The Role of Technetium Scintigraphy in the Non-Invasive Diagnosis of Transthyretin Cardiac Amyloidosis

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Abstract

Technetium scintigraphy, specifically using technetium-99m-labeled bone-seeking tracers such as Tc-PYP, Tc-DPD, and Tc-HMDP, plays a crucial role in the non-invasive diagnosis of transthyretin cardiac amyloidosis (ATTR-CA). This imaging modality has been validated for its high sensitivity and specificity in detecting myocardial amyloid deposits, particularly in patients with heart failure and echocardiographic or cardiac MRI findings suggestive of cardiac amyloidosis.

The diagnostic utility of technetium scintigraphy is particularly significant when combined with blood and urine tests to exclude monoclonal protein, thereby differentiating ATTR-CA from light chain (AL) amyloidosis. The American College of Cardiology and other Multisocietal guidelines support the use of technetium scintigraphy for the non-biopsy diagnosis of ATTR-CA in the appropriate clinical context.[1]

Technetium scintigraphy can achieve a specificity and positive predictive value of 100% for ATTR-CA when there is grade 2 or 3 myocardial radiotracer uptake and no evidence of a monoclonal protein in serum or urine. [2] This imaging technique is also valuable for early detection of cardiac involvement before echocardiographic changes become apparent, and it correlates well with the severity of cardiac involvement as assessed by echocardiography, ECG, and cardiac biomarkers.

In summary, technetium scintigraphy is a cornerstone in the diagnostic pathway for ATTR-CA, providing a reliable, non-invasive alternative to endomyocardial biopsy when used in conjunction with appropriate biochemical testing.

1. INTRODUCTION

Cardiac amyloidosis, particularly transthyretin cardiac amyloidosis (ATTR-CA), is a progressive and often fatal condition characterized by the deposition of amyloid fibrils in the myocardium. Early and accurate diagnosis is crucial for the management and treatment of this disease. Technetium scintigraphy, using technetium-99m-labeled bone-seeking tracers such as Tc-PYP, Tc-DPD, and Tc-HMDP, has emerged as a highly sensitive and specific non-invasive imaging modality for diagnosing ATTR-CA.

Technetium scintigraphy has been shown to reliably detect myocardial amyloid deposits, with a high positive predictive value when combined with the absence of monoclonal protein in serum and urine. This imaging technique can differentiate ATTR-CA from light chain (AL) amyloidosis, thereby reducing the need for invasive endomyocardial biopsies. The American Society of Nuclear Cardiology (ASNC), American Heart Association (AHA), and other societies have endorsed the use of technetium scintigraphy in their multimodality imaging guidelines for cardiac amyloidosis.[3]

Recent studies have demonstrated that technetium scintigraphy not only aids in the diagnosis but also correlates with the severity of cardiac involvement, as assessed by echocardiography, ECG, and cardiac biomarkers.[4] This imaging modality is particularly valuable for early detection, even before echocardiographic changes become apparent, and can guide therapeutic decisions.

In summary, technetium scintigraphy is a cornerstone in the non-invasive diagnosis of cardiac amyloidosis, particularly ATTR-CM, when used in conjunction with appropriate biochemical testing to exclude AL amyloidosis.

2. REVIEW

2.1. Cardiac Amyloidosis

Cardiac amyloidosis is a progressive infiltrative cardiomyopathy caused by the extracellular deposition of amyloid fibrils in the myocardium. This deposition leads to thickening and stiffening of the ventricular walls, resulting in restrictive physiology and heart failure. The condition is often under recognized and can mimic other forms of heart disease, such as hypertrophic cardiomyopathy or constrictive pericarditis. [5-8]

There are two primary types of cardiac amyloidosis based on the precursor protein involved:

2.1.1. *Immunoglobulin Light Chain (AL) Amyloidosis*

This type is caused by the deposition of misfolded monoclonal immunoglobulin light chains, typically produced by clonal plasma cells in the bone marrow. AL amyloidosis is associated with a rapidly progressive clinical course and poor prognosis if untreated. [5-8]

2.1.2. *Transthyretin (ATTR) Amyloidosis*

ATTR amyloidosis results from the deposition of misfolded transthyretin (TTR) protein. It is further subdivided into:

• Wild-type ATTR (ATTRwt): Occurs due to the deposition of wild-type TTR and predominantly affects elderly individuals.

