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The Canadian Association of Nuclear Medicine

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CANM Cardiac Amyloid PYP Imaging Guidelines

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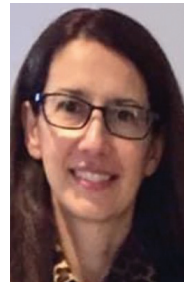


INTRODUCTION

Amyloidosis is a group of diseases in which normal or abnormal proteins breakdowns, known as amyloid fibrils, build up in tissue. Physicians have known about the anatomic and clinical effects of these proteins deposition for many centuries. Such have been described since at least 1639 when Nicolao Fontano reported a case of sago spleen in the journal Responsionum & Curationum Medicinalium. The term "amyloid" was coined in 1838 by Matthias Schleiden, a German botanist, to describe a normal amylaceous constituent of plants. There are about 30 different known types of amyloidosis related to genetic or acquired specific protein misfoldings. They are grouped into localized and systemic forms and their symptomatology depends on which organs are affected. The four most common systemic amyloidosis are the light chain (AL), inflammatory (AA), dialysis (Aβ2M), and hereditary and old age (ATTRwt) types.

The incidence of AL amyloidosis is about 3–13 per million people per year and of AA amyloidosis about 2 per million people per year with the majority onsetting between 55 and 60 years old. Diagnosis may be suspected when protein is found in the urine, organ enlargement is present, or polyneuropathy develops and is confirmed by tissue biopsy. Treatment is geared towards decreasing the amount of the involved protein. Without treatment the prognosis is quite bleak and the average life expectancy between 6 to 48 months.

CARDIAC AMYLOIDOSIS

Cardiac amyloidosis also known as stiff heart syndrome is a form of restrictive infiltrative cardiomyopathy that confers significant mortality. It can be inherited or familial. It is rare before the age of 40. While its incidence is similar in men and women, its prevalence is higher in men than in women. Accurate estimates of the incidence and prevalence of cardiac amyloidosis are lacking. Improved awareness and advances in imaging over the past 3 decades have shown that it is substantially underdiagnosed.

The vast majority of cardiac amyloidosis are of the acquired monoclonal immunoglobulin light chain (AL) type or the familial or mutation transthyretin (ATTR) type. Light chain (AL) amyloidosis refers to the misfolding of monoclonal light chains produced by plasma cells that deposit in organs. In transthyretin amyloidosis, the transthyretin protein produced by the liver which transport thyroxine and retinol dissociates into monomers and misfolds with monomers and dimers and protofilaments depositing in various organs. The heart might be affected in up to 50 percent of patients with systemic light chain (AL) amyloidosis and ATTRwt might account for as many as 30% of patients with heart failure. The accumulation of amyloid fibrils in the myocardial interstitium increases the thickness and mass of the ventricular wall and results in progressive diastolic and systolic dysfunction. Amyloid deposition in the heart may occur in the atria, ventricles, perivascular space, valves and conduction system.

DIAGNOSIS OF CARDIAC AMYLOID

Cardiac symptomatology is nonspecific, and patients often present with heart failure such as dyspnea and leg edema. The key clinical features which heighten the suspicion of cardiac amyloid include without being limited to: established AL or ATTR diagnosis in non-cardiac organ, carpal tunnel syndrome, nephrotic syndrome, peripheral sensorimotor neuropathy and/or neuronal autonomic dysfunction, unexplained increased left ventricular wall thickness, preserved left ventricular ejection fraction with low flow aortic gradient aortic stenosis.

Challenges for the clinical diagnosis of cardiac amyloidosis are related to the relative rarity of the disease, the different potential origins of myocardial hypertrophy, the unfamiliarity with proper diagnostic algorithms, and the absence of definitive treatment.

The formal diagnosis of cardiac amyloid requires histological confirmation with an endomyocardial biopsy that demonstrates apple-green birefringence when stained with sulfate Alcian Blue or Congo Red and viewed with a polarizing microscope. Myocardial biopsy is invasive and although the risks of serious complications is limited it is performed in few centers. A combination of clinical, laboratory, electrocardiographic and imaging methods is commonly used instead.

In a patient with a known plasma cell dyscrasia and AL amyloidosis the combination of serum BNP (B-type natriuretic peptide) and troponin can be useful to stratify prognosis and guide treatment strategies. Low voltage, axis deviation, left ventricular hypertrophy criteria, pseudo infarction pattern T waves abnormalities, atrial fibrillation and other rhythm disturbances can be seen on the ECG

Albeit not necessarily specific, the echocardiographic hallmarks of cardiac amyloid include ventricular wall thickness, small left ventricular chamber volume, valve thickening, atrial enlargement and signs of elevated filling pressures with a restrictive diastolic filling. Speckle-tracking echocardiography and left ventricular longitudinal strain measurement by tissue Doppler have emerged as useful clinical tools for the identification of cardiac amyloidosis to differentiate the different forms of ventricular wall thickening. The relative preservation of apical strain and the segmental strain bulls-eye pattern can be a good indicator of cardiac amyloidosis.

