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REVIEW ARTICLE

# Pyrophosphate Scintigraphy: Use in the Diagnosis and Monitoring of Cardiac Amyloidosis

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## Abstract

Cardiac amyloidosis (CA) is a progressive condition marked by the accumulation of amyloid fibrils in cardiac tissue, resulting in cardiac dysfunction and, ultimately, heart failure. Pyrophosphate scintigraphy has emerged as a promising tool for the early detection and monitoring of CA, providing valuable insights into the disease's extent and severity. This review examines the current use of pyrophosphate scintigraphy in distinguishing between different types of amyloidosis, assessing risk levels, and monitoring patients with CA. It underscores the clinical significance and prospects of this imaging technique.

## Introduction

Systemic amyloidosis is a disease caused by the deposition of misfolded proteins in extracellular tissue. Although 95% of cardiac amyloidosis (CA) is caused by light chain (AL) or transthyretin (ATTR), the International Society of Amyloidosis (ISA) has identified more than 40 precursors that can cause the deposition of such proteins in various tissues and organs.[1]

In CA, the deposition of insoluble protein fibrils occurs in the myocardial interstitium, damaging myocardial function. The pathophysiological process is defined by an infiltrative restrictive cardiomyopathy that affects diastolic function and ventricular compliance.[2] This condition often involves electrophysiological abnormalities, disrupting normal electrical conduction and resulting in various altered electrocardiographic patterns.[2]

In the diagnostic investigation of CA, it is important to be aware of "red flags" such as heart failure with preserved ejection fraction (HFpEF) in men over 65 years old and interventricular septal thickness > 12 mm, bilateral carpal tunnel syndrome, reduction of antihypertensive doses in previously hypertensive patients or intolerance to angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs) and beta blockers, symptoms of sensory or motor peripheral neuropathy.[3] Moreover, it is essential to differentiate between the types of amyloidosis based on the deposited precursor protein, as the treatment differs between the two main causes and results in distinct outcomes.[3]

The American College of Cardiology (ACC) recommends that the initial investigation of CA through imaging tests be performed using Doppler echocardiography. Moreover, important additional imaging methods include cardiac magnetic resonance (CMR) with late gadolinium enhancement images and scintigraphy with 99mTc-pyrophosphate, which eliminates the need for biopsy in cases of ATTR, as long as the presence of immunoglobulin ALs is safely ruled out.[3]

In view of the progress in treatments for CA, there are some ongoing studies monitoring the response to treatment.[4] The AMYTRE study will evaluate microvascular damage in patients after treatment with Patisiran through measured coronary flow reserve in CZT SPECT equipment. Martinez-Naharro employed CMR with T1 mapping and assessment of tissue characterization and extracellular volume to monitor amyloid overload, which is not specific to amyloidosis and can be utilized for monitoring purposes.[5] Other studies have used 18F-Florbetapir and

## Keywords

Amyloidosis; Radionuclide Imaging; Diagnosis; Nuclear Medicine.

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**Central Illustration: Pyrophosphate Scintigraphy: Use in the Diagnosis and Monitoring of Cardiac Amyloidosis**

