The mosaic of the cardiac amyloidosis diagnosis: role of imaging in subtypes and stages of the disease

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Cardiac amyloidosis is a rare, infiltrative cardiomyopathy that presents with thickened ventricular walls and progressive heart failure. The morphological findings and clinical features are shared with many other diseases (i.e. hypertrophic cardiomyopathy, ‘athlete’s heart’, Fabry disease, and hypertensive cardiomyopathy), and misdiagnosis occurs frequently. Cardiologists have many instruments that can help reach a correct diagnosis in a relatively short time. As tiles of a mosaic are placed to create an image, thoughtful and smart use of the different diagnostic tools available allows the opportunity to identify amyloid infiltration of the myocardium. When the myocardium is involved, prognosis is poor, so identification of its involvement is crucial for disease management. The diagnostic process begins with an accurate evaluation of clinical elements and includes cardiovascular imaging (echocardiography, magnetic resonance, and nuclear medicine), electrocardiography, serological assays, and myocardial biopsy; only the appropriate integration of these instruments can reveal the diagnosis to an expert physician. The latest improvements in non-invasive diagnostic techniques with increased diagnostic power have reduced the need for biopsy.

Keywords
Cardiac amyloidosis • Cardiac magnetic resonance • Echocardiography • Nuclear medicine imaging

Introduction

Amyloidosis is a systemic or localized disease characterized by deposition of anomalous fibrillar proteins in a variety of tissues causing structural alterations and functional impairment. Fibrils originate from the misfolding of an altered precursor protein that precipitates in the extracellular matrix where it assumes a proteolytic resistant beta-sheet structure; the amorphous material generated is called ‘amyloid’. To date, 28 precursor proteins have been identified; however, subtypes light chain amyloidosis (AL), transthyretin (TTR) amyloidosis, systemic secondary amyloidosis, and systemic senile amyloidosis are the most common.¹–⁵ Amyloidotic deposition can affect myocardium, valves, and coronary vessels, leading to structural and functional alterations.³

Diagnostic process: from clinical presentation to myocardial biopsy

Clinical presentation
Close to 90% of patients with amyloidosis experience fatigue, weight loss, and present with edema. The clinical presentation depends on the amyloid deposit in the vessels, kidneys, liver, nerves, and heart.⁶–⁹ Cardiac involvement is frequent in AL, systemic senile, and TTR amyloidosis but rare in the systemic secondary variant. Cardiac amyloidosis begins with a subclinical stage due to initial amyloid deposition that is characterized by mild and unspecific cardiac symptoms.¹⁰ Observations in this phase include focal deposition of amyloid [atria, atrioventricular valves, intramural left ventricular (LV) deposition], mild LV wall thickness (<15 mm), mild diastolic dysfunction, and an impairment of only LV longitudinal function (subclinical stage). Progression of amyloid deposition causes a marked thickening of the LV wall (>15 mm) and the typical stage is characterized by heart failure (HF) with preserved systolic function, sometimes with a restrictive diastolic pattern (typical ‘hypertrophic’ stage). The disease evolves to end-stage congestive HF with biventricular systolic impairment and arrhythmias (end-stage). Angina could be present because of amyloid infiltration of the small intramyocardial vessels. Syncope is common and a consequence of both autonomic failure and arrhythmias; when activity-related syncope occurs, prognosis is poor. The most frequent arrhythmias are atrial fibrillation, sinus
dysfunction, and atrioventricular blocks. The degree of cardiac involvement, clinical presentation, and prognosis are strongly related to the particular subtypes of cardiac amyloidosis. Particularly, wild-type TTR has less cardiac involvement and a good prognosis with respect to mutant TTR. On the contrary, AL cardiac amyloidosis has a very poor prognosis with respect to wild-type TTR and mutated TTR.

Electrocardiography

The most common electrocardiogram (ECG) finding of cardiac amyloidosis is represented by low QRS voltages (Figure 1). The diagnosis of low voltages is correct when the sum of three peripheral lead voltages is ≤0.15 mV. Other cardiac amyloidosis findings are poor R-wave progression in precordial leads and pseudonecrotic Q waves, atrial fibrillation, and atrioventricular block.

