

ORIGINAL RESEARCH

Cardiac Diffusion Tensor Imaging May Detect Early Cardiac Amyloidosis in Carpal Tunnel Syndrome



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ABSTRACT

BACKGROUND Cardiac amyloidosis (CA) occurs when amyloid fibrils deposit in the myocardium, leading to diastolic dysfunction and subsequent heart failure. An early symptom of systemic amyloidosis is carpal tunnel syndrome (CTS). The prevalence of CTS in patients with transthyretin amyloidosis has been shown to be up to 50%, with CTS preceding clinically overt CA by 5 to 10 years on average.

OBJECTIVES This study applied cardiac diffusion tensor imaging (cDTI) to patients with CTS who underwent carpal tunnel release surgery and had confirmed amyloid deposition on tenosynovial biopsy in an attempt to screen for early CA.

METHODS cDTI was performed on 20 patients with CTS with confirmed tenosynovial amyloid, 20 patients with CA, 20 patients with hypertrophic cardiomyopathy, and 20 healthy controls. The diffusion scheme was an electrocardiogram-gated, free-breathing, second-order, motion-compensated spin echo acquisition obtained in systole. Mean diffusivity (MD), fractional anisotropy (FA), helix angle transmural, absolute sheetlet angle, T1, and T2 were calculated from respiratory motion-corrected images.

RESULTS MD was significantly elevated in CA compared to CTS (1.79 ± 0.16 vs 1.63 ± 0.09 , $P = 0.0016$), and in CTS compared to healthy controls (1.63 ± 0.09 vs 1.51 ± 0.10 , $P = 0.0016$). FA was significantly reduced in CA compared to controls (0.25 ± 0.052 vs 0.31 ± 0.057 , $P = 0.0044$) and CTS compared to controls (0.24 ± 0.027 vs 0.31 ± 0.057 , $P = 0.0004$). cDTI outperformed T1 and T2 in distinguishing between healthy myocardium and those of the CA and CTS groups.

CONCLUSIONS MD and FA were significantly different between healthy patients and those with CA or CTS, suggesting that cDTI may detect evidence of myocardial microstructural alterations consistent with possible early CA. (JACC Adv. 2026;5:102562) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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**ABBREVIATIONS
AND ACRONYMS****ATTR** = transthyretin
amyloidosis**CA** = cardiac amyloidosis**cDTI** = cardiac diffusion tensor
imaging**CMR** = cardiac magnetic
resonance**CTS** = carpal tunnel syndrome**E2A** = absolute sheetlet angle**FA** = fractional anisotropy**HA** = helix angle**HAT** = HA transmural**HCM** = hypertrophic
cardiomyopathy**LV** = left ventricle**MD** = mean diffusivity**MRI** = magnetic resonance
imaging**PYP** = pyrophosphate**SPECT** = single-photon
emission computed
tomography

Amyloidosis is a systemic disease caused by the deposition of amyloid fibrils with misfolded protein, most commonly immunoglobulin light chains amyloidosis or transthyretin amyloidosis (ATTR). Cardiac amyloidosis (CA) occurs when these amyloid fibrils deposit in the myocardium, which leads to a restrictive cardiomyopathy and subsequent heart failure. Studies have shown that cardiac involvement in amyloidosis has a poor prognosis: the median life expectancy historically of untreated patients was 6 to 12 months in light chain amyloidosis and 3 to 5 years in wild-type ATTR amyloidosis.¹ Therapeutic treatments for CA are most effective when initiated before the onset of significant symptoms of cardiac dysfunction.² Early diagnosis, however, is challenging as symptoms of heart failure may not present until more advanced stages of CA.³

Historically, the gold standard of diagnosis of CA was an endomyocardial tissue biopsy showing positive Congo red staining

with the characteristic apple-green birefringence under polarizing light, with subsequent amyloid typing with immunohistochemistry or mass spectrometry.⁴ However, a noninvasive approach has been developed using nuclear scintigraphy with bone-avid radiotracers such as technetium pyrophosphate (PYP).⁴ A noninvasive diagnosis of ATTR-CA can be made in the context of grade 2 or grade 3 cardiac uptake on a PYP scan confirmed with single-photon emission computed tomography (SPECT) combined with negative testing for a monoclonal protein.⁵

Although bone-avid nuclear scintigraphy using ^{99m}Tc-phosphate derivatives has been found to have high specificity, its ability to pick up early ATTR-CA is in question. False-positive scans due to blood pool uptake and lack of SPECT imaging can lead to erroneous diagnosis.⁶ Furthermore, it involves radioactive exposure, and positive scans can still occur with rare forms of non-ATTR CA and have also been seen in hydroxychloroquine toxicity, to name a few examples.

Cardiac diffusion tensor imaging (cDTI)⁷ is an in vivo, noninvasive, and contrast-free imaging technique that can assess cardiac amyloid infiltration by analyzing myocardial microstructure.⁸ Key parameters obtained from cDTI include mean diffusivity (MD), fractional anisotropy (FA), helix angle (HA), and absolute sheetlet angle (E2A). MD reflects the degree of restriction of water diffusion within the

myocardium with higher values representing less restriction.⁸ FA is a scalar value between 0 to 1, with a value of 0 indicating that diffusion is isotropic whereas a value of 1 indicates that diffusion is anisotropic.⁸ HA is the angle between the local cardiomyocyte orientation and the circumferential directions in the wall of the left ventricle (LV). HA transmural (HAT) is the slope of HA transmurally from the endocardium to the epicardium. E2A is the orientation of the myocardial sheetlet structures relative to the epicardial wall of the LV. cDTI is noninvasive and does not expose patients to radiation, providing an advantage in the diagnosis of CA and potentially in the detection of early cardiac amyloid.

