Diffusion Tensor Cardiovascular Magnetic Resonance in Cardiac Amyloidosis

Khalique: DT-CMR in cardiac amyloidosis

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Background
Cardiac amyloidosis (CA) is a disease of interstitial myocardial infiltration, usually by light chains (AL) or transthyretin (ATTR). We used diffusion tensor cardiovascular magnetic resonance (DT-CMR) to non-invasively assess the effects of amyloid infiltration on the cardiac microstructure.

Methods
DT-CMR was performed at diastole and systole in 20 CA, 11 hypertrophic cardiomyopathy (HCM) and 10 control subjects with calculation of mean diffusivity (MD), fractional anisotropy (FA) and sheetlet orientation (second eigenvector angle, E2A).

Results
MD was elevated and FA reduced in CA compared with both controls and HCM (p<0.001). In CA, MD was correlated with ECV ($r=0.69, p=0.004$) and FA was inversely correlated with circumferential strain ($r=0.65, p=0.02$). In CA, diastolic E2A was elevated and E2A mobility was reduced compared with controls (both $p<0.001$). Diastolic E2A was correlated with amyloid burden measured by ECV in ATTR, but not AL.

Conclusions
DT-CMR can characterise the microstructural effects of amyloid infiltration and is a contrast free method to identify the location and extent of the expanded disorganised myocardium. The diffusion biomarkers MD and FA effectively discriminate CA from HCM. DT-CMR demonstrated that failure of sheetlet relaxation in diastole correlated with ECV in ATTR, but not AL. This indicates that different mechanisms may be responsible for impaired contractility in CA, with an amyloid burden effect in ATTR, but an idiosyncratic effect in AL. Consequently, DT-CMR offers a contrast-free tool to identify novel pathophysiology, improve diagnostics and monitor disease through non-invasive microstructural assessment.

Key Words: heart, amyloid, diffusion, magnetic resonance imaging
CLINICAL PERSPECTIVE

Cardiac amyloidosis (CA) is a disease of myocardial infiltration by light chain (AL) or transthyretin (ATTR) fibrils that disturb the microstructure. It is often misdiagnosed, difficult to discriminate from its mimic hypertrophic cardiomyopathy (HCM), but requires tailored therapy depending on the subtype. Prompt diagnosis and treatment is critical as prognosis can be as poor as 6 months. The gold standard of diagnosis is histology, but cardiac biopsy carries both risk and sampling bias, so there has been a drive towards non-invasive diagnosis. Diffusion tensor cardiovascular magnetic resonance (DT-CMR) offers in-vivo non-invasive assessment of the myocardial microstructure. The diffusion biomarkers mean diffusivity (MD) and fractional anisotropy (FA) offer information on freedom of water diffusion and microstructural organisation. Sheetlet dynamics can also be assessed. In this study, we demonstrate that MD and FA discriminate between CA and both healthy and HCM hearts. Both MD and FA are highly specific and could offer a contrast-free tool to help identify CA. This study also found novel abnormalities in sheetlet dynamics that differed between AL and ATTR, suggesting that contractile impairment may have different underlying mechanisms depending on the CA subtype. DT-CMR is a novel tool that offers deeper understanding of the pathophysiology of CA and offers potential in the diagnosis and monitoring of cardiac amyloidosis.
INTRODUCTION

Amyloidosis is an infiltrative disease in which cardiac involvement portends a poor prognosis. The myocardium is typically infiltrated by misfolded immunoglobulin light chains (AL) or transthyretin protein (ATTR), either in its native or mutant form. Prompt and accurate diagnosis is critical, as the different amyloid subtypes require different treatments. However, differentiating cardiac amyloidosis (CA) from its mimics, such as hypertrophic cardiomyopathy (HCM) and distinguishing between subtypes can be difficult. Reports describe over a third of CA patients are misdiagnosed, often as HCM and differentiating HCM from CA remains a clinical problem. The gold standard for diagnosis of CA is biopsy, but there is now an increasing drive towards non-invasive diagnosis. Such current techniques do not yield information on the microstructure of the myocardium nor on the interplay between the amyloid fibrils and the microstructure, which is a dynamic that is poorly understood.

