Title
Cardiac Amyloidosis: Diagnosis and Treatment Strategies.

Journal
Current oncology reports, 19(7)

ISSN
1534-6269

Authors
Tuzovic, Mirela
Yang, Eric H
Baas, Arnold S
et al.

Publication Date
2017-07-01

Peer reviewed

Curr Oncol Rep (2017) 19:46
DOI 10.1007/s11912-017-0607-4

Cardiac Amyloidosis: Diagnosis and Treatment Strategies

Mirela Tuzovic[1] · Eric H. Yang[1] · Arnold S. Baas[2] · Eugene C. Depasquale[2] · Mario C. Deng[2] · Daniel Cruz[2] · Gabriel Vorobiof[1,3]

Abstract Cardiac amyloidosis in the United States is most often due to myocardial infiltration by immunoglobulin protein, such as in AL amyloidosis, or by the protein transthyretin, such as in hereditary and senile amyloidosis. Cardiac amyloidosis often portends a poor prognosis especially in patients with systemic AL amyloidosis. Despite better understanding of the pathophysiology of amyloid, many patients are still diagnosed late in the disease course. This review investigates the current understanding and new research on the diagnosis and treatment strategies in patients with cardiac amyloidosis. Myocardial amyloid infiltration distribution occurs in a variety of patterns. Structural and functional changes on echocardiography can suggest presence of amyloid, but CMR and nuclear imaging provide important complementary information on amyloid burden and the amyloid subtype, respectively. While for AL amyloid, treatment success largely depends on early diagnosis, for ATTR amyloid, new investigational agents that reduce production of transthyretin protein may have significant impact on clinical outcomes. Advancements in the non-invasive diagnostic detection and improvements in early disease recognition will undoubtedly facilitate a larger proportion of patients to receive early therapy when it is most effective.

Keywords Cardiac amyloidosis · Transthyretin amyloidosis · AL amyloidosis · Echocardiography · Cardiac magnetic resonance imaging · Nuclear imaging

This article is part of the Topical Collection on *Cardio-oncology*

Electronic supplementary material The online version of this article (doi:10.1007/s11912-017-0607-4) contains supplementary material, which is available to authorized users.

✉ Gabriel Vorobiof
gvorobiof@mednet.ucla.edu

Mirela Tuzovic
mtuzovic@mednet.ucla.edu

Eric H. Yang
ehyang@mednet.ucla.edu

Arnold S. Baas
abaas@mednet.ucla.edu

Eugene C. Depasquale
edepasquale@mednet.ucla.edu

Mario C. Deng
mdeng@mednet.ucla.edu

Daniel Cruz
dcruz@mednet.ucla.edu

[1] Division of Cardiology, Department of Medicine, Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA

[2] Ahmanson-UCLA Cardiomyopathy Center, Department of Medicine, Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA

[3] Cardiovascular Center, 100 Medical Plaza, Suite 545, 100 UCLA Medical Plaza, Los Angeles, CA 90095, USA

Introduction and Epidemiology

Systemic amyloidosis is caused by tissue infiltration of insoluble proteins, disrupting normal organ function leading to a variety of disease manifestations. Virtually any organ can be affected including the heart, kidney, lung, peripheral nervous system, liver, eyes, skin, and blood vessels. Systemic amyloidosis with cardiac involvement (CA) portends a poor prognosis with eventual development of congestive heart failure, angina, and arrhythmias. There are many types of systemic amyloidosis worldwide; however, three main subtypes account for the majority of cases in the United States: light chain amyloidosis (AL), senile systemic amyloidosis (wtATTR), and hereditary

Published online: 20 May 2017

(familial) amyloidosis (mATTR). Although the amyloidogenic protein is different in AL versus ATTR, the underlying mechanism of cardiac involvement is similar and they are not distinguishable by light microscopy (Fig. 1D) [1].

The exact prevalence of CA is not known as the diagnosis is often overlooked. The diagnosis of CA can be challenging as signs and symptoms of clinical CA may often be non-specific and subtle in the early disease course. High level of clinical suspicion is necessary for diagnosis, and a lack of familiarity may delay diagnosis until end stages. A study examining the autopsy examination of 109 patients with a diagnosis of heart failure with preserved ejection fraction (HFpEF) without clinically apparent amyloid involvement demonstrated that 19% of those patients had LV amyloid deposition, suggesting that wtATTR may play an unrecognized but important role in HFpEF [2]. Early recognition of amyloidosis may be critical for intervention prior to manifestation of end-stage complications. This review examines the pathogenesis, diagnostic strategies, and treatment with a focus on recent research and current understanding in the use of cardiac imaging modalities for the diagnosis and prognosis of CA.

Pathogenesis and Subtypes

AL Amyloidosis

AL amyloidosis is caused by a plasma cell dyscrasia that may occur alone or be associated with multiple myeloma. In this disease, monoclonal plasma cells produce an abnormal immunoglobulin that becomes insoluble in serum due to protein misfolding, and subsequently deposits in tissue. AL amyloidosis commonly affects the heart and kidneys, although other organ involvement occurs frequently. Myocardial amyloid deposition leads to cardiomyocyte necrosis and interstitial fibrosis [1]. AL amyloid infiltration can be seen in both ventricles, atria, valves, and blood vessels [3]. Direct circulating light chain toxicity is also felt to be an important cause of cardiac dysfunction due to oxidative stress [4]. AL amyloidosis due to production of a lambda light chain is three times more common than due to a kappa light chain. Disease onset is typically near the sixth decade of life and occurs commonly in both men and women [5]. Cardiac AL amyloidosis is an aggressive disease with a median survival of 4 months [5].

Hereditary Amyloidosis (mATTR)

Hereditary amyloidosis is an inherited disease most commonly caused by production of a mutant transthyretin protein. Transthyretin is a transport protein found in serum and is normally produced by the liver. Seventy-five different mutations of the transthyretin protein are known to cause disease, of which 44 involve the heart. The most common mutations are replacement of valine by methionine at position 30 (V30M) and replacement of valine by isoleucine at position 122 (V122I) [6]. V122I is found in 4% of the African-American population and is the most common mutation seen

