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Wild-type Transthyretin Cardiac Amyloidosis: Novel Insights from Advanced Imaging

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Abstract

Amyloidosis is caused by extracellular deposition of abnormal protein fibrils, resulting in destruction of tissue architecture and impairment of organ function. The most common forms of systemic amyloidosis are light-chain (AL) and transthyretin-related (ATTR). ATTR can result from an autosomal dominant hereditary transmission of mutated genes in the TTR (ATTRm) or from a wild-type form of disease (ATTRwt), previously known as senile cardiac amyloidosis (SCA). With the aging of the worldwide population, ATTRwt will emerge as the most common type of cardiac amyloidosis that clinicians encounter. Diagnosis of systemic amyloidosis is often delayed, either due to the false assumption that it is a rare disease, or due to misdiagnosis as a result of mistaking it with other conditions. Clinicians must integrate clinical clues from history, physical exam, and common diagnostic tests to raise suspicion for ATTRwt. The historical gold standard for diagnosis of cardiac amyloid is endomyocardial biopsy (EMB) with pathological distinction of precursor protein type, but this method often results in delayed diagnosis given the limited availability of expertise to perform and interpret the EMB. Emerging noninvasive imaging modalities provide easier, accurate screening for ATTRwt. These modalities include: advanced echocardiography, using strain imaging and the myocardial contraction fraction; nuclear scintigraphy, which can differentiate between ATTR and AL cardiac amyloid; and cardiac magnetic resonance, using extracellular volume measurement, late gadolinium enhancement, and distinct T1 mapping. These novel approaches reveal insights into the prevalence, clinical course, morphological effects, and prognosis of ATTRwt.

Introduction

Amyloidosis is caused by extracellular deposition of abnormal protein fibrils, resulting in destruction of tissue architecture and impairment of organ function[1]. Amyloidosis may be localized or systemic, and is categorized by the type of precursor protein[2]. Clinical

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manifestations of systemic amyloidosis depend on the site of amyloid deposition. The most common forms are light-chain (AL) and transthyretin-related (ATTR). AL amyloidosis is caused by deposition of immunoglobulin light chains resulting from an underlying plasma cell dyscrasia[3,4]. ATTR can result from an autosomal dominant hereditary transmission of mutated genes in the TTR protein (there are more than 100 known mutations in the gene) or as a wild-type form of disease (with a normal TTR sequence)[4,5]. TTR is produced by the liver and in the mutated state deposits in the peripheral nervous system, causing familial amyloid polyneuropathy (FAP), or the myocardium, causing familial amyloid cardiomyopathy (FAC).

Epidemiology

The most common TTR mutation in the United States is Val122Ile (Valine to Isoleucine substitution at position 122). TTR amyloid predominantly affects individuals of African American descent; Val122lle mutation prevalence has been reported in 3.43% of African Americans under age 65[6]. Wild-type TTR (ATTRwt), previously known as Senile Cardiac Amyloidosis (SCA), is caused by deposition of amyloid fibrils formed from misfolded TTR proteins, and has been described almost exclusively in older adult males[1-3]. While AL Amyloid is a relatively rare disorder, with approximately 3,000 new cases in North America annually[4], ATTRwt is rapidly increasing in recognition. Wild-type TTR deposits are already found in >25% of people over age 80 at autopsy, and its percentage of clinical representation at amyloid centers is rapidly accelerating[7]. Additionally, with the aging of the worldwide population, ATTRwt will likely become the most common type of cardiac amyloidosis (CA) encountered by clinicians.

Impediments to Diagnosis

Despite its clinical importance, the diagnosis of cardiac amyloidosis can be delayed or missed altogether. Several factors may be responsible. First, there is the assumption that amyloid is a rare condition. Indeed, AL amyloid is rare; only 30-50% of patients with AL amyloid have cardiac involvement[4] and there are an estimated 10,000 patients with AL in United States. ATTRwt, however, is not rare, and universally involves the heart. Second, there still exists an erroneous belief that cardiac amyloid is untreatable and that current management has no impact on outcomes. However, accurate diagnosis is critical for guiding amyloid-directed therapies as well as management of amyloid sequelae, especially heart failure and arrhythmias. Third, cardiac amyloidosis can be clinically subtle. Extra-cardiac manifestations such as peripheral neuropathy may predominate and become the clinical focus[1]. Diagnosis of ATTRwt-CA can also be confounded by the high prevalence of monoclonal proteins that occur with advancing age; up to 20% of elderly patients with TTR cardiac amyloidosis have concomitant monoclonal gammopathy of undetermined significance[1]. Symptoms of ATTRwt-CA are relatively non-specific, and are often attributed to the syndrome of heart failure. Indeed, recent investigations have shown that a significant percentage of patients with HFPEF have ATTRwt cardiac amyloidosis[8,9]. In fact, many of the clinical disorders with which ATTRwt-CA is associated – including HFPEF, aortic stenosis, stroke, atrial fibrillation, syncope, and angina – are especially common in the elderly, and the underlying cause is often not defined. Fourth, the phenotypic heterogeneity of amyloidosis often causes protean, non-specific symptoms (e.g. fatigue) or extra-cardiac

manifestations that prompt care with a non-cardiac specialist. Finally, the necessity of target organ tissue histological diagnosis with confirmation of amyloid type is often associated with delays in diagnosis, because of the expertise required for both EMB and precursor protein confirmation by mass spectroscopy.