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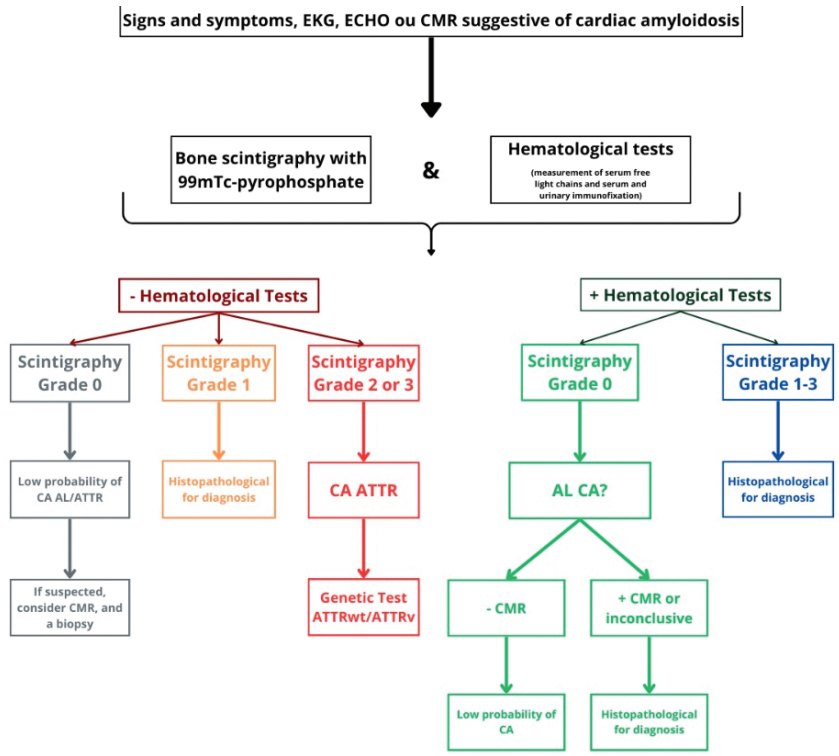


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18F-Florbetaben to differentiate between AL amyloidosis and ATTR using imaging techniques.[6,7] Therefore, this review aims to examine the primary molecular imaging techniques, highlighting recent advancements in the understanding of CA for diagnosis, monitoring, and identification of amyloidosis types.

## Method

A literature review spanning the last 10 years was conducted in Pubmed, Scopus and Google Scholar scientific databases. Relevant studies that addressed the imaging techniques used in CA were selected.

The inclusion criteria were as follows:

1. Type of Study: Original articles, systematic reviews, meta-analyses and consensus of expert committees were considered.
2. Language: The research includes articles in English language only.
3. Imaging Technology: Studies that used Nuclear Medicine to evaluate CA were included.
4. Focus: The scope of the research was restricted to CA.

Exclusion Criteria: Studies with small sample sizes, isolated case reports, and articles with unrelated results were excluded.

This systematic review aims to elucidate the current understanding of imaging techniques used in CA and contribute to the progress of medical knowledge in this area.

## Diagnosis of CA

Early diagnosis of CA is crucial for initiating timely and appropriate treatment, as the prognosis worsens with the advancement of heart disease.[1] When clinical suspicion of amyloidosis arises, imaging methods become invaluable for enabling a non-invasive diagnosis.[2] These CA diagnostic techniques include electrocardiography, echocardiography, CMR, and nuclear imaging methods like pyrophosphate scintigraphy with technetium (PYP).[8,9]

ECG patterns that raise suspicion for CA include (1) low voltage QRS complexes, (2) pseudo infarction criteria in the septal wall, and (3) conduction abnormalities, such

as bundle branch block and atrioventricular conduction defects.[10] However, the diagnosis of amyloidosis by ECG is challenging because it has patterns similar to those of other myocardial infiltrative diseases.[10] Algorithms that are easy to apply in clinical practice can be employed to improve sensitivity, such as that proposed by Schrutka et al., who described patterns that increase the chance of diagnosing CA with an odds ratio of 7.66 (95% CI: 5,47 – 10,72).[11] However, it is important to consider that typical CA patterns on the ECG are not conclusive for diagnostic and are considered to be red flags. These findings are often the starting point for continuing to investigate the disease with other imaging methods.

Newer approaches apply artificial intelligence (AI) to evaluate the ECG, which may be relevant for detecting patterns not easily identified by the human eye. Grogan et al. developed an AI method trained with data from the Mayo Clinic and obtained an area under the receiver-operating-characteristics (ROC) curve of 0.91 (95% CI: 0.90 – 0.93), in addition to predicting CA more than six months in advance of the clinical diagnosis in 59% of patients with CA or suspected CA.[12]

Echocardiography is often one of the initial tests requested when CA is suspected, given its widespread availability and ability to estimate various parameters of interest that may exhibit suggestive patterns in patients with amyloidosis. These findings typically manifest in the disease's advanced stages and primarily resemble restrictive cardiomyopathy of the infiltrative type.[13] Among the parameters assessed in echocardiography, several are associated with an amyloidosis pattern, including thickening of the left ventricle (LV) walls, thickening of the interatrial septum and mitral valve leaflets, reduction in the LV cavity's diastolic diameter, and the LV apical sparing pattern in longitudinal strain (also known as the "cherry on top" sign, indicating exclusive strain preservation at the apex).[13,14]