Cardiovascular magnetic resonance (CMR) is a key tool in the diagnosis and assessment of CA. Late gadolinium enhancement (LGE), T1 mapping and extracellular volume (ECV) are used for diagnosis and to locate and quantify the extent of myocardial infiltration and the related prognosis. ECV is considered superior to T1 as it is specific for the extracellular space, is less sensitive to oedema and is considered a direct measure of amyloid burden. However, due to the risk of nephrogenic systemic fibrosis, gadolinium is unsuitable for patients with significant renal impairment, a feature of approximately a quarter of newly diagnosed AL patients. LGE acquisition also requires expertise due to the perturbation by amyloid of gadolinium kinetics. Diffusion tensor cardiovascular magnetic resonance (DT-CMR) is a novel in-vivo tool that has potential to assess amyloid infiltration by examining the microstructure of the myocardium. It is a histologically validated and contrast-free technique that probes the diffusion of water in the myocardium to infer the
helical arrangement of cardiomyocytes through helix angle (HA) and the dynamic sheetlet reorientation through the cardiac cycle via the secondary eigenvector angle (E2A). These sheetlets consist of aggregated cardiomyocytes have a wall-parallel orientation in diastole and reorient to a more wall-perpendicular alignment in systole and are integral to the process of wall thickening. DT-CMR also characterises the myocardial integrity and organisation by mean diffusivity (MD) and fractional anisotropy (FA) respectively. MD reflects the freedom of water diffusion within the myocardium and FA is a scalar value between 0 and 1. A value of zero means that diffusion is isotropic, i.e. it is unrestricted (or equally restricted) in all directions. The aims of this study therefore were to use DT-CMR to assess the microstructural changes in CA and identify the potential role of DT-CMR in the clinical challenge of differentiating CA from its mimic HCM.

METHODS

Study Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. This study received approval from the National Research Ethics Committee. All participants gave written informed consent. CA patients with preserved renal function (eGFR >30mL/min) were prospectively recruited from the National Amyloidosis Centre, Royal Free Hospital, London. All patients underwent a comprehensive clinical assessment including clinical evaluation, echocardiography, serum and urine biochemistry including N-terminal pro-b-type natriuretic peptide (NT-proBNP), SAP scintigraphy and assessment of hematologic disease by serum free light chain (FLC) assay along with serum and urine immunofixation electrophoresis. Patients with ATTR amyloidosis also underwent technetium-labeled bone scintigraphy using 3,3-diphosphono-1,2-propanodicarboxylicacid
Cardiac ATTR was defined as the combination of typical features on CMR, grade 2 or 3 cardiac uptake on 99mTc-DPD scintigraphy in the absence of monoclonal gammopathy, or in the presence of monoclonal gammopathy, a cardiac biopsy positive for ATTR. Cardiac AL amyloidosis was defined as the combination of typical features on CMR and biopsy proven systemic AL amyloidosis on cardiac or non-cardiac biopsy. HCM was diagnosed in accordance with the 2014 ESC guidelines. Data from 4 HCM and 5 controls subjects had been acquired from a previous study. Participants were age and sex matched between groups.

