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Research Article

Difference Uptake of ^{99m}Tc-Pyrophosphate vs ^{99m}Tc-Methylenediphosphate in Detecting Cardiac Amyloidosis; First Experience in Hasan Sadikin General Hospital

Perbedaan Penangkapan *^{99m}Tc-Pyrophosphate* vs *^{99m}Tc- Methylenediphosphate* dalam Mendeteksi Amyloidosis Jantung; Pengalaman Pertama di RSUP Hasan Sadikin

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Abstract

Cardiac Amyloidosis (CA) is a disorder caused by deposits of insoluble fibrils in the myocardium and an underdiagnosed cause of heart failure. The standard for diagnosis CA is biopsy but this procedure is rarely performed. Recent advances in cardiac radionuclide imaging, in particular using bone-seeking agents such as ^{99m}Tc-Pyrophosphate (PYP) and ^{99m}Tc-Methylenediphosphate (MDP), can help to diagnose CA and also can differentiate Immunoglobulin Light Chain-Associated Amyloid (AL) from Amyloidosis Transthyretin-Related (ATTR). It is important to distinguish between these two types of amyloidosis because the treatment and prognosis of each type is different. This study aimed was to investigate the uptake characteristic of both tracers in CA. Three patients suspected of having cardiac amyloidosis underwent two cardiac radionuclide imaging examinations using those two different radiopharmaceuticals. The cardiac images were analyzed quantitatively and semi-quantitatively based on ASNC (American Society of Nuclear Cardiology) criteria. Results of this study found that the three patients showed the uptake of ^{99m}Tc-PYP gave a visual score of 1 while the uptake of ^{99m}Tc-MDP gave a visual score of 0. As a conclusion, cardiac radioactivity uptake of ^{99m}Tc-PYP was better than those of ^{99m}Tc-MDP based on quantitative as well as semi-quantitative (visual assessment).

Keywords: *cardiac amyloidosis; cardiac imaging; ^{99m}Tc-PYP; ^{99m}Tc-MDP*

Abstrak

Amiloidosis jantung merupakan suatu gangguan akibat deposit fibril yang tidak dapat larut pada miokardium dan merupakan penyebab gagal jantung yang jarang terdiagnosis. Diagnosis baku pada penyakit ini adalah biopsi, tetapi tindakan ini masih jarang dilakukan. Perkembangan terkini pada pencitraan sidik jantung dengan radionuklida terutama penggunaan *bone-seeking agents* seperti *^{99m}Tc-Pyrophosphate* (PYP) and *^{99m}Tc-Methylenediphosphate* (MDP) dapat digunakan untuk membantu diagnosis amiloidosis serta membedakan *Immunoglobulin Light Chain-Associated Amyloid* (AL) dan *Amyloidosis Transthyretin-Related* (ATTR).

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Membedakan kedua tipe dari amiloidosis ini sangat penting oleh karena penatalaksanaan dan prognosis dari masing-masing tipe sangat berbeda jauh. Tujuan studi ini adalah untuk menginventigasi karakteristik penangkapan antara kedua radiofarmaka tersebut. Tiga pasien dengan sangkaan amiloidosis jantung dilakukan pemeriksaan sidik jantung dengan dua radiofarmaka yang berbeda. Pencitraan jantung tersebut dianalisa secara kuantitatif dan semi kuantitatif berdasarkan kriteria ASNC (*American Society of Nuclear Cardiology*). Hasil studi ini didapatkan ketiga pasien menunjukkan penangkapan radioaktivitas dari ^{9m}Tc-PYP memberikan *visual score* 1 sedangkan penangkapan radioaktivitas dari ^{99m}Tc-MDP memberikan *visual score* 0. Sebagai simpulan, penangkapan radioaktivitas pada jantung oleh ^{9m}Tc-PYP lebih baik dari ^{99m}Tc- MDP berdasarkan penilaian kuantitatif maupun semikuantitatif (penilaian visual).

