentiate TTR cardiomyopathy from other subtypes. In addition, the absence of tracer uptake does not rule out amyloid cardiomyopathy.

The authors of a large study of 1217 patients that underwent radionuclide scintigraphy, either ^{99m}Technetium-3,3-disphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), ^{99m}Technetium pyrophosphate (^{99m}Tc-PYP) or ^{99m}Tc-hydroxymehtylene diphosphonate (^{99m}Tc-HMDP) proposed a non-invasive diagnostic criteria for TTR cardiomyopathy[33]. TTR was suggested by a score of 2 or 3 with the use of the Perugini visual score of myocardial radiotracer enhancement (Table 1). Grade 2 or 3 enhancement was shown to be 90% sensitive and 97% specific for TTR cardiomyopathy using this scoring system. Furthermore, when grade 2 or 3 uptake is

combined with absence of monoclonal proteins in serum or urine testing, the diagnostic accuracy improves further. A specificity and positive predictive value of 100% has been demonstrated in this regard. This was consistent among all three of the radiotracers used in the study.

Interestingly, while absence of abnormal cardiac uptake of radionucleotide tracer confers a prognostic benefit, Perugini grade stratification at diagnosis has yet to show prognostic significance in TTR cardiomyopathy[34]. These observations are further supported by a study of a large cohort of patients undergoing scintigraphy for non-cardiac reasons. Of 12521 patients included, myocardial tracer uptake was demonstrated in 0.36%[6].

Despite the added value of nuclear scintigraphy in the diagnostic pathway of amyloid cardiomyopathy, there remains low penetrance and high variability in its utilization[35], thus indicating a greater need for standardization in technique between centres.

^{99m}Tc-DPD scintigraphy

^{99m}Tc-DPD scintigraphy is a highly sensitive technique for imaging TTR cardiomyopathy. In a study utilizing ^{99m}Tc-DPD scintigraphy, all 158 patients with TTR and clinical cardiac involvement demonstrated cardiac tracer uptake[36]. In the diagnosis of TTR cardiomyopathy, a study comparing 15 patients with TTR cardiomyopathy to 10 patients with AL-related cardiomyopathy revealed both sensitivity and specificity of 100% in identifying the TTR cohort using ^{99m}Tc-DPD scintigraphy[37]. Another more recent study comparing a larger group of 45 patients with TTR cardiomyopathy to 34 with AL cardiomyopathy and 15 controls again showed high levels of accuracy with positive and negative predictive values of 88% and 100% using a visual score of ≥ 2[38]. ^{99m}Tc -DPD use as a modality in diagnosing and differentiating TTR from AL cardiomyopathy has also been supported by a study of a small Australian cohort of 13 TTR patients, all showing diagnostic tracer uptake, while 25% of patients with AL-related cardiac involvement showed uptake[39].

^{99m}Tc-DPD has been observed to distribute predominantly in the cardiac septal and basal segments and lowest uptake is found in the apical and apico-antero-lateral segments[40].

Furthermore, reasonable intermodality agreement ^{99m}Tc-DPD has been shown with cardiac magnetic resonance (CMR) in the identification of TTR cardiomyopathy. Significantly improved estimation of cardiac involvement was seen using ^{99m}Tc –DPD scintigraphy when compared to late gadolinium enhancement (LGE) on CMR in a study of 18 patients diagnosed with TTR. These consecutively diagnosed patients had a mean age of 50 years, 56% were female and 56% were asymptomatic[41]. Interestingly, amyloid fibril composition has been shown to affect the result of ^{99m}Tc-DPD scintigraphy. Among 55 biopsy-proven TTR patients, all of those with type A fibrils, and none of those with type B, showed tracer uptake. Type B fibrils were associated with early-onset V30M mutation and in patients carrying the Y114C mutation in inherited TTR, whereas type A was noted in all other mutations currently examined as well as in acquired TTR cardiomyopathy[42].

^{99m}Tc-PYP scintigraphy

^{99m}Tc-PYP is currently the most commonly used form of nuclear scintigraphy. There is growing evidence behind its use of as a cardiac tracer in TTR. In a large multicenter study of 171 patients with CA, 121 due to TTR, ^{99m}Tc-PYP showed 91% sensitivity and 92% specificity in diagnosing TTR cardiomyopathy[43]. Another study demonstrated the ability of ^{99m}Tc -PYP cardiac imaging to distinguish AL from TTR cardiomyopathy with a sensitivity of 97% and specificity of 100% when heart-to-contralateral ratio of > 1.5 was used[44]. Furthermore, ^{99m}Tc-PYP scintigraphy showed reduced uptake in the apical segments of the LV in TTR. This correlates with apical sparing of longitudinal strain seen on echocardiography[45].

