Cardiac Magnetic Resonance derived Extracellular Volume Mapping for the quantification of hepatic and splenic amyloid

Short title: Quantifying extra-cardiac amyloid with ECV mapping

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Abstract

Background. Systemic amyloidosis is characterised by amyloid deposition that can involve virtually any organ. Splenic and or hepatic amyloidosis occurs in certain types, in some patients but not others, and may influence prognosis and treatment. Serum amyloid P component (SAP) scintigraphy is uniquely able to identify and quantify amyloid in the liver and spleen, thus informing clinical management, but it is only available in only two centres globally. The aims of this study were to examine the potential for extracellular volume (ECV) mapping performed during routine cardiac magnetic resonance (CMR) to: (1) detect amyloid in the liver and spleen; and (2) estimate amyloid load in these sites using SAP scintigraphy as the reference standard.

Methods. 533 patients referred to the National Amyloidosis Centre, London, between 2015 and 2017 with suspected systemic amyloidosis who underwent SAP scintigraphy and CMR with T1 mapping were studied.

Results. The diagnostic performance of ECV to detect splenic and hepatic amyloidosis was high for both organs (Liver: AUC-0.917, 95%-CI 0.880-0.954, liver ECV cut-off=0.395, Sensitivity 90.7%, Specificity 77.7%, $p<0.001$; Spleen: AUC-0.944, 95%-CI 0.925-0.964, spleen ECV cut-off=0.385, Sensitivity 93.6%, Specificity 87.5%, $p<0.001$). There was good correlation between liver and spleen ECV and amyloid load assessed by SAP scintigraphy ($r=0.504$, $p<0.001$; $r=0.693$, $p<0.001$, respectively). There was high interobserver agreement for both the liver and spleen (ECV liver ICC 0.991, 95%-CI 0.984-0.995, $p<0.001$; ECV spleen ICC 0.995, 95%-CI 0.991-0.997, $p<0.001$) with little bias across a wide range of ECV values

Conclusions. Our study demonstrates that ECV measurements obtained during routine cardiacMR scans in patients with suspected amyloidosis can identify and measure the magnitude of amyloid infiltration in the liver and spleen, providing important clues to amyloid type and offering a non-invasive measure of visceral amyloid burden that can help guide and track treatment.

Keywords: extra-cardiac, amyloidosis, SAP, extracellular volume, mapping, magnetic resonance

Condensed abstract

This large study of patients referred with suspected amyloidosis demonstrates the very high diagnostic performance of ECV mapping performed during routine cardiac MR studies to identify and assess the severity of hepatic and splenic amyloidosis. This additional information is freely and immediately available, providing important pointers on amyloid type, prognosis and clinical management options as well as a means to specifically track the response to treatment of amyloid load in these organs. These findings have the potential to immediately impact clinical practice.

Abbreviations List:

AL: light chain

SAP: serum amyloid P component

MR: magnetic resonance

LGE: late gadolinium enhancement

ECV: extracellular volume

NAC: National Amyloidosis Centre

ROI: region of interest

AUC: area under the curve

ROC: receiver operating characteristic

CI: confidence interval

ICC: Intraclass correlation coefficient

ATTR: Transthyretin

ApoAI: apoliprotein AI

LECT 2: leukocyte chemotactic factor 2

Introduction

The systemic amyloidoses are characterized by deposition of misfolded, aggregated fibrillary proteins, which occupy and expand the extracellular space damaging the structure and function of vital organs. The most serious and commonly diagnosed type is systemic light chain (AL) amyloidosis.[1] AL amyloidosis is caused by the deposition of amyloid fibrils derived from monoclonal free immunoglobulin light chains and is a multi-system disorder that frequently involves the kidneys, liver, spleen, soft tissues, nervous system and heart.[2]Treatment of AL amyloidosis comprises chemotherapy directed towards the underlying clone of plasma cells in the bone marrow along with supportive care of failing organs; one or several organ systems may be affected, with multi-organ involvement and a large liver amyloid load being adverse predictors of patient prognosis[2]. However, it has lately become apparent that wild-type (non-hereditary) transthyretin (ATTR) amyloidosis is most prevalent cause of cardiac amyloidosis, but in contrast to AL type it does not involve visceral organs. Rare hereditary forms of ATTR amyloidosis such as the V30M genetic variant can very occasionally involve the spleen.[3]

