Comparison of planar with tomographic pyrophosphate scintigraphy for transthyretin cardiac amyloidosis: Perils and pitfalls

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Background. **Tc-99m pyrophosphate (PYP) SPECT is recommended for indeterminate findings on planar imaging. We aimed to compare the findings on planar PYP scintigraphy alone to that of routinely performed PYP SPECT.**

Methods. **PYP scintigraphy data of 133 patients (53% men; mean age 76 years) were evaluated. SPECT was routinely performed following 1-hour planar imaging, in all cases. Semiquantitative visual score and heart-to-contralateral (H/CL) ratio were determined in all patients as recommended.**

Results. **PYP images from 35 patients (26%) were considered to be positive based on SPECT myocardial uptake. Among them, 20 (57%) had a H/CL ratio ≥1.5 and 34 had a visual score ≥ 2. SPECT identified myocardial uptake in one patient with a visual score < 2 and refuted the presence of myocardial uptake in two patients with a visual score ≥ 2. Visual score correlated well with SPECT ($r = 0.94$; $P < .0001$) and had an accuracy of 98% for tomographic myocardial uptake. Addition of H/CL ratio reduced the diagnostic performance of visual score.**

Conclusions. **Planar-derived visual score has an excellent accuracy for tomographic myocardial uptake, though it misclassifies a small proportion of patients. H/CL ratio decreases the diagnostic certainty of planar imaging. Tomographic imaging prevents misdiagnoses and should always be performed. (J Nucl Cardiol 2021;28:104–11.)**

Key Words: Amyloid heart disease • SPECT • Image analysis

The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarizes the contents of the paper and is free for re-use at meetings and presentations. Search for the article DOI on SpringerLink.com.

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Abbreviations	
PYP	Techneticum-99m pyrophosphate
TTR-CA	Transthyretin cardiac amyloidosis
H/CL	Heart-to-contralateral
ASNC	American Society of Nuclear Cardiology
SPECT	Single photon emission computed tomography
LVEF	Left ventricular ejection fraction

INTRODUCTION

Technetium-99m pyrophosphate (PYP) scintigraphy has a high diagnostic accuracy for transthyretin cardiac amyloidosis (TTR-CA), obviating the need for endomyocardial biopsy.[1] A Perugini score of $\geq$ 2 and the absence of a monoclonal protein in serum and urine have been shown to have a specificity of 100% for diagnosis of TTR-CA.[1,2] Additionally, a heart-to-contralateral (H/CL) ratio of $\geq$ 1.5 at 1 hour on planar imaging has a high diagnostic accuracy for differentiating TTR-CA from light-chain cardiac amyloidosis.[3] Consequently, per American Society of Nuclear Cardiology (ASNC) expert consensus recommendation the current diagnostic paradigm for TTR-CA incorporates both the assessment of visual score and H/CL ratio for the diagnosis of TTR-CA.[4]

Several nuclear cardiology laboratories are routinely performing PYP single photon emission computed tomography (SPECT),[5–7] even though the recommendations suggest to perform in cases when planar findings are indeterminate. Conceivably, performance of SPECT in all patients could improve reader confidence for image interpretation, as myocardial uptake of PYP would be confirmatory for TTR-CA. Additionally, the recommended diagnostic approach with PYP imaging was developed using data from populations with biopsy proven TTR-CA and thus may not be applicable in contemporaneous clinical practices when biopsies are performed less frequently. In this report, we present the distribution of abnormal PYP scintigraphy findings among patients suspected with TTR-CA, and the diagnostic performance of planar PYP scintigraphy when compared to that of PYP SPECT.