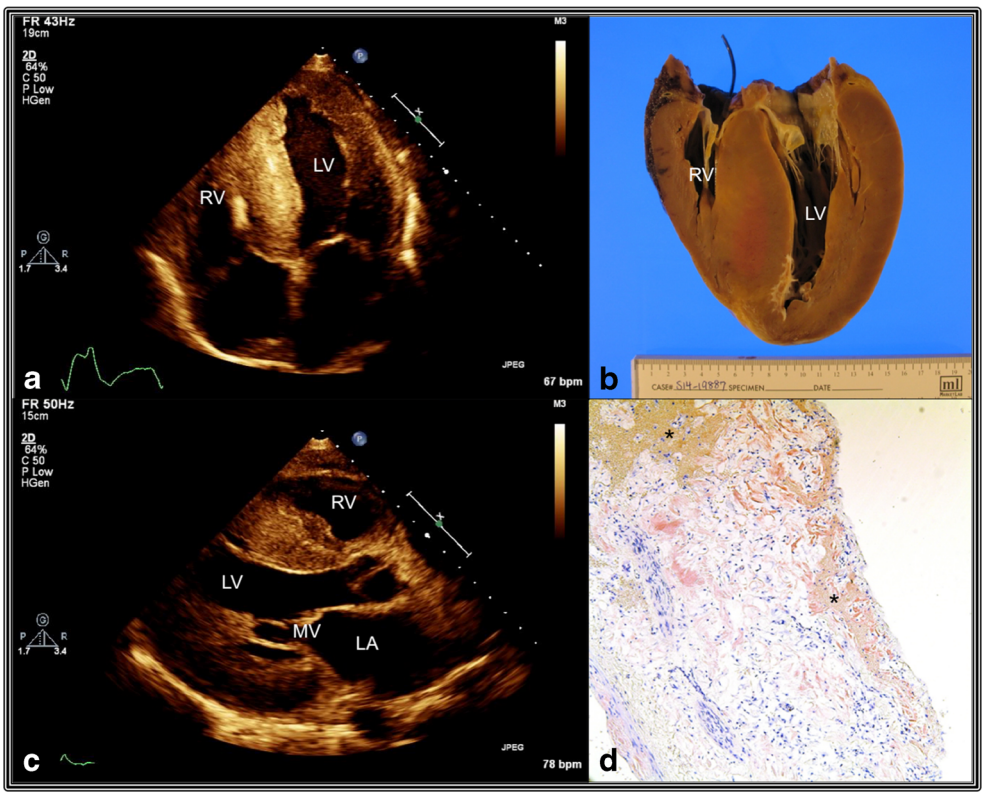

Fig. 1 Cardiac images showing the correlation between echocardiography and the gross anatomy and histopathology after cardiac explant of a patient with mATTR who underwent orthotopic heart transplantation. **a** Transthoracic echocardiogram, apical four chamber view demonstrating thickened left and right ventricular walls. **b** Explanted heart showing significant increase in right and left ventricular wall thickness. **c** Transthoracic echocardiogram, parasternal long axis view demonstrating thickened left ventricular walls. **d** Histopathology of the left ventricular wall showing positive Congo red staining (noted with *asterisk*) consistent with amyloid infiltration. *LA* left atrium, *LV* left ventricle, *MV* mitral valve, *RV* right ventricle

in the Unites States [7]. Transthyretin mutations are inherited in an autosomal dominant pattern; thus, both men and women are commonly affected. The age of disease onset and clinical manifestations are variable and dependent on the specific mutation. Symptoms of congestive heart failure typically occur in the sixth decade of life [7].

Senile Systemic Amyloidosis (wtATTR)

Senile amyloidosis is caused by infiltration of the wild-type transthyretin protein. Disease onset tends to be much later than either AL or hereditary amyloidosis, primarily affecting patients over the age of 65 years. It affects men disproportionately to women at a ratio of 20:1. Prior studies have found about a 25% prevalence of wtATTR infiltration in people over the age of 80 years on autopsy; however, not all of the infiltration is clinically significant [8]. In contrast to AL and hereditary amyloidosis, it is not uncommon for patients with senile amyloid to have normal voltage on electrocardiography (ECG) [6]. Cardiac infiltration in wtATTR tends to have a less aggressive course than AL amyloidosis with a median survival of 75 months [1].

Histologic Evaluation

The pattern of amyloid infiltration within the myocardium varies among patients. Recent studies have attempted to identify and characterize different patterns of ventricular infiltration within and between amyloidosis subtypes in order to improve interpretation of diagnostic imaging. Evaluation of nine explanted or autopsied hearts of patients with amyloid cardiomyopathy showed that amyloid infiltration is heterogeneous without significant difference between the amyloid subtypes. Three patterns of amyloid deposition were evident: diffuse, mainly subendocardial, and mainly segmental. Endocardial involvement was more common in these patients, suggesting that amyloid deposition occurs in an endo-to-epicardial direction [3]. In contrast, a different study of 216 patients with cardiac amyloidosis demonstrated distinct patterns of amyloid distribution between AL amyloidosis, which showed a reticular/pericellular pattern, and ATTR, which showed patchy infiltration. This study also suggested a maximum threshold for myocardial amyloid burden since no patient showed a burden >60% for AL amyloidosis and >70% for ATTR (median burden was 30.5%) [9••].

Diagnosis

Early diagnosis of cardiac amyloidosis is crucial since outcomes are especially poor with late diagnosis. Many symptoms and signs raise suspicion for CA. CA most commonly presents with symptoms of heart failure; however, angina also occurs often due to intramyocardial vessel infiltration. Low voltage on ECG (defined as ≤1 mV in all precordial leads or ≤0.5 mV in all limb leads) with evidence of left ventricular wall thickening suggests a diagnosis of amyloid (Fig. 1B). Pseudoinfarction pattern and conduction delays are also common ECG patterns [5]. Cardiac biomarkers, such as NT-pro brain natriuretic peptide (BNP) and troponin, are sensitive markers of cardiac dysfunction and are commonly abnormal in amyloidosis. There is insufficient data on the utility of biomarkers in the diagnosis and treatment response assessment in amyloidosis especially in ATTR. Elevated troponins have been shown to be associated with a worse prognosis in patients with systemic amyloidosis [10]. In AL amyloidosis, troponin and NT-proBNP have been incorporated into the amyloidosis staging system [11, 12]. Echocardiography is often helpful showing LV wall thickening and evidence of restrictive ventricular filling (Figs. 1 and 2). However, since the symptoms and signs mentioned above are not specific to amyloidosis, a definitive diagnosis of amyloid requires a biopsy specimen and histologic analysis showing a positive Congo red stain with apple-green birefringence under polarized light (Fig. 1D). A biopsy specimen can be obtained from any involved tissue. CA is considered present if there is either a positive endomyocardial biopsy or a positive non-cardiac biopsy in a patient who has evidence of clinical, laboratory, or echocardiographic abnormalities consistent with amyloid [13].

Once the diagnosis of amyloidosis is confirmed, the subtype must be identified since treatment can vary considerably. AL amyloidosis is confirmed with testing for serum free light chains (FLC) and serum and urine protein electrophoresis/immunofixation [13]. If ATTR is suspected, then DNA analysis is performed to identify the mutant form [6].

While tissue biopsy remains the gold standard for diagnosis of amyloidosis, there is increasing interest in using non-invasive cardiac imaging techniques to potentially diagnose CA earlier, which can have a tremendous effect in clinical outcomes. Various imaging modalities with different advantages and disadvantages (Table 1) have been utilized and studied to varying degrees in CA, with most studies looking at small patient populations.

