Nuclear imaging of cardiac amyloidosis. 'We've only just begun'

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Cardiac amyloidosis is an infiltrative/restrictive cardiomyopathy caused by the abnormal extracellular deposition of protein fibrils in the myocardium which most commonly presents as heart failure with preserved ejection fraction. The clinical presentation often overlaps with other more common cardiovascular diseases (for example, hypertrophic cardiomyopathy, hypertensive heart disease, aortic stenosis) leading to missed and/or delayed diagnosis.[1,2] The type of cardiac amyloidosis depends on the deposited precursor proteins.[2] The most common deposited precursor proteins include immunoglobulin light chains, transthyretin, and serum amyloid A, with light chain (AL) and transthyretin amyloidosis (ATTR) being the most common forms seen in clinical practice.[2] ATTR has 2 subtypes, hereditary/mutant ATTR caused by a hereditary amino acid mutation in the transthyretin molecule and senile or wild-type ATTR (ATTR-wt) seen with advancing age. Patients with AL and ATTR cardiac amyloidosis have overlapping imaging features on echocardiography and cardiac MRI. It is clinically important to differentiate these subtypes since they have different clinical courses (milder clinical presentation for ATTR with slower progression), prognosis (AL is much worse), and therapies (chemotherapy for AL and liver or heart-liver transplantation for familial ATTR).[3] This differentiation may gain additional importance in the near future with the introduction of novel therapies that target the transthyretin protein and therefore would be specific for the treatment of the ATTR subtype.[4] The diagnosis is often confirmed either by demonstrating amyloid deposits on endomyocardial biopsy or by demonstrating histologic amyloid deposits on biopsy from extracardiac tissues (e.g., abdominal fat pad, rectum, etc.) in patients with clinical/imaging suspicion of cardiac involvement.

Endomyocardial biopsy coupled with immunohistochemistry or mass spectroscopy, the current gold standard for diagnosis of cardiac amyloidosis, is invasive and requires expertise. While echocardiography and cardiac MRI are clinically used in the evaluation of cardiac amyloidosis, their findings are not specific. Further, they are unable to differentiate between the amyloid subtypes (AL versus ATTR), which can be better addressed by nuclear imaging.[1] Several SPECT and PET agents have been investigated including ^{99m}Technetium 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD)[5,6] ^{99m}Tc pyrophosphate (^{99m}Tc-PYP), 99mTc-labeled aprotinin, ^{11}C-labeled Pittsburgh compound B (^{11}C-PIB),[7,8,9] ^{18}F-Florbetapir[10,11] among others (reviewed in Ref[4]). While not useful for the diagnosis of cardiac amyloidosis, ^{123}I mIBG has been shown to identify cardiac sympathetic denervation that is known to occur in the early stages of ATTR-type amyloidosis.[16]

For PET imaging, the most commonly used cardiac tracers include ^{11}C-PIB and ^{18}F-florbetapir. A pilot study by Antoni and colleagues showed obvious ^{11}C-PIB uptake in the LV wall of all 10 patients with cardiac amyloidosis (7 AL and 3 ATTR subtypes), whereas no LV uptake was seen in any of the 5 healthy controls.[7] In half of the patients, ^{11}C-PIB uptake was also visually detectable in the right ventricular wall.

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Semiquantitative assessment demonstrated significantly larger ^{11}C-PIB retention index in the patients with known cardiac amyloidosis than in healthy volunteers. However, the investigators did not specifically compare the retention index between ATTR and AL patients.[7] Hence, the ability of ^{11}C-PIB to differentiate between the amyloid subtypes is uncertain. More recently Kero and colleagues have demonstrated the feasibility of accurate software-based semiautomatic analysis of cardiac ^{11}C-PIB uptake and retention index in patients with cardiac amyloidosis.[9] From a practice stand point, widespread clinical use of ^{11}C-PIB PET is limited to centers with onsite cyclotron given the short half-life of ^{11}C of 20 minutes.

