

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,300

Open access books available

130,000

International authors and editors

155M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com



Diagnosis of Cardiac Amyloidosis Using Non-Invasive Technics

Eva Strickler, Ernest Tsiaze, Gerrit Hellige, Dominik Zumstein, Dominik Waldmeier and Nisha Arenja

Abstract

Amyloidosis is a rare multiorgan disease defined by a process of irreversible, extracellular accumulation of fibrillar proteins in the tissues, including the heart. Cardiac involvement is seen in most forms of amyloidosis, but it is frequently present and clinically significant in light chain (AL)-amyloidosis as well as transthyretin amyloidosis (ATTR). Cardiac amyloid accumulation leads to a restrictive filling pattern, which must be differentiated from other forms of restrictive and hypertrophic cardiomyopathies due to consequences for the treatment. Evolving knowledge of the disease has led to a definite diagnosis of the cardiac amyloidosis (CA) using non-invasive and low-risk diagnostic features, such as scintigraphy (gamma scan) and cardiovascular magnetic resonance (CMR) imaging using late gadolinium enhancement (LGE) and T1 mapping technics. The availability and diagnostic accuracy of these technics has reduced the need for cardiac biopsy. In the following chapter, we will describe common types of CA, the basic concepts, and updates of non-invasive diagnostic features.

Keywords: Cardiac Amyloidosis, Diagnosis, Non-Invasive Technics, Imaging Modalities

1. Introduction

1.1 Common types of amyloidosis

Amyloidosis is an infiltrative disease defined by extracellular accumulation of fibrillar proteins in the tissues, including the heart (cardiac amyloidosis (CA)). Lately, about 30 different types of amyloidosis have been described, each due to a specific misfolded protein [1]. Some types of amyloidosis are hereditary others are caused by abnormal organ or plasma cells producing a precursor protein. Additional causes involve long-term dialysis or inflammatory diseases. The disease is classified as “localized amyloidosis” and “systemic amyloidosis”.

The main subtypes of amyloidosis are summarized in the following:

- **Light chain amyloidosis (AL, primary amyloidosis):** AL-amyloidosis represents the most common type of amyloidosis with a prevalence of >0.3 per 100,000 of the general population. The incidence is estimated at 8.9–12.7 per million person-years [2]. The age at manifestation is usually between 60 and 69 years. Precursor protein in AL-amyloidosis is a misfolded immunoglobulin light chain produced by plasma cells. Deposition of misfolded proteins can

occur in virtually any organ system. However, in most cases, the heart and kidneys are involved. Cardiac involvement is described in more than 70% of the cases with a mortality rate of up to 50% per year after the first episode of an acute heart failure [3]. The development of AL cardiomyopathy is caused by the AL amyloid-associated lysosomal dysfunction, oxidative stress, and induction of autophagy (direct toxicity) [4].

- **Amyloid transthyretin (ATTR)-amyloidosis:** ATTR-amyloidosis is a life-threatening and progressive type of amyloidosis. Two forms of ATTR can be distinguished, the mutant transthyretin (**ATTRm**, referred to as familial or hereditary transthyretin amyloidosis (FTA)) and the wild-type amyloidosis (**ATTRwt**, known as well as senile systemic amyloidosis). The precursor protein is amyloid transthyretin (TTR), a transport protein, which usually carries thyroid hormone thyroxine (T4) and retinol-binding protein bound to retinol in serum and cerebrospinal fluid.
- **ATTRm** is an autosomal dominant condition caused by mutations in the TTR gene with abnormal secreted by the liver and deposited in various organs. The type and severity of organ involvement defines its prognosis. ATTRm is clinically heterogeneous and causes a broad spectrum of symptoms. Most often patients suffer from mixed clinical phenotype consisting of sensory and motor impairment and multiple organ failure [5]. Although the exact prevalence of ATTRm is unknown, recently published data reported a global prevalence as high as 38,000 persons [5]. In African Americans ATTR-CA is frequently associated with the mutation Val142Ile (formerly known as Val122Ile), which is carried by 10% of African Americans with heart failure with reduced ejection fraction (HFrEF) and by 1.5–3.5% of the general African American population [6]. In the general Caucasian population this mutation is extremely rare (< 0.005%) [7, 8].
- **ATTRwt** is the most common cause of CA, particularly in the elderly. In a population-based autopsy study Tanskanen M, et al. showed its presence in 25% of subjects aged >85 years [9]. Several studies presented concomitant ATTRwt-amyloidosis in patients with severe aortic stenosis and heart failure with preserved ejection fraction (HFpEF) [10]. The prevalence among patients, who underwent transcatheter aortic valve implantation (TAVI) was reported in 8–16% [11]. However, the prevalence in patients with (paradoxical) low-flow, low-gradient aortic stenosis was reported much higher, with up to 30% [12]. The amyloid protein is being stored in every structure of the heart including myocardium, valves, and coronary arteries. The accumulation of dysfunctional proteins in the extracellular space of the myocardium leads to stiffening of the muscle and impairs the diastolic function of the heart. Heart failure occurs due to a restrictive filling pattern and impaired systolic function. Common arrhythmias resulting from structural changes usually include atrial fibrillation, atrioventricular block (AV), and sudden cardiac death (SCD) due to bradyarrhythmia or tachyarrhythmia [13].
- **Serum amyloid A amyloidosis (SAA, secondary amyloidosis):** An acute-phase protein produced in the liver represents the precursor protein of SAA. An inflammatory disease, such as autoimmune and autoinflammatory disease, chronic infections, or cancer disease may trigger its production. The most commonly affected organs are the kidneys, liver and spleen. Cardiac involvement in SAA is rarely described in the literature [14].

- **Localized amyloidosis:** In localized amyloidosis the amyloidogenic protein is deposited at the site of production and not transported via bloodstream. Localized amyloidosis is usually light chain associated, but also serum amyloid A protein and TTR have been reported as localized disease. Localized immunoglobulin AL-amyloidosis is a rare disease. In a large study by the Mayo clinic 403 of 5551 AL patients (7%) were found for localized immunoglobulin AL-amyloidosis [15]. In this study, the median follow-up for survival and progression were 72 and 39 months. Localized amyloidosis is characterized by deposition of amyloid in a limited area of an anatomical region, such as isolated atrial amyloidosis caused by the precursor protein of atrial natriuretic factor (ANF) [16]. All tissues may be involved, but localized amyloidosis typically involves the laryngo-tracheobronchial tree, skin and urogenital tract.

