Simultaneous Tc-99m PYP/Tl-201 dual-isotope SPECT myocardial imaging in patients with suspected cardiac amyloidosis

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Received Jan 23, 2019; accepted Feb 28, 2019
doi:10.1007/s12350-019-01753-5

Introduction. **Assessment of myocardial uptake of Tc-99m-pyrophosphate (Tc-99m PYP) is pivotal in distinguishing transthyretin-associated cardiac amyloidosis (ATTR) from light chain amyloid (AL). It is often difficult to differentiate myocardial uptake from blood pool radioactivity with planar imaging or SPECT. We studied whether simultaneous dual-isotope Tc-99m PYP/Tl-201 SPECT improves assessment of Tc-99m PYP uptake compared to single-isotope SPECT.**

Methods. **Simultaneous Tc-99m PYP/Tl-201 dual-isotope SPECT was acquired in 112 patients studied for possible cardiac amyloidosis. Visual interpretation was performed by two observers on single-isotope followed by dual-isotope SPECT. Heart-to-contralateral lung ratio (H/CL) of myocardial counts quantified by single-isotope and dual-isotope SPECT was compared between ATTR, AL, and no amyloidosis groups.**

Results. **In 112 patients (39 ATTR and 26 AL patients, and 47 no amyloidosis), a lower proportion of no amyloidosis and AL patients were classified visually as equivocal with dual-isotope SPECT compared to single-isotope SPECT (2% vs 19%, P=0.02 and 8% vs 35%, P= 0.04, respectively). H/CL measurements with single-isotope and dual-isotope were lower in AL and no amyloidosis patients vs ATTR patients (P<0.05). Interobserver agreement of visual assessment was improved with dual-isotope SPECT ($P = 0.03$). AUCs for detection of ATTR by visual assessment and H/CL quantification were higher with dual-isotope (0.94 and 0.95, respectively) compared to single-isotope SPECT (0.84, P=0.001 and 0.92, P=0.02).**

Conclusion. **Tc-99m PYP/Tl-201 SPECT improves visual differentiation of ATTR and AL amyloidosis compared to single-isotope SPECT. Visual assessment and H/CL quantitation with**

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12350-019-01753-5) contains sup plementary material, which is available to authorized users.

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JNC thanks Erick Alexanderson MD, Carlos Guitar MD, and Diego Vences MD, UNAM, Mexico, for providing theSpanish abstract; Zhuo He BS, Haipeng Tang MS, Min Zhao MD, PhD; and Weihua Zhou PhD, for providing the Chinese abstract; andJean-Luc Urbain MD, PhD, CPE, Past President CANM, Chief Nuclear Medicine, Lebanon VAMC, PA, for providing the Frenchabstract.

1071-3581/$34.00

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dual-isotope SPECT provide similar discrimination between patients with ATTR and AL amyloidosis. (J Nucl Cardiol 2020;27:28–37.)

Spanish Abstract

Introducción. **La evaluación de la captación miocárdica de Tc-99m-pirofosfato (Tc-99m PYP) es fundamental para distinguir la amiloidosis cardíaca asociada a transtiretina (ATTR) del amiloide de cadena ligera (AL). A menudo es difícil diferenciar la captación miocárdica de la radioactividad del pool sanguíneo con imágenes planares o SPECT. Nosotros estudiamos si el SPECT dual simultáneo con isótopos Tc-99m PYP/Tl 201 mejora la evaluación de la captación de Tc-99m PYP comparado con el SPECT con isótopo simple.**

Métodos. **El SPECT simultáneo con isotopo dual Tc-99m PYP / Tl-201 se adquirió en 112 pacientes estudiados para una posible amiloidosis cardíaca. La reconstrucción de la imagen y la interpretación visual se realizaron en el isótopo único seguido del SPECT de isótopo dual. Se comparó la relación entre corazón y el pulmón contralateral (H/CL) de la cuantificación de cuentas miocárdicas por isotipo simple y SPECT de isótopo dual entre los grupos de ATTR, AL y el grupo sin amiloidosis.**

Resultados. **en 112 pacientes (39 pacientes con ATTR, 26 pacientes con AL y 47 sin amiloidosis), una menor proporción de pacientes sin amiloidosis y con AL, se clasificaron visualmente como equívocos con SPECT de isótopo dual en comparación con SPECT de isótopo único (4% vs 16% *P*=0.04 y 8% vs 34%, *P*=0.03 respectivamente). Las mediciones de H/CL con isótopo simple e isótopo dual fueron más bajas en pacientes con AL y sin amiloidosis en comparación a los pacientes con ATTR (*P*<0.05). La concordancia intra/interobservador de la cuantificación de H/CL fue mejorada con SPECT de isótopo dual (*P*=0.04 y 0.02, respectivamente). El AUC para la detección de ATTR por evaluación visual y la cuantificación de la relación H/CL fueron mayores en el grupo de isótopo dual (0.94 y 0.95, respectivamente) en comparación con SPECT de isótopo único (0.84, *P*=0.001 y 0.92, *P*=0.02).**

Conclusión. **el SPECT Tc-99m PYP/Tl-201 mejora la diferenciación visual de la amiloidosis ATTR y AL en comparación con el SPECT de isótopo único. La evaluación visual y la cuantificación de la relación H/CL con SPECT de isótopo dual proporcionan una discriminación similar entre los pacientes con amiloidosis asociada a ATTR y AL. (J Nucl Cardiol 2020;27:28–37.)**