Although many studies indicate an association between apical sparing and CA, this pattern is not always found. A study by Wali et al. sought to evaluate the prevalence of this pattern in patients with CA, concluding that approximately 1/3 of patients had apical sparing.[15] Although some echocardiography parameters indicate the possibility of CA, they are not specific and may relate to other cardiomyopathies with ventricular hypertrophy. In this context, some studies suggest the use of AI to differentiate between types of amyloidosis. For example, Zhang et al. proposed an AI method based on texture characteristics of images to distinguish CA from other conditions like hypertrophic cardiomyopathy, uremic cardiomyopathy, and hypertensive heart disease.[16]

Magnetic resonance imaging plays a role in diagnosing CA by assessing myocardial tissue characteristics and cardiac involvement. CMR can provide valuable diagnostic insights by evaluating both cardiac morphology and function, thus facilitating the differentiation of CA from other cardiomyopathies.[13] Various CMR parameters, such as delayed gadolinium enhancement, extracellular volume, and the R1 myocardium-light ratio on post-contrast T1 maps, have been studied for their diagnostic accuracy in detecting CA. In the study by Kidoh et al., the techniques of extracellular volume and R1 myocardium-light ratio on T1 map were evaluated for detection of CA, in which the area values under the ROC curve were respectively 0.99 (95% CI: 0.97 – 1.00) and 0.98 (95% CI: 0.95 – 0.99), with no difference between the two techniques for this objective ($p = 0.10$).[17] Dohy et al. evaluated the use of CMR for diagnosing AL-type CA and found a specificity of 88% and 100% sensitivity for late gadolinium enhancement. In comparison, global strain reduction with apical sparing showed low sensitivity (6%) but very high specificity (100%). Another highly diagnostic finding is a septal wall thickness > 15 mm, which can differentiate CA from the AL type of hypertensive heart disease with a sensitivity of 91% and a specificity of 89%.[18]

One limitation of CMR is its inability to differentiate between TTR and AL types of CA. In this regard, Germain et al. proposed the use of an AI model to attempt this classification, comparing its performance with that of human readers.[19] While one of the models showed slightly better results than human evaluation (75% accuracy vs. 67.5%), neither achieved sufficient accuracy for clinical use. Therefore, other modalities are needed for this differentiation.

Endomyocardial biopsy is the most sensitive method for detecting amyloid deposits and allows for the detection of concomitant diseases and classification by type.[20] Congo red staining is used for characterization, showing an anomalous apple-green birefringence under polarized light.[20] For AL amyloidosis, less invasive procedures such as subcutaneous fat or salivary gland biopsies can confirm the diagnosis in 50%-80% of cases. However, for ATTR, endomyocardial biopsy is the preferred method for histopathological diagnosis despite being riskier and requiring greater expertise.[21]

Based on studies that have explored the use of tracers, mainly bisphosphonates, to evaluate CA, Perugini et al. conducted a pilot study aiming to differentiate between

ATTR and AL types of CA using scintigraphy with 3,3-diphosphate-1,2-propanedicarboxylic-99mTc acid (DPD-Tc$^{99m}$).[21] The study indicated a higher uptake of the tracer by ATTR patients, suggesting a potential correlation with this type of amyloid deposit. Since then, other studies have expanded the knowledge base of this technique, as this pilot study was conducted with only 25 patients. It is worth mentioning that in the original study by Perugini et al.,[21] there were only 10 patients with AL amyloidosis and none exhibited accumulation of bone radiotracer in the myocardium. However, subsequent studies have shown that a significant portion of patients with AL amyloidosis also exhibit an accumulation of bone radiotracers, which shows that cardiac scintigraphy with bone radiotracer alone is not enough to diagnose CA-ATTR and is necessary to rule out the presence of AL amyloidosis by investigating the presence of free ALs.[22]

