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ORIGINAL ARTICLE

Global and Regional Reduction of Myocardial Perfusion in Patients with Transthyretin Type of Cardiac Amyloidosis: A Dual SPECT Study Using ^{99m}Tc Pyrophosphate and ^{201}Thallium

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Abstract

***Purpose*: We aimed to clarify the clinical characteristics of global and regional myocardial perfusion in patients with transthyretin type of cardiac amyloidosis (ATTR) using dual single-photon emission computed tomography (SPECT) with ^{99m}Tc pyrophosphate (PYP) and ^{201}TL (TL).**

***Methods*: Consecutive 178 (mean age 78 ± 12, male 79) patients known or suspect of ATTR who underwent PYP-TL dual SPECT were retrospectively enrolled. Patients were categorized according to the visual grading for planar PYP uptake using Perugini grading, and the patients with grade greater than or equal to 2 were analyzed. In planar analysis, the heart/contralateral ratio (H/CL) for PYP, and heart/lung ratio (H/L) for TL were obtained to evaluate global myocardial uptake. In TL-SPECT polar map analysis, the heterogeneity of myocardial uptake was evaluated using segmental mean %uptake. Cardiac function and left ventricular function and end-diastolic ventricular mass (LVmass) were measured by echocardiography.**

***Results*: Among 178 patients, 39 patients showed PYP uptake with grade 2 or 3 and H/CL >1.3 (81 ± 5 ys, male 28). Of those, 4 patients showed significant perfusion defect in TL scan. Among 35 patients without perfusion defect, H/L showed a significant inverse correlation to H/CL, and LVmass (r=-0.3, p=0.02; r=-0.4, p=0.03. 95% confidence interval -0.4 to 0.2, and -0.7 to -0.04 for H/CL and LVmass). Polar map analysis demonstrated significantly lower mean %uptake for TL in septum compared to lateral (79.4 ± 8.4 vs. 84.3 ± 6.2, p=0.006 for TL in septum vs. lateral, respectively).**

***Conclusion*: In ATTR, TL uptake surrogated the reduction of global myocardial perfusion. A significant regional heterogeneity was observed with a notable reduction in septum despite the diffuse hypertrophy.**

Keywords: Cardiac amyloidosis, Myocardial perfusion, Pyrophosphate, SPECT, Transthyretin
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Cardiac amyloidosis is characterized as restricted cardiomyopathy caused by amyloid fibril deposition in the extracellular space of the myocardium, illustrating concentric ventricular remodeling and decreased cardiac output (1). Cardiac amyloidosis commonly demonstrates heart failure with preserved ejection fraction (HFpEF) or mildly reduced EF with cardiac signs, symptoms as clinical manifestations, and may be diagnosed as the result of screening in patients who manifest extracardiac signs of amyloidosis (2). Transthyretin type of cardiac amyloidosis (ATTR) is categorized into hereditary and wild-type amyloidosis, and autopsy studies have indicated that the prevalence of cardiac wild-type ATTR is greater than previously estimated (3). Therefore, the more frequent use of non-invasive imaging technique such as bone

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seeking tracers and cardiac magnetic resonance imaging (CMR) have resulted in a marked rise in diagnoses in the past few years, particularly in the super-elderly population (4). Given the impact of ATTR on prognosis and the availability of new disease-modifying therapies, timely diagnosis using appropriate imaging techniques is essential to improveboth quality of life and prognosis in these diseases. The use of ^{99m}technetium-labeled-pyrophosphate (PYP) scintigraphy and abnormal cardiac uptake in patients with proven cardiac amyloidosis was firstly demonstrated in 1983 (5). Subsequent work has provided greater clarity on the biological basis for the different "Perugini" grades of uptake reported in the original study (6). To date, late gadolinium enhancement in CMR plays a key role for the diagnosis of ATTR as well as differentiating other cardiomyopathies. However, the use of contrast materials is contraindicated to renal dysfunction, and frequently repeated breath-hold acquisition may cause patient discomfort. In nuclear cardiology, dual single-photon emission computed tomography (SPECT) using various probes and perfusion with ^{201}TL have been frequently employed for the detection of either ischemic or non-ischemic disease. PYP and TL dual-tracer SPECT had been historically used for acute myocardial infarction in Japan. Due to the diffuse myocardial disease, myocardial perfusion may present non-remarkable finding in ATTR, while several representative cases show heterogenous myocardial PYP uptake (7). In the present study, the clinical significance of TL SPECT in use with PYP scan for ATTR was investigated.