Kata kunci: amiloidosis jantung; sidik jantung; ^{99m}Tc-PYP; ^{99m}Tc-MDP

Introduction

Amyloid deposits in the myocardium are called cardiac amyloidosis and are an underdiagnosed cause of Heart Failure with preserved Ejection Fraction (HFpEF). Cardiac amyloidosis is one of the causes of cardiac morbidity and mortality as the result of restrictive cardiomyopathy, heart failure, and death.[1] There are two types of amyloidosis that are most clinically challenging: *Immunoglobulin Light Chain-Associated Amyloid* (AL) and *Amyloidosis Transthyretin-Related* (ATTR).[2] Cardiac involvement in AL CA and ATTR CA can present similar clinical manifestations (usually progressive heart failure, arrhythmias or conduction disease, and infrequently chest pain) and imaging presentation. Nuclear scintigraphy offers a non-invasive imaging modality for assessing suspected CA with a evidence showing the potential for an earlier diagnosis of CA compared to echocardiography and CMR, the ability to measure amyloid burden, differentiate between CA types, and provide a prognostic.[3] Distinguishing between the various types of CA is very important because the treatment and prognosis of AL CA and ATTR CA are vastly different.[3] This study aimed was to investigate the uptake characteristic of both tracers in detecting cardiac amyloidosis.

Methods

Cardiac radionuclide imaging for patients with suspected cardiac amyloidosis has never been performed in Indonesia. In this study, three patients with suspected cardiac amyloidosis were referred for cardiac radionuclide imaging. The patients underwent two examinations in one week using two different radiopharmaceuticals, which were ^{99m}Tc-Pyrophosphate (PYP) and ^{99m}Tc-Methylenediphosphate (MDP). The patients received a dose of 20 mCi each of both radiopharmaceuticals. Planar and SPECT imaging were performed in 1 and 3 hours post injection

of radiopharmaceutical. Quantitative and semi-quantitative images analysis was done based on ASNC (American Society of Nuclear Cardiology) 2019 criteria.

Results

Case I

A 44 years old woman presented with shortness of breath for three days. The patient had a history of heart disease at a young age and a Caesarean surgery due to impaired heart function. The patient's father and sister had a history and died because of heart disease. The patient had no complain of chest pain. Blood pressure, heart rate, and respiration rate were 120/80 mmHg, 40 beats/min, and 24 times/min, respectively. Echocardiography showed concentric left ventricle hypertrophy and dilated left atrium (Figure 1). Due to the symptoms of bradycardia, a temporary pacemaker was placed. She was diagnosed with suspected cardiac amyloidosis with a differential diagnosis of hypertrophic cardiomyopathy. The patient was referred to Nuclear Medicine Department for cardiac radionuclide imaging (Figure 1 and 2).

