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Interpretation and Reporting of Cardiac Scintigraphy with Bone-Avid Tracers in Suspected Transthyretin Cardiac Amyloidosis (ATTR-CA)

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INTRODUCTION

Cardiac scintigraphy with bone-avid tracers, 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (Tc-99m DPD), 99mTc-pyrophosphate (Tc-99m PYP), and 99mTc-hydroxymethylene diphosphonate (Tc-99m HMDP or Tc-99m HDP), is the cornerstone of an imaging-based diagnostic pathway for accurate, non-invasive confirmation of transthyretin cardiac amyloidosis (ATTR-CA). While imaging protocols previously emphasized planar imaging and computation of the heart-to-contralateral lung (H/CL) ratio on anterior planar view for confirmatory diagnosis,[1] recent recommendations recognize findings on planar imaging to result in incorrect image interpretation and highlight tomographic evaluation on SPECT or SPECT/CT to be the diagnostic standard.[2,3] Tomographic imaging allows direct visualization of tracer uptake in the myocardium and avoids interpretations.

While current guidelines recommend imaging 3-hours after tracer injection, there is increasing evidence of similar diagnostic accuracy when imaging is performed at 1 or 3 hours after tracer injection.[4,5] If imaging is performed at 1 hour after tracer injection and excessive blood pool activity limits accurate assessment of myocardial tracer uptake, then repeat imaging at 3-hours should be performed.

Myocardial tracer uptake can be seen in some cases with light chain amyloidosis (AL-CA).[6] Thus, it is imperative to recommend assessment of plasma cell dyscrasia when reporting imaging findings (whether suggestive or not suggestive of ATTR-CA). This can be done by quantitation of serum kappa and lambda light chains and by performing serum and urine immunofixation electrophoresis.

STEPWISE APPROACH TO INTERPRETATION OF CARDIAC SCINTIGRAPHY WITH BONE-AVID TRACERS

Step 1: Confirmation of myocardial tracer uptake

- Assess cardiac or chest SPECT reconstruction to confirm myocardial uptake **(Figure 1)**[7]
- Differentiate blood pool activity from myocardial tracer uptake **(Figure 2)**
- If myocardial tracer uptake is confirmed on SPECT, then proceed to Step 2.

Planar imaging and H/CL are insufficient to diagnose ATTR-CA

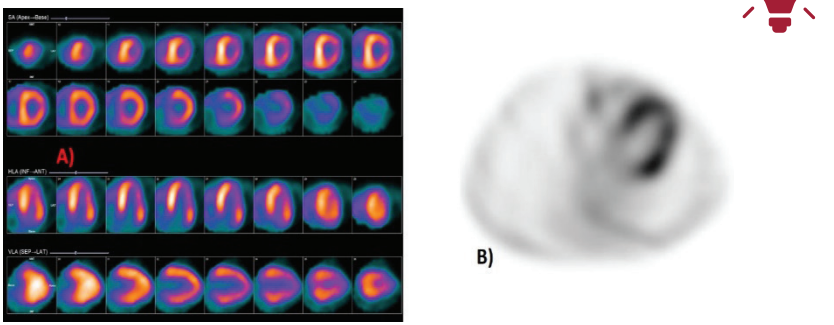

Figure 1: A) Cardiac and B) Chest SPECT confirming tracer uptake in the myocardium.

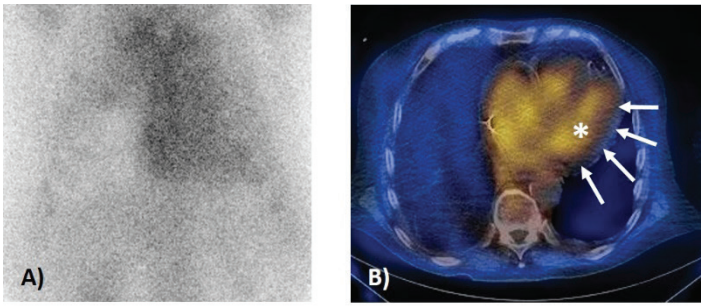

Figure 2: A) Anterior planar image depicting tracer activity in the heart, which is (B) confirmed to be excessive blood pool activity on SPECT/CT. * Depicts blood pool activity, and arrows delineate the myocardium.

Step 2: Semi-quantitative visual score (Perugini Score) (Figure 3)

Grade 0: No myocardial uptake and normal bone uptake
Grade 1: Myocardial uptake less than rib uptake
Grade 2: Myocardial uptake equal to rib uptake
Grade 3: Myocardial update greater than rib uptake

Grade 0 Grade 1 Grade 2 Grade 3

Figure 3: Semi-quantitative visual grades on chest SPECT reconstruction.

