Turk Kardiyol Dern Ars 2020;48(5):514-521 doi: 10.5543/tkda.2020.90914

INVITED REVIEW

Cardiac scintigraphy-centered diagnostic process in transthyretin cardiac amyloidosis

Transtiretin kardiyak amiloidozda kardiyak sintigrafi odaklı tanısal süreç

İlknur Ak Sivrikoz, M.D.,[1] Yüksel Çavuşoğlu, M.D.[2]

[1]Department of Nuclear Medicine, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Turkey;
[2]Department of Cardiology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Turkey

Summary– Cardiac amyloidosis (CA) is a progressive infiltrative cardiomyopathy. Amyloid fibrils in the form of misfolded endogenous proteins accumulate in the heart, as well as the kidneys, liver, and gastrointestinal tract. The most common forms of CA are transthyretin (TTR) and immunoglobulin light chain amyloidosis (AL). CA has long been thought to be a rare disease. However, recent reports have suggested that 13% of heart failure patients with a preserved ejection fraction and 16% of advanced-age patients with severe aortic stenosis have TTR-CA. Patients with TTR-CA have a poor prognosis, with a median survival of 2–4 years; however, early diagnosis and novel therapeutic options have been shown to significantly improve the prognosis. Scintigraphy using bone isotopes is considered a highly reliable and easy-to-use method in the diagnosis of TTR-CA. This is a review of the role of scintigraphic imaging with technetium-99m- labeled bisphosphonates in the diagnostic work-up process of TTR-CA and the applicable protocols.

Özet– Kardiyak amiloidoz (KA), ilerleyici infiltratif bir kardiyomiyopatidir. Katlanması bozulan endojen proteinlerin amiloid fibriller şeklinde kalpte ve bazen beraberinde böbrek ve karaciğerde birikimi ile ortaya çıkar. En sık gözlenen KA formları, transtiretin (TTR) ve immünglobulin hafif zincir (AL) amiloidozudur. KA bugüne kadar nadir görülen bir hastalık olarak düşünülmüştür. Ancak yeni veriler korunmuş ejeksiyon fraksiyonlu kalp yetersizliği olgularının %13 ve yüksek riske sahip ciddi aort darlığı bulunan yaşlı olguların %16'sında TTR-KA bulunduğunu göstermektedir. TTR-KA olguları kötü prognoza sahiptir. Bu hastaların ortalama sağ kalım süresi 2–4 yıl olarak bildirilmektedir. Erken tanı ve tedavi yaklaşımları ile prognozun anlamlı düzeltilebildiği gösterilmiştir. Kemik ajanları ile yapılan sintigrafi, TTR-KA tanısında oldukça güvenilir ve uygulaması kolay bir yöntem olarak gösterilmektedir. Bu belgede, TTR-KA tanısal sürecinde kemik ajanları ile yapılan sintigrafinin rolü ve uygulama protokolleri gözden geçirilmiştir.

Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy for which there is growing awareness.[1] CA results from the myocardial deposition of misfolded endogenous proteins in the form of amyloid fibrils.[2] CA may be accompanied by amyloid deposition in the kidneys, liver, or gastrointestinal tract. However, the diagnosis of CA is often overlooked or ignored in clinical practice, and the condition is frequently confounded with hypertensive left ventricular hypertrophy (LVH) or hypertrophic cardiomyopathy.[1,2] The diagnosis of amyloidosis is challenging. Therefore, highly accurate, simple, and widely available diagnostic methods are needed. Recently, the value of cardiac scintigraphy with bone imaging agents has been recognized in the diagnosis transthyretin (TTR) CA. Radioactive bone scintigraphy is of central significance in the diagnostic process of TTR-CA with a diagnostic performance of almost 100%, eliminating the need for a biopsy.[2] However, awareness among clinicians about the role of scintigraphy in the diagnosis of TTR-CA is inadequate. There is a remarkable lack of experience with the nuclear isotopes to be used in bone scintigraphy, the scintigraphy protocols, and the interpretation of data obtained from the procedure. This review is a discussion of the role of bone scintigraphy in the diagnosis of TTR-CA, as well as protocols to be used in the performance and interpretation of scintigraphy scans.

Cardiac Amyloidosis From the Clinical Point of View

To date, several types of amyloidosis (AA amyloi-

Received: April 17, 2020 *Accepted:* June 02, 2020
Correspondence: Dr. Yüksel Çavuşoğlu. Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Eskişehir, Turkey.
Tel: +90 222 - 239 29 79 e-mail: yukselc@ogu.edu.tr

dosis, familial amyloid polyneuropathy, atrial amyloidosis, etc.) have been found to involve the heart, but TTR-related CA and immunoglobulin light chain amyloidosis (AL)-CA are the most common types encountered in clinical practice.[2] There are 2 types of TTR–related CA: mutant transthyretin (mTTR)-CA and wild type transthyretin (wtTTR)-CA.