METHODS

We conducted a retrospective study of patients who underwent PYP scintigraphy between June 2016 to March 2020 at two inner city hospitals. Demographic, clinical, and imaging data of patients referred for PYP imaging were collected via review of electronic medical records. Institutional Review Board approval was obtained from University at Buffalo/Buffalo General Medical Center, Buffalo, NY, and from Stroger Hospital of Cook County, Chicago, IL, for the conduct of this study. Performance of PYP imaging was guided by the clinical suspicion of TTR-CA by treating clinician, based on a combination of the following features—suspicious echocardiographic findings (including abnormal strain imaging with an apical sparing pattern), repeated heart failure admissions, syncope, atrial arrhythmias, or heart block. PYP scintigraphy was performed in accordance with ASNC Expert Consensus Recommendation, using 15-20 mCi dose of PYP, followed by planar imaging at 1-hour after radioisotope injection.[4] Imaging was performed on a dual-headed sodium-iodide General Electric NM 830 SPECT camera, with acquisition of 1 million counts per view. As a part of the laboratory imaging protocol, nongated SPECT (180° orbit; step-and-shoot approach) was routinely performed immediately after planar imaging.

Semiquantitative visual scoring of planar images was performed in accordance with the method suggested by Perugini et al.[2] A region of interest (ROI) was drawn over the precordium on anterior planar view, and copied to the contralateral chest. Care was taken to maintain similar location of the two ROI on either side of the sternum, while avoiding areas of hot spots such as due to rib fractures. H/CL ratio was calculated as a ratio of the average heart counts and average contralateral counts from these ROIs. Tomographic reconstruction was performed in a standard manner, in a fashion similar to that of myocardial perfusion SPECT. In cases with none or equivocal myocardial uptake on planar images, ROI for tomographic reconstruction were positioned in standard locations on anterior and lateral orientations. Visualization of left ventricular walls on tomographic images, either diffuse or focal, was considered to indicate myocardial PYP uptake.[5] When tracer uptake in myocardial segments was not visualized on tomographic images, the counts noted on planar images were ascribed as being blood pool. As a part of diagnostic protocol for TTR-CA, all patients underwent immunologic evaluation of abnormal light chains in urine and serum. PYP scintigraphy was considered to be positive when there was tomographic evidence of myocardial uptake.[5] SPECT evidence of myocardial uptake, along with a lack of abnormal immunoglobulin light chains, was considered to be the diagnostic reference standard of TTR-CA. Access to routine genetic testing was not available till late 2018 and thus data on the presence or absence of genetic mutations were not available on all patients.

Statistical Analyses

Statistical analyses were performed using a t-test and Chi-square test for continuous and categorical data, respectively. Pearson's correlation coefficient was used to determine the correlation between planar and SPECT findings. A P value of $< .05$ was considered to represent statistical significance. All statistical analyses were performed on STATA version 15 (College Station, TX).

Table 1. Demographic and clinical characteristics of patients referred for Tc-99m pyrophosphate scintigraphy stratified by myocardial uptake on SPECT

	PYP SPECT negative (n = 98)	PYP SPECT positive (n = 35)	*P* value
Demographics			
Mean age, years	74 ± 13	81 ± 9	.004
Men	52%	57%	.60
African American	73%	89%	.15
Clinical characteristics			
Troponin-T (ng/mL)	0.55 ± 1.77	0.45 ± 1.70	.34
BNP (pg/mL)	1282 ± 1535	1169 ± 1069	.65
Low ECG voltage[a]	58%	65%	.001
History of CAD	55%	43%	.23
Echocardiography variables			
LV ejection fraction	55 ± 16	48 ± 18	.04
Septal wall thickness (cm)	1.4 ± 0.4	1.6 ± 0.3	.009
LV mass index (gm/m^2)[b]	127 ± 50	154 ± 49	.01
Diastolic dysfunction ≥ stage II[c]	44%	71%	.002
Apical sparing strain pattern[d]	38%	91%	.0001
Planar PYP scintigraphy variables			
Mean H/CL ratio	1.1 ± 0.1	1.6 ± 0.2	< 0.0001
Mean visual score	0.5 ± 0.5	2.8 ± 0.5	< .0001