Echocardiography

The hallmark of CA on echocardiography is a range of diastolic abnormalities in the setting of ventricular wall thickening due to amyloid infiltration. ATTR and AL amyloidosis are not morphologically distinguishable on echocardiography [14]. Early studies using echocardiography showed that the majority of patients with CA have

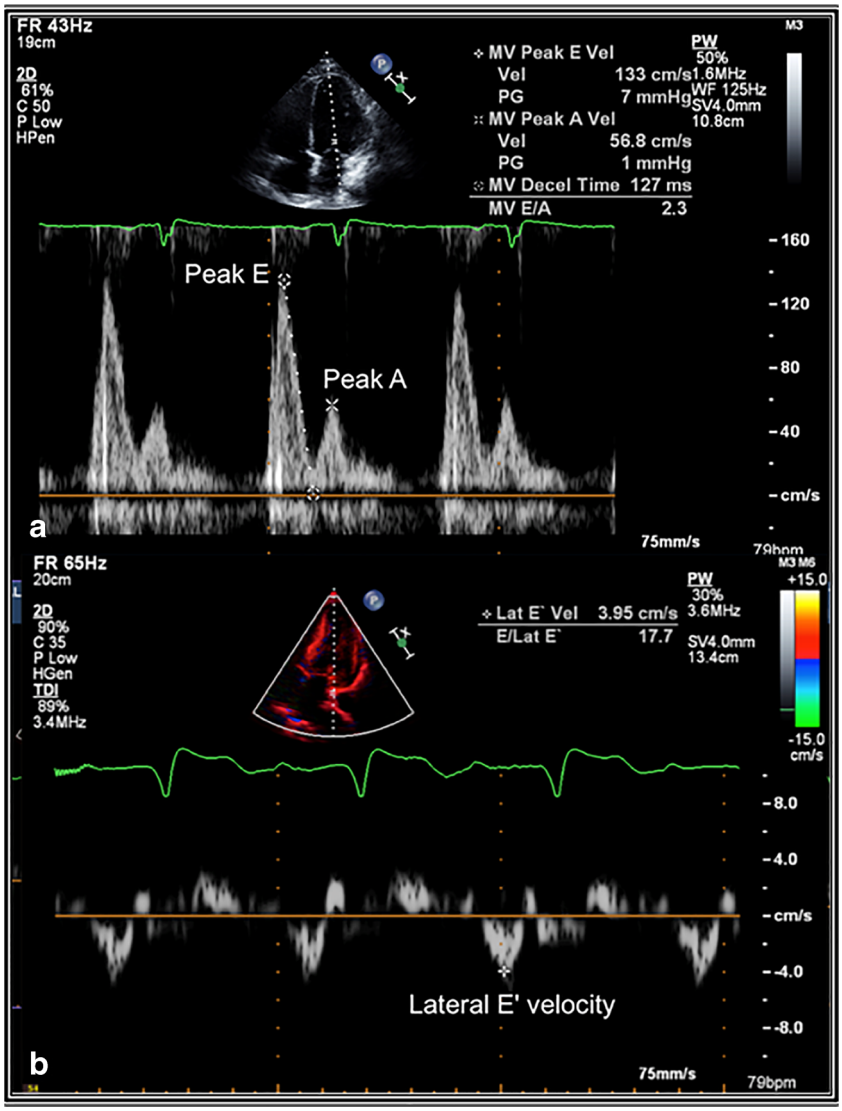

Fig. 2 Transthoracic Spectral Doppler echocardiography at the mitral valve inflow showing (**a**) increased peak E (early) to peak A (late) ventricular filling velocity ratio and (**b**) decreased lateral E′ velocity suggestive of restrictive left ventricular filling in a patient with mATTR. Normal range: E/A ratio <2.0, lateral E′ velocity >10 cm/s

concentric LV wall thickening (Fig. 1), although asymmetric septal thickening can occur [15]. The LVEF is often normal even in the presence of congestive heart failure. The evolution of abnormal LV diastolic filling patterns in CA was first described by Klein et al. in a study of 53 patients with primary systemic amyloidosis. These patients had deleterious changes in LV filling as measured by transmitral peak early (E) and late (A) flow velocity and E/A ratio with increasing progression of cardiac disease (Fig. 2). In advanced cardiac disease, a restrictive filling pattern was evident with significant changes in diastolic parameters including deceleration time and systolic versus diastolic pulmonary vein peak flow velocities [16]. Similar diastolic function abnormalities in patients with AL amyloid cardiomyopathy were later reported by Koyama et al. [17]. Systolic dysfunction can result but requires significant cardiomyocyte necrosis and extensive fibrosis, such as found in advanced disease.

Myocardial Strain

Strain is a non-invasive, reliable, and quantitative assessment of myocardial deformation with vast clinical applications including early detection of cardiac dysfunction in a variety of pathological conditions. Multiple recent studies have shown that strain abnormalities can be an early marker of CA often before symptoms of congestive heart failure [2, 17, 18]. Impairment in longitudinal LV strain is present across all three amyloidosis subtypes and these abnormalities correlate with other standard echocardiographic parameters [19]. Furthermore, there is a specific pattern of change in strain in CA, which is described as a basal to apical gradient of strain abnormalities with relative "sparing," i.e., relatively normal values, of apical segments (Fig. 3). The presence of an "apical sparing" pattern also has prognostic implications being predictive of a lower rate of major adverse cardiac events [19].

Table 1 Comparison of echocardiography, CMR, and nuclear imaging in cardiac amyloidosis

Modality	Advantages	Disadvantages
Echocardiography	No ionizing radiation Readily available Cost-effective Superior assessment of valvular disease, diastolic dysfunction, and hemodynamics Extensive literature Increased sensitivity for detecting early disease using strain pattern	Operator dependent and quality dependent on patient acoustic windows Requires geometric assumptions Cannot distinguish amyloid subtypes No cut-off values are sensitive or specific enough for CA diagnosis
CMR	No ionizing radiation Superior spatial resolution with 3D images of cardiac anatomy and tissue characterization More reproducible than echocardiography with accurate assessment of left and right ventricular function No acoustic window interference from bone or air	Underestimates degree of amyloid severity in diffuse disease Limited availability and high cost Requires patient cooperation with long examination times Not typically compatible with metallic implants Gadolinium contraindicated in advanced kidney disease Cannot distinguish subtypes
Nuclear imaging with Tc-PYP or Tc-DPD	Can distinguish ATTR from AL High sensitivity for ATTR even in early disease	Radiation exposure makes it less suitable for serial follow-up monitoring Modest specificity

The apical sparing strain pattern has been shown to distinguish amyloid from other causes of LV hypertrophy such as aortic stenosis and hypertrophic cardiomyopathy. In one study, a relative apical LS value of 1.0, defined as the average apical LS/(average basal LS + average mid-LS), showed a sensitivity of 93% and specificity of 82% for differentiating CA from hypertrophic cardiomyopathy, aortic stenosis, and LV hypertrophy. In regard to the different CA subtypes, apical sparing is seen in both ATTR and AL amyloidosis; however, apical strain was noted to be significantly lower in ATTR: −17.5 ± 5.2 in AL versus −14.5 ± 4.8 in ATTR [20••]. The systolic longitudinal base to apex strain gradient in a patient with shortened diastolic time of <200 ms may be helpful in distinguishing amyloid versus multiple other causes of concentric LV hypertrophy [21].

Prognosis

Abnormal Doppler-derived LV diastolic filling variables including deceleration time and increased E/A ratio are important predictors of survival in CA. The combination of an E/A ratio >2.1 and a deceleration time <150 ms has been shown to be more strongly associated with mortality than 2D measurements of LV thickness and fractional shortening in patients with biopsy-proven systemic amyloidosis [22]. Low voltage on ECG in combination with a reduced LVEF identifies patients at highest risk of cardiac death [23]. Strain as a prognostic indicator has not been well studied in ATTR; however, in AL amyloidosis, mean basal LV longitudinal strain and global longitudinal strain (LS) are significant predictors of survival [24, 25].

