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Imaging in systemic amyloidosis

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Background: Diagnosis of systemic amyloidosis remains challenging. Histology, the current gold standard for diagnosis of amyloidosis provides limited information on the extent of the disease and is not useful for monitoring. Non-invasive imaging modalities offer an easy way to evaluate whole-body amyloid burden, accurately identify organ involvement, quantify and monitor disease progression and response to treatment.

Sources of data: A literature search was performed using PubMed on the subjects of 'amyloid imaging', 'SAP scintigraphy', 'imaging in cardiac amyloidosis', 'cardiac MRI', 'PET and amyloidosis' and 'nuclear imaging in amyloidosis'.

Areas of agreement: ^{123}I-SAP scintigraphy is the best and the only modality in routine clinical use for assessing the extent and distribution of visceral amyloid deposition in all types of amyloidosis. Echocardiography remains the most important tool for assessing cardiac amyloidosis but cardiac magnetic resonance imaging is becoming increasingly valuable. Bone-seeking tracers like ^{99m}Tc-DPD and pyrophosphate are beginning to have a role in imaging transthyretin cardiac amyloidosis.

Limitations: Specificity of each of the imaging modalities limits the utility of any one imaging method for all types of amyloidosis for all organs.

Growing points and further research: ^{99m}Tc-DPD has a high sensitivity and specificity to cardiac transthyretin amyloid deposits and its role in early diagnosis of this condition is under investigation. Further studies are needed with ^{123}I-mIBG to assess its utility in patients with early cardiac autonomic neuropathy. Positron emission tomography with tracers used for Alzheimer's disease imaging is an area of increasing interest in systemic amyloid imaging.

Keywords: imaging/systemic amyloidosis/SAP/DPD/PET/CMR

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Introduction

Amyloidoses are a heterogeneous group of diseases resulting from unstable circulating proteins, which give rise to extracellular deposition of insoluble amyloid fibrils leading to progressive organ dysfunction. Amyloid deposition can occur in any organ: heart, lungs, liver, kidneys, skin, bones, peripheral or autonomic nerves are commonly involved. There are currently over 30 different proteins known to cause amyloidosis.[1] Amyloidosis can be classified in several ways: hereditary or acquired, by means of the precursor proteins and the distribution of amyloid deposits (localized or systemic). Light-chain amyloidosis (AL) is the most common form of systemic amyloidosis and other forms are as follows: secondary (AA type), senile systemic or wild-type transthyretin (ATTR-wt), familial (hereditary type) and haemodialysis-related (beta2-microglobin) amyloidosis. Senile systemic amyloidosis caused by deposition of ATTR-wt mainly in the heart is an increasingly recognized condition and may become the commonest type of systemic amyloidosis in the near future.

Diagnosis is frequently delayed due to the insidious nature of the disease leading to advanced organ dysfunction having occurred by the time a patient presents. Cardiac involvement is the main cause of mortality and morbidity in amyloidosis. Early diagnosis and detection of affected organs would be invaluable. Histological demonstration of amyloid deposition is the gold standard for the diagnosis of amyloidosis. Sampling errors, invasive nature of biopsies and procedure-related high-risk complications are impediments. Moreover, histology cannot provide information on amyloid distribution, extent and disease progression. It is therefore necessary to develop non-invasive imaging modalities to evaluate visceral amyloid load, quantify and monitor disease progression and response to treatment.

Much progress has occurred in the development of non-invasive imaging methods over the last decade. These include positron emission tomography (PET) tracers, cardiac magnetic resonance imaging (CMR) and novel methods of cardiac assessments by echocardiography. We review some of the established and novel methods of imaging for patients with amyloidosis. Table 1 details the assessment and investigations of a patient with amyloidosis.

Serum amyloid P component scintigraphy

Serum amyloid P (SAP) is a non-fibrillar glycoprotein of the pentraxin family and is found in all types of amyloid deposits. SAP in circulating

Table 1 Assessment of patients and monitoring of patients with amyloidosis.