The utility and value of various imaging modalities within the field of amyloidosis have evolved and expanded over recent years, substantially improving clinical assessment of patients, not only in terms of diagnosis and characterisation of organ involvement but also in terms of evaluating response to existing and novel treatments. The development of serum amyloid P component (SAP) scintigraphy in 1987 represented a major advance in the management of systemic amyloidosis by enabling the specific demonstration of amyloid deposits within solid visceral organs by exploiting the specific molecular affinity of SAP, a normal plasma protein, to all types of amyloid deposit.[4] SAP scintigraphy involves gamma camera image acquisition following the administration of ^{123}I-labeled purified human SAP and is highly sensitive for identifying amyloid deposits in the liver and spleen, which are common in AL amyloidosis but do not occur in wild-type ATTR.[3] This was validated against histologically proven amyloidosis. [4] SAP scintigraphy also enables visceral amyloid deposits to be quantified, with serial studies having uniquely yielded objective evidence for regression of amyloid following treatments that suppress production of amyloid fibril precursor proteins [5-7] . Limitations of SAP scintigraphy include its inability to image amyloid in the moving hollow heart and necessity for

ionising radiation, but its major drawback is that it is only available in two centres throughout the world. There is no other validated non-biopsy method for diagnosing or quantifying liver or spleen amyloidosis, and even biopsies cannot provide a meaningful estimate of whole organ amyloid load.

A more recent and now widely available imaging technology has been cardiac magnetic resonance imaging (MR), which with late gadolinium enhancement (LGE) techniques has become the cornerstone of non-invasive diagnostic pathways for the diagnosis of cardiac amyloidosis.[8-10] Cardiac MR with measurement of the myocardial extracellular volume (ECV) allows the continuum of cardiac amyloid infiltration to be measured.[11-14] In a small pilot study using cardiac MR technology, we measured the ECV of extra-cardiac organs, demonstrating good correlation between amyloid load as detected by SAP scintigraphy with ECV measurements from MR[15]

The objectives of the present study were to assess the potential for ECV mapping, performed during routine cardiac MR scans to (1) detect amyloid in the liver and spleen, and (2) to measure severity of amyloid accumulation in these organs as assessed against the current reference standard SAP scintigraphy.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Population

The study population comprised 533 patients referred to the National Amyloidosis Centre (NAC), Royal Free Hospital, London, United Kingdom between 2015 and 2017 with suspected systemic amyloidosis. All patients underwent six-minute walk test, echocardiography, SAP scintigraphy and cardiac MR with T1 mapping and ECV quantification within a 3-day integrated visit. Patients were managed in accordance with the Declaration of Helsinki and provided written informed consent with approval from the Royal Free Hospital ethics committee (ref: 06/Q0501/42).

Cardiac MR

All participants underwent cardiac MR on a 1.5-T clinical scanner (Magnetom Aera, Siemens Healthcare, Erlangen, Germany). A standard volumetric study was performed followed by a native T1