Chinese Abstract

前言. 评估**Tc-99m-pyrophosphate(Tc-99m PYP)**的心肌摄取是鉴别甲状腺素转运蛋白相关型**(ATTR)**和轻链型**(AL)**心脏淀粉样变的关键。然而,平面或**SPECT**断层显像难以从血池放射性摄取中辨识心肌摄取情况。本研究通过与单核素**SPECT Tc-99m PYP**比较,探讨同步双核素**Tc-99m PYP/TI-201 SPECT**能否提高 **Tc-99m PYP**心肌摄取的评价能力。

方法. 对**112**名疑似心脏淀粉样变的患者进行同步**Tc-99m PYP/TI-201** 双核素**SPECT**显像。分别采用单核素与双核素**SPECT**数据进行重建和视觉评估。比较**ATTR, AL**和无心脏淀粉样变三组之间单、双核素**SPECT**心/对侧肺放射性计数比值**(H/CL)**的差异。

结果. 在**112**名患者**(39**名**ATTR, 26**名**AL,**以及**47**名无淀粉样变患者)中,采用双同位素**SPECT**视觉评估对无心脏淀粉样变和**AL**判断不确定的比率要低于单核素**SPECT**的比率**(**分别为**4% vs 16%, *P*=0.04** 和**8% vs 34%, *P*=0.03)**。不论单/双核素**SPECT**计算的**H/CL**比值,在**AL**和无淀粉样变患者中均低于**ATTR**患者**(*P*<0.05)**。使用双核素**SPECT**提高了观察者自身和观察者间的一致性**(**分别为**p=0.04** 和**0.02)**。采用双核素**SPECT**视觉评估和和**H/CL**比值检测**ATTR**的**AUC**值**(**分别为**0.94**和**0.95)**要高于使用单核素**SPECT**的结果**(0.84, *P*=0.001** 和**0.92, *P*=0.02)**。

结论. Tc-99m PYP/Tl-201 SPECT提高了单核素**SPECT**视觉分析鉴别**ATTR**和**AL**的能力。双同位素**SPECT**的视觉评估和**H/CL**定量分析对鉴别**ATTR**和**AL**效能相当。 **(J Nucl Cardiol 2020;27:28–37.)**

French Abstract

Contexte. **L'amyloïdose cardiaque à la transthyrétine (ATTR) est une cardiomyopathie rare mais sous-diagnostiquée. Son diagnostic histologique invasif, peut être avantageusement remplacé par la scintigraphie planaire au pyrophosphate de technetium (99mTc-PYP).**

Malheureusement, les cameras a detecteurs de cadmium zinc telluride ne peuvent pas generer des images planaires. A ce jour aucune validation du diagnostic de l'ATTR par imagerie non planaire n'a été proposée et validée. Nous avons développé et validé un protocole utilisant la caméra cardiaque CZT de GE pour le diagnostic de l'ATTR.

Méthodes. **43 sujets (24 ATTR, 19 non-ATTR) ont été étudiés avec une camera double tête Philips en imagerie planaire et la caméra cardiaque CZT de General Electric. L'absorption myocardique du 99mTc-PYP a été quantifiée en utilisant le rapport classique entre les activités cardiaque et thoracique droite controlaterale (H / CL). Les acquisitions CZT ont été quantifiées par 2 lecteurs indépendamment des données planaires. La sensibilité et la spécificité de la scintigraphie au CZT ont été analysées sur base du seuil diagnostique (H/CL) de 1.5. L'analyse statistique de McNemar's et le coefficient de corrélation de Pearson ont été calculés.**

Résultats. **nous n'avons pas observé de différence significative pour l'identification positive de l'ATTR parmi les sujets étudiés (76,7% d'hommes, âgés de 77±9 ans) entre les deux modalités scintigraphiques. De plus nous avons observé une forte corrélation entre les rapports par imagerie CZT et planaire (r=0,92, P<0,0001), avec faible variabilité intra- (ICC=0,89 (0,80-0,94)) et inter-observateur (ICC=0,80 (0,65-0,89)). La scintigraphie au CZT a montré une sensibilité et spécificité de 100% pour le diagnostic de l'ATTR.**

Conclusion. **L'imagerie CZT au 99mTc-PYP est aussi sensible et spécifique que l'imagerie planaire pour le diagnostic de l'ATTR. Ces résultats sont cliniquement importants compte tenu de la prévalence des caméras CZT dans les centres de médecine nucléaire, de l'émergence de thérapies ATTR modificatrices de la maladie, et de l'addition de cette nouvelle modalité diagnostique. (J Nucl Cardiol 2020;27:28–37.)**

Key Words: Cardiac amyloidosis · transthyretin · ATTR · Tc-99m-pyrophosphate · Tl-201 · SPECT

Abbreviations	
AL	Primary light chain amyloid
ATTR	Transthyretin-associated amyloid
AUC	Area under receiver-operating characteristic curve
ROC	Receiver-operating characteristic
ROI	Regions of interest
SPECT	Single-photon emission computed tomography
Tc-99m-pyrophosphate	Tc-99m PYP

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INTRODUCTION

Cardiac amyloidosis is a progressive infiltrative disease that is highly prevalent among the elderly. The prevalence may be as high as 25% in patients over 80 years of age with a male predominance[1–3] and 13% in patients with heart failure and preserved EF.[4] The disease is characterized by the accumulation of amyloid fibrils in the extracellular matrix resulting in a restrictive cardiomyopathy. The two major types of cardiac amyloidosis—transthyretin-associated amyloid (ATTR) and primary light chain amyloid (AL) are associated with different therapies.[5,6] Treatment of AL includes immunotherapy and autologous stem cell transplantation.[5,7] For ATTR amyloidosis, multiple new treatments for ATTR are being investigated.[8–11] Importantly, in 2018, a large randomized trial showed that treatment with tafamidis is associated with marked reduction in all-cause mortality and cardiac hospitalization as well as improvement in exercise capacity and quality of life.[4] Tafamidis is now commercially available for ATTR therapy.

