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Molecular Imaging of Cardiac Amyloidosis

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Abstract

Purpose of Review The aim of this review is to give an update on the molecular imaging tools currently available as well as to discuss the potential roles and limitations of molecular imaging in cardiac amyloidosis.

Recent Findings Molecular imaging plays a central role in the evaluation of patients with suspected cardiac amyloidosis. It can be used to diagnose and distinguish between the different types of cardiac amyloidosis. The diagnostic properties of bone scintigraphy are such that it allows reliable diagnosis of transthyretin cardiac amyloidosis without the need of endomyocardial biopsy in a significant proportion of patients. Furthermore, molecular tracers assessing amyloid plaque burden and sympathetic innervation may be useful for the non-invasive evaluation diagnosis and risk stratification of patients with suspected cardiac amyloidosis.

Summary Cardiac amyloidosis is an under-recognized cause of left ventricular hypertrophy and heart failure in the elderly. The role of molecular imaging in cardiac amyloidosis is expected to grow considering the arrival of new therapies and molecular imaging probes.

Keywords Positron emission tomography · SPECT · Cardiac amyloidosis · Transthyretin · Bone scintigraphy

Introduction

Cardiac amyloidosis (CA) is a collection of diseases, inherited or acquired, characterized by deposition of amyloid in the myocardial extracellular matrix [1]. Amyloid is composed for the most part of fibrils formed by the deposition of insoluble serum proteins and, to a lesser extent, by the amyloid P component and other glycoproteins [2]. The exact mechanisms by which amyloid deposition causes cardiac dysfunction are not completely understood and likely go beyond simple physical replacement of the structurally normal tissue by amyloid [3]. Different types of cardiac amyloidosis have been described and are classified based on the precursor protein accumulating in the myocardium. The overwhelming majority of cardiac amyloidosis cases are caused by either light chains or transthyretin [2]. The generally accepted nomenclature for the different types of cardiac amyloidosis is to use the letter "A" followed by the protein abbreviation. Light-chain amyloidosis is abbreviated as "AL" and transthyretin amyloidosis as "ATTR" [1]. The superseded terminology "primary amyloidosis" and "secondary amyloidosis" should be avoided.

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Light-Chain Amyloidosis

Light-chain (AL) amyloidosis is a systemic disease with an incidence of approximately 1 per 100,000 person, affecting both males and females, typically in their fifties. Between 30 and 50% of patients with AL amyloidosis will present symptomatic cardiac involvement [4, 5]. Kidney, liver, and peripheral neurological involvement is frequently seen, and isolated cardiac involvement is relatively rare, representing less than 5% of cases [2]. AL amyloidosis is a hematological disease caused by deposition of light chains, or more frequently light-chain fragments, produced by clonal plasma B cells originating from the bone marrow and is associated with different lymphoproliferative disorders such as multiple myeloma [6]. When left untreated, AL cardiac amyloidosis has a very poor prognosis with survival of a few months only. With appropriate chemotherapy and supportive treatments, the medial survival can be prolonged to over 5 years [6].

Transthyretin Amyloidosis

Transthyretin (ATTR) amyloidosis is caused by deposition of misfolded transthyretin, a protein produced by the liver which transports the thyroid hormone thyroxine and the vitamin retinol. Transthyretin is sometime referred to as prealbumin because it precedes albumin on protein electrophoreses although it is not a precursor of albumin. ATTR amyloidosis can be caused by a genetic mutation in the transthyretin gene resulting in accumulation of misfolded transthyretin in tissue. This form of amyloidosis is referred to as mutant or familial ATTR (ATTRm). Over 100 different mutations in the TTR gene have been identified so far. Common mutations include the familial amyloid polyneuropathy (FAP) type I (ATTR V30M), more prevalent in Portugal, Japan, and Sweden, and the Val122Ile mutation, affecting mostly people of African descent [1, 6–8]. ATTR cardiac amyloidosis can also be caused by accumulation of non-mutant misfolded transthyretin proteins, in which case it is referred to as wild-type amyloidosis (ATTRwt). Transthyretin folding can be perturbed by various factors such as pH level, impaired proteolysis, increased temperature, presence of metal ions, and osmolytes [9]. The incidence of ATTRwt increases with age and is practically exclusively seen in patients 65 years or older as it takes decades to accumulate sufficient misfolded TTR to cause organ dysfunction. The exact prevalence of ATTR cardiac amyloidosis is unknown, but the consensus is that the disease is an under-recognized cause of left ventricular hypertrophy (LVH) and heart failure (HF) in the elderly [5, 10]. Indeed, postmortem studies demonstrated that a quarter of adults older than 80 years of age and a third of patients with HF with preserved ejection fraction (HFpEF) have abnormal amyloid deposition [11, 12]. The current management of patients with ATTR cardiac amyloidosis relies mostly on supportive care and, ultimately, cardiac transplantation. However, several new promising molecules targeting the precursor protein and fibril deposits are currently in late-phase trials. An accurate and reliable non-invasive diagnostic tool allowing evaluation of disease activity, response to therapy, and evaluation of patients' prognosis will likely have a major role to play in future clinical trials and patients' selection for new therapy.