Cardiovascular Magnetic Resonance has the intrinsic ability to characterize tissue particularly when enhance with gadolinium-based contrast agents. Late gadolinium enhancement of thickened left ventricular walls and documentation of expansion of the extracellular space can contribute to the diagnosis, monitor the amyloid fibrils load and treatment response.

Molecular Imaging of cardiac amyloid with PET amyloid tracers such as 18F-florbetapir, 18F-florbetaben and 11C-Pittsburgh B radiophar-maceuticals has been used to image and quantitate amyloid deposits in the heart. They appear to have high sensitivity and specificity. They are not widely available and expensive. Sympathetic denervation in cardiac amyloidosis has been demonstrated with Metaiodobenzylguanidine (MIBG) SPECT in patients with ATTR. It is an indirect nonspecific imaging marker and it is not recommended for clinical use.

CARDIAC AMYLOID IMAGING WITH BONES TRACERS – PYROPHOSPHATE

Pyrophosphate is a ubiquitous metabolic byproduct of many intracellular processes found in most cells. Pyrophosphate acts as a potent inhibitor of calcification; it antagonizes the ability of inorganic phosphate to crystallize with calcium to form hydroxyapatite by occupying some of the inorganic phosphate sites on the surface of nascent growing hydroxyapatite crystals.

Radiolabeled biphosphonate derivatives such as ^{99m}Tc-bisphosphonate complexes, ^{99m}Tc-methylenediphosphonate (^{99m}Tc-MDP), and ^{99m}Tc-hydroxymethylenediphosphonate (^{99m}Tc-HMDP, are among avid bone seeking radiopharmaceuticals that have been used for many decades in nuclear medicine. They are all related to pyrophosphate binding to nascent hydroxyapatite crystals and reflecting calcium deposits and bone turnover. In soft tissues, their accumulation is thought to result from absorption on calcium salt surface.

Over the past decades, different bone tracers including 99mTcpyrophosphate (^{99m}Tc-PYP), ^{99m}Tc- HMDP) , and ^{99m}Tc-3,3- diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), have been used for the imaging of cardiac amyloidosis with ^{99m}TC PYP being the only compound approved by Health Canada for clinical use.

In a seminal article published in 1982 already, Wizenberg et al described the value of positive myocardial technetium-99m-pyrophosphate scintigraphy in the noninvasive diagnosis of cardiac

amyloidosis. Falling into desuetude largely because of the absence of therapies cardiac nuclear imaging with PYP has witnessed a true renaissance with the emergence of new therapies.

In cardiac amyloidosis, Tc-99m pyrophosphate binds to microcalcifications associated with amyloid deposits in ATTR with high affinity, allowing early diagnosis of ATTR cardiac amyloidosis. Because it shows minimal affinity for amyloid deposits in AL cardiac amyloidosis, it allows distinction between the two types.

In addition to its high sensitivity and specificity above 90%, quantitative assessment of Tc-99mpyrrophospate uptake in ATTR cardiac amyloid disease uptake provides additional prognostic information on major adverse cardiac event (MACE)–free survival, increased acute heart failure, and mortality

PATIENTS SELECTION

Nuclear cardiac imaging with Tc-99m pyrophosphate is currently indicated in the following groups of patients:

- Individuals with heart failure and unexplained increase in left ventricular wall thickness.
- African-Americans/Canadians over the age of 60 years with heart failure, unexplained or with increased left ventricular wall thickness (>12 mm).
- Individuals over the age of 60 years with unexplained heart failure and preserved left ventricular ejection fraction.
- Individuals, especially elderly males, with unexplained neuropathy, bilateral carpal tunnel syndrome or atrial arrhythmias and signs/symptoms of heart failure.
- Evaluation of cardiac involvement in individuals with known or suspected familial amyloidosis.
- Individuals whose findings are suspicious for cardiac amyloidosis on cardiac magnetic resonance or echocardiography.

SCINTIGRAPHIC PROCEDURE

Considerations

Planar pyrophosphate imaging is simple and rapid to perform. Visual interpretation and quantitation of tracer uptake is straightforward. It has been proven useful for the identification of ATTR cardiac amyloidosis with sensitivity and specificity above 90%.