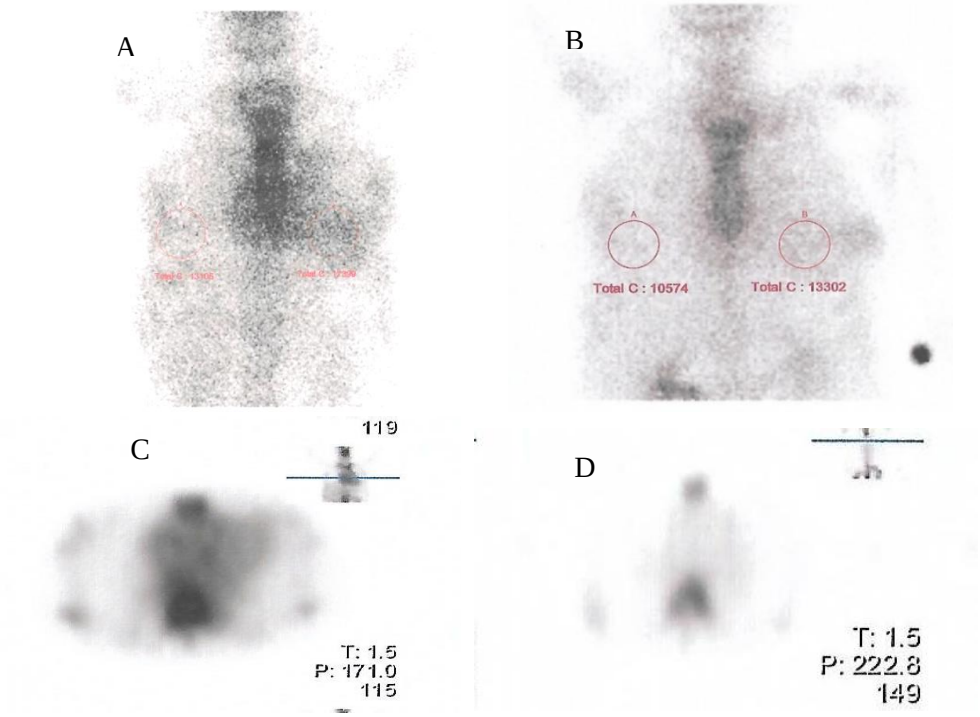

Figure 1 (Case I) Cardiac Radionuclide Imaging 1-Hour Post Radiopharmaceutical Injection

A. Planar Image of ^{99m}Tc-PYP with Heart and Contralateral Lung Ratio of 1.32; B. Planar Image of ^{99m}Tc-MDP with Heart and Contralateral Lung Ratio 1.25; C. SPECT Image of ^{99m}Tc-PYP; D. SPECT Image of ^{99m}Tc-MDP

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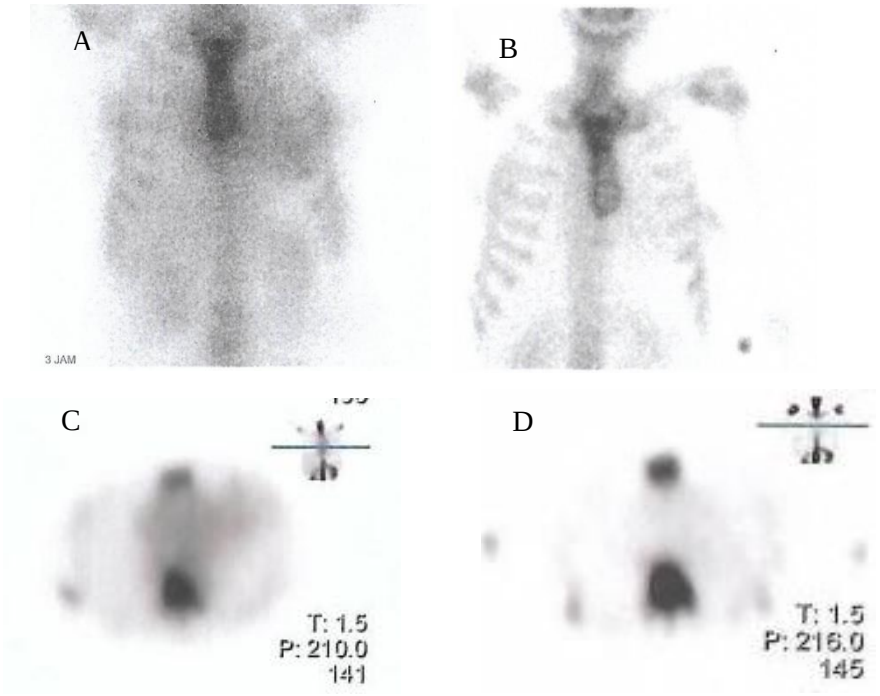

Figure 2 (Case I) Cardiac Radionuclide Imaging 3 Hours Post Radiopharmaceutical Injection

A. Planar Image of ^{99m}Tc-PYP; B. Planar Image of ^{99m}Tc-MDP; C. SPECT Image of ^{99m}Tc-PYP; D. SPECT Image of ^{99m}Tc-MDP

Three-hour planar and SPECT images post ^{99m}Tc-PYP injection was better with visual score 1 (heart uptake less than rib uptake) compared to ^{99m}Tc-MDP with visual score 0 (no uptake). Based on this study, it can be concluded that those images are equivocal for ATTR amyloidosis, and different uptake of both tracers was observed.

Case II

A 39-year-old woman complained of shortness of breath and palpitation for three years, which worsened in the last two months. The patient had a history of frequent syncope in 2014 and stroke in 2017. Blood pressure, heart rate, and respiration rate were 110/70 mmHg, 40 beats/min, and 24 times/min, respectively. Echocardiography showed left ventricle hypertrophy with mild mitral and tricuspid regurgitation. A temporary pacemaker was placed due to symptomatic bradycardia. She was diagnosed with suspected cardiac amyloidosis with a differential diagnosis of hypertrophy cardiomyopathy. The patient was referred for cardiac radionuclide imaging (Figure 3 and 4).

