Cardiac Amyloidosis Imaging, Part 2: Quantification and Technical Considerations

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^{99m}Tc-pyrophosphate imaging has been around for a long time. In the 1970s, it was used to image recent myocardial infarction. However, it has recently been recognized for its value in detecting cardiac amyloidosis, leading to widespread use across the United States. Increased use led to considerable procedure variability. As the evidence base to support formal guidelines was being developed, experts from several professional medical societies issued imaging and interpretation recommendations titled "ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: part 1 of 2—Evidence Base and Standardized Methods of Imaging." To reach a consensus on a protocol that would benefit the bulk of laboratories, the experts considered several parameters and radiotracer kinetics. The most critical parameters concerned injection-to-imaging delay and planar imaging versus SPECT. Accordingly, the standardized protocol recommends the injection of 370–740 MBq (10–20 mCi) of ^{99m}Tc-pyrophosphate with imaging 3 h later. Planar images of the chest are acquired in the anterior and lateral views accompanied by SPECT images. Both the planar and the SPECT images are used to semiquantitatively grade the degree of myocardial uptake compared with the amount of uptake in the ribs using a 0–3 scale. A grade of 2 or 3 on the SPECT images is considered positive for cardiac amyloidosis. The planar images are used to calculate a heart–to–contralateral-lung ratio. A ratio greater than 1.3 at 3 h helps to confirm the diagnosis of cardiac amyloid if the SPECT images have positive findings. This article is part of a 3-part series in this issue of the *Journal of Nuclear Medicine Technology*. Part 1 details the etiology of cardiac amyloidosis and ^{99m}Tc-pyrophosphate imaging acquisition parameters. Part 2, this article, describes the procedure evolution over 50 y, image processing, and quantification. It further discusses radiotracer kinetics and 2 important technical considerations: injection-to-imaging delay and planar imaging versus SPECT. Part 3 covers study interpretation along with cardiac amyloidosis diagnosis and treatment.

Key Words: 3-h imaging; heart–to–contralateral-lung ratio (H/CL); semiquantitative scoring; blood pool; cardiac amyloidosis

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Historically, cardiac amyloidosis was believed to be rare, affecting fewer than 200,000 people in the United States (*1*). However, recent improvements in noninvasive diagnostic imaging have revealed a previously unknown population of patients with the disease. The contemporary literature suggests a high prevalence of cardiac amyloidosis in patients with heart failure of unknown etiology (*2*). The recognition of a higher prevalence and the availability of new treatment options has led to a resurgence of interest in ^{99m}Tc-pyrophosphate cardiac amyloidosis imaging. ^{99m}Tc-pyrophosphate imaging is easy to perform, widely available, and effective in screening and detecting cardiac amyloidosis early in the disease process when treatment is more beneficial.

This article is the second part of a 3-part series in this issue of the *Journal of Nuclear Medicine Technology*. Part 1 reviews the etiology of cardiac amyloidosis and the ^{99m}Tc-pyrophosphate acquisition protocol (*3*). Part 2, this article, describes image processing and quantification and justifies the recommended protocol. Part 3 discusses ^{99m}Tc-pyrophosphate imaging interpretation and cardiac amyloidosis diagnosis and treatment opportunities (*4*).

BRIEF REVIEW OF CARDIAC AMYLOIDOSIS

Cardiac amyloidosis, a form of restrictive heart disease, is caused by the deposition of amyloid fibrils (misfolded proteins) in extracellular myocardial tissue (*5*). The accumulation of amyloid fibrils causes the myocardium to thicken and stiffen, leading to diastolic dysfunction and, eventually, heart failure. Two primary types of amyloidosis—transthyretin amyloidosis (ATTR) and immunoglobulin light-chain

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amyloidosis (AL)—account for nearly 95% of all cardiac amyloidosis diagnoses.

Cardiac ATTR can be further subdivided into 2 main types: wild type, previously called senile, and variant, also called mutant (*6*). In wild-type ATTR, transthyretin proteins misfold as part of the aging process, whereas variant ATTR protein misfolding is caused by hereditary variants of the transthyretin gene. Therefore, if cardiac ATTR is identified, variant ATTR must be distinguished from wild-type ATTR through genetic sequencing of the transthyretin gene.

Although the patient presentation of cardiac AL and ATTR is often clinically similar, the two have a vastly different disease progression and treatment (*7*). AL is treated with chemotherapy and immunotherapy to suppress light-chain production. ATTR is treated by managing heart failure and arrhythmias and initiating new disease-modifying pharmacotherapies. Thus, diagnosing and differentiating between AL and ATTR are critically important.

PROCEDURE EVOLUTION

Cardiac imaging with bone-seeking radiotracers has been around for over 50 y. In the 1970s, ^{99m}Tc-pyrophosphate, ^{99m}Tc-bis-phosphonate (^{99m}Tc-DPD), and ^{99m}Tc-hydroxymethylene diphosphonate were used for myocardial infarct imaging because of their assumed binding to calcium deposits (*8*).