However planar images for the diagnosis of cardiac amyloidosis have limitations. Notably:

a. They only allow a visual assessment and quantitative planar quantification of tracer uptake

b. They do not define regional differences in myocardial tracer deposition.

c. They do not account for tracer uptake unrelated to amyloidosis: calcified valves, mitral annulus calcification, calcified thrombus, pericardial calcification.

d. They may be impacted by tracer uptake in skeleton and blood pool activity.

SPECT imaging, particularly with CT attenuation and anatomic mapping, overcomes these limitations and determines the exact localization of tracer uptake. SPECT and particularly SPECT/CT images allow a more quantitative tracer uptake evaluation, the generation of polar maps of raw counts and the determination of relative tracer intensity. Apical sparing is important to detect as it impacts prognosis. Higher apical sparing ratios have been shown to be associated with a significantly better survival.

Based on our personal experience and the expert consensus recommendation for currently available guidelines (ASNC, EANM, SNMMI) we recommend the following, acquisition, processing and interpretation for the performance of Tc-99m-pyrrophosphate scintigraphic studies

Acquisition Procedure

Procedure	**Parameters**
Patient Preparation	None; no fasting required
Radiopharmaceutical	10-20 mCi of Tc-99m-Pyrrophosphate with dose gently guidelines in pediatric population
Administration	Intravenous injection
Time between injection and imaging	1 hr. for planar and SPECT/(CT) and delayed planar (and SPECT/(CT)) if needed and/or persistent blood pool activity
IMAGING PARAMETERS	
Collimators	Low Energy, high resolution
Energy Window	140 keV with 15-20% window
Matrix	64 x 64 minimum
Pixel Size	3.5 – 6.5 mm
Patient Position	Supine or sitting depending on the type of cameras used; arms above shoulders or supported
Field of view	At least cardiac or chest with optional whole body planar
PLANAR IMAGING PARAMETERS	
Views	Anterior, lateral and left anterior oblique
Image duration (count based)	750,000 counts
Magnification if needed	1.46
SPECT PARAMETERS	
Angular range	360 degrees
Detector configuration	180 degrees
ECG Gating	none
Views per detector	40
Time per stop	20 seconds
Magnification	1.0
Reconstruction	Filtered back projection or iterative reconstruction
(CT PARAMETERS)	
Equipment/Vendor based	CT for attenuation correction & anatomic mapping. Low-dose CT transmission scan (10 mA, 120 kVp, free tidal breathing) over the heart

Images Processing-Interpretation

On planar or spect images, a visual semiquantitative analysis assess the cardiac uptake relative to the ribs with a grade 0 exhibiting no uptake, a grade 1 showing uptake less than bone, a grade 2 where cardiac uptake is equal to bone uptake and a grade 3 with cardiac uptake greater than bone uptake.

Visual score

0: absent myocardial uptake
1: myocardial uptake < bone
2: myocardial uptake = bone
3: myocardial uptake > bone

Using this scoring system, the sensitivity for ATTR amyloid has been reported to be as high as >99%, while the specificity was 86%. Grade 2 or 3 tracer uptake on imaging, coupled with the absence of a monoclonal protein, had a specificity and positive predictive value for ATTR amyloidosis of 100%.

The Quantitative analysis of planar images involved the drawing of a region of interest (ROI) over the heart, copying and mirroring the region on the contralateral chest and the calculation of the heart-to-contralateral ratio mean counts per pixel.

$$\text{Heart/Controlateral Ratio (H/CL)} = \frac{\text{Heart ROI Total Counts}}{\text{Contralateral ROI Total Counts}}$$

Cardiac AL amyloidosis have a ratio that is consistently less than 1.5 while patients with clinical cardiac amyloid disease have a ratio of 1.5 or above on 1hr. post injection planar images.

Attention should be paid not to include extracardiac uptake in the cardiac ROI and the right ventricle on the contralateral chest when uptake is also present in that cavity. The greater the ratio the poorer the 5-year patient's survival.

Reporting

Parameters	**Content**
Patient Demographics	name, age, sex, ethnicity current problem/symptoms and relevant history reason for the test, date of study
Ancillary Tests	Labs results, EKG, prior imaging procedures, biopsy results if available
Nuclear Procedure Detail	Radiopharmaceutical dose Interval between IV injection and imaging Planar, SPECT, SPECT/CT protocol Reconstruction method
Images Findings	Image quality, visual interpretation, grading score, quantitative ratio
Images Ancillary findings	Abnormal Uptake outside the heart if any Abnormal CT Findings if any
Impression	Normal/abnormal study Suggestive/not suggestive/equivocal for cardiac ATTR Recommend additional evaluation as appropriate

PROGNOSIS-TREATMENT

The presence and severity of amyloid cardiomyopathy is the major factor influencing prognosis of affected subjects. Management of cardiac amyloidosis is best performed in specialized centers, or at least in consultation with such a center. Treatment requires a twofold approach: management of cardiac-related complications due to amyloid deposition (which is similar regardless of the specific type of amyloid) and treatment of the underlying disease to suppress new amyloid formation (which is targeted for each specific form).