• Hereditary ATTR (ATTRv): Caused by mutations in the TTR gene and can present with either cardiomyopathy or sensory/autonomic polyneuropathy, depending on the specific mutation. [5-8]

The American College of Cardiology (ACC) emphasizes the importance of differentiating between these types due to their distinct clinical courses, prognoses, and treatment approaches. [9]

2.2. Pathology of Transthyretin Amyloidosis

TTR, formerly known as pre-albumin, is a protein made up of four β-sheet-rich monomers that circulate together as a tetramer, carrying molecules like thyroxine and holo-retinol binding protein (RBP). The choroid plexus produces a smaller amount of TTR tetramer for the cerebrospinal fluid, and retinal pigmented epithelial cells produce it for the vitreous humor of the eye. The liver, however, is the main source, secreting TTR tetramer into the bloodstream. When TTR misfolds and aggregates in these fluids, it leads to tissue dysfunction and clinical signs of ATTR amyloidosis. [10]

The TTR gene is located on chromosome 18. ATTRv (variant) is characterized by single amino acid changes in the 127 amino acid sequence of TTR, which destabilize the tetramer and increase its tendency to aggregate. The ATTRv notation uses shorthand for the normal amino acid at a specific position, followed by the substituted amino acid (e.g., Val30Met means methionine replaces valine at position 30). Although Val30Met is commonly used, genetic test results that include the 20 amino acid signal peptides refer to this as pV50M. In ATTRwt (wild type), the TTR gene is normal. The aging process may contribute to the instability and aggregation of the wild-type protein, though the exact cause is unclear. Since thyroid hormone is found in less than 5% of TTR, it doesn't significantly influence TTR's tendency to aggregate. [11]

On the other hand, holo-RBP binds and stabilizes tetrameric TTR, suggesting that low levels of holo-RBP could be a risk factor for ATTR-CM. The formation of TTR amyloid begins when the tetramer breaks down into monomers, a process that may involve proteolysis. These monomers can partially denature and misassemble into various aggregate forms, including amyloid fibrils. In ATTR-CM (cardiomyopathy), this aggregation leads to the buildup of stiff TTR amyloid fibrils in the heart, causing stiffness and dysfunction. Additionally, non-amyloid aggregates may also be toxic to cells in ATTR-CM, similar to what is observed in AL amyloidosis.[12]

2.3. Pathology of AL Amyloidosis:

ALSystemic amyloidosis is defined by the extracellular deposition of fibril-forming monoclonal immunoglobulin light chains (LCs), of which the lambda isotype is most frequently found. A small, lazy plasma cell clone typically secretes these light chains. A conformational shift that results in an unstable conformation in the secondary or tertiary structure of the aberrant monoclonal LC is part of the pathophysiology. Because of its instability, the LC folds abnormally and becomes rich in β-

sheets. These monomers stack up to create amyloid fibrils.

These amyloid fibrils cause architectural disruption and direct cytotoxicity when they deposit in different tissues and organs, which results in organ failure and malfunction. Usually, only the heart and kidneys are impacted; cardiac involvement frequently results in restrictive cardiomyopathy and renal involvement resulting in Nephrotic syndrome [13].

2.4. Population Affected

(ATTR) Amyloidosis

Though they usually develop between the ages of 30 and 80, the onset of symptoms might vary greatly.

Those with the V30M mutation typically experience symptoms between the ages of 20 and 40, while those with the V122I mutation may experience symptoms later in life, frequently after 60 [9].

(AL) Amyloidosis

In the United States, the estimated incidence of AL amyloidosis, also known as immunoglobulin light chain amyloidosis, ranges from 9.7 to 14.0 instances per million person-years. Adults are the main victims, usually between the ages of 60 and 70. Males are more likely than females to be affected [14].

2.5. Presentation of Amyloidosis

Aortic Stenosis

When the aortic valve narrows, it prevents blood flow from the heart, a condition known as aortic stenosis (AS) occurs. AS might make diagnosis and therapy more difficult for individuals with cardiac amyloidosis (CA). Amyloid protein buildup in the heart causes cardiac tissue to stiffen and lose its function, which is the hallmark of CA.

A significant percentage of people with cardiac amyloidosis have AS. Research has indicated that approximately 8–16% of people with CA also have AS; in these circumstances, (ATTRwt) cardiac amyloidosis is more common than (AL) amyloidosis [15].

2.6. Hypertrophic Cardiomyopathy

Amyloid buildup in the heart can cause restrictive cardiomyopathy, although it can also occasionally mimic hypertrophic cardiomyopathy in appearance.