Circulating biomarkers

Brain natriuretic peptide (BNP) is the active molecule obtained from the cleavage of the N-amino terminal fragment (NT-proBNP). NT-proBNP is an inactive element but produced in equimolarity to active BNP. BNP and NT-proBNP are widely recognized as markers of HF. Although the elevation of ventricular filling pressure is the main cause for the release of BNP, it is possible that direct damage of the ventricular myocytes could increase the level of BNP in patients with cardiac amyloidosis. Cardiac troponin is the most sensitive biomarker of myocardial injury. Recently, several studies demonstrated that high levels of cardiac troponin T and I have a strong predictive power in diagnosis and prognosis of cardiac amyloidosis.

Histological assay

Abdominal fat biopsy is a highly sensitive (<70% of AL amyloidosis) and specific instrument to diagnose amyloidosis. Other tissues that allow relatively non-invasive biopsy procedures are minor salivary glands, gingiva, rectum, and skin. Despite imaging development, endomyocardial biopsy remains the gold standard technique to diagnose cardiac amyloidosis in patients with HF.

Need for cardiac imaging

Although clinical evaluation and extracardiac biopsy allow the diagnosis of systemic amyloidosis, accurate evaluation of myocardial involvement in patients with amyloidosis is extremely complex, particularly at the subclinical phase. Imaging techniques were introduced with the aim to identify with high accuracy specific forms of cardiac amyloidosis (i.e. 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid ([99mTc-DPD] to diagnose TTR cardiac amyloidosis) and to evaluate early structural [i.e. focal delayed contrast enhancement (DCE) at cardiac magnetic resonance (CMR)] or mechanical (i.e. longitudinal strain) abnormalities. Only an appropriate use of these techniques guides the clinician towards the proper management of these patients.

Nuclear medicine techniques

Although different features of heart involvement can be assessed by nuclear medicine techniques, the most useful information in patients with amyloidosis is obtained through the imaging of myocardial innervation by 123I-metaiodobenzylguanidine ([123I-mIBG]) or by using radiopharmaceuticals that image amyloid deposits. Myocardial defects in [123I-mIBG] activity seem to correlate with impaired cardiac sympathetic nerve endings due to amyloid deposits and with clinical severity of disease. Namely, 123I-mIBG heart-to-mediastinum ratio is reduced and washout rate is increased in patients with cardiac amyloidosis. Moreover, it has been demonstrated that [123I-mIBG] scintigraphy can detect cardiac denervation in TTR amyloidosis in early stage, before signs of amyloidosis are evident on echocardiography. Furthermore, in a recent study evaluating the prognostic value of [123I-mIBG] scintigraphy in 143 patients with TTR amyloidosis, Coutinho et al. found that heart-to-mediastinum ratio is an independent prognostic predictor of survival.

At present, nuclear medicine imaging of cardiac amyloid deposition is predominantly accomplished with bone-seeking radiotracers (panel C in Figures 2 and 3), such as 99mTc-pyrophosphate ([99mTc-PYP]), 99mTc-hydroxymethylene-diphosphonate ([99mTc-HDP]), and 99mTc-DPD, which may differentiate AL from TTR cardiac amyloidosis with significant implications for prognosis, therapy, and genetic counselling. In particular, using [99mTc-PYP] imaging, Bokhari et al. found that subjects with TTR cardiac amyloidosis had a significantly higher semiquantitative cardiac visual score as well as a higher quantitative score than those in the AL cohort. They reported that using a heart-to-contralateral chest ratio >1.5, consistent with intensely diffuse myocardial tracer retention, had a 97% sensitivity and 100% specificity for identifying TTR cardiac amyloidosis. Rapezzi et al. found 99mTc-DPD accumulation in 45/45 cases of TTR cardiac amyloidosis, no radiotracer uptake in 15/15 unaffected controls, and only a mild degree of radiotracer uptake in 11 of 34 patients with AL-related cardiac amyloidosis. As a further positive issue, it has been demonstrated that both 99mTc-DPD and 99mTc-HDP scintigraphy are capable to identify amyloid deposition.
in the myocardium of patients with TTR cardiac amyloidosis (i.e. TTR-familial amyloid polyneuropathy and systemic senile amyloidosis) across a wide spectrum of morphologic/functional cardiac involvement allowing an early diagnosis of the disease, even before the appearance of echocardiographic abnormalities. Moreover, in a recent study by Minutoli et al., LV segmental extension of myocardial amyloid deposition as demonstrated by 99mTc-DPD imaging was often larger than that revealed by visual analysis of DCE-CMR. Indeed, although 99mTc-DPD imaging and DCE-CMR have similar capability to identify patients with myocardial amyloid deposition, cardiac amyloid infiltration burden can be significantly underestimated by visual analysis with DCE-MRI with respect to 99mTc-DPD imaging. Finally, myocardial uptake of bone-seeking radiotracers is correlated with disease severity and has been demonstrated to be a prognostic determinant of “cardiac” outcome in TTR cardiac amyloidosis, either alone or in combination with LV wall thickness.