In the early 1980s, it was reported that Tc-99m pyrophosphate (Tc-99m PYP), a standard bone scanning radiopharmaceutical, is taken up in both the left and right ventricles in patients with cardiac amyloidosis.[11] While Tc-99m PYP appeared to show very high specificity, its clinical application was limited, due to apparent low sensitivity for the disease. Later, it was shown that Tc-99m PYP myocardial uptake is observed in patients with ATTR but not in the AL variant,[12] explaining its low sensitivity for cardiac amyloidosis. Until recently, biopsy was often required for distinguishing ATTR and AL amyloidosis. Presently, due to the high sensitivity and specificity, myocardial uptake of Tc-99m PYP is now considered sufficient to establish the diagnosis of cardiac ATTR amyloidosis without the need for biopsy.[13] With the recognition of the high prevalence of ATTR, the recently available effective therapy, and the now central role of Tc-99m PYP imaging in the diagnostic pathway, there has been rapid growth in Tc-99m PYP myocardial imaging.

While planar Tc-99m PYP imaging is most commonly used for the evaluation of cardiac amyloidosis,[5]

SPECT is increasingly being employed and is the only way of imaging with CZT camera systems. SPECT improves the distinction of myocardial uptake from residual blood pool activity and is less affected by variable activity in ribs that can affect planar Tc-99m PYP assessment.[5,14] With standard SPECT, however, distinguishing blood pool from myocardial uptake and identification of myocardial boundaries remains imprecise, limiting visual interpretation of myocardial Tc-99m PYP uptake. With virtually all currently available SPECT cameras, simultaneous dual-isotope imaging with Tl-201 and Tc-99m PYP can be performed, without significant contamination from Tl-201 photons. We tested the hypothesis that simultaneous dual-isotope SPECT with Tc-99m PYP and Tl-201, providing distinct definition of myocardial boundaries, improves interpretation of Tc-99m PYP when compared to single-isotope SPECT.

METHODS

This is a retrospective study of consecutive patients who underwent simultaneous dual-isotope Tc-99m PYP/Tl-201 SPECT at Cedars-Sinai Medical Center. ATTR was diagnosed by the absence of free light chains in the serum and a positive endomyocardial biopsy or two or more of the following criteria: clinical heart failure, positive extracardiac tissue biopsy, echocardiographic features of left ventricular hypertrophy with restrictive filling, and MRI findings of myocardial infiltration. AL was diagnosed by the presence of abnormal serum free light chains or clonal cells in the bone marrow and one of the following criteria which included clinical symptoms of heart failure, evidence of myocardial infiltration with cardiac MRI, or a restrictive filling pattern by echocardiography.[15,16] The no amyloidosis group was comprised of patients with suspected cardiac amyloidosis without evidence of amyloidosis on subsequent clinical follow-up. The study was approved by the institutional review board and patients provided written informed consent.

Simultaneous Dual-Isotope Tc-99m PYP/Tl-201 SPECT Myocardial Imaging

The imaging protocol prescribed an intravenous injection of 20 mCi of Tc-99m PYP followed 4 h later with injection of 1 mCi of Tl-201, SPECT. Imaging was performed using a dual-detector Anger gamma camera using a low-energy, high-resolution collimator with energy windows centered at 70 KeV for Tl-201 and 140 KeV for Tc-99m PYP and 20% and 15%. A non-gated SPECT acquisition was acquired at 40 seconds per stop for 32 frames per detector over 180 degrees in a 64x64 matrix. Projection data were separated into separate datasets for Tl-201 and Tc-99m PYP using the nuclear medicine image-processing workstation (ADAC/Philips Pegasys, Milpitas, CA) and imported into QPS software (Cedars-Sinai, Los Angeles, CA) for the reconstruction of SPECT.

Image Reconstruction and Analysis

SPECT Image Reconstruction. Tc-99m PYP SPECT images were reconstructed by an expert nuclear cardiology technologist (M. H.). Image reconstruction was performed using OSEM iterative method (12 iteration 4 subsets) with a filtered back projection prefilter. For Tc-99m PYP, a Butterworth filter with cutoff frequency of 0.4 cm^{-1} and order of 0.5 was used, and for Tl-201, a Butterworth filter with cutoff frequency of 0.4 cm^{-1} and order of 10 was used. Images were reoriented along the long axis of the left ventricle (LV) in the axial and sagittal views to create short axis, vertical long axis, and horizontal long axis images using commercially available software (QPS, Cedars-Sinai, Los Angeles, CA.). For the single-isotope method, processing of Tc-99m PYP images was performed without the use of Tl-201 images as a reference for localizing the position and orientation of the heart. The reconstruction was performed with both the entire field of view (FOV) including the heart and contralateral lung[17] and FOV restricted to the heart. When the heart was not clearly visualized, the orientation of the heart was surmised by using the ribs, spine, and the sternum as landmarks. For the dual-isotope method, Tc-99m PYP images were processed with the use of myocardial Tl-201 uptake to define the position and orientation of the heart. Tl-201 reconstruction parameters were the same as for Tc-99m, except Butterworth filter with cutoff frequency of 0.4 cm^{-1} and order of 10 was used. With both approaches, myocardial contours were determined automatically and were adjusted manually when appropriate.