Cardiac amyloidosis can manifest clinically as conduction system dysfunction, arrhythmias, or heart failure. Rarely, it may present with asymmetric septal hypertrophy and thicker left ventricle, two characteristics of hypertrophic cardiomyopathy. [16] Due to the comparable echocardiographic features of cardiac amyloidosis and HCM, such as left ventricular hypertrophy and granular flashing of the myocardium, this overlap may make the diagnosis more difficult.[17].

2.7. Carpel Tunnel Syndrome

The most prevalent nerve entrapment symptom caused by ATTR amyloidosis is carpal tunnel syndrome. Deposits in the soft tissues might result from this condition. More ATTR cases than AL result in deposits in the flexor retinaculum and tenosynovial tissue within the carpal tunnel, which typically cause bilateral symptoms. About 50% of individuals with ATTRwt-CM who are referred to have carpal tunnel syndrome. Carpal tunnel syndrome symptoms are a common early manifestation of ATTR-CM and often occur 5 to 10 years before overt manifestation-[9].

2.8. Lumbar Spinal Stenosis

Lumbar spinal stenosis is associated principally with ATTRwt-CM. Amyloid deposition causes thickening of the ligamentum flavum which leads to compression and narrowing of the spinal canal.

2.9. Diagnosis

For several reasons, the diagnosis of ATTR-CM presents difficulties for the clinician.

First, other prevalent conditions such hypertensive heart disease, aortic stenosis, or hypertrophic cardiomyopathy may be responsible for the clinical phenotype of wall thickening and HF.

Second, because ATTR-CM is sometimes confused with the AL type, it is thought to be rare.

Third, medical professionals do not know which diagnostic algorithm to use.

Several significant clinical indicators of ATTR-CM presence have been reported. A "natural cure" for hypertension, such as the requirement to reduce the dosage or stop antihypertensive medication, is one indicator. Similarly, in cases of recently diagnosed HF, amyloidosis should be taken into consideration if β-blockade is intolerable.

It is important to actively investigate any history of HF associated with lumbar spinal stenosis,

carpal tunnel syndrome, and biceps tendon rupture. Although it can also happen in AL and sporadically in ATTRwt, the presence of inexplicable peripheral or autonomic neuropathy raises the chance of ATTRv amyloidosis.

When a low-voltage electrocardiographic signal is present together with increasing left ventricular wall thickness, ATTR-CM can be distinguished from hypertensive or hypertrophic cardiomyopathy. Nevertheless, only 25–40% of ATTR-CA patients satisfy the low-voltage requirements.

There should be heightened clinical suspicion in any patient presenting with low-flow, low-gradient aortic stenosis, or unexplained increased left or right ventricular wall thickness.

The currently accepted echocardiographic diagnostic threshold for cardiac amyloidosis is an interventricular septal wall thickness >12 mm [19].
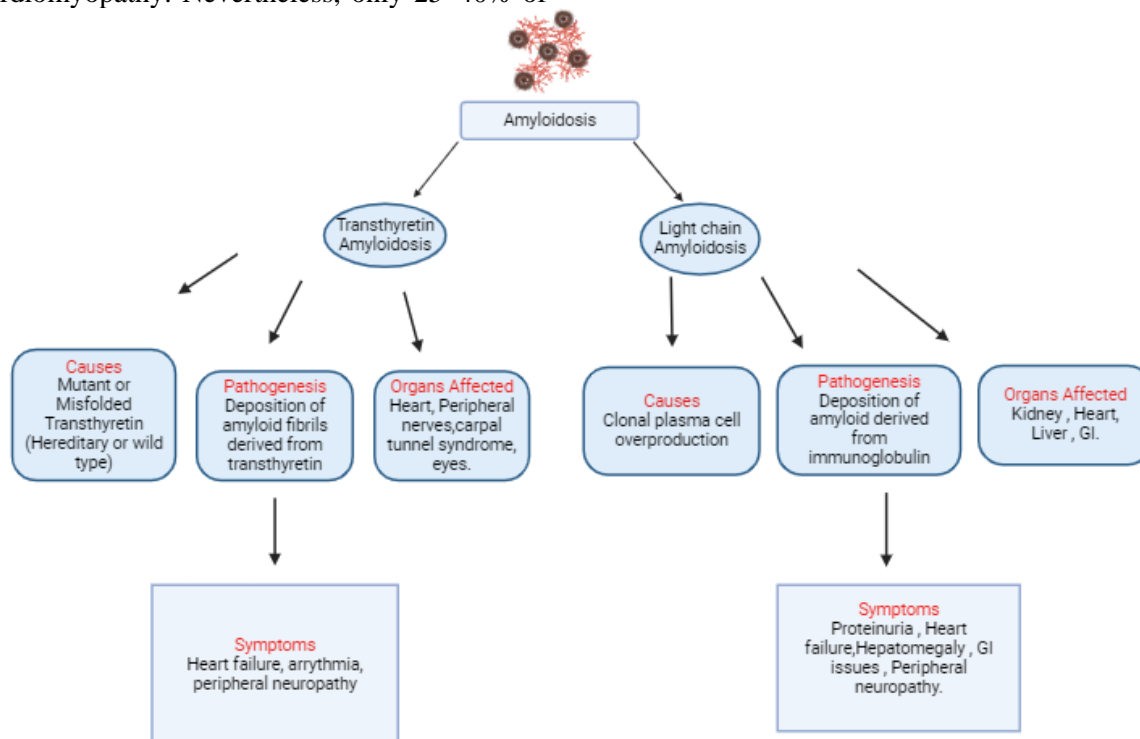
In ATTR-CA, echocardiographic evaluations of cardiac deformation—more especially, decreased longitudinal systolic strain—are helpful. The left ventricular apical region exhibits more normal strain in contrast to values that get worse as one move toward the mid and basal regions, exhibiting a characteristic pattern of "apical sparing". When separating amyloid heart disease from other etiologies, aberrant ratios of apical to basal strain or apical to basal plus mid-ventricular strain can be quantified with good diagnostic accuracy [20].