The clinical use of positron emission tomography, which has the advantages of absolute quantification and higher resolution, probably will be gained by the increasing investigation of tracers that sensitively and specifically binds to amyloid fibrils.

**Echocardiography**

The main 2D echocardiographic findings observed in the typical ‘hypertrophic’ stage of cardiac amyloidosis include: symmetric LV and right ventricular (RV) thickening, dilated atria, pericardial effusion, valvular thickening (particularly in wild-type or mutant TTR cardiac amyloidosis), and ‘granular sparkling’ appearance (Supplementary data online, Video S1). Although these findings are common in the typical stage of cardiac amyloidosis, they have low accuracy in the early stage of cardiac amyloidosis and in discriminating cardiac amyloidosis from other causes of LV hypertrophy.

In order to obtain an early and definite diagnosis of cardiac amyloidosis, it is necessary a multiparametric evaluation, which also includes data of segmental systolic function (longitudinal, radial, and circumferential), right ventricular, and ventricular diastolic function.

**Figure 2:** Case 1. Subclinical stage. A 42-year-old woman with somatic polyneuropathy, no cardiac symptoms, and positive results of genetic testing for transthyretin familial amyloid polyneuropathy (Thr49Ala). Echocardiographic findings show a mild increase of LV thickness (12 mm) on four chambers view (A), a normal longitudinal function (S wave 0.08 cm/s) on TDI (D) and a moderate diastolic dysfunction (pseudonormal E/A pattern and E/E’ 10). Longitudinal deformation by 2D strain imaging (E) shows a very mild impairment of global longitudinal deformation (−19.1, normal value >−19.7). Furthermore, a lower deformation in basal segments with respect to apical segments can be found. MRI with late gadolinium enhancement in horizontal long-axis view (B) shows focal enhancement of right atrium and left atrium (with arrow). Technetium-99m-diphosphonate scan shows faint cardiac radiotracer uptake (arrows).
Tissue Doppler and two-dimensional strain rate and strain imaging
The analysis of segmental myocardial deformation derived by tissue Doppler imaging (TDI) and 2D strain imaging (2D-S) plays a crucial role in early diagnosis and prognostic evaluation of patients with cardiac amyloidosis.24 Serial investigations revealed that longitudinal deformation detected by TDI is impaired early in patients with cardiac amyloidosis.25 Porciani et al.25 observed a strong correlation between LV thickness and longitudinal dysfunction investigated by TDI in patients with cardiac amyloidosis and mild amyloid infiltration. Lindqvist et al.26 found that TDI was accurate in the detection of myocardial involvement in familial amyloidotic polyneuropathy patients with no clinical signs of HF. These data were further confirmed by Koyama et al.,27,28 who showed a lower longitudinal function, derived by TDI, in patients with typical stage of cardiac amyloidosis compared with amyloidotic patients without heart involvement. Particularly, longitudinal myocardial deformation at the base and mid LV was significantly decreased in asymptomatic cardiac amyloidosis patients with and without increased wall thickness.29

The clinical relevance of longitudinal dysfunction detected by TDI is confirmed by an adverse outcome in patients with depressed longitudinal peak systolic septal deformation.29

All these observations support the notion that impairment of longitudinal function by TDI plays a major role in the pathophysiology of cardiac amyloidosis and may be present even before congestive HF occurs and sometimes even in subjects without increased LV wall thickening.