TTR is a plasma transport protein synthesized in the liver that transports the thyroid hormone and retinol. mTTR-amyloidosis may result from any of more than 130 mutations defined in the gene-encoding TTR protein, and may present with cardiac involvement and/or neuropathy, based on the mutation underlying the disease.[3] Genetic analysis does not reveal any mutation in wtTTR-amyloidosis, which predominantly occurs in the cardiac phenotype. However, both types of TTR-related amyloidosis are characterized by TTR deposition.

TTR-CA may not be as rare as previously believed. In a recently published study, wtTTR amyloidosis was detected in 13.3% of patients aged 60 years or older who presented with heart failure with preserved ejection fraction (HFpEF) and LVH (≥12 mm).[4] Autopsy findings support indications that amyloid deposition may be found in 32% of individuals aged >75 years and 8% of individuals aged <75 years, and the incidence of wtTTR may increase with age.[5,6] wtTTR-CA has been reported in 16% of elderly patients with calcific aortic stenosis. Indeed, wtTTR-CA typically occurs in the elderly (>60 years of age).

Although mTTR amyloidosis is quite a rare condition, a relatively higher prevalence of several mutations has been reported for certain geographic regions, societies, and races.[7] For instance, the prevalence of a Val30Met mutation has been reported at 1:538 in Northern Portugal and 4% in Northern Sweden. The prevalence of a Thr60AlaTTR mutation has been reported at 1.1% in Northern Ireland, and the prevalence of a Val122Ile mutation has been reported to vary between 3% and 4% in African-Americans. However, the age of onset and the appearance of the clinical manifestations of CA may vary among people with mutated TTR.

As with mTTR amyloidosis, AL-CA is a rare type of amyloidosis. The prevalence of AL-CA has been estimated at 3 to 5 per million in the USA, 10 per million in the UK, and 3.2 per million in Sweden.[8–10] Symptomatic cardiac involvement occurs in 30% to 50% of patients with AL amyloidosis.

AL-CA has the poorest prognosis among all of the types of amyloidosis.[11] The mean overall survival is about 6 months, whereas the mean overall survival in patients with TTR-related amyloidosis is estimated at 27 months. In addition, mTTR-CA is associated with a poorer survival compared with wtTTR-CA. One study has reported a mean overall survival of 43 months for wtTTR-CA and 26 months for mTTR-CA.[12] However, early detection and specific treatment may prolong survival by many years. Amyloid subtyping is of great importance in determining specific treatments. Once a diagnosis of AL-CA is made, hematologic/oncologic therapies (such as chemotherapy, stem cell therapies, etc.) addressing the underlying etiology should be initiated immediately, whereas specific therapies (tafamidis, etc.) preventing amyloid protein deposition should be considered once a diagnosis of wtTTR/mTTR-CA is made.

Abbreviations:

AL	*Immunoglobulin light chain amyloidosis*
CA	*Cardiac amyloidosis*
DPD	*3,3-diphosphono-1,2-propanodicarboxilic acid*
ECG	*Electrocardiogram*
ECHO	*Echocardiography*
EMB	*Endomyocardial biopsy*
H/L	*Heart to contralateral lung ratio*
HMDP	*Hydroxymethylene diphosphonate*
HFpEF	*Heart failure with preserved ejection fraction*
I-123	*Iodine-123*
LGE	*Late gadolinium enhancement*
LVH	*Left ventricular hypertrophy*
MDP	*Methylene diphosphonate*
MIBG	*I-123 metaiodobenzylguanidine*
mTTR	*Mutant transthyretin*
PET	*Positron emission tomography*
PYP	*Pyrophosphonate*
SPECT	*Single-photon emission computerized tomography*
Tc99m	*Technetium-99m*
TTR	*Transthyretin*
wtTTR	*Wild type transthyretin*

Clinical Characteristics of Potential Candidates for Cardiac Amyloidosis

Within the scope of cardiology, patients with HFpEF along with ventricular wall thickening and elderly patients with nonrheumatic severe aortic stenosis are considered potential candidates for TTR-CA.[1–3] These patients typically present with symptoms associated with HFpEF. Normotension/hypotension in a previously hypertensive patient or intolerance to beta-blockers/angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers should suggest CA. Paresthesia in the extremities, orthostatic hypotension, a history of carpal tunnel syndrome, and syncope are also among the manifestations suggesting CA. CA should be investigated in patients with unexplained LVH, and particularly in elderly patients with new-onset hypertrophic cardiomyopathy.[1,2] CA should be taken into consider-

ation in conduction abnormalities leading to syncope in the elderly. Although a low voltage electrocardiogram (ECG) is typical for CA, a lack of agreement between the voltage of the ECG and the wall thickness observed with echocardiography (ECHO) should also suggest amyloidosis.[1–3] Patients with LVH accompanied by valve thickness or pericardial effusion should be considered candidates for amyloidosis.

Diagnostic Work-up in Cardiac Amyloidosis

ECHO is the most widely used method in the diagnostic workup of CA. Characteristic ECHO findings for CA include ventricular, interatrial septal, and valvular thickening; pericardial effusion; and biatrial dilatation.[13] A "sparkling" appearance of the thickened wall, which is specific to amyloidosis, can be identified by an experienced echocardiographer. Abnormal diastolic parameters are among the early findings. The global longitudinal strain is reduced. Apical sparing accompanied by a decreased global longitudinal strain is considered specific to CA and differentiates CA from other causes of hypertrophy.[14] Yet while ECHO may reveal many important findings of CA, none of these findings is diagnostic.