A multicenter study (USA and Europe) with 1,217 patients with suspected CA was conducted to evaluate the diagnostic power of this scintigraphy method with bone markers (DPD, pyrophosphate and Hydroxymethylene diphosphonate labeled with Tc$^{99m}$), in which there was prior evidence of its craving for amyloid deposits. However, the molecular basis of this process is not known.[23] The results reported by Gillmore et al. indicated a positive predictive value of 100% (95% CI: 98% - 100%) for the diagnosis of ATTR-type amyloidosis, if monoclonal gammopathy has been ruled out (through testing for free ALs in plasma and urine).[23] Therefore, for patients in whom AL-type amyloidosis has been ruled out, pyrophosphate scintigraphy is a diagnostic method with very high specificity, meaning there is no need for endomyocardial biopsy for confirmation and consequently reducing the risks for the patient and improving their prognosis.

## Role of 99mTc-Pyrophosphate Scintigraphy in CA

The 99mTc-Pyrophosphate (PYP) is a radiopharmaceutical discovered in the 70s. PYP was initially used for skeletal imaging due to its ability to fixate in regions of osteogenesis, being soon replaced by more stable markers for bone studies. However, researchers soon noted its application in the detection of necrotic cardiac areas, especially in the acute phase of acute myocardial infarction.[24] The uptake of compounds labeled with metastable technetium 99 in calcium deposits in patients with Amyloidosis was observed in the late 70s, allowing the use of 99mTc-PYP and other phosphate-derived compounds in the evaluation of this disease.[25]

Wizenber et al.[26] and Falker et al.[27] demonstrated the sensitivity of 99mTc-PYP in the diagnosis of CA, correlating uptake with positive biopsies and morphological changes in the LV, as assessed by echocardiography. However, heterogeneous results in other studies raised doubts about this correlation. As previously mentioned, Perugini et al. used a visual scoring method to analyze scintigraphic images. Their study demonstrated that TTR amyloidosis cases exhibited abnormal cardiac uptake of the radioactive tracer, with intensity surpassing that of the costal arches.[21] The imaging protocol with 99mTc-PYP involves administering

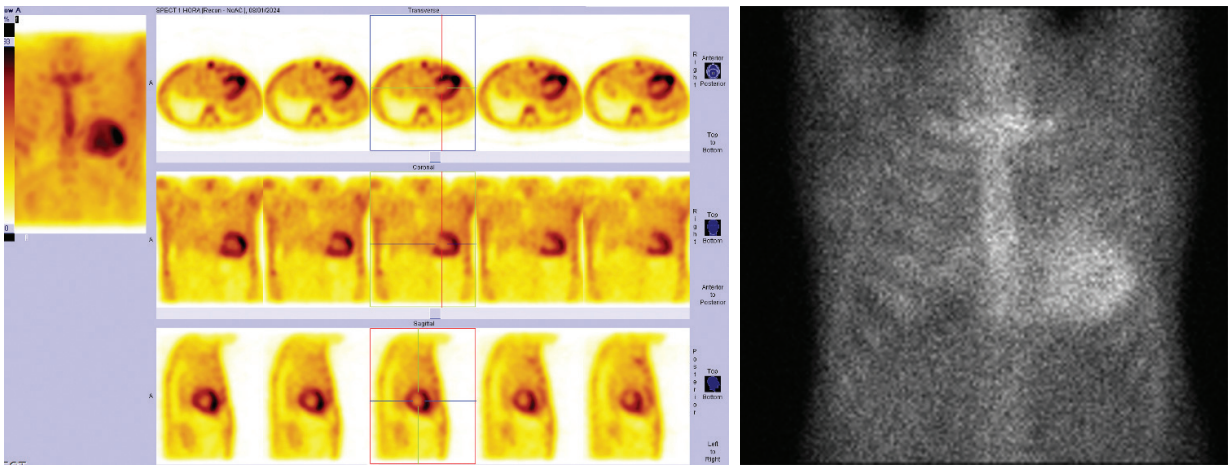

**Figure 1 – Chest image of scintigraphy with bone tracer marked with 99mTechnetium. In the images shown, 99mTc-PYP was used, evidencing Perugini grade 3 cardiac uptake (more intense than the ribs and with reduced uptake in the skeleton).**