However, TDI has many of the typical limitations of techniques based on Doppler effect, including angle dependence and noise interference.

The introduction of speckle tracking analysis allowed limitations linked to deformation analysis performed by TDI to be overcome. Speckle tracking permits evaluation of the myocardial deformation...
thanks to the analysis of acoustic interferences created by interaction between ultrasounds and tissues (speckles). The dedicated software is able to evaluate not only longitudinal function but also the radial and the circumferential ones. Twist, untwist, and torsion are other parameters of deformation connected to the opposite rotation of the base of the heart and apex.

Sun et al. reported that global longitudinal, circumferential, and radial deformations detected by 2D strain were significantly lower in patients with advanced cardiac amyloidosis compared with controls, hypertrophic cardiomyopathy (HCM), and hypertensive heart disease. Di Bella et al. showed that epicardial circumferential strain was significantly lower in patients with TTR cardiac amyloidosis than in patients with HCM.

Recently Quarta et al., analysing myocardial deformation by 2D-S in patients with AL and TTR cardiac amyloidosis, observed that despite a preserved LV ejection fraction, longitudinal deformation was severely impaired at basal and mid LV segments while apical longitudinal strain was preserved irrespective of the etiology of CA and the degree of wall thickening. Interesting, systemic senile amyloidosis (wild type TTR) was characterized by greater LV wall thickness and lower ejection fraction with respect to AL and mutated TTR. However, patients with systemic senile amyloidosis had a similar prognosis with respect to mutated TTR and a longer survival with respect to AL cardiac amyloidosis.

An interesting study carried out by Baccouche et al. compared late gadolinium enhancement evaluated by CMR with three-dimensional strain by echocardiography; they found that radial strain was strongly correlated with the severity of the myocardial involvement.

The more severe infiltration of the basal segments determined a clear basoapical gradient (‘inverse pattern’), with lower deformation in basal segments with respect to apical segments. This condition has been observed in CA and could be used to differentiate it from other causes of LV hypertrophy. Patients with HCM had a reduced, but still preserved, basoapical gradient. Therefore, the basoapical radial strain gradient displayed oppositional characteristics in cardiac amyloidosis and HCM, suggesting a ‘function pattern-based’ differentiation with a sensitivity of 83% versus the CMR-derived diagnosis.

Left ventricular rotational mechanics, investigated in patients with systemic amyloidosis, showed that LV twist and untwist rate enhances before LV hypertrophy is developed.

Data from both TDI and 2D-S highlight that patients with cardiac amyloidosis show a greater impairment of basal segments than apical ones.

Finally, in clinical practice, the greater impairment of basal segments with respect to apical ones from TDI and/or 2D-S can help clinicians in diagnosing cardiac amyloidosis (Figure 4).

For the most part, the studies highlighted that strain is useful in the distinction between cardiac amyloidosis and other diseases characterized by LV hypertrophy, myocardial deformation is usually more reduced in cardiac amyloidosis than in other forms of cardiac hypertrophy, and, moreover, the greater impairment of basal segments with respect to apical ones can further help clinicians in differential diagnosis of cardiac amyloidosis. However, larger studies are needed to determine clear and reliable reference values.

### Left ventricular diastolic dysfunction

Cardiac amyloidosis is usually described as a typical example of ‘restrictive cardiomyopathy’ characterized by high filling pressures and restrictive mitral inflow pattern. Recently, many authors revealed that these findings are common only in advanced cardiac amyloidosis. In this stage, a markedly increased wall thickness associated with a restrictive filling pattern characterized by markedly shortened deceleration time and high early (E-wave) velocity and relatively low atrial (A-wave) velocity is usually observed.

Many studies revealed that in cardiac amyloidosis, the degree of amyloid infiltration is related to diastolic dysfunction, which progresses from an abnormal relaxation pattern in the early stage, through a pseudonormal pattern, to a restrictive filling pattern in the late stage (E/A > 2, deceleration time < 150 ms). The onset of a restrictive pattern is an important and independent prognostic indicator of (poor) outcome in cardiac amyloidosis.