When compared with ECHO, cardiac magnetic resonance imaging (MRI) may provide more valuable diagnostic information for CA.[15,16] Cardiac MRI has an important role in the noninvasive diagnosis of CA because it can provide information about tissue characteristics in addition to high-resolution morphological and functional assessment of the heart. In cases of wall thickening, MRI may help differentiate CA from other causes of cardiomyopathy. In addition to findings that are identifiable using ECHO, the most important diagnostic findings for CA that may be provided by MRI include global subendocardial fibrosis at the initial stage and transmural fibrosis at advanced stages as revealed with late gadolinium enhancement (LGE)-imaging and increased extracellular volume as revealed using T1 mapping. As with ECHO, MRI alone cannot serve to make a diagnosis of CA, even though the diagnostic sensitivity and specificity of LGE imaging for CA is 80% and 94%, respectively, when compared with an endomyocardial biopsy (EMB). MRI is particularly useful when ECHO findings are inconclusive or indefinite. However, MRI cannot differentiate AL-CA from TTR-CA. Kidney impairment, which is very common among patients with amyloidosis, can also limit the use of contrast agents. Furthermore, cardiac MRI may not be available in every healthcare center, and when available, an experienced MRI team is needed.

EMB is a very sensitive and specific method (about 100% for each) and has been considered the gold standard in the diagnosis of CA.[17] However, considering the invasive nature of the procedure, EMB should be performed only if there is a strong suspicion of CA. Furthermore, the procedure is associated with a risk of complications, and a specific specialty is required to interpret the histological examination. Furthermore, a negative EMB cannot exclude amyloidosis. Due to the risk of complications associated with EMB, other tissue/organ (e.g., subdermal fat tissue, labial, rectal, renal tissue, etc.) biopsies are often performed to diagnose amyloidosis. However, the lack of adequate amyloid deposition in corresponding tissues/organs may yield a negative result, and it must be remembered that negative results cannot exclude CA.[18]

Genetic analysis is usually performed for amyloid typing and family scanning once a diagnosis of amyloidosis has been made. Serum and urine protein electrophoresis, immunofixation, and serum and urine light chain testing should be done to diagnose or rule out AL-CA.[1,2] ECG and N-terminal pro B-type natriuretic peptide/B-type natriuretic peptide and cardiac troponin measurements may provide additional evidence to support the diagnosis of amyloidosis.

Radionuclide Imaging

Three main groups of radioisotope-labeled agents are used to identify amyloid deposition noninvasively with conventional radionuclide techniques: iodine-123 (I-123)-labeled serum amyloid P component, technetium-99m (Tc-99m)-labeled aprotinin, and Tc-99m-labeled bone agents. The use of I-123-labeled serum amyloid P component and Tc-99m-labeled aprotinin is limited by low cardiac image quality.[20] Bone imaging agents, such as Tc-99m-labeled pyrophosphonate (PYP), 3,3-diphosphono-1,2-propanodicarboxilic acid (DPD), and hydroxymethylene diphosphonate (HMDP) are widely accepted radioactive agents to be used in radionuclide imaging and the noninvasive diagnosis of CA.[21]

It has long been known that myocardial uptake of Tc-99m-labeled PYP derivatives occurs in patients with

CA.[22–25] In the early 1980s, increased myocardial uptake of bone imaging agents and ECHO findings suggestive of CA were reported for the first time in patients with biopsy-confirmed extracardiac amyloidosis.[24] Intense activity was incidentally detected in the cardiac region during bone scanning in a patient with CA at our center, and this case report was published in 2000.[26] Bone imaging agents show a high affinity for calcium. The underlying mechanism of increased uptake of diphosphonates in amyloidosis may be associated with an increased calcium concentration in tissues where amyloid deposition occurs.[26] The amyloid P component is a calcium-dependent protein that binds amyloid fibrils together.[27]

The P component is found in all forms of amyloid and may be associated with diphosphonate binding to calcium in amyloid fibrils. Cardiac scintigraphy with bone agents, such as Tc-99m PYP, Tc-99m DPD, and Tc-99m HMDP, is an essential tool in the management of patients with CA.[28–30] All 3 agents have proven valuable in studies of cardiac involvement in amyloidosis. However, Tc-99m PYP has US Food and Drug Administration approval and has become prominent in studies demonstrating precise diagnostic accuracy for TTR-CA. Although methylene diphosphonate (MDP) is a commonly used radionuclide for bone scanning in practice, this agent has a low sensitivity in cardiac imaging. This may be the result of the higher bone mineral affinity of bisphosphonates that contain a hydroxyl group, such as DPD or HMDP. Therefore, the diagnostic performance of MDP is lower in the detection of patients with grade 1 or even grade 2 amyloidosis due to the low calcium deposit content and the use of MDP is not recommended in cardiac imaging. In fact, there are case reports in the literature regarding intense myocardial uptake with PYP in cases missed using Tc-99m MDP scintigraphy.[31] In our center, we have also had cases showing significant myocardial uptake of PYP but not Tc-99m MDP. The other 2 agents (DPD, HMDP) have been approved for use in Europe. Although the molecular structures of Tc-99m DPD and Tc-99m PYP are similar, these 2 isotopes differ in pharmacokinetics.[32] The imaging protocols for Tc-99m DPD/HMDP include images obtained 3 hours after radiotracer injections. On the other hand, only 10% of the injected dose remains in the heart at 1 hour after a Tc-99m PYP injection. Therefore, images should be obtained within 1 hour of the Tc-99m PYP injection to diagnose CA.