A red flag early symptom of systemic amyloidosis is carpal tunnel syndrome (CTS).⁹ The prevalence of CTS in patients with ATTR has been shown to be as high as 50%, with CTS preceding the diagnosis of clinically overt CA by between 5 to 10 years on average.¹⁰⁻¹³ This study therefore applied cDTI to patients with CTS who underwent carpal tunnel release surgery and had confirmed amyloid deposition on tenosynovial biopsy, along with patients with CA, hypertrophic cardiomyopathy (HCM), and healthy controls, in an attempt to screen for early CA. Earlier detection of CA would allow for the earlier initiation of treatment and better patient outcomes.

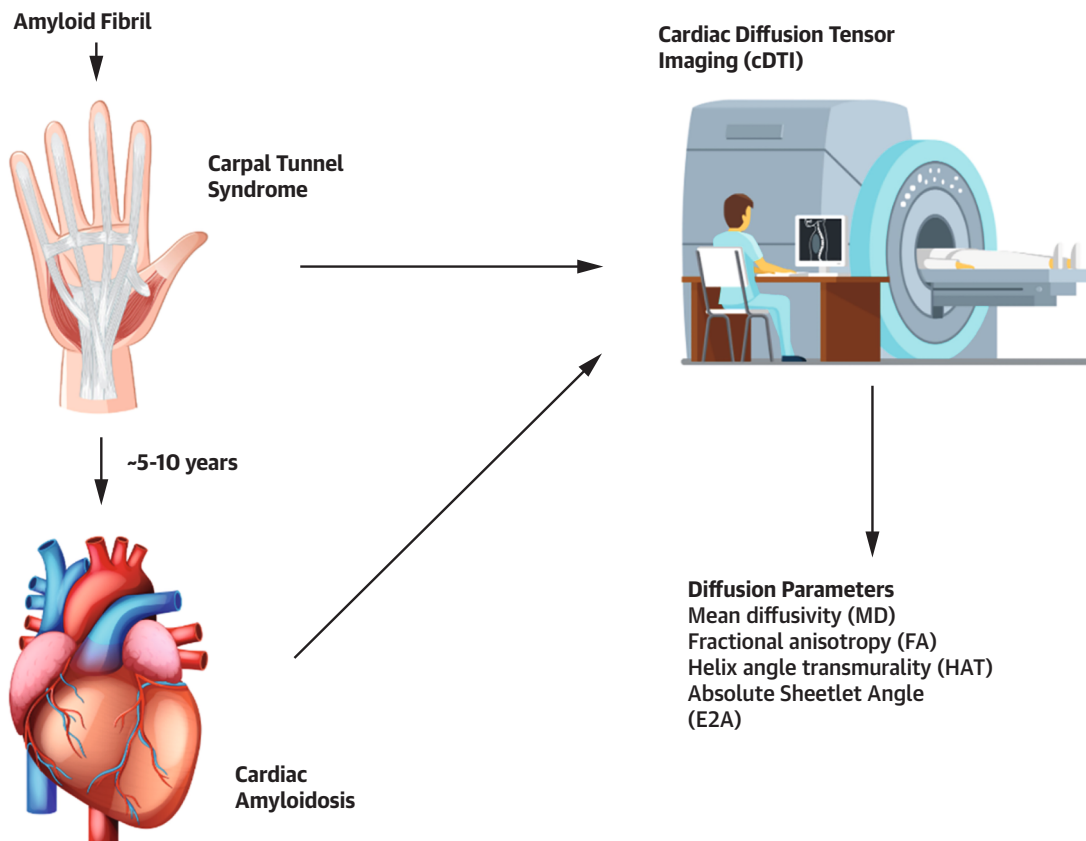
METHODS

PATIENT RECRUITMENT. This study was performed under a Cleveland Clinic Institutional Review Board approved protocol. Patients with the following inclusion criteria underwent cDTI: 1) between the ages of 18 to 85; and 2) provision of written informed consent. The following exclusion criteria were utilized: 1) vulnerable populations, including prisoners; 2) contraindications to cardiac magnetic resonance (CMR) imaging as determined by standard magnetic resonance imaging (MRI) protocols; and 3) decisionally impaired (eg, dementia, cognitive disability). Volunteers were compensated for their time.

Diagnosis of amyloidosis at the time of carpal tunnel release surgery was based on tenosynovial biopsy which was stained with Congo red, and subsequent amyloid typing was attempted using laser microdissection and mass spectrometry. Diagnosis of CA was done with a cardiac workup, including biomarkers, echocardiography, and a PYP scan. Diagnosis of HCM was based on an unexplained wall thickness >15 mm in the context of a highly suggestive cardiac MRI and/or genetic testing, or >13 mm in the presence of a family history. This group was

CENTRAL ILLUSTRATION Cardiac Diffusion Tensor Imaging May Detect Early Cardiac Amyloid

Patients with cardiac amyloidosis, carpal tunnel syndrome with tenosynovial amyloid, and healthy controls underwent cDTI; N = 20 for each group



MD and FA for the LV myocardium were significantly different between healthy patients and those with CA or CTS

- MD was highest in CA, followed by CTS, and lowest in healthy patients
- FA was lowest in CA and CTS, and highest in healthy patients

These results suggest that cDTI can detect evidence of microstructural alterations consistent with possible early cardiac amyloidosis

- Earlier detection provides the opportunity for earlier treatment initiation
- cDTI avoids the invasiveness of a myocardial biopsy and the radiation exposure of PYP