Methods

Patients

This is a single center, retrospective study. Patients suspect or known ATTR who underwent PYP-TL dual SPECT between 2013 Jan and 2022 Dec were enrolled. The patient demographics including family history, risk factor, other myocardial disease was collected from medical record. This study was approved by institutional review board in Fukushima Medical University (No. C-T2022-0348).

Transthoracic echocardiography

Echocardiographic examinations were conducted at time of SPECT scan or within 6 months. The measurement has been performed in routine procedures using EPIQ7 (Phillips co., ltd, Netherlands), Vivid E05 (GE Medical Systems, Chicago). Left ventricular ejection fraction (LVEF) was estimated using the biplane Simpson method. LV wall mass was calculated using established formula obtained elsewhere (8). Asymmetric septal hypertrophy was assessed with short axis view, based on an established definition (the ratio of septal to lateral wall thickness over 1.3), the measurement in short axis cine-MR was preferentially employed if CMR was performed within 6

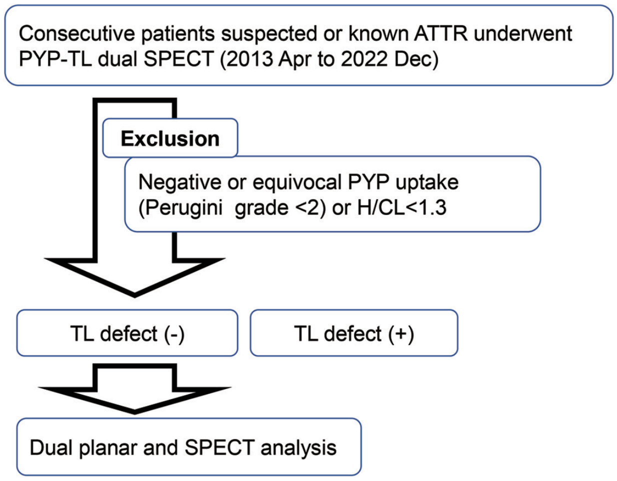

Figure 1 Chart for patient enrollment.
Patient enrollment of the study is shown. Consecutive 178 patients were enrolled in the study. Using visual Perguini grading, grade 2 or 3 was defined positive PYP uptake to enroll into analysis. After enrolling positive PYP uptake, the patients were not enrolled into planar and SPECT analysis when a regional significant defect was observed.

months.

PYP-TL dual SPECT

PYP-TL dual SPECT was performed using 3-head gamma detector SPECT system (GCA 9300R, Canon medical systems, Tokyo, Japan), equipped with low-energy high-resolution collimators.

The imaging protocol for PYP and TL dual scan was as follows. First, 370MBq of PTP was administrated intravenously, and the patients were stand-by for approximately 180 min for acquisition. 111MBq of TL was administrated 15min prior to dual planar and SPECT scan. Planar acquisition was done for 5 min, followed by SPECT scan. Energy window was 140KeV ± 20%, and 71KeV ± 20% for PYP and TL. Scatter correction was not applied to the TL planar image. The parameters for SPECT acquisition were as follows matrix 64*64, 4 angle for step and shoot with 90 views in circular orbit, zoom 1.0. Filtered back projection with Butterworth filter 0.41 for reconstruction.

Image analysis

The patient enrollment was described in Figure 1. Planar images were assessed by two experienced radiologists (OH, and SS) for visual grading among enrolled consecutive 178 patients, and the cases with Perugini score less than 2, or with the blood pool uptake confirmed by trans-axial SPECT image were excluded from analysis. The patients with normal perfusion (summed defect score for TL less than 3) were enrolled for planar and SPECT image analysis. Schematic presentations for planar and SPECT analysis were shown in Figure 2. Region of interest (ROI) was placed with circle was