1.2 Cardiac amyloidosis

CA is a leading cause of restrictive cardiomyopathy due to interstitial deposits of amyloid impairing the elasticity and contractility of the myocardium and leaving

Amyloid subtype	Precursor protein	Origin	Affected Organs	Clinical signs	Therapy
Light chain amyloidosis (AL)	Mono-clonal light chain	Plasma cells in bone marrow	Heart, kidneys, liver, nerves, gastro-intestinal tract, liver, soft tissue	periorbital hematoma, macro-glossia, proteinuria, weight loss	Chemotherapy
Hereditary transthyretin variant amyloidosis (ATTR_v, familial or hereditary transthyretin amyloidosis (FTA))	Trans-thyretin mutation	Liver	Heart, kidneys, peripheral and autonomic nervous system, gastro-intestinal tract	Sudden cardiac death, arrhythmia, syncope, dysautonomia (orthostatic hypotension) peripheral sensory-motor neuropathy	Tafamidis, or 2-(3,5-dichlorophenyl)-benzoxazole 6-carboxylic acid; Promising pharmacologic strategies to stabilize TTR
Transthyretin wild-type amyloidosis (ATTR_{wt}, senile systemic amyloidosis)	Abnormal Trans-thyretin	Liver	Heart and peripheral nervous system	Heart failure, spinal stenosis, bilateral carpal tunnel syndrome	
Amyloid A amyloidosis	Serum amyloid A	Liver	Liver, kidneys, heart (rare)	Heart failure	Treatment of underlying inflammatory process
Apolipo-protein AA amyloidosis	Mutation in Apolipo-protein A1 gene		Liver, kidneys, heart	Heart failure, proteinuria, hematuria, edema, hepatosplenomegaly	Liver transplantation
Isolated atrial amyloidosis	Atrial natriuretic factor	Heart	Heart only	atrial fibrillation/arrhythmia	no specific therapy available

Table 1.
 Overview of the main subtypes of amyloidosis with the possibility of cardiac involvement.

the muscle stiff. Early findings include abnormal myocardial relaxation, gradually advancing to restrictive filling pattern, with signs and symptoms of heart failure. As specified above, the most common types of CA are AL and ATTR-amyloidosis (**Table 1**). An early diagnosis is of paramount importance in order to start the adequate treatment according to the disease, which determines the patient's prognosis.

Previously, the gold standard of CA diagnosis was a histological analysis of endomyocardial tissue. The invasive nature of an endomyocardial biopsy (EMB) limits its routine application. The following immediate or late complications are associated with EMB: pericardial effusion with or without tamponade, arrhythmias, tricuspid valve damage, pneumothorax, pulmonary embolism, nerve paralysis, bleeding complications, creation of an arteriovenous fistula, venous thromboembolism, and infections [17]. Major complications caused by EMB are described with a rate of 1% even when performed in large centers by experienced operators [18–20]. The cause of death is often perforation with tamponade.

Advances in imaging protocols have led to them being primarily used in daily clinical routine. The following chapter provides diagnostic steps for patients with CA including the most recent literature.

2. Non-invasive diagnostic techniques

2.1 Standard 12-lead electrocardiography (ECG) and Holter-ECG monitoring

The diagnostic procedure starts with a simple electrocardiogram (ECG), which may already provide clues for the presence of CA. Historically, CA is a condition associated with low voltage in the ECG, which usually is defined as a peak-to-peak QRS amplitude of less than 5 millimeters in the limb leads and/or less than 10 millimeters in the precordial leads [21].

Rapezzi et al. analyzed ECG recordings of AL, ATTRm and ATTRwt-amyloidosis and found significant differences among the three groups for low QRS voltage and left bundle-branch block [22]. Left bundle-branch block was frequently present in ATTRwt (40%), while in AL low QRS voltage was more common (25% ATTR versus 60% in AL). Boldrini et al. assessed the prevalence of intraventricular and atrioventricular conduction delays in a cohort of 344 AL patients. Intraventricular conduction delay due to myocardial amyloid deposits was associated with worse systolic function, higher mortality, and higher levels of cardiac biomarker [23]. Further 276 patients with a diagnosis of systemic amyloidosis, admitted to the Beijing Union Medical College Hospital from January 2000 to December 2011, were evaluated by Cheng and colleagues [24]. The study reported atrial arrhythmia, low voltage on limb leads, AV-block, and pseudo-infarct pattern as the most present ECG pattern in CA than control groups. In summary, the study data suggests a high specificity and a positive predictive value of low voltage on limb leads and pseudo-infarct pattern for the diagnosis of CA. However, these features are only observed in some CA patients (50% AL and 30% ATTR) and often in a later stage of the disease [25].

The most frequent arrhythmias in CA are atrial fibrillation (45–65%), ventricular tachyarrhythmias (ventricular tachycardia 9.9% and ventricular fibrillation 0.7%) and AV conduction delays (3.5%) [26]. The risk of SCD is increased, especially in advanced disease. The Austrian hot spot mutation His108Arg is linked to an increased incidence of ventricular tachycardia [27]. The proarrhythmic substrate for ventricular arrhythmias in CA is left ventricular fibrosis leading to micro- and macro-reentrant circuits [28]. Therefore, Holter-ECG monitoring is recommended in CA at initial presentation and follow-up.

Although electrophysiological studies (EPS) do not serve as a diagnostic tool, research supports their prognostic relevance. For example, in a study by Reisinger et al., 92% had a prolonged His-ventricular (HV) interval (>55 ms), which was identified as an independent predictor of SCD on multivariate analysis among patients with AL [29]. In a recently published study by Orini et al., ventricular conduction and repolarization abnormalities were more pronounced in AL compared to ATTR-amyloidosis [30].

In conclusion, in patients with AL and ATTR-amyloidosis, ECG and Holter-monitor are important tools to diagnose AV conduction delays as well as atrial and ventricular arrhythmias. Implantation of a permanent pacemaker system is recommended in patients meeting the established criteria for device implantation [31]. EPS should be considered in the setting of unexplained syncope due to the fact of common HV prolongation in absence of AV-Block in the 12-lead ECG. Patients with AL-amyloidosis have a higher risk to develop arrhythmias and suffer from a poor prognosis. However, implantable cardioverter defibrillator (ICD) for primary prophylactic therapy did not show a survival benefit in AL-CA. Their use may be considered in patients with AL or ATTR associated CA complicated with ventricular arrhythmias causing hemodynamic instability, who are having a life expectancy of more than one year with good functional status [32–34].

