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MINIREVIEWS

Diagnostic and prognostic value of cardiac imaging in amyloidosis

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Abstract

Amyloidosis is an infiltrative disease caused by extracellular protein deposition that has accumulated a lot of scientific production in recent years. Different types of amyloidosis can affect the heart. Transthyretin amyloidosis and light chain amyloidosis are the two most common types of cardiac amyloidosis. These entities have a poor prognosis, so accurate diagnostic techniques are imperative for determining an early therapeutic approach. Recent advances in cardiac imaging and diagnostic strategies show that these tools are safe and can avoid the use of invasive diagnostic techniques to histological confirmation, such as endomyocardial biopsy. We performed a review on the diagnostic and prognostic implications of different cardiac imaging techniques in cardiac amyloidosis. We mainly focus on reviewing echocardiography, cardiac magnetic resonance, computed tomography and nuclear imaging techniques and the different safety measurements that can be done with each of them.

Key Words: Cardiac imaging techniques; Transthyretin cardiac amyloidosis; Immunoglobulin light-chain amyloidosis; Echocardiography; Magnetic resonance imaging; Nuclear imaging

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Core Tip: Cardiac amyloidosis is a disease with a poor prognosis. However, in recent years, specific therapies have been developed. When implemented in the early stages of the disease, they are associated with an improvement in the quality of life and survival. The use of cardiac magnetic resonance, echocardiography, computed tomography and nuclear imaging techniques allows an early diagnosis. In this review, we define in detail the implication of each imaging technique in cardiac amyloidosis.

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INTRODUCTION

Amyloidosis is a systemic infiltrative disease characterized by extracellular amyloid deposition, which causes a structural and functional alteration at different organs. Amyloid comes from up to 30 different types of misfolded precursor proteins. Only five directly affect the heart: Light chain, transthyretin, apolipoprotein A, fibrinogen and serum amyloid-protein A; Although, most cases of cardiac amyloidosis (CA) will be caused by the first two proteins[1]. The different proteins involved allow classifying the different types of amyloidosis, which have different clinical expression, prognosis and treatment.

Light chain amyloidosis (AL) is a plasma cell dyscrasia characterized by inappropriate production of only one type of light chain. Deposition of these proteins can be evidenced not only in the heart but also in the kidneys, nervous system, gastrointestinal system and soft tissues[2].

Transthyretin amyloidosis (ATTR) originates from the accumulation of transthyretin (a transporter molecule for thyroxine and retinol-bound protein) that mainly comes from the liver and whose principal deposit is limited to cardiac tissue, soft tissues and the nervous system[3]. Within this type of amyloidosis, two subtypes are classified based on the presence or absence of a mutation in the transthyretin gene: Variant transthyretin amyloidosis (ATTRv) and wild-type transthyretin amyloidosis (ATTRwt).

The early diagnosis of this pathology is essential due to its worse prognosis when it affects the heart and the existence of treatments that can modify the evolution of these patients[4].

This review aims to describe the different imaging tools for CA diagnosis and the prognostic value of the different approaches.

EPIDEMIOLOGY

For years, AL has been considered the most frequent subtype of amyloidosis. However, an increase in ATTR diagnoses has been evidenced recently. The incidence of AL is estimated to be around three to five patients per million per year[5]. The overall prevalence of ATTRv is around 5000–10000 persons, although it is endemic in areas such as Portugal, Sweden or specific areas of Japan[6]. The controversy started when trying to define the prevalence of ATTRwt. Classically it was considered a rare disease; however, a prevalence of 16% has been observed in patients with severe aortic stenosis undergoing transcatheter aortic valve replacement[7], 13.3% in patients hospitalized with heart failure with preserved ejection fraction and left ventricular hypertrophy (LVH) greater than or equal to 12 mm[8] and up to 25% in autopsies of patients > 85 years[9]. These results imply that it is an underdiagnosed disease, especially in older people.

Both subtypes show high morbidity and mortality in the short term. For ATTR-CA,

the TRACS study found a median survival from diagnosis of 25.6 mo for ATTRv and 43.0 mo for ATTRwt[10]. Likewise, cardiac involvement in AL (found in up to 50%-70% of patients[11]) determines a worse prognosis with a median survival of 6 mo in patients with heart failure and untreated disease[12,13].

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Amyloid can infiltrate any cardiac structure. Mainly, the deposit occurs in both ventricular walls increasing wall thickness, progressively altering the ventricular compliance and generating diastolic dysfunction. Also, amyloid can infiltrate the atrial walls, heart valves and conduction tissue. Clinically it can manifest as heart failure, cardiac conduction alteration, valve dysfunctions or with supraventricular arrhythmias such as atrial fibrillation.

As previously exposed, CA is a systemic disease that can involve multiple organs. ATTR-CA can cause glaucoma due to eye protein deposition. In the nervous system it causes varying degrees of ascending symmetric sensory-motor polyneuropathy (mainly ATTRv) and sometimes affecting the autonomic nervous system causing dysautonomia with orthostatic hypotension, erectile dysfunction, urinary incontinence and gastrointestinal symptoms. A greater predisposition to deposit protein in soft tissues frequently causing carpal tunnel syndrome (even bilateral), lumbar canal stenosis due to deposit in the yellow ligament, atraumatic rupture of the biceps tendon (Popeye's sign on physical examination), quadriceps tendon rupture and Dupuytren's contracture[1,3] has been observed in ATTRwt.

The deposits of the monoclonal protein in LA can affect not only the organs previously described but also the kidney. It causes monoclonal gammopathies of renal significance that leads from the development of a nephrotic syndrome to kidney failure. In 5% of patients, gastrointestinal deposits cause clinical manifestations of gastrointestinal malabsorption, and in 15% of patients the deposit is in the liver with the development of hepatomegaly/splenomegaly and different grades of organ dysfunction[2].

Classically, diagnosis of CA required pathological confirmation of amyloid deposition in the myocardium obtained through endomyocardial biopsy. However, thanks to the algorithm published in 2016 that joins the determination of monoclonal proteins in blood and urine together with the performance of a ^{99m}Tc-labeled phosphate scintigraphy, it is possible to perform the noninvasive diagnosis of patients with ATTR-CA[8,14]. Nowadays, different hospital protocols have adapted the algorithm published by an expert consensus in order to reduce the invasive approach (Figure 1).

CARDIAC IMAGING

Cardiac imaging is playing an increasingly important diagnostic and prognostic role in amyloidosis. It allows reducing the invasive approach thus decreasing the number of endomyocardial biopsies performed to confirm the diagnosis. In this review we analyze the different cardiac imaging tools.

ECHOCARDIOGRAPHY

Transthoracic echocardiography (TTE) is an accessible and harmless technique for the patients, so it is usually the first study performed to rule out cardiac involvement in amyloidosis.

As previously described, amyloid deposition causes thickening of both ventricles. The characteristic pattern was defined as concentric; however, in several studies different patterns such as the asymmetric septal were observed[15]. Multiple studies suggest that the measurement of 12 mm or more in the long parasternal axis at the level of the interventricular septum, in the absence of alternative causes of LVH, is the cut-off point for suspecting CA[16]. The appearance of the left ventricle (LV) wall has been classically described with the term "sparkling." However, it is not diagnostic of CA because multiple situations can simulate this appearance.

Other findings that can be observed in CA are valve or interatrial septum thickening, biatrial dilatation and mild pericardial effusion. Valve involvement, objectified in the mitral and tricuspid valves in 50% of patients and in the aortic valve

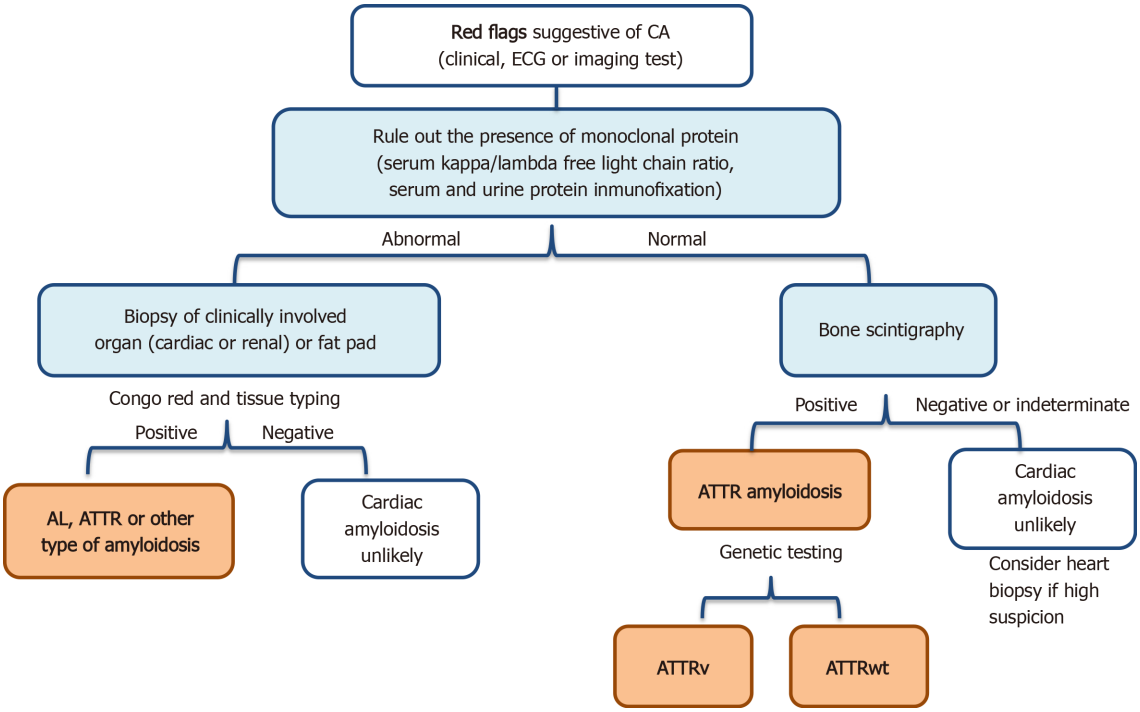

Figure 1 Algorithm for diagnostic patients with suspected cardiac amyloidosis[78]. AL: Light chain amyloidosis; ATTR: Transthyretin amyloidosis; ATTRv: Variant transthyretin amyloidosis; ATTRwt: Wild-type transthyretin amyloidosis; CA: Cardiac amyloidosis; ECG: Electrocardiogram.