mapping 4-chamber long-axis image and three short axis slices using a modified look-locker inversion recovery sequence after regional shimming. After a bolus of contrast (0.1 mmol/kg of gadoterate meglumine, Dotarem, Guerbet S.A., France) and standard LGE imaging, T1 mapping was repeated 15 minutes post-contrast using the same slice locations with the modified look-locker inversion recovery sequence, to produce automated inline ECV mapping reconstruction. T1-mapping protocols used 5s(3s)3s and 4s(1s)3s(1s)2s sampling, pre- and post-contrast, respectively.[16] Image analysis was performed offline using Osirix MD 9.0 (Bernex, Switzerland).For ECV measurement, a single region of interest (ROI) was drawn in the liver and spleen on left ventricular short axis ECV maps (analysis performed by MB and MF). The ECV error map was used to confirm that the ROI was drawn in areas with lowest error (Figures 1 and 2). Non-parenchymal anatomic structures were carefully excluded. Data pertaining to a specific organ was excluded if the organ was not imaged or imaged incompletely affecting reliability of ROI measurement. Inter-observer reproducibility was performed in fifty patients by 2 blinded observers (MF and MB).

SAP scintigraphy protocol

As part of the routine assessment at the NAC, all patients since 1990 have undergone SAP scintigraphy which is the sole reference standard for assessment of amyloid burden in the spleen and liver. Anterior and posterior whole-body images were acquired following administration of ^{123}I-SAP using a General Electric Infinia Hawkeye or Discovery 670 gamma camera (GE, Milwaukee, Wis) with extended low-energy general-purpose (ELEGP) collimators. A single physician (P.N.H) with more than 30 years of experience of over 30,000 studies, scored liver and splenic amyloid burden by visual assessment into four categories (no visceral organ uptake on SAP scintigraphy, small, moderate and large amyloid loads respectively). [4, 7]

Statistical methods

All continuous variables were tested for normal distribution (Shapiro-Wilk test). Baseline characteristics are expressed as mean (standard deviation) when normally distributed and median (interquartile interval) when non-normally distributed. Spearman's rank correlation coefficient was

calculated between liver and spleen SAP scores and corresponding ECV measurements. The diagnosis endpoint was defined as the presence of moderate or large amyloid load on SAP scintigraphy. Discrimination, distinguishing between patients who do and do not experience the endpoint, was evaluated by determining the area (AUC or *c*-statistic) under the receiver operating characteristic (ROC) curve. The optimal cut off value was defined as the point with the highest sum of sensitivity and specificity and was calculated using the Youden and Liu methods. Area under the curve (AUC) with its associated confidence interval (CI), predictive probabilities, sensitivity and specificity were calculated. Inter-observer variability was assessed by calculating the intraclass correlation coefficient (ICC) with 95% confidence intervals (CI) and Bland Altman analysis (as expressed as bias +/- 2 standard deviations for limit of agreement). A probability value of <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics Version 25 (IBM, Somers, New York).

Results

Five hundred and thirty-three patients with ECV Mapping and SAP scintigraphy were retrospectively analysed. Of the 533 patients in the study population, the median age was 69 (IQR 59 to 76), the mean BMI was 27.28 (SD 4.93) with 347 (65%) males and 186 females (35%). The final diagnosis was systemic AL amyloidosis in 250 patients (46.9%), transthyretin (ATTR) amyloidosis in 111 patients (20.8%) (91 ATTR wild type, 20 ATTR hereditary amyloidosis), other rare types of systemic amyloidosis in 2 patients (1 apolipoprotein AI (ApoAI), 1 leukocyte chemotactic factor 2 (LECT 2)), localized amyloidosis in 43 (8.1%) (31 with localised AL, 3 with localised ATTR, 9 unconfirmed) and no systemic amyloidosis in 127 patients (23.8%). (Figure 3).

Of the 111 patients with a final diagnosis of ATTR amyloidosis, 83% (92/111) had a biopsy, of whom 36% (33/92) had a positive result. Of the 250 patients with AL amyloidosis, (241/250) 96% had a tissue biopsy, of whom 91% (220/241) had a positive result.