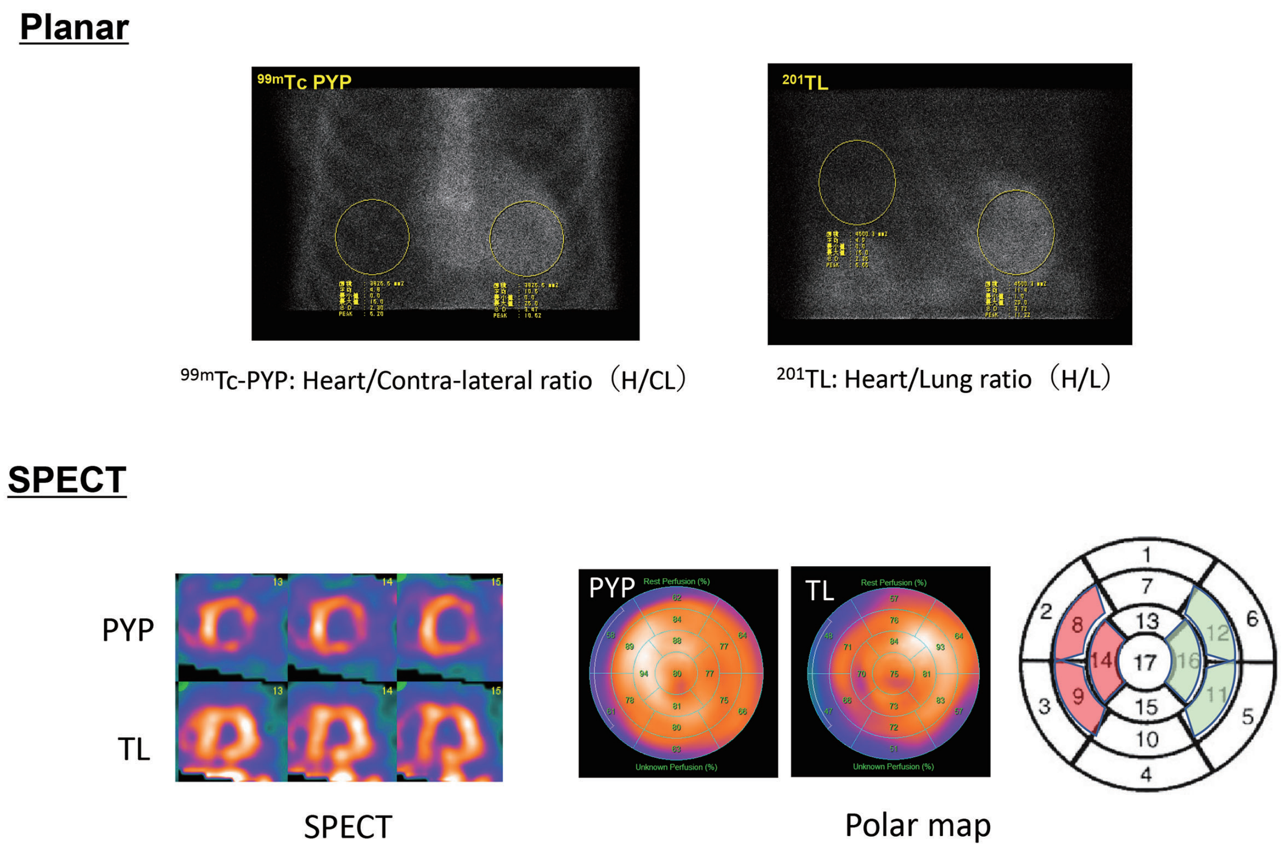

Figure 2 Image analysis for planar and SPECT-polar map.
The schematic images for planar and SPECT-polar map analysis for PYP and TL are shown. ROI was placed with circle was drawn in left ventricle for PYP. In TL planar images, circular ROI was placed for left ventricle and the center of right upper lung not to include liver. In SPECT analysis, mean %uptake in 17 segment model was calculated. The 17 segments were allotted into 4 regions; anterior (seg 7 and 13), septal (seg 8, 9, and 14), inferior (seg10 and 15), and lateral region (seg 11, 12, and 16), and mean value of each region was calculated.

drawn in left ventricle according to the studies by Bokhari et al (9, 10). In TL planar images, circular ROI was placed for left ventricle and the center of right upper lung not to include liver according to the study by Takeishi et al (11). In SPECT analysis, mean %uptake from American Heart Association 17 segment model was used (QPS. Ceders-Sinai Medical Center, LA). The 17 segments were allotted into 4 regions; anterior (seg 7 and 13), septal (seg 8, 9, and 14), inferior (seg10 and 15), and lateral region (seg 11, 12, and 16), and mean value of each region was calculated.

