Cardiac Amyloidosis Imaging, Part 1: Amyloidosis Etiology and Image Acquisition

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Cardiac amyloidosis is a systemic form of amyloidosis in which protein-based infiltrates are deposited in myocardial extracellular space. The accumulation of amyloid fibrils causes the myocardium to thicken and stiffen, leading to diastolic dysfunction and, eventually, heart failure. Until recently, cardiac amyloidosis was considered rare. However, the recent adoption of noninvasive diagnostic testing, including ^{99m}Tc-pyrophosphate imaging, has revealed a previously undiagnosed sizable disease prevalence. Light-chain amyloidosis (AL) and transthyretin amyloidosis (ATTR), the 2 primary types, account for 95% of cardiac amyloidosis diagnoses. AL results from plasma cell dyscrasia and has a very poor prognosis. The usual treatment for cardiac AL is chemotherapy and immunotherapy. Cardiac ATTR is more chronic, usually resulting from age-related instability and misfolding of the transthyretin protein. ATTR is treated by managing heart failure and using new pharmacotherapeutic drugs. ^{99m}Tc-pyrophosphate imaging can efficiently and effectively distinguish between ATTR and cardiac AL. Although the exact mechanism of myocardial ^{99m}Tc-pyrophosphate uptake is unknown, it is believed to bind to amyloid plaque microcalcifications. ^{99m}Tc-pyrophosphate imaging has a 97% sensitivity and nearly 100% sensitivity for identifying cardiac ATTR when the AL form of the disease is ruled out through serum free light-chain and serum and urine protein electrophoresis with immunofixation testing. Although there are no published ^{99m}Tc-pyrophosphate cardiac amyloidosis imaging guidelines, the American Society of Nuclear Cardiology, Society of Nuclear Medicine and Molecular Imaging, and others have published consensus recommendations to standardize test performance and interpretation. This article, part 1 of a 3-part series in this issue of the *Journal of Nuclear Medicine Technology,* describes amyloidosis etiology and cardiac amyloidosis characteristics, including the types, prevalence, signs and symptoms, and disease course. It further explains the scan acquisition protocol. Part 2 of the series focuses on image/data quantification and technical considerations. Finally, part 3 describes scan interpretation, along with the diagnosis and treatment of cardiac amyloidosis.

Key Words: cardiac amyloid imaging; cardiac amyloidosis; transthyretin; light-chain; ^{99m}Tc-pyrophosphate

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Amyloidosis is a collection of diseases characterized by deposits of protein-based infiltrates within the body's tissues. There are several amyloid subtypes based on the type of protein deposited (*1*). Until recently, cardiac amyloidosis was considered rare in the United States. However, the increased use of noninvasive diagnostic testing, such as ^{99m}Tc-pyrophosphate imaging, has led to increased diagnoses of what may have otherwise been unrecognized cases of cardiac amyloidosis (*2*). Attention to detail is imperative when gathering the patient's history, administering the radiopharmaceutical, and acquiring images to ensure quality and accurate diagnosis of the disease.

This article is the first part of a 3-part series in this issue of the *Journal of Nuclear Medicine Technology* examining the utility of ^{99m}Tc-pyrophosphate imaging to diagnose cardiac amyloidosis. Part 1 begins with a discussion of the etiology of amyloidosis in general and then details cardiac amyloidosis, including information about the types, prevalence, signs and symptoms, and disease course. The last section of part 1 outlines the ^{99m}Tc-pyrophosphate image acquisition protocol. Part 2 explains the processing and quantification of ^{99m}Tc-pyrophosphate scans, including semiquantitative grading and heart–to–contralateral-lung ratios, and discusses several protocol technical considerations (*3*). Finally, part 3 concludes the series by discussing scan interpretation, cardiac amyloidosis diagnosis, and treatment (*4*).

WHAT IS AMYLOIDOSIS?

Amyloidosis refers to a collective group of rare diseases in which there are deposits of protein-based infiltrates

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within the extracellular tissue space (*1*). Proteins perform a wide range of essential functions throughout the body, such as catalyzing chemical reactions, providing structural support, regulating cellular membrane transport, protecting against diseases, and coordinating cell signaling pathways (*5*). It is estimated that there are as many as 100,000 different proteins in the human body (*6*). Proteins fold and bend into precise shapes based on the sequence of amino acids. A protein's specific function is directly related to its 3-dimensional shape.