SAP scintigraphy. 385 out of 533 (72.2%) patients had no visceral organ uptake on SAP scintigraphy. Sixty-seven patients (12.6%) had both liver and spleen involvement, 4 patients had only liver involvement (0.75%) and 77 (14.4%) patients had only spleen involvement. (Figure 4) Of the patients

with isolated spleen involvement, 1 patient had ApoA1 amyloidosis and 1 had LECT 2 amyloidosis. All remaining patients with spleen or liver involvement had AL amyloidosis. Among patients with ATTR amyloidosis, none had extracardiac visceral involvement. In patients with any liver involvement, 27 (38%) had small amyloid load, 18 (25.3%) had moderate amyloid load and 26 (36.6%) had large amyloid load. In patients with any spleen involvement, 63 (43.4%) had small amyloid load, 62 (43.1%) had moderate amyloid load, and 19 (13.2%) had large amyloid load.

Spleen and Liver ECV mapping

Extra-cardiac ECV measurement of the liver and spleen was possible in 493 (92.5%) patients. The liver in 19 patients (3.6 %) and spleen in 24 patients (4.5%) could not be measured due to absent or incomplete imaging affecting reliable ROI measurement. There was good correlation between liver ECV and SAP amyloid burden in the liver as assessed by SAP scintigraphy ($r= 0.504$, $p<0.001$) and between spleen ECV and amyloid burden in the spleen ($r= 0.693$, $p<0.001$) (Figure 5) in patients with systemic AL amyloidosis.

Diagnostic Accuracy

The diagnostic performance of ECV to detect any degree of amyloid infiltration (mild, moderate or large) of liver and spleen amyloid loading was as follows: Liver AUC 0.833, 95% CI 0.782-0.884, liver ECV cut-off = 0.395, Sensitivity 74.3%, Specificity 79.3% $p<0.001$; Spleen AUC 0.898, 95% CI 0.864-0.931, spleen ECV cut-off = 0.355, Sensitivity 83.9%, Specificity 82.8%, $p<0.001$. (Figure 6). The diagnostic performance of ECV to detect clinically significant liver amyloid loading (moderate and large amyloid load) was high (AUC 0.917, 95% CI 0.880-0.954, liver ECV cut-off = 0.395, Sensitivity 90.7%, Specificity 77.7%, $p<0.001$), and similarly the diagnostic performance of ECV to detect clinically significant splenic amyloid loading (moderate and large amyloid load) was high (AUC 0.944, 95% CI 0.925-0.964, spleen ECV cut-off = 0.385, Sensitivity 93.6%, Specificity 87.5%, $p<0.001$). (Figure 6). This accuracy to detect clinically significant (moderate and large amyloid loading) persisted in the subgroup of systemic AL amyloidosis to identify patients with moderate and large liver amyloid load (AUC 0.891, 95% CI 0.841-0.942, liver ECV cut-off = 0.435, Sensitivity 79.1%, Specificity

82.4%, p<0.001) and to identify patients with moderate and large spleen amyloid load (AUC 0.882, 95% CI 0.839-0.924, spleen ECV cut-off = 0.385, Sensitivity 93.5%, Specificity 75.5%, p<0.001). For inter-observer reproducibility, liver and spleen ECV measurement was carried out by two blinded observers in 50 patients (MF and MB). There was high interobserver agreement for both the liver and the spleen (ECV liver ICC 0.991, 95% CI 0.984-0.995, p<0.001, ECV spleen ICC 0.995, 95% CI 0.991-0.997, p<0.001) with little bias across a wide range of ECV values (Bias ECV liver: -0.002, 95% CI -0.040-0.036; bias ECV spleen 0.000, 95% CI -0.028-0.028). (Figure 7).

Conclusions and discussion

Our study of a large cohort of patients with systemic amyloidosis demonstrates for the first time that liver and spleen ECV mapping obtained during the course of a routine clinical cardiac MR study can identify the presence and measure the magnitude of amyloid infiltration in the liver and spleen. This additional clinical information, available immediately and readily, has potential not only to support the type of amyloid under investigation, since hepatic and splenic amyloid is frequent in AL but does not occur in the prevalent wild-type ATTR type, but also to inform clinical management strategies and to serially track amyloid load and response to therapies in these non-cardiac sites.

