Tc-99m-PYP imaging for cardiac amyloidosis: Defining the best protocol before the flood gates burst

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WHAT IS CARDIAC AMYLOIDOSIS AND WHY IS IT IMPORTANT TO MAKE A DIAGNOSIS?

Cardiac amyloidosis can be caused by deposition of immunoglobulin light chains produced by a clonal plasma cell disorder (AL) or liver produced transthyretin protein (ATTR). The most prevalent form of ATTR is the wild-type caused by age-related transthyretin misfolding (ATTRwt) with the autosomal dominant gene mutation variant being less common ($ATTR_v$). Since there are now effective treatments for ATTR-CA, early accurate diagnosis is key as treatment is more effective if started early in the natural history of the disease. Left untreated after diagnosis, survival for AL is < 6 months and 3-5 years for ATTR. To date, the diagnosis of cardiac amyloidosis continues to be made in patients with advanced disease. More needs to be done to improve awareness of its clinical manifestations and the potential of therapeutic intervention to improve prognosis.[1]

HOW IS A DIAGNOSIS OF CARDIAC AMYLOIDOSIS MADE?

Once ATTR-CA is suspected, a definitive diagnosis can usually be achieved on endomyocardial biopsy or non-invasively on bone scintigraphy with either Technetium-99m pyrophosphate (Tc-99m- PYP), Tc-99m-diphosphono-1,2-propanodicarboxylic acid (Tc-99m-DPD) or Tc-99m-hydroxymethylene diphosphonate (Tc-99m-HMDP) in the absence of abnormal light chains on serum free light chain assay and immunofixation of the serum and urine.[2] The exact molecular mechanism underlying myocardial transthyretin amyloid uptake of ^{99m}Tc-labeled bone agents is not known but it has been hypothesized to be due to binding of calcium in transthyretin amyloid fibrils to the phosphate domains in these radiotracers. Although echocardiography and cardiac magnetic resonance imaging maybe suggestive of CA, endomyocardial biopsy or Tc-99m bone scintigraphy are required to make a diagnosis.

HOW ACCURATE IS TC-99M IMAGING FOR CA?

In 2002, Puille et al showed that whole body ^{99m}Tc-DPD scintigraphy was a valuable diagnostic aid to evaluate the severity of ATTR-CA and the risk of associated complications[3]. In 2005, Perugini et al showed that whole body ^{99m}Tc-DPD scintigraphy was 100% sensitive and 100% specific for diagnosing ATTR-CA[4]. ^{99m}Tc-DPD is not approved in the USA; however, ^{99m}Tc-PYP is readily available. ^{99m}Tc-PYP is currently approved for blood pool imaging (GI bleed and gated cardiac blood pool studies), cardiac imaging (detection of acute MI), and bone scintigraphy. In the late 70's and early 80's, ^{99m}Tc-PYP was employed to diagnose myocardial infarction. In early 80's bone scintigraphy with ^{99m}Tc-PYP identified cardiac amyloid

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in single case reports and small cohort studies. Some of the initial single-center cohort studies demonstrated variable utility. In 2013, Bokhari et al. used ^{99m}Tc-PYP planar chest imaging instead of whole body imaging and demonstrated high sensitivity (97%) and specificity (100%) for diagnosing ATTR-CA[5].

HOW STANDARDIZED IS TC-99M IMAGING AND INTERPRETATION FOR CA?

The variables that must be considered in performing and interpreting 99mTc-PYP bone tracer cardiac scintigraphy studies are listed in Table 1. Detailed recommendations for these variables have not been made by professional medical societies and there is great variability in the published literature and in clinical practice. The 99mTc-PYP dose in published studies has varied from 10 to 25 mCi and the most recent ASNC guidelines recommend 10-20 mCi. Once injected, 99mTc-PYP is cleared from the blood pool at a variable rate that is dependent, in part, on bone metabolism and renal function. High bone metabolism and normal renal function results in rapid clearance. High blood pool activity may influence semi-quantitative and quantitative interpretation and given the poor spatial resolution of SPECT it is often difficult to discriminate between blood pool and uptake in adjacent myocardial walls. The injection to scan time has varied from 1 to 3 hours and the ASNC Practice Points recommend planar imaging at 1 hour with SPECT or planar imaging optional at 3 hours. Early imaging is more convenient for patients and laboratories, but may negatively influence overall study quality and accuracy due to persistent blood pool. Approximately half of sites perform a 1-hour scan and if excess blood pool activity is seen, then a delayed 3-hour scan is performed. This practice requires review of the images before the patient leaves the imaging laboratory in case blood pool is present and delayed images are needed. The remaining sites perform a delayed 2 or 3-hour planar and/or SPECT scan.