Statistical analysis

Statistical analysis was performed using Prism ver. 8 (Graphpad inc., Belgium). A spearman correlation coefficient was plotted for H/CL, H/L ratio, and echo data. Mann-Whitney test was done for SPECT analysis. Two-tailed P value <0.05 was defined statistically significant.

Results

Among 178 patients, 39 patients showed PYP uptake with grade 2 or 3 and H/CL >1.3 (81 ± 5 ys, male 28). Of those, 4 patients showed significant perfusion defect in TL scan. Thirty-five patients were enrolled for planar and SPECT analysis. Demographics of enrolled patients is shown in Table 1. Forty percent of the patients had severe aortic stenosis; 6 patients (16%) had a recent history of a significant congestive heart failure. Fifteen had asymmetric septal hypertrophy (ASH), and the rest showed diffuse left ventricular hypertrophy in echocardiography. As shown in Table 2, mean PYP grade 2.7 ± 0.4, H/CL was 1.6 ± 0.3. In the analysis with normal TL perfusion, H/L was 2.6 ± 0.8, and overt right ventricle (RV) uptake was observed in 13 patients. In comparison between with or without RV uptake, H/L was significantly lower in patients with RV uptake compared to those without (1.8 ± 0.4 vs. 2.5 ± 0.8, p=0.009). Figure 3 showed the result of planar image analysis for PYP and TL. H/L showed a significant inverse correlation to H/CL (r=-0.34, p=0.02, 95% confidence interval -0.4 to 0.2), and also showed a significant inverse correlation to LV wall mass, while not to LVEF (r=-0.4, p=0.03, 95% confidence interval -0.7 to -0.04). Additionally, we compared H/L between enrolled PYP positive patients and the patients who were excluded due to negative PYP uptake (grade 0, n=80), and a significant difference was observed (2.6 ± 0.8 vs 2.8 ± 0.6, p=0.02) (Supplemental Figure 1, left).

Table 1 Patient demographics (n=35)

	n(%)
Age	81 ± 5
Male	28(72)
AS	15(40)
History of HF	6(16)
Echocardiography	
LVEF (%)	47.6 ± 13.3
LVEDV(mL)	97.4 ± 34.5
LVESV(mL)	52.5 ± 29.6
LV mass(g)	213.1 ± 61.0
ASH	15(40)
Diffuse LVH	24(60)

AS, aortic stenosis; HF, heart failure; LVEF, left ventricular ejection fraction; EDV, endo-diastolic volume, ESV, endo-systolic volume; ASH, asymmetric septal hypertrophy; LVH, left ventricular hypertrophy

Table 2 Planar and SPECT analysis

^{99m}Tc PYP (3hr)		
Perugini grading	2.7 ± 0.4	
H/CL	1.6 ± 0.3	
Uptake pattern		
Septal		22
Diffuse		17
^{201}TL (3hr)		
H/L	2.6 ± 0.8	
Summed defect score	2.6 ± 0.2	
RV uptake+	13 (35)	
Segmental mean% uptake		
Anterior (seg 1,7,13)	80.3 ± 12.3	
Inferior (seg 4,10,15)	70.8 ± 9.1*	
Septal (seg 8,9,14)	79.4 ± 8.4$	
lateral (seg 11,12,16)	84.3 ± 6.2	

*p<0.0001 compared to others
$p=0.006 compared to lateral
H/CL, heart to contralateral ratio; H/L, heart to lung ratio; RV, right ventricle