PYP, Tc-99m pyrophosphate; *SPECT*, single photon emission computed tomography; *BNP*, brain natriuretic peptide; *ECG*, electrocardiogram; *CAD*, coronary artery disease; *LV*, left ventricular; H/CL, heart-to-contralateral
[a]Low ECG voltage defined by a QRS amplitude ≤ 5 mm in all the limb leads and/or ≤ 10 mm in all the precordial leads
[b]Calculated using Devereux method
[c]Based on American Society of Echocardiography Guidelines and Standards
[d]Apical sparing strain pattern was defined by a ratio of average apical to the sum of average mid and basal strain >1

RESULTS

A total of 133 patients underwent PYP imaging for diagnosis of TTR-CA. The mean age of the cohort was 76 ± 12 years with 53% being men and 77% of the patients being African American. The average left ventricular ejection fraction (LVEF) was 53% ± 17%, and average left ventricular wall thickness was 1.5 ± 0.4 cm. A total of 35 patients (26%) were considered to have a positive PYP scintigraphy based on tomographic evidence of myocardial PYP uptake. Only one patient had focal uptake, predominantly involving the septum, while uptake was diffuse in the remainder of the population. None of these patients had evidence of abnormal immunoglobulin light chains. Demographic, clinical, and imaging characteristics of patients stratified by a positive PYP scan are presented in the Table 1. Patients with positive PYP SPECT were older and had a lower ejection fraction and a greater left ventricular mass and septal wall thickness. Additionally, these patients had a greater prevalence of low voltage on electrocardiogram, diastolic dysfunction grade 2 or higher, and apical sparing pattern on strain echocardiography, when compared to those with a negative PYP SPECT.

The mean H/CL ratio (1.6 vs 1.1, $P < .0001$) and mean visual score (2.8 vs 0.5, $P < .0001$) were significantly greater among those with a positive PYP SPECT when compared to those with a negative PYP SPECT, respectively. Thirty-five (26%) patients had a visual score ≥ 2 and 21 (16%) had a H/CL ratio ≥ 1.5. Distribution of visual score and H/CL ratio, stratified by PYP SPECT results, is shown in Figure 1. Despite evidence of myocardial uptake on PYP SPECT (n = 35), 15 patients (43%) had a H/CL ratio < 1.5. One patient had an H/CL ratio of 1.9 with a visual score of 0 and no myocardial uptake on SPECT (Figure 2). This patient had severe eccentric mitral regurgitation with large right pleural effusion resulting in marked reduction in contralateral counts and an erroneous elevation in H/CL ratio. The correlation of H/CL ratio with visual score and with SPECT was 0.79 ($P < .0001$) and 0.78 ($P < .0001$), respectively.

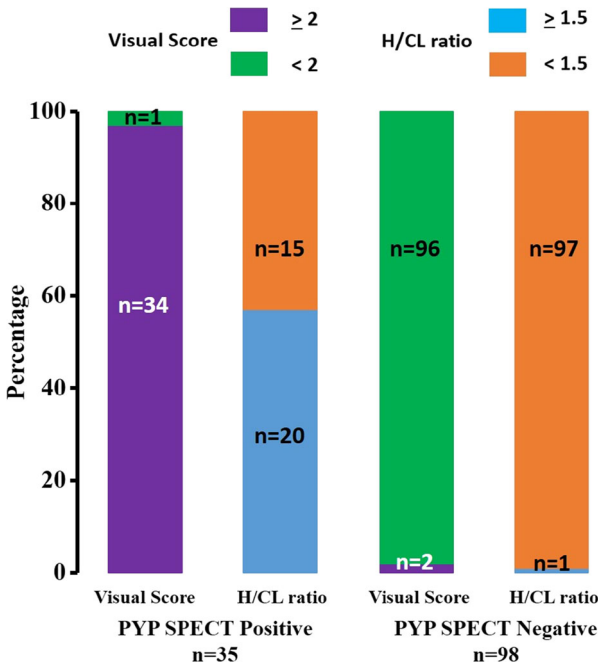

Figure 1. Distribution of planar findings, stratified by Tc-99m pyrophosphate SPECT results.