Confirmation of presence of amyloid	• Biopsy of suspected site if feasible and safe • Fat aspirate or rectal biopsy • SAP scintigraphy, if available
Confirmation of type of amyloid and detecting the underlying disorder	• Typing the amyloid fibrils in the biopsy—immunohistochemistry or laser capture micro-dissection and mass spectrometry • Supported by the following for confirmation: ○ Light-chain amyloid (AL), underlying plasma cell dyscrasia ○ Serum/urine electrophoresis (SPEP) and immunofixation ○ Serum-free light chains ○ Bone marrow examination • Hereditary amyloid—appropriate gene sequencing to detect mutations in proteins known to cause hereditary amyloidosis (fibrinogen alpha chain, transthyretin, lysozyme, apolipoprotien A1, gelsolin) • Secondary AA amyloid—assess underlying inflammatory disorder
Assessment of distribution and degree of organ dysfunction	• Tests of organ function: liver function tests, serum creatinine, eGFR, 24-h proteinuria, serum albumin • Systemic amyloid burden—^{123}I SAP scintigraphy if available—assess amyloid deposition in liver, spleen, kidneys, adrenals, localised soft tissue deposits and bones • Cardiac amyloid: ○ ECG and 24-h Holter monitor if indicated ○ Echocardiogram ○ CMR with gadolinium contrast (EQ-CMR if available) ○ Suspected transthyretin amyloidosis: ^{99m}TcDPD or PYP scan • Cardiac disease stage—NT-proBNP and troponin T/I • Neuropathy ○ Nerve conduction studies ○ Autonomic function studies
Disease progression and response to treatment monitoring	• Individualized as per assessment of distribution and extent of organ involvement by appropriate tests of organ function • AL amyloid: monitoring the monoclonal protein by serum-free light chains or SPEP • AA amyloid monitoring ongoing inflammatory activity by serial CRP or SAA levels. • Appropriate imaging—^{123}I SAP scintigraphy, echocardiography, CMR or ^{99m}TcDPD scintigraphy

plasma is in a constant equilibrium with SAP in the amyloid deposits. Hawkins *et al*.[2,3] developed the concept of using radiolabelled SAP as a tracer imaging for amyloid deposits. Injected radiolabelled SAP localizes rapidly and specifically to amyloid deposits in proportion to the amount of amyloid deposited. SAP labelled with ^{123}Iodine (^{123}I-SAP) is used in routine clinical practice at the UK national amyloidosis centre for *in vivo* imaging of amyloid deposits. SAP scintigraphy was reported to have 90% sensitivity in AA and AL amyloidosis.[4] The tracer does not accumulate in healthy subjects or in patients with non-amyloid diseases and is rapidly catabolized and the label excreted.[5] A number of studies over the years have confirmed that this is a safe and non-invasive technique providing information on the presence, distribution and extent of amyloid deposits of all types and its utility in monitoring of treatment responses.[6] The patients are generally scanned 24 h after injection of the radiotracer to allow time for equilibration and clearance from blood pool. The dose of radiation is small and comparable to a plain X-ray of the lumbar spine.[3]

The ^{123}I-SAP images are analysed in a semi-quantitative way by comparing each organ to the normal blood-pool distribution. SAP scintigraphy enables identification of visceral amyloid deposits,[3] including those in the liver, kidneys, spleen, adrenal glands and bones. It can identify amyloid deposits in organs that have not been suspected clinically (e.g. liver or adrenals) and in anatomic sites that are not available for biopsy (e.g. spleen). SAP scintigraphy will identify liver involvement in over 30% of cases not detected by standard tests of liver function or size (Fig. 1).[7] The patterns of organ involvement on SAP scan may give clues to, but is not diagnostic of, the amyloid fibril type since there is substantial overlap in the patterns of organ involvement. Significant uptake in bones is a feature almost unique to AL amyloidosis.[3]

Scintigraphic estimation of whole-body amyloid load can provide information on prognosis. Patients with AL amyloidosis and a large amyloid load have a higher risk of complications associated with chemotherapy, peripheral blood stem cell or solid organ transplantation.[8,9] Measurements of whole-body amyloid load also correlates with prognosis in AA amyloidosis.[7] It was by use of SAP scintigraphy that regression of amyloid deposits was conclusively demonstrated *in vivo* where it was possible to reduce or eliminate the supply of fibril precursors. Serial SAP scintigraphy is a useful guide to monitor regression/progression of amyloid deposits—identifying the need for further therapy or confirming adequacy of therapy. This is useful in all types of systemic amyloidosis including patients with AA,[10] AL,[11] Ab2M (b2-microglobulin),[12] AFib (fibrinogen A alpha chain)[13] and AApoA1 (apolipoprotein A1)[14] of amyloidosis.