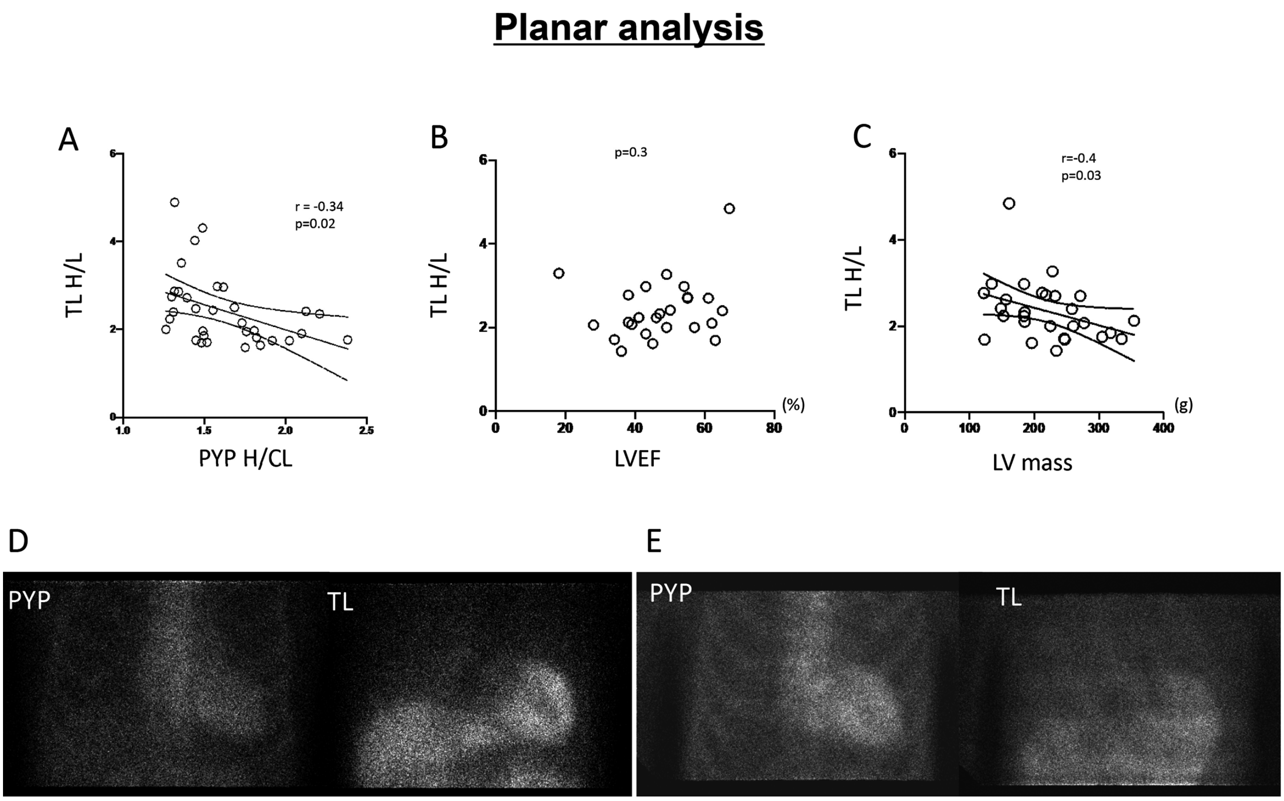

Figure 3 Planar image analysis.

The result of planar image analysis for PYP and TL are shown. H/L showed a significant inverse correlation to H/CL (r= -0.3, p=0.02, 95% confidence interval -0.4 to 0.2). H/L showed a significant inverse correlation to LV wall mass, while not to LVEF (r=-0.4, p=0.03, 95% confidence interval -0.7 to -0.04). The lower panel of figure 4 showed representative cases for the planar images for reduced and preserved TL in patients with ATTR. D showed preserved TL H/L uptake ratio with positive PYP uptake (PYP H/CL and TL H/L were 1.3 and 2.0). E showed a marked uptake in PYP and reduced TL cardiac uptake (PYP H/CL and TL H/L were 1.8 and 1.6).

The lower panel of Figure 3 showed representative cases for the planar images in patients with ATTR. D showed preserved TL H/L uptake ratio with positive PYP uptake (PYP H/CL and TL H/L were 1.3 and 2.0). E showed a marked uptake in PYP and reduced TL cardiac uptake (PYP H/CL and TL H/L were 1.8 and 1.6). In SPECT analysis for PYP and TL, all cases were available for TL, while 25 cases were available for PYP (10 cases failed in polar map reconstruction due to extracardiac uptake such as bone). The regional mean %uptake of TL showed significant reduction in septal wall compared to lateral in all cases (79.4 ± 8.4% vs. 84.3 ± 6.2%, $p<0.0001$, Table 2), and this statistical difference was also observed in non-ASH, diffuse hypertrophy (78 ± 11.0% vs. 86 ± 12.3%, $p=0.006$). On the contrary, PYP polar map analysis showed a significant higher uptake in septal wall compared to lateral wall (86 ± 7.0% vs. 69 ± 8.0%, $p < 0.0001$) (Figure 4 upper right). Additionally, we performed TL polar map analysis for the patients with PYP negative to compare to those with PYP positive, and found a significant difference in %uptake of septal wall between PYP negative and positive (82.2 ± 5.8 vs. 79.4 ± 8.4, $p=0.01$ for PYP negative and positive, respectively) (Supplemental Figure 1 middle and right). The lower panel of Figure 4 showed representative cases for PYP and TL polar map analysis. A showed a case with a significant ASH in cardiac MRI. A marked septal hypertrophy was observed in cine MRI, and PYP showed relatively elevated uptake in septum. Conversely, TL showed reduced uptake in corresponding septal wall. B showed ATTR with diffuse hypertrophy. Cine MRI demonstrated mildly hypertrophied left ventricle without ASH. However, PYP demonstrated a remarkable elevated uptake in septal wall. C showed the case with significant TL defect in inferior wall and positive PYP uptake, which was excluded from analysis. Cine MRI demonstrated ASH, and gadolinium perfusion study showed perfusion defect in inferior wall. Late gadolinium enhancement study revealed that undistinguishable lower signal intensity in inferior wall corresponding to perfusion defect in diffuse hyperintensity in LV, where was overt in TL scan.

