The current status of quantitative SPECT/CT in the assessment of transthyretin cardiac amyloidosis

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Nuclear medicine bone scans differentiate ATTR cardiomyopathy (ATTR-CM) from light chain cardiac amyloidosis and other myocardial disorders, helping to make the diagnosis without biopsy. Standard bone scans are not absolutely quantitative, so are assessed by comparing the heart to other tissues. The standard visual scoring system compares heart to bone. This accurately diagnoses ATTR-CM and has been validated in a multicenter study, but has limitations. Semiquantitative techniques including heart/contralateral thorax (H/CL) and heart/whole body ratio (H/WB) improve on visual scoring but still rely on extracardiac sites as comparators. Absolute quantitation of myocardial uptake using quantitative SPECT should help overcome these shortcomings. In ATTR-CM, this technique is practical, accurately makes the diagnosis and provides information that is not identical to visual scores. However, more work needs to be done. The reproducibility in ATTR-CM must be tested. Larger studies need to be undertaken to determine whether quantitative SPECT measurements can assess prognosis, disease progression or treatment response. As ATTR-CM is relatively uncommon multicenter trials will help recruit enough subjects to answer these questions. Accurate measurement techniques are needed in ATTR-CM to enable appropriate use of proven therapy and to conduct trials of new therapeutic agents. Quantitative bone scans offer a promising avenue.

Key Words: Transthyretin cardiac amyloidosis • Bone scan • Quantitation

INTRODUCTION

Transthyretin (ATTR) cardiac amyloidosis is associated with heart failure.[1] Nuclear medicine bone scans differentiate ATTR cardiac amyloidosis from light chain (AL) cardiac amyloidosis and other myocardial disorders with increased left ventricular wall thickness.[2-4] In appropriately selected individuals, bone scans can diagnose ATTR cardiomyopathy (ATTR-CM) without endomyocardial biopsy.[1,5] The technetium 99m (Tc) labeled phosphate-based agents hydroxymethylene diphosphonate (HMDP), pyrophosphate (PYP) and 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) have equivalent diagnostic accuracy for detecting ATTR-CM,[2,6,7] though it is worth remembering that the images produced by these different agents are not identical.[8] Given recent developments in bone scan imaging technology it is timely to consider how best to report cardiac bone scans.

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VISUAL SCORING

Standard bone scans are not absolutely quantitative, so cardiac images are assessed using relative indices, with heart uptake being compared to other tissues. The most widely used index is a visual comparison of cardiac uptake to bone giving scores 0–3 with 0 representing no myocardial disease.[9] This accurately identifies ATTR-CM [9,10] and has been validated in a multicenter study.[2] But there are limitations. The bone that acts as the comparator has not been constant across reported studies, producing reporter and referrer confusion. This has been addressed in a recent expert consensus, with a comparison of myocardium to rib being defined as standard.[11] Although visual scores distinguish 2 groups with clearly different prognoses (those with ATTR-CM and those without), they have not proven useful in risk stratification of individuals with proven ATTR-CM.[10,12] Given that prognosis in wtATTR, the most common subtype of ATTR, is determined by the stage of cardiac involvement rather than the nature of extracardiac disease,[13] why isn't this reflected in the visual score?

ATTR is a systemic disease and abnormal protein is deposited at sites other than myocardium, so bone scan uptake can be seen at extracardiac sites. In ATTR related to genetic mutations (mATTR), the extracardiac sites are determined by the syndrome that accompanies the specific mutation, with neural involvement being common and preceding cardiac involvement in some subtypes.[14] In ATTR with normal wild type genotype (wtATTR), neural involvement is not typically part of the clinical syndrome. The increased incidence of carpal tunnel syndrome in wtATTR appears to relate to ATTR deposition in tenosynovial tissues.[15] Synovial deposition also probably plays a role in large joint arthropathy: individuals with wtATTR have an increased rate of knee and hip replacements.[16] Tendinopathy with ATTR deposition is associated with an increased risk of spontaneous biceps tendon rupture.[17] Skeletal muscle uptake can be intense with DPD,[18] but appears to be less marked with HMDP (personal observation) and is not a feature of PYP scans.[19] Bone scan uptake in fat is variably seen, partly because amyloid fat deposition varies between subtypes of amyloidosis: amyloid is present in abdominal fat biopsy in 84% of cardiac AL, 45% of mATTR-CM but only 15% of wtATTR-CM.[20] Deposition of ATTR occurs in the lungs and can cause bone scan uptake.[21] In wtATTR, unlike in AL, specific renal involvement with amyloid is uncommon.[22] Hepatic uptake can occur in mATTR [23] but is not a common feature of bone scans in wtATTR (personal observation).