Single- and Dual-isotope SPECT Visual Interpretation. Tc-99m PYP SPECT images were visually interpreted in two ways by experienced nuclear cardiologists (O.M. and S.C.) who were unaware that dual-isotope imaging had been performed. First, all Tc-99m PYP SPECT images (single-isotope SPECT) were assessed. We then informed the readers of the dual-isotope protocol. The readers were provided the Tl-201 images along with the Tc-99m PYP images displayed both with and without the contours derived from the Tl-201 and with the Tl-201 images. For both approaches, myocardial uptake was graded on a 0 to 3 scale with 0 (no myocardial uptake), 1 (mild/less than rib), 2 (moderate/equal to rib) and 3 (higher/greater than rib). Myocardial uptake that could not be clearly distinguished from blood pool was given a grade of 1. Scans with scores of 1 were considered equivocal, and scans with scores 2 or 3 were considered abnormal.

Quantitative Assessment of H/CL Ratio. Quantification of heart-to-contralateral lung (H/CL) ratio with single- and dual-isotope SPECT was performed from images reconstructed with the entire FOV. Tc-99m PYP uptake measured in counts was quantified using regions of interest (ROI) placed over the entire heart and the contralateral lung.[17] For assessment of intraobserver agreement, reconstruction of raw images and quantification of H/CL was performed twice by M.H. for both the single-isotope and dual-isotope methods. H/CL ratios quantified from single-isotope and dual-isotope methods by M.H. and O.M. were compared for evaluation of interobserver agreement.

Statistical Analysis

Statistical analyses were performed with STATA software (version 13 StataCorp LP) and MedCalc software (version 17.9.6). All data were tested for normal distribution using the Kolmogorov-Smirnov test. Continuous variables are expressed as mean±standard deviation. For comparison between two groups, Mann-Whitney's U test was used, and Kruskal-Wallis test was used for comparison between three groups. Wilcoxon signed-rank test was used to compare myocardial Tc-99m PYP counts with the single- and dual-isotope methods in ATTR, AL, and no amyloidosis. Interobserver agreement of visual assessment and H/CL ratio were expressed as a kappa statistic and intraclass correlation coefficient (ICC) respectively. Fisher *r*-to-*z* transformation was used to compare intraclass correlation coefficients. Difference in visual assessment of Tc-99m PYP uptake between single- and dual-isotope SPECT images was evaluated by chi-square test. Logistic regression analysis was used to test the performance of H/CL ratio and quantitative assessment of SPECT by single- and dual-isotope methods for detection of ATTR amyloidosis. The logistic models were compared using receiver-operating characteristic (ROC) analysis and pairwise comparisons according to Delong et al.[18]

RESULTS

Patient Characteristics

The cohort was comprised of 112 patients (76% male) with mean age of 75±9 years, including 39 patients with ATTR amyloidosis [37 wild type and 2 ATTR mutant], 26 patients with AL amyloidosis, and 47 patients who proved to have no amyloidosis (no amyloidosis) (Table 1). Patients underwent imaging for evaluation of heart failure (29%), reduced ejection fraction (27%), dyspnea (15%), and abnormal ECG (2%), and findings suggesting amyloidosis based on echocardiography or history of extracardiac amyloidosis (24%). ATTR was diagnosed by endomyocardial biopsy (n=12) and by extracardiac biopsy (n=8) (Table 2). Sites of extracardiac biopsy were from bladder, lung, bone marrow, skin, abdominal fat, muscle, and the lip. ATTR mutation was diagnosed by genetic testing (n=2). Cardiac MRI with evidence for myocardial infiltration[15] was available in 12 patients with ATTR and 8 patients with AL.

Visual Interpretation of Tc-99m PYP Uptake Using Single- and Dual-Isotope SPECT

The comparative results of the single- and dual-isotope visual interpretations are shown in Figure 1. In the 112 patients, a lower proportion were classified as equivocal with dual-isotope SPECT (P=0.007). In no amyloidosis and AL patients, 19% and 35%, respectively, were considered equivocal with single-isotope SPECT. With dual-isotope SPECT, there was a decrease in studies classified as equivocal (P=0.02 in no amyloidosis and P=0.04 in AL). An example of an AL patient with equivocal Tc-99m PYP uptake on single-isotope SPECT reclassified as normal using dual-isotope SPECT is shown in Figure 2. Among ATTR patients, only 2% were considered equivocal with single-isotope SPECT and with dual-isotope SPECT (P=0.5).