Cardiac Magnetic Resonance Imaging

In recent years, cardiac magnetic resonance imaging has generated a lot of interest as a potential diagnostic technique for CA. In contrast to echocardiography, cardiac magnetic resonance imaging (CMR) is not dependent on good acoustic windows, has higher spatial resolution, and provides tissue characterization. Studies have shown that certain late gadolinium enhancement (LGE) patterns on CMR are highly sensitive and specific for CA and may even precede morphologic increases in LV wall thickness [26]. Gadolinium contrast agents preferentially distribute in the extracellular space. LGE images are acquired approximately 10 min after gadolinium administration, and, due to a rapid washout in normal myocardium, enhancement is typically only seen in myocardium with abnormal distribution kinetics and an expanded extracellular space such as in the setting of amyloid infiltration. Regional differences in LGE reflect differences in distribution of amyloid deposits and can be used to estimate myocardial amyloid burden [19].

Patterns of Late Gadolinium Enhancement Seen in Cardiac Amyloidosis

Multiple studies confirm that LGE patterns in patients with cardiac amyloid distribution on CMR are heterogeneous varying from non-specific patchy enhancement to more specific patterns such as global subendocardial enhancement or difficulties with myocardial nulling (Fig. 4). CMR utility in CA was first reviewed in a study of 29 patients with biopsy-proven amyloidosis. Sixty-nine percent (20/29) of the amyloid patients had a characteristic pattern of global subendocardial late enhancement. Presence of late enhancement correlated with other markers of amyloid deposition such as LV and RV mass index and LVEF [27]. In a larger study of 251 patients with multiple myeloma referred for CMR due to concern for CA based on heart failure symptoms, systemic amyloidosis, or abnormalities in cardiac biomarker, ECG, or echocardiography, 30% (75/251) of patients had a LGE pattern suggestive of CA. These patients had several different patterns of infiltration including diffuse subendocardial or transmural

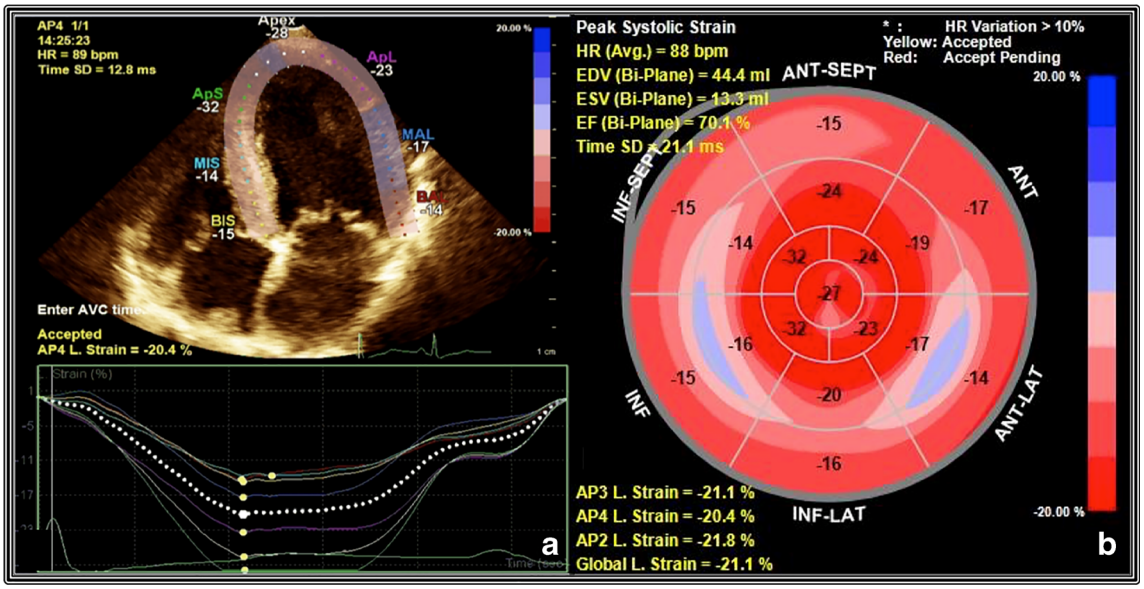

Fig. 3 **a** Myocardial strain imaging by speckle tracking echocardiography of a 71-year-old male patient with wtATTR. Transthoracic echocardiogram, apical four chamber view. The apical segments demonstrate better strain (between −23 and −32) in comparison to the mid- and basal segments (between −14 and −17). **b** Polar plot of a 2D representation of the left ventricle in 17 segments. The strain value for each segment is noted on the figure. There is apical sparing demonstrated by the preserved strain values in the apical LV segments compared to the reduced strain values in the outer LV segments (i.e., mid- and basal left ventricular segments). *BIS* basal inferoseptal segment, *MIS* mid-inferoseptal segment, *ApS* apical septal segment, *Apex* apical segment, *ApL* apical lateral segment, *MAL* mid-anterolateral segment, *BAL* basal anterolateral segment

pattern (55%) and focal or patchy patterns (26%); the remaining 19% of patients had suboptimal nulling [26]. Similar findings were reported in 18 patients with positive genetic testing for ATTR, 56% (10/18) of whom had positive LGE with the following enhancement patterns: subendocardial circumferential (13%), focal (75%), and diffuse (13%) [28]. Another subsequent study examined 53 patients with mATTR amyloid and showed that patterns of LGE were either diffuse (32%), focal (26%), or circumferential (2%), with diffuse pattern only seen in patients with cardiac symptoms [29].

Differentiating Subtypes of Cardiac Amyloidosis

Although CMR cannot fully distinguish between amyloid subtypes, small studies have attempted to delineate differences in LGE patterns that could elucidate the amyloid subtype. Subendocardial LGE occurs more commonly in AL, and transmural LGE more commonly in ATTR. One study showed that subendocardial LGE was present in 39% of AL versus 24% of ATTR patients, and transmural LGE was present in 27% of AL versus 63% of ATTR patients [30]. A second study similarly described that global subendocardial pattern was present in 39% of AL and 12% of ATTR, but extensive transmural LGE was higher in ATTR than AL [31••]. In addition, mATTR showed greater enhancement in the RV free wall as well as the atria. Based on these findings, a LGE scoring system called the Query Amyloid Late Enhancement (QALE) was devised to distinguish ATTR from AL. This score was able to detect ATTR from AL with a sensitivity of 87% and specificity of 96%; however, reproducibility of the QALE score between two independent observers was only fair [31••].