Proteins must maintain their specific shape (*5*). If the protein loses its normal shape, or misfolds, it cannot function properly. Usually, when proteins misfold, the body disassembles and removes them with specialized enzymes called proteasomes. However, if the body does not remove the misfolded proteins, they can accumulate within various organs in the extracellular tissue. In amyloid disease, long, unbranched strings of misfolded proteins, called fibrils, several micrometers in length, have an extremely stable structure resistant to dismantling and removal by cellular processes (*2*).

The accumulation of amyloid fibrils eventually impairs the affected organ's function. Think of it like a neighborhood with a stockpile of broken-down, junked cars parked on the streets (the amyloid fibrils are the junked end-product of the misfolded proteins). The junked cars stockpile, blocking the parking places and the driving lanes for normally operating cars. Eventually, traffic ceases, and the neighborhood shuts down. In amyloid, the fibrils displace normally functioning structures in a similar fashion.

Amyloid fibrils can deposit in any tissue or organ in the body, such as the brain, skin, or heart, causing amyloidosis (*5*). Different clinical manifestations and diseases result, depending on the organ and protein deposited (*2*). For example, the deposition of β-amyloid proteins between brain neurons creates plaques that block communication and disrupt cell function in Alzheimer disease. As another example, deposits of serum amyloid A protein in the kidney or liver can cause long-term inflammatory conditions.

Over 30 different amyloid diseases have been identified. Interestingly, all amyloid is morphologically or structurally similar despite the abnormal protein involved. How amyloid can be morphologically homogeneous compared with the heterogeneity of organ involvement and clinical syndromes is a mystery.

TYPES

Classification of amyloid is based on the abnormal protein involved and whether it is confined to a single organ (localized) or spread throughout the body (systemic) (*5*). Localized, or organ-specific, amyloidosis involves a single organ. Although it can occur in any organ or tissue, amyloidosis frequently affects the skin, bladder, eyes, lungs, or brain. Alzheimer disease, which affects the brain, is the most recognized localized form of the disease.

The most common types of systemic amyloidosis include monoclonal immunoglobulin light-chain amyloidosis (AL), transthyretin amyloidosis (ATTR), and serum amyloid A amyloidosis. AL is caused by an overabundance and misfolding of light-chain proteins. Light-chain proteins are antibody components or immunoglobulins (immune system proteins in serum and cells) produced by plasma cells in the bone marrow that fight off infection. There are 2 types of light chains: κ and λ.

Although light-chain amyloid fibrils can build up in any organ, they most frequently affect the heart and kidneys. However, light-chain fibrils can also accumulate in peripheral nerves (e.g., carpal tunnel syndrome), liver, skin, and the gastrointestinal system. AL is acquired and typically diagnosed in individuals over 50 y old. It is lethal because of its rapid progression (Fig. 1).

ATTR results from the misfolding of the transthyretin protein, a protein that used to be called prealbumin. The ATTR protein is generated by the liver and involved in the transportation of thyroxine (a hormone secreted by the thyroid gland affecting digestion, heart function, muscle function, brain development, and bone maintenance) and retinol-binding protein (a protein responsible for transporting vitamin A) (*7*). ATTR can affect multiple organs, including the heart, peripheral nerves, and autonomic nervous system. When amyloid is deposited in the autonomic nervous system, it can affect bladder, digestive, and genital function.

Serum amyloid A amyloidosis is caused by misfolding of serum amyloid A protein and fibril formation. Serum amyloid A protein is produced in the liver and is involved in inflammatory responses. It commonly deposits in the kidney and liver and can affect individuals at any age. It can be involved in long-term inflammatory conditions such as rheumatoid arthritis, Crohn disease, tuberculosis, or osteomyelitis.

Because many types of amyloidosis can affect different and multiple organs and tissues, causing a plethora of symptoms, it can be challenging to diagnose. For example, amyloidosis affecting the kidneys can cause fatigue, as can amyloidosis affecting the heart. As another example, amyloidosis of the heart can cause shortness of breath, but so can amyloidosis of the respiratory system.

WHAT IS CARDIAC AMYLOIDOSIS?

Cardiac amyloidosis is a systemic form of amyloidosis in which the protein-based infiltrates deposit in myocardial tissue along with other tissues throughout the body. The accumulation of amyloid fibrils causes the myocardium to thicken and stiffen, leading to diastolic dysfunction. Diastolic dysfunction progresses to restrictive cardiomyopathy and, eventually, congestive heart failure (*8*).

