Nuclear imaging of cardiac amyloidosis

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Amyloidosis is a multi-system disorder affecting various organs and histologically defined by deposition of abnormal proteins (amyloid fibrils) with characteristic staining pattern. Cardiac involvement may be seen with AL amyloidosis, characterized by deposition of light chains, and TTR amyloidosis, characterized by deposition of transthyretin, either genetically abnormal (mutant transthyretin, familial form of cardiac amyloidosis) or normal (wild-type transthyretin-wt, senile systemic amyloidosis). Cardiac amyloidosis (CA) is an under-diagnosed clinical entity affecting 50% of the patients with AL amyloidosis, in almost all patients with wt-TTR amyloidosis and with variable frequency of cardiac involvement in mutant-TTR amyloidosis depending on the underlying mutation.[1,2] Under-diagnosis is partly due to the inherent difficulty in making a definitive diagnosis of CA, for which endomyocardial biopsy remains the gold standard. Tissue-based diagnosis, however, is an invasive approach and it is not uncommon for patients either to be considered too high of a risk to undergo biopsy, or refuse biopsy. In these cases, diagnosis of CA relies on (a) obtaining tissue from a different site (abdominal fat pad, salivary glands etc.) and (b) identifying signs indicative of CA on cardiac magnetic resonance imaging. Another reason why diagnosis of CA is challenging is because its cardinal echocardiographic features (increased ventricular wall thickness, impaired diastolic function) are also frequently seen with other common disorders, most notably hypertensive heart disease and other restrictive cardiomyopathies.

Despite the difficulty in identifying patients with the disorder, it is important not only to identify patients at early stages of the disease in order to institute appropriate therapy, but also to differentiate between AL-CA and TTR-CA subtypes. The latter is due to their differing prognosis, AL-CA carrying the worst and wt-TTR generally believed to have the most favorable prognosis in terms of patient survival.[3,4] Timely intervention and initiation of treatment is also essential. In the past, it was common belief that no effective therapy for CA existed; however, this is no longer the case. Patients with AL-CA may see improvement in their survival of up to 12 years with appropriate chemotherapy.[5,6] The traditional treatment for TTR-CA is liver transplantation, with novel pharmacological agents under development.[7] In the face of these advances and prognostic implications of CA, it is essential to make the correct diagnosis using prompt and reliable non-invasive imaging modalities. This will allow not only for differentiation amongst the subtypes of CA (AL versus TTR), but also from other myocardial disorders with similar imaging characteristics, such as hypertensive heart disease and other restrictive cardiomyopathies, for which distinctively different management is required.

In the recent years, scientific interest has focused on the use of nuclear cardiac imaging for the early detection of CA. Planar imaging alone or with single-photon emission computed tomography (SPECT) using non-amyloid-specific, bone-avid radiotracers (^{99m}Tc-DPD [3,3-diphosphono-1,2-propanodicarboxylic acid], ^{99m}Tc-MDP [methylene diphosphonate], ^{99m}Tc-HMDP [hydroxymethylene diphosphonate], and ^{99m}Tc-PYP [pyrophosphate]) have been found to be more effective in detecting TTR myocardial deposits.[8-17] Recent data

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indicate that the increased level of microcalcifications may explain the enhanced affinity of bone-seeking tracers for TTR over AL amyloidosis.[18] Amyloid-specific, positron emitting ^{18}F- and ^{11}C-tagged tracers have been used successfully with positron emission tomography (PET) imaging for the identification of both AL and TTR subtypes of CA.[19,20] However, there still remains some overlap in the diagnoses of AL and TTR-CA and the best strategy for approaching patients with suspected CA is yet to be defined.

In this issue of the *Journal of Nuclear Cardiology,* Capelli et al retrospectively assessed the diagnostic value of 99 mTc-HMDP in addition to thorough work-up (echocardiography, biomarkers, ECG, cardiac MRI) in a relatively small cohort (N = 65) of patients with biopsy proven CA ($N = 26$ AL CA; $N = 39$ TTR CA).[21] Importantly, all patients underwent planar ^{99m}Tc-HMDP total body scintigraphy and not SPECT imaging. All patients with TTR-CA had cardiac uptake of Tc-HMDP based on visual/qualitative evaluation using the Perugini score ($N = 3$ grade 1—mild cardiac uptake, inferior to bone uptake, $N = 16$ grade 2—moderate cardiac uptake associated with attenuated bone uptake and $N = 20$ grade 3—high cardiac uptake with decreased or absent bone uptake). Quantitative assessment using the heart retention-to-whole body retention ratio (HR:WBR) showed that patients with TTR-CA had a significantly higher HR:WBR value compared to AL-CA (6.2 ± 1.4 vs 2.2 ± .4, $P = .0001$) and also when compared to patients with left ventricular hypertrophy (LVH) not related to CA (6.2 ± 1.4 vs 1.6 ± .7, $P = .0001$). HR:WBR between AL-CA and LVH patients did not differ significantly, but more importantly did not overlap with the respective value for TTR-CA patients. The authors concluded that ^{99m}Tc-HMDP total body scintigraphy is an accurate tool to diagnose TTR-CA with a Perugini score of ≥2 carrying 100% specificity and 93% sensitivity and a cut-off of 3.3 for HR:WBR carrying a 100% accuracy for TTR-CA, based on ROC curve analysis. Therefore, ^{99m}Tc-HMDP could be considered an effective radiotracer to correctly identify patients with TTR-CA and differentiating them from AL-CA and LVH.