Like this, in late gadolinium enhancement computed tomography (CMR) amyloidosis is suggested by the failure to attenuate or "null" the cardiac signal or by the presence of extensive subendocardial or transmural enhancement patterns, with sensitivity and specificity approaching 85% to 90% [21].

While both echocardiography and CMR are helpful in distinguishing amyloidosis from non-amyloid illnesses, they are not able to accurately distinguish ATTR-CM from AL [22].

The gold standard for CA diagnosis is still endomyocardial biopsy, which is almost 100% sensitive and specific if biopsy specimens are taken from several sites (more than four are advised) and examined by Congo red staining for the presence of amyloid plaques [23].

Definitive identification of the misfolded precursor protein must be determined by either immuno histochemistry.

2.10. Technetium Scintigraphy

The only imaging modality that can accurately diagnose ATTR-CM without the need for invasive cardiac biopsy is nuclear scintigraphy using bone-avid radiotracers. Three technetium-labeled radiotracers have been evaluated clinically for CA.

These include Tc-99m- PYP (available in the United States) and Tc-99m−3, 3-

diphosphono-1, 2-propanodicarboxylic acid (DPD) or Tc-99m−hydroxymethylene diphosphonate (HMDP), the latter 2 of which are available in Europe [9].

The mechanism of myocardial uptake in ATTR-CM is not clear but is possibly related to binding of the radiotracer to microcalcifications, with some evidence that these are more abundant in ATTR than AL fibrils [24].

When using 99mTc-scintigraphy to image cardiac amyloidosis, radiotracer ranging from 10 to 25 mCi is injected intravenously. Planar and single-photon emission computed tomography (SPECT) imaging are then performed after one or three hours. Both qualitative and quantitative grading systems are used to assess the level of uptake in the myocardium on planar imaging. The following qualitative scores connect the uptake of the heart to that of the rib bones: grade 0 indicates no uptake, grade 1 indicates mild uptake, less than rib, grade 2 indicates moderate uptake, equal to rib, and grade 3 indicates severe uptake, greater than rib.

The detailed description of quantitative scores is based on the heart to contralateral (H/CL) ratio or the heart to whole body ratio [24]. The H/CL ratio needed to identify a positive test is lower at 3 hours (1.3) than it is at 1 hour (1.5) because the isotope's myocardial retention diminishes with time.

Additional SPECT imaging, with or without computed tomography, is required to confirm that uptake is in the myocardium and not in the blood pool or an extracardiac focus because these tracers are also blood pool agents. Even while the imaging test parameters at one and three hours do not seem to differ considerably, early planar imaging is linked to a larger frequency of blood pool confounding signals, which results in more false positives [25].