The limitations of ^{123}I-SAP scintigraphy include the cost of ^{123}I, availability of SAP (a purified virally inactivated plasma derived component), inability to image hollow, diffuse or small structures such as gastrointestinal tract,

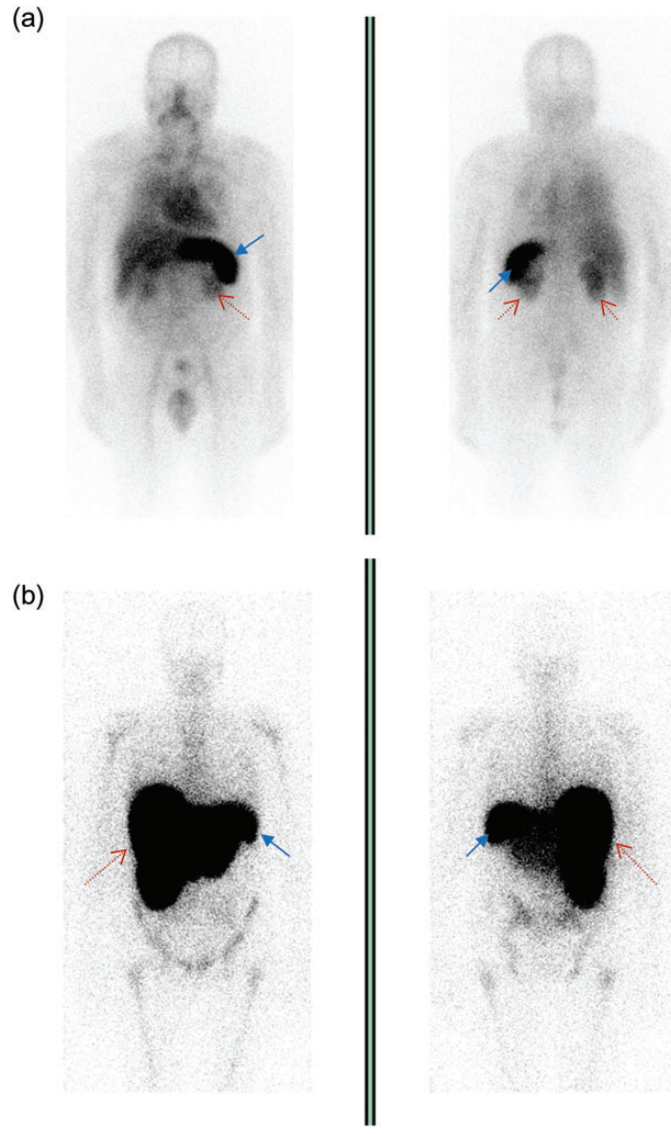

Fig. 1 Whole-body ^{123}I-serum amyloid P component scintigraphy. (**a**) Anterior and posterior whole-body scan in a patient with fibrinogen A alpha chain hereditary amyloidosis. Amyloid deposits are present in the spleen (→) and kidneys (⇢) (seen more clearly on the posterior scan). (**b**) Anterior and posterior whole-body scan in a patient with AL amyloidosis. Amyloid deposits are present in the liver (⇢) and the spleen (→). There is also uptake in the bones which is rarely seen in other types of systemic amyloidosis. The large amyloid deposits in the liver obscure the visualization of kidneys and adrenal glands on planar imaging.

skin or nervous system and most critically, its inability to image the heart. There are many plausible factors that may account for the major limitation of labelled SAP studies in imaging amyloidotic heart muscle, including movement artefact, ventricular blood-pool content and possibly the most

important factor being a lack of a fenestrated endothelium in the myocardium, hindering access of the large 127 kDa SAP molecule to the amyloidotic interstitium within the available timescale of the short half-life of ^{123}I isotope.[4]

Currently, ^{123}I-SAP scintigraphy remains the best and only modality in routine clinical use for assessing the extent and distribution of amyloid deposition in all types of amyloidosis.[3] It is routinely available in the UK National Amyloidosis Centre, University College London (UK) and the University Medical Centre, Groningen (the Netherlands).

Echocardiography

Echocardiography has been used for the diagnosis of cardiac amyloidosis over the last 25 years. The features in patients with advanced cardiac amyloidosis are characteristic (Fig. 2). Echocardiography has diagnostic and prognostic significance in established disease; however, early diagnosis is challenging.[15] Although there are many echocardiographic features in cardiac amyloidosis, none is highly specific in isolation. A combination of several features is usually required and must be interpreted in the context of clinical findings and other investigational methods.