Bone Scintigraphy Imaging and Interpretation in Cardiac Amyloidosis

Depending on the radiotracer used in scintigraphy for CA, planar and single-photon emission computerized tomography (SPECT) images are obtained at 1 hour and 3 hours after a Tc-99m PYP injection. The first step of the analysis includes a visual assessment of cardiac uptake on the planar and SPECT images. Once cardiac uptake is confirmed, 2 approaches may be adopted. The first approach includes quantitative analysis by calculating the heart to contralateral lung (H/L) uptake ratio at 1 hour post injection. A ratio of ≥1.5 is considered positive for TTR-CA, and an H/L ratio of <1.5 is deemed negative. The second approach

Table 1. Semi-quantitative visual grading; cardiac uptake scoring at hour 3

Grade	Tc-99m PYP cardiac uptake
Grade 0	No cardiac uptake
Grade 1	Cardiac uptake less intense than the sternum
Grade 2	Cardiac uptake intensity similar to the sternum
Grade 3	Cardiac uptake intensity greater than the sternum

PYP: Pyrophosphonate; Tc99m: Technetium-99m.

Table 2. Cardiac Tc-99m PYP uptake analysis

Quantitative assessment	The heart (H) to contralateral lung (L) ratio on planar or single-photon emission computed tomography (SPECT) images at 1 hour post injection: An H/L ratio of ≥1.5 is deemed positive for transthyretin (TTR)-cardiac amyloidosis (CA), and an H/L ratio of <1.5 is regarded as negative for TTR-CA.
Semi-quantitative assessment	Grade 2 to 3 uptake on planar or SPECT images at 3 hours post injection is considered positive for TTR-CA, and Grade 0–1 uptake at 3 hours post injection is deemed negative for TTR-CA.

Although grade 2 to 3 or an H/L uptake ratio >1.5 suggests TTR amyloidosis, protein electrophoresis, or serum light chain testing should be performed to exclude immunoglobulin light-chain amyloidosis (AL), as any grade of myocardial uptake of 99mTc-PYP may occur in AL-CA. PYP: Pyrophosphonate; Tc99m: Technetium-99m.

is a semi-quantitative visual scoring system based on comparisons between cardiac uptake and bone uptake (usually in the sternum, or on the rib) on images obtained at 3 hours post injection. A scoring system has been defined as grade 0 as no cardiac uptake (excludes TTR-CA), grade 1 reveals cardiac uptake that is less intense than that seen in the sternum, grade 2 uptake is signified by a cardiac uptake intensity similar to that of the sternum, and grade 3 is defined by a cardiac uptake intensity that is greater than that of the sternum (Table 1). A grade 2 or 3 uptake and an H/L ratio of >1.5 strongly suggest TTR-CA (Table 2). A grade 1 uptake and an H/L ratio of 1-1.5 raise suspicion of TTR-CA (Fig. 1). If DPD or HMDP is used in the scintigraphy, the intensity of the uptake is graded using a semi-quantitative visual scoring system.

Diagnostic Value of Bone Scintigraphy in Cardiac Amyloidosis

Perugini et al.[33] reported that a visual grade of ≥2 for myocardial uptake of Tc-99m DPD uptake had a sensitivity of 100% for TTR-CA and a specificity of 100% in the differentiation of TTR- from AL-CA and control subjects. In a meta-analysis of 529 patients with TTR-CA,[34] the sensitivity and specificity of Tc-99m-labeled bone agents was reported to be 92.2% and 94.5%, respectively, though different agents were used in the included studies. In another study that evaluated 857 patients with histologically confirmed amyloidosis (EMB in 374 patients) and 360 patients with non-amyloid cardiomyopathy (1217 in total), the sensitivity and specificity of cardiac scintigraphy for TTR-CA was found to be 99% and 98%, respectively.[35] Furthermore, in the absence of monoclonal protein in the serum and urine, grade 2 and grade 3 myocardial uptake on scintigraphy had a sensitivity and a positive predictive value of 100% for TTR-CA. Cardiac scintigraphy provides critical information about CA, whereas ECHO and MRI offer additional structural and functional characterization. Scintigraphy detects cardiac involvement in amyloidosis earlier and with greater accuracy compared with ECHO and MRI.[36] It also provides information about the intensity of myocardial amyloid deposition and prognosis. The presenting symptoms of CA are rarely specific, and early diagnosis may be challenging. However, early detection and treatment of CA are among the principles for improving the prognosis. Cardiac Tc-99m PYP/DPD/HMDP scintigraphy should be considered for the early detection of TTR-CA in patients with specific features for TTR-CA, such as unexplained LVH, HFpEF, advanced age, degenerative severe aortic stenosis, family history of amyloidosis, or bilateral carpal tunnel syndrome (Fig. 2).

