Diffusion Tensor Cardiovascular Magnetic Resonance in Cardiac Amyloidosis

BACKGROUND: Cardiac amyloidosis (CA) is a disease of interstitial myocardial infiltration, usually by light chains or transthyretin. We used diffusion tensor cardiovascular magnetic resonance (DT-CMR) to noninvasively 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, and 10 control subjects with calculation of mean diffusivity, fractional anisotropy, and sheetlet orientation (secondary eigenvector angle).

RESULTS: Mean diffusivity was elevated and fractional anisotropy reduced in CA compared with both controls and hypertrophic cardiomyopathy ($P<0.001$). In CA, mean diffusivity was correlated with extracellular volume ($r=0.68$, $P=0.004$), and fractional anisotropy was inversely correlated with circumferential strain ($r=-0.65$, $P=0.02$). In CA, diastolic secondary eigenvector angle was elevated, and secondary eigenvector angle mobility was reduced compared with controls (both $P<0.001$). Diastolic secondary eigenvector angle was correlated with amyloid burden measured by extracellular volume in transthyretin, but not light chain amyloidosis.

CONCLUSIONS: DT-CMR can characterize the microstructural effects of amyloid infiltration and is a contrast-free method to identify the location and extent of the expanded disorganized myocardium. The diffusion biomarkers mean diffusivity and fractional anisotropy effectively discriminate CA from hypertrophic cardiomyopathy. DT-CMR demonstrated that failure of sheetlet relaxation in diastole correlated with extracellular volume in transthyretin, but not light chain amyloidosis. This indicates that different mechanisms may be responsible for impaired contractility in CA, with an amyloid burden effect in transthyretin, but an idiosyncratic effect in light chain amyloidosis. Consequently, DT-CMR offers a contrast-free tool to identify novel pathophysiology, improve diagnostics, and monitor disease through noninvasive microstructural assessment.
Cardiac amyloidosis (CA) is a disease of myocardial infiltration by light chain or transthyretin fibrils that disturb the microstructure. It is often misdiagnosed, difficult to discriminate from its mimic hypertrophic cardiomyopathy, 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 noninvasive diagnosis. Diffusion tensor cardiovascular magnetic resonance offers in vivo noninvasive assessment of the myocardial microstructure. The diffusion biomarkers mean diffusivity and fractional anisotropy offer information on freedom of water diffusion and microstructural organization. Sheetlet dynamics can also be assessed. In this study, we demonstrate that mean diffusivity and fractional anisotropy discriminate between CA and both healthy and hypertrophic cardiomyopathy hearts. Both mean diffusivity and fractional anisotropy 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 light chain and transthyretin CA, suggesting that contractile impairment may have different underlying mechanisms depending on the CA subtype. Diffusion tensor cardiovascular magnetic resonance is a novel tool that offers deeper understanding of the pathophysiology of CA and offers potential in the diagnosis and monitoring of CA.

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.1,2 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.1–3 Reports describe over a third of patients with CA are misdiagnosed, often as HCM and differentiating HCM from CA remains a clinical problem.2–5 The gold standard for diagnosis of CA is biopsy, but there is now an increasing drive towards noninvasive diagnosis.6,7 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.8–10 Late gadolinium enhancement, T1 mapping, and extracellular volume (ECV) are used for diagnosis and to locate and quantify the extent of myocardial infiltration and the related prognosis.9 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.11–13 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 patients with AL.14 Late gadolinium enhancement acquisition also requires expertise due to the perturbation by amyloid of gadolinium kinetics. Diffusion tensor CMR (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 and the dynamic sheetlet reorientation through the cardiac cycle via the secondary eigenvector angle (E2A).15–17 These sheetlets consisting 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.15 DT-CMR also characterizes the myocardial integrity and organization by mean diffusivity (MD) and fractional anisotropy (FA), respectively.16,18 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, that is, 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. Patients with CA with preserved renal function (estimated glomerular filtration rate >30 mL/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 NT-proBNP (N-terminal pro-B-type natriuretic peptide), estimated glomerular filtration rate, serum amyloid P scintigraphy,19 and assessment of hematologic disease by serum free light chain assay along with serum and urine immunofixation electrophoresis. Patients with ATTR amyloidosis