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Amyloid fibrils deposit all over the body, including the carpal tunnel, leading to carpal tunnel syndrome. Carpal tunnel syndrome is considered a red flag symptom of early systemic amyloidosis and can precede cardiac involvement of amyloidosis by 5 to 10 years on average. Therefore, patients with amyloid found in the tenosynovium represent a population at risk for the development of cardiac amyloidosis. We thus performed cardiac diffusion tensor imaging on patients with tenosynovial amyloid found during carpal tunnel release surgery who did not yet have evidence of cardiac involvement, as well as patients with confirmed cardiac amyloidosis, to determine cardiac diffusion tensor imaging's ability to screen for early cardiac amyloidosis. By analyzing differences in mean diffusivity and fractional anisotropy, there is evidence to suggest that cardiac diffusion tensor imaging can detect microstructural changes consistent with possible early cardiac amyloid involvement. Designed by Freepik. CA = cardiac amyloidosis; CTS = carpal tunnel syndrome; LV = left ventricle; PYP = pyrophosphate.

TABLE 1 Baseline Characteristics of Study Patients

	CTS (n = 20)	CA (n = 20)	P Value	HCM (n = 20)	P Value	Healthy (n = 20)	P Value
Age, y	73 ± 6	67 ± 10	0.028	56 ± 13	<0.001	52 ± 15	<0.001
Male	12 (60%)	15 (75%)		12 (60%)		12 (60%)	
Female	8 (40%)	5 (25%)		8 (40%)		8 (40%)	
Amyloid subtype	ATTR: 8 (40%) Untyped due to low amyloid yield: 12 (60%)	ATTR: 17 (85%) AL: 3 (15%)					
BMI, kg/m ²	30.51 ± 5.00	29.62 ± 4.59	0.561	29.29 ± 3.77	0.389	26.42 ± 5.56	0.019
Diabetes	6 (30%)	3 (15%)		2 (10%)		0 (0%)	
Hypertension	14 (70%)	8 (40%)		9 (45%)		1 (5%)	
Coronary artery disease	6 (30%)	4 (20%)		1 (5%)		0 (0%)	
Systolic blood pressure (mm Hg)	127.1 ± 17.79	124.3 ± 14.16	0.585	125.95 ± 12.29	0.813	119.42 ± 20.69	0.216
Diastolic blood pressure (mm Hg)	73.75 ± 8.16	71.00 ± 8.25	0.296	77.3 ± 9.63	0.216	76.08 ± 9.66	0.415
LV wall septal thickness (mm)	12.74 ± 2.48	17.14 ± 4.01	<0.001	14.80 ± 3.03	0.024	9.44 ± 1.44	<0.001
LV end-diastolic volume (mL)	138.48 ± 30.00	176.24 ± 42.33	0.003	155.28 ± 39.07	0.136	144.36 ± 46.37	0.637
Indexed LV end-diastolic volume (mL/m ²)	66.64 ± 13.03	82.05 ± 17.57	0.003	75.57 ± 13.86	0.043	73.00 ± 17.58	0.202
LV end-systolic volume (mL)	55.73 ± 17.66	96.70 ± 31.46	<0.001	62.02 ± 19.22	0.288	59.65 ± 23.25	0.552
Indexed LV end-systolic volume (mL/m ²)	26.70 ± 7.61	45.15 ± 14.51	<0.001	29.87 ± 7.70	0.198	30.02 ± 8.70	0.207
LV stroke volume (mL)	82.75 ± 20.07	79.54 ± 27.60	0.677	93.26 ± 25.48	0.156	84.71 ± 25.93	0.791
Indexed LV stroke volume (mL/m ²)	39.94 ± 9.50	36.90 ± 12.04	0.381	45.082 ± 9.69	0.098	42.98 ± 10.43	0.341
LV ejection fraction (%)	60.04 ± 8.20	45.15 ± 14.93	<0.001	60.16 ± 6.94	0.960	59.10 ± 5.14	0.667
LV mass (g)	108.46 ± 34.97	171.48 ± 48.64	<0.001	136.00 ± 36.92	0.020	89.67 ± 32.39	0.086
Indexed LV mass (g/m ²)	51.82 ± 13.82	79.88 ± 20.68	<0.001	65.62 ± 14.52	0.004	46.69 ± 10.81	0.199
LV cardiac output (L/min)	5.54 ± 1.43	5.17 ± 1.94	0.497	6.07 ± 1.53	0.265	5.37 ± 1.35	0.701
LV cardiac index (L/min/m ²)	2.68 ± 0.67	2.40 ± 0.82	0.245	2.94 ± 0.57	0.194	2.74 ± 0.50	0.750

Values are mean ± SD or n (%). P values are in comparison to the carpal tunnel syndrome group.
AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; BMI = body mass index; CA = cardiac amyloidosis; CTS = carpal tunnel syndrome; HCM = hypertrophic cardiomyopathy; LV = left ventricle.

