Quantitative PYP metrics: separating the wheat from the chaff

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The non-biopsy diagnosis of cardiac transthyretin (ATTR) amyloidosis by bone scintigraphy and the introduction of an effective drug treatment in tafamidis have disrupted the field of cardiac amyloidosis.[1,2] The prevalence of cardiac ATTR amyloidosis has increased substantially, with patients more often diagnosed at an earlier stage of the disease and having significantly lower mortality.[3] The widespread implementation of bone scintigraphy into daily clinical practice, and earlier detection of cardiac ATTR amyloidosis, continuously challenge its diagnostic performance.[4] On top, nuclear cardiologists are approached by clinicians with novel unmet questions: What is the amyloid burden in this patient? How does it affect the prognosis? Did the cardiac amyloid burden progress over time? To what extent did he or she respond to tafamidis?

Clinically, myocardial uptake of technetium-99m (^{99m}Tc)-labeled bone-seeking radiotracers is primarily assessed visually in comparison to rib uptake (i.e., Perugini score).[5] A visual score equal to or greater than 2 is classified as positive. In the absence of a monoclonal protein in serum or urine, this method has a diagnostic accuracy of 89% with sensitivity of 74% and a specificity of 100%.[1] Secondly, to minimize interrater variability, the myocardial-to-contralateral lung uptake ratio (H/CL ratio), a semiquantitative metric, has been introduced. Here, counts from a circular region of interest (ROI) over the heart are divided by counts from an ROI over the contralateral chest (to account for background and rib activity).[5] A ratio of $\geq$ 1.5 at 1 hour or $\geq$ 1.3 at 3 hours are classified as positive. In a multicenter study among amyloid referral centers, these thresholds had an area under the curve (AUC) of 0.960 with a sensitivity of 91% and a specificity of 92%.[6] In addition to its diagnostic value, the semiquantitative method assists in the risk stratification of cardiac ATTR amyloidosis: patients with H/CL ratio $\geq$ 1.6 have an eightfold high increase in mortality compared to those with H/CL ratio $<$ 1.6.[6] These qualitative and semiquantitative methods of image assessment have advanced the field of ATTR amyloidosis tremendously. However, to address the evolving unmet needs, absolute quantitation of radiotracer uptake to estimate the amyloid burden is critical. Thanks to the refinement of single-photon emission computed tomography (SPECT) technology by cadmium-zinc-telluride (CZT)-based detectors, the absolute radiotracer uptake can be quantified by standardized uptake values (SUV),[7] similar to positron emission tomography (PET). These absolute metrics correlate strongly ($r \sim$ 0.8-0.9) with

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extracellular volume, an indirect but established marker of amyloid burden in cardiac magnetic resonance.[7]

The major challenge for all of these methods—visual, semiquantitative and quantitative—is blood pool radiotracer activity.[4] In the visual assessment, misinterpretation of blood pool activity as cardiac uptake can be minimized by adding SPECT/CT to planar scintigraphy as well as by delaying acquisition to 3 hours after injection.[5] However, the optimal approach to exclude blood pool activity in the (semi-)quantitative evaluation has not yet been established.

In the current issue of the Journal, Ikoma et al.[8] have tested the diagnostic accuracy of the heart-to-mediastinum ratio (H/M ratio) with endomyocardial biopsy as the standard of reference in 30 patients undergoing ^{99m}Tc-pyrophosphate (PYP) SPECT/CT. Half of the patients (n = 15) had biopsy-proven cardiac ATTR amyloidosis; the rest of the patients suffered from dilated cardiomyopathy, hypertrophic cardiomyopathy, aortic stenosis, hypertensive heart disease, cardiac sarcoidosis, cardiac light chain (AL) amyloidosis and isolated atrial amyloidosis. The H/M ratio was calculated on SPECT/CT images by dividing the maximal SUV from a volume of interest (VOI) drawn over the heart by the maximal SUV from a VOI drawn just under the aortic arch including the ascending aorta. It had an AUC of 0.982, with a sensitivity of 100% and a specificity of 93%. On the contrary, the planar H/CL ratio had an AUC of 0.947 with a sensitivity of 80% and specificity of 80%, and visual grading had a sensitivity of 100% and specificity of 67%. Although the AUC is numerically higher for the H/M ratio than for the H/CL ratio, the authors did not compare the two values statistically because of the low sample size. After excluding the single case with cardiac AL amyloidosis, the sensitivity of the H/M ratio fell to 93%. Based on these findings, the authors argue that the H/M ratio ''has the potential to be a novel indicator for cardiac ATTR amyloidosis''.

The authors should be congratulated for their innovative study. A specific strength of this study is that all patients had histological confirmation of the underlying disease. However, as for every study, there are certain weaknesses and limitations that need to be highlighted. First, the small sample size precluded a direct statistical comparison of the H/M ratio to the H/CL ratio and the visual scoring. Even if statistically significant in a larger sample size, the introduction of the H/M ratio might not be clinically relevant for the diagnostic performance since the implementation of SPECT/CT itself helps identifying blood pool activity in the majority of cases. Moreover, the sole use of H/M ratio to diagnose amyloidosis can be limiting as it can be driven by a low mediastinal activity; to avoid false positive diagnosis, as with the planar H/CL ratio, this SPECT metric should be applied after visual confirmation of myocardial uptake of radiotracer on SPECT/CT.[5] Second, the small difference in the two AUC's might also be explained by the fact that a ratio in two-dimensional imaging (i.e., H/CL ratio in planar scintigraphy) is compared to a ratio in three-dimensional imaging (i.e., H/M ratio in SPECT/CT). Third, in their main analysis, the patient with cardiac AL amyloidosis was not excluded but did negatively affect the diagnostic performance of the H/M ratio, as outlined in the supplemental material. Despite these limitations, the H/M ratio seems to be a reasonable and easy way to account for blood pool activity. It takes the same lines as the recently published ''cardiac pyrophosphate activity (CPA)'' where thresholds for abnormal cardiac activity were directly derived from left ventricular blood pool activity.[9] CPA not only improved the diagnostic accuracy over visual scoring and the H/CL ratio, but was also associated with heart failure hospitalizations. In contrast, ''indexed LV counts''—a metric very similar to the H/M ratio where mean total LV counts were divided by the mean blood pool counts from 3 ROIs in the proximal, mid, and distal ascending aorta—did not predict outcome.[10]

In summary, quantifying myocardial uptake of bone-seeking radiotracers using SPECT/CT emerges as a tool to estimate cardiac amyloid burden and hopefully to improve the management of patients with cardiac ATTR amyloidosis. However, blood pool activity remains a major challenge for the quantitation of disease activity by radionuclide imaging. While the H/M ratio may be added to the list of promising metrics, the wheat has yet to be separated from the chaff.

Disclosures

Authors have no conflicts to disclose.

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