Amyloidosis is a systemic disease in which different organs are involved in different types of the disease, but organ involvement also differs greatly among individuals with particular types, most notably AL amyloidosis. Although cardiac involvement is usually the main driver of prognosis in AL and ATTR amyloidosis, by far the two most common types, the ability to identify and serially measure visceral amyloid load has not generally been possible. Standard cross-sectional imaging is widely used to ascertain enlargement of an amyloidotic organ but is not at all specific. ^{123}I-SAP scintigraphy is very sensitive and specific for evaluating amyloid in large solid organs[6] and is considered the current reference standard and the only clinically validated method to assess presence and degree of amyloid infiltration in the spleen and liver. Organ uptake of injected radiolabelled SAP correlates with the amount of amyloid[4], mirroring the endogenous biodistribution of this normal plasma protein, and SAP scans are diagnostic of amyloid in all patients with AA and AL amyloidosis in whom there is clinically significant involvement of the liver or spleen [3]. At our centre and at the University of Groningen, ^{123}I-

SAP scintigraphy has been used routinely in the assessment of patients with suspected or proven amyloidosis and for serially monitoring visceral amyloid load for over 30 years.[17] However, the technical complexity of this procedure, high cost and lack of a commercial supply of pure clinical grade SAP protein has limited its availability to just two academic centres internationally. Therefore, there is no measure of visceral organ infiltration to inform clinical care or to follow in clinical trials in the vast majority of amyloidosis patients globally.

Since myocardial involvement is the main recognised cause of morbidity and mortality in most patients with amyloidosis, there has been substantial interest in cardiac imaging. Cardiac MRI with ECV mapping is emerging as the reference standard to visualize and quantify the continuum of cardiac amyloid deposition.[8, 12, 13] A few years ago, we performed a small pilot study that explored the potential role of ECV mapping in assessing the degree of amyloid infiltration within the liver and the spleen, showing good correlation between ECV and amyloid load ascertained by SAP scintigraphy, demonstrating the proof of concept that measurement of extra-cardiac ECV is technically feasible, with potential to track amyloid infiltration.[15] However, these results were based on ECV measurements using infusion gadolinium protocols (infusion for at least 30 min, starting 15 min after bolus administration) and multi-breath hold T1 weighted approaches, making the analysis extremely cumbersome, operator dependent and only accessible to skilled operators, therefore rendering routine implementation of this technique in clinical practice impracticable. Ascertainment of ECV has evolved greatly over time, with bolus-only techniques and ECV maps available on the scanner within a few seconds of post contrast image acquisition.[18] The ECV of the liver and the spleen is visualized immediately and a single ROI per organ delivers the amyloid burden in percentage on the left ventricular short axis stack images without any further acquisition (Figures 1 and 2). This provides not only a true quantitative estimate of amyloid burden in the liver and spleen, but also represents a significant advantage over SAP scintigraphy which is only semi-quantitative, with a degree of overlap between different grades, as opposed to ECV which is a continuous measure. Our results demonstrated a slightly higher diagnostic accuracy with spleen ECV compared to liver ECV, a finding which most likely reflects the susceptibility of the liver to the effects of venous congestion. Despite this, an integrated assessment of both liver and spleen amyloid burden is required to fully characterize the

patient's clinical phenotype. T1 mapping is available on scanners from all manufacturers potentially permitting early, wide adoption with no added cost as the measurement of spleen and liver ECV can be performed with a single ROI on routine images acquired during a CMR scan. We confirm here for the first time that inline ECV maps, acquired during the course of a routine cardiac MR performed to evaluate the possibility and characterisation of cardiac amyloidosis, can readily provide a reliable estimate of amyloid burden in the liver and the spleen.