2.2 Cardiac biomarker and laboratory parameter

In suspected CA further laboratory parameters are needed. Due to an underlying plasma cell dyscrasia in AL-amyloidosis, a monoclonal gammopathy is detected by electrophoresis and immunochemical measurements of specific isotypes or free light chains (FLC) pairs. The spike of light chains is referred as “Bence Jones protein”. For detection of even small amounts of FLC a serum fluorescence lifetime correlation spectroscopy and a serum FLC (sFLC) assay are of great additional value [35]. If monoclonal proteins are identified, the patient should be referred to a hematologist for further evaluation including a bone marrow biopsy. In case, an AL-amyloidosis can be ruled out, the next step should involve Technetium (Tc)-labeled cardiac scintigraphy (for further details see chapter 2.5).

Incorporation of sFLC differentiation into the current staging system for AL-amyloidosis improves risk stratification therapy optimization. Increased values of cardiac biomarkers such as brain natriuretic peptide (BNP), N-terminal brain natriuretic peptide (NT-proBNP), and Troponin (TnI, TnT) are used as screening parameters for cardiac involvement and clinical outcome. They might also assess the treatment response. In general, natriuretic peptides and Troponin levels are commonly elevated in CA, with a mild elevation seen in ATTR and higher levels in AL due to a cardiotoxic effect of light chains. The Mayo classification consists of TnT, NT-proBNP, and FLC-ratio (difference between light chain kappa and lambda) and helps estimating cardiac involvement and prognosis in AL patients [36].

2.3 Echocardiography

Echocardiography is an essential screening tool for CA and speeds up diagnosis. The most important finding represents the ventricular hypertrophy associated with amyloid self-aggregation (**Figure 1**). However, left ventricular (LV) wall thickening may also be seen in other conditions, such as long-standing arterial hypertension, high-grade aortic stenosis, hypertrophic cardiomyopathy (HCM) or storage diseases such as Fabry’s disease. Therefore, further echocardiographic characteristics such as thickening of the atrial septum, valvular leaflets, as well as enlarged atria and pericardial effusion raise suspicion towards CA. Furthermore, assessment of

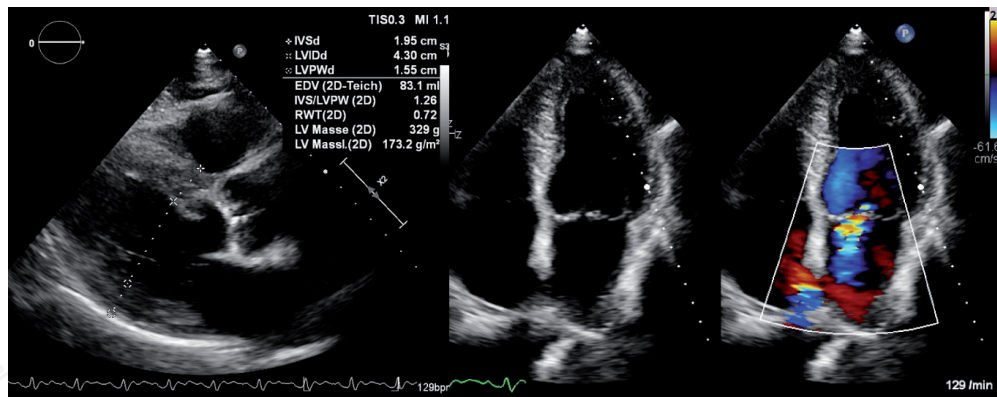


Figure 1. Echocardiographic imaging showing a parasternal long axis view of a left ventricular hypertrophy and an apical 4-chamber view demonstrating mitral regurgitation.

diastolic function is a useful evaluation tool for CA. Diastolic dysfunction usually appears before pathologic measurements of left or right ventricular (RV) walls and it is the hallmark of amyloid heart disease [37]. A restrictive filling pattern is found in up to one-third of the CA population. According to the European classification of cardiomyopathies, CA may be regarded either as restrictive or hypertrophic cardiomyopathy based on the severity of diastolic filling impairment [38]. Based on hypertrophy and diastolic function parameters Aimo et al. developed a simple score named AMYLOidosis Index (AMYLI), as the product of relative wall thickness (RWT) and E/e' ratio, for initial screening of CA patients (AMYLI <2.22 excludes the diagnosis in patients undergoing a diagnostic screening for CA) [39]. However, this score needs further validation and is currently not in use for clinical routine.

Historically, “sparkling myocardium” is associated with CA. Granular sparkling is seen in approximately 25% of CA patients, which is attributed to increased echogenicity of the amyloid protein [40]. However, scanning with tissue harmonic frequencies imparts increased echogenicity of myocardium in general and granular sparkling may be overdiagnosed. In general, “speckled appearance” alone is not diagnostic of CA, since HCM, end-stage renal disease, harmonic imaging, and glycogen storage disease produce similar appearance [41].

Speckle tracking as an advanced echocardiography technic is a useful tool to differentiate CA from other causes of LV hypertrophy including other storage diseases. Myocardial speckle tracking-based strain imaging of the LV can help in the differential diagnosis and the presence of relative apical sparing may indicate CA. While left ventricular ejection fraction (LVEF) is preserved at early stages of CA, the longitudinal systolic contraction is already impaired [40]. Typically, the longitudinal strain at the basal and the mid ventricular segments is reduced, while the longitudinal apical strain of the LV is preserved (apical sparing). Preserved apical strain can be visualized using the strain ratio or the bull’s eye plot (**Figure 2**) [42]. The pathophysiological basis of the apical sparing is not fully understood, but advanced imaging has shown evidence of amyloid deposition preferably in the basal and mid ventricular segments. In addition, a normal value of the global longitudinal strain (GLS) is known as a positive predictor for survival [43].

Although concomitant RV free wall hypertrophy is suggestive of infiltrative cardiomyopathy, an additional RV apical sparing pattern has been shown to distinguish CA from other storage diseases. Arvidsson et al. examined RV global and segmental strain of 42 subjects with ATTR amyloidosis. Patients with ATTR amyloidosis showed an apex-to-base RV strain gradient with relative apical sparing [44], RV involvement has been shown to occur most commonly after LV infiltration and has implications for prognosis [45].