On the contrary, only 1 patient with a positive PYP SPECT had a visual score of 1 (Figure 3). Visual score was considered as being falsely negative in this patient. Similarly, two patients with a visual score ≥ 2 showed no tomographic evidence of myocardial PYP uptake, but only LV blood pool activity, and therefore, the study was reclassified as being negative. Both patients had a severely reduced left ventricular ejection fraction. One of these patients underwent repeat imaging at 3 hours, which showed a visual score of 2 with no SPECT evidence of myocardial PYP uptake (Figure 4). Visual score in these two patients was considered to be falsely positive. Nonetheless, there was excellent correlation between visual score and PYP SPECT (r = 0.94, $P <$ .0001). Considering tomographic evidence of PYP uptake as the imaging standard, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of visual score alone for TTR-CA were 97%, 98%, 94%, 99% and 98%, respectively. When the suggested classification of visual score ≥ 2 and H/CL ratio ≥ 1.5 was used to identify a positive PYP study, the sensitivity, specificity, PPV, NPV, and accuracy of this criteria were 57%, 95%, 80%, 85% and 85%, respectively.

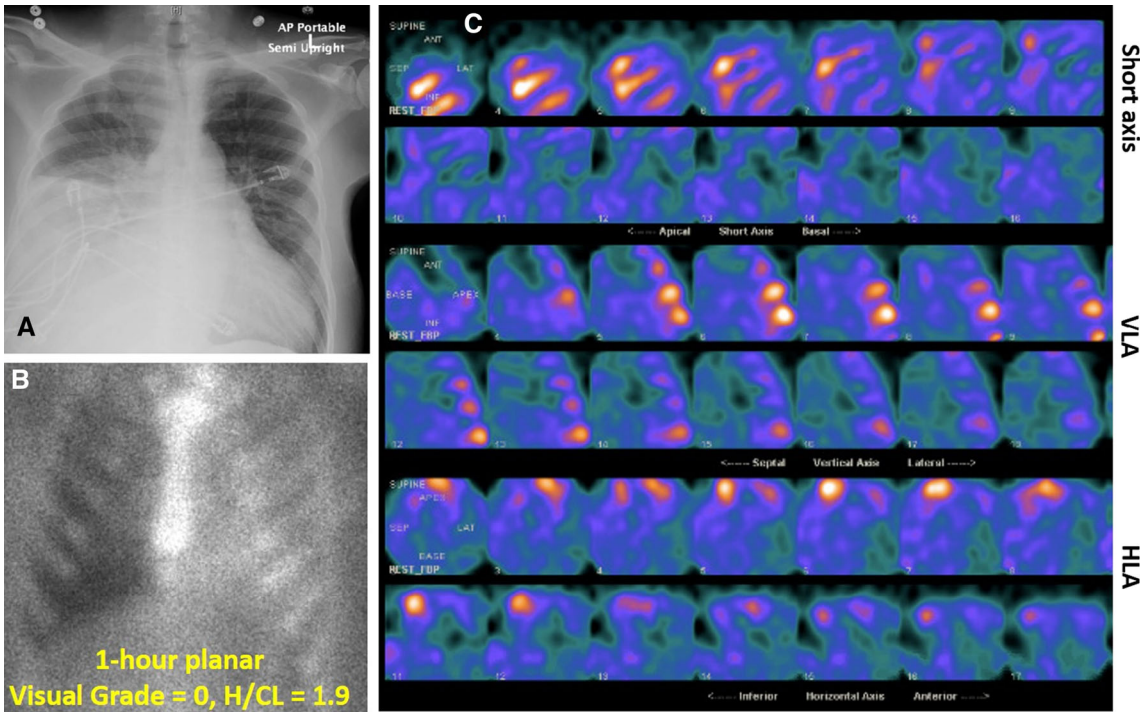

Figure 2. Erroneous elevation in heart-to-contralateral ratio in a patient with large right pleural effusion. Chest x-ray (**A**), demonstrating a large right pleural effusion. Anterior planar PYP image (**B**) depicting no cardiac PYP activity, which is confirmed on PYP SPECT (**C**).