Interestingly, although diastolic dysfunction is a common finding, restrictive filling pattern is unusually observed in cardiac amyloidosis. Rapezzi et al. have studied diastolic function, using both invasive haemodynamic measures and Doppler echocardiography, of the

![Figure 4: Myocardial deformation in different stages of cardiac amyloidosis. Green = normal strain; yellow = mild–moderate strain impairment; red = severe strain impairment). Note the longitudinal dysfunction in mid and basal LV segments both in subclinical (longitudinal mild dysfunction < 19%) and typical stage.](image)
three main systemic types of cardiac amyloidosis (AL, TTR-familial amyloid polyneuropathy, and TTR wild-type); they observed that the majority of patients in each group did not display restrictive filling pattern. Particularly, groups showed relevant haemodynamic differences, with AL patients most often displaying abnormal values in the different measures of diastolic function.

Many studies showed that peak early diastolic velocity (E’) by TDI already is decreased in patients with systemic amyloidosis and normal wall thickness (early stage) and further decreases with the advent of LV thickening (typical stage) and in the late phase of cardiac amyloidosis (end-stage).

Another clinical application of TDI to the evaluation of diastolic function is the ability of E’ to discriminate cardiac amyloidosis (marked reduced) with respect to constrictive pericarditis (normal or mild reduced). 36

Some authors described a higher sensitivity of TDI in comparison with the strain rate in detecting the decrease of the E’ velocity in patient with advanced cardiac amyloidosis. 24,37

Therefore, in clinical evaluation of cardiac amyloidosis, diastolic dysfunction is a common finding but the restrictive mitral pattern is observed only in the few cases with massive deposition of amyloid in the end-stage phase of cardiomyopathy; parameters derived from TDI are more accurate in detecting the alteration of the diastolic function in the early stage of the disease.

Recently, Liu et al. 38 tried to combine data from strain imaging and diastolic function to obtain a more accurate differentiation between cardiac amyloidosis and other causes of concentric LV hypertrophy. He observed that combination of systolic septal longitudinal base-to-apex strain gradient (septal apical to basal LSsys ratio >2.1) with a shortened diastolic deceleration time of early filling wave (<200 ms) aids in differentiating cardiac amyloidosis from other causes of concentric LV hypertrophy.

Particularly, diastolic dysfunction can be an important independent prognostic indicator of (poor) outcome in cardiac amyloidosis. 35

Finally, in clinical evaluation of cardiac amyloidosis, diastolic dysfunction is a common finding but the restrictive pattern is observed only in the few cases with severe deposition of amyloid, typical, and end-stage phases of cardiomyopathy.

**Right ventricular dysfunction**

It has been reported that RV dysfunction is common in cardiac amyloidosis and indicates poorer outcome. 39,40 Reduced tricuspid annular plane systolic excursion was associated with more severe LV involvement, higher NT-pro-BNP peptide levels, and poorer survival. 41 Right ventricular dysfunction in patients with cardiac amyloidosis using both TDI and strain imaging was significantly reduced in cardiac amyloidosis compared with controls and was a significant independent predictor of poor prognosis. 42

**Cardiac magnetic resonance imaging**

Cardiac magnetic resonance imaging, having higher spatial resolution than nuclear medicine and echocardiography, is an excellent tool to obtain a detailed view of morphofunctional (volumes, ejection fraction, and mass) parameters of LV and RV as well as of atrial and ventricular thickness. 32,43 Delayed contrast enhancement CMR obtained 10–20 min after injection of gadolinium is a robust tool to identify myocardial damage (scar, fibrosis) in many heart diseases. Delayed contrast enhancement occurs as a result of altered gadolinium washout kinetics in the damaged myocardium (slow washout) with respect to normal surrounding tissue (fast washout). Therefore, myocardial damage appears as a hyperintense area due to the presence of gadolinium, while normal myocardium appears as a hypointense area.