- **Grade 0** is not consistent with ATTR-CA. If AL-CA is excluded, further evaluation, including endomyocardial biopsy, in patients with high suspicion of CA may be required.[6]
- **Grade 1** uptake can be observed in AL-CA or may reflect early ATTR-CA. Further evaluation, including endomyocardial biopsy should be considered to clarify the diagnosis in patients with high suspicion of CA.
- **Grade 2 or Grade 3** uptake is consistent with ATTR-CA, AFTER exclusion of plasma cell dyscrasia, as any degree of uptake can be seen with AL-CA.

Step 3 (Optional): Quantitation of myocardial tracer uptake

Quantitation of myocardial tracer uptake by determination of H/CL ratio (**Figure 4**) was previously regarded as a diagnostic tool to confirm ATTR-CA and differentiate it from AL-CA. Recent evidence suggests H/CL ratio to be inadequate for diagnosis of ATTR-CA, and as such should not be employed for that purpose. However, quantitation of myocardial tracer uptake may have value in assessing status of disease and may be performed as an optional step, but should NOT be used to confirm or refute a diagnosis of ATTR-CA.

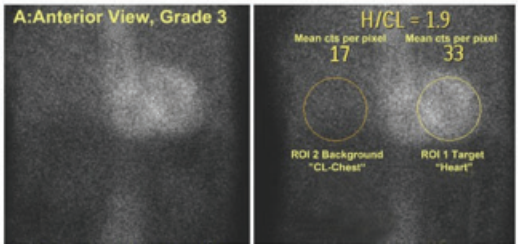

Figure 4: Quantitation of myocardial tracer uptake (optional).

Notes:

- Recent literature de-emphasizes the use of the H/CL ratio for diagnosis.[8] Diagnosis should only be made based on the visual grade from SPECT or SPECT/CT images.
- Observations that require careful consideration prior to interpreting and reporting these studies:
  a. Excess blood pool activity on planar and SPECT images being interpreted as positive scans.
  b. Missed diagnosis of AL amyloidosis, if serum free light chain and serum and urine immunofixation electrophoresis studies are not recommended in the final report.
  c. Tc-99m PYP/DPD/HMDP uptake can be observed in cases of myocardial injury including pericarditis, myocardial infarction seen as regional uptake and chemotherapy or drug associated myocardial toxicity.
  d. Normal physiologic uptake of Tc-99m bone tracers can be seen in breast tissue. Degenerative processes in the thoracic spine can account for extra cardiac activity. Parenchymal lung changes can show Tc-99m bone tracer uptake on planar images, and objects located anterior to the myocardium can attenuate uptake.

TABLE 1. SOURCES OF FALSE INTERPRETATIONS ON SPECT RECONSTRUCTION OF CARDIAC SCINTIGRAPHY WITH BONE-AVID TRACERS

False Positive Studies	False Negative Studies
Excessive blood pool activity	Genetic mutations with low sensitivity for Tc-99m bone tracers (Ser77Tyr, Phe64Leu)
Recent myocardial injury (pericarditis, myocardial infarction)	Early disease
Breast tissue uptake	Tracer washout at 3 hours
Parenchymal lung changes	ATTR-CA with only Type B fibrils
Rib fracture	
Metastatic lesions	
Hydroxychloroquine toxicity	
Exclusion of monoclonal proteins is required for a definitive diagnosis to avoid misdiagnosis and inappropriate treatment. **False interpretations are increased if planar imaging is used to determine myocardial tracer uptake.**	

STANDARDIZED REPORTING OF CARDIAC SCINTIGRAPHY with BONE-AVID TRACERS

Parameter	Elements
Demographics	Patient name, age, sex, reason for test, date of study, prior imaging, biopsy results, if available
Methods	Imaging technique, radiotracer dose, mode of administration, interval between injection and scan, scan technique (SPECT, Planar - optional)
Findings	Image quality, visual scan interpretation, semi-quantitative interpretation in relation to rib uptake
Ancillary Findings	Whole-body imaging if planar whole-body images are acquired (optional); Interpret CT for attenuation correction if SPECT/CT scanners are used (recommended)
Conclusions	1. Summarize interpretation of imaging findings: a. Negative for myocardial tracer uptake b. Positive for myocardial tracer uptake 2. State whether the imaging findings are suggestive for ATTR-CA if results for ruling out light chain disease are available; if not, then, 3. Recommend to rule out light chain amyloidosis by quantitation of serum kappa and lambda light chains and by performing serum and urine immunofixation electrophoresis **Negative:** No myocardial tracer uptake and semi-quantitative visual Grade 0 in patients with low suspicion of disease **Positive:** If myocardial uptake of Tc-99m PYP/DPD/HMDP (HDP) is visually confirmed[6] **Suggestive of ATTR-CA:** Presence of myocardial tracer uptake on cardiac SPECT and AL amyloidosis has been ruled out.