**Image Acquisition**

CMR was performed at 3T (Magnetom Skyra, Siemens, Erlangen). Retro-gated balanced steady state free precession (bSSFP) images were acquired for volumetric analysis and identification of a mid-ventricular slice suitable for DT-CMR. The DT-CMR protocol has been described fully. In summary, a cardiac diffusion weighted stimulated echo acquisition mode (STEAM) single shot echo planar imaging (EPI) sequence was used for an 8mm thick slice with 6 diffusion encoding directions at b=600 s/mm² (minimum 8 averages systole and 10 diastole) and also at b=150 s/mm² (minimum two averages) fat saturation, TR=2RR intervals, TE=25ms, SENSE parallel imaging acceleration factor 2, echo train duration 13ms, acquired in-plane spatial resolution=2.8×2.8 mm², reconstructed to 1.4×1.4 mm². Data was acquired in diastole and systole and each breath-hold lasted 18 heart-beats. Strain data was obtained from 2D cine spiral displacement encoding with stimulated echoes (DENSE) data acquired using a reduced field of view technique. Data were acquired during breath-hold, 30ms temporal resolution, 3.3×3.3mm² spatial resolution, 8mm slice thickness and TE/TR= 1ms/15ms with 2 encoding directions (0.06cycles/mm). T1 mapping used a Modified Look Locker Imaging sequence. LGE imaging was performed using Gadobutrol.
(Gadovist 1.0mmol/ml solution for injection at 0.1mmol/kg). A phase sensitive inversion recovery sequence was employed.

**Diffusion tensor analysis**

DT-CMR data were processed with custom software built using MATLAB (Mathworks, Massachusetts, USA), as described previously. Diffusion tensors were calculated for each voxel in systole and diastole. From these quantitative maps of FA and MD were generated. For quantification, data was first analysed on a per-patient basis, using global values for the whole LV slice. Next the slice was divided into 12 equal segments for regional analysis. Thresholds for abnormal MD and FA were set at 95th percentiles from the control cohort (1.34 x10^-3 mm²/s and 0.48 respectively). These thresholds were utilised to calculate the sensitivity and specificity of MD and FA in distinguishing CA from HCM. The upper threshold of ECV was set at 32.9%, being 1.97 standard deviations above the mean in an age and sex corrected cohort of healthy subjects scanned at 3T.

Next, orientations of the principal and secondary diffusion ellipsoid axes (E1 and E2) were calculated for each tensor, according to the local cardiac orthogonal coordinate system of each voxel. E2A is defined as the absolute angle between the projection of E2 in the cross-myocyte plane, and the local wall tangent plane. It is considered a DT-CMR measure of sheetlet orientation. Quantitative maps of the absolute E2A at each voxel were generated.

**Image analysis**

Volumetric analysis was performed using CMRtools (Cardiovascular Imaging Solutions, London). Results were indexed to body surface area. Strain measurements were calculated from DENSE images using MATLAB software (University of Virginia). Peak global LV radial and circumferential strain were calculated from the mid short axis slice and
longitudinal strain from the horizontal long axis acquisition. T1 and ECV maps were generated using CMR42 (Circle Cardiovascular Imaging, Calgary) and provided global values to match the globally reported DT-CMR values.

**Statistical analysis**

Statistical analysis used SPSS Statistics software (v26), IBM, NY, USA. Data were tested for normality and the Mann-Whitney or independent t-tests were used for comparative analysis accordingly. Correlation coefficients (r) were calculated to describe the relationship between diffusion biomarkers, and strain and ECV. The diagnostic accuracy of MD and FA for discriminating CA from HCM was examined by ROC analysis.

**RESULTS**

**Study population**

Twenty-three CA, 11 HCM and 10 control subjects were recruited. Data from three CA patients was not analysable due to claustrophobia, frequent ectopy and poor breath-holding. Despite recruitment of patients with preserved renal function, 1 CA patient could not receive gadolinium due to an eGFR<30mL/min. T1 data was missing in 3 CA patients due to technical issues. Of the 20 CA patients, 10 had ATTR and 10 AL. Average number of breath-holds was 12 in systole and 14 in diastole (including reference images). Baseline characteristics are shown in table 1.