This is important for several reasons. In terms of diagnosis, spleen and liver ECV measurement would enable the identification of patients with systemic amyloidosis with spleen or liver involvement but no cardiac involvement. In our cohort, 17% of patients fell into this category. The presence of expanded ECV in the liver and/or spleen helps both to identify these patients, but also to corroborate the diagnosis of cardiac involvement when amyloid deposits in the heart are at a very early stage. Evidence of significant expansion of the ECV in the liver and/or spleen also helps to differentiate between AL and ATTR amyloidosis, virtually excluding the latter. Liver infiltration has never been described in ATTR amyloidosis, and the presence of spleen infiltration has only been described in a small proportion of patients with very rare genetic variants, such as V30M. [3] In terms of patient management, knowledge of spleen and liver amyloid infiltration helps in choosing risk-adapted treatment approaches. Splenic and liver infiltration is very common in AL and the extent of amyloid infiltration in these organs has prognostic implications and influences treatments; for example, a large amyloid load in patients with AL amyloidosis is associated with a higher risk of complications related to chemotherapy, peripheral blood stem cell or solid organ transplantation. [19, 20]

Within a clinical cardiac MR protocol, we can thus now assess the cardiac, splenic and hepatic amyloid burden without any further imaging, enabling a much more comprehensive assessment of organ involvement in patients with systemic amyloidosis, improving the diagnosis of patients with systemic amyloidosis, but also identifying liver and/or spleen involvement with those with absence of or very early cardiac involvement. Our findings have an immediate impact on clinical practice since cardiac MR with T1 mapping is now available from all cardiac MR manufacturers and T1 mapping is considered a standard approach in patients with suspected amyloidosis. The findings from this study might also extend beyond clinical utility. The development of therapies to reduce production of

amyloid or enhance its clearance has gained substantial momentum[21] . In a phase 1 clinical trial, after the depletion of circulating plasma SAP with the drug (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC) followed by infusion of IgG anti-SAP antibody targeting SAP in amyloid deposits, it was shown to be possible to effectively track treatment response and regression of amyloid infiltration in the liver by ECV and SAP scintigraphy.[22] Several more molecules are being developed that are able to specifically suppress amyloid production or enhance the clearance of amyloid deposits. The widespread availability to track changes in amyloid load in the spleen and liver overtime in visceral organs would represent a step change in drug development.

This study has several limitations. As ours was a retrospective analysis, in 3.6 % and 4.5% patients respectively, liver and spleen ECV could not be measured. This was due to absent or incomplete imaging affecting reliable ROI measurement. Secondly the shimming was done on the heart and not the liver and spleen. Potential off-resonance due to imperfect shim could lead to errors in estimates of T1 and ECV[23], estimated to be on the order of a few percent. The presence of fat in the liver may also influence the estimate of tissue T1.[24, 25] The present study did not incorporate fat saturation in T1-mapping. The ROIs were drawn to avoid large vessels, however it is unknown how much intravascular volume contributed to the estimate of extracellular space. In spite of these technical limitations, our results confirm this biomarker has very high diagnostic accuracy, proving to be the first, widely available imaging tool, to assess extra cardiac amyloid. Thirdly, prognostic outcome data is not available from this cohort. Multi-organ involvement in systemic AL amyloidosis has been proven to be a strong prognostic predictor,[2] therefore it is very likely that ECV of the liver and spleen will add important information in risk stratification and determining prognosis, but a further study will be needed to confirm the prognostic value of spleen and liver ECV measurement. Finally, the presence of liver fibrosis may also increase the ECV, but the degree of increase associated with liver fibrosis is minimal compared to that caused by amyloid infiltration. [26]

In conclusion, we report cardiac MR derived ECV mapping for the measurement of amyloid burden in the spleen and liver offering a much-needed non-invasive measure of extra-cardiac burden, without carrying any additional time to the current protocol, and also holds potential to become an important tool to monitor treatment response.