in 25%, has been related to a more advanced New York Heart Association functional class, lower left ventricular ejection fraction (LVEF) and was associated with reduced 5-year survival[17].

At first, it is important to use conventional ultrasonography. It allows us to obtain a high suspicion of amyloidosis. With conventional TTE, there are parameters that guide the differentiation between CA and hypertrophic cardiomyopathy (HCM). For example, in HCM, LVH is usually severe and asymmetric, generating an obstructive gradient in the outflow tract. However in CA, LVH is usually concentric, not so severe, without an obstructive gradient and sometimes with sparkling. Likewise, interatrial, pericardial involvement and the apical sparing are usually rare in HCM unlike in CA[18].

Diastolic function is impaired and in the advanced stages it presents a restrictive filling pattern. The deceleration time of transmitral E wave, E/A ratio of transmitral flow and D/S ratio of pulmonary venous flow were independent predictors of overall death[19].

Functional assessment of the LV can be carried out in different ways. CA predominantly affects diastolic function; thus it was traditionally related to normal or slightly depressed LVEF values. However, it has recently been observed in different series that up to 50% of patients with ATTRwt-CA had LVEF < 50%[20]. Small variations in LVEF may imply large myocardial amyloid deposits. For this reason, other parameters have been evaluated to detect early alterations in the correct functioning of the LV with low cardiac amyloid burden. In AL-CA patients with normal LVEF but symptomatic and with high cardiac biomarker values, parameters such as stroke volume index < 33 mL/min, myocardial contraction fraction (MCF) (calculated as a ratio between LV stroke volume and LV myocardial volume) < 34% and cardiac-index < 2.4 L/min/m^2 determine a higher mortality. Moreover, these measurements are altered before LVEF, so they provide earlier information[21]. Myocardial dysfunction from amyloidosis can prolong pre-ejection period leading to reduced ejection time, and its measurement has shown an important prognostic implication. The cut-off ≤ 240 ms had a specificity of around 90% in predicting 1-year cardiac mortality in AL-CA patients[22,23].

Right ventricle (RV) involvement has been studied as a prognostic factor in the evolution of the disease. It was observed that a ventricular area ratio ≤ 2 predicts survival in AL-CA patients[24]. In both AL-CA and ATTR-CA, reductions in RV fractional shortening, tricuspid annular plane systolic excursion (TAPSE), tissue Doppler systolic velocity and global RV longitudinal strain have been described. Of them, only TAPSE < 14 independently predicted 6 mo major adverse cardiac events[25].

Therefore, a simple technique such as measuring TAPSE is particularly useful in the prognostic evaluation of the disease.

Diastolic dysfunction progressively generates biatrial dilation, and it has been shown that patients with higher N-terminal pro b-type natriuretic peptide (NT-proBNP) and troponin values presented larger indexed 3D left atrial volumes and lower 3D left atrial total emptying fraction. A cut-off of 3D left atrial total emptying fraction < 34% combined with worse 3D peak atrial longitudinal strain had significantly lower 2-year survival[26].

Longitudinal (LS) and radial strain total values are reduced in CA. Phelan *et al*[27] described the regional variations in LS from base to apex in CA patients. Patients with CA typically present a marked decrease in longitudinal strain in the basal and midwall segments and a relative apical sparing (Figure 2). The relative apical longitudinal strain [average apical longitudinal strain/(average basal + mid longitudinal strain)] greater than 1 could differentiate CA from hypertrophic cardiomyopathy and aortic stenosis with high diagnostic precision (sensitivity 93%, specificity 82%). Along the same lines, Koyama *et al*[28] showed that the reduction of LV basal strain was an independent predictor of both cardiac and overall deaths. Different articles published later, defined other relevant diagnostic and prognostic strain measurements. Speckle-tracking-imaging derived global longitudinal early diastolic strain rate was superior to conventional diastolic parameters for predicting mortality in CA patients with preserved LVEF, increasing the risk of death fourfold with a cut-off value of 0.85[29]. RV strain analysis brings more prognostic information. Free-wall right ventricular longitudinal strain worse than 21.2% distinguishes between CA and other etiologies of cardiac hypertrophy[30].

LS and 2D-global LS provided incremental value to the combination of NT-proBNP, troponin and clinical parameters on survival in AL amyloidosis, and LS correlated strongly with the amyloid deposition measured histologically[31,32]. Strain is especially useful in early stages of the disease and could set up groups with a worse prognosis.

In summary, echocardiography can objectify cardiac infiltration in all its stages. The effect of strain and E/e' have high probabilities of being abnormal at low cardiac amyloid burden. However, indexed stroke volume, MCF and TAPSE are abnormal more gradually with the progressive amyloid infiltration. Finally, at high levels of cardiac infiltration, biatrial areas and biventricular ejection fraction are altered[33]. Echocardiography is an important resource to objectify cardiac involvement. The advantages of the use of conventional TTE are: Rapid and instantaneous diagnostic tool; technically simple and easily interpretable; high availability; and does not require radiation of the patient. Completing the study with the strain test can slightly prolong the duration of the procedure, but it has a greater interpretive difficulty and the availability of the software is lower, which limits its use. The combination of structural parameters such as the biventricular hypertrophy pattern, biatrial dilation, pericardial effusion, interseptal and valve thickening associated with functional parameters such as conventional diastolic function measurement, MCF and the strain parameters allow clinicians to perform a first diagnostic approach and provide prognostic data on the evolution of the disease.

CARDIAC MAGNETIC RESONANCE

Cardiac magnetic resonance (CMR) is a widely used technique today. It is a noninvasive tool that permits the evaluation of cardiac structure and function as well as characterization of the composition of interstitial tissue. To this aim, certain sequences are used, and it can be grouped into three categories: Functional/cine imaging; Noncontrast tissue imaging; and Postcontrast tissue imaging[34].

Cine sequences or functional assessment in patients with CA allow visualizing the morphology of the infiltrated myocardium (*i.e.* biventricular hypertrophy, valvular or interatrial septum thickening, pericardial effusion or biatrial dilation) and accurately assessing systolic and diastolic function. It is particularly important for the evaluation of the LV and the rest of the cardiac chambers. RV involvement is a predictor of mortality in CMR, as it had been shown previously in TTE[35]. With the disease progression towards advanced stages, there is an increase in the atrium volume and an alteration of their functioning. It occurs by direct infiltration of the amyloid fibrils in the atrium and indirectly by the increase in filling pressures secondary to diastolic dysfunction. Mohty *et al*[36] observed in patients with AL-CA that the reduction of the total left atrial emptying fraction was not only related to more advanced stages of the disease and with a worse functional class but also with an increase in 2-year mortality

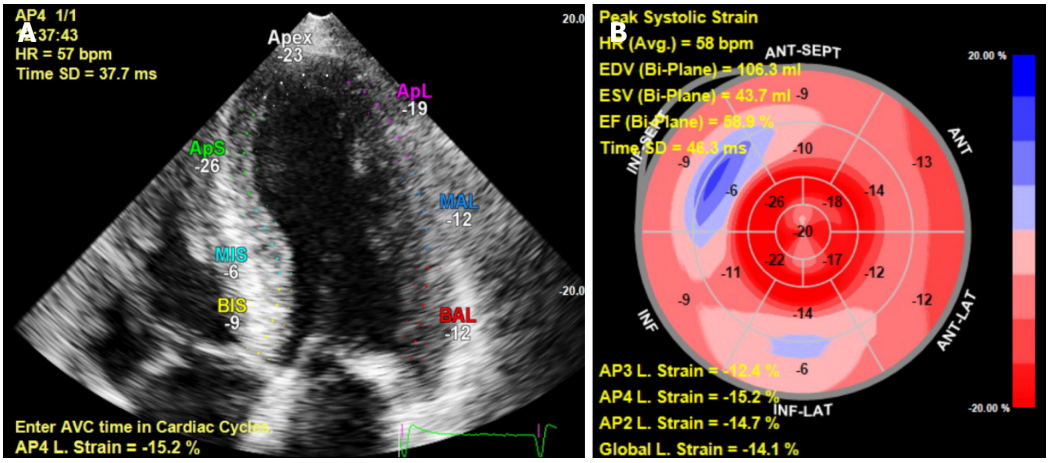

Figure 2 Transthoracic echocardiography imaging from a patient with transthyretin amyloidosis-cardiac amyloidosis. A: Strain imaging by transthoracic echocardiography; B: Reduced mid and basal values with apical sparing.

if its value decreased below 16%. In addition, the CMR also allows us to measure less frequently used parameters such as MCF and long axis strain. These new determinations can further stratify the risk in AL-CA patients with late gadolinium enhancement (LGE) uptake if the value of long axis strain exceeds 7% and the MCF value decreases below 52.6%. This subgroup of patients will have the greatest risk of death and heart transplantation[37].