**Sheetlet orientation (E2A)**

There were differences in the E2A orientations between CA and control groups, most notably in diastolic E2A (Figure 1A). Diastolic E2A (mean ± standard deviation) was significantly higher in CAs compared to controls; 45 ± 11° vs 25 ± 9°, p<0.001. Systolic E2A
was similar between CA and controls; 69 ± 6° vs 65 ± 5°, p=0.07. E2A mobility in CA was approximately half that of controls: 24 ± 11° versus 40 ± 7°, p<0.001. There was no significant difference in the biphasic E2A orientations or mobility between CA and HCM patients. E2A mobility significantly correlated with longitudinal strain in controls (r= 0.80, p=0.01, CI -1.34:-0.26), but this relationship was lost in CA (r= 0.11, p=0.64, CI -0.61:0.38) and HCM (r= 0.19, p=0.65, CI -1.17:0.79).

Figure 1B shows example E2A maps. Controls had a predominance of wall-parallel lower E2A (blue) in diastole and more wall-perpendicular higher E2A (red) in systole. In CA, the diastolic maps are similar to the maps in systole of controls, with predominance of red higher E2As. CA and HCM maps were similar in both cardiac phases.

**Diffusion biomarkers**

Both MD and FA discriminated CA patients from controls and HCM patients. Mean diffusivity was significantly higher in CA than controls and HCM (Figure 2A). Diastolic MD (mean ± standard deviation) was elevated at 1.43 ± 0.13 ×10^-3 mm²/s in CA patients, compared to controls and HCM (1.12 ± 0.11 and 1.19 ± 0.16 ×10^-3 mm²/s) respectively both p<0.001). Similarly, systolic MD was significantly elevated in CA compared to controls and HCM (supplementary table 1). Using a threshold of 1.34 ×10^-3 mm²/s, MD offered 91% specificity and 80% sensitivity, with an area under the curve of 0.88 in discriminating CA from HCM (figure 3A).

Conversely FA was significantly lower in CA compared to controls and HCM (Figure 2B). Diastolic FA was 0.43 ± 0.06 in CA, significantly reduced compared to controls and HCM (0.56 ± 0.05 and 0.53 ± 0.06 respectively, both p<0.001). This was true also in systole (supplementary table 1). Using a threshold of 0.48 FA offered 80% specificity and 82% sensitivity, with an area under the curve of 0.89 (figure 3B).
There was an inverse correlation between FA and circumferential strain in CA, indicating that strain is increasingly impaired as FA decreases ($r=0.65$, $p=0.002$, CI -1.03:-0.27).

**Diffusion parameters and ECV**

A clear relationship between the spatial distribution of MD, FA and ECV was observed in CA (Figure 4). Regions of elevated MD (orange-red) and reduced FA (green) matched with location and extent of abnormal ECV. This was present in both AL and ATTR patients. MD was positively correlated, and FA inversely correlated with ECV in both cardiac phases of CA patients. Figure 5A shows the correlation between ECV and diastolic MD ($r=0.68$, $p=0.004$, CI 0.26:1.10). For FA, the inverse correlation between ECV and diastolic FA was $r=-0.50$, $p=0.05$, CI -0.99:0.003(figure 5B). Using a 12-segment model including data from 15 CA and 11 HCM patients, there was co-location of areas of abnormal diffusion parameters with areas of elevated ECV (Figure 6).

**Helix angle**

Diastolic helix angle gradient (HAG) in degrees per percentage wall thickness was similar between CA ($0.76 \pm 0.15 \degree/\%$) and controls $0.73 \pm 0.1 \degree/\%$, $p=0.63$), but flatter than HCM ($0.91 \pm 0.17 \degree/\%$, $p=0.02$). The converse was true in systole, with HAG in CA patients being steeper than controls and not significantly different to HCM.