Clinical Clues to Diagnosis of ATTRwt

Cardiac amyloidosis is frequently misdiagnosed as hypertensive heart disease and hypertrophic cardiomyopathy (HCM), since their clinical and imaging feature can overlap[10]. A clinician whose differential diagnosis includes CA may discern findings that increase its likelihood. These include HFPEF in the absence of an elevated blood pressure, recent-onset hypotension (e.g. in a formerly hypertensive patient), intolerance of commonly-used cardiovascular medications such as ACE inhibitors or beta blockers, or a history of bilateral carpal tunnel syndrome. While dyspnea and lower extremity edema are common findings in heart failure, CA is often characterized by a predominance of findings related to right heart failure such as of hepatomegaly, ascites, abdominal boating/satiety and edema. Pulmonary edema, however, is quite rare[10]. CA patients may also have positive troponins, frequently without typical angina, prompting diagnostic evaluation for acute coronary syndrome, yet without obstructive lesions on coronary angiography. Angina, if present, may also be due to amyloid infiltration of small intramyocardial vessels or myocardiotoxicity from the amyloid deposits[11].

Prognosis, Treatment, and the Need for Better Diagnostics

ATTRwt is not a benign diagnosis. A prospective cohort study found the median survival of ATTRwt after diagnosis to be 43 months, with a decline in 6-minute walk test and ejection fraction (EF) over the first 18 months[12]. A recent prospective study found a similar median survival from time of biopsy of 46.7 months with a 5-year survival was 35.7%. Notably, 78% of the deaths were attributed to cardiac causes[13]. Fortunately, potential treatments for ATTRwt are in late phase clinical trials. Pharmacologic therapies include TTR stabilizers such as tafamidis and diflunisal, which have been shown to be effective for FAP[14,15]; RNA silencers and monoclonal antibodies are also being tested[16]. Regarding heart failure therapy, it is important to recognize that non-dihydropyridine calcium channel blockers are contra-indicated in patients with cardiac amyloidosis, as they cause significant negative inotropy and high degree heart block. Additionally, there is potential increased risk of digoxin toxicity, due to digitalis' binding of amyloid fibrils[17]. Diuresis is the mainstay of clinical management, while ACE inhibition and nitrates carry a greater risk of symptomatic hypotension. High dose beta blockade is also often poorly tolerated, due to fixed stroke volume and reliance on an increased heart rate to maintain cardiac output[18].

Yet, there is much still to learn about the actual prevalence and clinical course of the disease. As therapies emerge, imaging modalities may have a role not just in diagnostics, but also in monitoring disease progression or response. Newly developed non-invasive imaging methods have already provided novel insights into amyloid and associated conditions, such as heart failure with preserved ejection fraction (HFPEF), atrial fibrillation, and aortic stenosis with paradoxical low flow. This review will focus on the evaluation of ATTRwt

cardiac amyloid and the novel insights that have recently been garnered from a growing array of imaging modalities.

Classical Diagnostic Tests

Electrocardiography

Common diagnostic tools can assist in the detection of cardiac amyloidosis. Typical ECG changes reflect the displacement of myocardium with amyloid deposits, affecting the conduction system[3]. The classically reported ECG finding ascribed to CA is low QRS voltage (amplitude of ≤ 0.5mV in limb leads or ≤ 1.0 mV in precordial leads), especially in disproportion to a hypertrophic left ventricle (LV) seen on echocardiogram[3,5]. However, in ATTRwt, the sensitivity of low voltage in isolation is poor (< 30%), as the fibrils are less toxic to the myocardium than in AL, and up to 15% of subjects may even have electrocardiographic evidence of LVH[5,17,19,20]. The lack of sensitivity of the electrocardiogram is especially true among older adults with the Val122Ile mutation, which almost exclusively affects African-Americans, in whom the presence of increased QRS amplitude (independent of hypertension) can potentially confound detection of amyloid-related voltage decrements[20]. Irrespective of race, hypertension-related LVH can decrease sensitivity of low voltage as a diagnostic criterion for CA[5], as can left bundle branch block conduction abnormalities[17]. Diagnostic approaches that incorporate both ECG voltage with echocardiographically-determined wall thickness in order to calculate voltage-to-mass ratios have been shown to be sensitive and specific for diagnosing CA than voltage criteria alone[21]. Another classic sign on ECG is a pseudo-infarct pattern, either poor R-wave progression or QS waves in the precordial leads, yet these are reported more frequently in AL than ATTR[12,19].

Endomyocardial Biopsy

The current reference standard for diagnosis of cardiac amyloid involves EMB. This approach can be challenging, especially in context of large scale population-based screening. EMB is a procedure often restricted to centers with significant expertise in its performance, typically large referral centers with transplant programs[1]. While rare, procedural complications can include arrhythmia, perforation with pericardial tamponade, and pneumothorax[22]. In addition to technical expertise required for cardiac biopsy, pathologic expertise is required for accurate identification of amyloid and appropriate subtyping[23]. Histological staining using amyloid-specific stains (Congo red) reveals apple-green birefringence under polarized light. Pathologic verification of the amyloid precursor protein by immunohistochemistry and/or sequence analysis by mass spectroscopy should be performed for further diagnostic confirmation[1,3,5]. In ATTR, extra-cardiac biopsies can have low sensitivity, thereby emphasizing the need for accurate non-invasive screening tool[1]. The aforementioned limitations of ECG, EMB, or extra-cardiac biopsies to diagnose ATTRwt yields a need for accurate and practical diagnostic imaging techniques.

Insights from Novel Imaging for ATTRwt-CA

Non-invasive imaging is widely used for diagnosis and serial evaluation of patients with known or suspected cardiac amyloid. Traditional imaging methods have predicated diagnosis on cardiac morphology. Newly developed techniques have enabled more sensitive assessment of myocardial function, as well as quantitative evaluation of myocardial tissue characteristics that can be altered in the context of amyloid deposition. The following sections will provide an overview of advances in echocardiography, nuclear scintigraphy, and cardiac magnetic resonance as relevant to diagnosis and management of ATTRwt-CA.