Unlike TTE, CMR usually provides high image quality that allows differentiation of the endocardial border and greater definition of small displacements. Ochs *et al*[38] evaluated the prognostic value of different valve plane displacements. Traditionally, this measurement is reduced to TAPSE and inferoseptal mitral plane systolic excursion. However, it was found that the anterior aortic plane systolic excursion was the valve displacement that provided the best predictive value for transplant-free survival in AL patients. Therefore, cine sequences provide a global assessment with important prognostic and diagnostic information. It can even objectify the alteration of different parameters at low cardiac amyloid burden[39].

The strain can be analyzed by CMR to complete a deep study. Wan *et al*[40] noticed that the strain correlates well with the level of LGE uptake, and it may be an alternative to LGE in the group of patients where contrast should not be used (Table 1). They found that global longitudinal strain and global circumferential strain were significantly lower in the subendocardial and transmural than in no or nonspecific LGE group. They also found that the impaired global longitudinal strain was a robust predictor of all-cause mortality. Furthermore, they emphasized the utility of this tool in the early stage of the disease because in AL patients without cardiac involvement, basal segmental circumferential strain and radial strain were significantly impaired compared with those in healthy subjects.

One of the most worthwhile uses of CMR is the possibility of characterizing the tissue in a noninvasive way, for which the pre-contrast (native) T1 mapping, the postcontrast imaging-LGE and T1 mapping are used. In amyloidosis, the deposition of amyloid fibrils in the extracellular level causes an increase in the interstitial volume and a greater accumulation of gadolinium in that level.

The significant amyloid deposit alters the gadolinium kinetics. The gadolinium presents a rapid clearance from the intravascular space into the extracellular space. Thus the myocardial signal becomes hyperintense before the blood pool signal, unlike healthy patients. It is difficult to acquire and correctly interpret LGE images. Therefore, in the imaging acquisition of LGE the inversion time on the scanner needs to be adjusted to make the normal myocardium appear dark and the abnormal tissue bright. If the amyloid infiltration is diffusely distributed, then it is even more difficult to identify the optimal inversion time because of little or no normal tissue available to null the myocardium. There are some tools to overtake this issue like phase correction inversion recovery LGE imaging or quantitative T1 mapping. It has prognostic implications because there is an increased risk of death if it is impossible to obtain a normal myocardial signal on LGE using the look locker sequence (T1 sequence with different inversion times) with inversion time over 300 ms[41].

The typical pattern of LGE in amyloidosis is a diffuse subendocardial uptake, and it was described a transmural pattern enhancement and less frequently a focal patchy

Table 1 Early imaging tool for cardiac amyloidosis diagnosis

	Patients with renal impairment	Patients without renal impairment
TTE	MCF, cardiac-index, strain parameters, E/A ratio of transmitral flow	MCF, cardiac-index, strain parameters, E/A ratio of transmitral flow
CMR	Stroke volume index, global longitudinal and circumferential strain, T1 native	Stroke volume index, global longitudinal and circumferential strain, T1 native and ECV
CCT		ECV
Nuclear imaging		^{99m}Tc-DPD myocardial uptake, MIBG uptake

^{99m}Tc-DPD: ^{99m}Tc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid; CCT: Cardiac computed tomography; CMR: Cardiac magnetic resonance; ECV: Extracellular volume; MCF: Myocardial contraction fraction; MIBG: 123-iodine metaiodobenzylguanidine; TTE: Transthoracic echocardiography.

one. The gadolinium deposits usually involve the RV and the atrial walls. Controversy exists regarding the prognostic implication of gadolinium uptake in the myocardium. Maceira *et al*[42] noticed that the presence of LGE was not a robust predictor of death but they described a new method to measure gadolinium kinetics: The difference post-gadolinium intramyocardial T1 between subepicardium and subendocardium. If there is less difference between the subepicardium uptake and the subendocardium uptake, it implies that the amyloid infiltration is more diffuse. These patients had a worse survival when that difference was lower than 23 ms. Ruberg *et al*[35] founded in 28 AL patients with suspected heart disease that the LGE is highly sensitive and specific (86% and 86% respectively) for the identification of CA, and it correlated with high values of brain natriuretic peptide but did not predict survival. A clear correlation with high NT-proBNP values and the extent of LGE was observed without showing a direct relationship with survival[43]. However, multiple subsequent studies demonstrated a relevant prognostic implication of LGE in this disease. Diffuse subendocardial uptake detected using a modified LGE-CMR protocol with visual T1 assessment had high diagnostic precision (positive predictive value 93%, negative predictive value 90%), and it was significantly associated with 2-year mortality[44,45]. Fontana *et al*[46] observed the presence of a transmural pattern in ATTR and AL patients that predicted high risk of death in a follow-up period of 24 + 13 mo. All of this information was tested in a meta-analysis where it was found that in patients with known or suspected CA, LGE was associated with an odds ratio of 4.96 (95% confidence interval: 1.90 to 12.93) for all-cause mortality, without differences between both types of CA[47].

Wan *et al*[48] studied the RV gadolinium uptake in AL patients, and they showed that it was an independent predictor of survival during a period of 6 mo follow-up. Afterwards, the same investigation group[49] proposed a new CMR parameter, the query amyloid late enhancement score. It is a semiquantified measurement of LGE in both LV and RV, where higher values imply greater involvement. The query amyloid late enhancement score above 9 predicted worse survival, and it was especially useful in patients with a subendocardial LGE pattern because the query amyloid late enhancement score value above 9 defined a subgroup with a higher risk of death.

In patients with AL-CA, the diffuse pattern provides incremental prognosis over biomarker stage[50]. In patients with multiple myeloma the presence of LGE patterns included diffuse subendocardial, transmural and focal or patchy, and suboptimal nulling provides incremental prognosis for mortality prediction over biomarker stage, clinical and echocardiographic variables[51]. In patients with ATTR-CA, the presence of LGE increases the prognostic power over the functional New York Heart Association class[52]. This information suggests that the combination of conventional LGE images with clinical, biomarker and echocardiographic findings has an important prognostic role, and it improves the diagnostic accuracy in CA.

Noncontrast T1-mapping has the potential to detect and quantify cardiac involvement and could become a clinically useful diagnostic and prognostic tool, especially for impaired renal patients where the use of contrast has deleterious effects. The amyloid infiltration alters cardiac native signal. In ATTR and AL patients, it involves greater myocardial T1 native values. The increase of T1 values is not only due to interstitial expansion but also cellular hypertrophy. It could limit the ability of myocardial T1 values to distinguish CA from other cardiac hypertrophy etiologies, especially in early stages where there is little interstitial expansion[34]. Despite that, Karamitsos *et al*[53] proved that myocardial T1 was increased in AL amyloidosis even when cardiac involvement was uncertain or absent, showing that this tool could allow an early diagnosis of CA. The cut-off value of 1020 ms had high sensitivity and

specificity (around 90%) for identifying amyloid patients with possible or definite cardiac involvement. Higher T1 values were well correlated with decreased LVEF, decreased LV mass index and with worse diastolic function suggesting that T1 changes could reflect more severe cardiac involvement. At that time, there was still no clear information about the prognostic implication of native T1.

T1 mapping (Figure 3) with native T1 and extracellular volume (ECV) are recently developed quantitative parameters. Patients with AL and suspected cardiac involvement had increased values of native T1 and ECV, even in early stages where no LGE was demonstrated[54]. It emphasized that native T1 and ECV are more useful tools than LGE in early cardiac diagnosis. However, only the ECV had a significant prognostic implication with greater mortality if its value was above 44%. This tool was especially useful in subgroups with the same LGE pattern where the ECV could distinguish a high risk group[54]. Basal, mild and apical level of native T1 and ECV were quantified in a Wan *et al*[55] report. Basal ECV had the best prognostic value amongst myocardial T1 mapping parameters, and it increased in patients without LGE uptake, strengthening the concept that this tool is very useful in early disease stages. Later, relative to ATTR-CA, Martinez-Naharro *et al*[56] observed that both native T1 and ECV provided excellent diagnostic accuracy for identification of ATTR-CA, without difference between the two types of ATTR. Similar to AL, only ECV was an independently predictor of mortality. Both native T1 and ECV correlated with cardiac function parameters and with increasing cardiac uptake (assessed by bone scintigraphy). They noticed that due to the different biological information provided by native T1 and ECV measurements (ECV measures extracellular volume and native T1 measures the interstitial expansion and the cellular hypertrophy) that there were discrepancies in measurements depending on the level of cardiac infiltration. When amyloid burden was moderate or severe, there were discrepancies between the results of ECV and native T1. However at low level infiltration assessed by nondiagnostic ^{99m}Tc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) grade 1 uptake, there were consistent abnormal values of both myocardial T1 and ECV, proving that they had greater precision at low amyloid burden. Using these measurements, CMR could detect a phenotype of early amyloid infiltration. Unless the patient had impaired renal function, the ECV was a better T1 mapping parameter than native T1[54].