Several case studies published beginning in 1980 documented myocardial uptake of ^{99m}Tc-pyrophosphate in patients with amyloidosis and generated great excitement in the field. However, a study in 1987 quashed that excitement when Gertz et al. compared ^{99m}Tc-pyrophosphate myocardial uptake in patients with biopsy-proven amyloid (undefined subtypes) and observed myocardial uptake in only 3 of 14 subjects (*9*). The investigators further observed myocardial ^{99m}Tc-pyrophosphate uptake in only 17 of 20 patients with echocardiographic features of amyloidosis. The authors concluded that ^{99m}Tc-pyrophosphate imaging was not sensitive enough to diagnose cardiac amyloidosis. Thus, ^{99m}Tc-pyrophosphate imaging was not routinely used clinically because of a perceived lack of sensitivity and variable accuracy (*10*). In hindsight, this erroneous perception is now believed to be due to earlier studies using mixed patient populations with ATTR and AL subtypes.

Fortunately, astute investigators in the early 2000s comparing ^{99m}Tc-DPD imaging with endomyocardial biopsy results discovered that bone-seeking radiotracers demonstrated high myocardial uptake in cardiac ATTR but low to no uptake in cardiac AL (*8*). This finding led to the conclusion that bone-avid radiotracers such as ^{99m}Tc-pyrophosphate could be used to diagnose cardiac ATTR and differentiate it from cardiac AL in the absence of abnormal light chains on serum and urine analysis (*6*). The ability to diagnose cardiac ATTR and differentiate it from AL resulted in renewed interest in cardiac imaging with ^{99m}Tc-labeled bone-avid tracers.

Much of the early research and initial publications imaged patients 1 h after ^{99m}Tc-pyrophosphate injection, acquiring planar chest images in the anterior, left anterior oblique, and left lateral views. SPECT imaging was optional, as were planar images 3 h after injection. So naturally, many labs adopted variations of that protocol. Unfortunately, the lack of standardization created substantial confusion and potential misdiagnosis across the field.

CURRENT RECOMMENDED PROTOCOL

Currently, there are no published guidelines directing the performance of cardiac amyloidosis imaging, because the evidence base is still being developed (*6*). Much of the early research comprised small studies performed at single centers or larger multicenter studies that were limited in scope. Guideline development requires prospective, randomized clinical trials.

To address the lack of standardization and to decrease variation until guidelines can be established, the American Society of Nuclear Cardiology, the Society of Nuclear Medicine and Molecular Imaging, and several other professional medical societies joined to craft an expert opinion consensus. In 2019, the "ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: part 1 of 2—Evidence Base and Standardized Methods of Imaging" was published (referred to as the "consensus recommendations" in this article) (*6*). The consensus recommendations address not only nuclear cardiology imaging but also echocardiography and cardiac MRI.

In 2021, the American Society of Nuclear Cardiology and the other societies published an addendum to the consensus recommendations with refined, precise instructions for ^{99m}Tc-pyrophosphate imaging (*11*). The protocol described in this article and detailed in part 1 of this series (*3*) follows those recommendations.

ACQUISITION

The consensus recommendations prescribe a dose of 370–740 MBq (10–20 mCi) of ^{99m}Tc-pyrophosphate, ^{99m}Tc-hydroxymethylene diphosphonate, or ^{99m}Tc-DPD (not available in the United States) (*6*). ^{99m}Tc-pyrophosphate is most frequently used in the United States. The recommended time between injection and imaging is 3 h. At 3 h, anterior and lateral planar images of the chest are acquired for 750,000 counts. SPECT imaging, either a 180° or a 360° acquisition, is then performed. The overall parameters outlined in the 2021 American Society of Nuclear Cardiology addendum work well for most camera systems (Table 1) (*11*).

^{99m}Tc-DPD and ^{99m}Tc-hydroxymethylene diphosphonate are widely used outside the United States. No studies to date have directly compared the 3 tracers. However, the published literature suggests they can be used interchangeably. ^{99m}Tc-methyl diphosphonate use is not recommended. For simplicity, this article focuses on the use of ^{99m}Tc-pyrophosphate.

TABLE 1
^{99m}Tc-Pyrophosphate Cardiac Amyloidosis Imaging Parameters

Parameter	Characteristics	Standard/optional/preferred
Camera type	Large-field-of-view γ-camera	Standard
	Cadmium zinc telluride	Optional*
Energy peak	140 keV	Standard
Energy window	15%–20%	Standard
Collimator	Low-energy, all-purpose	Standard
Patient position	Supine	Standard
Field of view	Heart/chest	Standard
Injection-to-imaging time	3 h	Standard
	1 h	Optional
Planar		
Acquisition type	Static	Standard
	Whole-body imaging	Optional†
Detector configuration	90°	Standard
Views	Anterior and left lateral	Standard
Number of views	2	Standard
Counts per view	750,000	Standard
Matrix	256 × 256	Standard
Magnification	1.46	
SPECT or SPECT/CT*		
Acquisition type	Step and shoot or continuous	Standard
Patient position	Supine	Standard
	Upright	Optional
Orbit	180°/90°	Standard
	360°/180°	Optional
Matrix	128 × 128 (minimum, 64 × 64)	Standard
Magnification	1.46 (180° orbit)	Standard
	1.0 (360° orbit)	Optional
Pixel size	2.3–6.5 mm	Standard
Projections per detector	40/32	Standard
Time per projection	20 s/25 s	Standard
CT attenuation correction	Heart	Preferred