Echocardiography

Morphology and Function—Many previously described characteristics of ATTRwt-CA can be demonstrated by conventional 2D echocardiography. These findings include left and right ventricular (LV, RV) wall thickening, normal to small LV cavity – initially with preserved ejection fraction, bi-atrial enlargement, and a small pericardial effusion. ATTR-CA is characterized by progressively worsening diastolic dysfunction, ultimately to a restrictive pattern, with shorter deceleration time (<150ms) and high early (E-wave) and relatively low atrial (A-wave) velocities (E/A waves >2). Severity of diastolic dysfunctional has been reported to be proportional to magnitude of cardiac amyloid deposition[18]. A non-specific but frequently mentioned finding of ATTRwt-CA is a granular, speckled appearance of the myocardium. Speckling, however, has been shown to be dependent on data acquisition parameters (e.g. gain settings) and may not be apparent using relatively recent echocardiography machines[3,12,17,24].

Wall Thickness—Another basic echocardiography hallmark of ATTRwt-CA is increased wall thickness. Diagnostic suspicion should be increased when wall thickness is increased in the absence of a stimulus such as hypertension, predisposing hemodynamic factors (e.g. aortic stenosis), or genetic conditions (e.g. hypertrophic cardiomyopathy, Fabry's disease)[1,3,5,6,12]. While morphologic features of AL and ATTRwt can overlap, prior studies have reported patients with ATTRwt to manifest greater LV wall thickness than those with AL[2,25,26,27] – mean wall thickness of 17mm±2 versus 15mm±2 in a recent study[27]. Irrespective of diagnostic subtype, increased wall thickness in patients with amyloid is due to protein (AL or TTR) deposition rather than actual myocyte hypertrophy, thereby explaining concomitant “low voltage” on ECG[1,5].

Strain and Strain Rate—Advanced echocardiographic techniques reveal more sophisticated characteristics of ATTRwt-CA. Echocardiographic strain imaging, for example, provides a means of quantifying regional myocardial deformation. Longitudinal strain (LS) can be analyzed using tissue-Doppler imaging (TDI) and 2D speckle-tracking. Furthermore, 3D speckle-tracking can be used to differentiate between ATTRwt-CA and other hypertrophic diseases by potentially yielding improved assessment of global radial, circumferential, and longitudinal strain[1,3,5,6,15,25,28]. Radial and longitudinal strain have each been shown to be reduced in ATTRwt-CA as well as other conditions, although the pattern of strain decrement can be used to identify CA. A novel insight from strain imaging is that patients with ATTRwt-CA typically demonstrate marked decrease in LS in basal and

mid-wall areas with relative apical sparing, referred to as “cherry on top” or apical preservation[17] (**Figure 1**). Conversely, patients with HCM or aortic stenosis related LVH typically demonstrate reduced LS in regions of maximal hypertrophy[5,6,17,25,29]. Generally, abnormal LS portends a worse survival. Curiously, survival in ATTRwt is better than in AL despite similarly abnormal LS, likely due to the greater toxicity of AL amyloid[17,27].

Myocardial Contraction Fraction—Conventional measures of left ventricular function, notably the ejection fraction, are often initially normal/near-normal in CA. However, actual physiologic performance of the LV is not intact, due to amyloid-associated changes in ventricular remodeling (e.g. chamber size and wall thickness), reduced chamber capacitance and decreased chamber contractility. A novel metric of myocardial contraction, the myocardial contraction fraction (MCF), which is the ratio of stroke volume to myocardial volume, is frequently abnormal in ATTR-CA patients (Figure 2). Normal or “preserved” EF in ATTR-CA is due to a similar percentage decrease in both stroke volume and LV end-diastolic volume (LVEDV), which occurs as the ventricular wall thickens with concomitant decline in ventricular capacitance and upward shifts in the end diastolic pressure volume relation.[29] The MCF, while analogous to the ejection fraction in terms of being unitless and free of the need for indexation for body size, offers several distinct theoretical advantages. First, capitalizing on the fundamental principle that the myocardium is incompressible from end diastole to end systole, and by indexing the stroke volume to the myocardial volume, the MCF is an index of the volumetric shortening of the myocardium that is independent of chamber size and geometry. By eliminating chamber volume from the assessment of shortening, the MCF expresses the strain relationship only in terms of the heart structure which shortens, namely the myocardium. As a measure of myocardial shortening, the stroke volume is therefore most appropriately assessed relative to the myocardium (specifically to myocardial volume). The MCF, though operationalized prior to the advent and widespread measurement of strain using echocardiography, is highly correlated with global longitudinal strain[30]. The novel insight from MCF is that it is a better marker of pathology in ATTRwt cardiac amyloid than EF. In a recent study, MCF <30 in CA patients was associated with increased risk of death, while EF did not correlate[31]. Emerging data also suggest that MCF has superior diagnostic ability for ATTR-CA, i.e. correlates better with 99mTc-PYP positivity than ECG voltage-to-mass ratio[1,32].

Nuclear Scintigraphy

Several nuclear scintigraphy tracers are currently being evaluated for detection of cardiac amyloid. These include bone imaging agents such as (99m) Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) and (99m)Tc-pyrophosphate (99mTc-PYP).