Another sequence that it could be used in the diagnosis of CA is the T2-weighted imaging, and it is attractive because no gadolinium administration is needed. A decreased myocardial signal intensity compared with skeletal muscle in T2 images was associated with shortened survival. However, for a T2 ratio value less than 1.36 it had a weak sensitivity and specificity (63% and 73%, respectively) to predict cardiac involvement[57,58].

In conclusion, CMR would be a second step to complete the diagnostic study of a patient with suspected CA. It is an imaging technique that is not available in many hospitals, and the long duration of each study limits the number of studies that can be performed per day. Likewise, increasing the number of sequences further prolongs the duration of the test, which hinders accessibility. Another drawback is that it does not provide instant information as with TTE, and postprocessing is required to complete the entire test. However, the great advantage of this technique, in addition to the anatomical and functional cardiac characterization, is the tissue characterization and the absence of ionizing radiation on the patient. The use of contrast for gadolinium uptake sequences would cause kidney damage, but as previously exposed, it seems that the use of strain presents an adequate correlation with gadolinium uptake, which obviate this sequence in patients at risk of impaired kidney function. Therefore, the use of CMR establishes an early and accurate diagnostic approach in CA through measurement of MCF, strain parameters, native T1 and ECV. These measurements associated with an adequate assessment of the RV, atrial function and in non-contraindicated cases the pattern of LGE uptake have shown implications in the prognosis and mortality of the patient. Therefore, it is a fundamental tool in the diagnosis of CA.

CARDIAC COMPUTED TOMOGRAPHY

The usefulness of cardiac computed tomography (CCT) for the diagnosis of CA is unknown due to few trials. Nevertheless, it is commonly used to rule out the presence of other concomitant diseases. This tool, despite being more accessible than performing a CMR or a scintigraphy, has deleterious effects on the patient, such as the use of contrast and radiation exposure[34].

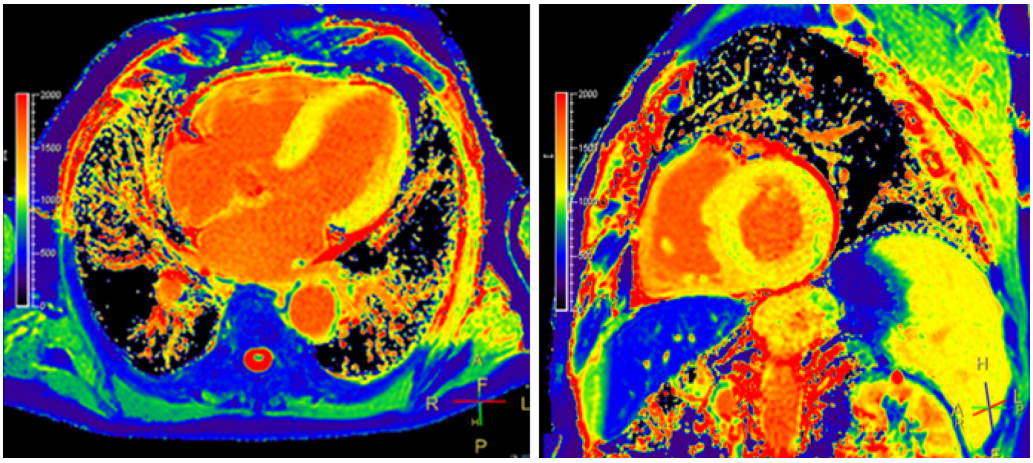

Figure 3 Native T1-mapping images. Abnormally elevated values of T1 native (1120 ms) in a patient with amyloidosis-cardiac amyloidosis.

Few studies have been published about the diagnosis of CA by CCT. Treibel *et al*[59] compared a small sample of 26 patients with AL and ATTR-CA with patients with severe aortic stenosis by quantifying the contrast distribution in the extracellular volume by CCT. They underwent a dynamic equilibrium CCT protocol with rapid contrast administration to quantify the ECV. The authors observed an adequate correlation between the ECV measured by CCT in the first 5 min and the ECV measured by CMR, with high diagnostic accuracy of CA and a great correlation with clinical and biochemical markers of disease severity. Furthermore, CCT had good results and was easier, quicker and more accessible than CMR.

To quantify the ECV by CCT it is necessary to obtain a combination of the hematocrit, pre- and postcontrast measurements. Treibel *et al*[60] simplified this technique to not require blood extraction, further facilitating the use of this method.

Despite the disadvantages of this technique with respect to ionizing radiation and the need to use contrast, the greater availability of this tool and the capacity of tissue characterization with the ECV measurement, makes the CCT an alternative to CMR in the diagnosis of cardiac infiltration by amyloid.

NUCLEAR IMAGING

None of the previous cardiac imaging tools gives us great information with regard to the type of CA. The main utility of the scintigraphy is to precisely differentiate the types of amyloidosis.

^{99m}Tc-DPD, ^{99m}Tc-labeled pyrophosphate (^{99m}Tc-PYP) and ^{99m}Tc-labeled hydroxymethylene diphosphonate were the different bone avid radiotracers used for ATTR-CA diagnosis[14]. Fibril deposits are composed of the precursor protein, heparin sulfate proteoglycan and a calcium dependent P-component. It is thought that the use of calcium for binding amyloid P and fibrils explains the uptake of ^{99m}Tc-bone avid tracers. Stats *et al*[61] histologically showed that hearts affected by ATTR-CA have higher microcalcification density compared to hearts with AL-CA, which may explain the higher uptake in the ATTR subgroup. This binding allows a semiquantitative (visual) scoring and a quantitative (heart to contralateral ratio) assessment of amyloid protein deposition.

The use of ^{99m}Tc-labeled hydroxymethylene diphosphonate allows us to distinguish cardiac involvement by transthyretin from other nonamyloid left ventricle hypertrophy, and it predicts acute heart failure and/or death[62]. However, the ability to differentiate between the two subtypes is limited, and its diagnostic utility compared to ^{99m}Tc-PYP and DPD is likely suboptimal.

In Europe, ^{99m}Tc-DPD is the only radiotracer approved for clinical use. Perugini *et al*[63] documented the high accuracy (around 100%) of ^{99m}Tc-DPD scintigraphy for distinction of AL and ATTR etiology (Figure 4). Subsequently, in patients with ATTR-CA, the ^{99m}Tc-DPD myocardial uptake proved to be a determinant of cardiac outcome, and it could also detect the myocardial involvement before visualization of morphological abnormalities by echocardiogram, which is very relevant in the early diagnosis of CA[64]. Regarding the different degrees of uptake in the semiquantitative

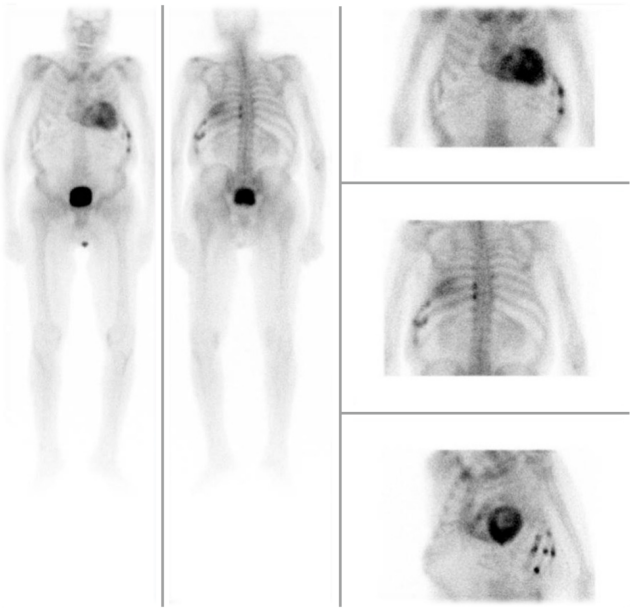

Figure 4 Planar scintigraphy showing intense cardiac uptake of ^{99m}Tc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid corresponding to a grade 3 in a patient diagnosed with cardiac amyloidosis-transthyretin amyloidosis.

measurement of the uptake of ^{99m}Tc-DPD, Hutt *et al*[65] showed a better survival in patients with grade 0 compared to grades 1, 2 and 3 with no differences in nonzero degrees.