Typical features of cardiac amyloidosis include concentric left ventricular (LV) wall thickening with right ventricular involvement, impaired biventricular long-axis function and thickened valves (particularly in wild-type or variant ATTR amyloid).[16] Other features suggestive of cardiac amyloidosis are increased echogenicity of the myocardium. The so-called 'granular speckling' appearance is not as obvious on later generation echocardiography machines. LV wall thickening together with a low electrocardiogram (ECG) voltage is suggestive of an infiltrative cardiomyopathy and amyloidosis is at the top of the differential diagnosis for patients with such combination. This simple combination is reported to have high sensitivity (72–79%) and specificity (91–100%) for amyloidosis.[17]

An LV ejection fraction is normal or nearly normal until late in disease. Long-axis function is typically lost early despite a preserved LV ejection fraction. Impaired systolic function is a late feature of the disease and carries a poor prognosis. Right ventricular dilatation is associated with more severe cardiac involvement and a median survival of only 4 months.[16] One of the main features is diastolic dysfunction on echocardiography, which may occur before the development of cardiac symptoms.[18] This is one of the most typical features and may be present in all patients with evidence of restrictive pattern on Doppler mitral inflow assessment. Pulsed wave Doppler studies have demonstrated a spectrum of diastolic dysfunction early in cardiac amyloidosis and precede the characteristic restrictive pattern. Longitudinal strain and strain rate analysis may