The history of nuclear scintigraphy to detect CA originates when Kula et al. (1977) visualized calcifications in amyloid deposits with 99mTc –diphosphanate[23]. In 1982, there was a report of two patients without acute myocardial infarction who demonstrated 99mTc-PYP myocardial uptake and confirmed cardiac amyloidosis, one diagnosed by EMB and the other at autopsy[32]. Yet, in the 1980s, sensitivity for detecting CA was determined to be poor, likely due to inability to differentiate AL and TTR cardiac amyloid, lack of a quantitative

scoring system for measuring myocardial tracer retention, and uncommon usage of advanced imaging at that time[17,23].

The two commonly used nuclear isotopes, 99mTc-DPD and 99mTc-PYP, both localize to cardiac TTR deposits. While 99mTc-DPD has been more widely studied, it is not available in the United States and in Canada. 99mTc-PYP, however, is FDA-approved for use in both planar and Single Photon Emission Computed Tomography (SPECT) imaging. It is speculated that both agents are taken up by TTR-infiltrated myocardium via a calcium-mediated mechanism[1,3,5]. While several studies show that 99mTc-DPD and 99mTc-PYP show only ATTR uptake and thus can differentiate from AL[33], there is some evidence that both can be taken up as well in patients with AL, albeit with less intense myocardial uptake. The reason for increased uptake in ATTR versus AL is unknown, but has been hypothesized to be due to higher amount of calcium, or longer duration of amyloid deposition, as ATTR-CA is more indolent and less myocardiotoxic than AL-CA. Bokhari et al. (2013) demonstrated that a 99mTc-PYP visual score of 2 or greater and a heart-to-contralateral ratio (HCL), a quantitative visual score measured one hour after injection, of greater than 1.5 can differentiate between ATTR and AL with sensitivity and specificity near 100%[34] (**Figure 3**). Nuclear scintigraphy results can also have prognostic value. Rapezzi et al. (2011) showed that an increased 99mTc-DPD heart-to-whole body ratio, another index of CA uptake, predicts poorer outcomes[35]. Similarly, increased uptake of 99mTc-PYP has been shown to correlate with disease severity such as wall thickness and LV mass[35]. High 99mTc-PYP uptake, though, as measured by the H/CL ratio, was recently shown to remain constant over time despite clinical progression of CA, which may reflect a threshold of amyloid burden beyond which the clinical course has been triggered, despite slowing of amyloid deposition[36].

Nuclear scintigraphy may ultimately obviate the need for biopsy to diagnose ATTR-CA and as has already yielded several new insights. First, prevalence of undiagnosed or misdiagnosed ATTR-CA is much higher than previously recognized. For example, among a cohort of 120 HPEF patients (≥ 60 years old) with LV hypertrophy (wall thickness ≥ 12mm), 13.3% showed a moderate-to-severe 99mTc-DPD uptake[15]. Additionally, preliminary data reveal that 16% of 75 patients with severe aortic stenosis, mostly men, had strong 99mTc-PYP uptake[37]. Discovering cardiac amyloid as the underlying etiology directs clinical focus on preventing or treating amyloid deposition rather than just the apparent cardiac disorders. Finally, the composition of precursor protein in CA (ATTR versus AL) has been shown to be more prognostic than the change in morphologic strain or myocardial function[27].

Cardiac Magnetic Resonance (CMR)

Cardiac magnetic resonance (CMR) is widely accepted as a non-invasive reference standard for cardiac function and structure. CMR entails no radiation exposure and provides excellent image quality independent of patient body habitus, making this modality well suited for cross-sectional study of patients with known or suspected amyloid. CMR has been shown to be more reproducible than echocardiography[38], enabling detection of subtle impairments in cardiac contractility. Prior validation studies have shown CMR to yield near exact agreement with ex-vivo chamber volumes as well as necropsy-quantified myocardial mass[39,40].

Importantly, the above indices can be quantified using non-contrast cine-CMR, which can be used to provide accurate quantification of amyloid-associated morphological changes (such as LVH, decreased chamber size, and atrial dilation) even in patients with contraindications to contrast use such as advanced renal insufficiency. Beyond cardiac function and remodeling, CMR can directly assess myocardial tissue characteristics. Post-contrast tissue characterization methods – including inversion recovery imaging for regional late gadolinium enhancement (LGE) and T1 mapping for extracellular volumes fractionation – have been used to diagnose amyloid and correspond to adverse clinical outcomes[41,42,43]. Thus, within a single exam, CMR can evaluate distinct facets of amyloid-related cardiomyopathy: myocardial structure, function, and tissue characteristics.

Late Gadolinium Enhancement—Post-contrast tissue characterization via LGE is predicated on increased gadolinium deposition (with consequent T1 shortening) in regions of increased myocardial extracellular volume. Multidisciplinary studies have shown patients with CA to demonstrate increased interstitial expansion on biopsy due to amyloid protein deposition, corresponding to LGE on CMR[44]. Novel insights from LGE on CMR include that amyloid-associated patterns of LGE can vary: subendocardial, mid-myocardial, or transmural in location, but typically occurs in a non-coronary arterial distribution. Diffuse subendocardial LGE, however, has been reported to be more common in the context of AL amyloid, although overlap can occur (**Figure 4A**). For example, among a cohort of 250 amyloid patients, subendocardial LGE was more prevalent in AL (39% in AL versus 24% in TTR, $p<0.05$) whereas transmural LGE was more common in TTR (63% versus 27% in AL, $p<0.001$)[45]. Similar results have been reported in retrospective datasets, which have reported LGE to be more extensive in patients with TTR (versus AL) amyloid[46]. Importantly, pattern of LGE can sometimes be challenging to differentiate from other infiltrative processes or from myocarditis. In this context, ancillary morphologic findings such as LVH can be of utility. Moreover, as amyloid-directed treatment varies based on subtype, CMR may be of greatest utility as an initial screening test, on which presence of LGE may prompt further testing (via biopsy or adjuvant testing) to establish amyloid sub-type (AL versus TTR) and guide tailored therapies.