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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-3,3-diphosphono-1,2-propanodicarboxylicacid scintigraphy in the absence of monoclonal gammopathy, or in the presence of monoclonal gammopathy, a cardiac biopsy positive for ATTR.7 Cardiac AL amyloidosis was defined as the combination of typical features on CMR and biopsy proven systemic AL amyloidosis on cardiac or noncardiac biopsy. HCM was diagnosed in accordance with the 2014 ESC guidelines.20 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 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.15 In summary, a cardiac diffusion-weighted stimulated echo acquisition mode single-shot echo planar imaging sequence was used for an 8 mm thick slice with 6 diffusion encoding directions at b=600 s/mm2 (minimum 2 averages) fat saturation, repetition time=2.8×2.8 mm2, reconstructed to 1.4×1.4 mm2, slice thickness and 10 diastole) and also at b=150 s/mm2 (minimum 8 averages systole and 10 diastole) and also at b=150 s/mm2 (minimum 2 averages) fat saturation, repetition time=2 RR intervals, echo time=25 ms, SENSE parallel imaging acceleration factor 2, echo train duration 13 ms, 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 data acquired using a reduced field of view technique.21

### DT Analysis

DT-CMR data were processed with custom software built using MATLAB (Mathworks, MA), as described previously.23 DTs were calculated for each voxel in systole and diastole. From these quantitative maps of FA and MD were generated.24 For quantification, data was first analyzed on a per-patient basis, using global values for the whole left ventricle 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 (1.34×10−3 mm/s and 0.48, respectively). These thresholds were used 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 SDs above the mean in an age and sex corrected cohort of healthy subjects scanned at 3T.25 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.15 Quantitative maps of the absolute E2A at each voxel were generated.

### Table. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Amyloid, n=20</th>
<th>HCM, n=11</th>
<th>P Value</th>
<th>Control, n=10</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67±8</td>
<td>63±9</td>
<td>0.16</td>
<td>69±5</td>
<td>0.62</td>
</tr>
<tr>
<td>Male sex</td>
<td>14/20 (70%)</td>
<td>8/11 (73%)</td>
<td>0.87</td>
<td>7/10 (70%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>119±14</td>
<td>133±15</td>
<td>0.01</td>
<td>137±26</td>
<td>0.06</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>72±11</td>
<td>75±8</td>
<td>0.43</td>
<td>79±13</td>
<td>0.12</td>
</tr>
<tr>
<td>Heart rate</td>
<td>64 [59 to 73]</td>
<td>54 [51 to 65]</td>
<td>0.04</td>
<td>64 [53 to 68]</td>
<td>0.45</td>
</tr>
<tr>
<td>Maximum wall thickness, mm</td>
<td>18 [15 to 21]</td>
<td>21 [19 to 23]</td>
<td>0.03</td>
<td>10 [8 to 11]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Indexed LV end-diastolic volume, mL/m²</td>
<td>74 [64 to 87]</td>
<td>83 [63 to 88]</td>
<td>0.73</td>
<td>73 [67 to 83]</td>
<td>0.91</td>
</tr>
<tr>
<td>Indexed LV end-systolic volume, mL/m²</td>
<td>30 [25 to 35]</td>
<td>19 [17 to 25]</td>
<td>0.01</td>
<td>24 [21 to 28]</td>
<td>0.06</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>58±11</td>
<td>72±7</td>
<td>0.001</td>
<td>68±3</td>
<td>0.002</td>
</tr>
<tr>
<td>Indexed LV mass, g/m²</td>
<td>111 [85 to 154]</td>
<td>110 [82 to 145]</td>
<td>1.00</td>
<td>62 [58 to 72]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Native T1, msec</td>
<td>1496±69</td>
<td>1367 [1329 to 1383]</td>
<td>&lt;0.001</td>
<td>1259±33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECV</td>
<td>0.52±0.09</td>
<td>0.29 [0.26 to 0.33]</td>
<td>&lt;0.001</td>
<td>1.00±0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak radial strain</td>
<td>0.29±0.11</td>
<td>0.36 [0.23 to 0.46]</td>
<td>0.12</td>
<td>0.51±0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak circumferential strain</td>
<td>−0.11 [−0.13 to −0.08]</td>
<td>−0.13 [−0.15 to −0.11]</td>
<td>0.18</td>
<td>−0.16 [−0.18 to −0.16]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak longitudinal strain</td>
<td>−0.06±0.03</td>
<td>−0.06 [−0.11 to 0.03]</td>
<td>0.80</td>
<td>−0.12±0.03</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as n (%), mean±SD, median [interquartile range].