Clinical Presentation

Patients with cardiac amyloidosis often present with non-specific symptoms related to heart failure such as dyspnea and leg edema. The disease is characterized by progressive increase in myocardial wall thickness due to accumulation of amyloid in the cardiac muscle, which leads to diastolic dysfunction and hypertrophy with paradoxically low voltage on ECG [13, 14]. Patients may also present with extracardiac symptoms such as peripheral and autonomic neuropathy. Detailed description of the clinical features of the different forms of amyloidosis is beyond the scope of this article and has been thoroughly reviewed elsewhere (see [6, 14]). Echocardiography is often the first imaging modality used to investigate patients with symptoms of heart failure. Frequently observed findings of cardiac amyloidosis on echocardiography include increased wall thickness, with LV wall thickness > 12 mm, and absence of LV dilatation. Impaired LV longitudinal strain with apical sparing, the so-called cherry on sundae pattern (Fig. 1), has also been associated with cardiac amyloidosis [15, 16]. While these findings can raise the suspicion of cardiac amyloidosis, they are not pathognomonic and further investigations are usually required to confirm or exclude the diagnosis of cardiac amyloidosis. Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) has been demonstrated to be useful at identifying CA. On CMR, in addition to the LVH, diffuse subendocardial LGE and non-infarct LGE patterns are seen (Fig. 2) [17]. Other features such as increased extracellular volume (ECV) and abnormal myocardial nulling on T1 mapping have been described to detect cardiac amyloidosis [18, 19]. In addition to its ability to detect cardiac amyloidosis, CMR also provide prognostic information beyond the conventional biomarkers [20]. Although CMR is the non-invasive modality of choice to image cardiac amyloidosis, it does have some limitations. The false negative rate of CMR for cardiac amyloidosis is relatively high, at 12% [21]. Diagnosis of cardiac amyloidosis relies on detection of fibrosis, which appears late in the disease after irreversible damage has occurred. Furthermore, CMR cannot reliably differentiate AL from ATTR cardiac amyloidosis [22]. Finally, CMR is contraindicated in some patients, such as those with impaired renal function, a relatively frequent comorbidity of the population in which amyloidosis is suspected.