*Parameters defined for γ-cameras as parameters for cadmium-zinc-telluride cameras have not been firmly established.
†Whole-body imaging is not useful when imaging with ^{99m}Tc-pyrophosphate. However, when using ^{99m}Tc-hydroxymethylenediphosphonate or ^{99m}Tc-DPD, whole-body imaging is useful to demonstrate soft-tissue uptake.

More information on imaging with ^{99m}Tc-DPD and ^{99m}Tc-HDMP is provided in a brief communication (*12*) published in this issue of the *Journal of Nuclear Medicine Technology*.

PROCESSING AND QUANTIFICATION

SPECT Reconstruction

The SPECT data are processed using the usual manufacturer's reconstruction algorithms. Filtered backprojection or iterative reconstruction may be used. The images are displayed in the short-axis, vertical long-axis, and horizontal long-axis views. The SPECT/CT images should be fused for attenuation correction and correlative interpretation.

The SPECT reconstructed images are crucial for distinguishing myocardial uptake from residual blood-pool activity and comparing myocardial uptake with bone uptake. The SPECT images are also helpful in identifying focal myocardial infarction and excluding overlapping bone hot spots from previous injuries.

Semiquantitative Visual Grading

The planar and SPECT reconstructed images are used to visually assess the degree of myocardial uptake versus the amount of uptake in the ribs. This comparison, first described by Perugini et al., is used to generate a semiquantitative visual score to diagnose the presence of cardiac amyloidosis or lack thereof (*13*).

A scale from 0 to 3 is used to grade uptake in the myocardium relative to the ribs (Table 2). Grade 0 represents no myocardial uptake and normal bone uptake. Grade 1 demonstrates myocardial uptake less than rib uptake. For grade 2, myocardial uptake is equal to rib uptake. Grade 3 is myocardial uptake greater than rib uptake, with little to no rib uptake (Fig. 1).

Heart–to–Contralateral-Lung Ratio (H/CL)

The anterior planar image is used to create an H/CL ratio (*10*). The ratio is determined from a circular region of interest drawn over the heart and a mirrored region of interest

TABLE 2
Semiquantitative Visual Scoring of ^{99m}Tc-Pyrophosphate Uptake in Myocardium Versus Ribs

Grade	Description
0	No myocardial uptake and normal bone uptake
1	Myocardial uptake less than rib uptake
2	Myocardial uptake equal to rib uptake
3	Myocardial uptake greater than rib uptake, with mild or absent rib uptake

on the opposite side of the chest (contralateral-lung region). The contralateral-lung region is used to account for background and rib activity. The total and absolute mean counts are computed for each region of interest. The H/CL ratio is calculated by dividing the mean counts in the heart by those in the contralateral chest region (Fig. 2).

The size of the heart region should be adjusted to maximize coverage of the myocardium (*14*). However, care must be taken to avoid including extraneous activity when drawing the region, ensuring the region does not include the adjacent lung or sternal activity. For example, including lung tissue in the heart region of interest—an area with no expected uptake—results in a lower ratio. Conversely, including sternal activity—a bony area with expected high uptake—results in an elevated ratio.

Care must also be taken when drawing the contralateral-lung region of interest on the right side of the chest. It should be placed over the flat area of the ribs above the diaphragm. Again, there should be no extraneous activity such as the right heart or sternum, nor should spine activity be included. In addition, the region of interest should not include increased rib activity from a prior injury. Furthermore, some patients may have an elevated liver extending into the lower ribs, which should also be excluded. The inclusion of increased activity from any of these scenarios will create an H/CL ratio that is spuriously low (Fig. 3).

If no myocardial uptake is seen on the planar and SPECT images (grade 0), calculating the H/CL ratio is unnecessary.

INTERPRETATION

The planar and SPECT images are evaluated to confirm diffuse uptake within the myocardium and not within the blood pool (*10*). A visual semiquantitative grade of 2 or 3 on the SPECT images is abnormal and strongly suggestive of cardiac ATTR. Conversely, grade 1 is equivocal for cardiac ATTR, and grade 0 does not suggest cardiac ATTR.

An H/CL ratio greater than or equal to 1.3 at 3 h is suggestive of cardiac ATTR if the SPECT study demonstrates myocardial uptake. Usually, if the semiquantitative score is positive (grade 2 or 3), the H/CL ratio is also positive (>1.3). However, if the results are discordant or if the semiquantitative score is equivocal (grade 1), the H/CL ratio can be helpful in deciding between grade 1 (equivocal) and grade 2 (positive). The H/CL ratio is not used in the interpretation if no myocardial uptake is seen on the SPECT images (grade 0).