Discussion

In this study, the reduction of global and regional myocardial perfusion was assessed using PYP and TL dual SPECT in patients with known or suspect of ATTR. Since the extent of global myocardial uptake of PYP should have surrogate the severity of the disease in ATTR, H/CL ratio has been recognized as a hallmark of the extent of fibril deposition and associated poor outcome (10). The result from our study, the ratio of heart to lung TL uptake showed significant reduction in ATTR according to the elevation of H/CL and LVmass. Global TL uptake in comparison to lung uptake has been historically used as surrogate marker for global reduction of perfusion in LV, or increased lung uptake due to pulmonary congestion. As shown in Table 1, 6 patients had a history of heart failure. In additional analysis in comparison to H/L of PYP negative subjects, H/L was significantly lower in patients with PYP positive than those with negative. In general, the prominent feature of cardiac amyloidosis is known as diffuse deposition of fibrils, resulting increased extracellular space. This pathological process may cause microvascular dysfunction and the loss of myocardial cell integrity (12). Although it is possible that the enrolled patients had lung congestion, our results indicated that the patients with PYP positive had global perfusion reduction due to myocardial damage. The findings in our study indicated that diffuse reduction of myocardial perfusion is one of the clinical characteristics of ATTR because hypertrophied myocardium generally represents elevated perfusion uptake (13). In SPECT analysis, regional heterogeneity in PYP was oppose to those of myocardial perfusion in TL. Interestingly, the heterogeneity of uptake particularly in septal and lateral was observed in both ASH type and diffuse hypertrophy. It is speculated that amyloid fibril predominantly deposits in septum, manifesting asymmetric uptake. Hypertrophic cardiomyopathy is known as differential diagnosis for ATTR, while demonstrating hyper-uptake in myocardial perfusion, and known to demonstrate transient defect under stress image surrogating microvascular dysfunction (13, 14). However, TL in ATTR showed significant reduction in septum either with or without ASH, this finding is new and may distinct findings from hypertrophied cardiomyopathy. Although there are limitations in spatial resolution, myocardial heterogeneity in perfusion imaging should be characteristics of ATTR regardless diffuse disease.

In our study, 4 cases were not enrolled into planar and SPECT analysis due to significant regional defect because perfusion defect might affect on the assessment of global uptake and regional heterogeneity. However, the regional perfusion defect commonly indicates myocardial damage including infarction or non-ischemic fibrosis. As shown in lower panel (C) of Figure 4, localization of regional fibrosis in diffuse high intensity signal in myocardium is difficult to discriminate, while TL perfusion defect clearly visualize transmural infarction. Since the prevalence of renal dysfunction in super-elderly population, the patients with severe renal dysfunction who is contraindicated for contrast-enhanced MRI can be allotted to TL-PYP dual SPECT as alternative non-invasive imaging technique. As a results of this study, there are other several advantages for dual SPECT. First, among PYP positive cases, 4 cases demonstrated significant myocardial perfusion defect indicated myocardial infarction. Considering ATTR is the disease prevalent among super-elderly, coronary artery disease may present as concomitant.