Beyond diagnosis, another novel insight from CMR is that LGE has been shown to stratify clinical prognosis among patients with known or suspected amyloid. Several LGE pulse sequences have been used for this purpose. Among a cohort of 154 patients (64 hypertensive, 90 suspected amyloid), White et al. (2014) demonstrated that diffuse LGE, assessed via an inversion time [TI] scout method for which TIs were sequentially increased to assess myocardial T1 shortening versus blood pool (**Figure 4B,C**), independently predicted mortality (hazard ratio: 6.0, 95% CI 3.0-12.1; $p < 0.0001$)[42]. Among a mixed cohort of 250 patients with AL and TTR amyloid, Fontana et al. (2015) reported that transmural LGE (on phase sensitive inversion recovery imaging) predicted subsequent mortality (hazard ratio, 5.4; 95% CI 2.1-13.7; $p<0.0001$) and remained an independent predictor of death after adjustment for N-terminal pro-brain natriuretic peptide, EF, stroke volume index, E/E', and LV mass index (hazard ratio, 4.1; 95% CI, 1.3-13.1; $P<0.05$). Of note, 15% of patients in this amyloid cohort had negative LGE; patients with negative LGE had lower LV mass, lesser diastolic dysfunction, and less advanced ECG and biomarker

(BNP) abnormalities.[46] In this context, it is possible that patients with biopsy-proven cardiac amyloid but negative LGE have less advanced disease – corresponding to improved outcomes – irrespective of biopsy results. Further studies are warranted to investigate.

T1 mapping—T1 mapping represents a new CMR approach that enables quantification of diffuse alterations in myocardial longitudinal relaxation (T1). Whereas amyloid itself produces increased T1 on pre-contrast imaging, post-contrast T1 is shortened due to amyloid-associated increments in extracellular volume of distribution (within which gadolinium can accumulate). A novel insight derived from T1 on CMR is that pre- and post-contrast T1 mapping data (obtained from regions of interest in the LV blood pool and myocardium) can be used to calculate myocardial extracellular volume (ECV) fraction, which holds the potential to provide a quantitative index of amyloid disease burden. Additionally, non-contrast T1 mapping has been shown to differentiate between patients with and without amyloid, as well as between patients with LVH of differing etiologies. Among a mixed cohort of patients with AL-CA, ATTRCA, hypertrophic cardiomyopathy (HCM), and normal controls, Fontana et al. (2014) reported that native T1 was higher in ATTR-CA than HCM and controls (1,097 ± 43 ms versus 1,026 ± 64 ms versus 967 ± 34 ms, respectively; both $p < 0.0001$), but lower than that in AL-CA (AL 1,130 ± 68 ms; $p = 0.01$). [47]

Another insight into the diagnosis and understanding of ATTR-CA arises from the revelation that ECV may even be elevated in patients with biopsy proven amyloid but negative LGE. For example, among a cohort of 36 patients with biopsy proven systemic amyloid (30 AL, 6 TTR) and 30 normative controls, Barison et al. (2015) reported ECV to be higher in amyloid patients versus controls (0.43 ± 0.12 versus 0.26 ± 0.04, $P < 0.05$), and notably even higher among amyloid patients without LGE (0.35 ± 0.10) as compared to controls ($P < 0.01$)[48]. Other studies have shown ECV to be useful for stratifying between amyloid subtypes, as evidenced by slightly higher ECV among patients with TTR versus AL amyloid ($p=0.008$)[49]. Ongoing research is aimed at testing prognostic utility of T1 mapping (inclusive of native T1 and calculated ECV), as well as relative utility of different CMR approaches for predicting therapeutic response among patients with AL and TTR amyloid[50].

Diagnosis Using Advanced Imaging—These novel imaging approaches can be incorporated into the diagnostic approach to a patient with cardiac amyloid. Once patient history and exam – including the clues described earlier – elicit enough clinical suspicion for CA, data from ECG and echocardiogram may support this diagnosis. CMR can also be used to confirm morphologic or functional changes typical of cardiac amyloid. For these patients, ruling out AL amyloid is imperative to avoid delaying vital therapies, and laboratory testing should include serum and urine protein electrophoresis with immunofixation as well as kappa and lambda free light chains. Natriuretic peptides and troponins could be used for staging purposes as well. If the immunologic bloodwork shows the presence of a monoclonal protein, these patients warrant histopathology confirmation of the diagnosis to exclude AL amyloid, although even in these patients a highly-positive scintigraphy scan may indicate ATTR-CA with concomitant monoclonal gammopathy, which is common with advanced age. If there is no evidence of a monoclonal protein by serum or urine protein

electrophoresis with immunofixation and kappa/lambda free light chains, high myocardial retention of the tracer on nuclear scintigraphy[51] is indicative of ATTR (and should be clarified into wild type versus mutant by genotyping), while low uptake is unlikely to represent cardiac amyloid, although with enough clinical suspicion an endomyocardial biopsy could still be justified[52]. (**Figure 5**)

Conclusion

Improved diagnostic screening for TTR cardiac amyloidosis is necessary, as the prevalence of ATTR-CA from wild type disease is significantly greater than previously known, and will continue to increase as the population ages. Classical methods of diagnosis that rely upon symptomatology, physical exam findings, ECG, and basic echocardiography, are either insensitive or nonspecific to confirm the diagnosis of ATTRwt-CA. The diagnostic gold standard, endomyocardial biopsy, is frequently considered too invasive or resource-intensive to adequately keep pace with the diagnostic need. Novel imaging modalities, though, have been shown to aid in early, non-invasive, and specific detection of ATTR-CA once the diagnosis is suspected. For example, advanced echocardiography strain patterns, which show characteristic apical sparing and a reduction in the ratio of stroke volume to myocardial volume (i.e. the MCF), are strongly suggestive of ATTRwt-CA. Additionally, nuclear scintigraphy is excellent at detecting ATTRwt-CA and differentiating it from AL via qualitative and quantitative scoring systems. Finally, CMR tissue characterization methods such as LGE and T1 mapping data can help to differentiate amyloid from other hypertrophic cardiac disease and stratify prognosis. These novel imaging modalities offer improved mechanisms for accurate diagnosis of ATTRwt-CA, enable a greater understanding of the disease and its progression, and can even aid in prognosis.