^{99m}Tc-pyrophosphate imaging is highly sensitive for diagnosing cardiac ATTR because of the high avidity of the radiotracer (*6*). As previously mentioned, uptake of ^{99m}Tc-pyrophosphate in AL is variable, but typically most AL cases demonstrate only low-grade ^{99m}Tc-pyrophosphate uptake. The reason for the disparity in ^{99m}Tc-pyrophosphate uptake between cardiac ATTR and cardiac AL is unknown. However, it is believed to be related to a higher calcium content in ATTR amyloid plaques, which are chronically deposited.

When myocardial uptake of ^{99m}Tc-pyrophosphate is demonstrated on

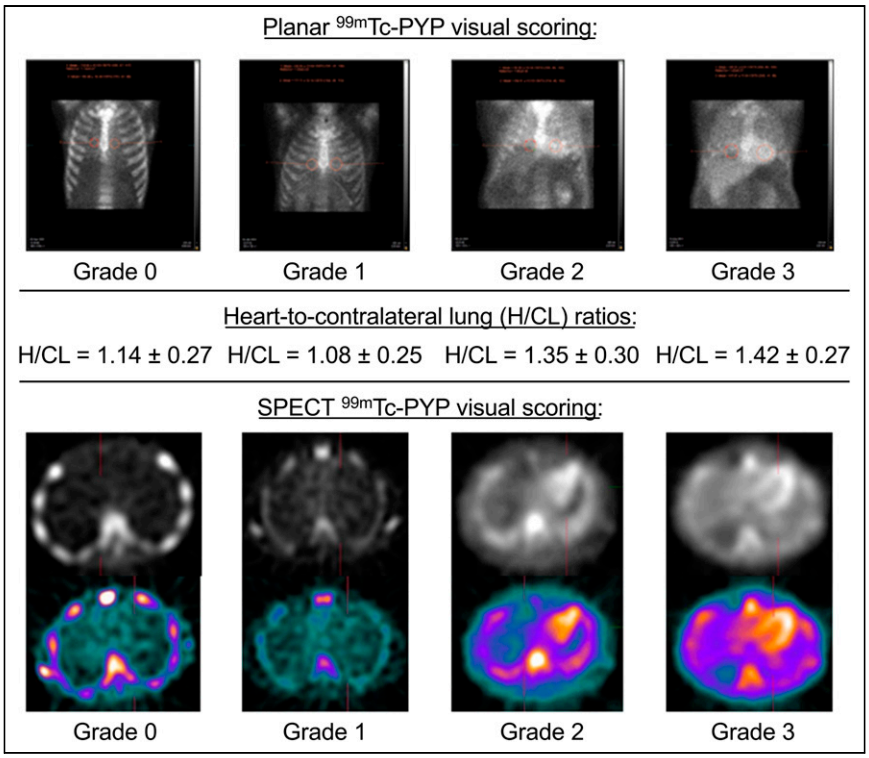

FIGURE 1. Semiquantitative visual grading. Both planar and SPECT images are used to visually score degree of cardiac amyloidosis. Amount of ^{99m}Tc-pyrophosphate uptake in myocardium is compared with that in ribs. Grade 0 (normal) = no myocardial uptake and normal bone uptake; grade 1 (equivocal) = myocardial uptake less than rib uptake; grade 2 (abnormal and suggestive of cardiac amyloidosis) = myocardial and rib uptake equal; grade 3 (abnormal and strongly suggestive of cardiac amyloidosis) = myocardial uptake greater than rib uptake; PYP = pyrophosphate.

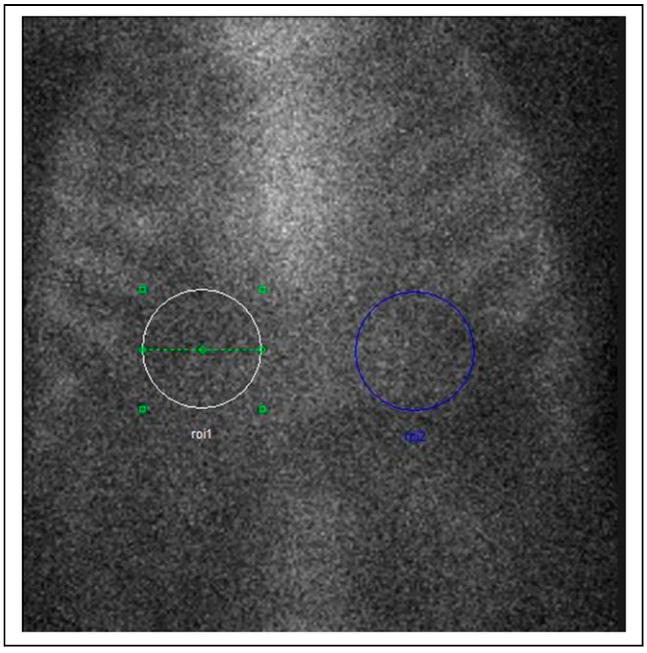

FIGURE 2. Correct region-of-interest placement for H/CL ratio. To accurately calculate H/CL ratio, circular region of interest (ROI) is placed over myocardium on 3-h anterior planar ^{99m}Tc-pyrophosphate image (blue circle). Size of heart region should be maximized to cover entire myocardium. For contralateral lung, equal-sized ROI is placed on opposite side of sternum on flat area of ribs (white circle). H/CL ratio is calculated by dividing heart region mean counts by contralateral chest region mean counts. (Courtesy of Saurabh Malhotra, MD, MPH.)