Until recently, cardiac amyloidosis was considered rare. However, the recent adoption of noninvasive diagnostic testing has revealed a previously undiagnosed sizable prevalence of the disease (*2*). Cardiac amyloidosis has been identified as a primary cause of heart failure, particularly unexplained heart failure with preserved ejection fraction (HFpEF) in

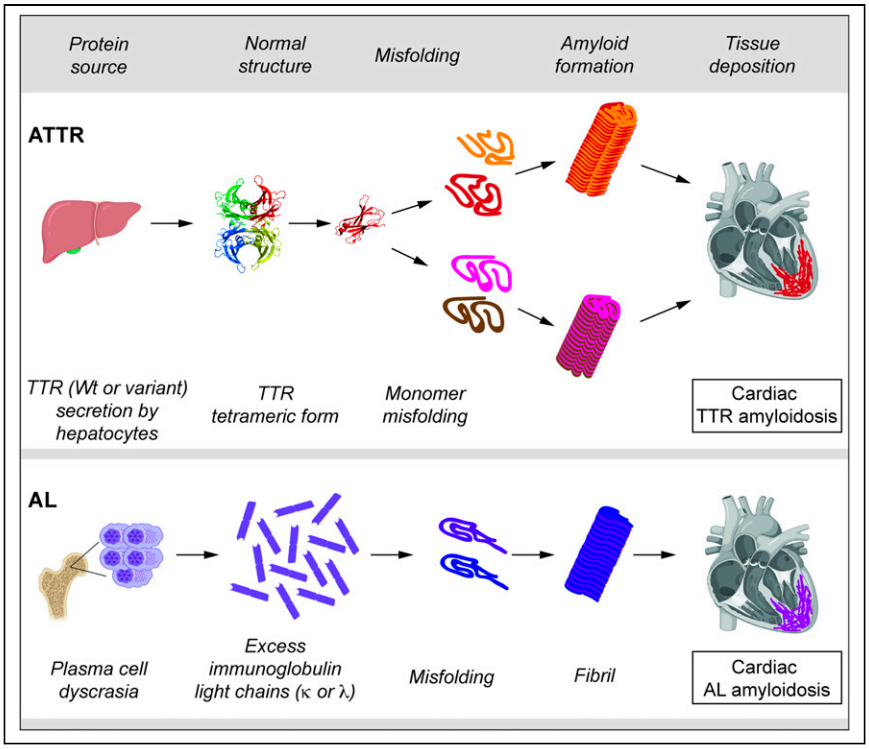

FIGURE 1. Amyloid molecular mechanisms and imaging characteristics. Source, protein, misfolding, fibril formation, and deposition are depicted for cardiac ATTR and AL. In ATTR (both wild-type and variant), transthyretin proteins are secreted by liver, fold abnormally, and form fibrils that are deposited in myocardium. In AL, immunoglobulin light-chain proteins misfold and form fibrils that are also deposited in myocardium. Echocardiography, CMR, and PET can detect both types of cardiac amyloidosis. However, nuclear imaging with bone-seeking tracers can differentiate between ATTR and AL, although there is evidence to suggest that a percentage of AL will be positive on nuclear imaging. TTR = transthyretin; Wt = wild-type. (Adapted from (*2*).)

the elderly (*9*). Cardiac amyloidosis is so unrecognized and underdiagnosed that recent research suggests most patients experience a delay of 2 or more years from when a patient first presents to a physician to when cardiac amyloidosis is diagnosed (*2*).

Two subtypes, AL and ATTR, make up approximately 95% of all cardiac amyloid diagnoses (Fig. 2) (*10*). Other forms of systemic amyloidosis, such as serum amyloid A amyloidosis, rarely affect the heart. The responsible proteins, the phenotypic expression (observable traits), therapy, and prognosis differ vastly between AL and ATTR. Therefore, differentiation between the two is essential. However, if left untreated, both types can lead to heart failure and reduced life expectancy (*11*).