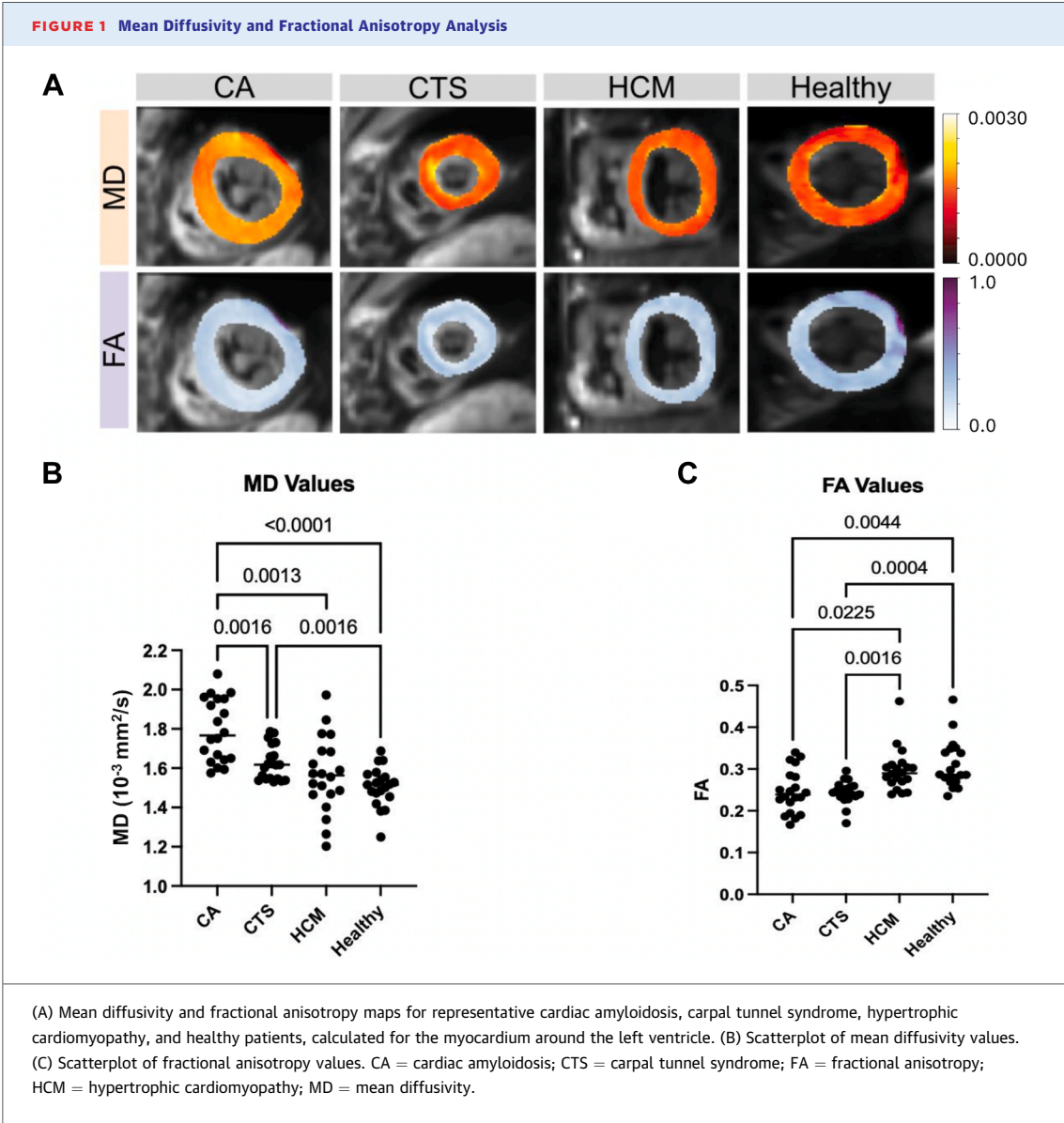
included since CA can oftentimes mimic features of HCM, such as left ventricular hypertrophy, making the differential diagnosis between these conditions challenging.¹⁴ Finally, healthy control participants were defined as patients with no history of existing heart disease or other chronic conditions.

IMAGE ACQUISITION. CMR was performed using 3T MAGNETOM Cima.X (Siemens Healthineers AG) with an 18-channel body coil. The system has a maximum possible gradient strength of 200 mT/m and a maximum slew rate of 200 mT/m/ms. cDTI used an electrocardiogram-gated, free-breathing, second-order, motion-compensated spin echo acquisition based on Stoeck et al¹⁵ obtained in systole (trigger delay = 50 ms).¹⁶ A ZOOMit pulse¹⁶ was used for inner volume excitation with a field of view of 350 mm and field of view phase reduction to 37.5%. Spectral attenuated inversion recovery fat suppression was used. The image resolution was 2.7 mm × 2.7 mm with a slice thickness of 8 mm. The matrix size was 128 × 48. Five slices were obtained with 12 diffusion

directions for both: 1 average low b = 50 s/mm² and 8 averages b = 500 s/mm², with an echo time of 59 ms. Scan duration was 540 heartbeats, with an average scan time of 8.34 minutes.

Native T1 and T2 mapping was also acquired in the same imaging session, with 3 slices acquired at apex, mid, and base. T1 mapping was performed with T1 modified look-locker inversion recovery.¹⁷ T2 mapping was performed with T2 fast low angle shot.¹⁸

CARDIAC MAGNETIC RESONANCE DATA ANALYSIS. Diffusion tensor calculation was performed in Python using a custom-built library. Diffusion-weighted images were retrospectively resampled by a factor of 2 (resolution = 1.85 mm × 1.85 mm). Respiratory motion correction was performed using the multitasking respiratory motion correction technique¹⁶ or symmetric and inverse-consistent deformable image registration.¹⁹ MD, FA, HAT, E2A were calculated from respiratory motion-corrected images.¹⁶ Global values of all parameters were calculated for the myocardium around the left ventricle from manual