Perspectives

Competency in patient care and procedural skills

The diagnostic accuracy of ECV mapping to detect hepatic and splenic amyloid infiltration has an immediate impact on patient care. Within a clinical cardiac magnetic resonance MR protocol, patients with systemic amyloidosis can undergo a comprehensive assessment of cardiac, splenic and hepatic amyloid burden without any further imaging.

Translational Outlook

Future research studying the role of ECV mapping in clinical trials to assess treatment response in patients with systemic amyloidosis is required to explore its full potential.

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Figure 1. SAP scintigraphy and ECV Mapping in a patient without any extra-cardiac amyloid deposition compared to a patient with liver and spleen amyloid deposits.

Figure Legend

a. SAP scan of a patient without any spleen or liver amyloid deposition; **b.** ECV map of the same patient demonstrates normal liver and spleen ECV values; **c.** SAP scan of a patient with large liver and spleen amyloid deposition; **d.** ECV map of the same patient demonstrates high liver and spleen ECV values.
SAP=Serum Amyloid P component; ECV= extracellular volume

Figure 2. ECV mapping in a patient without any extra-cardiac amyloid deposition compared to a patient with liver and spleen amyloid deposits.

Figure legend

a. Pre-contrast T1 map of a patient without any liver or spleen amyloid deposition; **a1**. ECV map of the same patient; **a2**. ECV Error map of the same patient; **b**. Pre-contrast T1 map of a patient with large liver and spleen amyloid deposition; **b1.** ECV map of the same patient; **b2**. ECV Error map of the same patient.
ECV= Extracellular volume; ROI=Region of interest

Figure 3. Flow diagram demonstrating final diagnosis in the overall population.

Figure legend

Flow diagram demonstrating the final diagnosis and presence of spleen, liver and/or cardiac amyloid involvement by cardiac magnetic resonance and SAP scintigraphy in all 533 patients analysed.

Figure 4. Pie chart demonstrating grades of uptake by SAP scintigraphy and corresponding ECV appearances on cardiac MRI.

Figure legend

Left panel a) ECV map of a patient with both splenic and hepatic amyloid infiltration b) ECV map of a patient with only splenic infiltration c) ECV map of a patient without splenic or hepatic infiltration d) ECV map of a patient with only hepatic infiltration. Right panel: Pie chart denoting distribution of organ distribution by SAP scintigraphy

ECV= Extracellular volume

Figure 5. Liver and Spleen extracellular volume fraction in patients with AL amyloidosis correlated to amyloid load assessed on SAP scintigraphy.

Figure legend: Mean extracellular volume fraction ± 2 SE (standard error) in patients with AL amyloidosis correlated to amyloid load assessed on SAP scintigraphy as none, mild, moderate and large in the liver (top image) and spleen (bottom image). Bonferroni adjustment was applied.

SAP=Serum Amyloid P component; CI = confidence interval; ECV= Extracellular volume

Figure 6. ROC curves for detecting amyloid load as assessed against SAP scintigraphy

Figure Legend

Top Panel: ROC curve for patients with mild, moderate and large liver amyloid load (left), and mild, moderate and large spleen amyloid load (right).

Bottom Panel: ROC curve for patients with moderate and large liver amyloid load (left), and ROC curves for patients with moderate and large spleen amyloid load (right).

ROC=receiver operator characteristic ECV= Extracellular volume; AUC= area under the curve;

CI =confidence interval

Figure 7 Bland Altman and Scatter Plots

Figure legend

Bland-Altman plots (left) and scatter plots (right) for inter-observer reproducibility of liver ECV (top) and spleen ECV (bottom).

ECV= Extracellular volume

Central Illustration

Figure Legend

533 patients with suspected systemic amyloidosis underwent SAP scintigraphy and CMR with T1 and ECV Mapping. The diagnostic performance of ECV to detect clinically significant hepatic and splenic amyloid loading was high, demonstrating for the first time that ECV mapping of the liver and spleen obtained during a routine cardiac MR can identify and measure the magnitude of extra-cardiac amyloid infiltration in patients with systemic amyloidosis.