Cardiac AL

AL results from plasma cell dyscrasia, the unregulated proliferation of a single plasma cell clone (*2*). AL prognosis, in general, is a function of the number and severity of organs involved. However, cardiac involvement harbors the worst prognosis because it has a rapid clinical progression and is rarely diagnosed before symptoms appear. Furthermore, the emergence of symptoms often signals advanced organ involvement (*12*). Unfortunately, cardiac AL, with its poor prognosis, has a median survival of 6 mo from the onset of heart failure if left untreated (*13*). Treatment focuses on symptom management and the suppression of additional light-chain production and usually entails chemotherapy and immunotherapy.

Fortunately, cardiac AL is relatively rare. Men and women are diagnosed at about the same rate, and diagnosis typically occurs in patients between the ages of 40 and 80 y (*2*). Cardiac AL can be associated with other immunoglobulin-related diseases, such as multiple myeloma (*9*).

Cardiac ATTR

Compared with cardiac AL, there is less evidence of direct toxic effects associated with cardiac ATTR. It is subdivided into wild-type ATTR, previously called senile amyloidosis, and variant, or hereditary, ATTR.

Wild-type ATTR is the most common type of cardiac amyloidosis and is considered a chronic disease that occurs with aging. Wild-type ATTR accounts for about 80% of cardiac amyloidosis cases. Although the overall prevalence in the general population has not been firmly established, on autopsy, nearly 30% of patients over 75 y old with HFpEF without an antemortem suspicion of amyloid disease were found to have wild-type ATTR (*14*). Similarly, wild-type ATTR has been found in 13% of hospitalized patients

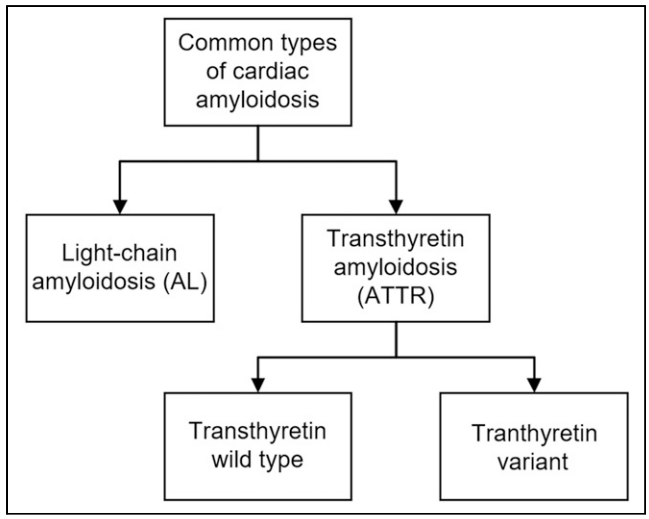

FIGURE 2. Common types of cardiac amyloidosis. Two kinds of amyloidosis account for approximately 95% of all cardiac amyloidosis cases: AL and ATTR.

with HFpEF and left ventricular wall thickness greater than 1.2 cm (*15*).

Wild-type ATTR occurs predominantly in people over 70 y old and affects men more often than women (*16*). Although the factors behind the lower prevalence in women have not been elucidated, one study suggested hormonal protection for women against wild-type ATTR (*17*). Wild-type ATTR is clinically associated with bilateral carpal tunnel syndrome, aortic stenosis, atrial fibrillation, and other conditions resulting in increased wall thickness (*1*). The median survival from diagnosis is 57 mo (*13*).

Variant ATTR is inherited from a genetic mutation in the transthyretin gene that affects the amino acid sequence and predisposes the protein to misfolding (*16*). Over 120 variant ATTR genotypic mutations have been identified (*18*). Worldwide, the most common mutation is V30M, which is associated more with sensory or autonomic neuropathy than with cardiomyopathy. In the United States, the V122I mutation, which is more likely to cause cardiomyopathy, is more common. Again, although the exact prevalence is unknown, it is estimated that 2 million people in the United States are carriers and that 3%–4% of African Americans carry the gene (*2*).

Like wild-type cardiac ATTR, variant cardiac ATTR is more common in men and is usually diagnosed between the ages of 55 and 75 y (*1*). It is also associated with bilateral carpal tunnel syndrome along with polyneuropathy. The median survival from diagnosis is 31 mo for the V122I form and 69 mo for other forms of variant ATTR (Table 1) (*13*).

