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Comparison of Static and Spect Images on Tc-99m-PYP Bone Scintigraphy in the Diagnosis of Cardiac Amyloidosis

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Abstract
Amyloidosis is a systemic disease characterized by the extracellular accumulation of amyloid fibrils caused by misfolding of proteins. Cardiac amyloidosis has the worst prognosis of the type of organ involvements. The most common forms of cardiac amyloidosis are immunoglobulin light chain amyloidosis (AL) and transtretin (TTR) amyloidosis. The developing diagnostic methods give the clinician early diagnosis of cardiac amyloidosis. Scintigraphic imaging with Technetium (Tc-99m) labelled biphosponates may faciliate early detection of cardiac involvement and distinguish various forms of cardiac amyloidosis. Bone scintigraphy for evaluation of cardiac amyloidosis especially for ATTR type amyloidosis is one of the most sensitive imaging prosedures in recent years. In our study, we compared the 1st and 3rd hour planar and SPECT imaging to investigate the importance of the 3rd hour and the necessity of SPECT in cardiac amyloidosis (CA) imaging, which is one of the controversial topics from the Nuclear Medicine perspective.

Keywords**:** *cardiac amyloidosis, Tc-99m PYP, SPECT, Planar, Imaging, scintigraphy.*

Introduction

Cardiac amyloidosis is a progressive cardiomyopathy that occurs as a result of the accumulation of endogenous proteins whose folding is disrupted in the form of amyloid fibrils in the heart and often in the kidneys, liver, gastrointestinal tract and soft tissues. It causes dysfunction in organs. Cardiac amyloidosis is a disease for which diagnostic awareness is increasing. However, in daily clinical practice, the diagnosis is often skipped or ignored. It can sometimes be confused with hypertrophic cardiomyopathy or hypertensive left ventricular hypertrophy due to infiltrative myocardial hypertrophy that occurs in the clinical course of the disease. Difficulties in the diagnostic process and limitations in specific treatments for amyloid constitute the most important obstacles in the clinician's path to diagnosis. It has been shown that the prognosis can be significantly improved with early diagnosis and treatment approaches. In recent years, diagnostic imaging

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methods such as cardiac MRI, bone scintigraphy, and echocardiography, genetic analysis, biopsy and histopathological tests provide the clinician with the opportunity for early diagnosis. Magnetic resonance imaging (MRI) is recommended in patients with suspected cardiac amyloidosis. MRI can detect early cardiac amyloidosis before the development of left ventricular hypertrophy, but cannot distinguish cardiac AL from ATTR (1,2,3). Bone scintigraphy examination for amyloidosis, which has become one of the most important diagnostic imaging methods and has become widely used in recent years, has high sensitivity, especially for ATTR amyloid diagnosis. The bone scintigraphy protocol includes both 1st and 3rd hour static and SPECT imaging, and visual and semiquantitative evaluations are made through these images. The necessity of long examination times should be discussed in daily practice, both for patient comfort and because of the distruption of routine gamma camera daily workflow. In our current study, we aimed to investigate the contribution and necessity of 1st and 3rd hour static and SPECT imaging in bone scintigraphy.

Materials and Methods:

A total of 85 patients, 55 men (mean age: 67) and 30 women (mean age: 72) between the ages of 27-95, who were referred to our clinic with suspicion of CA between November 2022 and January 2024, were examined after Tc-99m PYP injection at 1st and 3rd hour static and SPECT images. No special patient preparation was required for bone scintigraphy. Imaging was performed with 99mTc-PYP agent in all patients included in the study. We obtained heart/contralateral lung (CL) ratios by drawing ROIs from the area compatible with the heart and CL in planar images. We determined grade values by visually evaluating the heart area and ribs in SPECT images.

Results

Quantitatively, there were 13 patients in whom we obtained values of 1.5 and above from the static images at the 1st hour, and 11 patients at the 3rd hour (Table 1).

Table 1. Number of patients obtained by quantitative evaluation in static imaging

	>1,5	**<1,5**
1ST HOUR	**13**	**72**
3RD HOUR	**11**	**74**

We observed that the 3rd hour value dropped below 1.5 in 3 patients whose 1.5 value was observed at the 1st hour. The value became positive at the 3rd hour in one patient. We had 14 positive and 71 negative patients in total. In 84 patients, 1st hour values were correlated with patient outcome (98.8%). At the 3rd hour, the values of 82 patients were correlated with the results (96.4%). The Grade scores we created by visualizing the 1st and 3rd hour SPECT images semi-quantitatively are shared in Table 2.