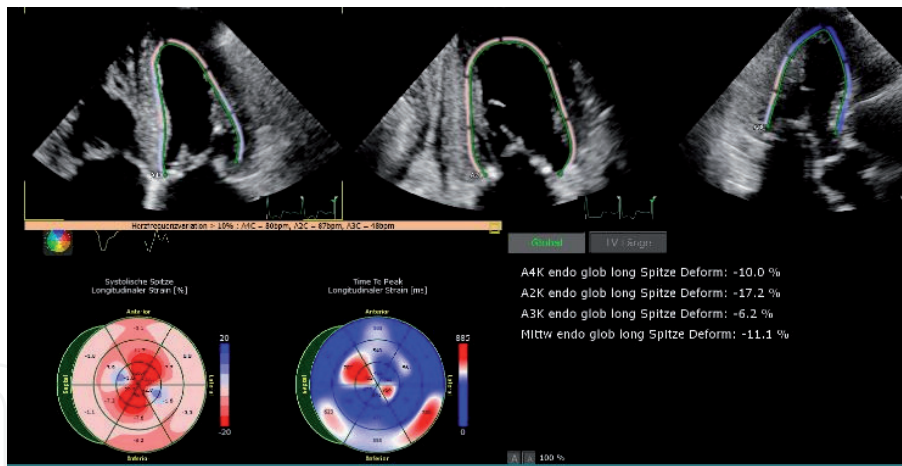


Figure 2.
Automated strain imaging using speckle-tracking algorithm.

To distinguish CA from other storage diseases, the following echocardiographic features may be helpful: presence of LV thickening, enlargement of the left atrium with wall thickening, lower E/e' , longer transmitral early filling wave deceleration time, reduced longitudinal strain in all myocardial segments with presence of relative apical sparing, additional RV hypertrophy with apical sparing pattern and mild pericardial and pleural effusion.

In summary, echocardiography using standard and speckle tracking imaging can provide many features suggesting amyloid heart disease though none of them are absolutely specific and further diagnostic tests are needed to accurately diagnose CA. Nevertheless, the presence of several echocardiographic findings increases the likelihood of the diagnosis, especially the combination of increased wall-thickness of the non-dilated LV with a restrictive filling pattern, biatrial enlargement, thickened valves, and pericardial effusion.

2.4 Cardiovascular magnetic resonance (CMR)

If echocardiographic findings hint at the presence of CA, cardiovascular magnetic resonance (CMR) is used to provide further support for the suspected diagnosis by evaluation of cardiac function and morphology using steady-state free precession (SSFP) sequences, tissue characterization via late gadolinium enhancement (LGE) and T1 mapping. CMR can characterize amyloid deposition in the extracellular tissue via LGE. In general, the phenomenon of LGE is explained by higher regional gadolinium concentration in the extracellular space and reduced distribution kinetics than in normal myocardium. In CA, the interstitium is substantially expanded by amyloid fiber accumulation, which is demonstrated by LGE in the myocardium with a dominant subendocardial distribution (**Figure 3**) [46, 47]. In a study by Pennell et al., a diffuse subendocardial LGE was observed in 69% [48]. Next to subendocardial different, other distribution patterns, ranging from the global transmural LGE to patchy focal LGE, have been described. The differences in the LGE pattern, especially the “patchy distribution” was explained by incorrect TI settings [49].

Suboptimal “myocardial nulling” is characteristic of CA. It describes the impossibility of adjustment of inversion time to discriminate the blood pool from the myocardium. An inversion recovery pulse sequence is used to null the myocardial signal during delayed-enhanced imaging. Usually, the blood pool reaches the null point before normal myocardium. However, this relationship is reversed in CA. Phase-sensitive inversion recovery (PSIR) reconstruction is emerging as the most accurate method to overcome this problem and assess LGE in CA. This technique

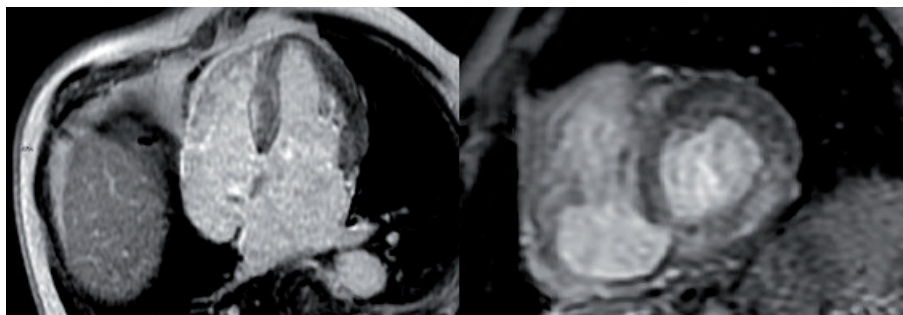


Figure 3. Cardiovascular magnetic resonance imaging of myocardial late gadolinium enhancement with pronounced septal and basal distribution.

eliminated the difficulties of accurate TI selection, because tissue with the least gadolinium always appears nulled [50].

Krombach et al. described in 2007 another technic for the evaluation of CA using CMR [51]. The authors presented a measurement of myocardial T1 mapping values without application of LGE in identifying interstitial amyloid infiltration. Using this parameter, a sensitivity of 80% and a specificity of 94% was achieved in the study to diagnose CA. Determination of native and postcontrast (after application of the contrast agent) T1 mapping, allows for calculation of the extracellular volume (ECV), which correlates well with histological findings based on cardiac biopsies [52]. Meanwhile, several studies have demonstrated an increase in native T1 relaxation time as well as ECV of the myocardium in CA [53]. However, the diagnostic significance of ECV is limited due to overlap with other myocardial diseases associated with LV hypertrophy. Therefore, thresholds for native T1 relaxation time and ECV have not been established yet [54].

Due to the above-described comprehensive technical features, CMR represents an alternative to biopsy and has become an established part of the standard clinical pathway for CA diagnosis. In addition, it may provide prognostic information for patients with a confirmed diagnosis.

2.5 Cardiac scintigraphy

Tc-labeled cardiac scintigraphy provides incremental value to echocardiography and CMR, because of the ability to distinguish ATTR CA from other forms of LV hypertrophy [55]. Radionuclides have affinity towards myocardial amyloid deposits, especially towards myocardial ATTR. The binding of the radiotracer towards myocardial ATTR is supposed to be due to microcalcifications [56]. Three different technetium-labeled radiotracers are used for the diagnosis of ATTR-CA: ^{99m}Tc -PYP (^{99m}Tc -labeled pyrophosphate), ^{99m}Tc -DPD (^{99m}Tc -labeled 3,3-diphosphono-1,2-propanodicarboxylic acid), and ^{99m}Tc -HMDP (^{99m}Tc -labeled hydroxymethyl diphosphonate). Grading systems for the degree of uptake in the myocardium on planar imaging are quantitative and qualitative. Qualitative scores are based on the heart to contralateral lung uptake (H/CL) ratio with ^{99m}Tc -PYP or the heart to whole body ratio with ^{99m}Tc -DPD and ^{99m}Tc -HMDP (Figure 4) [57].