Table 1. Consideration for optimal 99mTc-PYP imaging for cardiac amyloidosis

1.Tc-99m PYP dose
2. Time from injection to imaging
3. Planar vs SPECT
4. Chest vs whole body
5. With or without CT attenuation correction
6. Interpretation
Quantitative Heart to Contralateral lung (H/CL) ratio on planar
Semi-Quantitative on SPECT and planar

Both planar and SPECT acquisition using large or small field-of-view systems may be performed. The majority of sites perform planar imaging of the chest (anterior and lateral views using a 90-degree detector configuration). A limited number of sites perform whole body imaging. Dedicated small field-of-view cardiac cameras may not acquire the complete chest to allow good comparison to rib uptake or perform heart to contralateral ratio (H/CL) quantitative analysis. Positioning is critical. SPECT imaging is performed using 360 or 180-degree acquisition and only a limited number of sites use CT attenuation correction (CTAC). Some sites perform SPECT imaging alone.

Image interpretation may use a semi-quantitative method with a visual score on planar or SPECT imaging comparing uptake by the myocardium to bone and typically is graded 0 to 3 (grade 0: absent myocardial uptake, grade 1: myocardium< rib uptake, grade 2: myocardium = rib uptake, grade 3 myocardium: > rib uptake). Quantitative H/CL on planar images is measured by drawing a region of interest (ROI) over the left ventricle and the same or similar sized ROI over the contralateral chest.[6] The size of the region, use of the same region moved from the heart to the opposite lung versus independently drawn regions, and whether to include or exclude right ventricle is not standardized. Similarly, the cutoff values for H/CL have not been standardized. Despite failure to standardize these techniques published reports have demonstrated high sensitivity (97%) and specificity (100%) for diagnosing ATTR-CA. Large number of sites also perform SPECT imaging and use a similar semi-quantitative visual score and grading as in planar imaging. When CTAC is used, fused images allow better delineation between persistent blood pool activity and uptake in the myocardium that maybe difficult to identify on planar or SPECT. In addition, these images may identify abnormal bone uptake and the CTAC maps provide information on boney abnormalities and lung, large vessel and cardiac abnormalities.

WHAT DID WE LEARN FROM THE CURRENT PUBLICATIONS?

In this issue, we have 2 papers that attempted to address some of the options listed in Table 1, but unfortunately fall short in some aspects. Régis et al injected a dose of 20-25 mCi 99mTc-PYP in 122 patients with clinical suspicion of CA and followed some of the ASNC Practice Point recommendations: planar and SPECT images at 1 hour on which they calculated a planar H/CL ratio and an additional SPECT at 3 hours with semi-quantitative visual scoring on the 1 and 3 hour SPECT studies. (NEED REFERENCE

FROM JOURNAL). Planar images were not acquired at 3 hours and CTAC was done and used for localization but further details on the benefits of CTAC were not provided. Endomyocardial biopsy or clinical conformation of the presence or absence of ATTR-CA was not available in all cases. On the 1 hour planar images the following cutoffs for the diagnosis of CA were used: An H/CL ratio < 1.00 as negative. 1.00 to < 1.5 as equivocal and > 1.5 as positive.