2.11. Studies Supporting the Data

In a Multicenter planar study 171 participants (121 with ATTR cardiac amyloidosis and 50 with non-ATTR cardiac amyloidosis [34 with AL amyloidosis and 16 with nonamyloid heart failure with preserved ejection fraction]; 86% male; median [IQR] age, 73 years [65-79 years]) demonstrated 91% sensitivity and 92% specificity for detecting ATTR cardiac amyloidosis with an area under the curve of 0.960 (95% CI, 0.930-0.981)An H/CL ratio of 1.6 or greater was associated with worse survival among patients with ATTR cardiac amyloidosis [26].

1,217 individuals who received cardiac scintigraphy with these 3 agents and were referred for suspicion of CA were the subject of a later worldwide multicenter collaboration study. In this study, 360 individuals were later diagnosed with nonamyloid cardiomyopathy, while 857 patients obtained histological proof of amyloid. For the diagnosis of ATTR-CM, it was discovered that the presence of any cardiac radiotracer uptake (grade 1, 2, or 3) has a sensitivity of >99% and a specificity of 86% [27].

Twenty-one patients (8 AL and 13 ATTR) completed the study. Median age was 58 and 70 years for AL and ATTR patients respectively, and 19 (90.5%) were male. 99^mTc-DPD scintigraphy was positive in 2 (25%) of AL, and 13 (100%) of ATTR patients. Grade of cardiac uptake, and mean H: WB (0.1249 v. 0.0794) was greater in the ATTR cohort (p-value < 0.001 and 0.001 respectively). No statistically significant correlation was identified between H: WB and echocardiographic parameters. There was a significant positive correlation between H: WB and the PR interval on ECG (p = 0.026). [28]

Table1. *Showing the key findings of studies*

Study	No: of Participants	Sensitivity	Specificity	Key Findings
Multi center Planar Study (171) Participants [26]	121 With ATTR, 50 With Non-ATTR.	91%	92%	H/CL ratio of 1.6 or greater associated with worse survival in ATTR patients.
Worldwide multicenter collaboration study (1,217 Participants) [27]	857 With histological proof of amyloid, 360 with non-amyloid cardiomyopathy	>99%	86%	Any cardiac radiotracer uptake (grade 1,2, or 3) indicates ATTR-CM.
Australian Study (21Participants) [28]	8AL,13 ATTR	100% in ATTR, 25% in AL	Not Reported	Greater H:WB ratio

3. LIMITATIONS OF STUDY

3.1. False Positives

Grade 2 or 3 myocardial uptake seen in a recent history of acute myocardial infarction, AL amyloidosis, apolipoprotein AI amyloidosis (AApoAI), apolipoprotein AII amyloidosis (AApoAII), apolipoprotein A-IV amyloidosis (ApoAAIV), or β2-microglobulin amyloidosis (Aβ2M), hypertrophic cardiomyopathy, hydroxychloroquine toxicity, and cardiac blood pools are potential false-positive cases in 99mTc-PYP scintigraphy for ATTR-CM. For 99mTc-DPD and 99mTc-HMDP scintigraphy, case reports of false-positive myocardial uptake after intravenous iron doses have been published [24].

3.2. False Negatives

On the other hand, instances of potential false-negative cases include ATTRv-CM with a low sensitivity for 99mTc-labelled bone radiotracer scintigraphy (Ser77Tyr or Phe64Leu mutation), inadequate amyloid deposits, rib fractures, valvular/annular calcifications, recent myocardial infarction, delayed or premature acquisition in 99mTc-PYP scintigraphy, and initial diagnosis of cardiac pools with myocardial deposits. Potential causes such as errors in scintigraphy imaging time or interpretation, errors in biopsy sampling or pathological diagnosis, deposits of proteins other than TTR (e.g., AL), and ATTRv-CM with a low sensitivity in 99mTc-PYP scintigraphy should be suspected and investigated in case of inconsistencies between planar 99mTc-PYP scintigraphy results and biopsy findings [24].

4. CONCLUSION

Cardiac scintigraphy using technetium is an evolving test. Initially, it showed great promise based on data from carefully selected groups of patients. However, as its use has become more widespread, the accuracy has decreased, leading to more cautious optimism. To reduce the risk of misdiagnosis, it's essential to follow established guidelines for performing and interpreting the test and to use it only in appropriate clinical situations. It's important to remember that 99mTc-PYP, 99mTc-DPD, and 99mTc-HMDP scintigraphy cannot alone confirm or rule out the diagnosis of cardiac amyloidosis; it should be part of a broader diagnostic approach.

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