Cardiac scintigraphy with Tc-99m PYP/DPD/HMDP has a very low diagnostic value in AL-CA. There is little (grade 1 uptake) or no myocardial uptake in AL-CA. This difference may be explained by a longer course of the disease and a greater amount of amyloid fibril and calcium deposition in TTR-CA compared with AL-CA. However, a negative Tc-99m PYP/DPD/HMDP scintigraphy cannot exclude AL amyloidosis. Therefore, if ECHO/MRI findings suggest CA despite a negative or suspicious Tc-99m PYP/DPD/HMDP scintigraphy result, AL-CA should be investigated and excluded with protein electrophoresis as well as urine and serum light chain testing with immunofixation (Fig. 2). If both tests are negative, the available evidence suggests that CA is unlikely. In the event of positive Tc-99m PYP/DPD/HMDP scintigraphy findings along with abnormal laboratory results suggesting AL amyloidosis, the patient should be referred to a hematology/oncology clinic.

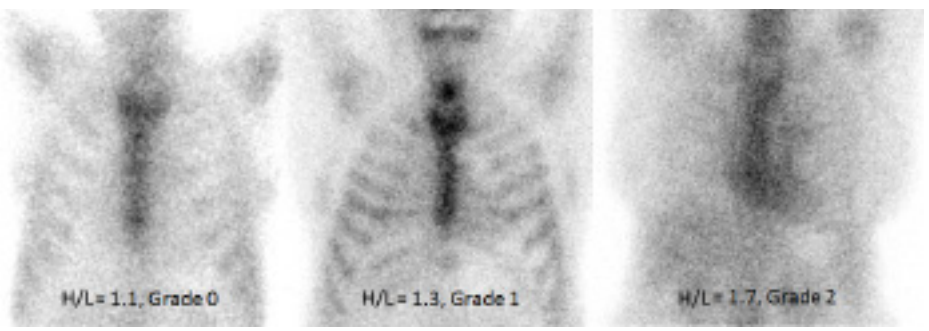

Figure 1. Grade 0 (on the left), Grade 1 (in the middle) and Grade 2 (on the right) cardiac uptake in Tc-99m PYP scintigraphy images

