Quantitative ATTR-cardiac amyloidosis SPECT/CT imaging: The time is now!

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Transthyretin (ATTR) cardiac amyloidosis (ATTR-CA) is a condition in which misfolded TTR proteins progressively accumulate in the heart as amyloid fibrils, leading to heart failure. In recent years there has been growing awareness of ATTR-CA, although it is still underdiagnosed. The most prevalent form of ATTR-cardiomyopathy, ATTRwt (wild type), was found in approximately 25% of patients older than 80 years on autopsy studies.[1] Other investigators have reported a prevalence of 13% in patients with heart failure with preserved ejection fraction[2] and 16% of elderly patients with severe aortic stenosis.[3] Until recently, ATTR-CA was considered untreatable, with disease management consisting of limited palliative care. Without ATTR-CA specific therapy, median survival for the two subtypes of ATTR-CA, hereditary and wild-type, was reported to be about 2.5[4] and 3.6[5] years, respectively.

Recently, disease-modifying therapies based on ATTR-CA stabilizing and silencing medications have become available. Among these, the release of the FDA-approved ATTR stabilizer, Tafamidis (Pfizer, New York, New York), was a significant advance. In a randomized trial, compared to placebo, Tafamidis was found to reduce mortality, morbidity, and cardiovascular-related hospitalizations in about 70% of patients.[6] Although Tafamidis stabilizes TTR protein preventing further cardiac amyloid deposition and slowing disease progression, it neither eliminates established amyloid deposits nor reverses altered cardiac function. Therefore, early diagnosis is crucial. Lifelong Tafamidis therapy comes at a very high cost, approximately $1.13 million per patient.[7]

Cardiac scintigraphy with bone-avid agents, i.e., ^{99m}Tc-PYP/DPD/HDMP (^{99m}*Tc*-pyrophosphate, ^{99m}*Tc*-3,3-diphosphono-1,2-pyrophosphate, and hydroxymethylene-diphosphonate, respectively), is an established powerful tool for noninvasive diagnosis of ATTR-CA. Current clinical practice relies on visual grading of the myocardial tracer uptake[8,9] of planar, SPECT-only, or SPECT/CT images. Most clinics use planar imaging, even though it is suboptimal due to the superimposition of blood pool and myocardial uptake. The visual grading scheme, a 0–3 scale introduced by Perugini,[10] is based on comparison of myocardial tracer uptake to that of bone. Grades 0 (no myocardial uptake) and 1 (myocardial uptake less than bone uptake) are considered negative, while grades 2 (myocardial uptake similar to bone uptake) and 3 (myocardial uptake higher than bone uptake) are considered positive. It is worth

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noting that even though grade 1 is considered normal, it can suggest early disease.

Because of the limitations of the visual grading approach, particularly for planar imaging, semi-quantitative metrics, such as the heart to contralateral lung (HCL) ratio and the heart to whole body ratio,[11,12] were introduced, leading to improved diagnostic accuracy and risk stratification.[13] Furthermore, increasing the time between tracer administration and image acquisition from 1 to 3 hours, improved the specificity (79% vs 100%) because of blood pool clearance.[13] However, these methods are inadequate for early diagnosis, identification of appropriate therapy candidates, and treatment monitoring.[8]

SPECT/CT imaging at 2–3 hour post injection has become the preferred imaging approach. In comparison to planar or SPECT-only scanning, SPECT/CT imaging is associated with enhanced diagnostic accuracy, improved reproducibility and repeatability, and reduced false positive rates because of better separation of blood pool and myocardial uptake.[14]

One of the major advantages of SPECT/CT imaging is its capability for absolute quantitation of tracer uptake. Quantitative imaging has the potential to enable earlier diagnosis, better risk stratification, improved selection of candidates for expensive treatments, and monitoring of treatment response and disease progression.[15] Absolute quantification of myocardial uptake by SPECT/CT requires CT-based attenuation correction (AC), scatter correction, resolution recovery, and scanner calibration. The scanner calibration procedure, analogous to that used for PET/CT, consists of regular acquisition of a cylindrical phantom uniformly filled with activity, and determination of the calibration factor to convert image counts per unit volume to activity concentration. Standardized uptake value (SUV) (based on weight) can then be calculated as tissue activity concentration divided by the injected activity per unit weight, with activity values decay-corrected to the same time. The low-dose CT image not only provides data for AC but can also be used to localize the SPECT activity concentration distribution and to guide segmentation, even when cardiac uptake is low or absent. It also facilitates automated or semi-automated myocardial segmentation via widely available software, thus offering superior repeatability and reproducibility compared to manual approaches.

Among the quantitation metrics, SUVmax, SUVmean, and SUVpeak have been the most investigated.[2,3,16–18] SUVmax is derived from a single voxel value within the myocardial region of interest (ROI); it is imprecise due to image noise. SUVmean represents the average SUV value within the myocardial volume, or a subvolume within the myocardium. SUVpeak is the mean within a subvolume of the myocardium, either centered on the voxel the maximum value or defined as the subvolume which yields the highest value. SUVpeak and SUVmean are more precise metrics, as they are calculated over multiple voxels. Two other promising metrics are the percentage of injected dose (%ID) and the cardiac amyloid activity (CAA), which in a study of heart failure patients with suspected ATTR-CA were strongly correlated with extracellular volume (ECV) derived from cardiac magnetic resonance imaging.[16] %ID is defined as the product of the mean activity concentration within the Left Ventricle (LV) Volume Of Interest (VOI) and the LV–VOI volume divided by the injected activity (with appropriate decay correction). CAA is the product of the mean SUV within the LV VOI and LV–VOI volume. CAA and %ID incorporate the volume as well as the magnitude of myocardial uptake and may, therefore, be more accurate representations of amyloid burden than are SUV-based metrics. Unlike the other metrics, %ID does not incorporate normalization for body weight and, therefore, may be more appropriate for highly sensitive tracers.