10 to 20 mCi of the radiopharmaceutical and acquiring images at 1 and 3 hours post-administration. Planar thoracic images are obtained to quantify myocardial uptake. In contrast, tomographic sections obtained through SPECT are crucial for confirming that the radiotracer accumulation occurs in the walls of the LV and not in the blood within the heart cavities (blood pool), which are common causes of false positives when analyzing planar images in isolation.[28]

The Perugini score classifies myocardial 99mTc-PYP uptake compared to the ribs in a planar image of the chest 3 hours after the injection on a semiquantitative scale from 0 to 3. The extensive study by Gillmore et al. revealed that Grades 2 and 3 uptakes, in the absence of monoclonal protein, exhibited 100% specificity and positive predictive value for ATTR-CA, obviating the need for invasive biopsy for diagnosis.[23]

While the mechanism behind 99mTc-PYP uptake in ATTR CA remains uncertain, the prevailing theory implicates calcium in amyloid fibrils. Despite this uncertainty, pyrophosphate scintigraphy proves to be a non-invasive method with high diagnostic accuracy, facilitating appropriate treatment. In addition to pyrophosphate scintigraphy, other diagnostic methods play crucial roles in the investigative process. Proper imaging protocol is vital to avoid false positives, as uptake observed in planar images should always be confirmed in tomographic scintigraphy (SPECT) images to distinguish uptake in the myocardium from uptake in the blood pool, which can lead to false positives. Furthermore, it is imperative to rule out monoclonal gammopathy, as up to 40% of AL amyloidosis cases may exhibit pyrophosphate uptake in the myocardium. Therefore, adherence to investigation algorithms is essential for accurately diagnosing the type of amyloidosis.[13]

## Prognostic Assessment and Monitoring of CA

Several imaging methods have been proposed for quantitatively assessing cardiac amyloid overload, which can help in prognostic stratification and monitoring disease progression.

Reviews of the literature have consolidated the use of multimodality imaging in evaluating CA.[29-31] For example, a systematic review by Cai et al., involving 955 patients across nine studies, suggests using this imaging modality to assess prognosis. They found relative risks for mortality of 1.33 (95% CI = 1.10; 1.60) for each 60 ms increase in T1 time, 1.16 (95% CI = 1.09; 1.23) for each 3% increase in ECV, and 5.23 (95% CI = 2.27; 12.02) for a below-average myocardial-skeletal ratio.[31] Pyrophosphate scintigraphy has been extensively studied to explore its ability to predict clinical outcomes and monitor disease progression.

Quantitative assessment of myocardial bone radiotracer activity appears to be a non-invasive measure that correlates with cardiac amyloid protein overload and may be useful for assessing disease progression or response to therapy. In a study by Miller et al., increased cardiac pyrophosphate activity in patients with ATTR cardiomyopathy was associated with a lower left ventricular ejection fraction (OR of 1.28) and a higher rate of hospitalizations for heart failure (hazard ratio of 1.29).[32] Similarly, Roshankar et al. found a significant hazard ratio for cardiac events and death due to increased tracer activity and volume of involvement.[33]

Further studies using pyrophosphate scintigraphy are necessary to validate its effectiveness in monitoring disease progression and response to targeted treatments, such as AMYTRE.[4] Additionally, quantitative assessment of bone radiotracer activity in the myocardium seems to be a non-invasive and promising approach for monitoring disease evolution and therapeutic responses. This potential was demonstrated in studies by Miller et al.[32] and Roshankar et al.[33] This evidence underscores the significance of integrating various imaging modalities for the optimal management of CA. Figure 2 contains an exemplary case in which the application of quantitative analysis tools for myocardial radiotracer uptake in sequential cardiac scintigraphy exams with 99mTc-Pyrophosphate, planar and SPECT showed a reduction in uptake over time.