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Brief summary

Wild-type transthyretin cardiac amyloid (ATTRwt), previously known as senile cardiac amyloidosis (SCA), is an under-recognized disease. Diagnosis of systemic amyloidosis is often delayed due to misdiagnosis or logistical difficulties related to the need for invasive methods. Emerging non-invasive imaging techniques can facilitate early and specific identification of ATTRwt. Advanced echocardiography, nuclear scintigraphy, and cardiac magnetic resonance have yielded important insights concerning prevalence, clinical course, and prognosis of ATTRwt.

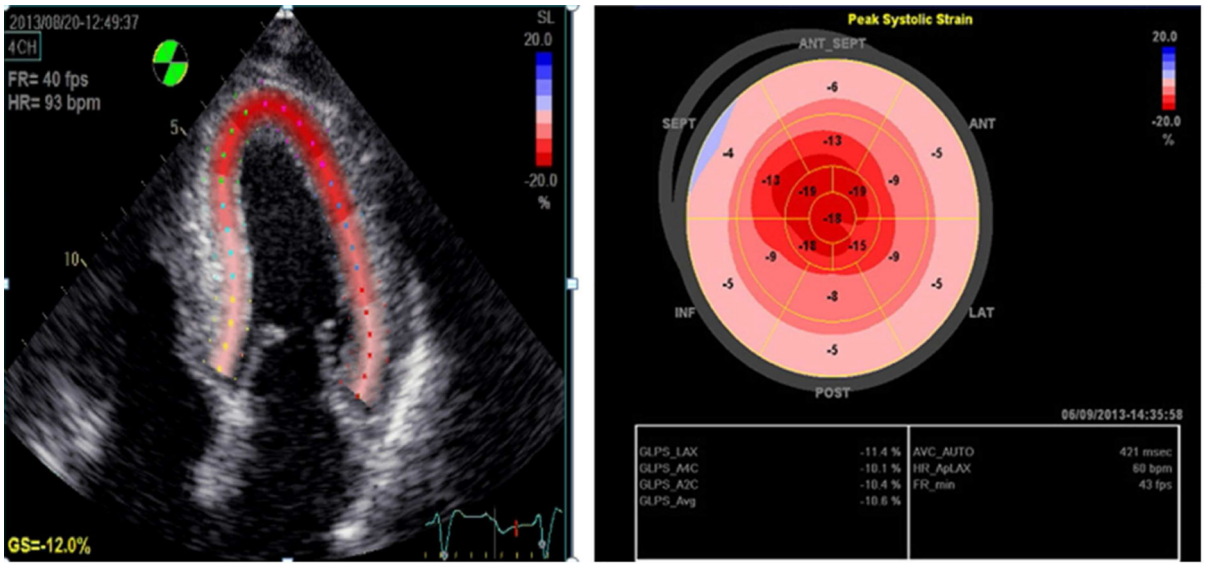


Figure 1. "Apical Sparing" Strain Pattern of ATTR Cardiac Amyloid on Echocardiogram

Patients with CA typically demonstrate marked decrease in longitudinal strain in basal and mid-wall areas with relative apical sparing, referred to as "cherry on top" or apical preservation.

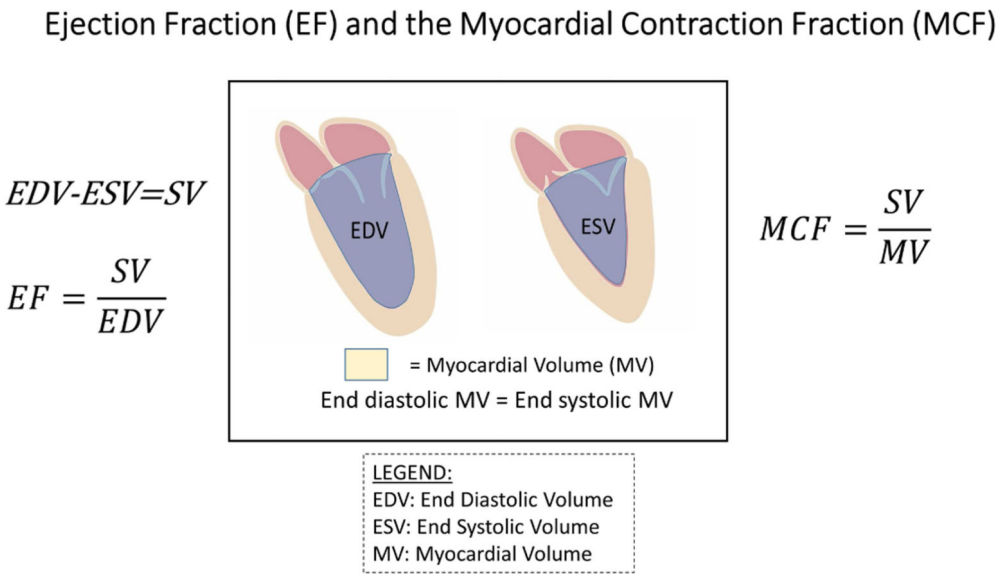
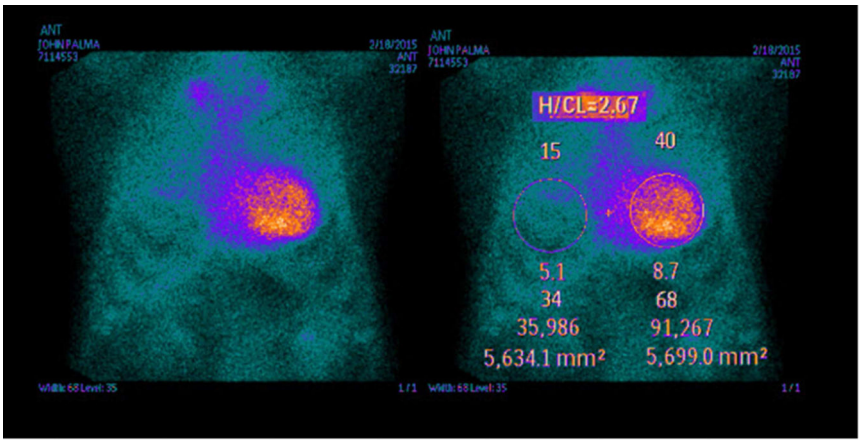