Table 2. Number of patients obtained by semiquantitative evaluation in SPECT imaging

	GRADE 0	GRADE 1	GRADE 2	GRADE 3
1ST HOUR	**0**	**66**	**14**	**5**
3RD HOUR	**1**	**75**	**9**	**0**

We observed that the Grade 3 value at the 1st hour decreased to Grade 2 at the 3rd hour in 5 patients, from Grade 2 to Grade 1 in 10 patients, and from Grade 1 to Grade 0 in 1 patient. When compared with the patient results, the 1st hour SPECT image gave similar results in 75 patients (88.23%). It was observed that it gave similar results (94.11%) in 80 patients at the 3rd hour. Planar and SPECT images of two different patients are shared in Figure 1 and Figure 2.

Figure 1: 1st and 3rd hour static images with a Heart/CL ratio > 1.5 in 76-years old male patient on Tc-99m PYP imaging

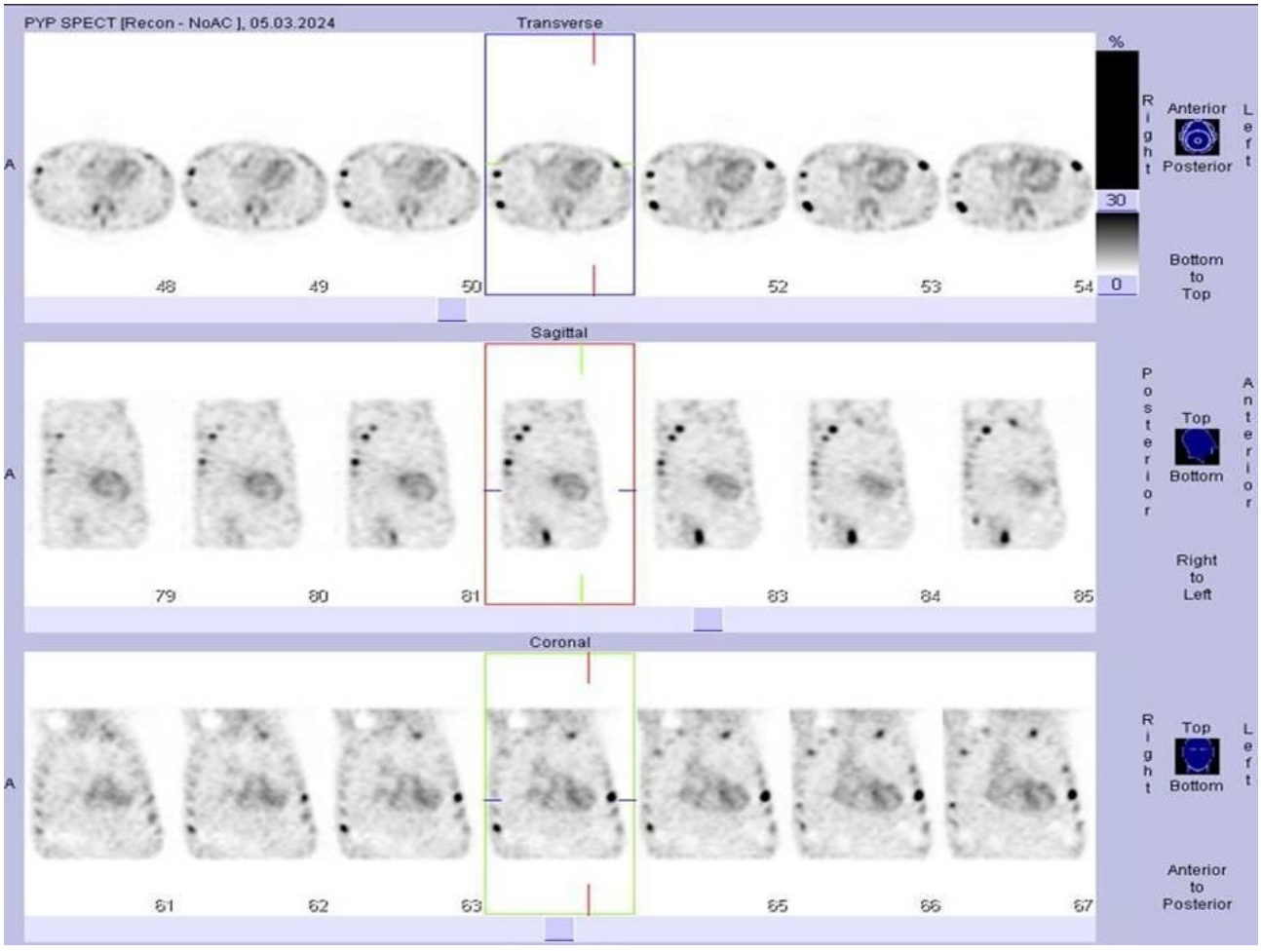

Figure 2: 1st hour SPECT imaging of a 90-year-old male patient whose cardiac involvement was scored as Grade 3. In this patient, we additionally observed activity involvements in areas corresponding to the ribs that may be compatible with fractures, and we took this into consideration when making a visual evaluation.