^{18}F-florbetapir, structurally distinct from PiB, was approved by the FDA in April 2012 for imaging beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive decline. ^{18}F-Florbetapir PET has shown promising results in a pilot study of 9 subjects with documented cardiac amyloidosis and 5 control subjects without amyloidosis.[10] All amyloid subjects and none of the control subjects demonstrated left and right ventricular ^{18}F-florbetapir uptake. ^{18}F-florbetapir myocardial uptake was diffuse and uniform in all but the one AL amyloid subject who was in remission. On quantitative assessment, the ^{18}F-Florbetapir myocardial retention index, target-to-background ratio, and LV myocardium to liver SUV ratio were significantly higher in cardiac amyloid subjects than in control subjects. Although the overall myocardial retention index tended to be higher in AL than in ATTR 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 ATTR amyloidosis. The higher median ^{18}F-florbetapir retention index in AL amyloid subjects over ATTR subjects was suggestive of a greater avidity for the light chain than for transthyretin protein. Osborne et al. propose a clinically useful 20 minutes imaging protocol with ^{18}F-Florbetapir PET and a simple analysis method for the assessment of cardiac amyloidosis.[11] On visual assessment, they noted differences in heart activity between three healthy controls and eight patients with cardiac amyloid involvement in as little as 10 minutes after injection. However, even in healthy controls, some background ^{18}F-Florbetapir activity remained in the heart and never fully cleared even after 80 minutes of uptake, a possible limitation in identifying early-stage cardiac involvement. Also visual comparison of control and cardiac amyloid subjects was problematic at later time points.[11] While the investigators demonstrate potential for ^{18}F-Florbetapir imaging in the stratification of AL from ATTR amyloid subtypes using liver and cardiac time activity curves, incorporation of the same in the everyday clinic setting seems challenging.

For SPECT imaging, the most widely used tracers include ^{99m}Technetium-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) and ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP). ^{99m}Tc-labeled aprotinin is a sensitive and specific modality to image cardiac amyloidosis,[11] but is not widely used since the withdrawal of aprotinin from the market due to concerns over safety.[10,12] Planar imaging with the bone-seeking ^{99m}Tc-DPD is widely used to diagnose ATTR in Europe[5,6] but the isotope is not currently approved for use in the United States. ^{99m}Tc-DPD cardiac uptake is absent in unaffected control subjects, absent or weak in AL subjects, and strong in ATTR subjects.[13,14] For patients with an echocardiographic or MRI definite or highly probable diagnosis of cardiac amyloidosis, absent ^{99m}Tc-DPD cardiac uptake is almost pathognomonic of the AL subtype, while strong cardiac uptake along with attenuated bone uptake is almost diagnostic of the ATTR subtype. Mild-to-moderate cardiac activity can be seen with both subtypes.[14]

In the United States, another bone-seeking agent, ^{99m}Tc-PYP, which is FDA approved (for bone imaging, as an adjunct in the diagnosis of acute myocardial infarction or as blood pool imaging agent), is readily available and has been the preferred radiopharmaceutical for assessment of cardiac amyloidosis. The mechanism of myocardial transthyretin amyloid uptake of ^{99m}Tc-PYP and ^{99m}Tc-DPD is unclear but it has been suggested that calcium in amyloid deposits binds to phosphate in these radiotracers.[4] ^{99m}Tc-PYP imaging has also been used to diagnose acute myocardial infarction since it localizes to the infarcted area (also by binding to calcium deposits) allowing for positive imaging of infarcted myocardium.[15] In the present issue of the journal, Bokhari and colleagues from Columbia University Medical Center, NY (doi:10.1007/s12350-016-0610-4) share their experience toward standardizing a ^{99m}Tc-PYP imaging protocol from 104 scans obtained in 45 patients with ATTR cardiac amyloidosis. Cardiac amyloid was confirmed by endomyocardial biopsies in 82% (37/45) of patients, and in the remaining patients by histologic documentation of Congo red staining in at least one involved organ with echocardiography-based evidence of amyloid cardiomyopathy. Since myocardial infarctions are mostly localized and cardiac amyloid infiltration is diffuse, only images with diffuse uptake were included. They evaluate multiple scans obtained using different counts (750 vs 2000 K), times to acquisition (1 vs 2-4 hours), processing matrix (256 vs 128), and ^{99m}Tc-PYP doses (30, 25, 20, 15, and 10 mCi) to arrive at an optimal protocol. They used a