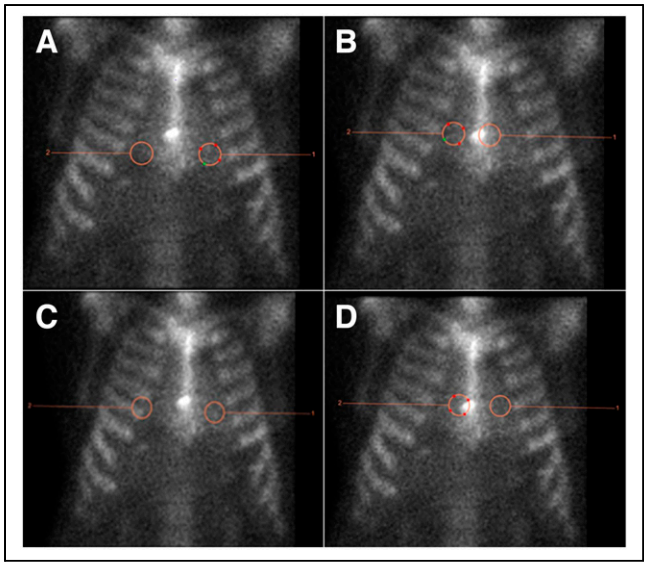

FIGURE 3. H/CL ratio incorrect region-of-interest placement. Three-hour anterior planar ^{99m}Tc-pyrophosphate images were used to demonstrate impact of incorrect region-of-interest placement on H/CL ratio. (A) Correct heart and contralateral-lung region-of-interest placement resulted in H/CL ratio of 1.18, which is negative for amyloidosis. (B) Incorrect heart region-of-interest placement including sternal activity but correct contralateral-lung region-of-interest placement. H/CL ratio was falsely elevated at 1.91, suggesting cardiac amyloidosis. (C) Correct heart region-of-interest placement but incorrect contralateral-lung region-of-interest placement over curvature of ribs resulting in falsely decreased ratio of 0.94 because of increased activity in contralateral-lung region of interest. (D) Correct heart region-of-interest placement but incorrect contralateral region-of-interest placement including sternal activity. Calculated H/CL ratio was falsely decreased at 0.67. Heart region of interest = 1. Contralateral-lung region of interest = 2.

imaging (grade 2 or 3), ATTR must be distinguished from AL (*11*). Cardiac AL can be ruled out by the absence of monoclonal proteins on serum and urine immunofixation and serum free light-chain assay.

A study by Gillmore et al. in 2016 of 1,217 patients with suspected cardiac amyloidosis (857 patients with histologically proven cardiac amyloidosis and 360 patients with non-amyloid cardiomyopathies) reported a 99% sensitivity and 86% specificity for cardiac ATTR (Table 3) (*15*). The false positives identified in the study were almost exclusively from myocardial uptake in patients with cardiac AL. Furthermore, patients with either grade 2 or grade 3 myocardial uptake and absence of monoclonal protein on serum and urine analysis had a 100% specificity and positive predictive value for cardiac ATTR.

The lack of myocardial uptake on ^{99m}Tc-pyrophosphate imaging (specificity) can be used to rule out cardiac amyloidosis and distinguish it from symptoms of other entities that mimic cardiac amyloidosis, such as hypertrophic cardiomyopathy (*16*).

TECHNICAL CONSIDERATIONS

Before the publication of the consensus recommendations, cardiac amyloidosis imaging was performed in a multitude of ways (*11*). To reach a consensus, the experts had to weigh the evidence for several technical factors and agree on an effective practical protocol. The most critical factors considered include the injection-to-imaging time (1 vs. 3 h) and planar imaging versus SPECT. Before we compare and contrast these options, a quick review of ^{99m}Tc-pyrophosphate kinetics is in order.

^{99M}TC-PYROPHOSPHATE KINETICS

In the absence of cardiac amyloidosis or a recent myocardial infarction, ^{99m}Tc-pyrophosphate does not accumulate in the myocardium. Furthermore, under normal circumstances, it clears rapidly from the blood pool and accumulates in the bone (*17*). Pharmacologically, 40%–50% is deposited within the bone in 1–2 h (*18*). The accumulation of ^{99m}Tc-pyrophosphate in the bone continues to increase, with bone uptake peaking at 2–3 h (*7*).