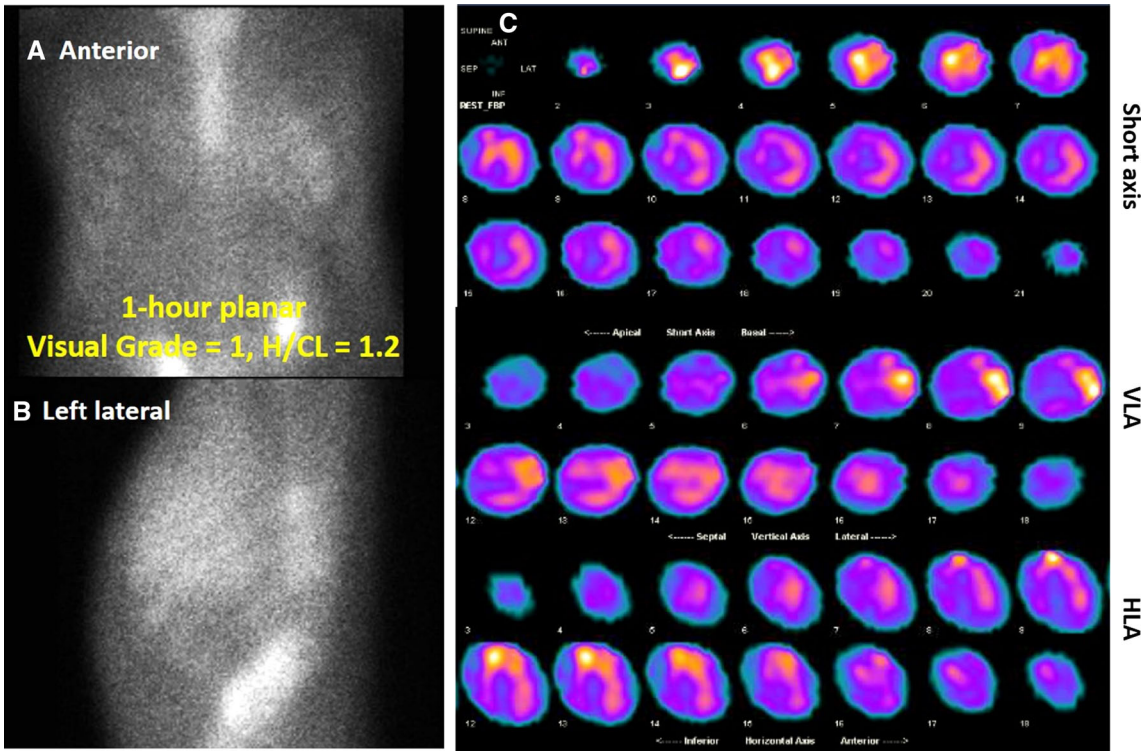

Figure 3. Confirmation of myocardial uptake by Pyrophosphate SPECT in a patient with a Perugini Score of 1. Anterior (**A**) and left lateral (**B**) planar images demonstrating mild PYP uptake, which was confirmed on PYP SPECT (**C**).