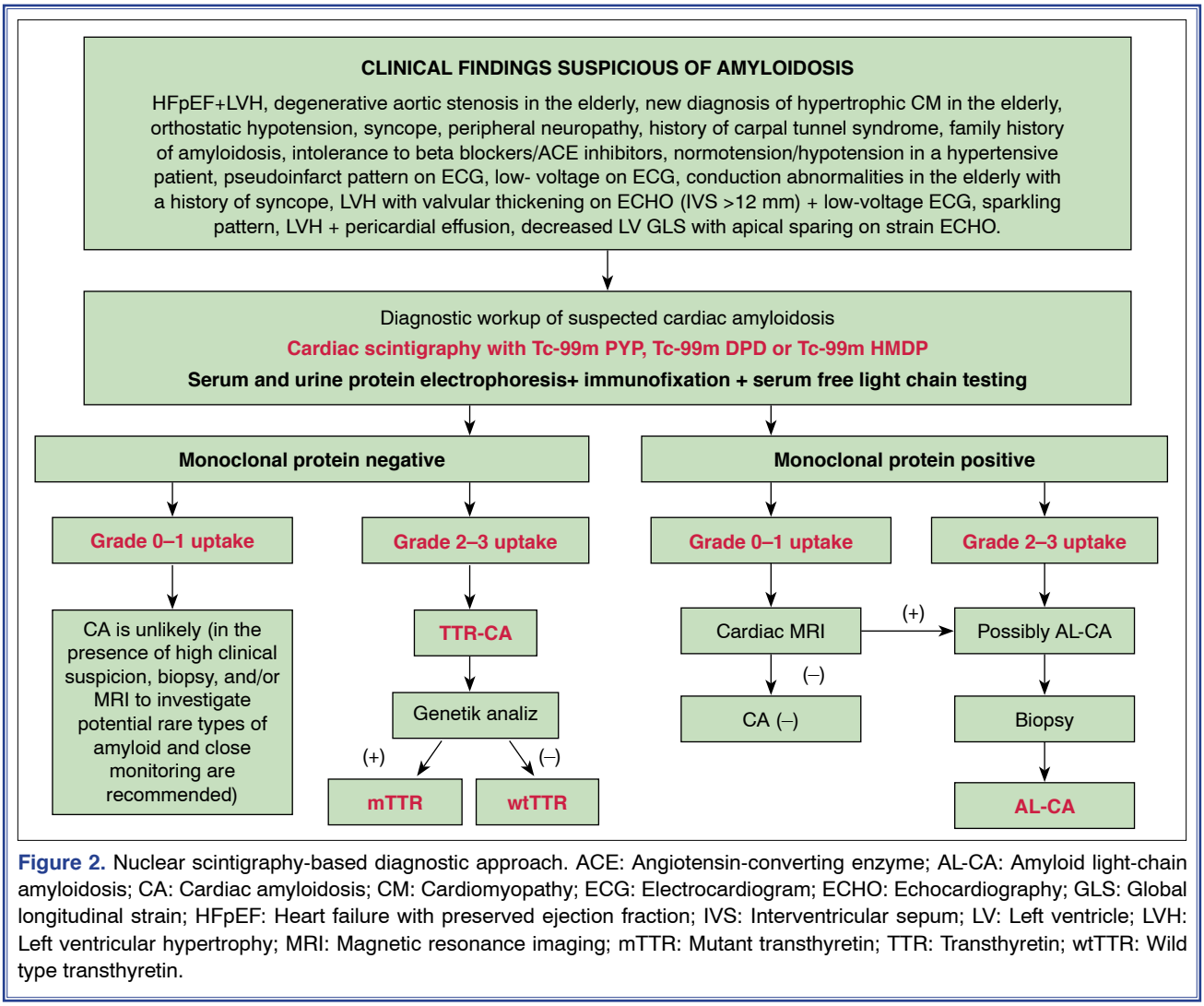

Figure 2. Nuclear scintigraphy-based diagnostic approach. ACE: Angiotensin-converting enzyme; AL-CA: Amyloid light-chain amyloidosis; CA: Cardiac amyloidosis; CM: Cardiomyopathy; ECG: Electrocardiogram; ECHO: Echocardiography; GLS: Global longitudinal strain; HFpEF: Heart failure with preserved ejection fraction; IVS: Interventricular sepum; LV: Left ventricle; LVH: Left ventricular hypertrophy; MRI: Magnetic resonance imaging; mTTR: Mutant transthyretin; TTR: Transthyretin; wtTTR: Wild type transthyretin.

Novel Radionuclide Techniques in Cardiac Amyloidosis

Advances in imaging techniques focus on the differentiation of CA from other hypertrophic phenotypes and the potency of differentiation as well as earlier and accurate diagnosis. The role of F-18 fluorodeoxyglucose, which is the most commonly used agent in positron emission tomography (PET) scanning, remains unclear.[37] In pilot studies of PET scanning using several amyloid-binding imaging agents, a higher myocardial uptake of the radiotracer has been reported in patients with CA compared with controls.[38–42] C-11 Pittsburgh Compound B is one of the first PET radiotracers developed for beta-amyloid imaging; however, it requires an on-site cyclotron due to its short half-life.[41,42] Subsequently, other amyloid-binding radiotracers, including F-18 florbetapir, F-18 florbetaben, and F-18 flutemetamol, have been developed and used to visualize amyloid deposition in patients with dementia; these agents have US Food and Drug Administration approval and are commercially available. A target to background (left ventricular myocardium/blood pool) ratio of >1.5 and a retention index of >0,025 min-1 have been the cutoff values determined to differentiate patients with CA from controls without CA.[38–40] These findings suggest that amyloid PET imaging may help to diagnose CA, assess treatment response, and differentiate TTR-CA from AL-CA in the future. Another critical benefit of amyloid PET imaging is that unlike ECHO or MRI, it has the potential to show systemic amyloid deposits in several organs and to measure the amyloid load in the whole body due to its ability to scan the whole

body in a single session.[42] However, further studies are needed to confirm these results.

Patients with amyloidosis are likely to develop autonomic dysfunction because of amyloid infiltration of myocardial and nerve conduction tissues and may develop rhythm disorders. Although amyloid infiltration of the cardiac autonomic system cannot be shown directly, autonomic myocardial denervation may be visualized using norepinephrine analogs such as I-123 metaiodobenzylguanidine (MIBG), I-124 MIBG, N-[3-bromo-4-3-[F-18] fluoro-propoxy)-benzyl]-guanidine LM1195, C-11 hydroxy-ephedrine, and I-123 MIBG, which accumulate at presynaptic sympathetic nerve terminals. MIBG scintigraphy can indirectly illustrate amyloid infiltration of the cardiac sympathetic system with a comparison of cardiac and mediastinal uptake ratios[43] and can identify innervation changes before the appearance of ECHO findings of the disease. Although there are limited available data, positive I-123 MIBG scintigraphy findings suggest that the risk for fatal arrhythmias may increase in CA.

Conclusion

Contrary to what was previously believed, TTR-CA is not a rare cardiomyopathy and there is an increasing awareness about the condition. A diagnostic work-up for CA should be performed in individuals with clinical high-risk characteristics such as HFpEF, advanced age, degenerative severe aortic stenosis, or ventricular hypertrophy. Cardiac scintigraphy is a widely used, cost-effective, and noninvasive modality that is of central importance in the diagnostic workup of CA. When performed and interpreted in line with recommended protocols and using appropriate bone imaging agents, it has a high diagnostic performance without a need of EMB. A holistic approach that includes the use of multimodal diagnostic tools may ensure high diagnostic sensitivity and specificity. However, large, prospective studies are needed to demonstrate the clinical benefit of cardiac scintigraphy in evaluating treatment response and predicting clinical outcomes.