The use of bisphosphonates with planar or SPECT bone scintigraphy in diagnosis of TTR-CA is not a novel concept. Since the seminal work by Perugini et al[8], a number of other studies have showed that ^{99m}Tc-DPD and ^{99m}Tc-PYP nuclear imaging is feasible and effective in detecting TTR-CA.[9,11,12,15-17] In addition to the traditionally used qualitative Perugini score which compares myocardial to bone uptake and the semi-quantitative HR:WBR,[8] Bokhari et al also showed that ^{99M}Tc-PYP imaging with a heart-to-contralateral lung ratio of >1.5 detected TTR-CA with a 97% and 100% sensitivity and specificity, respectively.[16] Negative and positive example images of TTR-CA with ^{99M}Tc-PYP imaging are depicted in Figures 1 and 2. Gillmore et al have conducted the largest multicenter study to date, showing that cardiac uptake (Perugini grades 1, 2 or 3) on planar imaging with bisphosphonates ($N = 877$ ^{99m}Tc-DPD, $N = 199$ ^{99m}Tc-PYP, $N = 141$ ^{99m}Tc-HMDP) is >99% sensitive and 68% specific for detecting TTR-CA, based on the subgroup of patients who had undergone endomyocardial biopsy.[17] The low specificity resulted largely from low-grade uptake in patients with cardiac AL or cardiac apolipoprotein A-I amyloidosis. The primary goal of the investigators was to assess the specificity and positive predictive value of a positive nuclear scan, so as to better differentiate TTR from AL-CA, given the significant differences in prognosis and treatment strategies.[17] Indeed, a combination of grade 2 or 3 Perugini score on nuclear bone imaging without a monoclonal protein identified on serum or urine immunoelectrophoresis and serum free light chain assay could reliably diagnose TTR-CA with 100% specificity and positive predictive value.[17,18] This was true among the three different bone tracers as well.[17] One of the conclusions of this study was that ^{99m}Tc-HMDP acts very similar to ^{99m}Tc-DPD and ^{99m}Tc-PYP, the two most widely used tracers.[17]

Despite the utility of the bone-seeking radiotracers in identifying myocardial involvement in TTR-CA, SPECT imaging falls short in the radioactivity quantification at affected sites and thus cannot be used in assessing disease burden and response to therapy. PET is a nuclear modality that can circumvent this problem and is now slowly starting to emerge as a promising tool in the management of CA. ^{11}C-PIB (Pittsburgh imaging compound) is a PET tracer able to detect and quantify β-amyloid fibrils in patients with Alzheimer's disease and was recently shown to also localize and quantify CA.[19] However, ^{11}C has a very short half-life of 20.4 min and needs a cyclotron for its production, precluding widespread clinical use. ^{18}F-florbetabir is a novel PET tracer, approved for imaging β-amyloid protein aggregates in patients with Alzheimer's disease and was recently shown to be useful in distinguishing AL- and TTR-CA from controls, but not AL from TTR-CA in a small pilot study ($N = 9$ CA, $N = 5$ controls) [20] (In the same study, ^{18}F-florbetabir also showed promise in quantifying disease activity.[20] Although the overall myocardial retention index tended to be higher in AL than in TTR patients, none of the indices tested (retention index, LV myocardial SUV, target to background ratio or LV myocardium to liver SUV ratio) clearly distinguished AL from TTR amyloidosis. The higher median ^{18}F-florbetapir retention index in AL amyloid subjects over ATTR subjects suggested a greater avidity for the light