**Comparison of ATTR and AL**

A subgroup analysis was performed, comparing ATTR and AL patients (supplementary table 2). ATTR patients had higher indexed LV mass (135 [107-159] vs 94 [71-114] g/m²) and lower EF (53 ± 11 vs 64 ± 10%). Radial and circumferential strains were
significantly impaired in ATTR compared to AL; 0.22 ± 0.06 vs 0.35 ± 0.12, p <0.01 and -0.10 [-0.12 to -0.07] vs -0.13 [-0.17 to -0.11], p=0.03 respectively. Systolic E2A was higher in AL compared to ATTR 72 ± 3° vs 66 ± 7°, p=0.02 (Supplementary Figure 1). Diastolic E2A and E2A mobility were similar between groups. Diastolic E2A was correlated with ECV (r=0.77, p= 0.03, CI 0.13:1.46) for the ATTR group, but not for the AL group (r= 0.05, p= 0.90, CI -1.03:0.93), as shown in Figure 7.

There were no significant differences between amyloid subtypes for FA and MD in both cardiac phases (Supplementary Figure 2). However, both AL and ATTR showed strong correlation of MD and ECV, significant in ATTR (r=0.76, p=0.03, CI 0.12:1.52), but not in AL (r=0.70, p=0.06, CI -0.02:1.33). There was a weak inverse correlation between FA and ECV, which was not statistically significant (ATTR; r=0.59, p=0.12, CI -1.22:0.18 and AL; r= 0.56, p=0.15, CI -1.44:0.28). FA and circumferential strain were correlated with r of 0.70, p=0.03, CI -1.60:-0.14) for AL, but non-significant correlation of r=0.52, p=0.12, CI -1.21:0.17 in ATTR.

**DISCUSSION**

Our study shows that DT-CMR detects abnormalities in myocardial microstructure and sheetlet behaviour in cardiac amyloid (CA). Previous work using DT-CMR in amyloid has been undertaken using a motion compensated spin echo approach and assessed ten patients with CA (8 AL and 2 ATTR), identifying elevated MD and lower FA in CA compared to healthy controls. However, the study was limited by only acquiring data in systole and could not capture important information about sheetlet dynamics. In our study we demonstrated that sheetlet mobility was reduced with an elevated diastolic E2A, suggesting
myocardial amyloid infiltration inhibits normal diastolic relaxation. The strong correlation between diastolic E2A and ECV in ATTR suggests that increasing amyloid burden causes greater limitation of sheetlet relaxation. In AL there was similar diastolic E2A, but a non-significant correlation with ECV, which might reflect a different mechanism of amyloid infiltration on sheetlet impairment. This supports the hypothesis that additional mechanisms beyond the burden of amyloid infiltration may contribute to the greater mortality in AL amyloidosis, such as light chain toxicity, previously proven by in vitro studies, or faster rate of amyloid deposition.31 Thus AL may have an idiosyncratic effect on sheetlet mobility and failure of relaxation. A similar pattern of elevated diastolic E2A and reduced sheetlet mobility in HCM was observed in this study and previous work.15,23 A different mechanism is implicated in HCM whereby impaired sheetlet relaxation is thought to relate to the underlying pathogenic sarcomeric mutations that increase myofilament sensitivity to calcium resulting in elevated cardiomyocyte tension.32,33

There were also significant differences between the MD (increased) and FA (reduced) in CA and the controls and HCM patients. The changes in FA and MD were co-located with amyloid burden. The ROC curves demonstrated that MD can provide 91% specificity with 80% sensitivity and thus may to help identify CA from other hypertrophic conditions. This would be valuable especially when ECV is not possible to obtain. Approximately a quarter of newly diagnosed AL patients have an eGFR <30mL/min contraindicating gadolinium contrast and thus preventing calculation of ECV.14