In ATTR, disease progression can be slowed or prevented by novel TTR-targeted therapies. Inotersen and patisiran are TTR RNA silencing agents that prevent the hepatic production of TTR protein.

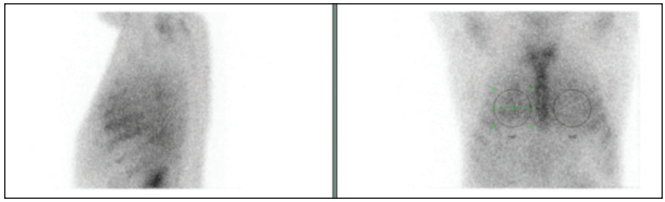
Inotersen is an antisense oligonucleotide and patisiran is a small interfering RNA molecule. Both agents have been studied in phase III clinical trials involving ambulatory patients with hATTR and polyneuropathy symptoms. Tafamidis is an oral TTR stabilizer that binds to TTR tetramers in circulation and prevents their breakdown into unstable amyloidogenic monomers.

In the Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT), Over 30 months, tafamidis was associated with a 32% reduction in mortality and a 30% reduction in cardiovascular hospitalization.

FIGURES

Figure 1. No evidence for Tc99m-PYP uptake

A. Planar Images

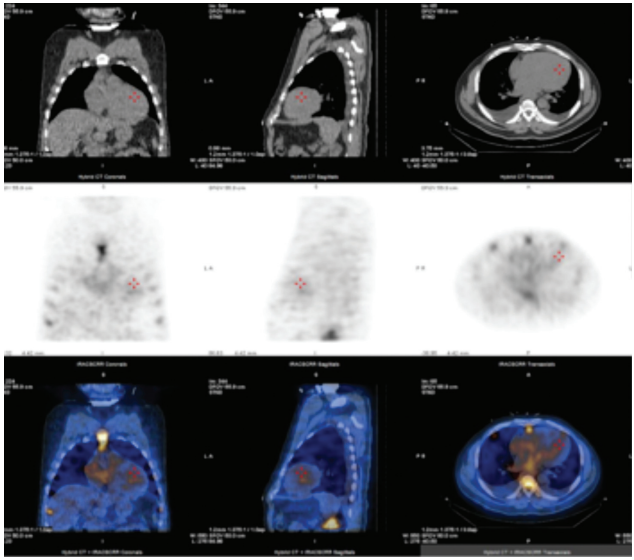


Left lat. and ant. Images showing no significant uptake at the level of the heart

Score: 0

Ratio: H/CL (total counts)= 41542/42316 = 0.98

B. SPECT/CT images



SPECT/CT images showing faint uptake in the ventricular cavities (blood pool)

Figure 2. left ventricle Tc99m-PYP uptake

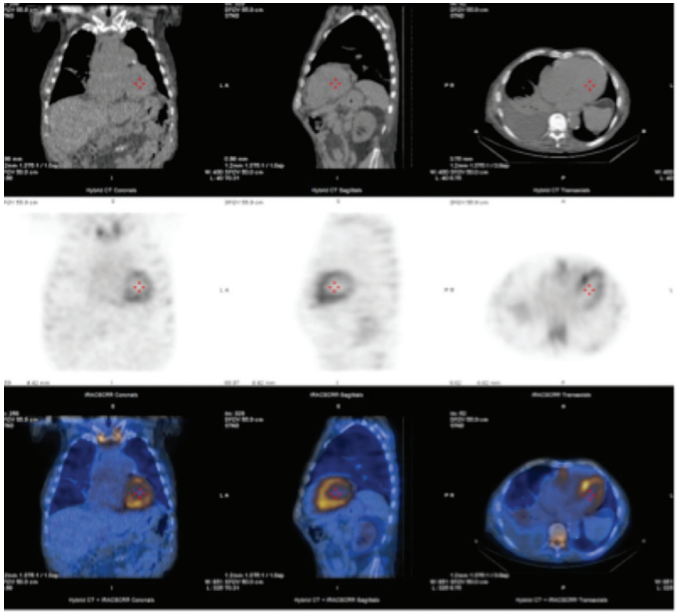
A. Planar Images

Left lat. And ant. images showing uptake at the level of the left ventricular walls.