H/CL Ratio Using Dual-Isotope, Single-Isotope SPECT in AL and ATTR Patients

Patients with ATTR had a higher H/CL ratio, 2.15±0.48 compared to no amyloidosis 1.19±0.34 and AL

Table 1. Patient characteristics

	Total	ATTR	AL	No amyloidosis	*P*
Number	112	39	26	47	
Age (years)	75±9	77±10	68±12	70±11	**0.03**
Male, *n* (%)	72, 75%	30, 91%	15, 60%	27, 71%	**0.02**
BMI (kg/m^2)	25±6	26±5	25±7	27±7	0.16
Hypertension, *n* (%)	62, 55%	19, 33%	15, 58%	28, 60%	0.31
Diabetes, *n* (%)	19, 17%	3, 8%	2, 8%	14, 43%	**0.02**
Dyslipidemia, *n* (%)	38, 34%	12, 31%	10, 38%	16, 34%	0.64
Cr (mg/dL)	2.1±2.0	1.9±1.7	2.1±1.9	2.3±2.2	0.40
Ejection fraction by echocardiography (%)	51±16	44±14	50±18	55±14	0.14
Anteroseptal thickness (cm)	1.4±0.4	1.7±0.4	1.3±0.2	1.3±0.4	**<0.01**
Posterior wall thickness (cm)	1.5±0.5	1.6±0.2	1.4±0.5	1.2±0.3	**<0.01**
LVIDd (cm)	4.4±0.5	4.5±0.6	4.6±0.7	4.3±0.8	0.57
LVIDs (cm)	3.5±0.6	3.3±0.8	3.4±0.5	3.5±0.7	0.81

BMI, Body mass index; *LVIDd*, left ventricular internal dimension in diastole; *LVIDs*, left ventricular internal dimension in systole
P values showing significant differences are given in bold

Table 2. Diagnosis of ATTR and AL

Diagnosis, *n* (%)	**ATTR (*n*=39)**	**AL (*n*=26)**
Normal serum light chain	39 (100%)	0
Abnormal serum light chain	0	26 (100%)
History of heart failure and suspicion for amyloidosis	16 (41%)	11 (42%)
Cardiac biopsy	8 (21%)	0
Extracardiac biopsy	12(31%)	4 (15%)
Bone marrow biopsy	2 (5%)	10 (38%)
Cardiac MRI features positive for infiltrative disease	12 (31%)	8 (31%)
Echocardiographic features positive for infiltrative disease	20 (51%)	8 (31%)

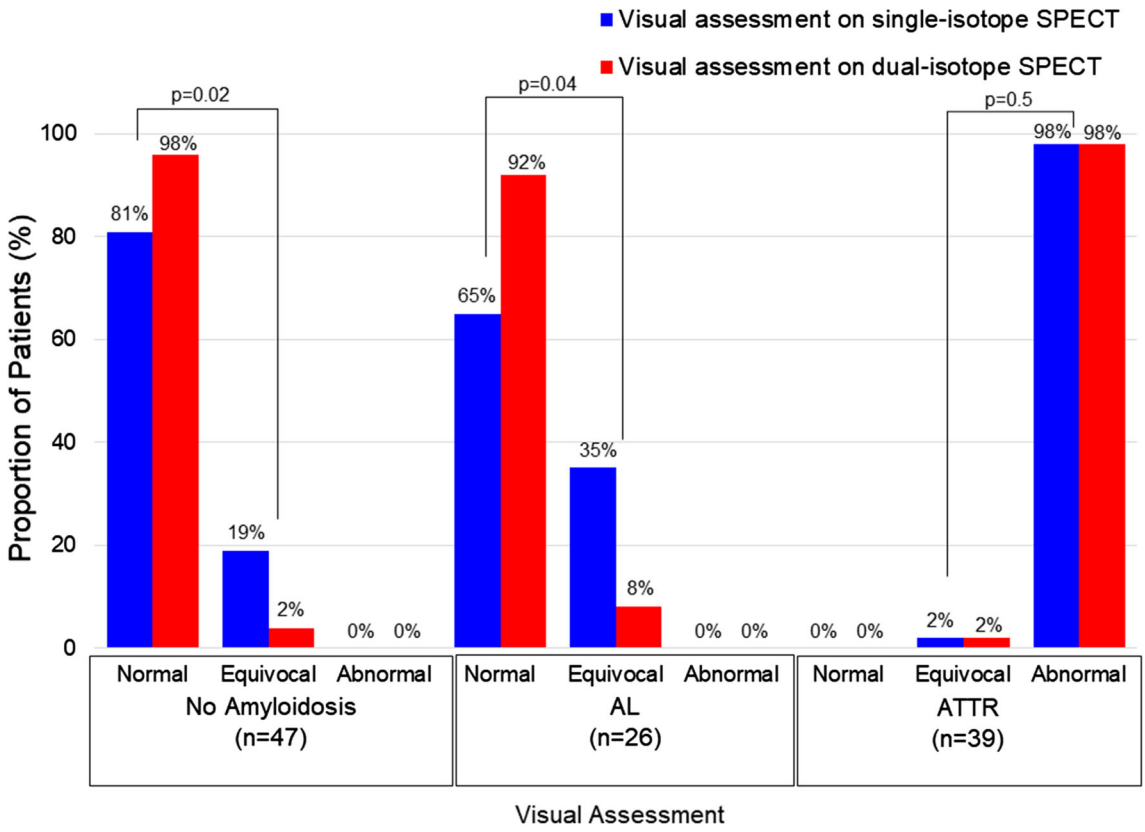

Figure 1. Visual interpretation of Tc-99m PYP single-isotope and dual-isotope SPECT in no amyloidosis, AL, and ATTR. Proportions of no amyloidosis, AL, and ATTR patients classified as normal, equivocal, and abnormal based on Tc-99m PYP uptake interpreted using visual assessment of single-isotope SPECT (blue bars) and dual-isotope SPECT (red bars). Dual-isotope methods significantly decreased the proportion of equivocal interpretations in both the no amyloidosis and AL groups compared to visual assessment of single-isotope SPECT.

patients 1.40±0.36, $P = 0.0008$ by single-isotope. Similar increase in H/CL ratio was seen in ATTR patients, 2.09±0.42, compared to no amyloidosis, 1.12±0.28, and AL patients, 1.29±0.51, P=0.01 by dual-isotope SPECT. The differences between H/CL ratio by single-isotope and dual-isotope were not statistically significant in no amyloidosis, P=0.19 AL, P=0.41, and ATTR, P=0.61 patients. An example of an ATTR patient with definitely abnormal Tc-99m PYP uptake by both single-isotope and dual-isotope SPECT is shown in Figure 3.