SIGNS AND SYMPTOMS OF CARDIAC AMYLOIDOSIS

If left untreated, all forms of cardiac amyloidosis eventually result in heart failure due to the restrictive nature of the disease and diastolic dysfunction. Thus, many patients experience the classic symptoms of heart failure, including shortness of breath during exertion and when lying down; swelling in the feet, ankles, and legs; orthostatic hypotension; irregular heart rhythms; lightheadedness; abdominal distension; and a sense of overall weakness and fatigue (*19*). If amyloid is deposited in the heart valves, it can lead to regurgitation or stenosis. It is not uncommon to discover that patients being treated for severe aortic stenosis also have ATTR. Treatment for both types of cardiac ATTR includes the management of heart failure symptoms and arrhythmias. In addition, new pharmacotherapeutic drugs are available that can help silence, stabilize, or break down errant proteins.

Because amyloidosis is a systemic disease, patients may—depending on the type of amyloidosis—experience other symptoms, often called red flags, such as numbness, tingling, or pain in the hands or feet. Patients with cardiac amyloidosis may have skin changes, such as thickness or easy bruising. Some patients with AL may demonstrate purple patches around the eyes (periorbital purpura), sometimes called panda or raccoon eyes (*20*). Macroglossia, an enlarged tongue that looks rippled along the edge, is a symptom in patients with AL (*21*). Finally, because AL can affect the kidneys and gastrointestinal tract, patients may experience increased or decreased urination, diarrhea, or constipation (*22*).

^{99M}TC-PYROPHOSPHATE SCAN ACQUISITION

Because cardiac amyloidosis eventually results in cardiac dysfunction, a debilitating disease, and because the treatment options vastly differ between ATTR and AL, it is critical to diagnose and differentiate between them. ^{99m}Tc-pyrophosphate imaging can efficiently and effectively distinguish between ATTR and cardiac AL. Although the exact mechanism underlying ^{99m}Tc-pyrophosphate uptake in cardiac amyloidosis is unknown, it has been hypothesized that ATTR amyloid plaque contains a higher concentration of microcalcifications that bind with the pyrophosphate, allowing for improved uptake on nuclear cardiac imaging (Fig. 3) (*23*). ^{99m}Tc-pyrophosphate imaging has a 97% sensitivity and nearly 100% specificity for identifying cardiac ATTR when the AL form of the disease is

TABLE 1
Cardiac Amyloidosis Subtypes and Clinical Characteristics

Subtype	Cause	Protein	Age range (y)	Sex frequency	Frequency of cardiac involvement	Other organ involvement or conditions	Associated conditions
AL	Plasma cell dyscrasia	Immunoglobulin light chain	40–80	Men = women	70%	Heart, kidney, gastrointestinal, tongue, nerves, liver, soft tissue	Multiple myeloma
Wild-type ATTR	Aging	Transthyretin	>70	Men > women	100%	Heart, peripheral nerves	Bilateral carpal tunnel syndrome, lumbar spinal stenosis, atrial fibrillation, biceps tendon rupture
Variant ATTR	Inherited genetic mutation	Transthyretin	55–75	Men > women	30%–100% (depending on mutation)	Heart, nerves	Bilateral carpal tunnel syndrome, polyneuropathy

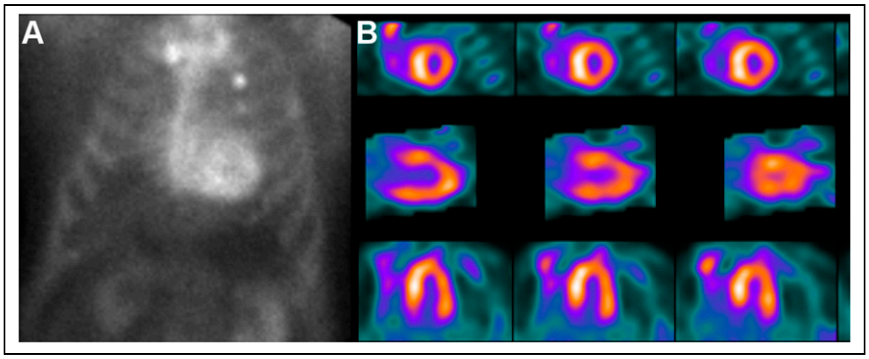

FIGURE 3. Abnormal planar and SPECT ^{99m}Tc-pyrophosphate cardiac amyloidosis scans. (A) ^{99m}Tc-pyrophosphate planar anterior image showing avid myocardial uptake. (B) SPECT short-axis (top), vertical long-axis (middle), and horizontal long-axis (bottom) images of same patient showing diffuse myocardial uptake. This scan is considered diagnostic of ATTR cardiomyopathy if serum and urine studies for AL are negative. (Reprinted from (*2*).)

ruled out by the serum free light-chain ratio and serum and urine protein electrophoresis with immunofixation tests (discussed in part 3).