In practice, the degree of apparent reduction in bone uptake, the main criterion used to distinguish grade 2 from grade 3 [11], might relate to having such intense cardiac uptake that activity is directed away from the skeleton, and hence represent severe myocardial disease. However, this is not the only possible explanation. Apparently, reduced skeletal uptake might also be because a high level of uptake at extracardiac disease sites has reduced availability of radiopharmaceutical for uptake in the skeleton. It could even relate to a thresholding issue—when there is intense extracardiac uptake (especially with intense musculotendinous uptake around shoulders and/or hips) the images may be thresholded to this intense uptake making the bones less discernible. This means that a patient may be allocated to grade 3 rather than 2 because of the degree of extracardiac disease rather than just the amount of uptake in the heart.

The mechanism by which bone scan radiopharmaceuticals are taken up and retained by the myocardium remains incompletely understood,[23] but it remains a reasonable hypothesis that more cardiac amyloid deposition will be associated with more bone scan uptake, that a greater amount of amyloid deposition is associated with a worse prognosis, and that changes in the amyloid burden can be assessed by changes in the amount of radiopharmaceutical uptake. The fact that that there is no difference in prognosis between visual grades 2 and 3 is disappointing, but is likely to be because the differentiation between these scores is determined by the amount of extracardiac ATTR deposition (which does not significantly affect prognosis) as well as by the amount of cardiac ATTR.

SEMIQUANTITATIVE INDICES

Attempts have been made to improve measurement of bone scan uptake with semiquantitative indices. Heart to contralateral thorax (H/CL) has been validated for 1 and 3 hour PYP scans in a multicenter study.[24] This study suggested H/CL has prognostic significance, however, there was only a small numerical difference between the cutoff value for diagnosis of ATTR and that related to poorer prognosis. For HMDP scans, Heart/Whole Body ratio (H/WB) improves on the visual score, and is more reliable than H/CL,[25] but its role in prognosis is not yet clear. Thus, semiquantitative techniques can improve on visual scores, but they still rely on extracardiac sites as comparators. This can be a problem when there is abnormal extracardiac uptake, whether this is caused by ATTR or other disease. For example, H/CL will be affected by uptake related to ATTR lung involvement, and with H/WB there can be error due to variation in musculoskeletal uptake. For example, wtATTR-CM tends to occur in older males

who are more likely to have intercurrent osteoblastic bone disease such as prostate cancer metastases, and the associated increased skeletal uptake causes an underestimate of H/WB compared to those with normal skeletons. The relative nature of these techniques also reduces accuracy in monitoring disease progression or treatment response due to variation in uptake in the comparator tissue over time—for example with prostate metastases skeletal uptake will vary with time depending on treatment—changing H/WB even when cardiac uptake is stable.

PET AND SPECT ABSOLUTE QUANTITATION

Absolute quantitation of myocardial uptake should help overcome these shortcomings. Quantitation can be achieved with PET, but to date the most commonly used PET bone scan agent, NaF, has not proven as useful in the assessment of cardiac ATTR as single-photon radiopharmaceuticals.[26] PET-based agents that image amyloid proteins can provide images of cardiac amyloid.[27] However, to date, studies using these agents are preliminary and have not yet provided information in ATTR-CM that has been shown to directly affect patient care, partly perhaps because PET is not as readily available as some other imaging techniques.

Another promising technique is quantitative SPECT which is now commercially available. The clinical adoption of this technique was initially limited by a number of technical challenges[28]. Phantom studies and technical advances have addressed many of these issues[29], and the technique is now making its way into clinical use. Quantitative SPECT images are reconstructed using commercially available software-incorporating CT-based attenuation correction, scatter correction and an appropriate iterative reconstruction technique. As with PET, the images represent parametric maps of radiopharmaceutical distribution with units of kBq/mL standardized to the time of injection, and can be corrected for injected dose and volume of distribution to give SUVs. Quantitative SPECT images can be displayed in conjunction with the CT component for anatomic localisation. In individuals without cardiac amyloidosis myocardial uptake is less intense than, or indistinguishable from blood pool on bone scan SPECT images.[30] VOIs can be drawn on the SPECT images, or on the CT images and then projected onto the SPECT images, allowing measurement of SUVs within various structures including myocardium, blood pool and individual bones.