What did they find? They found that using the 1-hour H/CL ratio with the above cutoffs, 81 patients (66%) had equivocal studies whereas with semi-quantitative SPECT only 10 patients (8%) were equivocal and there was 99% concordance between 1 and 3 hour SPECT acquisition. They concluded that the 1-hour planar H/CL ratio approach resulted in a high proportion of equivocal studies and that semi-quantitative SPECT at 1 or 3 hours produced fewer equivocal results. The reality is that the ASNC Practice Points rely on both the quantitative H/CL ratio and the semi-quantitative visual scoring with an equivocal study having a semi-quantitative visual score of 1 or H/CL ratio 1-1.5. There are many sites using an H/CL ratio of < 1.3 at 1 hour as negative and ratio of 1.3 to < 1.5 as equivocal. A high proportion of Régis et al. equivocal studies would have been negative if a ratio of < 1.3 was graded as negative. They concluded that SPECT imaging at 3 hours made image interpretation easier and more reliable due to better blood pool clearance. What about the value of CTAC? If you are doing SPECT at 1 hour or 3 hours, why wouldn't you do a simple anterior planar image to get the ratio?

Sperry et al. have a more balanced study design and imaged 109 consecutive patients with planar and SPECT/CT at 1 and 3 hours after injecting 15 ± 20% mCi of 99mTc-PYP. (NEED REFERENCE FROM JOURNAL). They found a very strong correlation between 1-hour and 3-hour planar H/CL ratios. They used a planar H/CL > 1.5 at 1 hour and > 1.3 at 3 hours as the cutoff for a positive study. In 17 patients (16%) there was a discordance between planar image interpretation (based upon semi quantitative score and H/CL ratio) and myocardial localization of radiotracer on SPECT/CT. SPECT/CT was very useful in separating myocardial uptake from persistent blood pool activity. The majority of discordant findings were a result of indeterminate planar results being reclassified based on SPECT/CT. The pattern of SPECT/CT uptake was identical at 1 and 3 hours in all cases. They concluded that SPECT/CT should be obtained in addition to planar images when performing nuclear scintigraphy for detection of cardiac amyloidosis and that a 1 hour planar and SPECT/CT appears optimal in terms of patient convenience and laboratory efficiency. They also observed low interobserver and intraobserver variability at 1 hour and 3 hours on H/CL ratios. Patient serum creatinine was not associated with differences at1 hour or 3-hour H/CL ratios in the entire cohort.

In a world without restrictions on 99mTc-PYP imaging for CA, the lowest possible dose of 99mTc-PYP would be injected and planar and SPECT/CT images acquired at 1 and 3 hours with planar whole body images at 3 hours. Interpretation would use H/CL on planar, semi-quantitative on planar and SPECT, CT for localization and separation of myocardium from blood pool, the whole body and SPECT bone images would be interpreted for non-cardiac bony abnormalities and the CT to further clarify any non-cardiac bony abnormalities and to look for coronary calcium, lung nodules, etc. Unfortunately, we live in a world with restrictions. Restrictions due to the patience of the patient; the need to reduce radiation exposure; and inefficiency of utilizing a camera for 3-5 hours for 1 study.

Since current imaging guidelines and practice points do not provide detailed recommendations down to this level of detail, Imaging Laboratories are left on their own to select the parameters listed in Table 1. They currently use imaging protocols at different time points and either planar, SPECT (with or without CT), or both imaging modalities. Even with the limitations of not having a gold standard for CA, what have we learned from these 2 papers? We learned that planar imaging should be performed to obtain a quantitative H/CL ratio. SPECT is needed for localization and semi-quantitative scoring and that SPECT/CT assists with localization in a small but important number of studies. Both of these studies are reassuring as they confirm that a 1-hour imaging protocol is equivalent to 3-hour protocol when incorporating SPECT/CT images. The radiotracer is rapidly taken up by the myocardium and bone, there is a relative increase in bone uptake over time and a peak in myocardial uptake at 1 hour followed by a slow decline. Multiple studies have shown that around 15%-20% patients have excess blood pool activity at 1-hour planar and SPECT images. In these patients a delayed 3-hour scan helps in differentiating between blood pool and myocardial uptake. Imaging at 1 hour is feasible but image review should be performed prior to letting the patient leave the laboratory.

What didn't we learn? We didn't learn the optimal 99mTc-PYP dose; the true accuracy of these studies at any imaging time, method of acquisition or analysis for diagnosis of CA or the real value of CTAC. We didn't learn the optimal cutoff values for H/CL. Updated guidelines incorporating the most current data are needed to help standardize the growing number of studies being performed for diagnosis of CA.

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