Protocol Note

In the literature, several radiopharmaceuticals and imaging protocols have been used for cardiac amyloidosis imaging over the past 40 y (*24*). However, with the recent renewed interest in radionuclide imaging, the multitude of protocols and lack of standardization have caused confusion and misdiagnosis. In response, the American Society of Nuclear Cardiology and several other professional medical societies, including the Society of Nuclear Medicine and Molecular Imaging, published "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" in 2019. The goal was to standardize performance and interpretation to improve quality and patient outcomes (*24*). In 2021, American Society of Nuclear Cardiology and the other societies published an addendum to the recommendations to further refine ^{99m}Tc-pyrophosphate imaging (*25*). The protocol described below follows those recommendations.

Indications and Contraindications

A variety of patient populations may be scheduled for ^{99m}Tc-pyrophosphate cardiac amyloidosis imaging. However, patients with certain diagnoses present more often than others. Many patients with suspected cardiac amyloidosis have classic symptoms of heart failure. These patients also often present with unexplained increased left ventricle thickness. Thus, the primary indication for ^{99m}Tc-pyrophosphate imaging is the evaluation of patients with heart failure and increased left ventricular wall thickness not associated with other conditions or reasons. ^{99m}Tc-pyrophosphate imaging is also indicated for men over 60 y old who may be African Americans or patients with HFpEF (*2*).

Patients with signs of heart failure and a history of bilateral carpal tunnel syndrome, unexplained neuropathy, or atrial arrhythmias are also candidates for ^{99m}Tc-pyrophosphate imaging (*19*). In addition, ^{99m}Tc-pyrophosphate imaging is indicated to differentiate variant from wild-type cardiac ATTR in patients with a suspected or known family history of amyloidosis. Finally, patients who are believed to have cardiac ATTR but have contraindications to cardiac MRI, such as implantable devices or renal insufficiency, are candidates for ^{99m}Tc-pyrophosphate imaging (*2*).

There are no known contraindications specific to ^{99m}Tc-pyrophosphate imaging other than the usual nuclear medicine procedure cautions related to pregnancy, breastfeeding, and other recent nuclear medicine scans.

Patient Preparation and Education

There are no specific patient restrictions before ^{99m}Tc-pyrophosphate imaging. Patients may eat, drink, and take their medications as usual. However, at the time of appointment scheduling, patients should be warned about the 3-h delay between injection and imaging.

A thorough patient medical history is crucial for accurate interpretation of ^{99m}Tc-pyrophosphate cardiac amyloidosis scans (*24*). The level of detail required is substantially more than necessary for other types of nuclear medicine scans. Thus, a standardized history sheet is useful in ensuring collection of complete information.

The patient interview should include past medical problems, specifically those related to heart failure and other cardiac diseases. The past medical history should also elicit information pertaining to bilateral carpal tunnel syndrome, lumbar spinal stenosis, orthopedic procedures, biceps tendon rupture, unexplained peripheral neuropathy, and autonomic dysfunction. In addition, the record needs to include any family history of amyloidosis, cardiomyopathy, or polyneuropathy.

Documentation of current symptoms, even if they do not seem heart-specific, is necessary to diagnose cardiac amyloidosis. Particular attention must be paid to signs and symptoms of heart failure, such as shortness of breath, lower-extremity edema, weakness, fatigue, or irregular heartbeat. Finally, the results of any previous diagnostic tests, including echocardiography, cardiac MRI, electrocardiography, and clinical laboratory testing, must be noted.

Radiopharmaceutical

A variety of ^{99m}Tc-diphosphonate and pyrophosphate bone-seeking agents, specifically ^{99m}Tc-pyrophosphate, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), and ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP), can be used to diagnose ATTR cardiomyopathy (*24*). In the

absence of cardiac amyloidosis or subacute myocardial infarction, these bone tracers do not accumulate in the myocardium. Thus, radionuclide imaging can differentiate cardiac amyloidosis from other conditions that mimic it, such as hypertrophic cardiomyopathy.