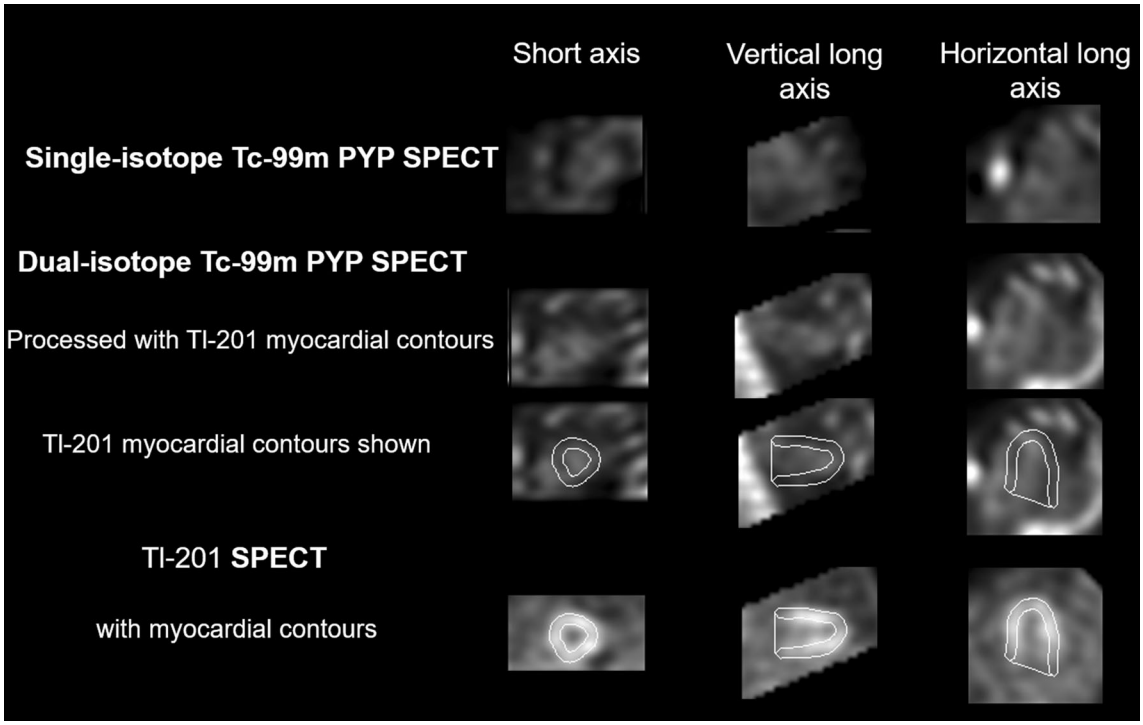

Figure 2. Example of an AL patient with equivocal myocardial Tc-99m PYP uptake with single-isotope method reclassified as normal by simultaneous dual-isotope SPECT. Tc-99m PYP SPECT with single-isotope method processed without knowledge of Tl-201 contours (first row), with knowledge of Tl-201 myocardial uptake from dual-isotope SPECT (second row), overlaid with myocardial contours derived from Tl-201 SPECT (third row) and Tl-201 SPECT with contours (fourth row) from a patient with AL. Regarding myocardial uptake of Tc-99m PYP, the single-isotope images were interpreted as equivocal, whereas the dual-isotope images with superimposed Tl-201 SPECT provide certainty that the Tc-99m PYP is confined to the blood pool.

Interobserver Agreement in interpretation in AL and ATTR Patients Using Dual- and Single-Isotope Methods

Among ATTR and AL patients, interobserver agreement of visual assessment was greater with dual-isotope method ($\kappa = 0.89$ [95% CI 0.78 to 1]) compared to the single-isotope method ($\kappa = 0.72$ [95% CI 0.56 to 0.87]), $P = 0.03$. Similarly, interobserver agreement for the quantification of H/CL of Tc-99m PYP uptake improved with the use of the dual-isotope method compared to the single-isotope method (ICC=0.91 [95% CI 0.88 to 0.99] vs ICC=0.85 [95% CI 0.79 to 0.91], P= 0.02).

Discrimination of ATTR by Visual Assessment and H/CL Ratio from Single-Isotope and Dual-Isotope SPECT

The area under the ROC curve (AUC) for detection of ATTR by visual assessment improved using the dual-isotope method (0.94, 95% CI 0.90 to 0.96) compared to the single-isotope method (0.84, 95% CI 0.81 to 0.89), $P<0.01$. AUC for differentiation of ATTR from AL by H/CL quantified using the dual-isotope method was increased (0.95, 95% CI 0.93 to 0.99) compared to the single-isotope method (0.92, 95% CI 0.84 to 0.98, P= 0.016) (Figure 4). There was no significant difference in the AUC of visual assessment of dual-isotope SPECT with AUC of H/CL quantification from dual-isotope method, P=0.34.