Porcari et al. with a study of 1422 patients demonstrated diffuse, as opposed to focal, right ventricle uptake of bone tracer on SPECT imaging was associated with poor outcomes in patients with ATTR-CM and is an independent prognostic marker at diagnosis.34 So, besides informing the presence and intensity of myocardial uptake of bone tracer agents it is very useful to discriminate the uptake in the right ventricle and its pattern to obtain the most prognostic information.

## Use of AI and Scintigraphy Images

Pyrophosphate scintigraphy has been integrated into AI models to enhance diagnostic precision and

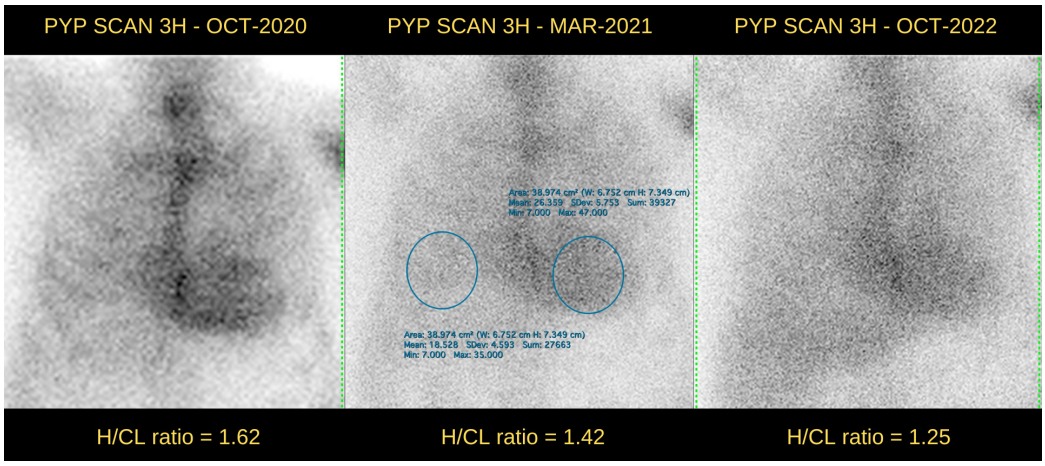


**Figure 2 – Illustrative images showing the decrease of 99mTc-pyrophosphate uptake in planar images after use of patisiran in a patient with hereditary cardiac amyloidosis (V142I).**

mitigate the subjectivity of human eye interpretation in image analysis. A recent study examined over 19,000 scintigraphic examinations using various tracers and protocols. The findings showed that AI-driven screening for uptake indicative of CA in scintigraphy patients was dependable, eliminating inter-rater differences, and offered prognostic value. These results have potential implications for identifying, referring, and managing patients clinically.[35]

## Final considerations

Pyrophosphate scintigraphy is a well-established, non-invasive diagnostic method for CA, particularly the ATTR form, and shows promise as a tool for monitoring disease progression. Its use has revolutionized the clinical approach to ATTR amyloidosis by enabling non-invasive diagnosis, thus eliminating the need for biopsy. However, caution is necessary due to potential false positives from AL amyloidosis and/or blood pool interference. The technique's potential for risk stratification and non-invasive monitoring of disease progression is also noteworthy. Future research should focus on investigating the prognostic potential of pyrophosphate scintigraphy and developing more precise quantitative assessments for monitoring disease progression and therapy response. This can be achieved through investment in prospective studies and clinical trials, ultimately leading to improved management and treatment of CA and benefiting patients directly.

## Author Contributions

Conception and design of the research: Mesquita CT, Yahiro DS, Simões M; acquisition of data: Mesquita CT, Yahiro DS, Rodriguez JGV, Azevedo Junior GL; analysis and interpretation of the data: Mesquita CT, Yahiro DS, Santos JFR, Machado LE, Rodriguez JGV, Azevedo Junior GL, Simões M; statistical analysis: Mesquita CT, Yahiro DS; writing of the manuscript: Mesquita CT, Yahiro DS, Santos JFR, Machado LE, Rodriguez JGV, Azevedo Junior GL; critical revision of the manuscript for intellectual content: Mesquita CT, Simões M.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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