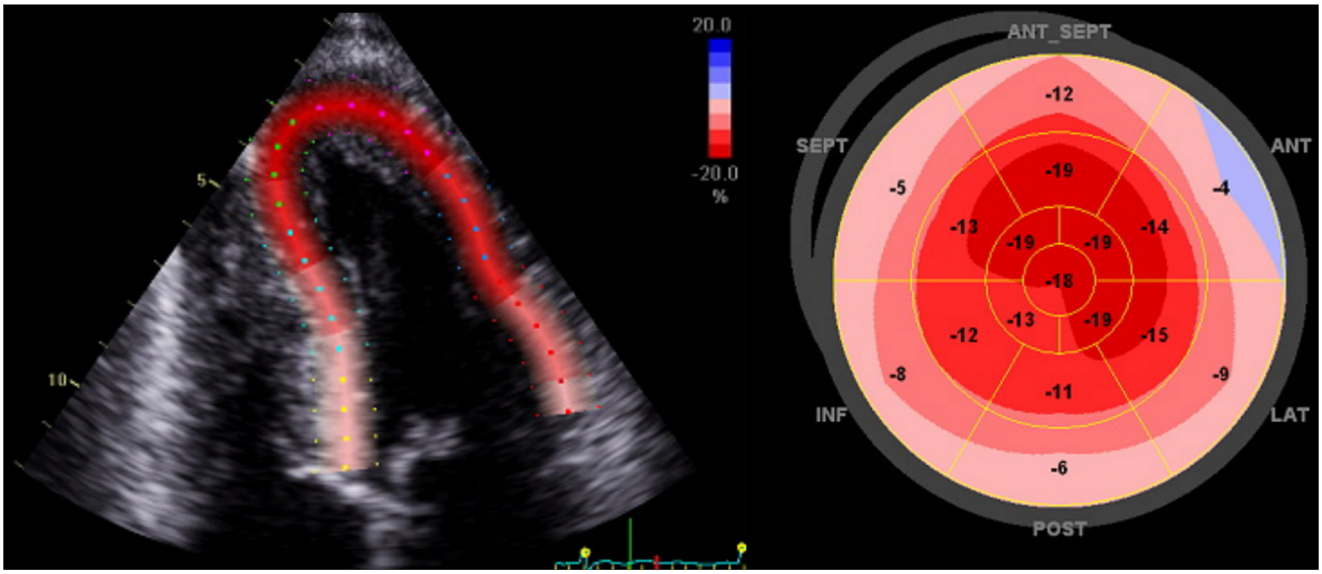

Fig. 1 Echocardiography longitudinal strain analysis of a 70-year-old male with biopsy-proven ATTR cardiac amyloidosis. Four-chamber view (*left*) and bull's-eye (*right*) images demonstrate impaired longitudinal strain predominantly affecting the basal segments of the left ventricle with sparing of the apex (cherry on sundae pattern)

Molecular Imaging

Bone Tracers

The first reports of molecular imaging in cardiac amyloidosis used bone-seeking agents and date from almost 40 years ago [23]. Those bone tracers are bisphosphate derivative labeled with the SPECT isotope ^{99m}Tc. Over the past decades, different bone tracers, including ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP), ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP), and ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), have been used in cardiac amyloidosis, with PYP being the only one approved for clinical use by the Food and Drug Administration. In soft tissues, bisphosphate derivative accumulation is thought to result from chemisorption on calcium salt surface [24]. In cardiac amyloidosis, bone tracers bind to microcalcifications associated with amyloid deposits in ATTR with high affinity, allowing early diagnosis of ATTR cardiac amyloidosis, before abnormalities can be seen on echocardiography [25]. Conversely, bone tracers show minimal affinity with amyloid deposits in AL cardiac amyloidosis, allowing distinction between the two types. Bone tracers were shown to identify patients with ATTR cardiac amyloidosis with sensitivity approaching 100% and specificity between 85 and 100% [26–29, 30••, 31••], with virtually all cases of false positive due to mild tracer uptake in AL subjects. In addition to its high sensitivity and specificity, quantitative assessment of bone tracer uptake provides additional prognosis information. It was shown that increased myocardial retention of the different bone tracers is associated with shorter major adverse cardiac event (MACE)–free survival, increased acute heart failure, and increased mortality [25, 32, 33].

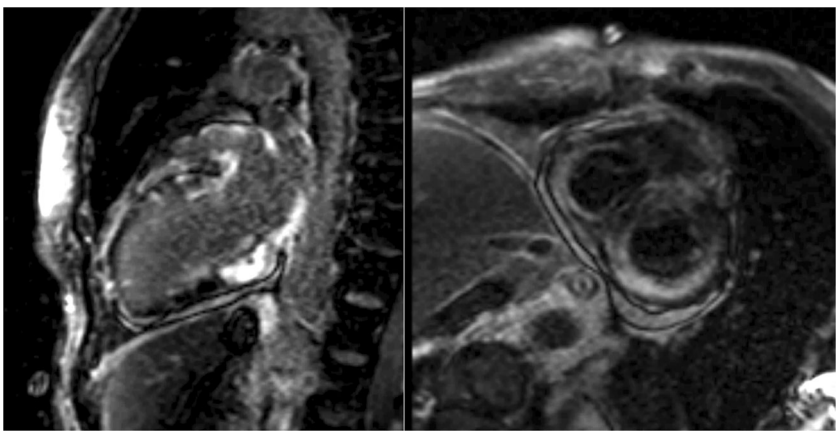

Fig. 2 Two-chamber (*left*) and short-axis (*right*) late gadolinium enhancement (LGE) CMR images of a 61-year-old female with multiple myeloma and AL cardiac amyloidosis demonstrate diffuse subendocardial LV LGE with basal predominance

Interpretation of bone scintigraphy with ^{99m}Tc-PYP, ^{99m}Tc-HMDP, or ^{99m}Tc-DPD relies on both visual and quantitative analyses. On visual analysis, uptake is typically categorized as absent, focal, or diffuse. ATTR cardiac amyloidosis usually presents as diffuse uptake while focal uptake can be seen in recent myocardial infarction. Quantitative or semi-quantitative image interpretation can be performed using two distinct methods. The first method consists of measuring the myocardial-to-contralateral (H/CL) ratio on planar images obtained 1 h after tracer injection (Fig. 3) [32]. To calculate H/CL ratio, 2 regions of interest (ROI) are drawn: one over the heart and one on the contralateral chest on planar images. The H/CL ratio is then obtained by dividing the mean counts in the heart ROI by the mean counts in the contralateral ROI. The H/CL ratio ≥ 1.5 is considered positive for ATTR cardiac amyloidosis [32]. The second method uses a grading system which relies on visual comparison of the myocardial and rib uptake on images acquired 3 h after tracer injection and can be used with both planar and SPECT images. Grade 0 is defined as absent myocardial uptake, grade 1 as myocardial uptake less than ribs, grade 2 as myocardial uptake similar to ribs, and grade 3 as myocardial uptake greater than ribs (Fig. 3). Grade ≥ 2 is considered positive for ATTR cardiac amyloidosis while grade 0 is considered negative for ATTR cardiac amyloidosis [34]. Grade 1 uptake could represent either ATTR or AL cardiac amyloidosis [34].

