THOUSAND WORDS ABOUT...

A thousand words about the imaging in cardiac amyloidosis

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ABSTRACT

Cardiac amyloidosis is an infiltrative disease which usually occurs under the form of restrictive cardiomyopathy. Advances in the treatment have changed the unfavorable outcomes of this disease. Thus, early diagnosis is essential. Recent advances in echocardiography and cardiac magnetic resonance have provided new modalities for the detection of cardiac amyloidosis. This summary discusses the role of imaging techniques in the diagnosis of cardiac amyloidosis.

Keywords: amyloidosis, echocardiography, myocardial strain imaging, cardiac magnetic resonance.

Introduction

Amyloidosis is characterized by the extracellular deposition of a structurally abnormal protein called 'amyloid' [1]. Cardiac amyloidosis (CA), or amyloid cardiomyopathy, refers to a group of inherited and acquired forms of amyloidosis involving the heart. Current classification of amyloidosis is based on a biochemical characteristic of amyloid fibrils [2]. Nomenclature includes a capital letter 'A', which denotes amyloid fibril protein, followed by a suffix that is an abbreviation of the parent or precursor protein name [3]. For example, for AL-type amyloidosis, the letter 'A' is a common index for amyloid and letter 'L' refers to an immunoglobulin light chain or light chain fragment.

CA occurs in two main forms, which accounts for 98% of clinical cases. The most common type (80% of cases) is AL-type amyloidosis, where the amyloid protein derives from misfolded immunoglobulin light chains.

The second most common type is transthyretin (ATTR) amyloidosis, resulting from the accumulation of the protein transthyretin. Transthyretin acts as a transport protein for thyroxine and retinol, and it is produced primarily in the liver. About 120 mutations in the TTR gene have been found to cause transthyretin amyloidosis. The most common mutation in patients with ATTR amyloidosis replaces valine with methionine at position 30 in the transthyretin protein (Val30-Met or V30M). V122I variant is another common mutation, mainly present in black Americans (3 to 4% of the population) or West African populations [4, 5]. ATTR amyloidosis accounts approximately for 18% of diagnosed cases of amyloidosis. This type of amyloidosis is further sub-divided into two types of disease: wild-type ATTR (ATTRwt) and hereditary (or mutant) ATTR (ATTRm) CA. Since the estimated survival form the onset of heart failure in patients with CA is of 3–4 years, early recognition is essential. These three most common forms of CA are described in **Table 1**.

Table 1. Characteristics of main types of cardiac amyloidosis

	AL amyloidosis	Acquired ATTR amyloidosis (wild type; senile amyloidosis)	Hereditary ATTR amyloidosis
Underlying reason	Plasma cell dyscrasia	Senile deposition of amyloid in myocardium	mutations in transthyretin gene (>100)
Precursor protein	Immunoglobulin light chains	Transthyretin, wild type (non-mutated, otherwise normal)	Mutated transthyretin (or prealbumin)
Percentage of cardiac amyloidosis (%)	80	18	
Age at manifestation (years)	> 40	> 60 (> 70)	30 to 70
Population	No specific population, both sexes	Older black men (mainly)	Afro-American, Afro-Caribbean, Portugal, Sweden, Japan
Course of disease	Poor prognosis, depending on specific organ involvement	Better prognosis, slower progression (compared to AL type)	
Organ involvement	One or more organs; In 50% of patients cardiac involvement	Mainly cardiomyopathy; Carpal tunnel syndrome; Involvement of other organs absent	Depending on mutation; cardiomyopathy, neuropathy, vitreous amyloidosis
Specific treatment	Chemotherapy (Bortezomib); Autologous bone marrow transplantation	Liver transplant, heart transplant Tafamidis	

The diagnosis of CA remains challenging due to its non-specific presentation. CA is considered a rare disease [6], which could also be the reason for misdiagnosis. Indeed, in the study by González-López et al. [7], the percent of the previous misdiagnosis was as high as 35%. Furthermore, ATTR amyloidosis seems also to be underdiagnosed [8]. Even if the majority of cases show a characteristic hypertrophic pattern, the full range of morphological findings in CA is more diverse. ATTR amyloidosis has been diagnosed in older patients with aortic stenosis [9] or patients with previously diagnosed hypertrophic cardiomyopathy [10]. No marked hypertrophy could also be observed [11]. Currently, noninvasive cardiac imaging including echocardiography and cardiac magnetic resonance are the first line modalities in the diagnosis of CA.