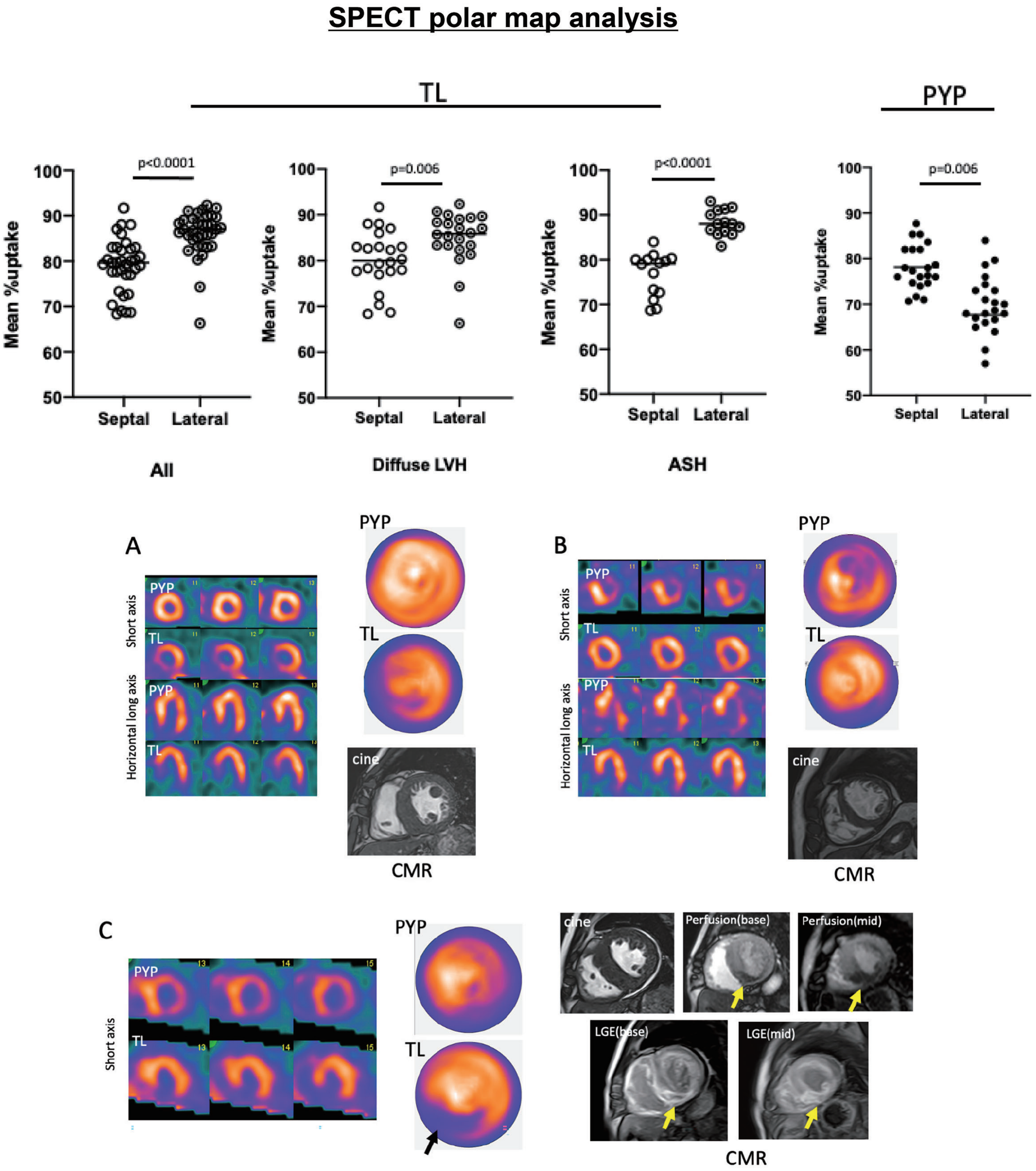

Figure 4 SPECT-polar map analysis.