For patients with amyloid; T1 n=17, ECV n=16. For patients with HCM; radial and circumferential strain n=10, longitudinal strain n=8. For controls; longitudinal strain n=9. ECV indicates extracellular volume; HCM, hypertrophic cardiomyopathy; and LV, left ventricle.
Image Analysis
Volumetric analysis was performed using CMRtools (Cardiovascular Imaging Solutions, London). Results were indexed to body surface area. Strain measurements were calculated from displacement encoding with stimulated echoes images using MATLAB software (University of Virginia). Peak global left ventricle 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. 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 receiver operating characteristic analysis.

RESULTS

Study Population
Twenty-three CA, 11 HCM, and 10 control subjects were recruited. Data from 3 patients with CA was not analyzable due to claustrophobia, frequent ectopy, and poor breath holding. Despite recruitment of patients with preserved renal function, 1 patient with CA could not receive

Figure 1. Diastolic secondary eigenvector angle (E2A) is elevated in cardiac amyloid.
E2A is an index of sheetlet orientation. The bars show mean and SD. In A, diastolic E2A in patients with amyloid (yellow and green) was significantly elevated compared with diastolic E2A in controls (blue), P<0.001. Example maps in (B) show a predominance of low E2A over the control left ventricle slice (blue) in diastole that changed to predominantly higher E2A in systole (more red pixels). In both cardiac amyloidosis and hypertrophic cardiomyopathy (HCM), the diastolic maps showed a greater extent of higher E2A in diastole (more red than blue). AL indicates light chains; and ATTR, transthyretin.
gadolinium due to an estimated glomerular filtration rate <30 mL/min. T1 data was missing in 3 patients with CA due to technical issues. Of the 20 patients with CA, 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.

**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±SD) was significantly higher in CAs compared with controls; 45±11° versus 25±9°, \( P<0.001 \). Systolic E2A was similar between CA and controls; 69±6° versus 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 patients with CA and HCM. E2A mobility significantly inversely correlated with longitudinal strain in controls (\( r=−0.80, \ P=0.01 \) [CI, −1.34 to −0.26]), but this relationship was lost in CA (\( r=−0.11, \ P=0.64 \) [CI, −0.61 to 0.38]) and HCM (\( r=−0.19, \ P=0.65 \) [CI, −1.17 to 0.79]).

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

In A, mean diffusivity (MD) was significantly higher in cardiac amyloidosis (\( P<0.001 \)) at both cardiac phases, with clear separation from hypertrophic cardiomyopathy (HCM) and controls. In B, fractional anisotropy (FA) was significantly reduced (\( P<0.001 \)) at both cardiac phases. A lower FA reflects greater disorganization of the underlying microstructure. AL indicates light chains; and ATTR, transthyretin.
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 patients with CA from controls and patients with HCM. MD was significantly higher in CA than controls and HCM (Figure 2A). Diastolic MD (mean±SD) was elevated at 1.43±0.13×10⁻³ mm²/s in patients with CA, compared with 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 with controls and HCM (Table I in the Data Supplement). 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 with controls and HCM (Figure 2B). Diastolic FA was 0.43±0.06 in CA, significantly reduced compared with controls and HCM (0.56±0.05 and 0.53±0.06, respectively, both \(P<0.001\)). This was true also in systole (Table I in the Data Supplement). 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 \((r=-0.65, \ P=0.002 \ [CI, -1.03 \text{ to } -0.27])\).

**Diffusion Parameters and ECV**

A clear relationship between the spatial distribution of MD, FA, and ECV was observed in CA (Figure 4).²⁹ 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 patients with CA. Figure 5A shows the correlation between ECV and diastolic MD \((r=0.68, \ P=0.004 \ [CI, 0.26 \text{ to } 1.10])\). For FA, the inverse correlation between ECV and diastolic FA was \(r=-0.50, \ P=0.05 \ (CI, -0.99 \text{ to } 0.003; \ Figure \ 5B)\). Using a 12-segment model including data from 15 CA and 11 patients with HCM, there was co-location of areas of abnormal diffusion parameters with areas of elevated ECV (Figure 6).