^{99m}Tc-PYP is the other tracer available in North America. Bokhari *et al*[66] proved that patients with ATTR-CA had a significantly higher uptake of ^{99m}Tc-PYP than AL-CA patients evaluated both semiquantitatively and quantitatively, and the elevated cardiac uptake was associated with an increase of all-cause mortality[14]. The heart to contralateral ratio > 1.5 had a sensitivity of 97% and a specificity of 100% for the diagnosis of ATTR-CA. In a period of 5 years, a heart to contralateral ratio of 1.6 or greater was associated with a significantly worse survival[67]. In relation to this tracer, Sperry *et al*[68] described an apical-sparing pattern and an increase in mortality dependent on regional distribution of LV ^{99m}Tc-PYP uptake. Patients with diffuse infiltration had more apical uptake and as a result a worse survival.

Gillmore *et al*[14] studied the uptake of these radiotracers in patients with suspected CA, and they found that a visual scoring of a radiotracer uptake grade ≥ 2 without monoclonal proteins on serum and urine analysis had a specificity and positive predictive value of 100% for ATTR-CA. As we explained previously, this information revolutionized the noninvasive diagnosis of CA, avoiding a large number of invasive procedures in these patients.

Positron emission tomography tracers are being investigated for the diagnosis of CA. The advantage over single-photon emission computed tomography tracers is that they allow quantification of the amyloid burden. To date the different tracers evaluated are 18F-florbetapir, 18F-florbetaben and 11C-Pittsburgh Compound-B in which a higher uptake has been observed in patients with amyloidosis compared to other types of cardiomyopathies. Regarding 18F-florbetapir the retention index and the uptake values in the LV myocardium was greater in patients with amyloidosis, and higher values have been observed in AL compared to ATTR hearts without significant differences[69]. Likewise, the increased uptake correlated with deterioration of biventricular function[70]. However, its prognostic involvement in the survival of these patients has not yet been demonstrated in multicenter studies, and it is a future research field.

In patients with amyloidosis, myocardial sympathetic denervation often precedes the neurological and cardiac manifestations, especially in ATTRv. Therefore, the detection of this situation could anticipate cardiac involvement[71]. 123-iodine metaiodobenzylguanidine (MIBG) imaging assesses myocardial sympathetic denervation, and the reduction of the myocardial uptake previously occurs before morphologic alterations visualized by TTE. An increased 5-year mortality rate in ATTR patients with a heart to mediastinum MIBG uptake ratio below 1.6[72] and worse liver transplant survival outcomes in ATTRv with a ratio lower than 1.43[73] has been observed. Even, cardiac sympathetic denervation documented by decreased MIBG

uptake is detected earlier than amyloid burden demonstrated by ^{99m}Tc-DPD scintigraphy in ATTRv patients, highlighting the importance of this tool for an early diagnosis in this subgroup of patients[74].

The disadvantage of scintigraphy, as well as CCT, is that it requires exposure to ionizing radiation. Advantages of this tool are the early diagnosis, even before the anatomical alterations are evident, and the ability to distinguish the different types of amyloidosis. Due to the advances in this technique, an algorithm has been developed that allows the diagnosis of ATTR-CA without the need for endomyocardial biopsy. Currently, it has positioned itself as one of the imaging techniques that contributes the most in the precise diagnosis of ATTR-CA.

MACHINE LEARNING

Before ending this review, we want to highlight the growth of machine learning and artificial intelligence in medicine in general and in diagnostic imaging in particular. It consists of using algorithms that learn from previous studies, identifying complex image patterns and later apply them in the diagnosis of different pathologies. In this way, we can shorten the duration of the different imaging techniques and increase diagnostic precision by reducing the interobserver variability of the tests[75,76].

The machine learning-based radiomics technique has been studied in different imaging tools (TTE, CCT, CMR and scintigraphy) with high diagnostic precision in acute myocardial infarction, HCM and RV abnormalities. However, the data about its applicability in the diagnosis of CA are limited. There was a study conducted by Zhang *et al*[77] that used automated cardiac image interpretation in patients diagnosed with CA. They evaluated myocardial structure, ventricular function and LS measured by TTE and compared it with segmentation and manual measurement. Using the cases with confirmed CA and matched controls, they found high diagnostic precision with an area under the curve of 0.87 (95% confidence interval: 0.83–0.91). It provides promising data that could revolutionize routine clinical practice. However, to implement the use of machine learning in CA, it is necessary to obtain more data about the diagnostic precision of the other imaging techniques as well as several studies to evaluate the ability of this technique to distinguish different cardiomyopathies.

CONCLUSION

Advances in cardiac imaging techniques not only allow for an accurate and early diagnosis, but also provides relevant prognostic information of patients. Given a clinical suspicion of cardiac involvement due to amyloidosis, initially an approximation study should be performed using TTE because it is the fastest and safest technique. TTE should evaluate simple measurements, such as TAPSE, whose alterations are relevant to patient mortality. Likewise, more complex measurements should be studied such as strain and MCF. They are altered in patients with low levels of myocardial infiltration, and it could modify their prognosis with the early establishment of treatment.

Subsequently, depending on the availability of the hospital, it would be advisable to perform a tissue characterization through CMR or CCT. The use of native T1 and ECV have a high diagnostic precision for CA and their alteration have already been observed in early stages of the disease. If renal function allows, then the use of the LGE imaging provides additional information on the prognosis, although it could be substituted for the strain analysis.

The noninvasive differentiation of amyloidosis types can be carried out with high precision through the ^{99m}Tc-DPD scintigraphy, and the detection of sympathetic denervation with decreased MIBG uptake anticipates the diagnosis of cardiac infiltration even before ^{99m}Tc-DPD myocardial uptake.

Finally, we hypothesize that cardiac imaging could replace invasive techniques in the CA diagnosis. Depending on the accessibility to the imaging techniques in the different hospital centers, multiple measurements with important prognostic implications in these patients can be selected.

REFERENCES

1 **González-López E**, López-Sainz Á, Garcia-Pavia P. Diagnosis and Treatment of Transthyretin Cardiac Amyloidosis. Progress and Hope. *Rev Esp Cardiol (Engl Ed)* 2017; **70**: 991-1004 [PMID: 28870641 DOI: 10.1016/j.rec.2017.05.036]

2 **Palladini G**, Merlini G. What is new in diagnosis and management of light chain amyloidosis? *Blood* 2016; **128**: 159-168 [PMID: 27053535 DOI: 10.1182/blood-2016-01-629790]

3 **Barge-Caballero G**, Barriales-Villa R, Crespo-Leiro MG. Cambio de paradigma en el diagnóstico y tratamiento de la amiloidosis cardiaca por transtirretina. *REC:CardioClinics* 2019; **54**: 9-12 [DOI: 10.1016/j.rccl.2018.12.007]

4 **Siddiqi OK**, Ruberg FL. Cardiac amyloidosis: An update on pathophysiology, diagnosis, and treatment. *Trends Cardiovasc Med* 2018; **28**: 10-21 [PMID: 28739313 DOI: 10.1016/j.tcm.2017.07.004]

5 **Gertz MA**. Immunoglobulin light chain amyloidosis diagnosis and treatment algorithm 2018. *Blood Cancer J* 2018; **8**: 44 [PMID: 29795248 DOI: 10.1038/s41408-018-0080-9]

6 **Schmidt HH**, Waddington-Cruz M, Botteman MF, Carter JA, Chopra AS, Hopps M, Stewart M, Fallet S, Amass L. Estimating the global prevalence of transthyretin familial amyloid polyneuropathy. *Muscle Nerve* 2018; **57**: 829-837 [PMID: 29211930 DOI: 10.1002/mus.26034]

7 **Castaño A**, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, Rubin J, Chiuzan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bokhari S, Maurer MS. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J* 2017; **38**: 2879-2887 [PMID: 29019612 DOI: 10.1093/eurheartj/ehx350]

8 **González-López E**, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015; **36**: 2585-2594 [PMID: 26224076 DOI: 10.1093/eurheartj/ehv338]

9 **Tanskanen M**, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, Singleton A, Kiuru-Enari S, Paetau A, Tienari PJ, Myllykangas L. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. *Ann Med* 2008; **40**: 232-239 [PMID: 18382889 DOI: 10.1080/07853890701842988]

10 **Ruberg FL**, Maurer MS, Judge DP, Zeldenrust S, Skinner M, Kim AY, Falk RH, Cheung KN, Patel AR, Pano A, Packman J, Grogan DR. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). *Am Heart J* 2012; **164**: 222-228. e1 [PMID: 22877808 DOI: 10.1016/j.ahj.2012.04.015]

11 **Merlini G**, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med* 2003; **349**: 583-596 [PMID: 12904524 DOI: 10.1056/NEJMra023144]

12 **Kyle RA**, Linos A, Beard CM, Linke RP, Gertz MA, O'Fallon WM, Kurland LT. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. *Blood* 1992; **79**: 1817-1822 [PMID: 1558973 DOI: 10.1182/blood.V79.7.1817.1817]

13 **Kyle RA**, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol* 1995; **32**: 45-59 [PMID: 7878478]

