

# Cardiovascular Nuclear Imaging in Cardiac Amyloidosis

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Nuclear imaging is a generic term for several imaging techniques. They all make use of small amounts of radioactive tracers administered to gain information about organs and tissues and represent an additional pillar in the diagnosis of CA. Nuclear imaging is not about functional, but more about structural assessment. While scintigraphy is two-dimensional or planar, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are three-dimensional.

cardiac scintigraphy

PET

cardiac amyloidosis

## 1. Introduction

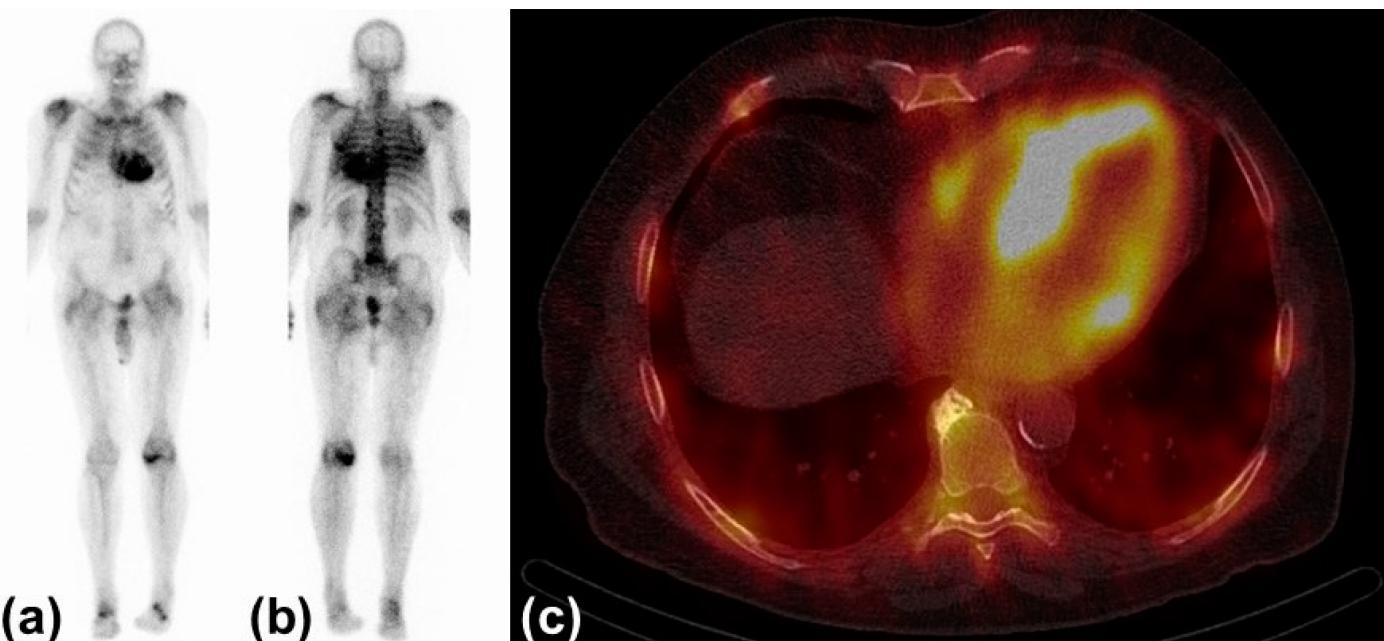
Cardiac amyloidosis (CA) is a disease characterized by deposition of misfolded protein fragments—called amyloid fibrils—in the heart. The two most frequent types of amyloidosis with cardiac involvement are light-chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) [1]. TTR amyloidosis incorporates two subtypes: ATTRv (variant or hereditary amyloidosis) stands for all hereditary forms, whereas ATTRwt (wild-type amyloidosis) is defined by sporadic mutations of the transthyretin gene [2]. Secondary amyloidosis is a rare type of amyloidosis with deposition of serum amyloid A. It generally appears along with inflammatory diseases such as rheumatoid arthritis [3].

Although AL and ATTR have similar effects on myocardial function and patients typically present with signs and symptoms of heart failure, they are different conditions with various therapeutic approaches. Thereby, early initiation of therapy is crucial for the prognosis [4]. This is particularly worthwhile given the recent significant developments of treatment options for both types of amyloidosis.

## 2. Scintigraphy and Single-Photon Emission Computed Tomography

Scintigraphy is recommended in patients with suspected CA due to findings from TTE and CMR. In addition, patients with confirmed ATTR neuropathy or a positive test for a TTR gene mutation are also advised to undergo scintigraphy. Otherwise, it should also be considered in case of unexplained left ventricular wall thickening, bilateral carpal tunnel syndrome, and for individuals with a family history of amyloidosis [5].