DISCUSSION

PYP scintigraphy is now considered as the diagnostic standard for TTR-CA. From an international, multicenter registry of patients who underwent endomyocardial biopsy, Gillmore et. al. reported a specificity of 100% of grade 2 or 3 score on bone scintigraphy for TTR-CA, in the absence of monoclonal proteins.[1] Similarly, H/CL ratio $\geq$ 1.5, another variable that is routinely evaluated on planar PYP scintigraphy, has been shown to have a 97% sensitivity and 100% specificity for differentiating TTR-CA from AL-CA.[3] Bone scintigraphy is relatively simple, widely available and can be readily performed by conventional sodium-iodide cameras. ASNC consensus recommendations for PYP scintigraphy consider a study to be positive if visual score is $\geq$ 2, while also highlighting a high diagnostic accuracy of a H/CL ratio $\geq$ 1.5.[4]

Despite the widespread recognition of excellent specificity conferred by a visual score $\geq$ 2, the sensitivity of any degree of myocardial uptake (grades 1, 2 or 3) of $>$ 99% is frequently ignored. Use of a planar visual score cut-off of $\geq$ 2 thus has the potential of missing the diagnosis of TTR-CA among those with milder uptake. Furthermore, historical data on application of PYP scintigraphy are derived from patients with biopsy proven TTR-CA. Thus, it is conceivable that, in current clinical practice, which is moving away from histological diagnosis of TTR-CA, these criteria may not maintain the perfect specificity that was previously reported.

With the wide adoption of PYP scintigraphy for diagnosis of TTR-CA, several limitations of the current diagnostic criteria have been identified.[6] Equivocal PYP uptake with a visual score of 1 can occur in patients with early TTR-CA. Our experience with one such patient is depicted in Figure 3. This case demonstrated the effectiveness of additional SPECT to planar imaging in identifying myocardial uptake, even when the study would have been classified as negative by both visual score of 1 and H/CL ratio of 1.2. In some patients, Perugini score can also be erroneously elevated with no tomographic evidence of myocardial PYP uptake.[8] This could be a result of low cardiac output, resulting in delayed clearance of blood pool activity.[9] Persistent blood pool activity can also be seen in patients with renal failure,[10] and delayed imaging at 3 hours is recommended if excess blood pool activity is identified at 1 hour.Though planar imaging is rapid and simple to