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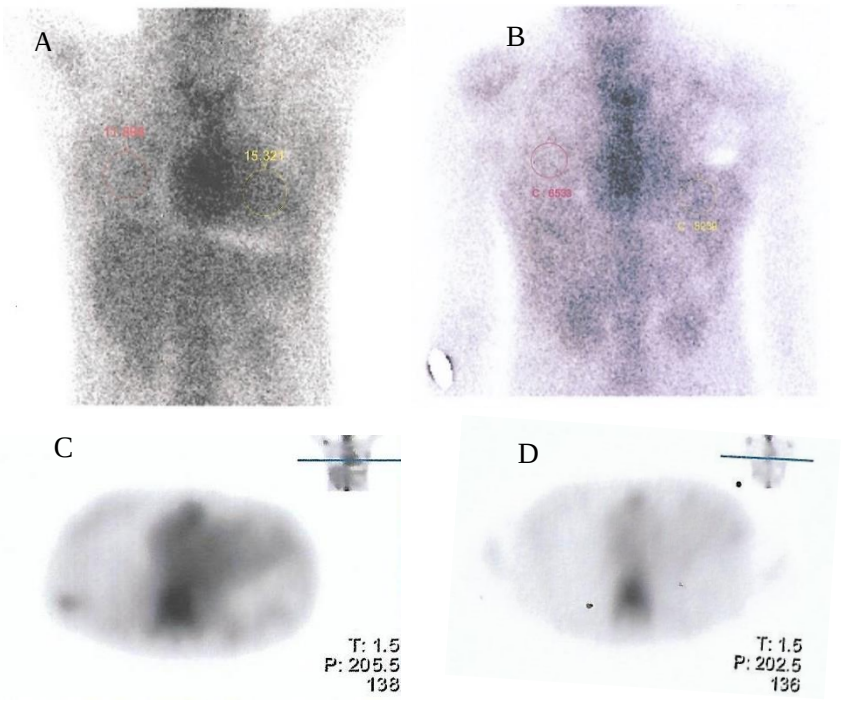

Figure 3 (Case II) Cardiac Radionuclide Imaging 1-Hour Post Radiopharmaceutical Injection

A. Planar Image of ^{99m}Tc- with Heart and Contralateral Lung Ratio of 1,28; B. Planar Image of ^{99m}Tc-MDP with Heart and Contralateral Lung Ratio 1,26; C. SPECT Image of ^{99m}Tc-PYP; D. SPECT Image of ^{99m}Tc-MDP

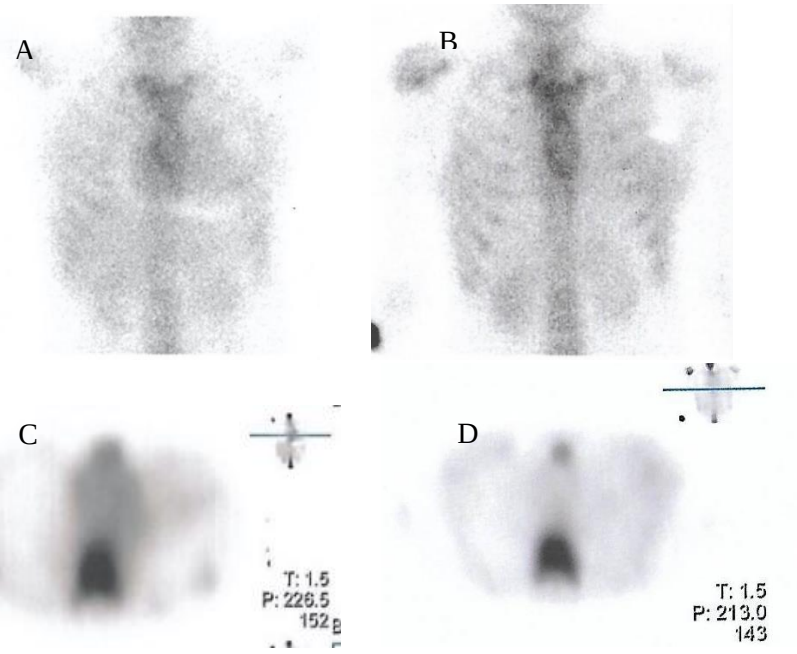

Figure 4 (Case II) Cardiac Radionuclide Imaging 3 Hours Post Radiopharmaceutical Injection