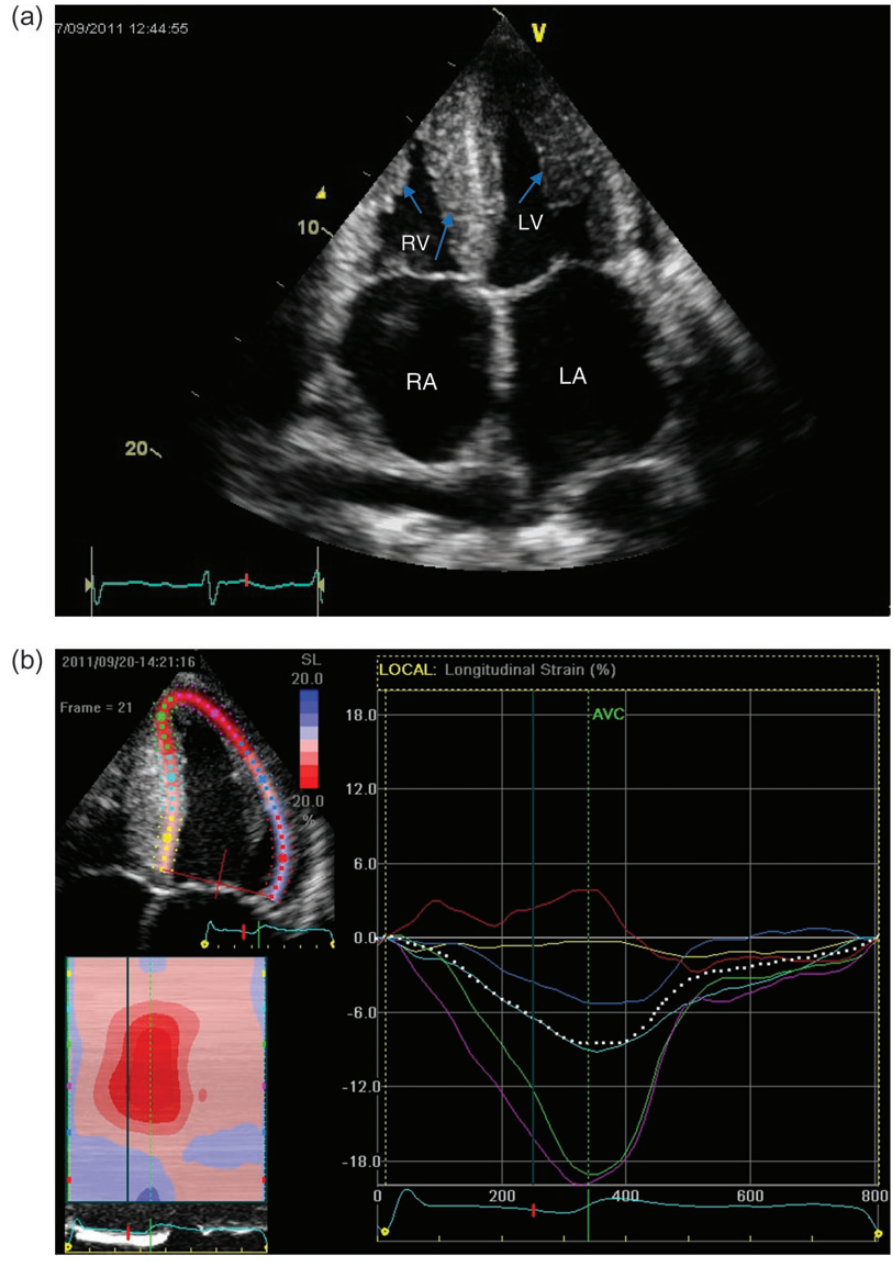

Fig. 2 Echocardiography in cardiac amyloidosis. (**a**) Two-dimensional echocardiography in a patient with advanced cardiac amyloidosis demonstrating the thickening of the interventricular septum, LV free wall as well as the right ventricle (→). There is bi-atrial enlargement giving an 'owl's-eye' appearance to the images. (**b**) Transthoracic echocardiogram with speckle tracking in a patient with cardiac amyloidosis. The LV wall is divided into six segments and the movement of the myocardium is tracked. This demonstrates that the base of the heart is affected to a much greater extent with limited contractile movement (red and yellow lines) compared with the apex (purple and green lines). On mapping, this demonstrates a characteristic 'bulls-eye' appearance (left lower image), which is rare in patients with other hypertrophic cardiomyopathies.

be abnormal in early amyloidosis.[19] Strain and strain rate imaging appear to be more sensitive than tissue Doppler, demonstrating long-axis dysfunction in early cardiac amyloidosis and confirming disproportionate impairment of longitudinal contraction despite apparently preserved fractional shortening (Fig. 2b).[19] LV longitudinal strain in particular may have a role in evaluating prognosis and response to treatment.[20]

Bisphosphonate bone tracers in amyloid imaging

Studies on cardiac amyloidosis imaging using bone-seeking radionuclide tracers were inspired following the observation of random myocardial uptake on routine bone scans during the 1970s and 1980s, which were later confirmed to be cardiac amyloidosis. A number of tracers have been used, including ^{99m}-technetium-labeled pyrophosphate, ^{99m}-technetium-methylene diphosphonate and ^{99m}-technetium-3,3,-diphosphono-1,2- propanodicarboxylic acid (^{99m}Tc-DPD). The exact mechanism of myocardial accumulation of bone-seeking tracers in cardiac amyloidosis remains unclear. A number of studies produced conflicting results with significant variations in diagnostic performance.[21] The use of bone-seeking tracers for amyloidosis was essentially abandoned in the 1990s due to these variable results.

The interest in the use of these tracers has recently been reignited by a report from colleagues in Italy demonstrating a high sensitivity and specificity of ^{99m}Tc-DPD in imaging cardiac transthyretin amyloid deposits. Perugini *et al.*[22] have reported 100% sensitivity and specificity of ^{99m}Tc-DPD in imaging deposits in ATTR variant and ATTR-wt. A number of centres[23] including our own have confirmed this finding (Fig. 3). ^{99m}Tc-DPD is also taken up in cardiac AL amyloidosis but only in half the cases with cardiac involvement and the uptake is generally low grade compared with avid high-grade in ATTR.

^{99m}Tc-DPD scintigraphy appears to be a valuable, accurate and inexpensive technique allowing non-invasive identification of senile systemic amyloidosis (ATTR-wt) related amyloidotic cardiomyopathy in elderly patients with unexplained concentric LV hypertrophy and a non-dilated LV (heart failure with a preserved ejection fraction). The mean LV wall thickness correlated with the cardiac tracer retention.[24] Rapezzi *et al.* demonstrated that ^{99m}Tc-DPD uptake was seen across a wide spectrum of cardiac involvement ranging from overt cardiomyopathy to cases with normal echocardiograms and normal or near-normal ECGs raising the intriguing possibility of using ^{99m}Tc-DPD as a screening test for senile cardiac amyloidosis. The true incidence of clinically significant myocardial deposits of ATTR-wt remains unknown. There may be a substantial burden of undiagnosed ATTR-wt amyloidosis in the elderly given the very high incidence of ATTR-wt deposits reported in autopsy studies

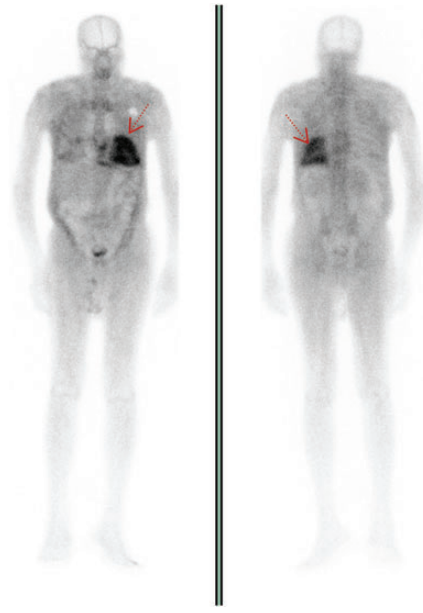

Fig. 3 ^{99m}TcDPD scintigraphy, in cardiac amyloidosis, in a patient with ATTR-wt cardiac amyloidosis. There is avid cardiac uptake with marked attenuation of the bone uptake (⇢).