Echocardiography in the diagnosis of CA

Echocardiography is the first-line screening tool, and virtually every patient with unexplained cardiac hypertrophy should be suspected of amyloidosis. Before harmonic imaging was commonly used, the echocardiographic pattern of sparkling myocardium was considered to be diagnostic for CA. However, myocardial speckling in amyloidosis has been shown to have low diagnostic sensitivity and specificity [12]. This echocardiographic phenomenon could also be found in hypertrophic cardiomyopathy, myocarditis, as well as in other infiltrative diseases of the myocardium. Most common echocardiographic representation of CA is the thickening of the left and right ventricular wall, thickening of the heart valves, and enlarged atria [13, 14] (**Figure 1**, **Video 1** – online). Extracellular deposition of amyloid fibrils contributes to ventricular stiffening and left ventricular diastolic dysfunction. Doppler analysis of mitral inflow reveals a restrictive pattern with a high E wave velocity and E/A ratio (**Figure 1**). Elevated E/e` ratio reflects the high filling pressures.

Although all these echocardiographic features are typical for CA, none of them are specific enough to be diagnostic.

Introduction of myocardial deformation analysis with the use of speckle tracking echocardiography significantly expanded the diagnostic potential of echocardiography. This technique utilizes the speckle pattern of two-dimensional gray-scale echocardiographic images. By grouping of the speckles into blocks and tracing it frame-by-frame, it allows measuring myocardial deformation in the longitudinal, circumferential and radial axis (**Figure 2**). During the last ten years, this modality has become a recognized method in the assessment of the left ventricular systolic function [15]. It has also been shown to be a valuable tool in the diagnosis of CA – the
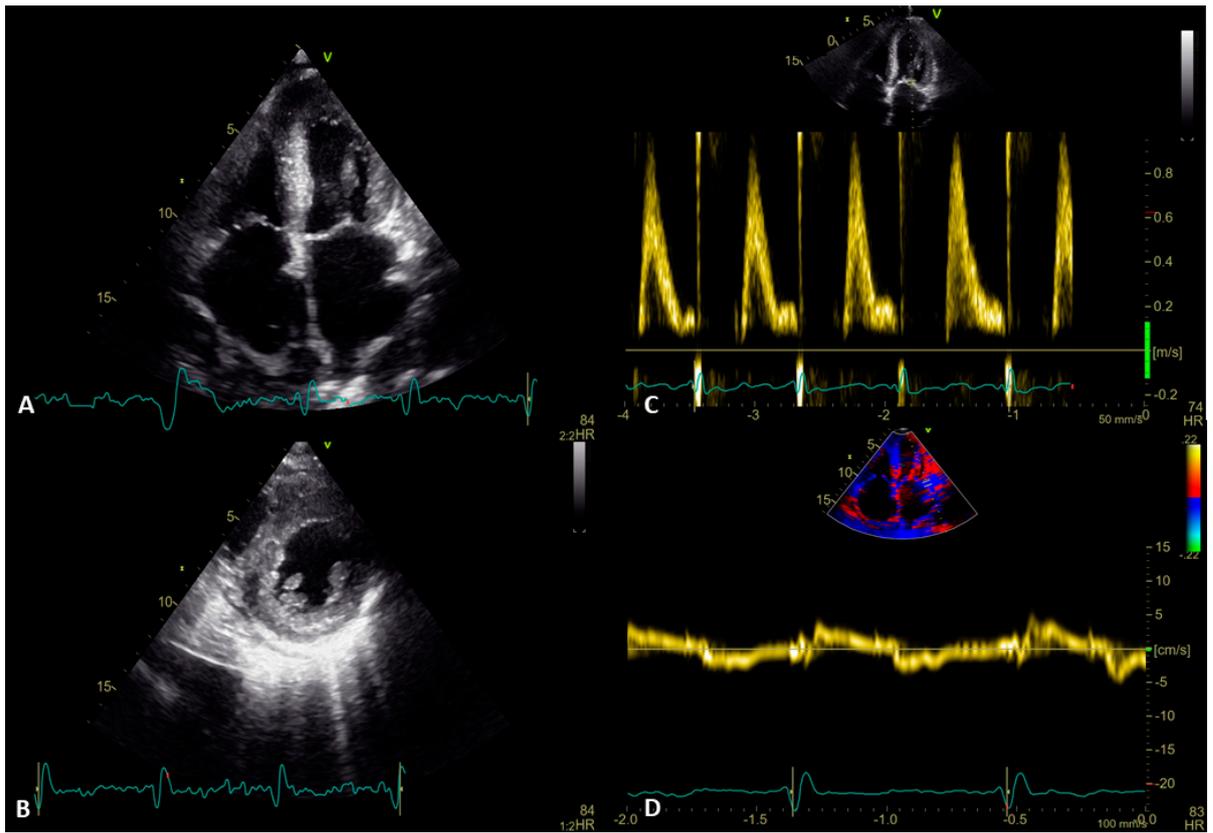
Figure 1. Echocardiographic image of cardiac amyloidosis. Panel A: apical four chamber view; thickening of the left ventricular wall, thickening of the heart valves, and enlarged atria thickened interatrial septum and pericardial effusion. Panel B: Parasternal short axis view: small, hypertrophied left ventricle. Panel. Doppler inflow of the mitral valve, high velocity of E-wave, no A-wave (atrial fibrillation) showing restrictive pattern of the mitral inflow. Panel D. Tissue Doppler echocardiography – decreased velocities of the myocardium
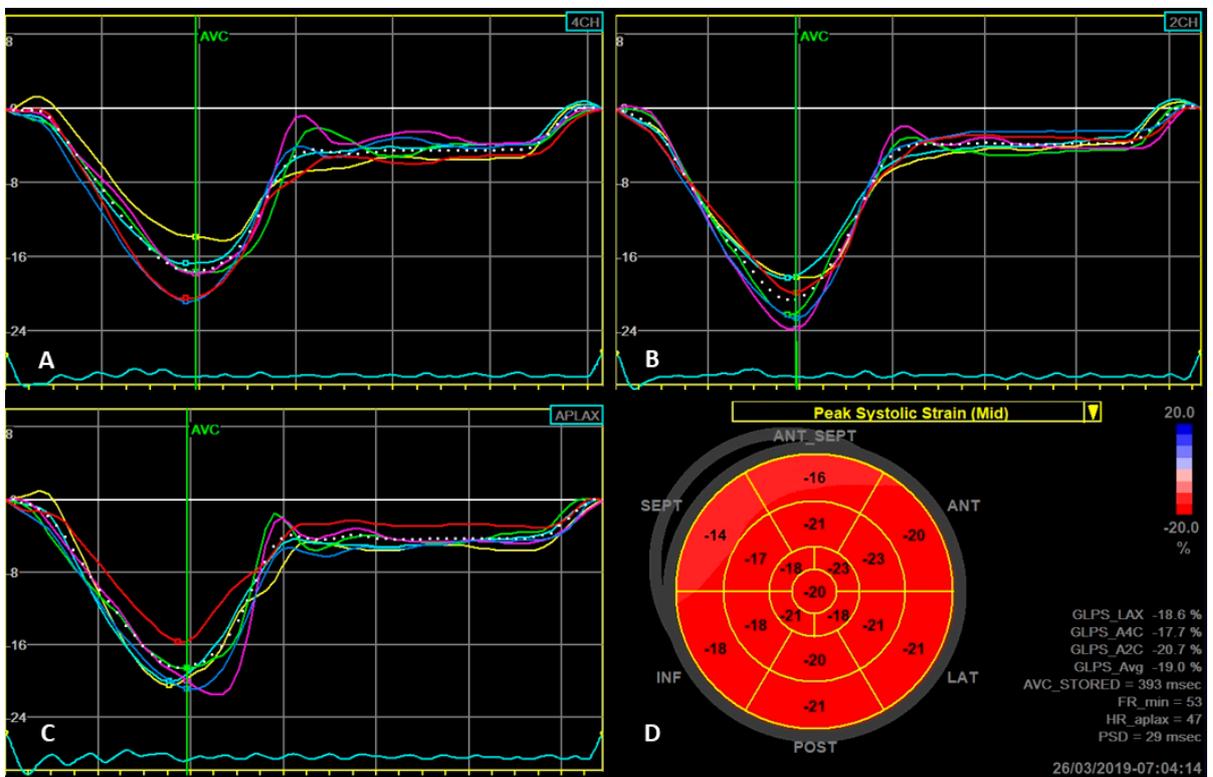
Figure 2. Normal values of longitudinal strain. Panels A, B and C show strain curves for left ventricular segments in apical four chamber-, two chamber and three chamber view, respectively. Dotted with line shows average value. Panel D – planar map of the peak systolic strain values for 17 segments of the left ventricle. Global longitudinal strain is – 19%.