Gillmore et al. assessed the diagnostic accuracy of all three above-mentioned tracers in 1,217 patients with suspected CA. Any myocardial radiotracer uptake was >99% sensitive and 86% specific for detecting ATTR-CA, with the majority of false-positive results from patients with AL-amyloidosis. A higher amount of myocardial radiotracer uptake (grade 2 or 3) and the absence of monoclonal proteins in serum or urine had nearly 100% specificity and 100% positive predictive value for ATTR-CA [55]. Imaging differentiation between AL and ATTR-amyloidosis

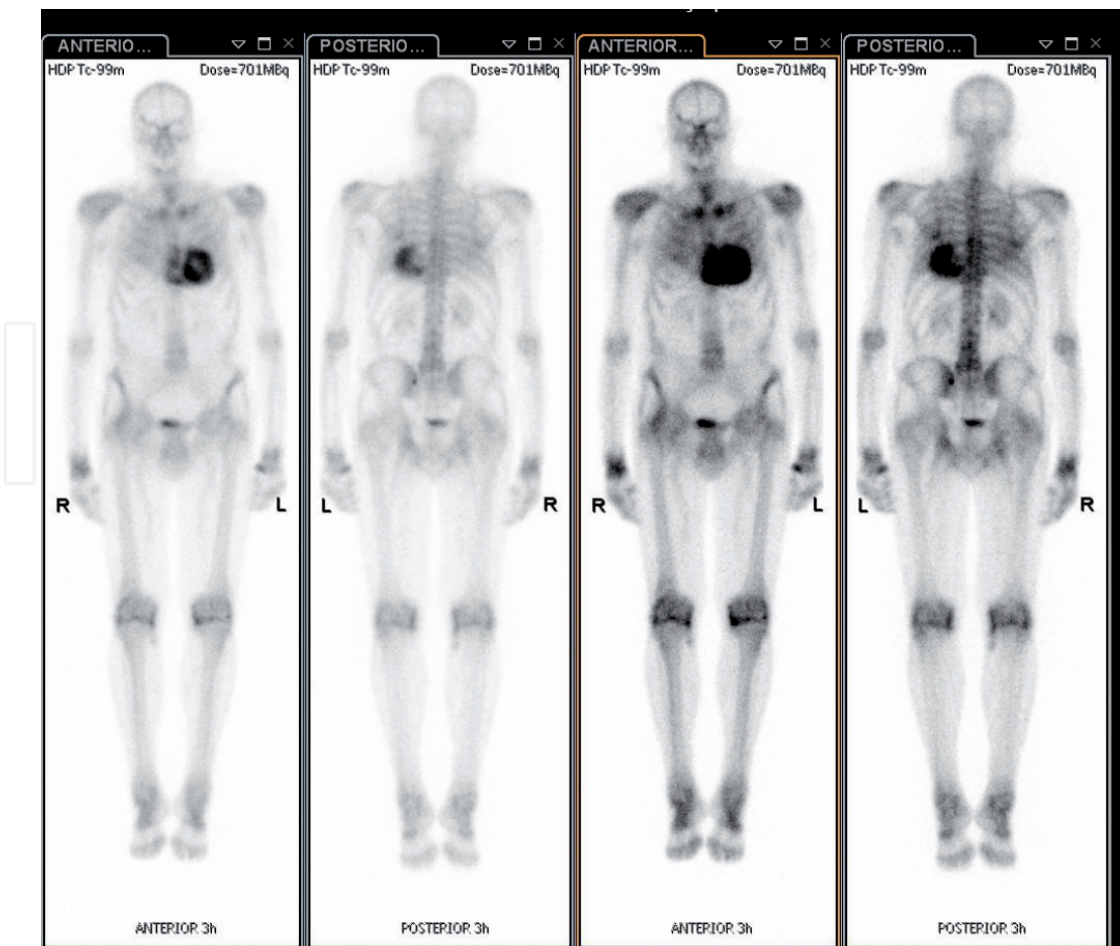


Figure 4.
^{99m}Tc-HMDP bone scintigraphy for diagnosis of cardiac amyloidosis.

is based on the ^{99m}Tc-PYP H/CL uptake ratio; a ratio of <1.5 favors AL, whereas a ratio of ≥1.5 favors ATTR [58]. Semi-quantitative evaluation using ^{99m}Tc-PYP planar imaging, a H/CL ratio of >1.5 at 1 h accurately distinguished ATTR from AL-CA with 97% sensitivity and 100% specificity and a whole-body retention of ^{99m}Tc-DPD at 3 h is highly sensitive and specific for ATTR-CA [59].

In conclusion, Tc-labeled cardiac scintigraphy can reliably diagnose ATTR-amyloidosis in the absence of tissue biopsy, especially in cases of high myocardial radiotracer uptake and after laboratory exclusion of AL-amyloidosis.

3. Conclusion

Cardiac involvement in amyloidosis has a high mortality rate. For instance, patients with AL-amyloidosis have a 50% survival rate per year after the first episode of acute heart failure. Rapid diagnosis and initiation of chemotherapy are crucial in these patients. Besides, ATTR-amyloidosis may benefit from novel therapeutic options to improve symptoms and survival. The following features should raise the suspicion of CA: patients above 60 years of age with a low-flow low-gradient aortic stenosis, unexplained LV hypertrophy or peripheral sensory neuropathy, and patients with monoclonal gammopathy or elevated FLC levels. Non-invasive imaging technics are valuable in the assessment of CA and should be used widely. Cardiac imaging findings in echocardiography, CMR, or Tc-labeled bone or cardiac scintigraphy, are specific enough to diagnose CA in the setting of a positive non-cardiac biopsy (**Figure 5**). EMB with histological analysis of myocardial tissue is not essential anymore.