DISCUSSION

Due to increased awareness of the high prevalence of cardiac ATTR amyloidosis, the availability of a new effective treatment,[4] and expert consensus that an abnormal Tc-99m PYP scan establishes the diagnosis of ATTR without needing biopsy,[13] Tc-99m PYP imaging has become one of the most rapidly growing imaging procedures in nuclear cardiology. While any Tc-99m PYP myocardial uptake has been shown to be greater than 99% sensitive for ATTR amyloidosis, low grade/equivocal Tc-99m PYP uptake (visual score 1)

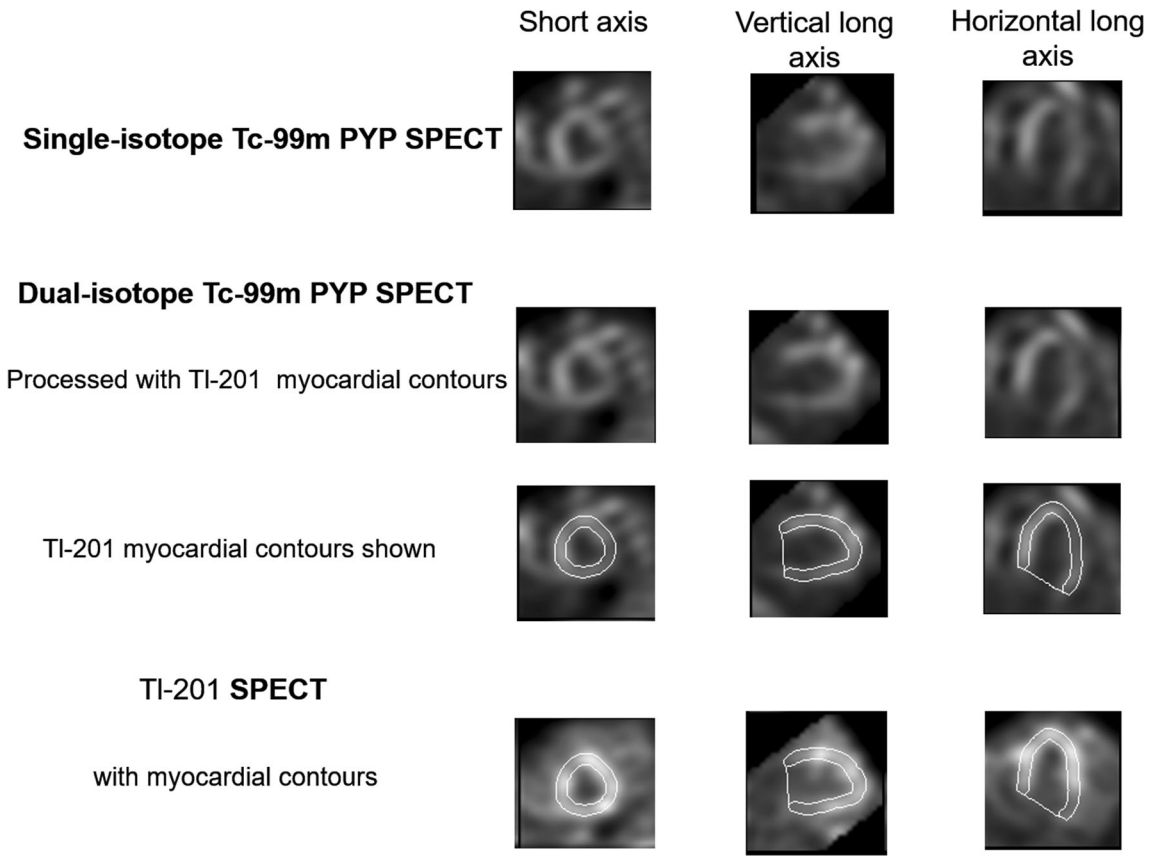

Figure 3. Example of an ATTR patient with abnormal Tc-99m PYP uptake using both single-isotope and simultaneous dual-isotope SPECT. SPECT images displayed in the same manner as shown in Figure 2 from a patient with ATTR. There is marked myocardial uptake of Tc-99m PYP on the single-isotope SPECT images. This figure illustrates that when studies are definitely abnormal, the dual-isotope approach does not contribute to overall interpretation.

results may reduce specificity (87%).[13] Further, the equivocal visual score has been reported to be associated with an adverse prognosis similar to that of scores of 2 or 3.[19] Thus, reducing the rate of equivocal visual interpretation by the dual-isotope method, shown in this study, has important clinical implications.

The Tc-99m PYP/Tl-201 dual-isotope SPECT method has been previously reported in a small number of patients by Yamamoto et al.[20]; however, the diagnostic and quantitative advantages of the dual-isotope approach over single-isotope SPECT were not evaluated. In this study, we show for the first time that the use of simultaneous dual-isotope Tc-99m PYP SPECT provides better visual discrimination of patients with ATTR from those with AL compared to single-isotope SPECT by reducing the number of cases classified as equivocal.