A. Planar Image ^{99m}Tc-PYP; B. Planar Image of ^{99m}Tc-MDP; C. SPECT Image of ^{99m}Tc-PYP; D. SPECT Image of ^{99m}Tc-MDP

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Three-hour planar and SPECT images post ^{99m}Tc-PYP injection was better with visual score 1 (heart uptake less than rib uptake) compared to ^{99m}Tc-MDP with visual score 0 (no uptake). Based on this study, it can be concluded that those images were equivocal for ATTR amyloidosis, and different uptake of both radiopharmaceuticals was observed. In cardiac radionuclide imaging using ^{99m}Tc-PYP, avoid area around the heart may indicate a pericardial effusion. However, cardiac radionuclide imaging using ^{99m}Tc-MDP in this study did not show that features due to the given diuretic.

Case III

A 61-year-old woman with chest pain and shortness of breath for three months. Patient had history of frequent syncope 3 months ago. Swelling on both feett was found 3 weeks ago. The patient had no symptoms of chest pain. Blood pressure, heart rate, and respiration rate were 130/80 mmHg, 80 beats/min, and 20 times/min, respectively. Echocardiography showed a *relative apical sparring* pattern on GLS (*global longitudinal strain*), and CMR (*cardiac magnetic resonance*) showed evidence of amyloidosis (*late gadolinium enhancement*: evidence of global endocardial fibrosis). Cardiac radionuclide imaging is performed to determine the type of amyloidosis (Figure 5 and 6).

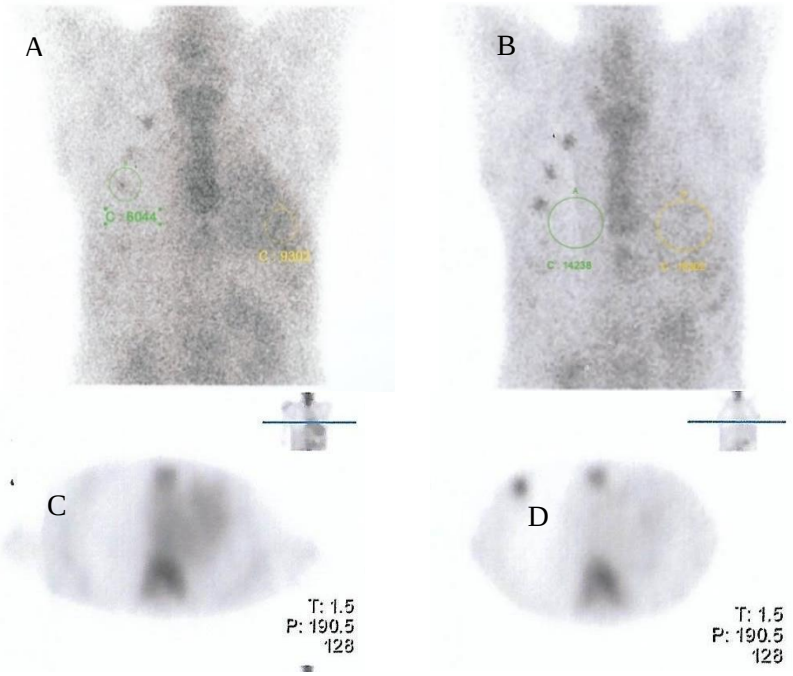

Figure 5 (Case III) Cardiac Radionuclide Imaging 1-Hour Post Radiopharmaceutical Injection

A. Planar Image of ^{99m}Tc-PYP with Heart and Contralateral Lung Ratio of 1,52; B. Planar Image of ^{99m}Tc-MDP with Heart and Contralateral Lung Ratio 1,27; C. SPECT Image of ^{99m}Tc-PYP; D. SPECT Image of ^{99m}Tc-MDP