The paper by Nichols et al. evaluates myocardial-to-blood pool uptake ratio (MBP), a semi-quantitative metric, for tracer uptake in CA.[19] In this single-center and single-observer retrospective study consisting of patients with suspected ATTR-CA, the authors assessed the reproducibility and diagnostic value of MBP derived from SPECT/CT and SPECT-only images. The reference standard was visual assessment from SPECT/CT images, and MBP was compared to a composite index and HCL evaluated from planar images. One major limitation emphasized by the authors is the use of visual assessment as the reference standard, making it impossible to compare the performance of the MBP against visual grading, as the true status of patients is unknown. The authors report a higher diagnostic accuracy (visual scores $\geq$ 2 considered positive) for MBP with SPECT/CT (99%) compared to SPECT-only (93%). SPECT/CT-derived MBP values were highly repeatable. Another limitation is the timing of the planar studies (1 hour post injection); although recommended by the imaging guideline at the time when the data were collected (2018), planar imaging is associated with a higher risk of confounding signal from the cardiac blood pools and, consequently, more false positives, introducing a bias into the authors' results.[8,9]

The paper has several strengths. The sample size is significant (318 patients), with a large subsample (191 patients) used to compare SPECT-only against SPECT/CT. The comparison of multiple approaches to evaluate tracer uptake in planar, SPECT-only, and SPECT/CT imaging highlights the current challenges in bone-avid

CA imaging and reinforces the superiority of SPECT/CT imaging for accurate diagnosis.

The semi-quantitative MBP metric is simple, straightforward, and accessible in routine practice, and it has the advantage of normalizing for blood activity concentration and, by extension, for injected activity. However, it has not been shown to be correlated with more accepted metrics of amyloid burden, such as ECV, and, thus, remain of limited value in the context of treatment monitoring, early diagnosis, and risk assessment. We can also regret the absence of results from quantitative metrics, such as SUV, CAA, and %ID, which have been shown to be strongly correlated with ECV. It is essential to understand that quantitative SPECT is available to all SPECT/CT (but not SPECT-only) system users. Scanner calibration procedures are straightforward and have been well-documented. The simplest approach consists of periodically scanning a cylindrical phantom filled with uniform Tc-99m activity concentration; from these data, a calibration factor converting counts per unit volume into activity concentration can be obtained. It is also worth mentioning that if an institution is performing such SPECT/CT calibration for oncologic imaging with ^{99m}Tc-labeled radiotracers, the calibration factors can also be applied to cardiac images.

The relatively small (16 mm-diameter) myocardial and blood pool circular ROIs used for MBP calculation were placed subjectively on a single transaxial slice, thus affecting the intra-reader repeatability and, presumably, inter-reader reproducibility (not evaluated in this paper). This is particularly true for SPECT-only images, for which CT images are not available to guide the ROI placement. This is reflected in the high limits of agreement for the intra-observer variability assessment of MBP, from .57 to − .61 with a mean difference of − .02, representing 285% and 305% of the mean difference, respectively. The variability of this metric implies limited utility for early diagnosis and for monitoring of disease progression and treatment response. Several recent studies utilizing semi-automated ROI definition have reported low limits of agreement (within 10% of the mean difference) for inter-reader reproducibility and intra-reader repeatability of HCL ratio measurements in bone-avid imaging[14] and retention index in ^{18}F-florbetapir PET/CT.[20]

An important weakness of the paper is that light chain cardiac amyloidosis (AL-CA) patients were not excluded from the study. The failure to exclude AL-CA is widely acknowledged as the most important cause of misdiagnosis, as AL-CA is associated with high mortality compared to ATTR and delays in treatment may associate with high morbidity and mortality. The failure to exclude AL-CA may have favorably skewed the results and could explain the increased MBP variability for the disease grade 3. It is thus critical to exclude AL-CA via serum/urine testing, or biopsy if a mono-clonal protein is present, as recommended by the recent imaging guidelines.[8,9]

The findings presented in this paper reinforce the widely recognized benefits of SPECT/CT over planar and SPECT-only imaging in the context of bone-avid tracer cardiac imaging in ATTR-CA. The semi-quantitative metric, MBP, was shown to perform well in classifying positive and negative cases, using visual grading from SPECT/CT images as the reference standard. However, this study did not evaluate the diagnostic accuracy of MBP because the true status of the patients was unknown. The future of bone-avid ATTR-CA imaging relies on the quantification of myocardial tracer uptake using robust automated or semi-automated techniques for ROI definition combined with meaningful metrics. These are the requirements for advances in detection of early disease, assessment of patient prognosis, monitoring disease progression, identifying appropriate candidates for existing and emerging therapies, and evaluation of treatment response. The time has come for quantitative SPECT/CT imaging to be established as the imaging modality of choice for diagnosis and monitoring of ATTR-CA.

Disclosures

Authors have no conflicts of interest to disclose.

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