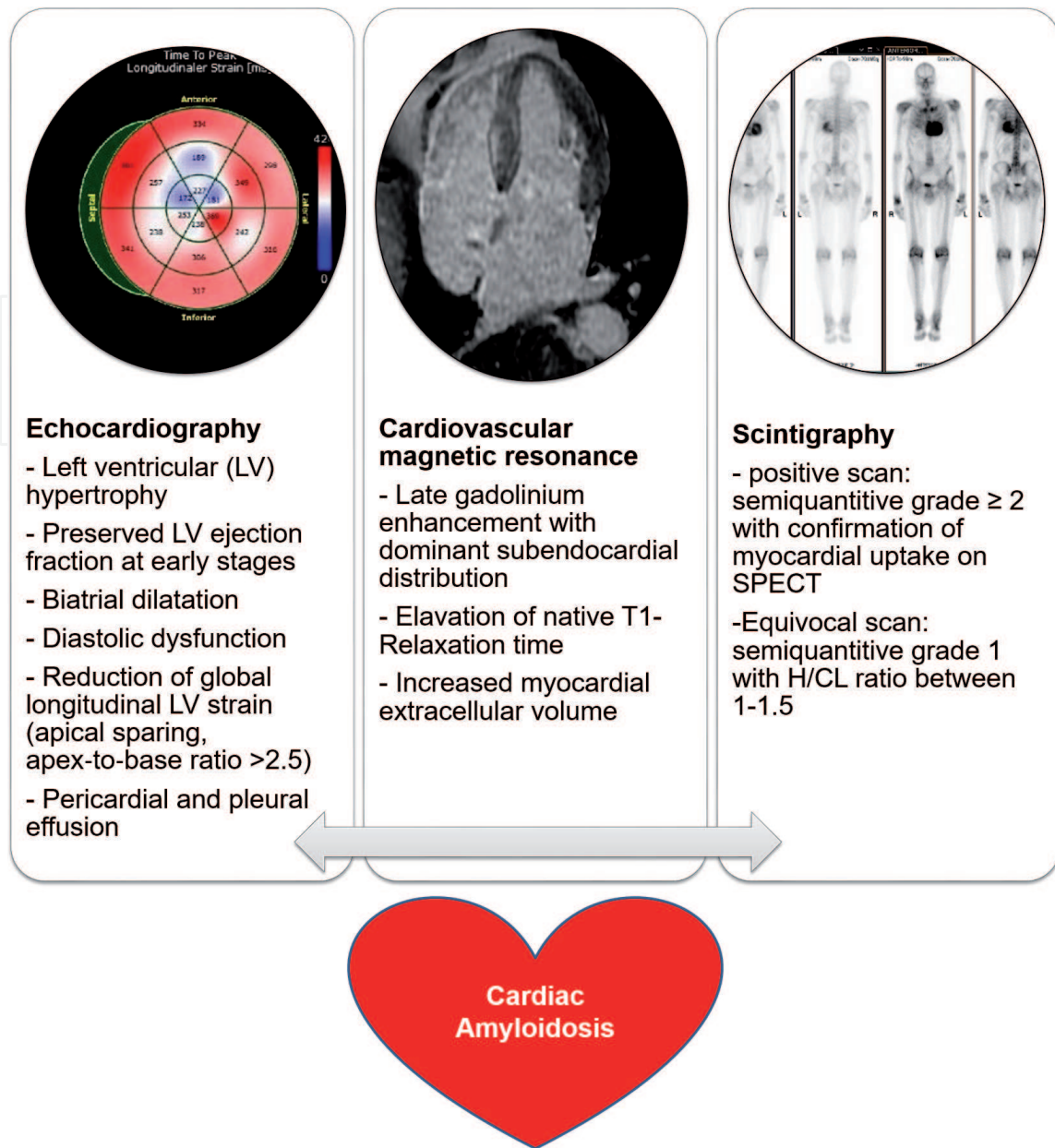


Figure 5.
Typical imaging features to diagnose cardiac amyloidosis.

Conflict of interest

NA and DZ has received meeting support from Pfizer.
The other authors declare no conflict of interest.

Abbreviations

AL	Light chain amyloidosis
AMYLI	AMYLoIdosis Index
ANF	Atrial natriuretic factor
ATTR	Amyloid transthyretin amyloidosis
ATTRm	Mutant transthyretin amyloidosis
ATTRwt	Transthyretin wild-type amyloidosis
AV	atrioventricular
BNP	Brain natriuretic peptide


CA	Cardiac amyloidosis
CMR	Cardiovascular magnetic resonance imaging
ECG	Electrocardiography
ECV	Extracellular volume
EMB	Endomyocardial biopsy
EPS	Electrophysiology study
ESC	European Society of Cardiology
GLS	Global longitudinal strain
HCM	Hypertrophic cardiomyopathy
HV	His-ventricular
ICD	Implantable cardioverter defibrillator
LGE	Late gadolinium enhancement
LVEF	Left ventricular ejection fraction
NT-proBNP	N-terminal brain natriuretic peptide
PSIR	Phase-sensitive inversion recovery
RV	Right ventricular
SAA	Serum amyloid A
SCD	Sudden cardiac death
sFLC	Serum free light chain
SPECT	Single photon emission computed tomography
SSFP	Steady-state free precession
T4	Thyroid hormone thyroxine
TAVI	Transcatheter aortic valve implantation
Tc	technicium
TDI	Tissue Doppler imaging
TnI	Troponin I
TnT	Troponin T
TTR	Transthyretin
⁹⁹ mTc-PYP	⁹⁹ mTc-labeled pyrophosphate
⁹⁹ mTc-DPD	⁹⁹ mTc-labeled 3,3- diphosphono-1,2-propanodicarboxylic acid
⁹⁹ mTc-HMDP	⁹⁹ mTc-labeled hydroxymethyl diphosphonate

Author details

Eva Strickler, Ernest Tsiaze, Gerrit Hellige, Dominik Zumstein,
Dominik Waldmeier and Nisha Arenja*
Kantonsspital Olten, Solothurner Spitäler AG, Olten, Switzerland