Importantly, not all bone tracers show equivalent diagnostic performance for CA. For example, the use of the widely available bone tracer ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) is considered inappropriate for the evaluation of patients with suspected ATTR cardiac amyloidosis as its sensitivity is inadequately low [26]. Recently, there has been interest in studying the use of ^{18}F-sodium fluoride (NaF) in cardiac amyloidosis. As opposed to other bone agents used for cardiac amyloidosis, NaF is a positron emission tomography (PET) tracer, with improved imaging properties allowing accurate quantification. The use of a PET tracer could lead to enhanced diagnostic performance, especially at the early stage of the disease. Although a case report described negative NaF PET in two subjects with ATTR cardiac amyloidosis [35], two small prospective studies showed accumulation of NaF in ATTR-CA and no significant uptake in controls and AL patients [36, 37•]. Of note, in both studies, the myocardial uptake was mild, only slightly higher than blood pool activity, highlighting the necessity of accurate quantitative assessment and protocol optimization with this tracer (Figs. 4 and 5). Further studies are required to confirm the utility of NaF PET for the diagnosis of ATTR-CA.

Amyloid Tracers

Various SPECT radiopharmaceuticals directly or indirectly targeting amyloidosis deposition were developed [38]. Although small studies suggested that such tracers, including iodine-labeled serum amyloid P protein and ^{99m}Tc-aprotinin, could play a role in the diagnosis of cardiac amyloidosis, they