Although ASNC guidelines have not required the use of SPECT for identification of Tc-99m PYP uptake in patients with cardiac amyloidosis, the use of SPECT is recognized as being highly useful.[5,12,20] Practice guidelines recognize that SPECT eliminates contamination from overlying rib and aids in distinguishing blood pool from myocardial uptake.[21] However, with single-isotope SPECT it still can be difficult to distinguish between blood pool and mild myocardial uptake as shown in this study. Our findings show that definition of myocardial boundaries based on automated assessment of Tl-201 affords the benefit of precisely delineating the myocardium from the blood pool using simultaneous Tl-201/Tc-99m PYP dual-isotope SPECT, due to its inherent perfect coregistration of the Tc-99m and Tl-201 images. In our study, the number of AL patients and patients with no amyloidosis interpreted visually as having equivocal uptake (therefore potentially being misclassified as possibly having ATTR) was substantially reduced. Of note, our imaging was routinely performed at 4 hours after Tc-99m-PYP injection in order to minimize blood pool radioactivity. The dual-isotope approach would be expected to have even greater impact in reducing the frequency of equivocal interpretations in scans performed at the recommended 1 hour or 3 hour delay times.[21]

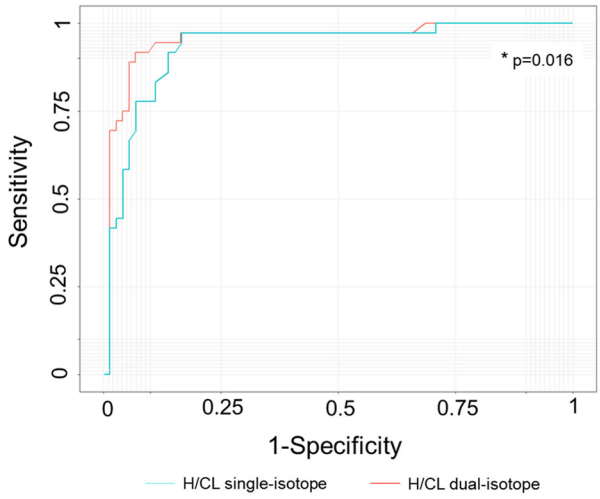

Figure 4. Receiver-operating characteristic curves for prediction of ATTR with H/Cl ratio from single-isotope and dual-isotope SPECT. The ROC curves for diagnosis of ATTR vs. AL using H/CL ratio from dual-isotope SPECT (red) and single-isotope SPECT (blue) are represented. There is a small increase in the AUC of H/CL quantified from dual-isotope SPECT compared to the AUC for diagnosis of ATTR using H/CL ratio from single-isotope SPECT (p=0.016).

The AUCs for detection of amyloidosis improved with dual-isotope SPECT compared to singe-isotope SPECT by both visual assessment and H/CL ratio; however, the AUCs were all high. A benefit of the H/CL method over visual assessment is that it allows the use of a threshold that represents abnormal uptake. It is possible that measurement of changes in H/CL ratio in patients with ATTR could be of use in assessing response to treatment. In a recent study of 20 patients with advanced ATTR amyloidosis, Castano et. al. found no difference in the H/CL ratio on planar Tc-99m PYP imaging on repeated study performed an average of 1.5 years after initial testing.[22] The authors noted, however, that the imaging technique may not have allowed detection of small but potentially clinically relevant changes in PYP uptake in the context of intense PYP uptake in their patients.

A unique benefit of the simultaneous dual-isotope method would be in its use with a commonly used CZT camera that uses focused imaging over the myocardium rather than imaging with similar sensitivity over the entire chest. For optimal imaging, the system relies on localization of the heart at the time of image acquisition. Accurate localization of the heart using Tc-99m SPECT PYP with this system is problematic when the myocardial uptake is low. Identification of the myocardium using the Tl-201 images in dual-isotope SPECT would afford accurate localization of the heart in all cases. Further, assessment of the H/CL with this system is problematic due to differences in counts related to the focused region of interest used for cardiac imaging, increasing the importance of accurate visual interpretation.

SPECT/CT systems may be ideal for Tc-99m PYP studies. They would improve the definition of the myocardial boundaries and would provide attenuation-corrected images for absolute quantitation of Tc-99m PYP uptake. Currently, however, most laboratories are not equipped with SPECT/CT, while virtually all laboratories performing SPECT MPI can perform simultaneous dual-isotope imaging.

New Knowledge Gained

Simultaneous dual-isotope SPECT with Tc-99m PYP and Tl-201 provides better discrimination of the myocardium from the blood pool, and thereby allows improved visual interpretation. The approach is particularly helpful in patients with equivocal Tc-99m PYP uptake.

Limitations

The study has several limitations. The number of patients in the study was modest. Myocardial biopsy was not available in most patients and we relied on a combination of clinical characteristics, serologic testing, and imaging data from MRI and echocardiography for diagnosis of ATTR and AL. The addition of Tl-201 to the Tc-99m PYP study is associated with an additional radiation dose. A lower dose of Tl-201 using standard gamma cameras may still allow accurate placement of myocardial contours; however, this was not assessed. Due to the high sensitivity of CZT cameras, their use should allow further reduction of the Tl-201 dose for the dual-isotope imaging.[23,24] Higher energy photons of Tl-201 are included in the Tc-99m energy window; however, due to their low abundance, this contamination is minimal.

CONCLUSION

By providing precise separation of myocardial from blood pool radioactivity, simultaneous dual-isotope Tl-201/Tc-99m PYP SPECT, easily performed with all SPECT systems, improves visual discrimination of patients with ATTR and AL amyloidosis compared to single-isotope SPECT.

Acknowledgements

This study was supported by a grant from the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation.

Disclosure

Drs. Berman and Slomka receive software royalties from Cedars-Sinai Medical Center. Tamarappoo, Otaki, Manabe, Hyun, Cantu, Arnson, Gransar, Hayes, Friedman, Thomson, Dey, Vescio, and Patel have reported that they have no relationships relevant to the contents of this manuscript to disclose.

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