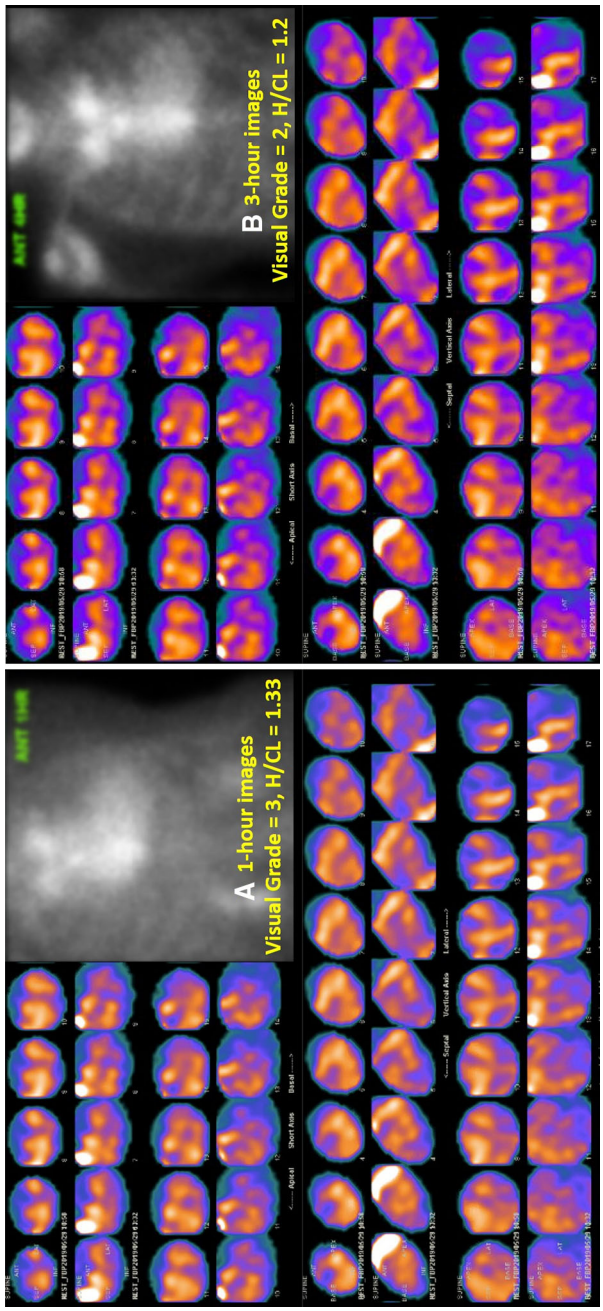

Figure 4. Persistence of blood pool activity on planar imaging at 3 hours, in a patient with severely reduced left ventricular function. PYP SPECT refuting the presence of myocardial isotope uptake, when activity was noted on (**A**) 1-hour and (**B**) 3-hour planar PYP imaging.

perform, planar images at 3 hours may still be indeterminate as shown in Figure 4. This patient, with severely reduced ejection fraction, was noted to have a visual score of 3 (H/CL ratio 1.3) and 2 (H/CL ratio 1.2), at 1-hour and 3-hour planar imaging, respectively, with no evidence of myocardial PYP uptake on SPECT. Thus, in the absence of SPECT, this study would have been categorized as being positive,[4] and the patient is falsely diagnosed with TTR-CA. Our experience indicates that SPECT should always be performed after planar imaging, as blood pool may not clear, even by 3 hours, to differentiate true myocardial uptake from residual blood pool activity. While 3-hour imaging is recommended if excessive blood pool activity is noted at 1 hour,[4] the need for repeat imaging could be circumvented by SPECT at 1 hour.

Similarly, there are several potential sources of error in the determination of H/CL ratio that can lead to false-positive or false-negative results.[9] Since this technique relies on extracardiac sites as comparators, disease states in which there is increased bone (metastasis) or skeletal muscle uptake can skew the ratio.[11] Extracardiac pathology such as pleural and pericardial effusions can lead to reduction in mean counts per pixel and erroneous results.[9] One of our patients had a large right pleural effusion, due to severe eccentric mitral regurgitation leading to diminished contralateral counts and falsely increased H/CL ratio (Figure 2). Other conditions that can lead to increased heart counts include mitral annular calcification and aortic valve calcification.[9] Abnormal focal uptake has been described in acute and subacute myocardial infarction, leading to abnormally high Perugini score and H/CL ratio.[9,4] H/CL ratio may be falsely low in patients who have had a large remote myocardial infarction as myocardial uptake of the tracer is limited to the non-infarcted segments.[4,12]

Our data suggest that the diagnostic utility of H/CL ratio is limited in contemporary clinical practice, as a substantial proportion of patients with SPECT evidence of PYP uptake have a ratio < 1.5. Contrary to this, our data suggest that only a fraction of patients will be misclassified if only visual score was relied upon, which is similar to that reported recently.[5,6] SPECT is now widely available in most laboratories performing radionuclide cardiac imaging, and PYP SPECT can be readily performed following planar imaging, in a manner similar to rest Tc-99m perfusion SPECT. While we routinely evaluated and reported planar PYP data, the early adoption of PYP SPECT by our laboratory allowed us to confidently classify test positivity based on SPECT alone. This approach has also been adopted by many similarly experienced nuclear cardiology laboratories,[5,6] even though guidelines do not emphasize routine SPECT acquisition. While the addition of SPECT increases the overall imaging time, performance of SPECT routinely after planar imaging improves diagnostic confidence and eliminates the need for 3-hour imaging for otherwise indeterminate studies, thus improving overall laboratory throughput, while maintaining diagnostic certainty.[5] Given the critical therapeutic consequences of misdiagnosis of TTR-CA, and the misclassification of a few patients by utilization of visual score alone, SPECT should be routinely performed as a part of PYP scintigraphy for TTR-CA.