Imaging Markers of Prognosis

Although there are inconsistencies in studies reporting the prognostic significance of LGE, the majority demonstrates that increased LGE is an important predictor of mortality. Austin et al. showed that diffuse delayed hyper-enhancement (DHE) on CMR in patients with suspected CA was a strong predictor of 1-year mortality (Wald chi-square statistic 4.91, $p = 0.03$) [32]. In patients with multiple myeloma, myocardial LGE on CMR was a predictor of mortality (HR 1.72, 95% CI 1.05–2.8, $p = 0.04$) [26]. In a study by Fontana et al., the presence of transmural LGE on CMR was an independent predictor of mortality in patients with either ATTR, AL or asymptomatic patients with mATTR (HR 4.1, 95% CI 1.3–13.1, $p < 0.05$) even after adjusting for NT-proBNP, LVEF, stroke volume index, E/e′, and LV mass index [30]. Maceira et al. did not show that the presence of LGE was an independent predictor; however, an intramyocardial T1 gradient of <23 ms was associated with worse outcomes with a median duration of follow-up of 623 days [33]. In contrast, in Ruberg et al.'s study of 28 patients with systemic amyloidosis, LGE was sensitive and specific for CA

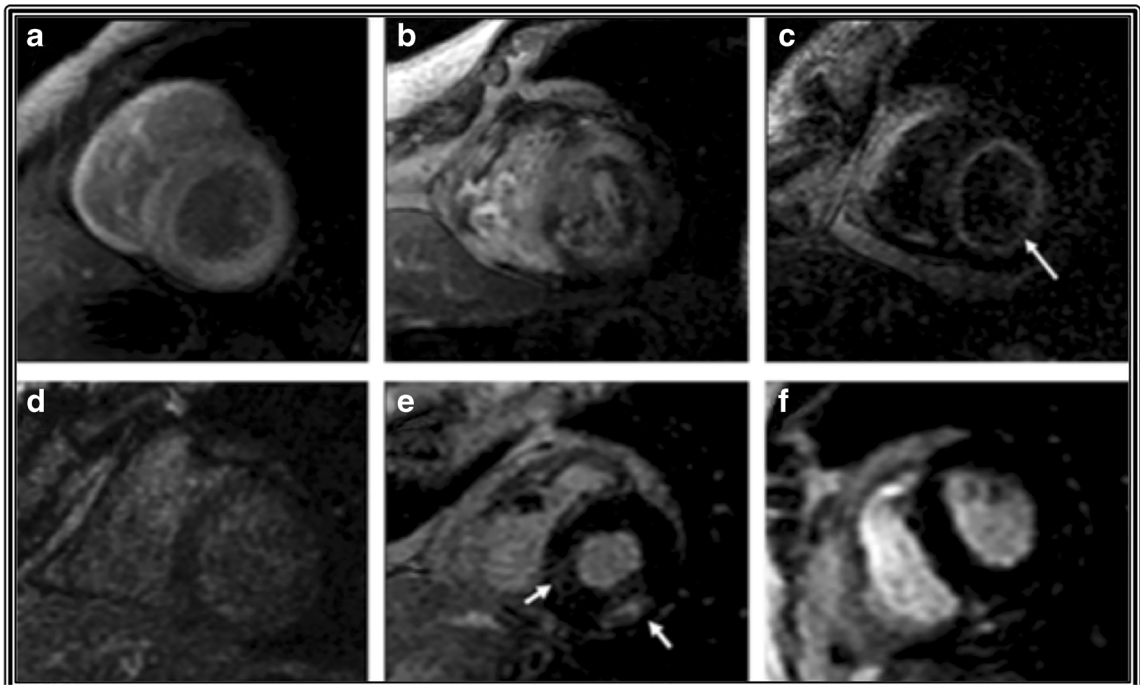

Fig. 4 Mid-ventricular short-axis LGE-CMR images in six patients with systemic amyloidosis. **a** Global transmural late gadolinium enhancement (LGE) in a homogeneous pattern in the left ventricle and right ventricle. The blood pool has a characteristic dark appearance commonly seen in cardiac amyloidosis. **b** Global transmural LGE in a heterogeneous pattern in the left ventricle and right ventricle. **c** Global subendocardial LGE (*arrow*) with dark blood pool. **d** Suboptimal myocardial nulling without discrete hyperenhancement. Normally, the LGE sequence forces normal myocardium to be nulled at an appropriately selected inversion time. The blood pool is darker than usual, and the image has poor signal-to-noise ratio with a grainy appearance, as has been described in cardiac amyloidosis. **e** Patchy focal LGE (*arrows*) in the basal inferolateral segment, and to a lesser extent in the inferoseptal segment. **f** Normally nulled myocardium. *CMR* cardiac magnetic resonance. Reprinted from JACC Cardiovascular Imaging, volume 3, number 2, Imran S. Syed, MD, James F. Glockner, MD, PhD, DaLi Feng, Philip A. Araoz, MD, Matthew W. Martinez, MD, William D. Edwards, MD, Morie A Gertz, MD, Angela Dispenzieri, MD, Jae K. Oh, MD, Diego Bellavia, MD, PhD, A. Jamil Tajik, MD, Martha Grogan, MD, Role of Cardiac Magnetic Resonance Imaging in the Detection of Cardiac Amyloidosis, pages 155–164, ©2010, with permission from Elsevier

and also correlated with heart failure, but it did not predict survival at a follow-up period of 29 months [34].

Limitations

LGE in patients with diffuse disease may limit the accuracy of CMR because LGE requires an inversion time to null normal myocardium. Homogeneity of amyloid infiltration can therefore lead to displaying only areas of higher amyloidosis distribution [28]. Alternative LGE sequences such as phase sensitive inversion recovery (PSIR) may improve this, as it is less sensitive to inversion time and less operator dependent [30].

Nuclear Imaging

Nuclear imaging has shown promise in facilitating the diagnosis of amyloid, particularly due to the ability to distinguish between subtypes. Many radiotracers have been investigated; however, ^{99m}technetium-phosphate derivatives (^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid or ^{99m}Tc-DPD, and Tc-pyrophosphate or Tc-PYP) have been the most studied. The mechanism of myocardial tracer uptake is not completely understood; however, phosphate-calcium binding appears to be an important factor. TTR amyloid accumulates more of these Tc-based tracers than AL. Although the reason for this is unclear, it is thought that a higher calcium content and longer duration of amyloid deposition in ATTR are contributing factors [35]. There are no studies that specifically compare imaging accuracy between the two tracers.

Tc-DPD

Nuclear imaging with Tc-DPD appears to have a very high sensitivity and specificity. ^{99m}Tc-DPD is the first radiotracer that showed the ability to distinguish AL from ATTR and may have prognostic significance [36, 37]. In one early study of 25 patients with either ATTR ($n = 15$) or AL ($n = 10$), ^{99m}Tc-DPD uptake had a sensitivity and specificity of 100% with echocardiography as the reference standard for amyloid recognition; no patients with AL showed tracer uptake [37]. A subsequent study evaluated 63 patients with biopsy-proven systemic ATTR either with or without echocardiographic evidence of amyloid cardiomyopathy. All patients with cardiac amyloid

showed moderate to severe tracer uptake including some patients without echocardiographic evidence of CA. The authors concluded that ^{99m}Tc-DPD may be useful in early disease detection. Univariate analysis of heart/whole body retention ratio (H/WB) correlated with prognosis (HR 7.2, CI 1.6–32.1, p = 0.009) [36]. This study was later expanded to include patients with AL amyloid as well as ATTR. In the follow-up study, ^{99m}Tc-DPD was still clearly useful in differentiating ATTR versus AL amyloid, as H/WB of late tracer uptake was higher in ATTR than AL subtypes. However, overall diagnostic accuracy was less than previously reported since one third of AL patients showed mild tracer uptake. Tracer uptake was assessed using a visual score of 0, 1, 2, or 3 which represents no, mild, moderate, or strong uptake, respectively. The positive and negative predictive values for a diagnosis of ATTR were 80 and 100% for a score of ≥1, 88 and 100% for a score of ≥2, and 100 and 68% for score of =3 [38••]. Tc-DPD is currently FDA approved and not available for clinical use in the United States.