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

References

1. Seferovic PM, Polovina M, Bauersachs J, Arad M, Gal TB, Lund LH, et al. Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019;21:553–76.
2. Çavuşoğlu Y, Özpelit E, Çelik A, İkitimur B, Kayıkçıoğlu M, Tokgözoğlu L, et al. Cardiac amyloidosis: Recent advances in the diagnosis and therapy. Turk Kardiyol Dern Ars. 2019;47:1–34. [CrossRef]
3. Guan J, Mishra S, Falk RH, Liao R. Current perspectives on cardiac amyloidosis. Am J Physiol Heart Circ Physiol 2012;302:H544–H52. [CrossRef]
4. González-López E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J 2015;36:2585–94.
5. Mohammed SF, Mirzoyev SA, Edwards WD, Dogan A, Grogan DR, Dunlay SM, et al. Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. JACC Heart Fail 2014;2:113–22. [CrossRef]
6. Tanskanen M, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. Ann Med 2008;40:232–9. [CrossRef]
7. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet 2016;387:2641–54.[CrossRef]
8. Kyle RA, Linos A, Beard CM, Linke RP, Gertz MA, O'Fallon WM, et al. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. Blood 1992;79:1817–22. [CrossRef]
9. Pinney JH, Smith CJ, Taube JB, Lachmann HJ, Venner CP, Gibbs SD, et al. Systemic amyloidosis in England: an epidemiological study. Br J Haematol 2013;161:525–32. [CrossRef]
10. Hemminki K, Li X, Försti A, Sundquist J, Sundquist K. Incidence and survival in non-hereditary amyloidosis in Sweden. BMC Public Health 2012;12:974. [CrossRef]
11. Connors LH, Prokaeva T, Lim A, Théberge R, Falk RH, Doros G, et al. Cardiac amyloidosis in African Americans: comparison of clinical and laboratory features of transthyretin V122I amyloidosis and immunoglobulin light chain amyloidosis. Am Heart J 2009;158:607–14. [CrossRef]
12. Ruberg FL, Maurer MS, Judge DP, Zeldenrust S, Skinner M, Kim AY, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). Am Heart J 2012;164:222–8.e1. [CrossRef]
13. Koyama J, Ikeda S, Ikeda U. Echocardiographic assessment of the cardiac amyloidoses. Circ J. 2015;79:721–34. [CrossRef]
14. Phelan D, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. Heart 2012;98:1442–8. [CrossRef]
15. Syed IS, Glockner JF, Feng D, Araoz PA, Martinez MW, Edwards WD, et al. Role of cardiacmagneticresonanceimaging in thedetection of cardiacamyloidosis. JACC CardiovascImaging 2010;3:155–64 [CrossRef]