14 **Gillmore JD**, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JL, Quarta CC, Grogan M, Lachmann HJ, Bokhari S, Castano A, Dorbala S, Johnson GB, Glaudemans AW, Rezk T, Fontana M, Palladini G, Milani P, Guidalotti PL, Flatman K, Lane T, Vonberg FW, Whelan CJ, Moon JC, Ruberg FL, Miller EJ, Hutt DF, Hazenberg BP, Rapezzi C, Hawkins PN. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. *Circulation* 2016; **133**: 2404-2412 [PMID: 27143678 DOI: 10.1161/CIRCULATIONAHA.116.021612]

15 **González-López E**, Gagliardi C, Dominguez F, Quarta CC, de Haro-Del Moral FJ, Milandri A, Salas C, Cinelli M, Cobo-Marcos M, Lorenzini M, Lara-Pezzi E, Foffi S, Alonso-Pulpon L, Rapezzi C, Garcia-Pavia P. Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. *Eur Heart J* 2017; **38**: 1895-1904 [PMID: 28329248 DOI: 10.1093/eurheartj/ehx043]

16 **Barros-Gomes S**, Williams B, Nhola LF, Grogan M, Maalouf JF, Dispenzieri A, Pellikka PA, Villarraga HR. Prognosis of Light Chain Amyloidosis With Preserved LVEF: Added Value of 2D Speckle-Tracking Echocardiography to the Current Prognostic Staging System. *JACC Cardiovasc Imaging* 2017; **10**: 398-407 [PMID: 27639764 DOI: 10.1016/j.jcmg.2016.04.008]

17 **Mohty D**, Pradel S, Magne J, Fadel B, Boulogne C, Petitalot V, Raboukhi S, Darodes N, Damy T, Aboyans V, Jaccard A. Prevalence and prognostic impact of left-sided valve thickening in systemic light-chain amyloidosis. *Clin Res Cardiol* 2017; **106**: 331-340 [PMID: 27933393 DOI: 10.1007/s00392-016-1058-x]

18 **Cardim N**, Galderisi M, Edvardsen T, Plein S, Popescu BA, D'Andrea A, Bruder O, Cosyns B, Davin L, Donal E, Freitas A, Habib G, Kitsiou A, Petersen SE, Schroeder S, Lancellotti P, Camici P, Dulgheru R, Hagendorff A, Lombardi M, Muraru D, Sicari R. Role of multimodality cardiac imaging in the management of patients with hypertrophic cardiomyopathy: an expert consensus of the European Association of Cardiovascular Imaging Endorsed by the Saudi Heart Association. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 280 [PMID: 25650407 DOI: 10.1093/ehjci/jeu291]

19 **Koyama J**, Ray-Sequin PA, Falk RH. Prognostic significance of ultrasound myocardial tissue characterization in patients with cardiac amyloidosis. *Circulation* 2002; **106**: 556-561 [PMID:

12147536 DOI: 10.1161/01.cir.0000023530.86718.b0]

20 **Grogan M**, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, Klarich KW, Miller WL, Maleszewski JJ, Dispenzieri A. Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. *J Am Coll Cardiol* 2016; **68**: 1014-1020 [PMID: 27585505 DOI: 10.1016/j.jacc.2016.06.033]

21 **Milani P**, Dispenzieri A, Scott CG, Gertz MA, Perlini S, Mussinelli R, Lacy MQ, Buadi FK, Kumar S, Maurer MS, Merlini G, Hayman SR, Leung N, Dingli D, Klarich KW, Lust JA, Lin Y, Kapoor P, Go RS, Pellikka PA, Hwa YL, Zeldenrust SR, Kyle RA, Rajkumar SV, Grogan M. Independent Prognostic Value of Stroke Volume Index in Patients With Immunoglobulin Light Chain Amyloidosis. *Circ Cardiovasc Imaging* 2018; **11**: e006588 [PMID: 29752392 DOI: 10.1161/CIRCIMAGING.117.006588]

22 **Migrino RQ**, Mareedu RK, Eastwood D, Bowers M, Harmann L, Hari P. Left ventricular ejection time on echocardiography predicts long-term mortality in light chain amyloidosis. *J Am Soc Echocardiogr* 2009; **22**: 1396-1402 [PMID: 19880277 DOI: 10.1016/j.echo.2009.09.012]

23 **Bellavia D**, Pellikka PA, Al-Zahrani GB, Abraham TP, Dispenzieri A, Miyazaki C, Lacy M, Scott CG, Oh JK, Miller FA Jr. Independent predictors of survival in primary systemic (Al) amyloidosis, including cardiac biomarkers and left ventricular strain imaging: an observational cohort study. *J Am Soc Echocardiogr* 2010; **23**: 643-652 [PMID: 20434879 DOI: 10.1016/j.echo.2010.03.027]

24 **Patel AR**, Dubrey SW, Mendes LA, Skinner M, Cupples A, Falk RH, Davidoff R. Right ventricular dilation in primary amyloidosis: an independent predictor of survival. *Am J Cardiol* 1997; **80**: 486-492 [PMID: 9285663 DOI: 10.1016/s0002-9149(97)00400-1]

25 **Bodez D**, Ternacle J, Guellich A, Galat A, Lim P, Radu C, Guendouz S, Bergoend E, Couetil JP, Hittinger L, Dubois-Randé JL, Plante-Bordeneuve V, Deux JF, Mohty D, Damy T. Prognostic value of right ventricular systolic function in cardiac amyloidosis. *Amyloid* 2016; **23**: 158-167 [PMID: 27348696 DOI: 10.1080/13506129.2016.1194264]

26 **Mohty D**, Petitalot V, Magne J, Fadel BM, Boulogne C, Rouabhia D, ElHamel C, Lavergne D, Damy T, Aboyans V, Jaccard A. Left atrial function in patients with light chain amyloidosis: A transthoracic 3D speckle tracking imaging study. *J Cardiol* 2018; **71**: 419-427 [PMID: 29153741 DOI: 10.1016/j.jjcc.2017.10.007]

27 **Phelan D**, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, Marwick TH, Thomas JD. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart* 2012; **98**: 1442-1448 [PMID: 22865865 DOI: 10.1136/heartjnl-2012-302353]

28 **Koyama J**, Falk RH. Prognostic significance of strain Doppler imaging in light-chain amyloidosis. *JACC Cardiovasc Imaging* 2010; **3**: 333-342 [PMID: 20394893 DOI: 10.1016/j.jcmg.2009.11.013]

29 **Liu D**, Hu K, Störk S, Herrmann S, Kramer B, Cikes M, Gaudron PD, Knop S, Ertl G, Bijnens B, Weidemann F. Predictive value of assessing diastolic strain rate on survival in cardiac amyloidosis patients with preserved ejection fraction. *PLoS One* 2014; **9**: e115910 [PMID: 25542015 DOI: 10.1371/journal.pone.0115910]

30 **Uzan C**, Lairez O, Raud-Raynier P, Garcia R, Degand B, Christiaens LP, Rehman MB. Right ventricular longitudinal strain: a tool for diagnosis and prognosis in light-chain amyloidosis. *Amyloid* 2018; **25**: 18-25 [PMID: 29260587 DOI: 10.1080/13506129.2017.1417121]

31 **Buss SJ**, Emami M, Mereles D, Korosoglou G, Kristen AV, Voss A, Schellberg D, Zugck C, Galuschky C, Giannitsis E, Hegenbart U, Ho AD, Katus HA, Schonland SO, Hardt SE. 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; **60**: 1067-1076 [PMID: 22883634 DOI: 10.1016/j.jacc.2012.04.043]

32 **Ternacle J**, Bodez D, Guellich A, Audureau E, Rappeneau S, Lim P, Radu C, Guendouz S, Couetil JP, Benhaiem N, Hittinger L, Dubois-Randé JL, Plante-Bordeneuve V, Mohty D, Deux JF, Damy T. Causes and Consequences of Longitudinal LV Dysfunction Assessed by 2D Strain Echocardiography in Cardiac Amyloidosis. *JACC Cardiovasc Imaging* 2016; **9**: 126-138 [PMID: 26777222 DOI: 10.1016/j.jcmg.2015.05.014]

33 **Knight DS**, Zumbo G, Barcella W, Steeden JA, Muthurangu V, Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Kotecha T, Francis R, Rezk T, Quarta CC, Whelan CJ, Lachmann HJ, Wechalekar AD, Gillmore JD, Moon JC, Hawkins PN, Fontana M. Cardiac Structural and Functional Consequences of Amyloid Deposition by Cardiac Magnetic Resonance and Echocardiography and Their Prognostic Roles. *JACC Cardiovasc Imaging* 2019; **12**: 823-833 [PMID: 29680336 DOI: 10.1016/j.jcmg.2018.02.016]

34 **White JA**, Fine NM. Recent Advances in Cardiovascular Imaging Relevant to the Management of Patients with Suspected Cardiac Amyloidosis. *Curr Cardiol Rep* 2016; **18**: 77 [PMID: 27319007 DOI: 10.1007/s11886-016-0752-7]

35 **Ruberg FL**, Appelbaum E, Davidoff R, Ozonoff A, Kissinger KV, Harrigan C, Skinner M, Manning WJ. Diagnostic and prognostic utility of cardiovascular magnetic resonance imaging in light-chain cardiac amyloidosis. *Am J Cardiol* 2009; **103**: 544-549 [PMID: 19195518 DOI: 10.1016/j.amjcard.2008.09.105]