Our report contrasts with recent reports on PYP scintigraphy. Contrary to our approach, Sperry et al. classified a planar PYP study with a visual score ≥ 2 and H/CL < 1.5 ratio as being indeterminate.[6] However, from their study, if only visual score cut-off of ≥ 2 at 1-hour was used to define test positivity, regardless of H/CL ratio, the diagnostic accuracy of visual score for SPECT evidence of PYP uptake would have been excellent at 96% (sensitivity and specificity of 89% and 100%, respectively) and similar to that reported by us. While Sperry et al. report a lack of congruence between planar and SPECT PYP data, they did not identify the cause of this finding. Our analysis of PYP scintigraphy highlights that this diagnostic uncertainty is mainly caused by H/CL ratio. Similarly, a recent report by Masri et al. focused on the comparison of 1-hour vs 3-hour PYP scintigraphy.[5] While they show excellent diagnostic performance of visual grade, similar to our report, they report excellent statistical measures of performance of H/CL ratio when compared to SPECT. This finding is in stark contrast to our data and also to that published by Sperry et al. In our population, 43% of the patient with a positive PYP SPECT had a H/CL ratio < 1.5 who would have been incorrectly classified as being indeterminate. Furthermore, we highlight the limitations of planar PYP scintigraphy by providing pertinent clinical examples. Additionally, our study combines data from two separate inner city hospital, where PYP imaging was performed in a consistent fashion, and also provides greater representation of women and minority populations.

LIMITATIONS

Our study is a retrospective analysis of unblinded data. All image analyses and reporting were performed by expert readers (JG, VS, RD. and SM) and are unlikely to influence categorization of SPECT data. However, it is possible that visual scoring of planar images could have been influenced by SPECT findings. Nonetheless, the prevalence of a positive PYP scintigraphy in our referral population was similar to that reported from referral cohorts at other tertiary care centers.[5,6] Except for a few early patients, we only

performed 1-hour imaging. This stemmed from our local experience and in initial comparison of 1-hour vs 3-hour images showing no diagnostic difference, which is now supported by recent data.[5] In our experience, 3-hour imaging hampered laboratory throughput and we circumvented the need for 3-hour imaging by instituting mandatory SPECT at 1-hour in all patients from the very beginning. Consistent with prevailing recommendations, tissue biopsy, the traditional ''gold standard,'' was not sought to confirm or refute TTR-CA. Additionally, the use of SPECT as a diagnostic standard for comparison with planar findings is arbitrary and not supported by biopsy evidence of TTR-CA, as opposed to that of planar imaging. Future studies maybe needed for validation of PYP SPECT as a diagnostic standard.

CONCLUSIONS

Semiquantitative visual scoring has a high diagnostic accuracy for TTR-CA, though the specificity is not 100% as previously suggested. H/CL ratio has poor correlation with both Perugini score and PYP SPECT and should not be employed for diagnosis of TTR-CA. Given its ability to distinguish blood pool activity from myocardial uptake, SPECT should be performed in all patients referred for PYP scintigraphy and not just reserved for those with an indeterminate planar study.

NEW KNOWLEDGE GAINED

H/CL ratio is the primary reason for an indeterminate result on planar PYP scintigraphy and should not be employed as a diagnostic criterion for TTR-CA. Perugini score correlates well with tomographic PYP uptake; however, some patients can be misdiagnosed by visual scoring alone. Given the wide availability of SPECT, tomographic imaging should be performed in all patients undergoing PYP scintigraphy.

Disclosures

Talal Asif, Javier Gomez-Valencia, Vasvi Singh, Rami Doukky, and Arlet Nedeltcheva have nothing to disclose. Saurabh Malhotra—Speakers Bureau: Pfizer and Akcea Therapeutics, and Advisory Board: Akcea Therapeutics

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