Score: 3

Ratio: H/CL (total counts)= 66611/45750 = 1.45

B. SPECT/CT Images



SPECT/CT Images showing uptake to the left ventricular walls, particularly the septum.

Figure 3. Blood Pool Activity

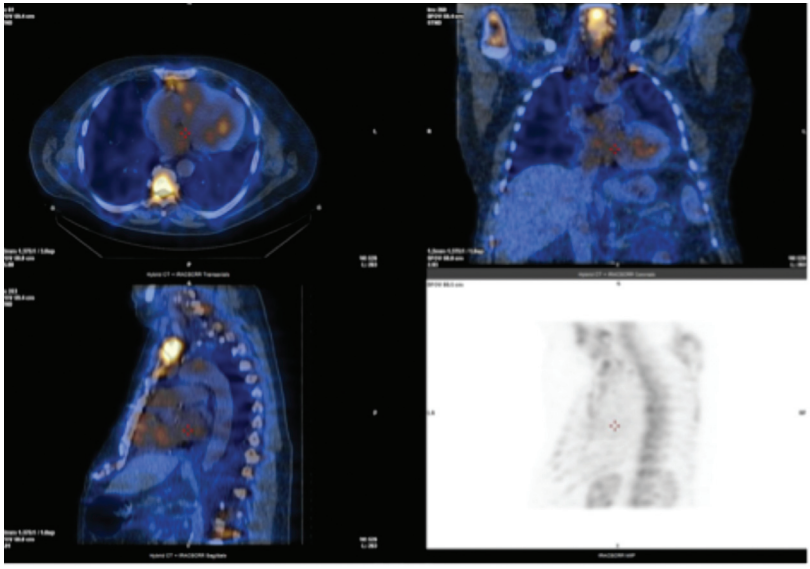
A. Planar Images

Left lat. And ant. images showing mild uptake at the level of the left ventricle.

Score: 2

Ratio: H/CL (total counts)= 56754/42882 = 1.3

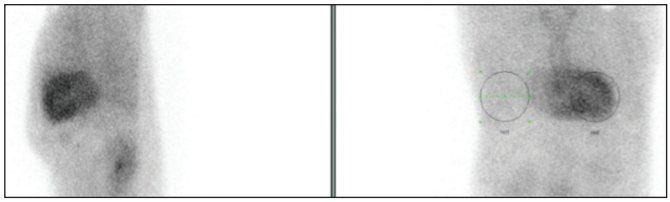
B. SPECT/CT Images



SPECT/CT Images showing no uptake to the left ventricular walls; there is mild to moderate uptake at the level of the ventricular cavities reflecting blood pool activity.

Figure 4. LV + RV tc-99m-PYP Uptake

A. Planar Images

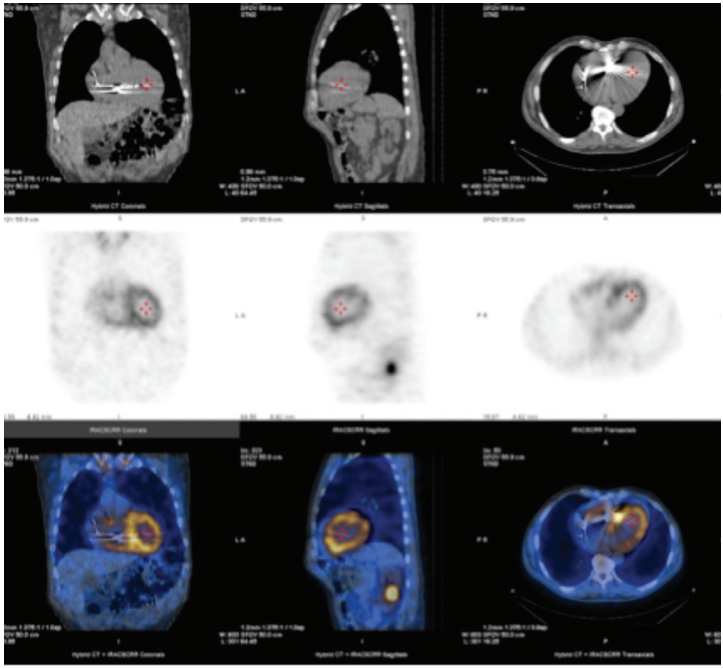


Left lat. and ant. Images showing uptake in both ventricles; there was also uptake in both atria (not shown here).

Score: 3

Ratio: H/CL (total counts)= 82466/37882 = 2.17

B. SPECT/CT Images



SPECT/CT images show significant uptake in both ventricles and faint uptake in the atria.

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