Tc-PYP

Tc-PYP is an alternative radiotracer that is available in the United States with sensitivity and specificity similar to that of Tc-DPD (Fig. 5). In one study of 45 patients with AL and either wtATTR or mATTR, the authors quantified ^{99m} Tc-PYP tracer uptake as a heart-to-contralateral (H/CL) uptake ratio. A ratio of >1.5, consistent with intensely diffuse myocardial retention, had 97% sensitivity and 100% specificity for identifying ATTR [39].

Other Radiotracers

Additional tracers currently used to quantify brain amyloid in Alzheimer's disease may be useful in the diagnosis of CA. C-BF-227, [11]C-PIB, and ^{18}F florbetapir in particular demonstrate myocardial uptake in CA but not in healthy volunteers [35]. These tracers may improve the quantification of CA; however, in contrast to Tc-PYP and Tc-DPD, these tracers do not differentiate between amyloid subtypes. A pilot study of 14 subjects (nine CA, five controls) demonstrated that ^{18}F florbetapir uptake, measured using standardized uptake values and myocardial retention index, can distinguish control subjects from patients with CA [40]. ^{18}F florbetapir is in advanced clinical development for CA with a clinical trial underway to assess if it can be used as a non-invasive measure of myocardial amyloid deposits [41].

Correlation Among Imaging Modalities

Large correlation studies comparing the diagnostic accuracy among different imaging modalities are lacking. One study compared all three amyloidosis subtypes using both echocardiography and CMR and showed that LS correlates with LGE and amyloid burden [19]. One study examined patients with familial transthyretin polyneuropathy with evidence of myocardial involvement who underwent echocardiography, CMR, and ^{99m}Tc-DPD. CMR abnormalities included increases in LV end-systolic diameter, increased anteroseptal and posterior wall thickness, increased LV mass, and lower LVEF. However, no difference in the LV end-diastolic diameter or MRI-derived diastolic function was observed. CMR underestimated amyloid burden in comparison to ^{99m}Tc-DPD. Based on this, Tc-DPD may be more sensitive than CMR; however, interobserver agreement in imaging findings may be lower for nuclear imaging (depending on the cardiac chamber), than for CMR [28]. Other studies support an association between the extent of transmural LGE by CMR with

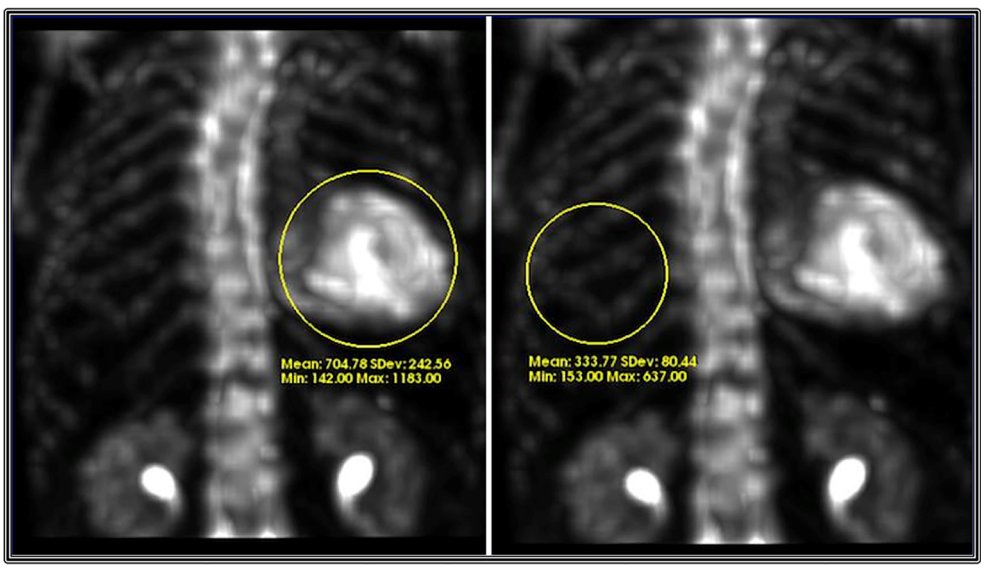

Fig. 5 Technetium pyrophosphate nuclear scan of a 79-year-old male patient demonstrating intense cardiac uptake (left panel) with a heart-to-contralateral (H/CL) uptake ratio of 2.1 consistent with wtATTR amyloidosis

abnormalities in echocardiographic LV end-diastolic volume, LV end-systolic volume, and left atrial size. Segments with extensive transmural enhancement (>50%) more commonly have severe hypokinesis or akinesis on echocardiography [42].

Treatment

Diuretics are central to the treatment of heart failure symptoms in all subtypes of CA. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are infrequently used because they can cause profound hypotension particularly in AL amyloidosis. Beta-blockers and calcium channel blockers have no proven benefit and are generally poorly tolerated. Digoxin should be avoided due to higher risk of digoxin toxicity likely due to avid binding of digoxin to amyloid fibrils. Symptoms of orthostatic hypotension may respond to compression stockings and treatment with the alpha-1 blocker midodrine [1, 6]. Pacemaker insertion may be required for conduction disease; however, pacemakers have not been shown to improve mortality [43]. Sudden cardiac death is common in patients with AL cardiac amyloidosis; however, death often occurs due to electromechanical dissociation as opposed to primary arrhythmias. The effectiveness of implantable cardioverter defibrillator (ICD) placement in CA remains unclear and it is not routinely recommended for primary prevention. Further studies are needed to help identify which subset of patients of CA may benefit from ICD placement [44, 45].

Routine use of heart transplantation in CA is controversial due to concerns about amyloid recurrence in the allograft. Prior studies have suggested worse post-transplant outcomes in patients with amyloidosis compared to patients transplanted for other indications [46, 47]. A more recent study suggests that similar intermediate-term post-transplant outcomes may be possible in patients with CA with careful patient selection, aggressive light chain suppression, and management of extracardiac disease [48].

AL Amyloidosis

Chemotherapy followed by autologous stem cell transplant is the target therapy for AL amyloidosis intended to eliminate the plasma cell clone producing the amyloidogenic protein. Severe cardiac involvement often precludes optimal chemotherapy administration; therefore, early diagnosis is crucial. In addition, a recent study by Kristen et al. found that once myocardial amyloid burden reaches a certain threshold, chemotherapy does not appear to improve outcomes [9].