global longitudinal strain (GLS) is impaired early in the course of the disease, even when left ventricular ejection fraction is preserved [16]. Importantly, the segmental longitudinal strain has an unusual and typical for CA pattern, with greater reduction of strain values in basal and mid segments of the left ventricle with relative sparing of apical segments (**Figure 3**). This phenomenon of 'apical sparing' is clearly visible on planar maps (so-called "bullseye") of segmental myocardial strain, and it is sensitive and specific for the diagnosis of CA [17].

ducible and accurate index to differentiate CA from other causes of LV thickening [20].

Cardiac magnetic resonance imaging

Cardiac magnetic resonance (CMR) is a very sensitive and specific tool for the diagnosis of CA. The main advantage of CMR over echocardiography is the ability of tissue characterization. The myocardial deposition of amyloid increases extracellular volume, which results in the accu-
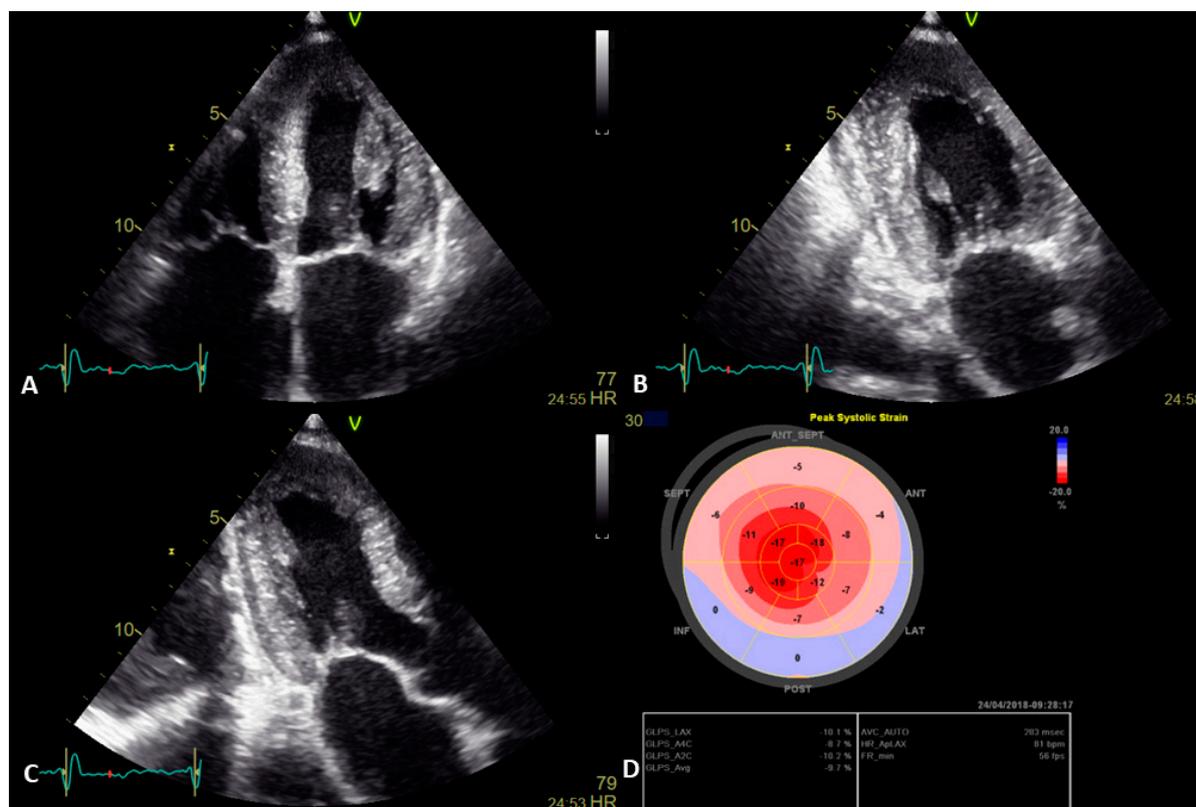
Figure 3. Global longitudinal strain in cardiac amyloidosis. Panels A, B, C show 2-dimensional apical four chamber-, two chamber, and three chamber view, respectively. In panel D, the strain map shows particular patterns suggestive of amyloidosis with relative preserved strain in apical segments and decreased on mid and basal level (apical sparing pattern).