36 **Mohty D**, Boulogne C, Magne J, Varroud-Vial N, Martin S, Ettaif H, Fadel BM, Bridoux F, Aboyans V, Damy T, Jaccard A. Prognostic value of left atrial function in systemic light-chain amyloidosis: a cardiac magnetic resonance study. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 961-969 [PMID: 27194782 DOI: 10.1093/ehjci/jew100]

37 **Arenja N**, Andre F, Riffel JH, Siepen FAD, Hegenbart U, Schönland S, Kristen AV, Katus HA, Buss SJ. Prognostic value of novel imaging parameters derived from standard cardiovascular magnetic resonance in high risk patients with systemic light chain amyloidosis. *J Cardiovasc Magn Reson* 2019; **21**: 53 [PMID: 31434577 DOI: 10.1186/s12968-019-0564-1]

38 **Ochs MM**, Fritz T, Arenja N, Riffel J, Andre F, Mereles D, Siepen FAD, Hegenbart U, Schönland S, Katus HA, Friedrich MGW, Buss SJ. Regional differences in prognostic value of cardiac valve plane displacement in systemic light-chain amyloidosis. *J Cardiovasc Magn Reson* 2017; **19**: 87 [PMID: 29121956 DOI: 10.1186/s12968-017-0402-2]

39 **Fontana M**, Ćorović A, Scully P, Moon JC. Myocardial Amyloidosis: The Exemplar Interstitial Disease. *JACC Cardiovasc Imaging* 2019; **12**: 2345-2356 [PMID: 31422120 DOI: 10.1016/j.jcmg.2019.06.023]

40 **Wan K**, Sun J, Yang D, Liu H, Wang J, Cheng W, Zhang Q, Zeng Z, Zhang T, Greiser A, Jolly MP, Han Y, Chen Y. Left Ventricular Myocardial Deformation on Cine MR Images: Relationship to Severity of Disease and Prognosis in Light-Chain Amyloidosis. *Radiology* 2018; **288**: 73-80 [PMID: 29664336 DOI: 10.1148/radiol.2018172435]

41 **Mekinian A**, Lions C, Leleu X, Duhamel A, Lamblin N, Coiteux V, De Groote P, Hatron PY, Facon T, Beregi JP, Hachulla E, Launay D; Lille Amyloidosis Study Group. Prognosis assessment of cardiac involvement in systemic AL amyloidosis by magnetic resonance imaging. *Am J Med* 2010; **123**: 864-868 [PMID: 20800158 DOI: 10.1016/j.amjmed.2010.03.022]

42 **Maceira AM**, Prasad SK, Hawkins PN, Roughton M, Pennell DJ. Cardiovascular magnetic resonance and prognosis in cardiac amyloidosis. *J Cardiovasc Magn Reson* 2008; **10**: 54 [PMID: 19032744 DOI: 10.1186/1532-429X-10-54]

43 **Lehrke S**, Steen H, Kristen AV, Merten C, Lossnitzer D, Dengler TJ, Katus HA, Giannitsis E. Serum levels of NT-proBNP as surrogate for cardiac amyloid burden: new evidence from gadolinium-enhanced cardiac magnetic resonance imaging in patients with amyloidosis. *Amyloid* 2009; **16**: 187-195 [PMID: 19922329 DOI: 10.3109/13506120903421538]

44 **Austin BA**, Tang WH, Rodriguez ER, Tan C, Flamm SD, Taylor DO, Starling RC, Desai MY. Delayed hyper-enhancement magnetic resonance imaging provides incremental diagnostic and prognostic utility in suspected cardiac amyloidosis. *JACC Cardiovasc Imaging* 2009; **2**: 1369-1377 [PMID: 20083070 DOI: 10.1016/j.jcmg.2009.08.008]

45 **White JA**, Kim HW, Shah D, Fine N, Kim KY, Wendell DC, Al-Jaroudi W, Parker M, Patel M, Gwadry-Sridhar F, Judd RM, Kim RJ. CMR imaging with rapid visual T1 assessment predicts mortality in patients suspected of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2014; **7**: 143-156 [PMID: 24412191 DOI: 10.1016/j.jcmg.2013.09.019]

46 **Fontana M**, Pica S, Reant P, Abdel-Gadir A, Treibel TA, Banypersad SM, Maestrini V, Barcella W, Rosmini S, Bulluck H, Sayed RH, Patel K, Mamhood S, Bucciarelli-Ducci C, Whelan CJ, Herrey AS, Lachmann HJ, Wechalekar AD, Manisty CH, Schelbert EB, Kellman P, Gillmore JD, Hawkins PN, Moon JC. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. *Circulation* 2015; **132**: 1570-1579 [PMID: 26362631 DOI: 10.1161/CIRCULATIONAHA.115.016567]

47 **Raina S**, Lensing SY, Nairooz RS, Pothineni NV, Hakeem A, Bhatti S, Pandey T. Prognostic Value of Late Gadolinium Enhancement CMR in Systemic Amyloidosis. *JACC Cardiovasc Imaging* 2016; **9**: 1267-1277 [PMID: 27568115 DOI: 10.1016/j.jcmg.2016.01.036]

48 **Wan K**, Sun J, Han Y, Luo Y, Liu H, Yang D, Cheng W, Zhang Q, Zeng Z, Chen Y. Right ventricular involvement evaluated by cardiac magnetic resonance imaging predicts mortality in patients with light chain amyloidosis. *Heart Vessels* 2018; **33**: 170-179 [PMID: 28840397 DOI: 10.1007/s00380-017-1043-y]

49 **Wan K**, Sun J, Han Y, Liu H, Yang D, Li W, Wang J, Cheng W, Zhang Q, Zeng Z, Chen Y. Increased Prognostic Value of Query Amyloid Late Enhancement Score in Light-Chain Cardiac Amyloidosis. *Circ J* 2018; **82**: 739-746 [PMID: 29093431 DOI: 10.1253/circj.CJ-17-0464]

50 **Boynton SJ**, Geske JB, Dispenzieri A, Syed IS, Hanson TJ, Grogan M, Araoz PA. LGE Provides Incremental Prognostic Information Over Serum Biomarkers in AL Cardiac Amyloidosis. *JACC Cardiovasc Imaging* 2016; **9**: 680-686 [PMID: 27209101 DOI: 10.1016/j.jcmg.2015.10.027]

51 **Bhatti S**, Watts E, Syed F, Vallurupalli S, Pandey T, Jambekar K, Mazur W, Hakeem A. Clinical and prognostic utility of cardiovascular magnetic resonance imaging in myeloma patients with suspected cardiac amyloidosis. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 970-977 [PMID: 27225804 DOI: 10.1093/ehjci/jew101]

52 **Migrino RQ**, Christenson R, Szabo A, Bright M, Truran S, Hari P. Prognostic implication of late gadolinium enhancement on cardiac MRI in light chain (AL) amyloidosis on long term follow up. *BMC Med Phys* 2009; **9**: 5 [PMID: 19416541 DOI: 10.1186/1756-6649-9-5]

53 **Karamitsos TD**, Piechnik SK, Banypersad SM, Fontana M, Ntusi NB, Ferreira VM, Whelan CJ, Myerson SG, Robson MD, Hawkins PN, Neubauer S, Moon JC. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2013; **6**: 488-497 [PMID: 23498672 DOI: 10.1016/j.jcmg.2012.11.013]

54 **Lin L**, Li X, Feng J, Shen KN, Tian Z, Sun J, Mao YY, Cao J, Jin ZY, Li J, Selvanayagam JB, Wang YN. The prognostic value of T1 mapping and late gadolinium enhancement cardiovascular magnetic resonance imaging in patients with light chain amyloidosis. *J Cardiovasc Magn Reson* 2018; **20**: 2 [PMID: 29298704 DOI: 10.1186/s12968-017-0419-6]

55 **Wan K**, Li W, Sun J, Xu Y, Wang J, Liu H, Dong Y, Cheng W, Zhang Q, Zeng Z, Zhou X, Han Y,

Chen Y. Regional amyloid distribution and impact on mortality in light-chain amyloidosis: a T1 mapping cardiac magnetic resonance study. *Amyloid* 2019; **26**: 45-51 [PMID: 30931628 DOI: 10.1080/13506129.2019.1578742]

56 **Martinez-Naharro A**, Kotecha T, Norrington K, Boldrini M, Rezk T, Quarta C, Treibel TA, Whelan CJ, Knight DS, Kellman P, Ruberg FL, Gillmore JD, Moon JC, Hawkins PN, Fontana M. Native T1 and Extracellular Volume in Transthyretin Amyloidosis. *JACC Cardiovasc Imaging* 2019; **12**: 810-819 [PMID: 29550324 DOI: 10.1016/j.jcmg.2018.02.006]

57 **Wassmuth R**, Abdel-Aty H, Bohl S, Schulz-Menger J. Prognostic impact of T2-weighted CMR imaging for cardiac amyloidosis. *Eur Radiol* 2011; **21**: 1643-1650 [PMID: 21720941 DOI: 10.1007/s00330-011-2109-3]