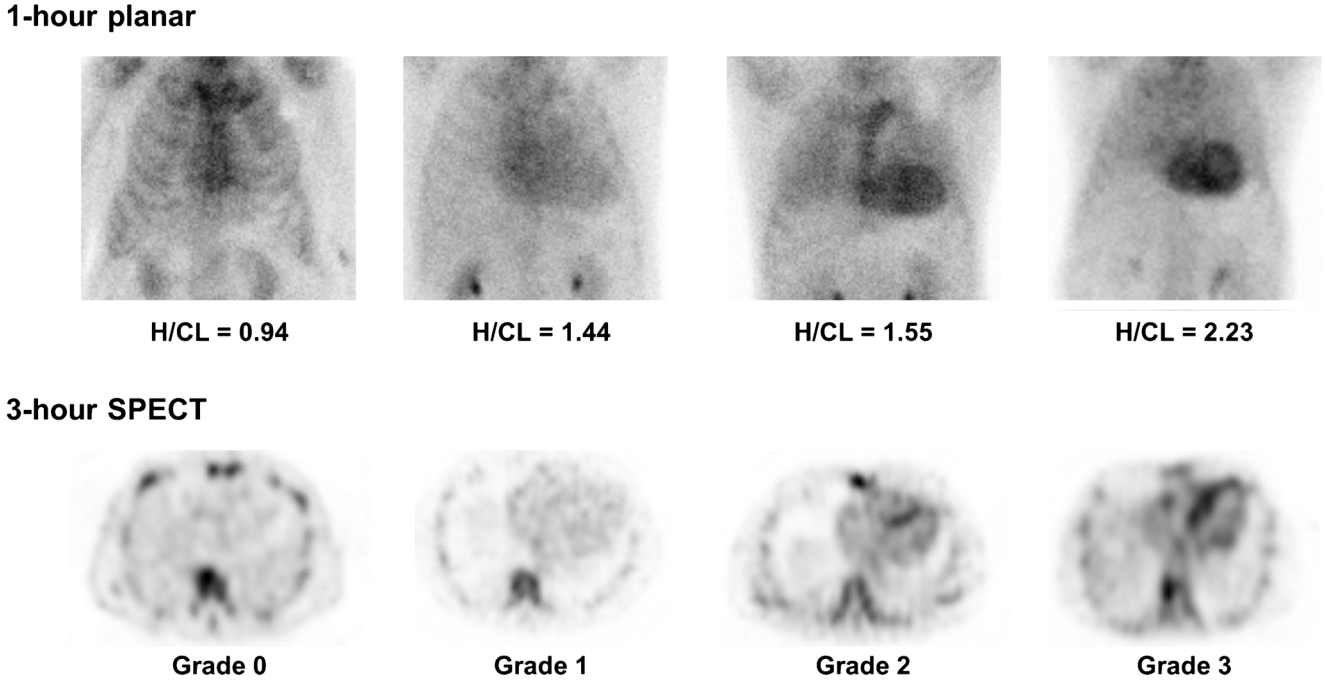

Fig. 3 Grading ^{99m}Tc-PYP uptake on planar bone scintigraphy performed at 1 h (*top*) and corresponding SPECT images obtained 3 h after tracer injection (*bottom*). Heart-to-contralateral (H/CL) ratio is calculated on 1-h planar images. On 3-h images, the myocardial uptake is compared with rib uptake: grade 0 = absent uptake; grade 1 = uptake less than rib; grade 2 = uptake equal to rib; and grade 3 = uptake greater than rib

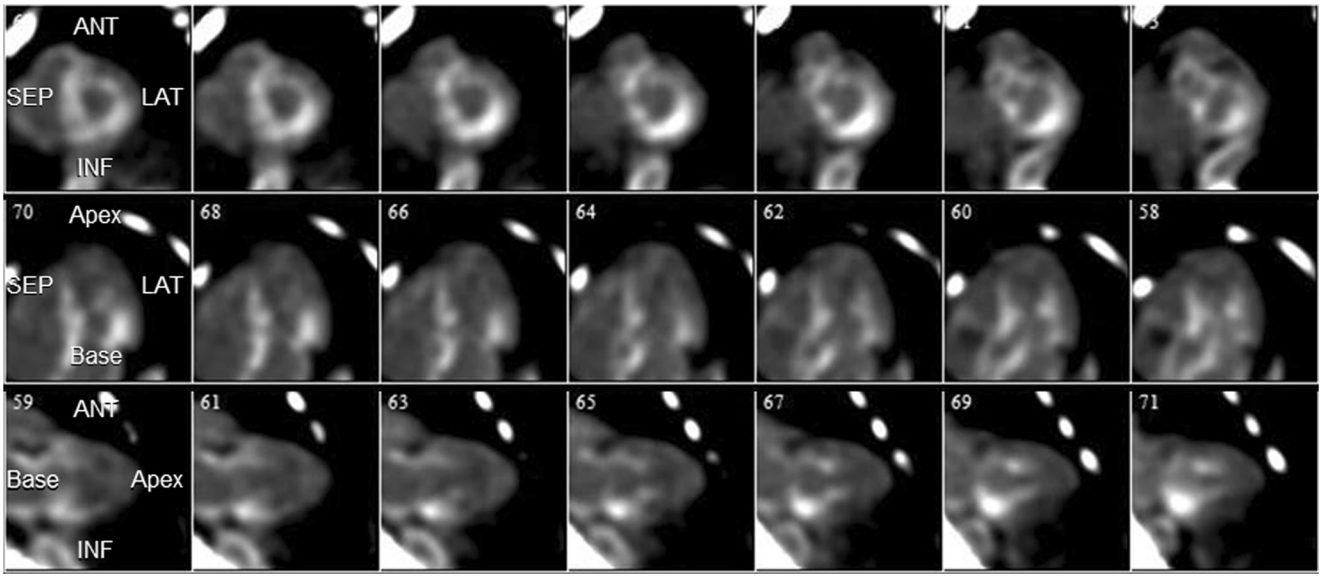

Fig. 4 ^{18}F-sodium fluoride (NaF) PET images of an 83-year-old male with ATTR cardiac amyloidosis showing increased biventricular and atrial NaF uptake in a patient with ATTR cardiac amyloidosis. The uptake is more intense in the basal segments with relative sparing of the apex and periapical segments

never reached widespread clinical acceptance and they are not readily available.