semiquantitative visual score (0 = no cardiac uptake, 1 = cardiac uptake less than ribs, 2 = cardiac uptake equal to ribs, 3 = cardiac uptake greater than ribs) to differentiate the AL (score 0, 1) from the ATTR subtype (score 2, 3). The optimal recommended protocol using 10 mCi ^{99m}Tc-PYP, scanning for 750 K counts at 1 hour and a 256 matrix, provided good to excellent image quality, low extracardiac activity, shortest overall study time, and lowest radiation exposure (3 vs 8-10 mSv). The proposed ^{99m}Tc-PYP quantitative methodology (heart-to-contralateral ratio) to diagnose ATTR was also relatively simple with 100% specificity and 97% sensitivity.

So how can nuclear imaging be incorporated in the diagnostic algorithm of cardiac amyloidosis? In the United States, the currently widely available tracers include ^{18}F-florbetapir and ^{99m}Tc-PYP. The pros of ^{18}F-florbetapir include its FDA approval (for imaging brain beta-amyloid plaque density in patients with cognitive decline), and its high diagnostic accuracy for ruling in cardiac involvement in the limited number of cardiac amyloidosis subjects studied. Its cons include reimbursement challenges by payers given its off-label use, and the somewhat limited availability of PET especially in smaller medical centers. For ^{99m}Tc-PYP, advantages include its FDA approval (for bone imaging, as an adjunct in the diagnosis of acute myocardial infarction or as blood pool imaging agent), its high diagnostic performance for the ATTR subtype, and its wide availability given access to gamma cameras even in small medical centers. ^{99m}Tc-PYP disadvantages include false positives in patients with prior myocardial infarction or cardiac contusions and the potential for false-negative scans in patients with early cardiac ATTR amyloidosis and in patients with AL cardiac amyloidosis if the diagnosis of amyloidosis has not been definitively made (i.e., subjects without histologic diagnosis and atypical echocardiographic and/or clinical findings). A reasonable approach proposed by Dorbala et al. would be to use ^{18}F-florbetapir as a cardiac amyloid-specific screening imaging test, which if positive can be followed by either a myocardial biopsy to confirm the diagnosis and for disease typing, since the imaging-based discrimination between amyloid subtypes is not reliable or by ^{99m}Tc-PYP imaging to confirm ATTR when suspicion of this subtype is high.[10] An alternative strategy if ^{18}F-florbetapir is unavailable would be starting with ^{99m}Tc-PYP imaging in patients with suspected ATTR. If the scan is positive, this confirms the diagnosis and if negative it suggests (but does not confirm) the AL subtype in patients with a firm clinical diagnosis of cardiac amyloidosis. In this scenario, a myocardial biopsy would be reserved to patients without a firm diagnosis of cardiac amyloidosis who have no or minimal ^{99m}Tc-PYP uptake.

What is needed to push the field further is data on the use of these agents for early diagnosis of cardiac amyloidosis which can help detect disease prior to its clinical manifestation. Development of tracers that are specific for the AL subtype of cardiac amyloidosis will help in confirming diagnosis without resorting to invasive procedures, therefore greatly simplifying the above-proposed algorithm. Finally, the use of imaging for treatment monitoring is an important area of research despite early data that suggest that serial ^{99m}Tc-PYP imaging may not be useful for quantification of amyloid burden over time at least in patients with advanced ATTR cardiac amyloidosis.[17] We therefore agree with Dorbala et al. and qualify their call that 'We've Only Just Begun.'[18]

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