**Helix Angle**

Diastolic helix angle gradient in degrees per percentage wall thickness was similar between CA (0.76±0.15˚/%) and controls 0.73±0.16˚/%, \(P=0.63\), but flatter than HCM (0.91±0.17˚/%, \(P=0.02\)). The converse was true in systole, with helix angle gradient in patients with CA being steeper than controls and not significantly different to HCM.

**Comparison of ATTR and AL**

A subgroup analysis was performed, comparing patients with ATTR and AL (Table II in the Data Supplement). Patients with ATTR had higher indexed left ventricle mass (135 [107–159] versus 94 [71–114] g/
m²) and lower EF (53±11 versus 64±10%). Radial and circumferential strains were significantly impaired in ATTR compared with AL; 0.22±0.06 versus 0.35±0.12, *P*<0.01 and −0.10 (−0.12 to −0.07) versus −0.13 (−0.17 to −0.11), *P*=0.03, respectively. Systolic E2A was higher in AL compared with ATTR 72±3° versus 66±7°, *P*=0.02 (Figure I in the Data Supplement). 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, −0.13 to 0.93]), as shown in Figure 7.

There were no significant differences between amyloid subtypes for FA and MD in both cardiac phases (Figure II in the Data Supplement). 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 to 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 to 0.18 and AL; *r*=0.56, *P*=0.15 [CI, −1.44 to 0.28]). FA and circumferential strain were correlated with *r* of 0.70, *P*=0.03 [CI, −1.60 to −0.14] for AL, but nonsignificant correlation of *r*=0.52, *P*=0.12 [CI, −1.21 to 0.17] in ATTR.

**DISCUSSION**

Our study shows that DT-CMR detects abnormalities in myocardial microstructure and sheetlet behavior in CA. Previous work using DT-CMR in amyloid has been undertaken using a motion-compensated spin echo approach and assessed 10 patients with CA (8 AL and 2 ATTR), identifying elevated MD and lower FA in CA compared with 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 nonsignificant 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 AL toxicity, previously proven by in vitro studies, or faster rate of amyloid deposition. This 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. 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.

Figure 5. Mean diffusivity (MD) and fractional anisotropy (FA) correlate with extracellular volume (ECV).
MD significantly correlated with ECV ($r=0.68$, $P=0.004$), suggesting MD reflects the expanded extracellular volume resulting from amyloid deposition (A). Conversely, the inverse correlation of FA with ECV had a $P$ value of 0.05 (B). AL indicates light chains; and ATTR, transthyretin.
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 receiver operating characteristic curves demonstrated that MD can provide 91% specificity with 80% sensitivity and thus may 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 patients with AL have an estimated glomerular filtration rate <30 mL/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 patients with ATTR, 35% were misdiagnosed, of whom a quarter were given the diagnosis of HCM.3 In another study of 233 patients with CA, 80 patients had been given incorrect prior diagnoses including HCM, heart failure, or arrhythmias.2 Similar imaging appearances contribute to this diagnostic challenge. A study of the different morphological phenotypes of ATTR demonstrated that 79% of patients displayed asymmetrical hypertrophy and only 18% the classically described concentric symmetrical hypertrophy.34 Reverse septal contour hypertrophy which is typically associated with HCM was present in a quarter of patients with ATTR. This creates a need to identify parameters that could help discriminate CA from HCM. FA and MD were significantly different between patients with CA and HCM 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 recognized that cardiac AL may regress with therapy and that this regression may be assessed via ECV.35 Newer disease-modifying treatments for ATTR, such as tafamidis, may offer a stabilizing effect preventing accumulation of misfolded amyloid proteins.36 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 orga-
nization as the amyloid protein infiltrates the myocardium. The correlation between decreasing FA and impaired circumferential strain reflects the interaction of disrupted microstructural organization on macroscopic function. FA is reported to be highest in the mesocardium, which is considered to represent the more uniform organization of the near circumferentially oriented cardiomyocytes, whose shortening contributes substantially to circumferential strain.\textsuperscript{16,37} 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 patients with ATTR, 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 patients with CA, although it would be expected that the normal subjects would have normal ECV. Thresholds for abnormal diffusion biomarkers need further validation.

**Conclusions**

DT-CMR offers novel insight into the interaction between amyloid infiltration and cardiac microstructure. FA and MD characterize the expanded and disorganized 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 shearlet relaxation and indicating that different mechanisms may be responsible in AL and ATTR.

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**Disclosures**

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**REFERENCES**


**ARTICLE INFORMATION**

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