More recently, different PET radiopharmaceuticals developed to detect brain amyloid, including ^{18}F-florbetapir, ^{18}F-florbetaben, and ^{11}C-Pittsburgh B (PiB), have been used to image amyloid deposits in the heart. These tracers have been shown to bind specifically to brain β-amyloid plaques, allowing diagnosis and follow-up of patients with Alzheimer's disease [39]. A pilot study of 14 subjects demonstrated that ^{18}F-florbetapir accumulates in the heart of patients with cardiac amyloidosis, with higher uptake in AL compared with that in ATTR, and no significant uptake was seen in the

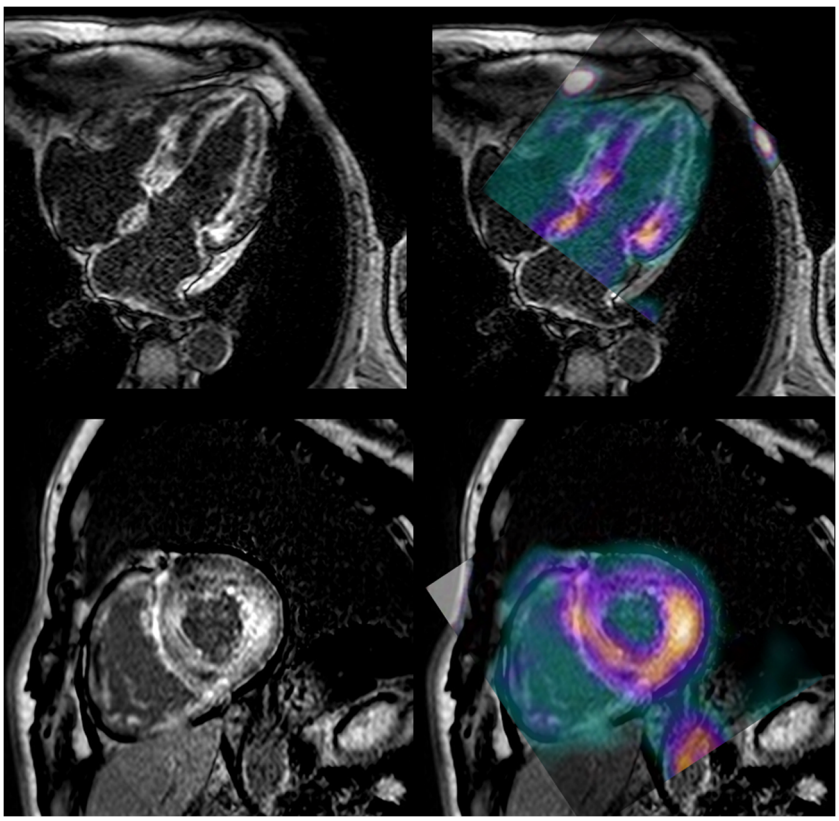

Fig. 5 MRI (*left*) and fusion ^{18}F-sodium fluoride (NaF) PET and MRI fusion images (*right*) of the 83-year-old male presented in Fig. 4. Increased NaF uptake is seen in the basal segments of the left ventricle and in the interauricular septum, corresponding to areas of late gadolinium enhancement on MRI

heart of healthy controls [40•]. Similar results were obtained with the ^{11}C-PiB [41•] and ^{18}F-florbetaben compounds [42]. These studies show that not only amyloid imaging can differentiate between healthy controls from patients with amyloidosis with high sensitivity and specificity; it can also differentiate between patients with cardiac amyloidosis from patients suffering from LVH due to hypertensive heart disease. It was shown that amyloid tracers bind specifically to myocardial amyloid deposit in both AL and ATTR cardiac amyloidoses, confirming that the uptake observed with these tracers is related to specific binding to amyloid deposits, without binding to interstitial fibrosis and infarct [43]. Further studies are required to assess the ability of amyloid plaque tracers to detect early disease and to evaluate if they can be used to monitor treatment response. As of now, lack of larger trials as well as costs and limited availability of these molecules is preventing its widespread clinical use.

Sympathetic Innervation

The SPECT tracer ^{123}I-metaiodobenzylguanidine (MIBG) is a norepinephrine analogue accumulating in sympathetic nerve endings. Unlike norepinephrine, MIBG undergoes minimal degradation and its accumulation in the nerve endings allows imaging and quantification of cardiac sympathetic innervation. It is used in various cardiomyopathies associated with dysautonomia such as HF, providing independent prognostic information and allowing assessment of response to therapy [44]. Demonstration of sympathetic denervation using MIBG in amyloidosis was first described in FAP, a form of ATTRm [45]. These results were later confirmed in a small prospective trial [46]. In cardiac amyloidosis, it is thought that decreased MIBG uptake is related to sympathetic denervation caused by the accumulation of amyloid [38]. In patients who are carriers of TTR mutations, decreased MIBG uptake was observed in absence of clinical evidence of cardiac amyloidosis [46, 47]. It was concluded that evaluation of cardiac sympathetic denervation by MIBG imaging could detect disease earlier than other modalities, including echocardiography and bone scintigraphy [48••]. Furthermore, in ATTRm cardiac amyloidosis, cardiac innervation assessment with MIBG was shown to be a strong and independent predictor of patient outcome [49, 50]. Abnormal late heart-to-mediastinal ratio has been demonstrated to be an independent prognostic predictor of 5-year mortality and is a predictor of survival following liver transplant [49, 51]. Given its ability to identify early disease, it has been suggested that MIBG could be used to screen patients with TTR mutation allowing earlier cardiac amyloidosis detection, before symptoms or function abnormalities occur. PET cardiac innervation tracers such as ^{11}C-HED and ^{124}I-MIBG could potentially outperform the conventional MIBG SPECT given their superior imaging properties; however, more studies are required to confirm this assumption [52].