Figure 2. Myocardial Contraction Fraction

The myocardial contraction fraction (MCF) is based on the principle that the myocardium is nearly incompressible and does not change volume significantly from end-diastole to end-systole. By indexing the stroke volume to the myocardial volume, the MCF is an index of the volumetric shortening of the myocardium that is independent of chamber size and geometry. The MCF, while analogous to EF in terms of being unitless and free of the need for indexation for body size, offers several theoretical advantages including expressing the strain relationship only in terms of that which shortens, namely the myocardium, thereby providing an ability to distinguish pathologic from physiologic hypertrophy.



Visual Cardiac Score
0 Absent Myocardial Uptake
1 Myocardial Uptake < Bone
2 Myocardial Uptake = Bone
3 Myocardial Uptake > Bone

Figure 3. Semiquantitative and Quantitative analysis of ^{99m}Tc-PYP Myocardial Uptake

Semiquantitative visual cardiac score was assigned 0-3 according to the scale detailed (A). The representative image demonstrates a visual cardiac score of 3. Quantitative heart-to-contralateral (H/CL) ratio was calculated by drawing a region of interest (ROI) over the heart, copying and mirroring it to the contralateral chest, and calculating the ratio of heart ROI mean counts to contralateral ROI mean counts (B). The representative image demonstrates H/CL ratio 40/15=2.67.

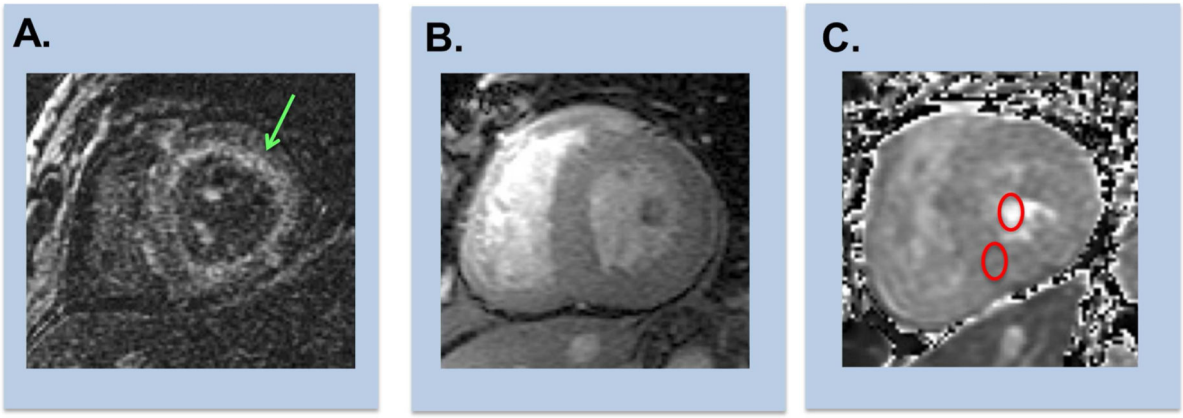


Figure 4. Representative Examples of Cardiac Amyloid on CMR

Representative examples of CMR evidenced enhancement patterns among patients with cardiac amyloid.

(A) Diffuse subendocardial enhancement (green arrow) on DE-CMR (inversion time [TI] 300msec).

(B) Diffuse transmural enhancement on DE-CMR (left [equivalent TI]).

(C) Corresponding T1 map enables quantification of extracellular volume fraction, which can be can be calculated via measurement of T1 in myocardium and blood pool (red circles) on matched pre- and post-contrast images.

