Quantitative SPECT in PYP imaging: Ready for prime time or too early to tell?

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^{99m}Tc pyrophosphate (PYP) imaging has revolutionized the field of cardiac amyloidosis in the last decade. PYP imaging obviates the need for endomyocardial biopsy and enables non-invasive diagnosis of transthyretin cardiac amyloidosis (ATTR-CA) in a carefully selected group of patients.¹ The approach to interpret PYP scan images necessitates integration of semi-quantitative and quantitative parameters that were initially described with predominantly planar imaging.² Planar imaging is simple and convenient, but carries important limitations including overlying bone uptake and cardiac blood pool uptake, which make accurate delineation of myocardial PYP uptake challenging. Therefore, ASNC guidelines for PYP imaging have made a strong recommendation to include SPECT.³ SPECT greatly improves diagnostic performance of PYP imaging and in most cases, allows for unequivocal ascertainment of myocardial PYP uptake.

SPECT has rapidly become an indispensable component of PYP imaging and therefore, the scientific community has demonstrated enthusiasm in developing SPECT-based quantitative techniques to evaluate the burden of myocardial PYP uptake.

Miller et al. have described a quantitative technique that allows for relative quantification of abnormal myocardial PYP uptake.⁴ Quantitative indices defined in

this study were namely cardiac pyrophosphate activity (CPA) and volume of involvement (VOI). The authors defined the threshold for abnormal myocardial PYP uptake as 1.5 times the left ventricular blood pool uptake. The rationale for this methodology is somewhat analogous to quantitative assessment of myocardial FDG uptake on PET,⁵ but it is important to note that FDG-PET lends to absolute quantification and measurement of standardized uptake values (SUVs), as opposed to the relative count-based evaluation Miller et al. described.

Other groups have used absolute quantitative techniques to assess the overall burden of myocardial uptake of other bone-avid tracers approved for cardiac amyloidosis imaging, namely ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD)⁶ and ^{99m}Tc-hydroxymethylene diphosphonate (HDP).⁷

In a study by Roshankar et al. published in this issue of the Journal of Nuclear Cardiology, the authors aimed to correlate previously described quantitative SPECT-based metrics in PYP imaging (CPA and VOI)⁴ to cardiac magnetic resonance imaging (CMR)-based indices of tissue characterization. CMR-based parameters of amyloid burden assessment included were native T1 mapping, late gadolinium enhancement (LGE), and extracellular volume (ECV). The authors also studied the association between these SPECT and CMR-based indices to adverse cardiovascular outcomes, albeit in a small study population. The study used a retrospective cohort design that included patients that underwent PYP imaging and CMR for evaluation of potential ATTR or AL cardiac amyloidosis (AL-CA). Standard diagnostic criteria using a combination of imaging data, laboratory evaluation, and endomyocardial biopsy were used to diagnose ATTR-CA and AL-CA. Of the 70 patients included in the study, 22 (31%) met diagnostic criteria for ATTR-CA, 11 (16%) for AL-CA, and the remaining 37 (53%) were used as controls.

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The authors demonstrated a statistically significant difference between CPA and VOI in ATTR-CA compared to AL-CA and controls, which is an expected finding since PYP imaging is known to have a high discriminatory value to differentiate ATTR-CA from AL-CA. The study reported modest correlations between CPA ($r^2 = .256$, $P = .027$), VOI ($r^2 = .348$, $P = .008$), HCL ratio ($r^2 = .214$, $P = .046$), and Perugini score ($r^2 = .391$, $P = .004$) with percent myocardial LGE in ATTR-CA patients. Among ATTR-CA patients, CPA ($r^2 = .509$, $P < .001$) and VOI ($r^2 = 0.586$, $P < .001$) had statistically significant correlations with average mid-myocardial T1, while HCL ratio ($r^2 = .147$, $P = .116$) and Perugini score ($r^2 = .115$, $P = .169$) did not. The authors reported that only VOI had a correlation with ECV ($r^2 = .515$, $P = .030$).

The composite outcome of heart failure hospitalization and cardiac death occurred in 12 patients in the ATTR-CA group over the mean follow-up of 1.2 years. After adjustment for age, CPA (adjusted HR 1.04, $P = .016$), VOI (adjusted HR 1.12, $P = .034$), and average myocardial T1 (adjusted HR 1.12, $P = .025$) were associated with higher risk of the composite outcome.

The authors present a timely and relevant study evaluating the correlation between quantitative SPECT-based metrics in PYP imaging and CMR-based indices of tissue characterized used in CA. It is important to note that the study has several limitations that are worth reviewing.

Retrospective study design and small sample size are inherent limitations of the study.

The study did not use SPECT-CT and there was no attenuation correction or scatter correction. Processing was performed using filtered back projection, instead of the more contemporary and superior iterative reconstruction technique.

CT allows for hybrid imaging and anatomic localization, which is incredibly valuable in cases where myocardial uptake is equivocal and significant blood pool is present. The authors used counts in the left ventricular blood pool to define a diagnostic threshold for abnormal myocardial uptake. However, it can be extremely challenging to accurately delineate blood pool uptake in some cases without availability of CT for anatomic localization.

Lack of SPECT-CT precluded assessment of absolute myocardial SUVs.^{8,9} Hence, the quantitative method developed by the authors is a relative quantification technique. The authors recognized that this technique does not add incremental value to enhance diagnostic accuracy when compared to the standard visual SPECT interpretation alone.

Biomarkers (troponin and n-terminal pro-B-type natriuretic peptide) have important diagnostic and

prognostic implications in cardiac amyloidosis.^{10,11} These biomarkers have been considered an indirect surrogate of amyloidosis burden.¹² In a study evaluating imaging-based quantitative indices of amyloid burden, lack of biomarker data is unexpected and not ideal.

Despite the small sample size, the authors studied clinical outcomes and were able to demonstrate a statistically significant correlation between the composite outcome and imaging-based quantitative indices. However, it is important to note that while the hazard ratios were adjusted for age, there were no adjustments for biomarker data or echocardiographic characteristics.

In summary, development of quantitative SPECT-based evaluation in PYP imaging is a highly relevant next step in refining the imaging modality that has completely transformed the diagnostic evaluation of ATTR-CA. Quantification of myocardial PYP uptake may have the potential to improve diagnostic accuracy, elucidate the possible spectrum or stages of myocardial involvement in ATTR-CA and enable serial imaging. Larger studies are needed to validate the technically most robust quantitative method and to evaluate the utility of follow-up imaging.

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