58 **Legou F**, Tacher V, Damy T, Planté-Bordeneuve V, Rappeneau S, Benhaiem N, Rosso J, Itti E, Luciani A, Kobeiter H, Rahmouni A, Deux JF. Usefulness of T2 ratio in the diagnosis and prognosis of cardiac amyloidosis using cardiac MR imaging. *Diagn Interv Imaging* 2017; **98**: 125-132 [PMID: 27692958 DOI: 10.1016/j.diii.2016.08.007]

59 **Treibel TA**, Bandula S, Fontana M, White SK, Gilbertson JA, Herrey AS, Gillmore JD, Punwani S, Hawkins PN, Taylor SA, Moon JC. Extracellular volume quantification by dynamic equilibrium cardiac computed tomography in cardiac amyloidosis. *J Cardiovasc Comput Tomogr* 2015; **9**: 585-592 [PMID: 26209459 DOI: 10.1016/j.jcct.2015.07.001]

60 **Treibel TA**, Fontana M, Steeden JA, Nasis A, Yeung J, White SK, Sivarajan S, Punwani S, Pugliese F, Taylor SA, Moon JC, Bandula S. Automatic quantification of the myocardial extracellular volume by cardiac computed tomography: Synthetic ECV by CCT. *J Cardiovasc Comput Tomogr* 2017; **11**: 221-226 [PMID: 28268091 DOI: 10.1016/j.jcct.2017.02.006]

61 **Stats MA**, Stone JR. 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; **25**: 413-417 [PMID: 27469499 DOI: 10.1016/j.carpath.2016.07.001]

62 **Galat A**, Rosso J, Guellich A, Van Der Gucht A, Rappeneau S, Bodez D, Guendouz S, Tissot CM, Hittinger L, Dubois-Randé JL, Plante-Bordeneuve V, Itti E, Meignan M, Damy T. Usefulness of (99m)Tc-HMDP scintigraphy for the etiologic diagnosis and prognosis of cardiac amyloidosis. *Amyloid* 2015; **22**: 210-220 [PMID: 26465835 DOI: 10.3109/13506129.2015.1072089]

63 **Perugini E**, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, Leone O, Farsad M, Ciliberti P, Bacchi-Reggiani L, Fallani F, Branzi A, Rapezzi C. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. *J Am Coll Cardiol* 2005; **46**: 1076-1084 [PMID: 16168294 DOI: 10.1016/j.jacc.2005.05.073]

64 **Rapezzi C**, Quarta CC, Guidalotti PL, Pettinato C, Fanti S, Leone O, Ferlini A, Longhi S, Lorenzini M, Reggiani LB, Gagliardi C, Gallo P, Villani C, Salvi F. Role of (99m)Tc-DPD scintigraphy in diagnosis and prognosis of hereditary transthyretin-related cardiac amyloidosis. *JACC Cardiovasc Imaging* 2011; **4**: 659-670 [PMID: 21679902 DOI: 10.1016/j.jcmg.2011.03.016]

65 **Hutt DF**, Fontana M, Burniston M, Quigley AM, Petrie A, Ross JC, Page J, Martinez-Naharro A, Wechalekar AD, Lachmann HJ, Quarta CC, Rezk T, Mahmood S, Sachchithanantham S, Youngstein T, Whelan CJ, Lane T, Gilbertson JA, Rowczenio D, Hawkins PN, Gillmore JD. Prognostic utility of the Perugini grading of 99mTc-DPD scintigraphy in transthyretin (ATTR) amyloidosis and its relationship with skeletal muscle and soft tissue amyloid. *Eur Heart J Cardiovasc Imaging* 2017; **18**: 1344-1350 [PMID: 28159995 DOI: 10.1093/ehjci/jew325]

66 **Bokhari S**, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. *Circ Cardiovasc Imaging* 2013; **6**: 195-201 [PMID: 23400849 DOI: 10.1161/CIRCIMAGING.112.000132]

67 **Castano A**, Haq M, Narotsky DL, Goldsmith J, Weinberg RL, Morgenstern R, Pozniakoff T, Ruberg FL, Miller EJ, Berk JL, Dispenzieri A, Grogan M, Johnson G, Bokhari S, Maurer MS. Multicenter Study of Planar Technetium 99m Pyrophosphate Cardiac Imaging: Predicting Survival for Patients With ATTR Cardiac Amyloidosis. *JAMA Cardiol* 2016; **1**: 880-889 [PMID: 27557400 DOI: 10.1001/jamacardio.2016.2839]

68 **Sperry BW**, Vranian MN, Tower-Rader A, Hachamovitch R, Hanna M, Brunken R, Phelan D, Cerqueira MD, Jaber WA. Regional Variation in Technetium Pyrophosphate Uptake in Transthyretin Cardiac Amyloidosis and Impact on Mortality. *JACC Cardiovasc Imaging* 2018; **11**: 234-242 [PMID: 28917675 DOI: 10.1016/j.jcmg.2017.06.020]

69 **Dorbala S**, Vangala D, Semer J, Strader C, Bruyere JR Jr, Di Carli MF, Moore SC, Falk RH. Imaging cardiac amyloidosis: a pilot study using ^{18}F-florbetapir positron emission tomography. *Eur J Nucl Med Mol Imaging* 2014; **41**: 1652-1662 [PMID: 24841414 DOI: 10.1007/s00259-014-2787-6]

70 **Law WP**, Wang W, Moore P, Mollee P, Ng A. Cardiac amyloid imaging with ^{18}F-florbetaben positron emission tomography: a pilot study. *Amyloid* 2017; **24**: 162 [PMID: 28434374 DOI: 10.1080/13506129.2017.1281120]

71 **Tanaka M**, Hongo M, Kinoshita O, Takabayashi Y, Fujii T, Yazaki Y, Isobe M, Sekiguchi M. Iodine-123 metaiodobenzylguanidine scintigraphic assessment of myocardial sympathetic innervation in patients with familial amyloid polyneuropathy. *J Am Coll Cardiol* 1997; **29**: 168-174 [PMID: 8996310 DOI: 10.1016/s0735-1097(96)00438-x]

72 **Coutinho MC**, Cortez-Dias N, Cantinho G, Conceição I, Oliveira A, Bordalo e Sá A, Gonçalves S, Almeida AG, de Carvalho M, Diogo AN. Reduced myocardial 123-iodine metaiodobenzylguanidine uptake: a prognostic marker in familial amyloid polyneuropathy. *Circ Cardiovasc Imaging* 2013; **6**:

627-636 [PMID: 23833285 DOI: 10.1161/CIRCIMAGING.112.000367]

73 **Algalarrondo V**, Antonini T, Théaudin M, Chemla D, Benmalek A, Lacroix C, Castaing D, Cauquil C, Dinanian S, Eliahou L, Samuel D, Adams D, Le Guludec D, Slama MS, Rouzet F. Cardiac Dysautonomia Predicts Long-Term Survival in Hereditary Transthyretin Amyloidosis After Liver Transplantation. *JACC Cardiovasc Imaging* 2016; **9**: 1432-1441 [PMID: 27838303 DOI: 10.1016/j.jcmg.2016.07.008]

74 **Piekarski E**, Chequer R, Algalarrondo V, Eliahou L, Mahida B, Vigne J, Adams D, Slama MS, Le Guludec D, Rouzet F. Cardiac denervation evidenced by MIBG occurs earlier than amyloid deposits detection by diphosphonate scintigraphy in TTR mutation carriers. *Eur J Nucl Med Mol Imaging* 2018; **45**: 1108-1118 [PMID: 29511839 DOI: 10.1007/s00259-018-3963-x]

75 **Martin-Isla C**, Campello VM, Izquierdo C, Raisi-Estabragh Z, Baeßler B, Petersen SE, Lekadir K. Image-Based Cardiac Diagnosis With Machine Learning: A Review. *Front Cardiovasc Med* 2020; **7**: 1 [PMID: 32039241 DOI: 10.3389/fcvm.2020.00001]

76 **Leiner T**, Rueckert D, Suinesiaputra A, Baeßler B, Nezafat R, Išgum I, Young AA. Machine learning in cardiovascular magnetic resonance: basic concepts and applications. *J Cardiovasc Magn Reson* 2019; **21**: 61 [PMID: 31590664 DOI: 10.1186/s12968-019-0575-y]

77 **Zhang J**, Gajjala S, Agrawal P, Tison GH, Hallock LA, Beussink-Nelson L, Lassen MH, Fan E, Aras MA, Jordan C, Fleischmann KE, Melisko M, Qasim A, Shah SJ, Bajcsy R, Deo RC. Fully Automated Echocardiogram Interpretation in Clinical Practice. *Circulation* 2018; **138**: 1623-1635 [PMID: 30354459 DOI: 10.1161/CIRCULATIONAHA.118.034338]

78 **Maurer MS**, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, Grogan M, Kristen AV, Lousada I, Nativi-Nicolau J, Cristina Quarta C, Rapezzi C, Ruberg FL, Witteles R, Merlini G. Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis. *Circ Heart Fail* 2019; **12**: e006075 [PMID: 31480867 DOI: 10.1161/CIRCHEARTFAILURE.119.006075]

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