Apical sparing could be expressed with the use of the formula: average longitudinal apical strain/(average basal longitudinal strain+average mid longitudinal strain). Furthermore, echocardiographic measurement of myocardial strain parameters can discriminate CA from the other causes of cardiac hypertrophy [18, 19]. Most recently, the dissociation between preserved left ventricular ejection fraction and reduced GLS (LVEF/GLS ratio), has been reported as a repro-

mulation of gadolinium contrast. For this reason, late gadolinium enhancement (LGE) imaging has been proven to be effective in identifying CA [21]. Although the typical pattern for CA is diffuse subendocardial LGE in a non-coronary artery territory distribution, transmural or focal patchy LGE could also be observed [22]. **Figure 4** shows common LGE patterns that may be encountered in patients with CA. Another promising technique is non-contrast T1 CMR. Of note, it is safe
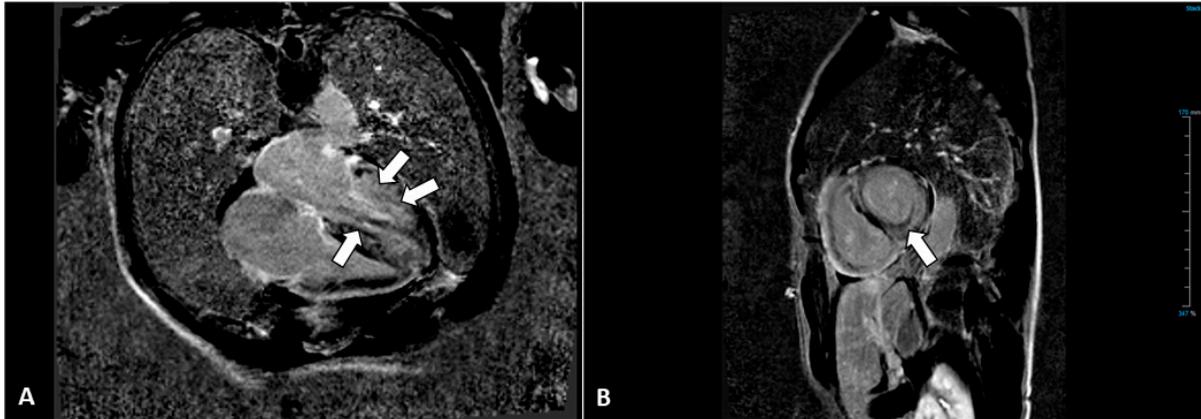
Figure 4. Cardiac magnetic resonance. Panel A: 4 -chamber view. LGE image. Diffuse amyloid infiltration with interstitial fibrosis of interventricular septum and lateral wall of left ventricle (arrows). Panel B: short axis view. LGE image. Subendocaridial amyloid infiltration in mid segment of left ventricle (arrow)

in patients with renal failure, which is a common problem in this group of patients. In this technique, the direct quantitative myocardial signal is measured before and after the application of contrast. It has been found that native myocardial T1 mapping has a high diagnostic accuracy for both types of CA (AL and ATTR), and is more sensitive for detecting early disease in gene mutation carriers than LGE imaging [23]. Furthermore, CMR allows differentiating between ATTR and AL amyloidosis [24].

The diagnosis of CA remains a diagnostic challenge. Reduced GLS with the unique regional deformation pattern is used for the initial diagnosis and differentiation from other types of cardiac hypertrophy. CMR with the LGE assessment could be applied for the confirmation of diagnosis.

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