*Address all correspondence to: nisha.arenja@spital.so.ch

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] J. D. Sipe *et al.*, “Nomenclature 2014: Amyloid fibril proteins and clinical classification of the amyloidosis,” *Amyloid*. 2014, doi: 10.3109/13506129.2014.964858.
- [2] G. Merlini *et al.*, “Systemic immunoglobulin light chain amyloidosis,” *Nat. Rev. Dis. Prim.*, 2018, doi: 10.1038/s41572-018-0034-3.
- [3] G. Merlini, D. C. Seldin, and M. A. Gertz, “Amyloidosis: Pathogenesis and new therapeutic options,” *Journal of Clinical Oncology*. 2011, doi: 10.1200/JCO.2010.32.2271.
- [4] K. Ablasser, N. Verheyen, T. Glantschnig, G. Agnetti, and P. P. Rainer, “Unfolding Cardiac Amyloidosis –From Pathophysiology to Cure,” *Curr. Med. Chem.*, 2018, doi: 10.2174/0929867325666180104153338.
- [5] H. H. Schmidt *et al.*, “Estimating the global prevalence of transthyretin familial amyloid polyneuropathy,” *Muscle and Nerve*, 2018, doi: 10.1002/mus.26034.
- [6] M. Grogan *et al.*, “Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System,” *J. Am. Coll. Cardiol.*, 2016, doi: 10.1016/j.jacc.2016.06.033.
- [7] F. Perfetto *et al.*, “The Val142Ile transthyretin cardiac amyloidosis: more than an Afro-American pathogenic variant,” *J. Community Hosp. Intern. Med. Perspect.*, 2015, doi: 10.3402/jchimp.v5.26931.
- [8] F. Cappelli *et al.*, “The Val142Ile transthyretin cardiac amyloidosis: Not only an Afro-American pathogenic variant? A single-centre Italian experience,” *J. Cardiovasc. Med.*, 2016, doi: 10.2459/JCM.0000000000000290.
- [9] M. Tanskanen *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, doi: 10.1080/07853890701842988.
- [10] P. P. Liu and D. Smyth, “Wild-Type Transthyretin Amyloid Cardiomyopathy: A Missed Cause of Heart Failure with Preserved Ejection Fraction with Evolving Treatment Implications,” *Circulation*. 2016, doi: 10.1161/CIRCULATIONAHA.115.020351.
- [11] P. R. Scully *et al.*, “Prevalence of Cardiac Amyloidosis in Patients Referred for Transcatheter Aortic Valve Replacement,” *Journal of the American College of Cardiology*. 2018, doi: 10.1016/j.jacc.2017.11.037.
- [12] J. Ternacle *et al.*, “Aortic Stenosis and Cardiac Amyloidosis: JACC Review Topic of the Week,” *Journal of the American College of Cardiology*. 2019, doi: 10.1016/j.jacc.2019.09.056.
- [13] E. González-López *et al.*, “Clinical characteristics of wild-type transthyretin cardiac amyloidosis: Disproving myths,” *Eur. Heart J.*, 2017, doi: 10.1093/eurheartj/ehx043.
- [14] C. Röcken and A. Shakespeare, “Pathology, diagnosis and pathogenesis of AA amyloidosis,” *Virchows Archiv*. 2002, doi: 10.1007/s00428-001-0582-9.
- [15] T. V. Kourelis *et al.*, “Presentation and Outcomes of Localized Immunoglobulin Light Chain Amyloidosis: The Mayo Clinic Experience,” *Mayo Clin. Proc.*, 2017, doi: 10.1016/j.mayocp.2017.02.016.
- [16] J. Guan, S. Mishra, R. H. Falk, and R. Liao, “Current perspectives on cardiac amyloidosis,” *American Journal*

of Physiology - Heart and Circulatory Physiology. 2012, doi: 10.1152/ajpheart.00815.2011

[17] Singh V, Mendirichaga R, Savani GT, Rodriguez A, Blumer V, Elmariah S, Inglessis-Azuaje I, Palacios I. Comparison of Utilization Trends, Indications, and Complications of Endomyocardial Biopsy in Native Versus Donor Hearts (from the Nationwide Inpatient Sample 2002 to 2014). *Am J Cardiol.* 2018 Feb 1;121(3):356-363. doi: 10.1016/j.amjcard.2017.10.021.

[18] Yilmaz A, Kindermann I, Kindermann M, Mahfoud F, Ukena C, Athanasiadis A, Hill S, Mahrholdt H, Voehringer M, Schieber M, Klingel K, Kandolf R, Böhm M, Sechtem U. Comparative evaluation of left and right ventricular endomyocardial biopsy: differences in complication rate and diagnostic performance. *Circulation.* 2010 Aug 31;122(9):900-909. doi: 10.1161/CIRCULATIONAHA.109.924167.

[19] Chimenti C, Frustaci A. Contribution and risks of left ventricular endomyocardial biopsy in patients with cardiomyopathies: a retrospective study over a 28-year period. *Circulation.* 2013 Oct 1;128(14):1531-1541. doi: 10.1161/CIRCULATIONAHA.13.001414.

[20] Bennett MK, Gilotra NA, Harrington C, Rao S, Dunn JM, Freitag TB, Halushka MK, Russell SD. Evaluation of the role of endomyocardial biopsy in 851 patients with unexplained heart failure from 2000-2009. *Circ Heart Fail.* 2013 Jul;6(4):676-684. doi: 10.1161/CIRCHEARTFAILURE.112.000087.

[21] G. B. Hannibal, "Interpretation of the low-voltage ECG," *AACN Adv. Crit. Care*, 2014, doi: 10.1097/NCI.0000000000000001.

[22] C. Rapezzi *et al.*, "Systemic cardiac amyloidosis: Disease profiles and

clinical courses of the 3 main types," *Circulation*, 2009, doi: 10.1161/CIRCULATIONAHA.108.843334.

[23] M. Boldrini *et al.*, "Prevalence and prognostic value of conduction disturbances at the time of diagnosis of cardiac AL amyloidosis," *Ann. Noninvasive Electrocardiol.*, 2013, doi: 10.1111/anec.12032.

[24] Z. Cheng, K. Zhu, Z. Tian, D. Zhao, Q. Cui, and Q. Fang, "The findings of electrocardiography in patients with cardiac amyloidosis," *Ann. Noninvasive Electrocardiol.*, 2013, doi: 10.1111/anec.12018.

[25] B. W. Sperry *et al.*, "Are classic predictors of voltage valid in cardiac amyloidosis? A contemporary analysis of electrocardiographic findings," *Int. J. Cardiol.*, 2016, doi: 10.1016/j.ijcard.2016.04.030.

[26] K. Sanchis *et al.*, "Atrial fibrillation and subtype of atrial fibrillation in cardiac amyloidosis: clinical and echocardiographic features, impact on mortality," *Amyloid*, 2019, doi: 10.1080/13506129.2019.1620724.

[27] M. Auer-Grumbach *et al.*, "Hereditary ATTR Amyloidosis in Austria: Prevalence and Epidemiological Hot Spots," *J. Clin. Med.*, 2020, doi: 10.3390/jcm9072234.

[28] D. K. Dawson *et al.*, "Prognostic role of CMR in patients presenting with ventricular arrhythmias," *JACC Cardiovasc. Imaging*, 2013, doi: 10.1016/j.jcmg.2012.09.012.

[29] J. Reisinger, S. W. Dubrey, M. Lavalley, M. Skinner, and R. H. Falk, "Electrophysiologic abnormalities in AL (primary) amyloidosis with cardiac involvement," *J. Am. Coll. Cardiol.*, 1997, doi: 10.1016/S0735-1097(97)00267-2.

[30] M. Orini *et al.*, "Noninvasive Mapping of the Electrophysiological

Substrate in Cardiac Amyloidosis and Its Relationship to Structural Abnormalities," *J. Am. Heart Assoc.*, 2019, doi: 10.1161/JAHA.119.012097.

[31] M. Brignole *et al.*, "2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association," *Europace*, 2013, doi: 10.1093/europace/eut206.