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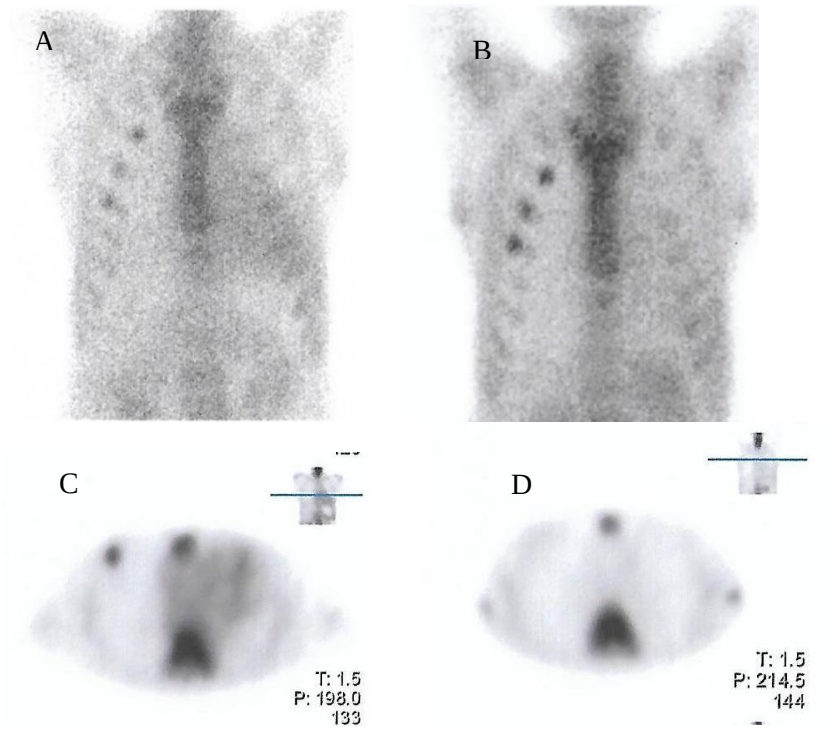

Figure 6 (Case III) Cardiac Radionuclide Imaging 3-Hours Post Radiopharmaceutical Injection

A. Planar Image of ^{99m}Tc-PYP; B. Planar Image of ^{99m}Tc-MDP; C. SPECT Image of ^{99m}Tc-PYP; D. SPECT Image of ^{99m}Tc-MDP

Three-hour planar and SPECT images post ^{99m}Tc-PYP injection was better with visual score 1 (heart uptake less than rib uptake) compared to ^{99m}Tc-MDP with visual score 0 (no uptake). Based on those studies, it can be concluded that those images suggested a Light Chain Amyloidosis and different uptake of both tracers was observed.

Discussion

Amyloidosis is a group of diseases characterized by the deposition of fibrils formed by different, insoluble proteins, that can infiltrate various tissues, leading to organ dysfunction.[4] Atrial, ventricular, valves, perivascular space, and conduction system are the anatomical distribution that amyloid can deposit in the heart.[5]

The diagnosis of amyloidosis relies on clinical suspicion. Unfortunately, the disease is often asymptomatic to an advanced stage and nevertheless, the symptoms can be very nonspecific.[6] Hence, there is often a delay in making the diagnosis.[2] There is a role for diagnostic modalities that arise in the diagnosis of cardiac amyloidosis such as electrocardiography (ECG), biomarkers (immunoglobulin and immunofixation), echocardiography, Cardiac Magnetic

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Resonance (CMR), and cardiac radionuclide imaging [5,7] Cardiac biopsy remains as the gold standard for diagnosis of cardiac amyloidosis,[8] but this is rarely performed.