Today, three bone avid radiotracers are used to perform scintigraphy in patients with suspected CA [6]. All of them are based on the radioisotope  $^{99m}\text{Tc}$  (Technetium).  $^{99m}\text{Tc}$ -pyrophosphate (PYP) is approved by the Food and Drug Administration (FDA) and mainly used in the United States (US).  $^{99m}\text{Tc}$ -hydroxymethylene diphosphonate (HMDP) and  $^{99m}\text{Tc}$ -3,3-diphosphono-1,2-propanodicarboxylicacid (DPD) are applied in Europe, but rarely or not utilized in the US. The radiotracers are injected intravenously. Whole-body planar images and chest or cardiac SPECT images are obtained two to three hours post-injection. The myocardial uptake of the tracer is then compared to the uptake of the rib cage (typically as a heart-to-bone and heart-to-contralateral ratio). It is graded from 0 to 3 according to the Perugini grading scale (0: no uptake, 1: uptake less than rib, 2: uptake equal to rib, 3: uptake greater than rib). Grades 2 and 3 are strongly suggestive for the presence of cardiac ATTR. Grade 0 is not suggestive, and Grade 1 is considered equivocal (Figure 1). Scintigraphy should always be accompanied by the performance of serum and urine immunofixation and serum-free light-chain studies. In September 2019, the American Society of Nuclear Cardiology (ASNC) and the European Association of Nuclear Medicine (EANM) published practice points regarding scintigraphy in CA.



**Figure 1.** Typical findings in scintigraphy and single-photon emission computed tomography: (a) Anterior view of  $^{99m}\text{Tc}$ -hydroxymethylene diphosphonate scintigraphy with myocardial uptake Perugini Grade 3. (b) Posterior view of the same study. (c) Left and right ventricular uptake of  $^{99m}\text{Tc}$ -hydroxymethylene diphosphonate in single-photon emission computed tomography.

In the late twentieth century, knowledge about scintigraphy for the diagnosis of CA was not consolidated. A study from 1987 by Gertz et al. serves as an example by showing that only a loose association between scintigraphy and CA was established [7]. Further research revealed, both in amyloidosis and scintigraphy, that microcalcifications are responsible for the selectivity of bone avid radiotracers in CA. The density of microcalcifications is higher in ATTR compared to AL [8].

A large study published in 2016 highlighted the performance of scintigraphy for the diagnosis of cardiac ATTR. The combined finding of Grade 2 or 3 radiotracer uptake in the absence of monoclonal protein in serum and urine is associated with a specificity and a positive predictive value for ATTR CA of 100%. Radiotracer uptake alone had a sensitivity of >99% and a specificity of 86% for ATTR CA. False positive cases almost exclusively occurred in patients with AL CA [9]. Especially in patients with advanced amyloid deposition, scintigraphy using bone avid radiotracers is the best available tool for the discrimination of AL and ATTR CA [10]. Scintigraphy therefore plays an important role in the guidelines for the diagnosis of CA of both the American Heart Association and the European Society of Cardiology [11][12].

In addition, radiotracer uptake correlates positively with all-cause mortality and negatively with survival free of cardiac adverse events [5]. Another approach, which is used to evaluate the forecast, is the assess autonomic dysfunction as a non-specific finding in patients with CA resulting in arrhythmias. Here, <sup>123</sup>I-metiodobenzylguanidine (MIBG) is used as a radiotracer, analogous to norepinephrine, to derive the cardiac-to-mediastinum ratio. In combination with the heart rate response to atropine, it can be used as a predictor of prognosis in patients with ATTR CA [10][13].

### 3. Positron Emission Tomography

<sup>11</sup>C-Pittsburgh Compound B, <sup>18</sup>F-Florbetapir, and <sup>18</sup>F-Florbetaben are amyloid-binding radiotracers. They were not designed for cardiac imaging but, i.e., for imaging of beta-amyloid deposits in the brain in Alzheimer's disease. PET is a functional nuclear imaging technique using computed tomography (CT) or magnetic resonance tomography (MRT), which is therefore not only eligible for CA but also systemic amyloidosis. Amyloid-binding radiotracers enable a quantification of the global amyloid burden but also of a regional burden, such as the myocardium. The parameters measured are the self-explanatory target-to-background ratio, myocardial standard uptake value (SUV, parameter to measure radioactivity of the studied tissue), and myocardial retention index (derived from SUV in different phases after radiotracer injection). The direct binding of the tracers to the agent causing the disease allows early detection of the disease, even before structural changes appear. Early detection is crucial for effective treatment. Distinction between the different types of CA is not feasible with this technique. Due to possible quantification of deposits, PET has the potential for serial imaging in order to monitor response to treatment [14].

Singh and Dorbala provide an overview of several studies conducted on PET in CA. The studies are limited by small sample sizes and a lack of standardized protocols for image acquisition. This can be illustrated with one specific publication commented on in the above work, which studied a new radiotracer (amyloid-binding <sup>18</sup>F-Flutemetamol) in only 17 patients undergoing PET (with CT or MRT). Images were acquired more than one hour after injection of the radiotracer, which is rather late compared to other amyloid-binding radiotracers. Only a small percentage of patients with CA showed relevant radiotracer uptake [15][16][17].

However, further research with larger sample sizes and standardized protocols is needed before PET is applied in clinical routine.

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