Approximately 10% of ^{99m}Tc-pyrophosphate is still in the blood pool at 1 h, according to the package insert (*18*). However, several clinical studies suggest that 15%–20% of patients still demonstrate significant blood-pool activity at 1 h (*10*). ^{99m}Tc-pyrophosphate blood-pool clearance is determined

TABLE 3
Sensitivity, Specificity, and Predictive Value Refresher

Measure	Description	Formula
Sensitivity	Probability that result will be positive when disease is present	TP/(TP + FN)
Specificity	Probability that result will be negative when disease is absent	TN/(TN + FP)
Accuracy	Number of correct findings	(TP + TN)/(TP + TN + FP + FN)
Positive predictive value	Probability that patients with positive result truly have disease	TP/(TP + FP)
Negative predictive value	Probability that patients with negative result do not have disease	TN/(TN+FN)

TP = patients with positive result who have disease; FN = patients with negative result who have disease; TN = patients with negative result who do not have disease; FP = patients with positive result who do not have disease.

by bone metabolism and renal function (*17*). Patients with slower bone metabolism or abnormal renal function may not clear the tracer quickly. Very elderly patients, even those with normal renal function, may also demonstrate delayed blood-pool clearance beyond 3 h.

In patients with cardiac ATTR or a recent myocardial infarction, myocardial uptake peaks at about 1 h after injection. After 1 h, the myocardial concentration slowly declines.

Myocardial Infarction

As a reminder, ^{99m}Tc-pyrophosphate was first used in the 1970s to image subacute myocardial infarction (*1*). ^{99m}Tc-pyrophosphate is taken up by calcium deposits within the infarcted myocardial tissue within the first 6 wk of injury (as opposed to uptake by the amyloid fibrils in the extracellular space in amyloidosis). Infarct uptake is typically regional as compared with the diffuse pattern seen in cardiac amyloidosis and, thus, must be excluded when interpretation is done using the SPECT images. In addition, it is essential to recognize that in regions of myocardial scarring—typically months to years after infarction—^{99m}Tc-pyrophosphate will not accumulate within the infarcted myocardium, and a large previous myocardial infarction may arbitrarily lower H/CL ratios and hinder interpretation of the SPECT images (*16*).

INJECTION-TO-IMAGING DELAY OF 1–3 HOURS

Imaging at 1 Hour After Injection

Realizing that peak myocardial uptake in amyloid fibrils occurs about 1 h after injection, it is tempting to want to scan at 1 h (*8*). One advantage to scanning at 1 h is that myocardial counts are at a peak, and the visual semiquantitative assessment may be more sensitive at 1 h. In addition, higher counts in the myocardium at 1 h after injection opens the potential for using lower doses. The consensus recommendations suggest the administration of 370–740 MBq (10–20 mCi) of ^{99m}Tc-pyrophosphate, ^{99m}Tc-DPD, or ^{99m}Tc-hydroxymethylene diphosphonate. Up to 925 MBq (25 mCi) of radiotracer have been used in the literature. The optimum activity of radiotracer is unknown because no research has been undertaken to answer this question, nor have there been any head-to-head comparisons of the 3 bone-seeking radiotracers (*17*).

An additional advantage of scanning 1 h after injection is increased lab efficiency and throughput. Having patients return 3 h after injection is more difficult from a scheduling perspective as the ^{99m}Tc-pyrophosphate cardiac amyloid patient will compete for myocardial perfusion scheduling slots. Finally, imaging at 1 h after injection is more convenient for patients because they are not confined to the waiting room for 3 h or forced to return for imaging.

The primary disadvantage of imaging at 1 h after ^{99m}Tc-pyrophosphate injection is increased blood-pool activity (*8*). Increased blood-pool activity can lower specificity (true-negative rate) by increasing the potential for false positives. In addition, visual assessment for cardiac ATTR may be less specific at 1 h after injection.

Imaging at 3 Hours After Injection

Imaging 3 h after radiotracer injection results in more bone uptake and less blood-pool activity (Fig. 4). The findings are more specific than 1-h imaging because of the potential for fewer false positives. With peak activity in the myocardium, albeit slowly decreasing, and peak activity in the bone, bone-to-heart ratios are more stable and consistent on images at 3 h after injection.

Although imaging is more specific at 3 h, the test may be less sensitive—there is always a trade-off between sensitivity and specificity. The H/CL ratio is lower at 3 h because of the slight decrease in myocardial counts over time. An H/CL ratio greater than or equal to 1.3 at 3 h is considered positive for cardiac ATTR, compared with a ratio of 1.5 at 1 h after injection. However, published data demonstrate low inter- and intraobserver variability with both 1- and 3-h planar H/CL ratios (*17*).

PLANAR IMAGING VERSUS SPECT

Planar Imaging

Planar imaging in the anterior and left lateral views is standard. The primary advantage of acquiring images in the planar view on a large-field-of-view camera is the broad ability to see the entire chest and rib cage. In addition, the anterior view provides an easy opportunity to calculate the H/CL ratio.