Metabolism

Fluorodeoxyglucose (FDG) is by far the most frequently used PET tracer worldwide. FDG is a glucose analogue routinely used to image inflammation, infection, and malignancies. Although some preliminary studies showed increased FDG uptake in organs affected by AL amyloidosis, including the heart, it is neither specific nor sensitive to detect cardiac amyloidosis, and therefore there is no current role for FDG in cardiac amyloidosis [53, 54].

Differentiating ATTR and AL

Distinction between AL and ATTR cardiac amyloidoses is crucial as treatment and prognosis of these two diseases are utterly different. The presence of monoclonal proteins alone cannot be used to differentiate AL from ATTR as prevalence of monoclonal gammopathy in the absence of AL cardiac amyloidosis is fairly high in the age group typically affected by ATTR cardiac amyloidosis [30••]. Echocardiographic features of AL and ATTR cardiac amyloidosis are similar and overlapping. Therefore, echocardiography cannot be used to distinguish the two types of cardiac amyloidosis [55]. Differences in LGE on CMR patterns have been shown to distinguish AL from ATTR cardiac amyloidosis, with prevalence of transmural LGE being significantly higher in patients with ATTR cardiac amyloidosis [56]. As well, native myocardial T1 is higher in AL while extracellular volume is higher in ATTR [22]. Although CMR criteria using LGE pattern developed to discern cardiac amyloidosis types have shown good discrimination [56], their clinical application is hampered by their low reproducibility, and currently, CMR cannot be used to reliably differentiate AL from ATTR cardiac amyloidosis [22]. In contrast, several studies demonstrated that bone scintigraphy can accurately and reliably distinguish between AL and ATTR cardiac amyloidoses [28, 30••, 32–35, 57]. This difference in uptake can be explained by the fact that ATTR amyloid is characterized by higher levels of microcalcification compared with AL amyloid [58]. The reasons why microcalcification content is higher in ATTR compared with that in AL are not completely understood and could be related to chronicity of ATTR compared with that of AL. Preliminary assessment of the PET bone tracer NaF displays results similar to other bone tracers with uptake significantly higher in ATTR compared with that in AL with minimal overlap [36, 37•]. On the other hand, the amyloid tracers demonstrate uptake in both ATTR and AL cardiac amyloidoses,