Discussion

Amyloidosis is a disease characterized by the aggregation of amyloid fibrils and their deposition in various organs. Proteins whose folding is disrupted cause aggregate formation and are stored (4). Structural defects in two protein precursors often cause amyloidosis. One of these is monoclonal immunoglobulin-derived light chain (AL) amyloid produced by bone marrow plasma cells; The other is ATTR, which originates from the TTR protein, which is a transporter for thyroid hormone and retinol, which are synthesized primarily in the liver (5). Amyloid fibrils can accumulate in the heart, kidney, liver, gastrointestinal tract, lung, and soft tissue. The type of organ involvement with the worst prognosis in systemic amyloidosis is cardiac amyloidosis. Echocardiography, cardiac magnetic resonance imaging and scintigraphic imaging with bone scintigraphy agents are imaging methods frequently used in the diagnosis of cardiac amyloidosis, differentiation of

amyloidosis types, follow-up of patients and determination of prognosis. Bone scintigraphy performed for the diagnosis of cardiac amyloidosis, especially for ATTR, shows a sensitivity of nearly 100% in the diagnosis of amyloidosis. Differential diagnosis of AL and ATTR is another area of use for bone scintigraphy. Although bone scintigraphy agents also show uptake in small amounts of AL amyloid, they are mostly specific for ATTR amyloid. Bone scintigraphy is used to show amyloid involvement that cannot be diagnosed by echocardiography and cardiac MRI. Cardiac involvement is prominent in the ATTR type of cardiac amyloidosis, probably due to calcium accumulation along with accumulation. In addition to cardiac involvement, involvement occurs in the gluteal, shoulder, chest wall and anterior abdominal wall, which are rich in muscle tissue (6,7). Pyrophosphonate (PYP) and 3,3-diphosphano-1,2-propanodicarboxylic acid (DPD) and hydroxydiphosphonate (HDP) linked agents, which are bisphosphonate compounds labeled with Tc-99m, are used. These radiopharmaceuticals are known to have high sensitivity in detecting cardiac involvement of ATTR amyloidosis (8,9,10). To distinguish AL from ATTR, 99m-Tc-PYP uptake is made by comparing the heart shadow with the contralateral lung tissue; A ratio < 1.5 is interpreted as AL, and a ratio $\geq$ 1.5 is interpreted as ATTR (11). Especially in screenings for the diagnosis of ATTR, 99mTc-PYP and 99mTc-DPD have the highest sensitivity and specificity (11). Cardiac involvement in scintigraphy is graded from Grade 0 to Grade III. While there is no involvement in Grade 0, the involvement in Grade III is as intense as bone involvement. Grade 0 scintigraphy indicates the absence of TTR type amyloidosis. Because grade 1 involvement on bone scintigraphy is seen in various types of CA, endomyocardial biopsy is indicated to confirm amyloidosis and define the type.

Based on the obtained data, we observed that the 1st hour provided more accurate results for static imaging and quantitative evaluation, while the 3rd hour provided more accurate results for SPECT imaging and semiquantitative evaluation. In the 1st hour planar imaging CA evaluation; It is a largely sufficient time in terms of the distribution of PYP throughout the body and is an indispensable parameter with its short waiting time and high accuracy. It was observed that the 3rd hour imaging was helpful to the 1st hour imaging by erasing the bloodpool activity of PYP and the involvement in the cardiac area and ribs was more evident in some patients. Visual imaging in SPECT images can give misleading results, especially in borderline positive or negative patients, as it is reporter dependent. Considering the age of the study patients, rib fractures and degeneration are common and appear to be a factor that makes visual evaluation difficult. In addition, it contributes to the planar view in determining the localization of the heart by distinguishing it from vascular structures and bone structures with which it may be superimposed, and in distinguishing local or diffuse myocardial involvement.

Conclusion

Drawing area of interest on planar images taken at the 1st and 3rd hour and using a combination of visual evaluation on SPECT images gives the most accurate and effective results. In the bone scintigraphy study for the diagnosis of amyloidosis performed with 99mTc-PYP, it is recommended to perform static imaging at the 1st hour and SPECT imaging at the 3rd hour, and it is thought that there is no need to perform a SPECT study at the 1st hour. Since there are rarely semiquantitative analysis results that give a ratio $\geq$ 1.5 at the 3rd hour, it is recommended to perform an additional static imaging at the 3rd hour and calculate the heart/CL ratio in this image as well.

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Authorship Contributions

Concept: E.A., P.P.O., Z.P.K., A.G., G.Y., **Design:** E.A., P.P.O., Z.P.K., A.G., G.Y., **Supervision:** E.A., P.P.O., Z.P.K., A.G., G.Y., **Data Collection and/or Processing:** E.A., P.P.O., G.Y.,**Analysis and/or Interpretation:** E.A., P.P.O., **Literature Review:** E.A., P.P.O., **Writer:** E.A.

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