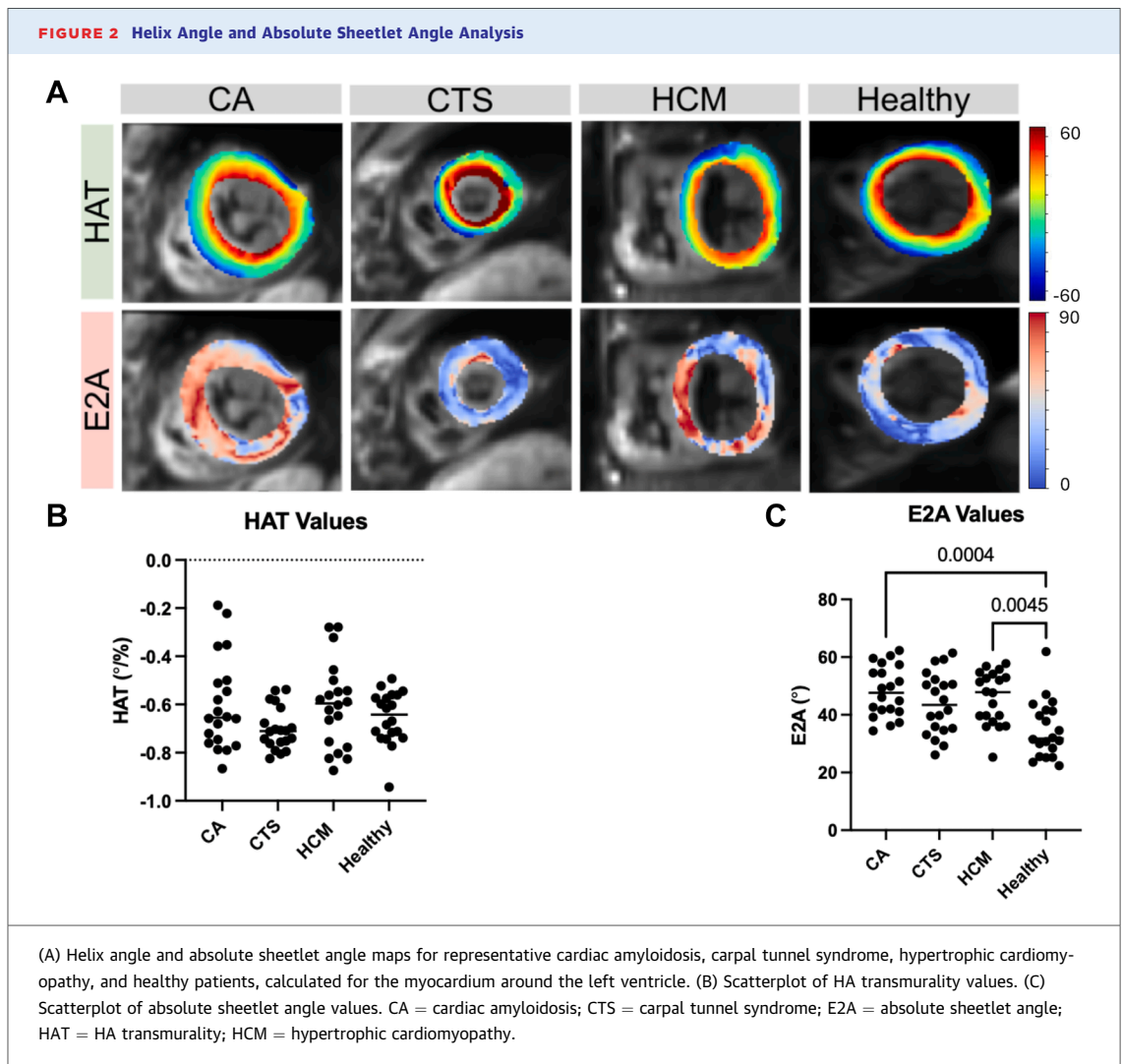
segmentations. Global T1 and T2 values in the LV myocardium were calculated from manual segmentations using Circle CVI42.²⁰

STATISTICAL ANALYSIS. Normality of the data was assessed visually using Q-Q plots. Data were found to be normal for the diffusion parameters. Brown-Forsythe and Welch analysis of variance was used to compare the means of MD, FA, HAT, E2A, T1, and T2 accordingly. A *P* value <0.05 was considered significant. Data are expressed as mean ± SD. A Dunnett T3 test was used as a post hoc multiple comparison test.

RESULTS

cDTI was performed on 20 patients with CTS with confirmed tenosynovial amyloid, 20 patients with CA, 20 patients with HCM, and 20 healthy controls (Central Illustration). Table 1 shows the baseline characteristics of patients in each of the 4 groups.

COMPARISON OF MD AND FA. Figure 1A depicts sample MRI overlay plots for MD and FA of representative patients with CA, CTS, HCM, and a healthy control. It can be appreciated that areas in the LV myocardium with elevated MD values correspond with areas of decreased FA.