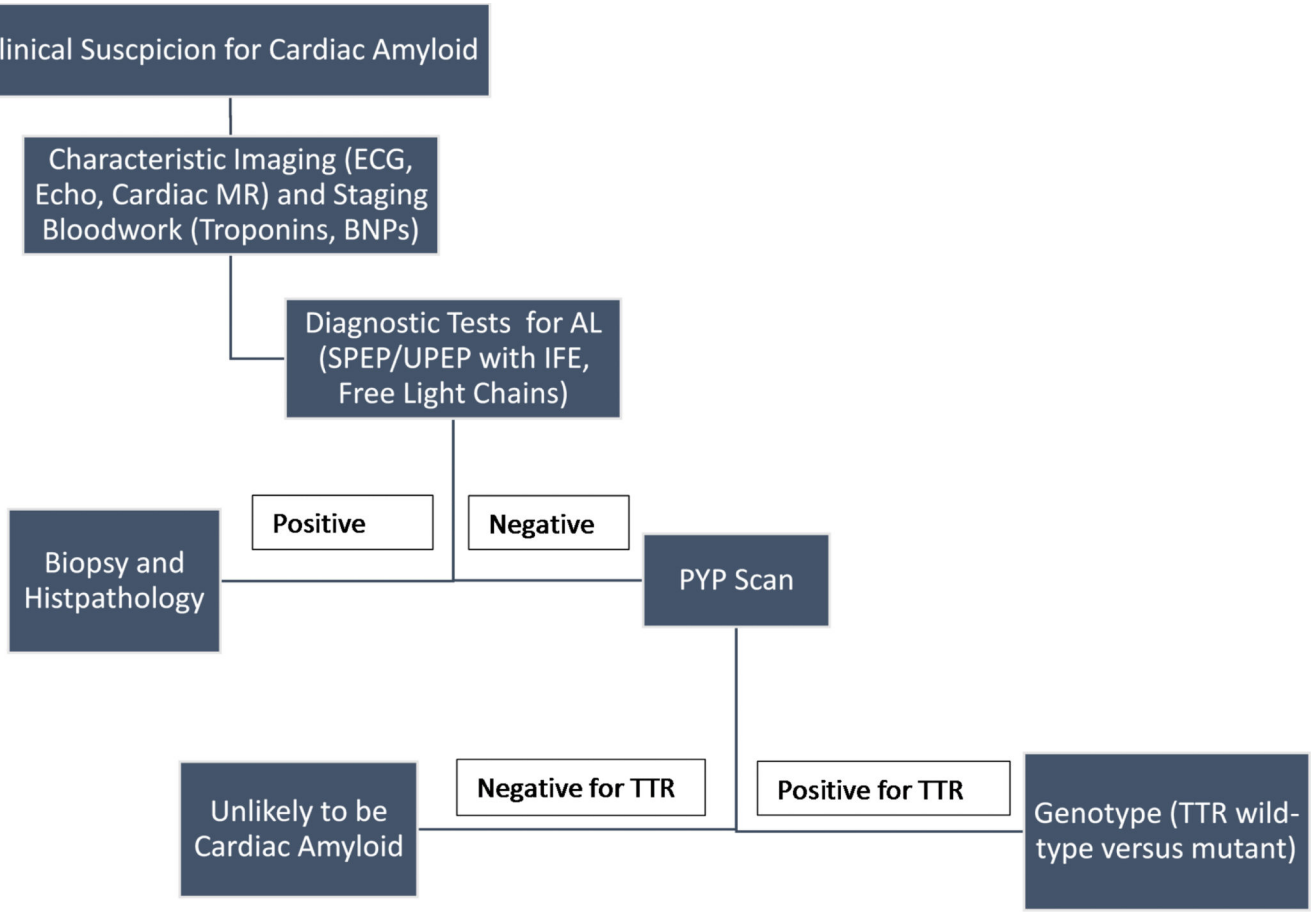


Figure 5.
Diagnosis Algorithm for ATTRwt Cardiac Amyloid using PYP scanning as an alternative to EMB

Table 1

Comparison of non-invasive imaging modalities for Cardiac Amyloidosis

Modality	Advantages	Limitations	Novel Insights
Echocardiography	- Widely available and relatively inexpensive - Can provide insight into morphological and functional cardiac changes - Emerging role for strain imaging for diagnosis and prognosis	- Best for assessing advanced LV remodeling (although diastolic dysfunction may suggest early changes) - Limited by patient-specific factors (e.g. windows, image artifacts) - Morphologic and functional changes non-specific (amyloid abnormalities may overlap with other cardiomyopathies, cannot differentiate ATTR from AL) - Strain imaging not widely clinically available	- LV Wall thickness of ATTR > AL, usually - Apical sparing very suggestive of cardiac amyloid - Strain imaging may be prognostic - Myocardial contraction fraction (MCF) may be useful for identification and is prognostic for ATTR
Nuclear (^{99m}Tc-PYP, ^{99m}Tc-DPD)	- Highly sensitive for TTR amyloid due to either mutation or wild type - Can differentiate ATTR from AL - ^{99m}Tc-PYP available for use in US and Canada	- Negative result does not exclude AL cardiac amyloid - Minimal radiation exposure (equivalent to mammogram) - ^{99m}Tc-DPD not FDA approved	- Prevalence of TTR cardiac amyloid is higher than previously recognized in conditions such as HFPEF and aortic stenosis - Extent of myocardial retention correlates with poorer prognosis - TTR amyloid deposits accumulate slowly - Clinical disease progression occurs despite lack of changes with imaging
CMR	- High spatial and temporal resolution - No radiation exposure, reproducible (excellent for serial assessment of function, morphology) - Cine-CMR and native T1 mapping do not require contrast - Tissue characterization may enable disease detection prior to advanced changes in LV morphology	- Contra-indicated in patients with ferromagnetic implants (e.g. pacemaker; frequently among CA patients with conduction disease) - Gadolinium contraindicated in patients with advanced renal insufficiency - Patients with claustrophobia or advanced HF may not tolerate CMR - LGE patterns non-specific; may require biopsy to establish diagnosis and distinguish amyloid subtypes (TTR, AL)	- LGE and ECV based tissue characterization provide incremental diagnostic utility beyond standard morphological indices (e.g. LVH, EF) - LGE pattern and ECV elevation magnitude may help to distinguish between amyloid subtypes (TTR and AL) - LGE and ECV stratifies prognosis (mortality) among amyloid patients independent of LV morphology, functional, and biomarker indices