Our work goes beyond the previous DT-CMR study in CA by addressing the clinical challenge of discriminating amyloid from HCM.30 High rates of misdiagnosis are seen in CA, in the region of 35%.2-4 In a cohort of 108 ATTR patients, 35% were misdiagnosed, of whom
In another study of 233 CA patients, 80 patients had been given incorrect prior diagnoses including HCM, heart failure, or arrhythmias. Similar imaging appearances contribute to this diagnostic challenge. A study of the different morphologic phenotypes of ATTR demonstrated that 79% of patients displayed asymmetric hypertrophy and only 18% the classically described concentric symmetric hypertrophy. Reverse septal contour hypertrophy which is typically associated with HCM was present in a quarter of ATTR patients. This creates a need to identify parameters that could help discriminate CA from HCM. FA and MD were significantly different between CA and HCM patients and offer new potential as biomarkers that could discriminate between CA and HCM. Prompt early diagnosis of CA is critical to facilitate prompt specific therapy, that is now available for both types of amyloidosis.

Furthermore, it has recently been recognised that cardiac AL may regress with therapy and that this regression may be assessed via ECV. Newer disease modifying treatments for ATTR, such as tafamidis may offer a stabilising effect preventing accumulation of misfolded amyloid proteins. MD and FA may offer a means to monitor amyloid burden longitudinally over time in renal failure patients.

The inverse relationship between FA and ECV may denote the increasing disruption of myocardial organisation as the amyloid protein infiltrates the myocardium. The correlation between decreasing FA and impaired circumferential strain reflects the interaction of disrupted microstructural organisation on macroscopic function. FA is reported to be highest in the mesocardium, which is considered to represent the more uniform organisation of the near circumferentially oriented cardiomyocytes, whose shortening contributes substantially to circumferential strain. Disturbing this arrangement may explain the impaired circumferential strain.
Limitations
This study is exploratory and has a limited cohort size with only univariate analyses. There are both mutant and wild-type ATTR patients, and AL patients are at different stages of their treatment regimes. Healthy volunteers did not receive gadolinium so examination of ECV relationships was limited to CA patients, although it would be expected that the normal subjects would have normal ECV. Thresholds for abnormal diffusion biomarkers need further validation.

Conclusion
DT-CMR offers novel insight into the interaction between amyloid infiltration and cardiac microstructure. FA and MD characterise the expanded and disorganised myocardium in CA without the need for gadolinium contrast and aid discrimination from HCM offering potential in diagnosis and disease monitoring, particularly in those with renal impairment. DT-CMR also offers deeper understanding of impaired contractility in amyloid, particularly highlighting failure of diastolic sheetlet relaxation and indicating that different mechanisms may be responsible in AL and ATTR.
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**FIGURE LEGENDS**

**Figure 1: Diastolic E2A is elevated in cardiac amyloid**

E2A is an index of sheetlet orientation. The bars show mean and standard deviation. In panel A diastolic E2A in amyloid patients (yellow and green) was significantly elevated compared to diastolic E2A in controls (blue), p<0.001. Example maps in panel B show a predominance of low E2A over the control LV slice (blue) in diastole that changed to predominantly higher E2A in systole (more red pixels). In both cardiac amyloidosis and HCM, the diastolic maps showed a greater extent of higher E2A in diastole (more red than blue).

**Figure 2: Diffusivity biomarkers differ significantly in cardiac amyloid**

In panel A, mean diffusivity (MD) was significantly higher in cardiac amyloidosis (p<0.001) at both cardiac phases, with clear separation from HCM and controls. In panel B, fractional anisotropy (FA) was significantly reduced (p<0.001) at both cardiac phases. A lower FA reflects greater disorganisation of the underlying microstructure.

**Figure 3: Receiver operating characteristic curves for diffusion biomarkers**

Panel A shows the ROC curve for mean diffusivity and panel B shows the ROC curve for fractional anisotropy.

**Figure 4: MD and FA map the location and extent of amyloid deposition**

Example maps from are shown. The left column shows control maps including a reference ECV map. The control MD map is blue and FA map is red. The second column shows HCM data; elevated ECV in the hypertrophied septum matching with elevated MD (red) and FA (green). The AL and ATTR maps show spatial co-location of the areas of elevated MD,
reduced FA and amyloid burden as shown by the ECV. Control ECV map is reproduced from [29], licensed under a Creative Commons Attribution (CC-BY) license.