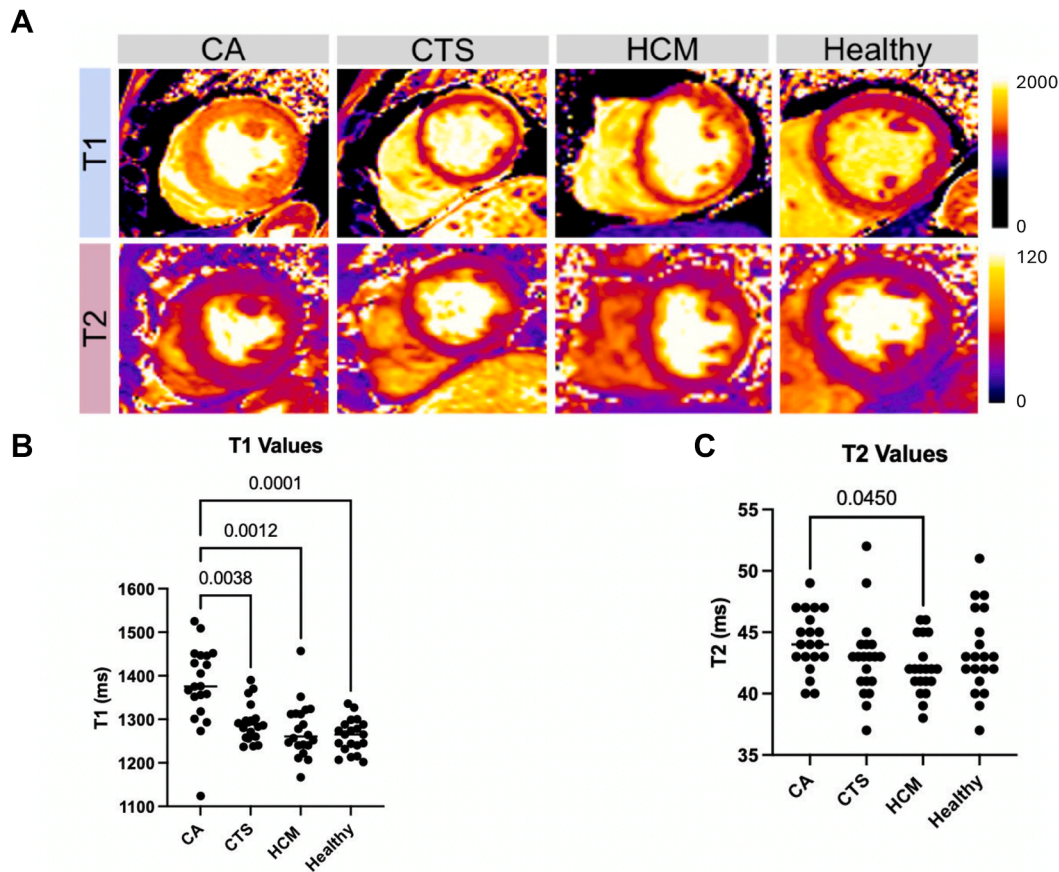
Figures 1B and 1C depicts scatterplots of the calculated MD and FA values for all patients in each of the 4 groups. MD was significantly elevated in patients with CA compared to patients with CTS (1.79 ± 0.16 vs $1.63 \pm 0.09 \mu\text{m}^2/\text{ms}$, $P = 0.0016$) (**Figure 1B**). Likewise, MD was significantly elevated in patients with CTS compared to healthy controls (1.63 ± 0.09 vs $1.51 \pm 0.10 \mu\text{m}^2/\text{ms}$, $P = 0.0016$) (**Figure 1B**). Patients with CTS thus had, on average, an intermediate MD value that was greater than healthy patients, but not as elevated as patients with confirmed CA. It is also noted that MD can discriminate between CA and HCM (1.79 ± 0.16 vs $1.57 \pm 0.19 \mu\text{m}^2/\text{ms}$, $P = 0.0013$) (**Figure 1B**), and that the HCM group showed the highest SD of MD values.

FA was significantly decreased in patients with CA compared to healthy controls (0.25 ± 0.052 vs

0.31 ± 0.057 , $P = 0.0044$) (**Figure 1C**), and in patients with CTS compared to healthy (0.24 ± 0.027 vs 0.31 ± 0.057 , $P = 0.0004$) (**Figure 1C**). FA could also discriminate patients with HCM (0.30 ± 0.051) from both patients with CA and CTS ($P = 0.0225$ and $P = 0.0016$, respectively). There was no statistically significant difference in the FA values between the CA and CTS groups.

COMPARISON OF HAT AND E2A. **Figure 2A** shows sample MRI overlay plots for parameters HA and E2A for representative patients from each group, and **Figures 2B and 2C** shows scatterplots of HAT and E2A values for each of the groups. HAT was not significantly different between CA, CTS, HCM, and healthy groups ($-0.60 \pm 0.19^\circ/\%$, $-0.70 \pm 0.087^\circ/\%$, $-0.60 \pm 0.18^\circ/\%$, and $-0.65 \pm 0.11^\circ/\%$, respectively)

FIGURE 3 T1 and T2 Analysis



(A) T1 and T2 maps for representative cardiac amyloidosis, carpal tunnel syndrome, hypertrophic cardiomyopathy, and healthy patients, calculated for the myocardium around the left ventricle. (B) Scatterplot of T1 values. (C) Scatterplot of T2 values. CA = cardiac amyloidosis; CTS = carpal tunnel syndrome; HCM = hypertrophic cardiomyopathy.

(Figure 2B) and had high SDs. E2A was significantly elevated in patients with CA compared to healthy patients ($48.14 \pm 8.78^\circ$ vs $34.88 \pm 9.86^\circ$, $P = 0.0004$) (Figure 2C). However, E2A did not differ statistically between CTS patients and healthy controls.

COMPARISON OF T1 AND T2. Figure 3A shows T1 and T2 maps for representative patients from each group, and Figures 3B and 3C shows scatterplots of the T1 and T2 values. T1 was found to be elevated in CA ($1,379 \pm 105$ ms) compared to CTS ($1,292 \pm 100$ ms, $P = 0.0038$) (Figure 3B), HCM ($1,275 \pm 90$ ms, $P = 0.0012$) (Figure 3B), and healthy ($1,262 \pm 105$ ms, $P = 0.0001$) (Figure 3B). T2 was only found to be significantly different between CA and HCM (44 ± 5 ms vs 42 ± 5 ms, $P = 0.0450$) (Figure 3C).

DISCUSSION

This study provides new insights into the use of cDTI to analyze myocardial microstructure in CA, with larger patient cohorts compared to previous works. In addition, this is the first study to investigate the use of cDTI as a tool to possibly detect early CA in patients with CTS, a key risk factor for CA, who have confirmed tenosynovial amyloid by biopsy but who do not yet meet the diagnostic criteria for cardiac involvement of amyloidosis using traditional diagnostic techniques with PYP scanning.