ATTR

Several investigational approaches to ATTR management are underway; however, transplantation of the liver, which produces the transthyretin protein, remains the gold standard of therapy. Tafamidis, a meglumine salt that has been shown to prevent breakdown of the transthyretin molecule, may decrease amyloid deposition [49, 50]; however, no placebo-controlled trials have been performed. Additional investigational drugs that decrease circulating levels of transthyretin are undergoing testing in clinical trials. Antitransthyretin small interfering RNA reduces the production of transthyretin and may have clinical benefit [51].

Conclusions

CA is a rare disease often with a poor prognosis. It commonly presents with non-specific symptoms and signs, and thus the diagnosis is often overlooked. However, early detection is critical since treatment effectiveness is greatest in early disease, particularly for AL and hereditary systemic amyloidosis. Echocardiography is the cornerstone of diagnosis, and evaluation for CA with newer metrics such as strain may provide significant advances in early recognition of CA.

CMR and nuclear imaging are useful diagnostic tools that can improve evaluation of presence and risk of CA. CMR enables high-resolution myocardial tissue characterization, assessment of amyloid burden, and appears to have prognostic significance. CA manifests with various patterns of LGE; none of which are specific to CA alone; therefore, CMR interpretation depends on integrating all clinical and diagnostic information. Nuclear imaging offers the best non-invasive technique for distinguishing CA subtypes, although specificity is modest. Several promising positron emission tomography (PET) radiotracers for the detection of CA are currently in clinical trials. There is little research on the correlation between imaging modalities, although they appear to offer similar yet complementary data.

Although newer chemotherapy regimens for AL have improved survival, treatment response still hinges on early diagnosis. Similarly, early identification of CA and timely liver transplantation have tremendous impact on survival in ATTR. New investigational agents that target transthyretin may have significant therapeutic benefit; however, their impact has not yet been established in clinical trials. Heart transplantation is offered to a minority of patients in experienced amyloid centers, although there is important concern for disease recurrence in the cardiac allograft. Ultimately, further studies are needed to help optimize patient selection and identify outcome predictors.

Compliance with Ethical Standards

Conflict of Interest Mirela Tuzovic, Eric H. Yang, Arnold S. Baas, Eugene C. Depasquale, Mario C. Deng, Daniel Cruz, and Gabriel Vorobiof declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Shah KB, Inoue Y, Mehra MR. Amyloidosis and the heart: a comprehensive review. Arch Intern Med. 2006;166(17):1805–13.
2. Mohammed S, Mirzoyev S, Edwards W, Dogan A, Grogan D, Dunlay S, et al. Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. JACC Heart Fail. 2014;2(2):113–22.
3. Leone O, Longhi S, Quarta C, Ragazzini T, De Giorgi L, Pasquale F, et al. New pathological insights into cardiac amyloidosis: implications for non-invasive diagnosis. Amyloid. 2012;19(2):99–105.
4. Brenner DA, Jain M, Pimentel DR, Wang B, Connors LH, Skinner M, et al. Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in the cellular oxidant stress. Circulation. 2004;94(8):1008–10.
5. Dubrey S, Cha K, Anderson J, Chamarthi B, Reisinger J, Skinner M, et al. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. QJM. 1998;91(2):141–57.
6. Dubrey S, Hawkins P, Falk R. Amyloid diseases of the heart: assessment, diagnosis, and referral. Heart. 2011;97(1):75–84.
7. Castano A, Drachman B, Judge D, Maurer M. Natural history and therapy of TTR-cardiac amyloidosis: emerging disease-modifying therapies from organ transplantation to stabilizer and silencer drugs. Heart Fail Rev. 2015;20(2):163–78.
8. Cornwell G, Murdoch W, Kyle R, Westermark P, Pitkanen P. Frequency and distribution of senile cardiovascular amyloid. A clinicopathologic correlation. Am J Med. 1983;75(4):618–23.
9.•• Kristen A, Brokbals E, Aus dem Siepen F, Bauer R, Hein S, Aurich M, et al. Cardiac amyloid load: a prognostic and predictive biomarker in patients with light-chain amyloidosis. J Am Coll Cardiol. 2016;68(1):13–24. **Patient with a late diagnosis of cardiac AL amyloidosis after extensive amyloid deposition may not have improvement in outcomes with chemotherapy**
10. Dispenzieri A, Kyle R, Gertz M, Therneau T, Miller W, Chandrasekaran K, et al. Survival in patients with primary systemic amyoidosis and raised serum cardiac troponins. Lancet. 24(361(9371)):1787–9.
11. Dispenzieri A, Gertz M, Kyle R, Lacy M, Burritt M, Therneau T, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol. 2004;22(18):3751–7.
12. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol. 2012;20(30(9)):989–95.
13. Gertz M, Comenzo R, Falk R, Fermand J, Hazenberg B, Hawkins P, 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, Tours, France, 18–22 April 2004. Am H Hematol. 79(4):319–28.
14. Dubrey S, Cha K, Skinner M, LaValley M, Falk R. Familial and primary (AL) cardiac amyloidosis: echocardiographically similar diseases with distinctly different clinical outcomes. Heart. 1997;78(1):74–82.
15. Siqueira-Filho A, Cunha C, Tajik A, Seward J, Schattenberg T, Giuliani E. M-mode and two-dimensional echocardiographic features in cardiac amyloidosis. Circulation. 1981;63(1):188–96.
16. Klein A, Hatle L, Burstow D, Seward J, Kyle R, Bailey K. Doppler characterization of left ventricular diastolic function in cardiac amyloidosis. J Am Coll Cardiol. 1989;13:1017–26.
17. Koyama J, Ray-Sequin PA, Falk RH. Longitudinal myocardial function assessed by tissue velocity, strain, and strain rate tissue Doppler echocardiography in patients with AL (primary) cardiac amyloidosis. Circulation. 2003;107(19):2446–52.
18. Liu D, Niemann M, Hu K, Herrmann S, Stork S, Knop S, et al. Echocardiographic evaluation of systolic and diastolic function in patients with cardiac amyloidosis. Am J Cardiol. 2015;108(4):591–8.
19. Ternacle J, Bodez D, Guellich A, Audureau E, Rappeneau S, Lim P, et al. Causes and consequences of longitudinal LV dysfunction assessed by 2D strain echocardiography in cardiac amyloidosis. JACC Cardiovasc Imaging. 2016;9(2):126–38.
20.•• Phelan D, Collier P, Thavendiranathan P, Popovic Z, Hanna M, Plana J, 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(19):1442–8. **Relatively preserved apical strain in the setting of significantly abnormal basal and mid ventricular strain is both a sensitive and specific finding for cardiac amyloidosis**
21. Liu D, Hu K, Niemann M, Herrmann S, Cikes M, Stork S, et al. Effect of combined systolic and diastolic functional parameter assessment for differentiation of cardiac amyloidosis from other causes of concentric left ventricular hypertrophy. Circ Cardiovasc Imaging. 2013;6(6):1066–72.
22. Klein A, Hatle L, Taliercio C, Oh J, Kyle R, Gertz M. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis: a Doppler echocardiography study. Circulation. 1991;83:808–16.
23. Kristen A, Perz J, Schonland S, Schnabel P, Kristen J, Goldschmidt H, et al. Non-invasive predictors of survival in cardiac amyloidosis. Eur J Heart Fail. 2007;9(6–7):617–24.
24. Koyama J, Falk R. Prognostic significance of strain Doppler imaging in light-chain amyloidosis. JACC Cardiovasc Imaging. 2010;3:333–42.
25. Buss S, Emami M, Mereles D, Korosoglou G, Kristen A, Voss A. Longitudinal left ventricular function for prediction of survival in systemic light-chain amyloidosis: incremental value compared with clinical biochemical markers. J Am Coll Cardiol. 2012;60:1067–76.
26. Bhatti S, Watts E, Syed F, Vallurupatti S, Pandey T, Jambekar K, et al. Clinical and prognostic utility of cardiovascular magnetic resonance imaging in myeloma patients with suspected cardiac amyloidosis. Eur Heart J Cardiovasc Imaging. 2016;17(9):970–7.
27. Maceira A, Joshi H, Prasad S, Moon J, Perugini E, Harding I, et al. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation. 2005;18:186–93.
28. Minutoli F, Di Bella G, Mazzeo A, Donato R, Russo M, Scribano E, et al. Comparison between (99m)Tc-diphosphonate imaging and MRI with late gadolinium enhancement in evaluating cardiac involvement in patients with transthyretin familial amyloid polyneuropathy. AJR Am J Roentgenol. 2013;200(3):W256–65.