[32] A. V. Kristen *et al.*, "Prophylactic implantation of cardioverter-defibrillator in patients with severe cardiac amyloidosis and high risk for sudden cardiac death," *Heart Rhythm*, 2008, doi: 10.1016/j.hrthm.2007.10.016.

[33] E. P. Hess and R. D. White, "Out-of-hospital cardiac arrest in patients with cardiac amyloidosis: Presenting rhythms, management and outcomes in four patients," *Resuscitation*, 2004, doi: 10.1016/j.resuscitation.2003.08.007.

[34] S. G. Priori *et al.*, "2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the Europe," *Europace*, 2015, doi: 10.1093/europace/euv319.

[35] M. A. Gertz *et al.*, "Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): A consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis," 2005, doi: 10.1002/ajh.20381.

[36] S. Kumar *et al.*, "Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain

measurements," *J. Clin. Oncol.*, 2012, doi: 10.1200/JCO.2011.38.5724.

[37] S. F. Nagueh *et al.*, "Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American society of echocardiography and the European association of cardiovascular imaging," *Eur. Heart J. Cardiovasc. Imaging*, 2016, doi: 10.1093/ehjci/jew082.

[38] P. Elliott *et al.*, "Classification of the cardiomyopathies: A position statement from the European society of cardiology working group on myocardial and pericardial diseases," *Eur. Heart J.*, 2008, doi: 10.1093/eurheartj/ehm342.

[39] A. Aimo *et al.*, "A simple echocardiographic score to rule out cardiac amyloidosis," *Eur. J. Clin. Invest.*, 2020, doi: 10.1111/eci.13449.

[40] E. D. Pagourelas *et al.*, "Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis: A Head-to-Head Comparison of Deformation and Nondeformation Parameters," *Circ. Cardiovasc. Imaging*, 2017, doi: 10.1161/CIRCIMAGING.116.005588.

[41] M. Boldrini *et al.*, "Multiparametric Echocardiography Scores for the Diagnosis of Cardiac Amyloidosis," *JACC Cardiovasc. Imaging*, 2020, doi: 10.1016/j.jcmg.2019.10.011.

[42] G. Y. Lee *et al.*, "Visual assessment of relative apical sparing pattern is more useful than quantitative assessment for diagnosing cardiac amyloidosis in borderline or mildly increased left ventricular wall thickness," *Circ. J.*, 2015, doi: 10.1253/circj.CJ-14-1328.

[43] S. J. Buss *et al.*, "Longitudinal left ventricular function for prediction of survival in systemic light-chain amyloidosis: Incremental value compared with clinical and biochemical markers," *J. Am. Coll. Cardiol.*, 2012, doi: 10.1016/j.jacc.2012.04.043.

- [44] S. Arvidsson, M. Y. Henein, G. Wikström, O. B. Suhr, and P. Lindqvist, "Right ventricular involvement in transthyretin amyloidosis," *Amyloid*, 2018, doi: 10.1080/13506129.2018.1493989.
- [45] Khor YM, Cuddy S, Falk RH, Dorbala S. Multimodality Imaging in the Evaluation and Management of Cardiac Amyloidosis. *Semin Nucl Med.* 2020 Jul;50(4):295-310. doi: 10.1053/j.semnuclmed.2020.01.001. Epub 2020 Feb 9. PMID: 32540027.
- [46] M. Fontana, "Prognosis in Cardiac Amyloidosis by LGE: Ready for Prime Time?*", *JACC: Cardiovascular Imaging.* 2016, doi: 10.1016/j.jcmg.2015.11.028.
- [47] M. Yazaki *et al.*, "Cardiac amyloid in patients with familial amyloid polyneuropathy consists of abundant wild-type transthyretin," *Biochem. Biophys. Res. Commun.*, 2000, doi: 10.1006/bbrc.2000.3203.
- [48] A. M. Maceira *et al.*, "Cardiovascular magnetic resonance in cardiac amyloidosis," *Circulation*, 2005, doi: 10.1161/01.CIR.0000152819.97857.9D.
- [49] M. Fontana *et al.*, "Prognostic value of late gadolinium enhancement cardiovascular magnetic resonance in cardiac amyloidosis," *Circulation*, 2015, doi: 10.1161/CIRCULATIONAHA.115.016567.
- [50] T. Pandey, K. Jambhekar, R. Shaikh, S. Lensing, and S. Viswamitra, "Utility of the inversion scout sequence (TI scout) in diagnosing myocardial amyloid infiltration," *Int. J. Cardiovasc. Imaging*, 2013, doi: 10.1007/s10554-012-0042-4.
- [51] G. A. Krombach *et al.*, "Cardiac amyloidosis: MR imaging findings and T1 quantification, comparison with control subjects," *J. Magn. Reson. Imaging*, 2007, doi: 10.1002/jmri.20917.
- [52] T. D. Karamitsos *et al.*, "Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis," *JACC Cardiovasc. Imaging*, 2013, doi: 10.1016/j.jcmg.2012.11.013.
- [53] A. Martinez-Naharro *et al.*, "Native T1 and Extracellular Volume in Transthyretin Amyloidosis," *JACC Cardiovasc. Imaging*, 2019, doi: 10.1016/j.jcmg.2018.02.006.
- [54] D. R. Messroghli *et al.*, "Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2 and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging," *Journal of Cardiovascular Magnetic Resonance.* 2017, doi: 10.1186/s12968-017-0389-8.
- [55] J. D. Gillmore *et al.*, "Nonbiopsy diagnosis of cardiac transthyretin amyloidosis," *Circulation*, 2016, doi: 10.1161/CIRCULATIONAHA.116.021612.
- [56] M. A. Stats and J. R. Stone, "Varying levels of small microcalcifications and macrophages in ATTR and AL cardiac amyloidosis: implications for utilizing nuclear medicine studies to subtype amyloidosis," *Cardiovasc. Pathol.*, 2016, doi: 10.1016/j.carpath.2016.07.001.
- [57] S. Dorbala *et al.*, "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," *J. Nucl. Cardiol.*, 2019, doi: 10.1007/s12350-019-01760-6.
- [58] Y. J. Kim, S. Ha, and Y. il Kim, "Cardiac amyloidosis imaging with amyloid positron emission tomography: A systematic review and meta-analysis," *J. Nucl. Cardiol.*, 2020, doi: 10.1007/s12350-018-1365-x.

[59] E. Perugini *et al.*, “Noninvasive etiologic diagnosis of cardiac amyloidosis using ^{99m}Tc -3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy,” *J. Am. Coll. Cardiol.*, 2005, doi: 10.1016/j.jacc.2005.05.073.

IntechOpen

IntechOpen