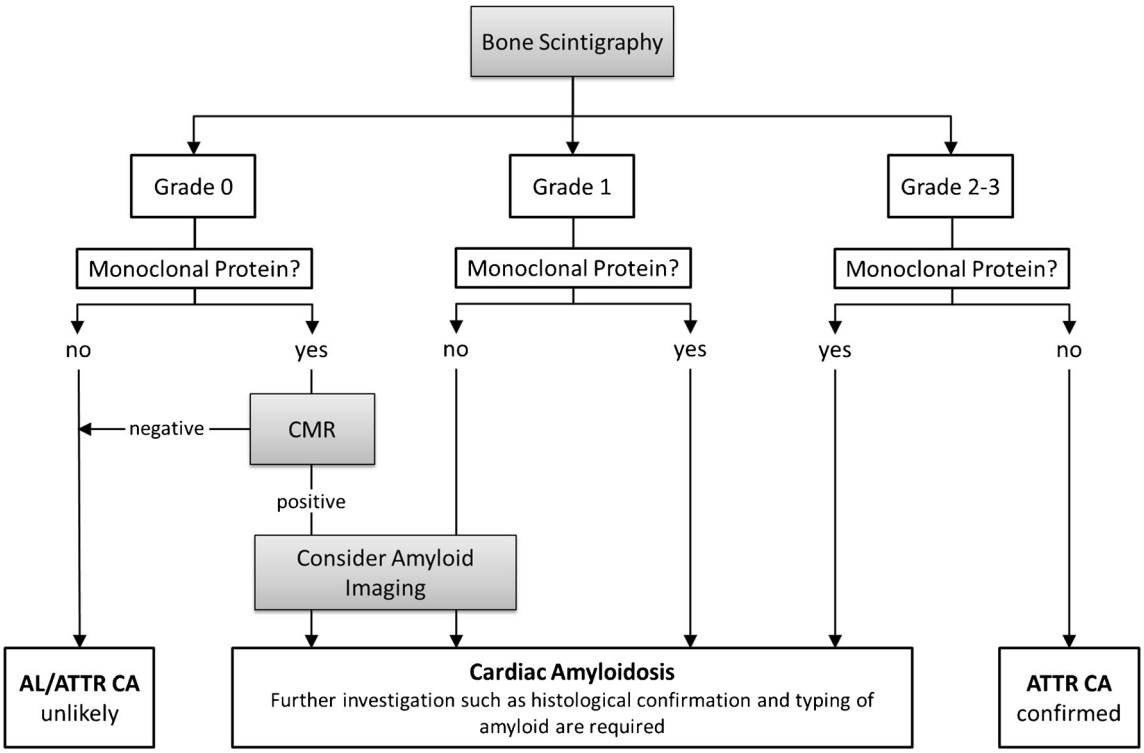

Fig. 6 Diagnostic algorithm based on bone scintigraphy with 99mTc-PYP/DPD/HMDP for patients with suspected cardiac amyloidosis (the figure created using data from [30, 62])

precluding its use for differentiation between ATTR and AL cardiac amyloidoses [40•, 42, 43].

Non-invasive Investigation of Cardiac Amyloidosis

Final diagnosis of cardiac amyloidosis is established by demonstration of the pathognomonic apple-green birefringence with polarized light on Congo red staining histopathology. Biopsy sample is usually obtained by endomyocardial biopsy (EMB) or from other tissues in which amyloid deposition occurs, such as subcutaneous fat. The yield of non-cardiac biopsies is relatively low in AL cardiac amyloidosis and even inferior in ATTR cardiac amyloidosis [59, 60]. EMB is considered the gold standard for the diagnosis of both AL and ATTR cardiac amyloidoses, and spectrophotometry is often required to differentiate AL and ATTR cardiac amyloidoses. However, EMB is an invasive procedure associated with a low but non-negligible complication risk, including perforation, tamponade, and arrhythmias [61]. There has been interest in developing a non-invasive approach allowing the diagnosis of ATTR cardiac amyloidosis without the use of EMB. Using the fact that bone scintigraphy has a sensitivity of nearly 100%, a high specificity, and that virtually all false positive studies are related to patients with AL cardiac amyloidosis, non-invasive investigation algorithms using bone scintigraphy have been proposed (Fig. 6) [6, 13, 30••, 62]. A non-invasive investigation algorithm, based on bone scintigraphy, MRI, and monoclonal protein screening, has been validated in a large multicentric study of 1217 patients investigated for suspicion of ATTR cardiac amyloidosis [30••]. The authors concluded that in patients with clinical suspicion of cardiac amyloidosis with abnormal echocardiogram and/or CMR and in the absence of monoclonal gammopathy, ATTR cardiac amyloidosis can be confidently diagnosed when grade 2 or 3 uptake is seen on bone scintigraphy. Conversely, in the same population, the absence of uptake on bone scan excludes ATTR cardiac amyloidosis. In the presence of monoclonal protein and grade 2 or 3 uptake on bone scintigraphy, further investigations are required to characterize the underlying disease. Although monoclonal proteins are relatively prevalent in the elderly investigated for cardiac amyloidosis, using the proposed non-invasive investigation algorithm, biopsy can be avoided in over 80% of patients in patients with grade 2–3 uptake [30••].

Conclusion

The prevalence of cardiac amyloidosis is likely significantly underestimated, and a significant proportion of elderly patients presenting cardiac symptoms unrelated to coronary artery disease might in fact suffer from cardiac amyloidosis.

Presently, the role of molecular imaging in cardiac amyloidosis relies mostly on bone scintigraphy. The ability of bone scintigraphy to diagnose ATTR cardiac amyloidosis with particularly high sensitivity and specificity, to differentiate ATTR from AL cardiac amyloidosis, to enable early diagnosis, and to provide prognostic information makes this modality valuable in the work-up of patients with suspected cardiac amyloidosis. With increased recognition of cardiac amyloidosis and arrival of new targeted therapies, the utilization of molecular imaging in cardiac amyloidosis is expected to expand. Evidence supporting the role of other molecular imaging tracers such as amyloid imaging and sympathetic innervation imaging is growing, and molecular imaging will likely play a greater role in the near future.

Compliance with Ethical Standards

Conflict of Interest Matthieu Pelletier-Galarneau, Gad Abikhzer, Genevieve Giraldeau, and Francois Harel declare that they have no conflict of interest.

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

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- •• Of major importance

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