29. Deux J, Damy T, Rahmouni A, Mayer J, Plante-Bordeneuve V. Noninvasive detection of cardiac involvement in patients with hereditary transthyretin associated amyloidosis using cardiac magnetic resonance imaging: a prospective study. Amyloid. 2014;21(4): 246–55.
30. Fontana M, Pica S, Reant P, Abdel-Gadir A, Treibel T, Banypersad S, et al. Prognostic value of late gadolinium enhancement cardiovascular magnetic resonance in cardiac amyloidosis. Circulation. 2015;132(16):1570–9.
31.•• Dungu J, Valencia O, Pinney J, Gibbs S, Rowczenio D, Gilbertson J, et al. CMR-based differentiation of AL and ATTR cardiac amyloidosis. JACC Cardiovasc Imaging. 2014;7(2):133–42. **Transmural LGE is more common in ATTR, and the Query Amyloid Late Enhancement (QALE) score, which represents the degree of LGE in the right and left ventricle, may help differentiate between AL and ATTR amyloidosis.**
32. Austin B, Tang W, Rodriguez E, Tan C, Flamm S, Taylor D, et al. Delayed hyper-enhancement magnetic resonance imaging provides incremental diagnostic and prognostic utility in suspected cardiac amyloidosis. JACC Cardiovasc Imaging. 2009;2(12):1369–77.
33. Maceira A, Prasad S, Hawkins P, Roughton M, Pennell D. Cardiovascular magnetic resonance and prognosis in cardiac amyloidosis. J Cardiovasc Magn Reson. 2008;10:54.
34. Ruberg F, Appelbaum E, Davidoff R, Ozonoff A, Kissinger K, Harrigan C, et al. Diagnostic and prognostic utility of cardiovascular magnetic resonance imaging in light-chain cardiac amyloidosis. Am J Cardiol. 2009;103(4):544–9.
35. Aljaroudi W, Desai M, Tang W, Phelan D, Cerqueira M, Jaber W. Role of imaging in the diagnosis and management of patients with cardiac amyloidosis: state of the art review and focus on emerging nuclear techniques. J Nucl Cardiol. 2014;21(2):271–83.
36. Rapezzi C, Quarta C, Guidalotti P, Pettinato C, Fanti S, Leone O, et al. Role of (99m)Tc-DPD scintigraphy in diagnosis and prognosis of hereditary transthyretin-related cardiac amyloidosis. JACC Cardiovasc Imaging. 2011;4(6):659–70.
37. Perugini E, Guidalotti P, Salvi F, Cooke R, 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(6):1076–84.
38.•• Rapezzi C, Quarta C, Guidalotti P, Longhi S, Pettinato C, Leone O, et al. Usefulness and limitations of 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in the aetiological diagnosis of amyloidotic cardiomyopathy. Eur J Nucl Med Mol Imaging. 2011;38(3):470–8. **Nuclear imaging with radiotracer ^{99m}Tc-DPD can help differentiate ATTR versus AL cardiac amyloidosis although the diagnostic accuracy is best when there is either no uptake or intense uptake.**
39. Bokhari S, Castano A, Pozniakoff T, Deslisle S, Latif F, Maurer M. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Imaging. 2013;6(2): 195–201.
40. Dorbala S, Vangala D, Semer J, Strader C, Bruyere J, Di Carli M, et al. Imaging cardiac amyloidosis: a pilot study using ^{18}F-florbetapir positron emission tomography. Eur J Nucl Med Mol Imaging. 2014;41(9):1652–62.
41. Brigham and Women's Hospital. Imaging cardiac amyloidosis: a pilot study using F-18 florbetapir positron emission tomography. 2012 Sep; Available from: https://clinicaltrials.gov/ct2/show/study/NCT01683825.
42. Perugini E, Rapezzi C, Piva T, Leone O, Bacchi-Reggiani L, Riva L, et al. Non-invasive evaluation of the myocardial substrate of cardiac amyloidosis by gadolinium cardiac magnetic resonance. Heart. 2006;92(3):343–9.
43. Mathew V, Olson L, Gertz M, Hayes D. Symptomatic conduction system disease in cardiac amyloidosis. Am J Cardiol. 1997;80(11): 1491–2.
44. Lin G, Dispenzieri A, Kyle R, Grogan M, Brady P. Implantable cardioverter defibrillators in patients with cardiac amyloidosis. J Cardiovasc Electrophysiol. 2013;24(7):793–8.
45. Kristen A, Dengler T, Hegenbart U, Schonland S, Goldschmidt H, Sack F, et al. Prophylactic implantation of cardioverter-defibrillator in patients with severe cardiac amyloidosis and high risk for sudden cardiac death. Heart Rhythm. 2008;5(2):235–40.
46. DePasquale E, Nasir K, Jacoby D. Outcomes of adults with restrictive cardiomyopathy after heart transplantation. J Heart Lung Transplant. 2012;31(12):1269–75.
47. Kpodonu J, Massad M, Caines A, Geha A. Outcome of heart transplantation in patients with amyloid cardiomyopathy. J Heart Lung Transpl. 2005;24:1763–5.
48. Davis M, Kale P, Liedtke M, Schrier S, Arai S, Wheeler M, et al. Outcomes after heart transplantation for amyloid cardiomyopathy in the modern era. Am J Transplant. 2015;15:650–8.
49. Bulawa C, Connelly S, Devit M, Wang L, Weigel C, Fleming J, et al. Tafamidis, a potent and selective transthyretin kinetic stabilizer that inhibits the amyloid cascade. Proc Natl Acad Sci. 2012;109(24):9629.
50. Said G, Grippon S, Kirkpatrick P. Tafamidis. Nat Rev Drug Discov. 2012;11(3):185–6.
51. Coelho T, Adams D, Silva A, Lozeron P, Hawkins P, Mant T, et al. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. NEJM. 2013;369(9):819–29.