To better identify myocardial damage (hyperintense area), it is needed to find a specific inversion time (usually 200–300 ms) to null the normal myocardial signal. This technical approach allows identification of normal myocardium as ‘nulled signal’ (hypointense), showing strong differing signal intensities with respect to myocardial damage and cavities. 44 The DCE areas can be observed both in ischaemic heart disease and in many cardiomyopathies such as HCM and Fabry disease. Usually, HCM shows a patchy DCE area located in the mid-wall of the hypertrophic segments; Fabry disease shows DCE in the basal inferolateral segment of the LV. 45

On the contrary, DCE images show atypical signal intensity in cardiac amyloidosis, determined by the distribution and severity of myocardial amyloid deposition and the faster clearance of gadolinium from the blood pool (Figure 3B). The peculiar gadolinium kinetics in amyloid heart walls are defined by the following patterns: (i) a diminished T1 difference between damaged myocardium and blood pool, and (ii) many myocardial DCE patterns due to the slow washout of gadolinium from interstitial space that is infiltrated and expanded by amyloid proteins. The diminished T1 difference causes similar signal intensities between myocardium and blood pool, causing difficulty in distinguishing myocardium cavities. To confirm this, the CMR protocol for cardiac amyloidosis calls for the acquisition of multiple images using different inversion times (i.e. 80–350 ms with a 30 ms increment). Further DCE CMR patterns include a myocardial enhancement distributed over the entire subendocardial circumference (global subendocardial circumference-DCE), a ‘zebra pattern’ consisting of a subendocardial and subepicardial DCE and a diffuse homogeneous myocardial enhancement sometimes with focal regions of higher DCE areas. 45,46

Furthermore, DCE CMR is able to identify areas of hyperintensity due to amyloid deposition in RV, atrioventricular valves, and thickened atria. 43

Vogelsberg et al. 46 reported that global subendocardial circumference-DCE pattern is the most frequent pattern observed in patients with biopsy-proven cardiac amyloidosis and shows high accuracy to detect cardiac amyloidosis. Others authors have shown that the 2 min post-gadolinium intramyocardial T1 difference between the subepicardium and subendocardium predict mortality; particularly, the lower the difference, the worse the prognosis. 47 Further main findings in cardiac amyloidosis are that DCE areas are not limited to the LV but usually involve the RV and atria. 43

Di Bella et al. 43 studied 16 TTR patients with familial amyloid polyneuropathy and showed unusual findings of cardiac amyloidosis. Particularly, the typical subendocardial circumferential-DCE pattern was observed only in one patient with advanced HF; asymptomatic patients with cardiac amyloid deposition detected by 99mTc-DPD scintigraphy showed a patchy intramural focal enhancement located in basal segments of inferolateral and inferior wall and areas of DCE in atria, atrioventricular valves, and RV.

Similarly, Syed et al. 47 observed both the typical subendocardial circumferential-DCE pattern and intramural focal DCE pattern in...
35 patients with cardiac amyloidosis; particularly, NYHA functional class, low voltage and pseudoinfarct pattern on ECG, LV and RV thickness, and cardiac troponin T and BNP levels were higher in patients with global subendocardial circumferential-DCE with respect to those with patchy intramural focal enhancement. These data support that the patchy intramural focal enhancement and DCE of atria, RV, and valves represent an early phase of myocardial amyloid deposition.

Recently, Dungu et al. highlighted the different CMR features in TTR and AL cardiac amyloidosis. Particularly, they showed an improved survival despite increased LV mass and more extensive LV and RV DCE in TTR with respect to AL cardiac amyloidosis.

Areas of DCE in atria and RV, typically found in asymptomatic TTR patients, are not observed in HCM and Fabry disease. Although subendocardial circumferential-DCE has high specificity in the identification of cardiac amyloidosis, the focal pattern cannot be considered specific. Therefore, the differential diagnosis has to include many other heart diseases; however, it is highly probable that the combined presence of focal LV-DCE and the involvement of other chambers or structures are due to cardiac amyloidosis.