In addition, there may be potential to diagnose early TTR cardiomyopathy. An observational study of carriers of inherited TTR mutations included 12 asymptomatic carriers with normal echocardiographic and biochemical parameters. Cardiac ^{99m}Tc-PYP uptake was abnormal by visual scoring, comparing cardiac to bone tracer uptake, in 84%. Grade 2 or 3 tracer avidity, indicating TTR deposition, was seen in 58%[46]. However, serial ^{99m}Tc-PYP scanning has not been shown to track disease progression accurately, as demonstrated in a small study, which showed no significant change in tracer uptake after 18 mo despite obvious clinical progression of disease[47].

POSITRON EMISSION TOMOGRAPHY

Radiolabelled amyloid ligands have previously been developed to investigate for

Table 1 Perugini visual scoring

Score	Cardiac uptake and bone uptake
Score 0	Absent cardiac uptake and normal bone uptake
Score 1	Mild cardiac uptake
Score 2	Moderate cardiac uptake accompanied by attenuated bone uptake
Score 3	Strong cardiac uptake with mild/absent bone uptake

amyloid deposits in the brain in Alzheimer's disease. These tracers have also shown some utility in amyloid cardiomyopathy. Its concomitant use with nuclear scintigraphy aids in confirming localization of tracer uptake in heart. A systematic review of six studies involving the use of positron emission tomography (PET) in amyloid cardiomyopathy, including 98 patients, demonstrated a pooled sensitivity of 95% and specificity of 98% in differentiating amyloid cardiomyopathy from controls[48]. Although the individual studies have been small, due to high levels of accuracy, the use of PET and scintigraphy may potentially aid in screening early phases of TTR cardiomyopathy where structural disease may not be apparent on echocardiography or CMR[49]. This requires further exploration. Evidence of PET studies utilizing various cardiac tracers are described below.

^{11}C-Pittsburgh compound B, a radiotracer commonly used in the investigation of Alzheimer's disease, has the ability to identify amyloid cardiomyopathy due to both type A and type B amyloid fibrils. While this method does not distinguish between TTR and AL, it may help identify certain patients with type B amyloid fibril disease, predominantly V30M mutation-associated TTR cardiomyopathy where ^{99m}Tc-DPD scintigraphy has shown a lack of tracer uptake. However, the mechanism of this is not fully known[42,50]. In addition, the utility of this compound is limited by its very short half-life and difficult production.

^{18}F-florbetaben PET has been shown to help identify patients with amyloid cardiomyopathy, due to TTR or AL. Percentage ^{18}F-florbetaben retention was shown to predict myocardial dysfunction in amyloid cardiomyopathy[51]. In another study of 14 patients, 9 with AL or TTR cardiomyopathy and 5 controls, ^{18}F-florbetapir uptake was seen in all patients with amyloid cardiomyopathy and none of the controls[49]. An autopsy study of 20 patients with autopsy-documented amyloid cardiomyopathy, either due to AL or TTR, and 10 controls, showed binding of ^{18}F-florbetapir, a similar tracer to ^{18}F-florbetaben, in myocardial sections in all amyloid cardiomyopathy patients and in none of the controls[52].

^{18}F-fluorine sodium fluoride is a PET tracer that has been shown, in a small study, to differentiate biopsy-proven TTR from AL cardiomyopathy and controls. Tracer uptake was shown to be present in all of the TTR cardiomyopathy patients and none of either the AL-related patients or controls[53]. This radioisotope was also able to quantify the degree and regional distribution of tracer uptake. However, another report of two patients with TTR cardiomyopathy did not show any uptake of this tracer[54]. The authors hypothesized that specific TTR mutation may influence radioisotope uptake. Therefore, while ^{18}F-fluorine sodium fluoride shows promise as a TTR-specific investigative and disease-monitoring tool, it requires further investigation in larger studies.