Although no studies to date have directly compared the 3 tracers, the published literature suggests they can be used interchangeably. ^{99m}Tc-DPD and ^{99m}Tc-HMDP are predominantly used in Europe because ^{99m}Tc-pyrophosphate is not available there. ^{99m}Tc-pyrophosphate is used in the United States because the Food and Drug Administration has not approved ^{99m}Tc-DPD and there is limited access to ^{99m}Tc-HMDP. ^{99m}Tc-methylene diphosphonate, although widely available in the United States, has a significantly lower sensitivity and should not be used for cardiac amyloid imaging.

The recommended dose is 370–740 MBq (10–20 mCi) administered intravenously. The total radiation exposure from a 555-MBq (15-mCi) dose is approximately 3 mSv (*26*).

^{99m}Tc-pyrophosphate clears from the blood pool, with rapid uptake in the bone and myocardium (*27*). Accumulation of ^{99m}Tc-pyrophosphate in the bone continues to increase over time. However, myocardial uptake in amyloid disease peaks at about 1 h and then slowly begins to decline. The ^{99m}Tc-pyrophosphate blood pool clearance rate depends on bone metabolism and renal function. The higher the bone metabolism along with normal renal function, the faster the ^{99m}Tc-pyrophosphate clears from the blood pool, improving the semiquantitative and quantitative interpretation of the study.

Acquisition

After intravenous injection of the ^{99m}Tc-pyrophosphate, both planar and SPECT images of the patient's chest are obtained 3 h later (*26*). Imaging is usually performed on a standard dual-head γ-camera using a 90° detector configuration (*27*). However, recent research demonstrated that ^{99m}Tc-pyrophosphate imaging and 3-dimensional semiquantitative analysis of the images is feasible using newer cadmium-zinc-telluride cameras (*28*).

Although imaging can be performed on a camera with a small field of view, positioning is more difficult (*27*) and the

TABLE 2
^{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, whole-body imaging when imaging with ^{99m}Tc-HMDP or ^{99m}Tc-DPD demonstrates soft-tissue uptake.

camera may not be large enough to image the complete chest so that rib uptake can be observed and the heart–to–contralateral-lung ratio calculated (described in part 2).

Patients are imaged supine with their arms above their head. For cameras with a large field of view, the patient's shoulders should be near the top of the field of view to visualize the entire ribcage (*25*). The planar images include the anterior and left lateral projections. Imaging parameters vary among equipment, but the overall parameters outlined in the 2021 addendum to the recommendations (*25*) work well for most camera systems (Table 2).

The SPECT acquisition should include as much of the chest as will fit within the field of view (*25*). Usually, with large-field-of-view cameras, a zoom of 1.46 is used. SPECT imaging may be performed using a 180° or 360° acquisition, and parameters for both are provided in Table 2. If SPECT/CT is available, CT attenuation correction is recommended.

Whole-body imaging is optional and has been shown to be of benefit, especially when imaging with ^{99m}Tc-DPD or ^{99m}Tc-HMDP (*26*). Whole-body imaging can demonstrate ^{99m}Tc-DPD or ^{99m}Tc-HMDP uptake in the shoulder and hip girdles, a specific indicator of systemic ATTR.

SUMMARY

The recent discovery of the sizable prevalence of cardiac amyloidosis in the population, especially in patients with heart failure of unknown origin or those with HFpEF, has led to a dramatic increase in the number of laboratories performing cardiac amyloidosis imaging, which has a high sensitivity and specificity when performed correctly. However, the lack of published guidelines delineating standardized imaging parameters and interpretation criteria for cardiac amyloidosis imaging led to considerable study variability and the potential for misdiagnoses. Thus, the American Society of Nuclear Cardiology, the Society of Nuclear Medicine and Molecular Imaging, and several other professional societies published consensus recommendations for performing and interpreting ^{99m}Tc-pyrophosphate cardiac amyloidosis imaging.

This article, part 1 of a 3-part series, explains the etiology and characteristics of cardiac amyloid disease so that technologists understand how the intricacies of the disease affect test performance. This article further provides a technical foundation for study acquisition. Part 2 details how to process and quantify the images and justifies some of the technical considerations of ^{99m}Tc-pyrophosphate cardiac amyloidosis imaging. Finally, part 3 puts acquisition and data quantification together to describe study interpretation and the diagnosis and treatment of cardiac amyloidosis.

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