(~25% of over 80 year olds on autopsy).[25] Early identification of senile cardiac amyloidosis is becoming relevant from a clinical perspective as there are novel drugs in development or early phase clinical trials which stabilize the transthyretin molecule or interfere with its production raising the exciting possibility of treating the disease for the first time.[26]

In summary, ^{99m}TcDPD scintigraphy is a useful and sensitive method of early identification of cardiac ATTR amyloid deposits, possibly at a stage when echocardiography, serum cardiac biomarkers and perhaps even CMR remain normal.[22] Although the sensitivity of ^{99m}TcDPD scintigraphy opens an immense potential for screening and diagnosis of cardiac ATTR, it is not a diagnostic test in isolation since uptake of ^{99m}Tc-DPD in the heart occurs in about half of the patients with cardiac AL amyloidosis. ^{99m}TcDPD, therefore, has to be interpreted in context with full assessment of a patient with amyloidosis and integrated with CMR, echocardiography, SAP scintigraphy as well biochemical assessment to increase its specificity and therefore its clinical usefulness.

^{99m}Technetium-labeled-aprotinin

^{99m}Technetium-labelled aprotinin imaging (^{99m}Tc-aprotinin) was developed with the knowledge that aprotinin, a low-molecular-weight

polypeptide protease inhibitor, is found in amyloid deposits of various organs including the heart. Its use is limited to imaging extra-abdominal organs as ^{99m}Tc-aprotinin is normally accumulated in the liver, spleen and kidneys making it appropriate for mainly cardiac amyloid imaging.[27] Several reports since 1995 have studied its use in patients with cardiac amyloidosis and found that they demonstrated mild–moderate accumulation of the tracer. But this was only 2-fold higher than background activity which was felt to be a limiting factor in clinical practice.[28] Unfortunately, aprotinin was derived from bovine lung tissue and the risk of bovine spongiform encephalopathy has limited the use of bovine products. This modality of imaging has been superseded by use of ^{99m}TcDPD scintigraphy and CMR.

^{123}Iodine-meta-iodobenzylguanidine

Meta-iodobenzylguanidine (mIBG) is a sympathetic neuronal tracer and an analogue of the false neurotransmitter guanetidine, and therefore of norepinephrine. It is used for the evaluation of myocardial autonomic innervation. It is retained in vesicles of sympathetic nerve endings. The washout is proportional to the normal sympathetic tone and the loss of sympathetic nerve endings leads to early washout. Its uptake in the myocardium is defined by the ratio of uptake in the heart to that in the mediastinum (heart to mediastinum ratio—HMR) on early and late images. Cardiac mIBG uptake has been shown to predict clinical outcomes of patients with heart failure, especially in diabetes and can detect diabetic cardiac autonomic neuropathy.[29]

Small studies have reported significantly reduced cardiac ^{123}I-mIBG uptake (low HMR and high washout rates) in patients with hereditary TTR amyloidosis. Cardiac amyloidosis in patients with familial ATTR amyloidosis is reported to have generally a preserved LV systolic function with congestive cardiac failure being a late feature of the disease.[30] They also have a higher incidence of cardiac conduction disturbances than AL patients.[31] It has been hypothesized that autonomic neuropathy may account for some of these features in addition to direct infiltration by amyloid deposits. The abnormalities on ^{123}I-mIBG provide indirect evidence of cardiac sympathetic autonomic neuropathy due to amyloidosis. It is reported that this technique may detect cardiac amyloid neuropathy in ATTR patients before the manifestation of echocardiographic features.[32] Further studies are needed with ^{123}I-mIBG to assess its utility in patients with ATTR as a complementary technique to ^{99m}TcDPD scintigraphy and also for detecting autonomic neuropathy in patients with AL amyloidosis. Since autonomic neuropathy causes significant morbidity and may contribute to mortality in a patient with amyloidosis, the

prognostic importance of early detection of autonomic neuropathy is likely to be significant but remains to be established.