Immunoglobulin Light Chain-Associated Amyloid (AL) and Amyloidosis Transthyretin-Related (ATTR) are the most common causes of cardiac amyloidosis.[5] However, differentiating between the various types of CA is crucial, since the treatment depends entirely on the amyloid type, and the prognosis of AL CA differs substantially from that of ATTR CA.[3,5,8]

In recent years, using cardiac radionuclide imaging has become the focus for early of CA. Planar imaging alone or with single-photon emission computed tomography (SPECT) using non amyloid-specific, bone seeking agent such as [^{99m}Tc-DPD (3,3-diphosphono-1,2-propanodicarboxylic acid), ^{99m}Tc-MDP, ^{99m}Tc-HMDP (hydroxymethylene diphosphonate), and ^{99m}Tc-PYP] have been known to be more effective in detecting ATTR myocardial deposits.[9]

The molecular mechanism underlying ^{99m}Tc-PYP uptake by myocardial transthyretin amyloid is unclear. A hypothesis proposed that ^{99m}Tc-PYP uptake in ATTR CA patients is due the presence of calcium bonds in transthyretin amyloid fibers to phosphate in these radiotracers. Calcium is found in both myocardial transthyretin amyloid fibrils and light chain amyloid fibrils. Therefore, the difference between ^{99m}Tc-PYP uptake in ATTR CA and AL CA may be due to an increase in the calcium content in transthyretin amyloid fibrils relatively higher than in AL fibrils, as well as an increased duration of accumulation of ATTR CA amyloid fibril due to the prolonged course of the disease.[10,11] Another hypothesis is that ^{99m}Tc-PYP can bind to ATTR amyloid fibrils more extremely than AL fibrils as a result of compounds containing higher calcium in ATTR hearts.[12] The characteristics of amyloidogenic fibrils in patients with ATTR cardiac amyloid may differ from those of AL amyloid, resulting in a higher ^{99m}Tc-PYP uptake rate.[12]

Based on ASNC criteria, interpretation of images can be done quantitatively or semi-quantitatively. The first quantitative method uses the heart to contralateral lung uptake ratio on planar image 1-hour post tracer injection. A positive result for ATTR amyloidosis is a heart to contralateral lung uptake ratio $\geq$ 1,5. The semi-quantitative method uses a visual score, which compares the tracer uptake between the myocardial and the rib. Visual score 0 is interpreted as absent of heart uptake, visual score 1 as heart uptake less than ribs, visual score 2 as heart uptake similar to ribs, and visual score 3 as heart uptake higher than ribs. ATTR amyloidosis is positive if the tracer uptake of the heart is equal to the rib (visual score $\geq$ 2).[8]

The best bone seeking tracers for detecting CA remains unclear as ^{99m}Tc-PYP is most commonly used in the USA, ^{99m}Tc-HMDP in France and ^{99m}Tc-DPD in other countries, including Italy and the UK.[13] Using ^{99m}Tc-MDP as a tracer for cardiac radionuclide imaging is controversial

due to low sensitivity.[7] However, the study conducted by Fukuzawa et al. and case report by Yang et al. and Fathala showed promising results using MDP for cardiac radionuclide imaging in detecting patients with amyloidosis.[14–16]

PYP and MDP are two bone-seeking agents available in our hospital that can be used for cardiac radionuclide imaging. In this study, three patients had cardiac radionuclide imaging using both tracers. The results showed a difference in cardiac radioactivity uptake of the two tracers. Martinez-naharro et al. and Ruberg-Berk described that ^{99m}Tc-binds preferentially to cardiac amyloid, although with avidity and sensitivity lower than ^{99m}Tc-PYP.[13,17] Less avidity and sensitivity of ^{99m}Tc-MDP may be due to lower bone mineral affinity, and the diagnostic performance of MDP is lower in detecting patients with grade 1 or even grade 2 amyloidosis because of the low content of calcium deposit.[18] Another study also showed ^{99m}Tc-PYP was positive in all seven patients with proven amyloidosis, but only four patients had ^{99m}Tc-MDP uptake.[19]

Conclusion

Cardiac radioactivity uptake of ^{99m}Tc-PYP was better than those of ^{99m}Tc-MDP based on quantitative as well as semi-quantitative (visual assessment). This study was the first experience in detecting cardiac amyloidosis using cardiac radionuclide imaging. Using bone seeking agents can help to diagnose cardiac amyloidosis. Further investigation with a larger number of subjects and cardiac biopsy as a gold standard is required.

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