CARDIAC COMPUTED TOMOGRAPHY

Currently, there is limited evidence regarding the utility of computed tomography (CT) in diagnosing TTR cardiomyopathy. Myocardial iodine concentration and ratio were increased in amyloid cardiomyopathy and can accurately distinguish amyloid cardiomyopathy from non-amyloid hypertrophic cardiomyopathy and healthy controls with an AUC of 0.99. At a threshold of 0.65, iodine ratio demonstrated a sensitivity of 100% and a specificity of 92% in diagnosing amyloid cardiomyopathy[55]. Myocardial extracellular volume measured using CT has been shown to accurately track laboratory and echocardiographic markers of amyloid cardiomyopathy severity and correlate with bone scintigraphy quantification of amyloid burden[56]. Furthermore, determining the myocardial extracellular volume previously required blood sampling to measure haematocrit level. However, recently, a methodology of calculating the extracellular volume, using a calculation involving the attenuation of blood, has eliminated the need for blood sampling from this process. This improves the feasibility of using CT as a potentially useful imaging modality in amyloid

cardiomyopathy[57].

CARDIAC MAGNETIC RESONANCE

Cardiac magnetic resonance (CMR) is a useful imaging modality in the diagnosis of amyloid cardiomyopathy. Its utility in assessing abnormal myocardial interstitium was described in 2005[58]. Characteristic features seen in amyloid cardiomyopathy were described as a subendocardial tram-line pattern on LGE imaging which can progress to transmural enhancement in later stages of the disease[59] (Figure 1). Alongside LGE, conventional sequences and non-contrast techniques including native T1 mapping can help diagnose amyloid cardiomyopathy and quantify amyloid burden, although caution should be applied in the setting of ectopic beats, which is not uncommonly associated with amyloid cardiomyopathy, but may result in overlapping blood pool and subsequent false positive diffuse elevation of T1 levels. Cardiac involvement in patients with inherited TTR can be seen in patients without clinical cardiac signs or increased LV wall thickness on CMR, suggesting a potential role in detecting pre-clinical amyloid cardiomyopathy in certain at-risk patients[60].

LATE GADOLINIUM ENHANCEMENT

LGE on CMR has been shown to be of high diagnostic value in amyloid cardiomyopathy and has achieved a diagnostic sensitivity of 85% and specificity of 92% in a meta-analysis of five studies[61]. Transmural pattern of LGE has been shown to be more associated with TTR than AL, although the classically described circumferential subendocardial or transmural LGE is not seen in most patients with amyloid cardiomyopathy. Other findings which are more suggestive of TTR include greater intraventricular septal wall thickness and right ventricular LGE[62]. These investigators also proposed a scoring system, derived from CMR with LGE, which differentiates TTR from AL with 87% sensitivity and 96% specificity[62].

Furthermore, the results of a study by Fontana and colleagues suggested that phase sensitive inversion recovery should replace conventional magnitude inversion recovery for LGE determination in the setting of amyloid cardiomyopathy. Phase sensitive inversion recovery helps to remove the potential confounder of incorrect inversion recovery time selection in diffuse infiltrative disease[63]. Higher proportion of left atrial LGE has been shown to have a strong association with amyloid cardiomyopathy and may help in differentiating amyloid cardiomyopathy from other cardiomyopathies. A sensitivity of 76% and specificity of 94% has been shown where left atrial LGE is > 33%, with significant reduction in left atrial emptying function[64].

However, LGE has some limitations in the investigation of amyloid cardiomyopathy. LGE does not enable assessment of diffuse changes in interstitial space secondary to amyloid deposition or quantitative assessment of expanded interstitium. This is due to inversion time adjustment to the least-enhancing myocardial region. As a result, absence of LGE does not confirm normal myocardium in amyloid cardiomyopathy[65]. Another limitation associated with gadolinium enhancement is the risk of nephropathy. Caution is warranted due to the high prevalence of renal impairment in patients with amyloid cardiomyopathy.

T1 MAPPING

T1 native mapping using non-contrast MRI has shown high levels of diagnostic accuracy in detecting AL cardiomyopathy. In a study of 53 AL amyloidosis patients, 28 patients with confirmed AL cardiomyopathy were compared to 36 healthy controls and 17 patients with aortic stenosis. Accuracy of 92% was seen using a non-contrast T1 cut-off of 1020 ms[66]. Compared to TTR cardiomyopathy, T1 elevations are higher in AL cardiomyopathy but similar diagnostic and disease-tracking performance has been shown in TTR. In TTR, T1 also correlates with left atrial area and with PR interval and QRS duration on electrocardiogram[67]. Quantification methods of myocardial T1, such as weighted mean shortened modified look-locker inversion recovery sequence T1 values have been shown to be significantly higher in amyloid cardiomyopathy when compared to healthy controls[68]. T1 mapping allows detection of diffuse myocardial disease and quantitative assessments, which are limited in LGE imaging[65].