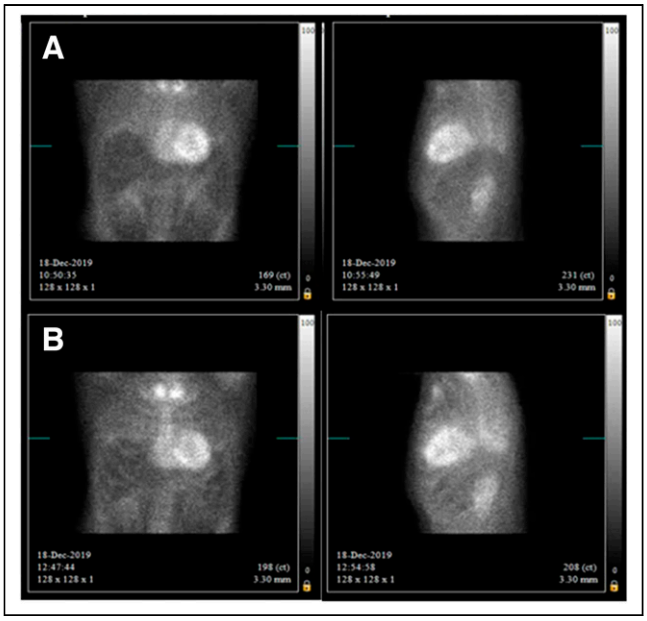

FIGURE 4. ^{99m}Tc-pyrophosphate image comparison at 1 vs. 3 h. (A) Anterior (left) and left anterior oblique (right) images acquired 1 h after injection. (B) Anterior (left) and left anterior oblique (right) images acquired 3 h after injection. Images acquired 3 h after injection demonstrate better soft-tissue clearance and greater bone uptake and definition than images acquired 1 h after injection. Hardly any bone uptake is discernable in 1-h images. In addition, myocardial uptake is similar on both 1- and 3-h images because peak myocardial uptake of ^{99m}Tc-pyrophosphate occurs about 1 h after injection. Peak bone uptake occurs 2–3 h after injection.

There are several disadvantages to planar imaging, especially planar-only (no SPECT) imaging. First, with planar imaging, diffuse myocardial uptake cannot be discerned from blood-pool activity within the ventricular cavity (Fig. 5). Additionally, overlying rib activity may falsely add counts to the heart region, or activity from the posterior side of the body may shine through (*19*).

Second, planar-only imaging, especially if performed at 1 h after injection, may result in lower specificity (more false positives) (*20*). For example, a study by Asif et al. retrospectively evaluated diagnostic accuracy and found that specificity decreased by 2% with planar-only imaging because patients were misclassified as having uptake in the myocardium on visual assessment when, in fact, the activity was within the blood pool (*21*). The investigators also found that the H/CL ratio was less sensitive in patients determined to be positive on SPECT evaluation. A study by Régis et al. confirmed this finding, demonstrating a higher proportion of equivocal studies with planar-only imaging and the use of the H/CL ratio (*22*). In view of these disadvantages, planar imaging alone should never be performed, because the findings are not diagnostic; the images should be used only as an adjunct to SPECT imaging.

SPECT Imaging

SPECT is the gold standard and overcomes most of the challenges associated with planar imaging, especially the primary confounder of cardiac blood-pool activity and the potential for false-positive results. SPECT allows for the clear discernment of myocardial uptake from blood pool. In addition, SPECT confirms the presence of diffuse myocardial uptake instead of regional uptake, providing for segmental evaluation of uptake (*19*).

SPECT permits the addition of CT for attenuation correction, consequently improving image quality and enhancing confidence in identifying myocardial tracer localization (*20*). SPECT/CT can also identify abnormal bone uptake and provide information about the large vessels and other heart abnormalities.