Cardiac magnetic resonance imaging

CMR imaging has been found to have an important role in the diagnosis and prognosis of cardiac amyloidosis.[33] Gadolinium is used as a contrast agent to characterize cardiomyopathies including cardiac amyloidosis. Gadolinium is distributed in the extracellular space which is hugely expanded in the myocardium due to amyloid fibril deposition. This leads to abnormal kinetics of gadolinium and can be exploited for diagnostic use in amyloidosis (Fig. 4). Global and subendocardial late gadolinium

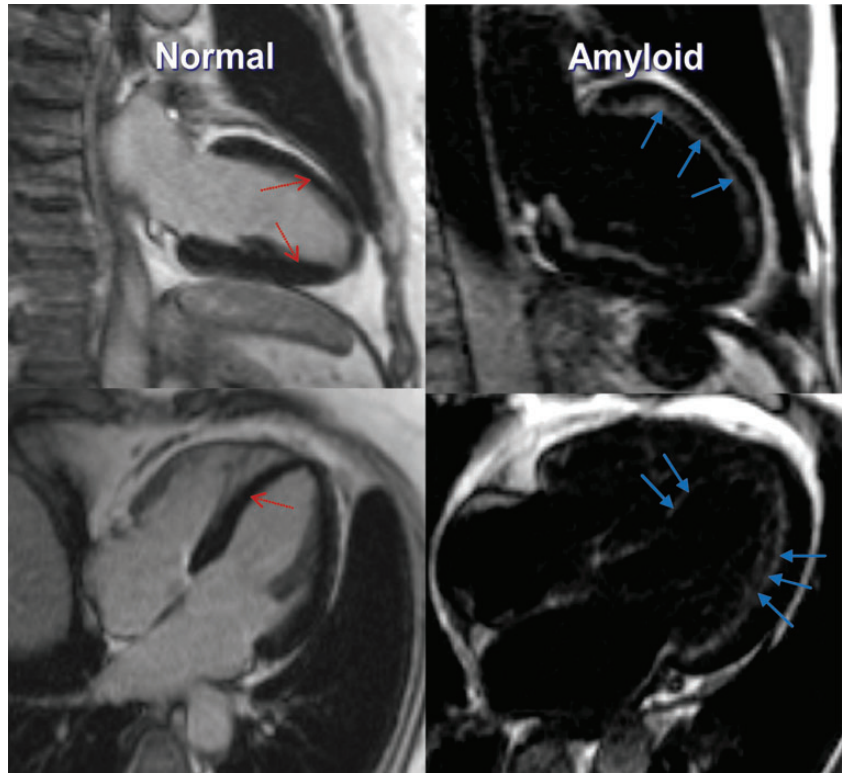

Fig. 4 Cardiac magnetic resonance images with late gadolinium enhancement in long axis (vertical) (top) and short axis (horizontal planes) (bottom) in a normal subject and a patient with cardiac AL amyloidosis. In a normal subject (left), signal from the myocardium is nulled and it appears black (⇢) without areas of white contrast that would indicate myocardial fibrosis or amyloidosis. In a patient with cardiac AL amyloidosis (right) using a similar sequence the expanded myocardial extracellular volume leads to nulling of both myocardium, blood pool and diffuse subendocardial enhancements (→)—which is characteristic of cardiac amyloid infiltration (images, courtesy of Dr Marianna Fontana and Dr James Moon, Heart Hospital, UCL, London).

enhancement occurs after gadolinium contrast injection in cardiac amyloidosis and has been correlated with histological evidence of amyloid deposition in the heart.[33] These features are seen in up to 80% of biopsy proven amyloid cases and are reported to correlate with prognosis.[33] CMR can also accurately define systolic function as well as reveal better morphological information on cardiac amyloidosis than echocardiography. CMR is especially useful when echocardiography is unhelpful in the presence of other 'hypertrophic' conditions of the heart such as severe hypertensive hypertrophy, hypertrophic cardiomyopathy, uremic cardiomyopathy and storage disorders. Although CMR now has a defined role in the diagnosis of cardiac amyloidosis, the utility of CMR in serial monitoring remains to be established.