Here, we demonstrate that cDTI has the potential to identify early CA in patients who have amyloid found in the tenosynovium at the time of carpal tunnel release surgery. Amyloid deposits in the extracellular

space, increasing the extracellular volume in which water can diffuse freely and, thus, increasing MD values. Likewise, the amyloid deposition causes more microstructural disorganization which decreases the directional dependence of water diffusion, causing lower FA values. MD was found to be significantly elevated in patients with CA compared to patients with CTS, and in patients with CTS compared to healthy controls. An intermediate MD value between that of CA and healthy patients suggests the possibility of myocardial microstructural alterations consistent with early amyloid involvement. FA was also found to discriminate between the myocardial microstructure of healthy patients compared to those with CTS. FA was found to be significantly lower in patients with CTS compared to healthy patients, and at comparable levels to patients with CA, further providing evidence for possible early CA. While other parameters like E2A and T1 could discriminate between the myocardium of healthy and patients with CA, they did not show evidence of statistically significant differences between the CTS and healthy patients. Of note, cDTI was able to distinguish between the myocardial microstructure of patients with CA and those with HCM.

Given that there are statistically significant differences in the diffusion parameters of patients with CTS vs healthy patients, and that these differences mimic those seen between CA vs healthy patients, cDTI has the potential to identify myocardial microstructural changes that can possibly represent early cardiac amyloid involvement. In particular, since none of the patients with CTS in this study met the diagnostic criteria for CA using a PYP scan, cDTI might have the possibility of detecting CA earlier than PYP. To definitively validate cDTI as an early marker of CA in patients with CTS would require endomyocardial biopsy.

CA has historically been associated with a poor prognosis and short life expectancies postdiagnosis. In recent years, novel treatments for ATTR-CA have been developed. Most notably, tafamidis, a TTR stabilizer, was the first medication approved by the U.S. Food and Drug Administration to treat cardiomyopathy caused by ATTR in 2019. Tafamidis treatment is most effective when initiated earlier in the disease progression.²¹ A study showed that there was a 41% reduction in the risk of all-cause mortality in patients who were treated with continuous tafamidis compared to patients who received a placebo for

30 months followed by tafamidis treatment.²¹ Therefore, earlier detection of CA using MD and FA values from cDTI and resultingly earlier intervention could provide the opportunity for improved patient outcomes.

STUDY LIMITATIONS. A limitation of this study is the difference in the average ages of the CA and CTS groups compared with the HCM and healthy groups. Symptomatic CA tends to present in the later decades of life, with the average age of diagnosis of 73 to 75 years.^{10,22} The average age of patients with CA in this study was 70. Similarly, studies have suggested that only increasing age is associated with a greater likelihood of undergoing carpal tunnel release surgery,²³ which is how the diagnosis of CTS with confirmed tenosynovial amyloid was obtained in this work. In contrast, healthy controls with no existing chronic conditions tended to be younger patients, resulting in difficulties with age-matching the cohorts. There were also differences in the prevalence of hypertension, coronary artery disease, and diabetes between the 4 groups. Although current literature does not show direct evidence that these factors are linked to changes in cDTI parameters, this possibility cannot be ruled out. As such, without further workup like endomyocardial biopsy, changes in myocardial microstructure in patients with CTS cannot be definitively attributed to early CA. Future studies should aim to include a larger sample size with adjusted analyses to account for differences in baseline characteristics. Another limitation was that, given the contrast-free CMR protocol design, differences in extracellular volume in CA and patients with CTS were unable to be investigated. Likewise, comparison of gadolinium-based CMR, the current gold standard for CA, could not be performed.

CONCLUSIONS

Diffusion parameters MD and FA for the left ventricular myocardium were significantly different between healthy patients and those with CA or CTS with tenosynovial amyloid but negative traditional testing for CA. These results suggest that cDTI can detect evidence of microstructural alterations consistent with possible early cardiac amyloid involvement without the invasiveness of a heart tissue biopsy or radiation exposure in technetium PYP scintigraphy scans, but will need validation with endomyocardial biopsy. Earlier detection of CA offers

the possibility of earlier treatment initiation and the improvement of CA prognosis.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: cDTI's noninvasive, radiation-free, and noncontrast nature makes it a convenient method to detect myocardial microstructural changes associated with CA. The results of this work support cDTI as a screening tool to identify patients at risk of CA who may warrant further evaluation with contrast-enhanced cardiac magnetic resonance or endomyocardial biopsy.

TRANSLATIONAL OUTLOOK: Future research should aim to determine the sensitivity of cDTI in patients with carpal tunnel syndrome for the diagnosis of eventual CA. It should also aim to determine how much earlier cDTI can detect CA compared to current conventional techniques.