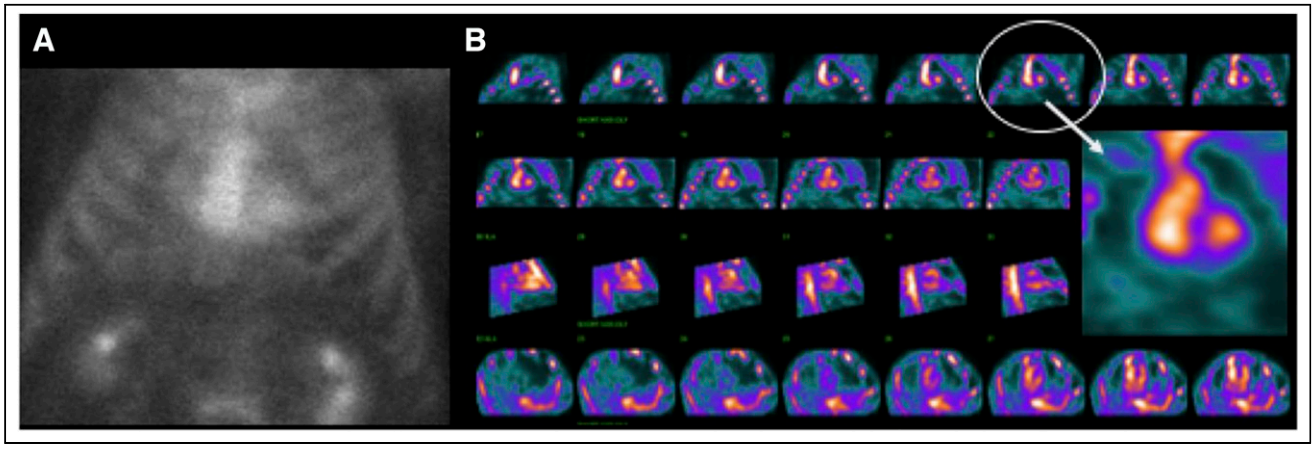

FIGURE 5. Planar vs. SPECT blood pool. On planar ^{99m}Tc-pyrophosphate images, blood pool cannot be differentiated from myocardial uptake. (A) Anterior planar image demonstrating diffuse uptake assumed to be myocardial uptake. Planar-only imaging cannot be used to differentiate blood-pool uptake from myocardial uptake. (B) SPECT images immediately after acquisition of planar images showing that ^{99m}Tc-pyrophosphate uptake is not localized to myocardium but is within ventricular cavity blood pool. Circle denotes coronal image best demonstrating residual blood pool. (Reprinted from (*1*).)

The addition of SPECT improves diagnostic performance. For example, a study by Régis et al. concluded that SPECT imaging 3 h after injection made interpretation more straightforward and reliable (*22*). The addition of SPECT to planar imaging using 1-h H/CL ratios reduced the number of equivocal studies from 66% to 8%. Furthermore, a study by Sperry et al. found 100% concordance in ^{99m}Tc-pyrophosphate SPECT between 1- and 3-h images (*23*). Finally, SPECT improves the positive predictive value (the likelihood that a patient with a positive test result has the disease) when added to planar imaging (*20*).

However, there are a few disadvantages of SPECT compared with planar imaging. The first is increased imaging time and potentially decreased laboratory efficiency. Second, presently there is no widely accepted method for quantifying SPECT images, though recent studies by Miller et al. and Roshankar et al. investigating techniques to quantitate SPECT cardiac amyloidosis data were promising (*24,25*). A third and final disadvantage of SPECT is the technical challenges in reconstructing data from images with low myocardial uptake.

TECHNICAL CONSIDERATIONS IN APPLICATION

The review of bone-seeking radiotracer kinetics and the research related to 1-h versus 3-h and planar imaging versus SPECT provides a solid rationale supporting the adoption of the consensus recommendations. We learned that myocardium and bone rapidly take up ^{99m}Tc-pyrophosphate. Myocardial uptake peaks about an hour after radiotracer injection and then slowly declines. Blood-pool activity should technically be low at 1 h. However, multiple studies show that 15%–20% of patients have high blood-pool activity at 1 h. Increased blood-pool activity decreases diagnostic specificity because of a potential increase in false positives. From these findings, it can be concluded that imaging at 3 h after injection is advantageous in differentiating between myocardial uptake and blood pool.

We also learned that planar imaging is necessary to calculate the H/CL ratio and observe the entire rib cage to assess bone uptake. However, planar imaging does not allow differentiation between blood-pool and myocardial uptake. SPECT imaging can differentiate between myocardial and blood-pool uptake and enables the assessment of diffuse versus regional uptake. SPECT can also be used to compare heart-to-rib uptake. Finally, SPECT increases study sensitivity by reducing the number of studies whose findings are interpreted as equivocal. Thus, both planar imaging and SPECT are advantageous for accurately interpreting ^{99m}Tc-pyrophosphate cardiac amyloidosis imaging.

CONCLUSION

In a perfect imaging world, ^{99m}Tc-pyrophosphate would completely clear from the cardiac blood pool in less than an hour and demonstrate high myocardial uptake in patients with cardiac amyloidosis. Unfortunately, our current imaging world is imperfect, and several parameters must be carefully optimized to maximize the quality of ^{99m}Tc-pyrophosphate imaging. In the absence of evidence-based guidelines (for which prospective randomized clinical trials must be conducted), laboratories across the United States were left on their own to choose an imaging protocol. As a result, various imaging protocols have been used across the United States, leading to confusion and potential misdiagnoses. To address this problem, experts from the American Society of Nuclear Cardiology, the Society of Nuclear Medicine and Molecular Imaging, and several other societies united to issue standardized consensus recommendations for cardiac amyloidosis imaging.

This article justifies the selection of 2–3 h after injection as the time point for imaging of ^{99m}Tc-pyrophosphate and details the requirement for both planar imaging and SPECT. The article also describes image processing and quantification and briefly explains how to interpret the results. Part 3 provides more detail on study interpretation combined with other clinical findings to diagnose cardiac amyloidosis. Specifically, part 3 explains how to differentiate between ATTR and cardiac AL and how to diagnose wild-type ATTR and variant cardiac ATTR. Finally, the series discusses the usual treatment of cardiac amyloidosis and new pharmacotherapies.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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