Polar map analysis for PYP and TL is shown. The regional mean %uptake of TL showed significant reduction in septal wall compared to lateral in all cases (68 ± 13% vs. 84 ± 8.0%, p<0.0001). Non-ASH type diffuse hypertrophy demonstrated showed significant reduction in septal wall compared to lateral (79.4 ± 8.4% vs. 84.3 ± 6.2%, p=0.006). On the contrary, PYP polar map analysis showed a significant higher uptake in septal wall compared to lateral wall (78.4 ± 7.0% vs. 69 ± 8.0%, p<0.0001). Lower showed representative cases for PYP and TL polar map analysis. Upper left showed a case with a significant ASH in cardiac MRI. A marked septal hypertrophy was observed in cine MRI, and PYP showed relatively elevated uptake in septum. Conversely, TL showed reduced uptake in corresponding septal wall. Upper right showed ATTR with diffuse hypertrophy. Cine MRI demonstrated mildly hypertrophied left ventricle without ASH. However, PYP demonstrated a remarkable elevated uptake in septal wall. Lower showed the case with significant TL defect in inferior wall and positive PYP uptake. Cine MRI demonstrated ASH, and gadolinium perfusion study showed perfusion defect in inferior wall. Late gadolinium enhancement study revealed that undistinguishable lower signal intensity in inferior wall corresponding to perfusion defect in diffuse hyperintensity in LV, where was overt in TL scan.

Hence, the findings from the result should be highlighted for novel insights for myocardial microcalcification and cell integrity.

There are several limitations to this study. It is a retrospective study and sample size is small. Prognostic follow-up is not available. Comorbidities such as undiagnosed endomyocardial infarction, symptomatic angina were not fully differentiated. In this study, scatter correction was not performed for TL acquisition because TL image was mainly used to localize the heart rather than the assessment of myocardial perfusion. Thus, it may have influenced the assessment of planar image analysis.

Conclusion

TL uptake in planar image surrogated the reduction of global myocardial cell integrity in ATTR. Regional heterogeneity with reduced septal uptake for myocardial perfusion contradicting PYP uptake was a unique phenomenon despite the diffuse myocardial disease.

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Conflicts of interest

None.

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References

1. Fontana M, Ćorović A, Scully P, Moon JC. Myocardial amyloidosis: The exemplar interstitial disease. JACC Cardiovasc Imaging 2019; 12: 2345–56.
2. Sperry BW, Hanna M, Shah SJ, Jaber WA, Spertus JA. Spironolactone in patients with an echocardiographic HFpEF phenotype suggestive of cardiac amyloidosis. JACC Heart Fail 2021; 9: 795–802.
3. Porcari A, Bussani R, Merlo M, et al. Incidence and characterization of concealed cardiac amyloidosis among unselected elderly patients undergoing post-mortem examination. Front Cardiovasc Med 2021; 8: 749523.
4. Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac amyloidosis: evolving diagnosis and management: A scientific statement from the American Heart Association. Circulation 2020; 142: e7–e22.
5. Fukushima K, Nakano S, Matsunari I. Cardiac amyloidosis: Current diagnostic strategies using multimodality imaging. Ann Nucl Cardiol 2020; 6: 67–73.
6. Dorbala S, Cuddy S, Falk RH. How to image cardiac amyloidosis. JACC Cardiovasc Imaging 2020; 13: 1368–83.
7. Lee C, Chao CJ, Agasthi P, et al. Global and regional variations in transthyretin cardiac amyloidosis: A comparison of longitudinal strain and ^{99m}Tc-pyrophosphate imaging. J Nucl Med Technol 2022; 50: 30–7.
8. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015; 28: 1–39.e14.
9. Bokhari S, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. ^{99m}Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Imaging 2013; 6: 195–201.
10. Castano A, Haq M, Narotsky DL, et al. Multicenter study of planar technetium 99m pyrophosphate cardiac imaging: Predicting survival for patients with ATTR cardiac amyloidosis. JAMA Cardiol 2016; 1: 880–9.
11. Takeishi Y, Chiba J, Abe S, Tomoike H. Ratio of lung to heart thallium-201 uptake on exercise and dipyridamole stress imaging in coronary artery disease: Implication of SPECT. Jpn Circ J 1993; 57: 379–87.
12. Ioannou A, Chacko L, Kotecha T et al. Myocardial ischaemia in cardiac amyloidosis: A change of perspective. Eur Heart J 2022; 43: ehac544.1761.
13. Huang G, Fadl SA, Sukhotski S, Matesan M. Apical variant hypertrophic cardiomyopathy “multimodality imaging evaluation”. Int J Cardiovasc Imaging 2020; 36: 553–61.
14. Abazid RM, Romsa JG, Warrington JC, Akincioglu C, Stodilka RZ, Vezina WC. Complementary role of hybrid imaging with SPECT myocardial perfusion and coronary CT angiography in hypertrophic cardiomyopathy. J Nucl Cardiol 2022; 29: 2716–20.