Further assessment of cardiac disease burden can be undertaken by measuring cardiac metabolic activity (CMA) and cardiac metabolic volume (CMV) which can be calculated from quantitative SPECT images using standard algorithms that identify voxels with uptake above certain thresholds within a defined volume of interest using techniques initially developed for total lesion glycolysis (TLG) and metabolic tumor volume (MTV) in oncology (Figure 1). These measurements have proven useful in FDG PET assessment of cardiac sarcoidosis[31] and would appear to carry promise for measuring cardiac amyloid burden. CMA and MTV are most reliably calculated when cardiac uptake is high, and so hold promise in assessing patients with known ATTR based solely on their cardiac uptake, offering a technical solution to the previously discussed grade 2 versus 3 issue. When there is no (or very low grade) myocardial uptake these algorithms are less accurate in defining the myocardium, hence are likely to be less useful in making the diagnosis of ATTR-CM.

To date, few published studies have used quantitative SPECT in ATTR-CM. In a small single-center study using HMDP, quantitative SPECT derived myocardial SUVmax accurately differentiated ATTR-CM from other cardiac diseases and this measurement was found to be sufficiently robust that a reference range for individuals without cardiac involvement could be developed, against which range a single potentially affected

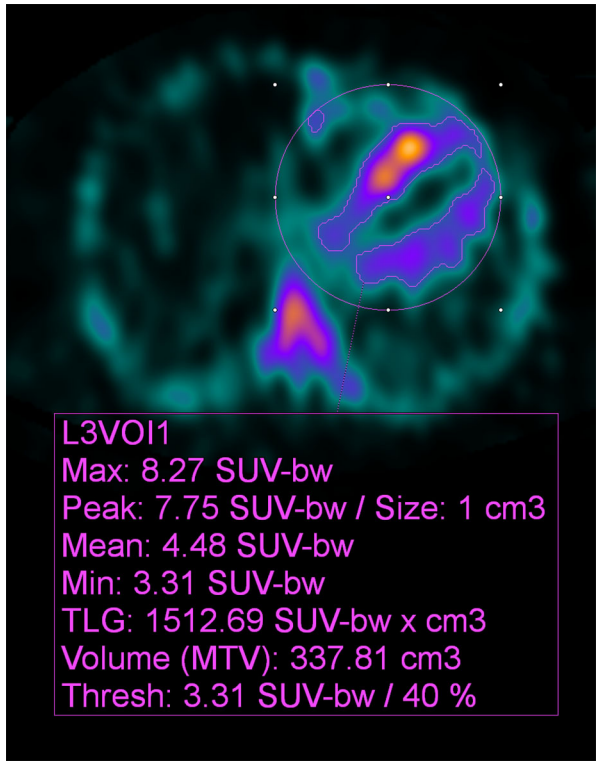

Figure 1. Transaxial quantitative SPECT image of the thorax showing sample measurements of myocardial uptake of HMDP (*TLG* total lesion glycoloysis = cardiac metabolic activity, *MTV* metabolic tumor volume = cardiac metabolic volume).

individual could be compared[30]. Caobelli et al. have now expanded on this preliminary work by showing that quantitative cardiac SPECT using DPD is practical, can make the diagnosis of ATTR-CM, and provides information that is not identical to visual score in grade 2 and 3 patients.[32]

THE FUTURE OF QUANTITATIVE BONE SCANS

More work needs to be done in this field. In quantitative SPECT, a regular QC process incorporating a NIST traceable calibration source can ensure measurement stability over time, and is a good first step in ensuring that different sites make equivalent measurements. It has also been proposed that quantitative SPECT should be subject to the same NEMA NU 2 QC process as PET.[33] If quantitative SPECT is to be used for progress assessment the reproducibility of measurements in individuals with ATTR-CM must be assessed. Larger clinical trials need to be undertaken to determine whether quantitative SPECT measurements can provide prognostic information in ATTR or play a role in assessing disease progression and treatment response. However, ATTR-CM is a relatively uncommon disease, so it is unlikely that a single site will rapidly obtain data from enough patients to conduct conclusive studies. Multicenter cooperative efforts are likely to be the best way to find answers to important clinical questions in ATTR-CM, including the role of quantitative SPECT.

Tafamidis has been proven to be efficacious in ATTR-CM [34] and treatments designed to reduce amyloid burden are in development. A recent Australian study looking at incidental cardiac uptake on bone scans performed for non-cardiac purposes suggested a prevalence of ATTR-CM of 4.2% in men aged 85 and over [35] confirming that ATTR-CM, and wtATTR-CM in particular, are not as uncommon as was previously believed, and are likely to be seen more frequently as the population ages. To meet the needs of these patients we need to develop readily accessible techniques that accurately identify these individuals in the community, and can assess their progress, to enable appropriate use of proven therapy and to assist in conducting dedicated trials of new pharmacological agents. Quantitative bone scans offer a promising avenue.

Disclosure

Dr. Ramsay acts as an unpaid advisor to Pfizer on cardiac imaging. He has no other potential conflicts of interest. Dr. Cuscaden has no conflicts of interest to declare.

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