REFERENCES

1. Nienhuis H, Bijzet J, Hazenberg B. The prevalence and management of systemic amyloidosis in Western countries. *Kidney Dis*. 2016;2(1):10-19. <https://doi.org/10.1159/000444206>
2. Martyn T, Rubio AC, Estep JD, Hanna M. Opportunities for earlier diagnosis and treatment of cardiac amyloidosis. *Methodist DeBakey Cardiovasc J*. 2022;18(5):27-39. <https://doi.org/10.14797/mdcvj.1163>
3. Martinez-Naharro A, Hawkins PN, Fontana M. Cardiac amyloidosis. *Clin Med*. 2018;18(2):s30-s35. <https://doi.org/10.7861/clinmedicine.18-2-s30>
4. Koike H, Okumura T, Murohara T, Katsuno M. Multidisciplinary approaches for transthyretin amyloidosis. *Cardiol Ther*. 2021;10(2):289-311. <https://doi.org/10.1007/s40119-021-00222-w>
5. Gillmore JD, Maurer MS, Falk RH, et al. Non-biopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation*. 2016;133(24):2404-2412. <https://doi.org/10.1161/CIRCULATIONAHA.116.021612>
6. Khor YM, Cuddy SAM, Singh V, Falk RH, Di Carli MF, Dorbala S. 99mTc bone-avid tracer cardiac scintigraphy: role in noninvasive diagnosis of transthyretin cardiac amyloidosis. *Radiology*. 2023;306(2):e221082. <https://doi.org/10.1148/radiol.221082>
7. Dall'Armellina E, Ennis DB, Axel L, et al. Cardiac diffusion-weighted and tensor imaging: a consensus statement from the special interest group of the society for cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2024;27(1):101109. <https://doi.org/10.1016/j.jocmr.2024.101109>
8. Khalique Z, Ferreira PF, Scott AD, et al. Diffusion tensor cardiovascular magnetic resonance in cardiac amyloidosis. *Circ Cardiovasc Imaging*. 2020;13(5):e009901. <https://doi.org/10.1161/circimaging.119.009901>
9. Kuznecova I, Mierkyte G, Janciauskas D, et al. Impact of carpal tunnel syndrome surgery on early diagnosis and treatment of transthyretin cardiac amyloidosis. *Medicina (Kaunas, Lithuania)*. 2023;59(2):335. <https://doi.org/10.3390/medicina59020335>
10. Shetty NS, Pampana A, Patel N, et al. Carpal tunnel syndrome and transthyretin amyloidosis in the all of us research program. *Mayo Clin Proc*. 2024;99(7):1101-1111. <https://doi.org/10.1016/j.mayocp.2023.11.016>
11. Milandri A, Farioli A, Gagliardi C, et al. Carpal tunnel syndrome in cardiac amyloidosis: implications for early diagnosis and prognostic role across the spectrum of aetiologies. *Eur J Heart Fail*. 2020;22:507-515. <https://doi.org/10.1002/ejhf.1742>
12. Maurer MS, Hanna M, Grogan M, et al. Genotype and pCarpal tunnel syndrome in cardiac amyloidosis: implications for early diagnosis and prognostic role across the spectrum of aetiologies/genotype of transthyretin cardiac amyloidosis. *J Am Coll Cardiol*. 2016;68(2):161-172. <https://doi.org/10.1016/j.jacc.2016.03.596>
13. Gertz MA, Benson MD, Dyck PJ, et al. Diagnosis, prognosis, and therapy of transthyretin amyloidosis. *J Am Coll Cardiol*. 2015;66(21):2451-2466. <https://doi.org/10.1016/j.jacc.2015.09.075>
14. Jiang S, Zhang L, Wang J, et al. Differentiating between cardiac amyloidosis and hypertrophic cardiomyopathy on non-contrast cine-magnetic resonance images using machine learning-based radiomics. *Front Cardiovasc Med*. 2022;9:1001269. <https://doi.org/10.3389/fcvm.2022.1001269>
15. Stoeck CT, Von Deuster C, Genet M, Atkinson D, Kozerke S. Second-order motion-compensated spin-echo diffusion tensor imaging of the human heart. *Magn Reson Med*. 2016;75(4):1669-1676. <https://doi.org/10.1002/mrm.25784>
16. Nguyen CT, Christodoulou AG, Coll-Font J, et al. Free-breathing diffusion tensor MRI of the whole left ventricle using second-order motion compensation and multitasking respiratory motion correction. *Magn Reson Med*. 2021;85(5):2634-2648. <https://doi.org/10.1002/mrm.28611>
17. Messroghli DR, Radjenovic A, Kozerke S, Higgins DM, Sivananthan MU, Ridgway JP. Modified Look-Locker inversion recovery (MOLLI) for high-resolution T1 mapping of the heart. *Magn Reson Med*. 2004;52(1):141-146. <https://doi.org/10.1002/mrm.20110>
18. Deichmann R, Adolf H, Nöth U, Morrissey S, Schwarzbauer C, Haase A. Fast T2-mapping with SNAPSHOT FLASH imaging. *Magn Reson Med*. 1995;33(4):633-639. [https://doi.org/10.1016/0730-725X\(95\)00004-Z](https://doi.org/10.1016/0730-725X(95)00004-Z)
19. Liu Y, Kara D, Garrett T, et al. Toward optimal inline respiratory motion correction for in vivo cardiac diffusion tensor MRI using symmetric and inverse-consistent deformable image registration. *Magn Reson Med*. 2025;94(2):724-734. <https://doi.org/10.1002/mrm.30485>

20. Circle Cardiovascular Imaging Inc. *cvi42 [Computer Software]*. Calgary, AB: Circle Cardiovascular Imaging Inc; 2025. Version v6.2.
21. Elliott P, Drachman BM, Gottlieb SS, et al. Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy. *Circ Heart Fail*. 2021;15(1):e008193. <https://doi.org/10.1161/CIRCHEARTFAILURE.120.008193>
22. Connors LH, Sam F, Skinner M, et al. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective, observational cohort study. *Circulation*. 2016;133(3):282-290. <https://doi.org/10.1161/CIRCULATIONAHA.115.018852>
23. Day CS, Makhni EC, Mejia E, Lage DE, Rozental TD. Carpal and cubital tunnel syndrome: who gets surgery? *Clin Orthop Relat Res*. 2010;468(7):1796-1803. <https://doi.org/10.1007/s11999-009-1210-2>

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