**Figure 5: MD and FA correlate with ECV**

MD significantly correlated with ECV (r=0.68, p=0.004), suggesting MD reflects the expanded extracellular volume resulting from amyloid deposition (Panel 4A). Conversely, the inverse correlation of FA with ECV had a p-value of 0.05 (Panel 4B).

**Figure 6: Segmental agreement of abnormal MD and FA with ECV derangement**

Using a 12-segment model for the LV slice, segments of elevated MD and reduced FA co-located with segments of raised ECV (>33%). The HCM and CA segments showed marked clustering, as shown in the grey boxes within which the ECV, FA and MD values are abnormal.

**Figure 7: Diastolic E2A correlates with ECV in ATTR, but not in AL**

There was a significant correlation between diastolic E2A and ECV in ATTR, (r=0.77 and p=0.03). However, this was not true for AL, where there was no correlation (r=0.05 and p=0.9). This suggests that there may be an amyloid dose-dependent relationship of diastolic E2A elevation in ATTR, but an idiosyncratic effect in AL.
Table 1: Baseline characteristics

|                          | Amyloid n=20 | HCM n=11 | p   | Control n=10 | p   |
|--------------------------|--------------|----------|-----|--------------|-----|
| Age                      | 67±8         | 63±9     | 0.16| 69±5         | 0.62|
| Male Sex                 | 14/20 (70%)  | 8/11 (73%)| 0.87| 7/10 (70%) | 1.00|
| Systolic blood pressure  | 119±14       | 133±15   | 0.01| 137±26      | 0.06|
| Diastolic blood pressure | 72±11        | 75±8     | 0.43| 79±13       | 0.12|
| Heart rate               | 64 [59:73]   | 54 [51:65]| 0.04| 64 [53:68]  | 0.45|
| Maximum wall thickness   | 18 [15:21]   | 21 [19:23]| 0.03| 10 [8:11]   | <0.001|
| Indexed LV end-diastolic | 74 [64:87]   | 83 [63:88]| 0.73| 73 [67:83]  | 0.91|
| Indexed LV end-systolic  | 30 [25:35]   | 19 [17:25]| 0.01| 24 [21:28]  | 0.06|
| LV ejection fraction (%) | 58±11        | 72±7     | 0.001| 68±3        | 0.002|
| Indexed LV mass (g/m²)   | 111 [85:154] | 110 [82:145]| 1.00| 62 [58:72]  | <0.001|
|                            | Mean (SD)       | Median (IQR) | P-value  |
|---------------------------|----------------|--------------|----------|
| **Native T1 (msec)**      | 1496±69        | 1367 [1329:1383] | <0.001  |
|                           | 1367 ± 33      | <0.001       |
| **ECV**                   | 0.52±0.09      | 0.29 [0.26:0.33] | <0.001  |
|                           | 0.29 ± 0.09    | <0.001       |
| **Peak radial strain**    | 0.29±0.11      | 0.36 [0.23:0.46] | 0.12     |
|                           | 0.51±0.16      | <0.001       |
| **Peak circumferential strain** | -0.11 [-0.13:-0.08] | -0.13 [-0.15:-0.11] | 0.18     |
|                           | -0.16 [-0.18:-0.16] | <0.001 |
| **Peak longitudinal strain** | -0.06 ±0.03   | -0.06 [-0.11:0.03] | 0.80     |
|                           | -0.12 ±0.03    | <0.001       |

*Data are presented as n (%), mean ± standard deviation, median [interquartile range]. †LV = left ventricle, RV = right ventricle. ‡For amyloid patients: T1 n=17, ECV n=16. For HCM patients: radial and circumferential strain n=10, longitudinal strain n=8. For controls; longitudinal strain n=9
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