16. Fontana M, Banypersad SM, Treibel TA, Abdel-Gadir A, Maestrini V, Lane T, et al. Differential Myocyte Responses in Patients with Cardiac Transthyretin Amyloidosis and Light-Chain Amyloidosis: A Cardiac MR Imaging Study. Radiology 2015;277:388–97. [CrossRef]
17. Siddiqi OK, Ruberg FL. Cardiac amyloidosis: An update on pathophysiology, diagnosis, and treatment. Trends Cardiovasc Med 2018;28:10–21. [CrossRef]
18. Flodrova P, Flodr P, Pika T, Vymetal J, Holub D, Dzubak P, et al. Cardiac amyloidosis: from clinical suspicion to morphological diagnosis. Pathology 2018;50:261–8. [CrossRef]
19. Fine NM, Arruda-Olson AM, Dispenzieri A, Zeldenrust SR, Gertz MA, Kyle RA, et al. Yield of noncardiac biopsy for the diagnosis of transthyretin cardiac amyloidosis. Am J Cardiol 2014;113:1723–7. [CrossRef]
20. Hawkins PN, Lavender JP, Pepys MB. Evaluation of systemic amyloidosis by scintigraphy with 123I-labeled serum amyloid P component. N Engl J Med 1990;323:508–13. [CrossRef]
21. Schaadt BK, Hendel HW, Gimsing P, Jønsson V, Pedersen H, Hesse B. 99mTc-aprotinin scintigraphy in amyloidosis. J Nucl Med 2003;44:177–83.
22. Falk RH, Lee VW, Rubinow A, Hood WB Jr, Cohen AS. Sensitivity of technetium-99m-pyrophosphate scintigraphy in diagnosing cardiac amyloidosis. Am J Cardiol 1983;51:826–30.
23. Gertz MA, Brown ML, Hauser MF, Kyle RA. Utility of technetium Tc 99m pyrophosphate bone scanning in cardiac amyloidosis. Arch Intern Med 1987;147:1039–44. [CrossRef]
24. Wizenberg TA, Muz J, Sohn YH, Samlowski W, Weissler AM. Value of positive myocardial technetium-99m-pyrophosphate scintigraphy in the noninvasive diagnosis of cardiac amyloidosis. Am Heart J 1982;103:468–73. [CrossRef]
25. Lo Presti S, Horvath SA, Mihos CG, Rajadhyaksha C, McCloskey V, Santana O. Transthyretin Cardiac Amyloidosis as Diagnosed by 99mTc-PYP Scanning in Patients with Acute Heart Failure and Preserved Ejection Fraction. Crit Pathw Cardiol 2019;18:195–9.[CrossRef]
26. Ak I, Vardareli E, Erdinĉ O, Kasapoğlu E, Ata N. Myocardial Tc-99m MDP uptake on a bone scan in senile systemic amyloidosis with cardiac involvement. Clin Nucl Med 2000;25:826–7.
27. Willerson JT, Parkey RW, Bonte FJ, Lewis SE, Corbett J, Buja LM. Pathophysiologic considerations and clinicopathological correlates of technetium-99m stannous pyrophosphate myocardial scintigraphy. Semin Nucl Med 1980;10:54–69.
28. Skinner M, Cohen AS, Shirahama T, Cathcart ES. P-component (pentagonal unit) of amyloid: isolation, characterization, and sequence analysis. J Lab Clin Med 1974;84:604–14.
29. Hutt DF, Quigley AM, Page J, Hall ML, Burniston M, Gopaul D, et al. Utility and limitations of 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in systemic amyloidosis. Eur Heart J Cardiovasc Imaging 2014;15:1289–98.
30. Pilebro B, Suhr OB, Näslund U, Westermark P, Lindqvist P, Sundström T. (99m)Tc-DPD uptake reflects amyloid fibril composition in hereditary transthyretin amyloidosis. Ups J Med Sci 2016;121:17–24. [CrossRef]
31. Masri A, Bukhari S, Ahmad S, Nieves R, Eisele YS, Follansbee W, et al. Efficient 1-Hour Technetium-99 m Pyrophosphate Imaging Protocol for the Diagnosis of Transthyretin Cardiac Amyloidosis. Circ Cardiovasc Imaging 2020;13:e010249.
32. Yang JC, Fox J, Chen C, Yu AF. Cardiac ATTR amyloid nuclear imaging-not all bone scintigraphy radionuclide tracers are created equal. J Nucl Cardiol 2018;25:1879–84. [CrossRef]
33. Perugini E, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. J Am Coll Cardiol 2005;46:1076–84. [CrossRef]
34. Treglia G, Glaudemans AWJM, Bertagna F, Hazenberg BPC, Erba PA, Giubbini R, et al. Diagnostic accuracy of bone scintigraphy in the assessment of cardiac transthyretin-related amyloidosis: a bivariate meta-analysis. Eur J Nucl Med Mol Imaging 2018;45:1945–55. [CrossRef]
35. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation 2016;133:2404–12.
36. Promislow SJ, Ruddy TD. The evolving landscape of nuclear imaging in cardiac amyloidosis. J Nucl Cardiol 2020;27:210–4.
37. Mekinian A, Jaccard A, Soussan M, Launay D, Berthier S, Federici L, et al. 18F-FDG PET/CT in patients with amyloid light-chain amyloidosis: case-series and literature review. Amyloid. 2012;19:94–8. [CrossRef]
38. Dorbala S, Vangala D, Semer J, Strader C, Bruyere JR Jr, Di Carli MF, et al. Imaging cardiac amyloidosis: a pilot study using ^{18}F-florbetapir positron emission tomography. Eur J Nucl Med Mol Imaging 2014;41:1652–62. [CrossRef]
39. Law WP, Wang WY, Moore PT, Mollee PN, Ng AC. Cardiac Amyloid Imaging with 18F-Florbetaben PET: A Pilot Study. J Nucl Med 2016;57:1733–9. [CrossRef]
40. Dietemann S, Nkoulou R. Amyloid PET imaging in cardiac amyloidosis: a pilot study using 18F-flutemetamol positron emission tomography. Ann Nucl Med 2019;33:624–8.
41. Driscoll I, Troncoso JC, Rudow G, Sojkova J, Pletnikova O, Zhou Y, et al. Correspondence between in vivo (11)C-PiB-PET amyloid imaging and postmortem, region-matched assessment of plaques. Acta Neuropathol 2012;124:823–31.
42. Ezawa N, Katoh N, Oguchi K, Yoshinaga T, Yazaki M, Sekijima Y. Visualization of multiple organ amyloid involvement in systemic amyloidosis using 11C-PiB PET imaging. Eur J Nucl Med Mol Imaging 2018;45:452–61. [CrossRef]
43. Noordzij W, Glaudemans AW, van Rheenen RW, Hazenberg BP, Tio RA, Dierckx RA, et al. (123)I-Labelled metaiodobenzylguanidine for the evaluation of cardiac sympathetic denervation in early stage amyloidosis. Eur J Nucl Med Mol Imaging 2012;39:1609–17. [CrossRef]

Anahtar sözcükler: Kardiyak amiloidoz; kemik sintigrafisi; tanı.

Keywords: Cardiac amyloidosis; bone scintigraphy; diagnosis.