T1 mapping can accurately identify patients with LGE-confirmed cardiac involvement in TTR and correlates well with the degree of amyloid deposition[69]. As a

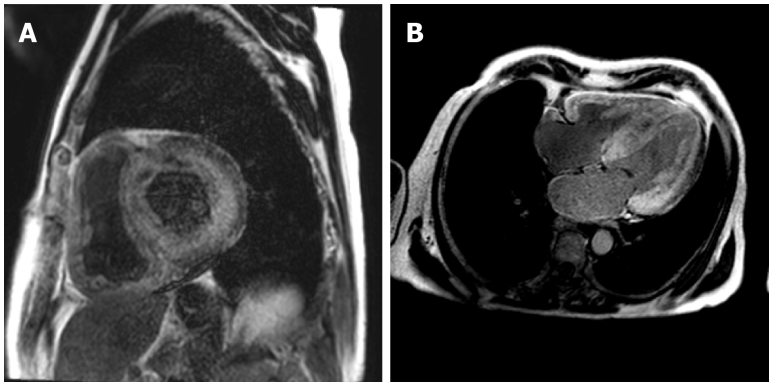

Figure 1 Cardiac magnetic resonance. A, B: Cardiac magnetic resonance demonstrating diffuse, circumferential and near transmural late gadolinium enhancement of the left ventricle in the 4-chamber (A) and short axis views (B), features which are characteristic of amyloid cardiomyopathy.

result, it can help improve detection rates of amyloid cardiomyopathy when used in combination with LGE sequences. It is also a particularly useful tool when contrast is contraindicated due to renal impairment and when LGE artefacts occur due to poor breath-holding and arrhythmias; diagnostic problems commonly seen in these patients.

MYOCARDIAL EXTRACELLULAR VOLUME

Myocardial extracellular volume is another cardiac mapping technique using CMR that is a validated indicator of myocardial fibrosis[70]. It involves T1 mapping acquisitions before and after T1-shortening contrast injection. Both T1 mapping and extracellular volume have recently been shown to perform well as diagnostic techniques in differentiating TTR from other causes of hypertrophic cardiomyopathy[71]. While not a specific feature of amyloid cardiomyopathy, it has been identified as a potential disease-marker to track therapeutic response in the reduction of hepatic amyloid burden following the use of anti-serum amyloid P component antibody in systemic amyloidosis[72].

Extracellular volume correlates with amyloid burden and has been shown to be an independent prognostic factor for survival in TTR cardiomyopathy patients[73]. Furthermore, extracellular volume has been suggested as a more robust marker in TTR cardiomyopathy when compared to T1 mapping as it has shown independent prediction of mortality, where T1 mapping has not[71]. In this regard, T1 mapping and extracellular volume are divergent when comparing TTR to AL cardiomyopathy. Extracellular volume is higher in TTR, reflecting proportionally more amyloid deposition. In contrast, native T1 levels, reflecting both interstitial and cellular changes, are lower in TTR[74]. However, these differing myocardial observations are poorly understood.

OTHER SEQUENCES

CMR-measured longitudinal strain can demonstrate the relative apical sparing and base-to-apex gradient in longitudinal strain, with significantly reduced global longitudinal strain, which is characteristic of amyloid cardiomyopathy[75]. Strain analysis using CMR can help diagnose LGE-positive amyloid cardiomyopathy patients while avoiding the need for contrast medium. Peak circumferential strain level and variability may be more sensitive when compared to LGE imaging in detecting early cardiac involvement in amyloid cardiomyopathy[76]. Basal segments strain parameters can accurately identify cardiac involvement in patients with amyloidosis[77].

Operator-independent heart deformation analysis using CMR has been shown to accurately reproduce radial and circumferential regional myocardial motion patterns, which correlate with feature-tracking indices in amyloid cardiomyopathy[78].

Reduced T2 ratio, comparing the T2 signal intensity of myocardium to skeletal muscle, has shown some utility in amyloid cardiomyopathy diagnosis and can predict mortality[79]. Myocardial oedema, as assessed by T2 mapping, is elevated in both TTR and AL cardiomyopathy, although to a higher degree in AL[80].

CONCLUSION

The use of multi-modality imaging in the diagnosis and management of suspected TTR cardiomyopathy is becoming increasingly accurate and necessary. In light of recent evidence for disease-specific therapeutic agents, high clinical suspicion coupled with earlier utilization of non-invasive imaging modalities are essential for diagnosing this insidious and elusive disease.

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