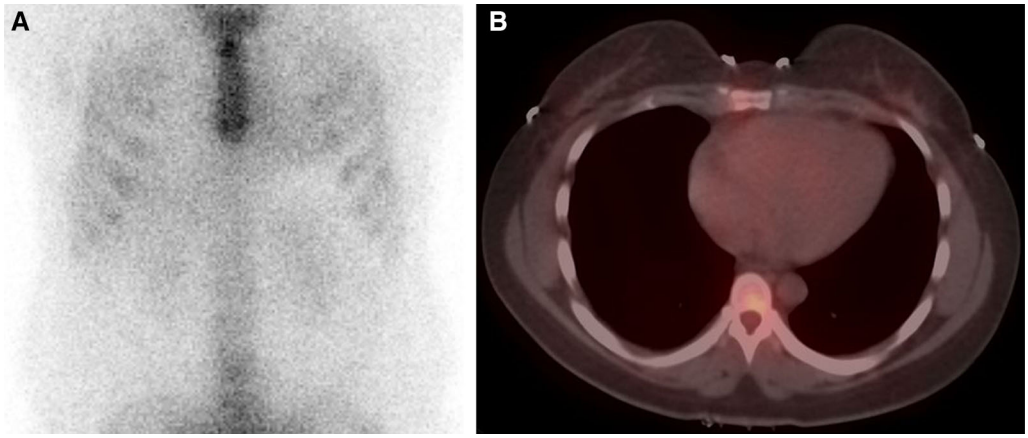

Figure 1. Negative ^{99m}Tc-PYP scan (Planar and axial SPECT/CT) with no appreciable myocardial tracer uptake (Perugini Score Grade 0).

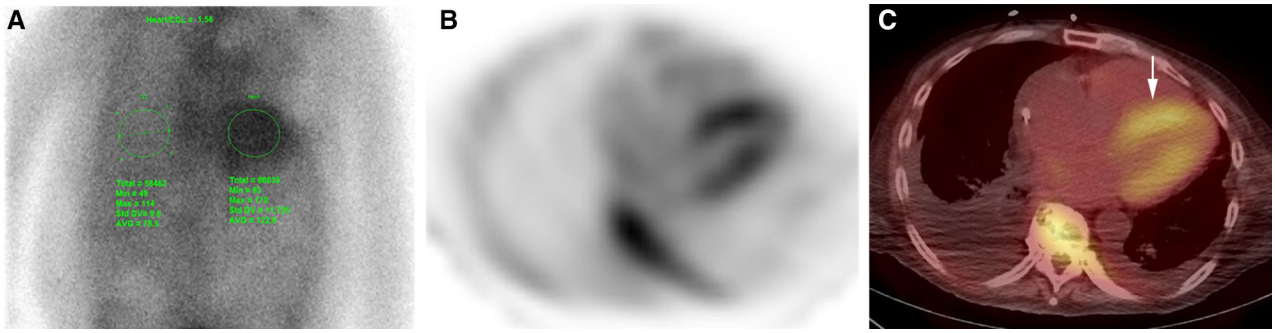

Figure 2. Positive ^{99m}Tc-PYP scan (Planar, axial SPECT and axial SPECT/CT) with prominent left ventricular myocardial tracer uptake (*arrow*) and decreased rib uptake (Perugini Score Grade 3). The heart to contralateral ratio is elevated at 1.56.

chain than for transthyretin protein. The authors suggest an approach of using ^{18}F-florbetabir PET as a screening step for CA (AL or TTR) and if positive, can be followed either by tissue diagnosis or ^{99m}Tc DPD or PYP scanning to confirm TTR myocardial deposits.[20] Similar findings have been reported with ^{18}F-florbetabir from other laboratories[22] and with another amyloid specific PET tracer, ^{18}F-florbetaben.[23]

The current study by Capelli et al[21] confirms earlier findings of smaller studies and case reports [13,14] as well as the large-scale study by Gillmore et al[17] showing the potential of ^{99m}Tc-HMDP nuclear imaging in patients with suspected TTR-CA, to reliably differentiate those from AL-CA and other causes of LVH. The biggest limitations, as the authors point out, are small sample size and lack of biopsy confirmation in several patients.[21] Their results are overall positive; however, there are a number of unanswered. Other than local availability, are there specific benefits of using ^{99m}Tc-DPD over ^{99m}Tc-PYP and ^{99m}Tc-HMDP and vice versa, such as ease of labeling (radiochemistry), differences in cost, image quality, radiation exposure etc.? It is also as important (if not more) to define a strategy of non-invasive assessment of patients with suspected CA. We agree with suggestions by Dorbala et al[20] for using 18F-florbetapir PET as a screening tool followed by bone scintigraphy or endomyocardial biopsy in positive cases, to help identify patients with AL CA (positive ^{18}F-florbetabir, negative ^{99m}Tc-DPD/PYP/HMDP) and TTR-CA (positive ^{18}F-florbetabir, positive ^{99m}Tc-DPD/PYP/HMDP). In addition to improving our diagnostic capability, more tools are needed to make early diagnosis which can help detect disease prior to its clinical manifestation, to better quantify disease severity, disease burden and response to therapy. ^{18}F-florbetabir appears promising; however, large-scale studies need to be undertaken to definitively establish its value in the management of cardiac amyloidosis. In conclusion, tailored nuclear imaging with PET and SPECT agents may simplify the diagnostic algorithm for cardiac amyloidosis while the PET radiotracer-derived quantitation offers the potential for imaging-guided management.

Disclosures

The authors declare that they have no conflict of interest.

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