New techniques are being developed to improve utility of CMR in cardiac amyloidosis. Equilibrium contrast CMR (EQ-CMR) is a quantitative technique where an infusion of gadolinium creates equilibrium between the amount of gadolinium in the myocardial interstitium and the plasma, allowing a numerical estimation of the myocardial interstitial volume. Interstitial space within the heart is expanded by fibrosis in many types of cardiac disease, however, EQ-CMR has recently demonstrated a higher extracellular myocardial volume in cardiac amyloidosis than in any other cardiac disease.[34] EQ-CMR may detect amyloid infiltration earlier than conventional MRI and can potentially provide a direct measure of the amyloid burden with scope for use in early diagnosis and disease monitoring.[34]

Computerized tomography

Standard computerized tomography (CT) scanning is useful to detect and monitor organomegaly in systemic amyloidosis but CT features are not specific to amyloidosis. CT scanning is important in patients with lymph node involvement (either isolated or as a part of systemic amyloidosis) to document extent of disease and response to treatment. CT is the imaging method of choice in amyloidosis localized to the respiratory tract. CT can provide quantitative assessment of airway narrowing in tracheobronchial amyloidosis, at presentation and follow-up, and establish disease extent by identification of any extraluminal manifestations. High-resolution CT is useful in diffuse pulmonary amyloidosis to identify and track the disease course in combination with serial pulmonary function tests

Positron emission tomographic in amyloid imaging

Positron emission tomography (PET) has a better resolution than planar whole-body imaging with standard radionuclides and has the advantage

of being quantitative. The role of PET radiopharmaceuticals in imaging systemic amyloidosis is limited. Much progress has been made in the non-invasive imaging of amyloid beta (β) plaques in Alzheimer's disease using PET. The PET tracers used for amyloid β imaging are based on the core structure of thioflavin-T, which is used for tissue staining of amyloid. Different derivatives of thioflavin-T have undergone intense studies including their suitability for brain imaging in animals and humans. The carbon-11-labeled Pittsburgh Compound-B (^{11}C-PiB) has been widely studied and was the first PET tracer used to selectively visualize amyloid β in living Alzheimer's disease patients.[35] Recently, florbetapir has been licensed by Food and Drug Administration, USA, for cerebral amyloid imaging in Alzheimer's disease. A case report suggested the detection of cardiac amyloid deposits in a patient with ATTR amyloidosis using ^{11}C-BF-227 (a PiB like compound) PET imaging.[36] Antoni *et al.*[37] recently reported myocardial ^{11}C-PiB uptake in 15 patients with cardiac amyloidosis but not in 5 healthy volunteers providing first evidence of using thioflavin-based PET tracers in systemic (cardiac) amyloid imaging. However, the study reported variable binding and further studies are in progress to assess the utility of such tracers for systemic amyloid imaging.

Fluorodeoxyglucose (^{18}F-FDG) is a standardized tracer in PET imaging and is widely available with excellent data on quantification. Standard ^{18}F-FDG-PET has been used to detect metabolic activity in amyloidosis. Amyloid deposits are metabolically inert but the infiltrating cells involved in amyloid formation in localized AL or macrophages involved in amyloid regression in both localized and systemic AL amyloidosis may have enough metabolic activity to be detected by ^{18}F-FDG . Case reports and small studies suggest that patients with localized AL amyloidosis show ^{18}F-FDG uptake at the sites of localized deposits allowing such deposits to be imaged for the first time and may provide a method for monitoring.[38] Another approach has been to use monoclonal antibodies (mAbs) to amyloid fibrils labelled with PET tracers. A phase I study using murine IgG1 mAb 11-1F4 labelled with ^{124}Iodine was studied in 18 patients with AL amyloidosis. Fifty per cent of the patients showed uptake in liver, lymph nodes, bone marrow, intestine or spleen (but not kidneys or heart). This is undergoing further studies.[39]

Conclusion

Early diagnosis of amyloidosis and identification of the affected organs have important clinical, therapeutic and prognostic implications. Tissue biopsy is the gold standard in diagnosis of amyloidosis at present. However, this has limitations and does not identify all affected organs—there is a need for non-invasive methods for screening, diagnosing and

monitoring treatment response in amyloidosis. There have been many developments of such non-invasive imaging modalities and our understanding as well as the ability of accurately imaging amyloid deposits has improved over the last decade. However, the marked disease variability in amyloidosis, the many types of amyloid fibril proteins and organ involvement represent a challenge. Any single test is not sufficient to make a diagnosis. A constellation of blood tests, ECG, echocardiogram, CMR, ^{99m}TcDPD, ^{123}I-SAP scintigraphy and tissue biopsy are currently necessary to make a reliable diagnosis and monitor disease progression. The very high sensitivity of ^{99m}TcDPD in imaging cardiac ATTR raises possibility of developing this as screening test for patients with senile transthyretin amyloidosis.

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