T1 mapping is an interesting application of T1-weighted imaging. T1 mapping requires acquisition of multiple images with different T1 to derive the T1 recovery curve. This approach permits acquisition of quantitative data of T1 tissue characterization; particularly, T1 mapping permits one to obtain, without use of gadolinium-based contrast agents (non-contrast or native T1 mapping), information about changes of myocytes and interstitium and, after gadolinium administration (contrast T1 mapping), information about the size of the extracellular space (myocardial interstitial disease).

Myocardial native T1 mapping has been shown to be accurate in detecting early cardiac involvement in both AL and TTR cardiac amyloidosis; furthermore, native T1 mapping can be used to track amyloidotic deposition. An important limitation of DCE technique is represented by the risk of nephrogenic systemic sclerosis in patients with renal impairment. Furthermore, CMR allows identification of both pericardial and pleural effusion (Supplementary data online, Video S1). These latter findings, usually, are observed in cardiac amyloidosis rather than in other cardiomyopathies with hypertrophic phenotypes.

**Practical application of cardiac imaging techniques**

In clinical practice, several clinical scenarios may occur in diagnosing cardiac amyloidosis.

SCENARIO A, patients with a definite diagnosis of systemic amyloidosis (e.g. positive fat biopsy) and no other possible causes of
abnormal cardiac findings: in this case, the evidence of abnormal ECG (i.e. low voltage) and/or LV wall thickening (> 12 mm), longitudinal dysfunction, E/E’ > 8 are satisfactory to diagnose cardiac amyloidosis.

SCENARIO B, patients with a definite diagnosis of systemic amyloidosis and other possible causes of increased LV thickness (e.g. hypertension): in this scenario, CMR (including DCE imaging) is needed. Scintigraphy using bone-seeking radiopharmaceuticals may be additionally performed in patients with TTR-related amyloidosis and non-conclusive CMR findings because of its high sensitivity in revealing amyloid deposition.22

SCENARIO C, patients with high risk to develop cardiac amyloidosis: this scenario includes subjects with a positive genetic test for TTR gene mutation or a disease carrying amyloid deposition, e.g. multiple myeloma, non-Hodgkin lymphoma, Waldenstrom macroglobulinemia, monoclonal gammapathy of unknown significance, chronic arthritis (particularly rheumatoid arthritis), ankylosing spondylitis, Crohn’s disease, hereditary periodic fevers and acquired or inherited immunodeficiencies, chronic renal failure, and long-term history of haemodialysis (non-TTR amyloidosis). Cardiac imaging using CMR and/or scintigraphy maybe used to reveal amyloid deposition.

SCENARIO D, patients with clinical and/or laboratory ECG and echocardiographic findings compatible with cardiac amyloidosis and without any known condition related to the development of amyloidosis: this scenario is very challenging, and it can be observed during echocardiographic examinations. Because of the heterogeneity of causes leading to amyloid deposition, diagnostic algorithm, and the need for imaging should be addressed by careful clinical evaluation. As far as cardiac imaging is concerned, when echocardiography and strain imaging reveal cardiac abnormalities, CMR with DCE should be the main diagnostic tool. Indeed, it is a ‘one stop shop’ technique that may disclose specific findings without radiation exposure. Scintigraphy using bone-seeking radiopharmaceuticals may be used as a non-invasive method to individuate TTR-related amyloidosis (Figure 5). Both CMR and nuclear medicine techniques allow prognostic evaluation. Biopsy should be considered in patients with HF when clinical features and cardiac imaging findings are not conclusive for cardiac amyloidosis.

Conclusions
Cardiac amyloidosis is a rare infiltrative cardiomyopathy resulting from a broad range of genetic, neoplastic, inflammatory, and autoimmune causes. The diagnostic process requires an accurate clinical evaluation, electrocardiography, serological assays, cardiac imaging, and biopsy. Although endomyocardial biopsy is the gold standard modality to diagnose cardiac amyloidosis, it is recommended in patients presenting with HF. Conversely, conventional echocardiography is the first line imaging modality in patients with clinical suspicion for cardiac amyloidosis and for follow-up patients. Advanced imaging, namely strain echocardiography, DCE CMR, and nuclear medicine techniques, is effective to non-invasively diagnose both early and advanced phases of cardiac amyloidosis.

Supplementary data
Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.

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