Adapted from: References 2, and 3, and the ASNC Practice Points https://www.asnc.org//Files/Guidelines%20and%20Quality/19110%202021%20ASNC%20Amyloid%20Practice%20Points%20PYP-MAY19-2022.pdf

Note: Tc-99m PYP, Tc-99m DPD and Tc-99m HMDP (HDP) are not FDA approved for diagnosis of ATTR-CA.

EXAMPLES OF CARDIAC SCINTIGRAPHY WITH BONE-AVID TRACERS REPORTING ATTR-CA

Tc-99m PYP Imaging Report; Jamieson Bourque, MD, MS, University of Virginia, Charlottesville, VA.

Interpretation Summary

- Myocardial uptake was negative with visual grade of 0.
- Findings are not suggestive of cardiac ATTR amyloidosis.

Evaluation for AL amyloidosis by serum free light chains, serum and urine immunofixation is recommended in all patients undergoing Tc-99m PYP imaging.

Results should be interpreted in the context of prior evaluation and referral to a hematologist or amyloidosis expert is recommended if either: a) Recommended echo/CMR is strongly suggestive of cardiac amyloidosis and Tc-99m PYP is not suggestive or equivocal and/or b) serum free light chains are abnormal or equivocal.

I have personally reviewed the nuclear images and agree with the documented findings and interpretation. I have edited the report as appropriate.

Jamieson Bourque, MD

ATTR Findings

Imaging Protocol Imaging was performed one hour and three hours after injection of 19.5 mCi of Tc-99m PYP. Tracer was injected into the Rt antecubital vein. Planar imaging was performed in the anterior, LAO and LLAT views. Single-photon emission computed tomography (SPECT) was subsequently performed. Planar and SPECT results were visually assessed. A quantitative heart-to-contralateral lung (H/CL) ratio was derived from the planar images. SPECT images were assessed for regional uptake and to differentiate myocardial uptake from blood pool and underlying rib activity.

Clinical Data The study was performed to assess for ATTR cardiac amyloid.

Imaging Results Myocardial uptake was negative. The visual grade was 0. The quantitative H/CL ratio is not reported given the visual grade of 0.

Conclusion Findings are not suggestive of cardiac ATTR amyloidosis.

Of note, a negative or positive Tc-99m PYP does not exclude AL amyloid. In addition, equivocal results could represent AL amyloid or early TTR amyloid.

Signed

Tc-99m HDP Imaging Report:
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PROCEDURE TYPE: Resting technetium-99m HDP SPECT/CT

INDICATION: Cardiac amyloidosis (E 85.4)

CLINICAL HISTORY: 83-year-old female with recurrent heart failure admissions, severe left ventricular hypertrophy and apical sparing pattern on echocardiogram, referred for a HDP scan for assessment of ATTR-CA.

SPECT IMAGING PROTOCOL: Resting myocardial imaging was performed 1-hour following intravenous injection of 13.0 mCi of technetium-99m HDP. After acquisition of initial planar images in the anterior, left anterior oblique and the left lateral positions, tomographic imaging was performed.

Attenuation correction: CT

Image quality: Adequate.

IMAGE INTERPRETATION: Planar images showed prominent cardiac uptake of technetium-99m HDP, at 1 hour after injection of the tracer. Tomographic reconstruction of the images confirmed diffuse myocardial uptake, with no significant blood pool activity. Semiquantitative visual score of the radioisotope uptake in the myocardium is Grade 3 at 1 hour after tracer injection. The heart-to-contralateral lung (H/CL) ratio was approximately 1.7.

Low dose CT performed for attenuation correction, depicts presence of moderate coronary artery calcification in a multivessel distribution.

Extracardiac UPTAKE: No significant extracardiac uptake.

CONCLUSIONS

1. This is a positive study. There is significant uptake of technetium-99m HDP in the myocardium.
2. Recommend assessment of paraproteinemia to rule out light-chain amyloidosis.
3. Consider genetic testing.
4. Calcific coronary artery disease is noted in a multivessel distribution, on low dose CT performed for attenuation correction.

Saurabh Malhotra, MD, MPH, FACC, FASNC

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