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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Atrial Lesion and Diastolic Dysfunction May Be Associated With Atrial Fibrillation in Patients With Cardiac Amyloidosis

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Background: Atrial fibrillation (AF) is a common arrhythmia associated with cardiac amyloidosis (CA). Diastolic dysfunction and atrial lesions have been reported in patients with AF fibrillation. We aimed to evaluate the diastolic function and atrial lesions in patients with CA and AF.

Methods and Results: We included 27 patients (mean age 72 years) with biopsy-confirmed CA. We analyzed the average E/e′ as diastolic function using echocardiography and atrial late gadolinium enhancement (LGE) as an atrial lesion using cardiac magnetic resonance imaging (CMRI). We compared these parameters among 20 patients with sinus rhythm (SR) and 7 with AF. Echocardiography examination showed that average E/e′ were larger in the AF group than in the SR group (average E/e′: AF, 21.3 [14.5–30.3]; SR, 14.2 [10.3–16.9]; P=0.0053). CMRI demonstrated that atrial LGE was more severe in the AF group than in the SR group (AF, 7/7 [100%]; SR, 11/21 [52.4%]; P=0.00228). Univariate logistic regression analysis showed that average E/e′ demonstrated significant association with AF in all patients (odds ratio 1.24; [95% confidence interval 1.03–1.51]; P=0.0251).

Conclusions: AF may be associated with atrial lesions and diastolic dysfunction in patients with CA.

Key Words: Amyloidosis; Atrial fibrillation; Echocardiography; Magnetic resonance imaging

Cardiac amyloidosis (CA) is caused by the extracellular deposition of misfolded proteins as insoluble amyloid fibrils in the heart. Atrial fibrillation (AF) is a common arrhythmia in patients with CA and an important cause of heart failure.[1,2] Amyloid deposition in the atrial myocardium and diastolic dysfunction have been discussed in association with AF.[3,4] However, no reports have been made on atrial lesions and diastolic function associated with AF in patients with CA. The present study aimed to evaluate the association between atrial lesion and diastolic function in patients with CA.

Methods

Study Population

We retrospectively studied 27 patients with CA who underwent cardiac magnetic resonance imaging (CMRI) at Nagasaki University between April 2019 and July 2024. CA was confirmed in all patients using cardiac or extracardiac biopsy. Patients with contraindications to gadolinium, MRI, or both, those with cardiac device insertion, or those with cardiomyopathy, including ischemic cardiomyopathy, were excluded from the study.

This study was approved by the Ethics Committee of Nagasaki University Hospital (23022010) and was conducted in accordance with the Declaration of Helsinki.

Standard Echocardiography Assessment

Echocardiography was performed using the GE Vivid E95 system (version 203; GE HealthCare, IL, USA); images were acquired from standard views. Cardiac function was assessed using transthoracic echocardiography. All standard echocardiography measurements were performed according to the European Association of Cardiovascular Imaging guidelines.[5]

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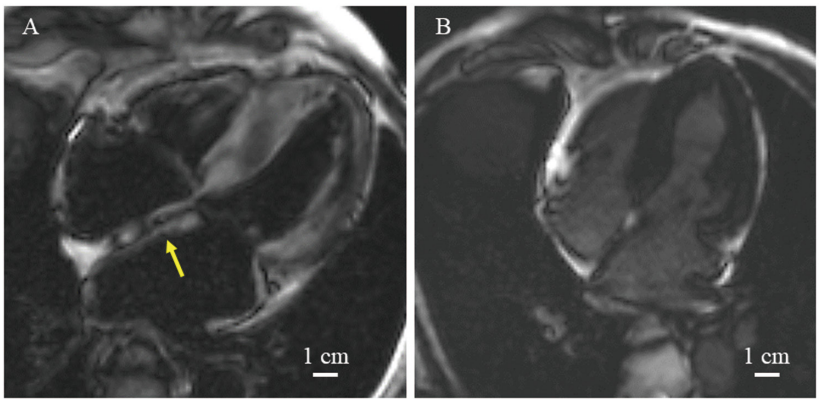

Figure. Severity of late gadolinium enhancement (LGE) of cardiac resonance images in patients with cardiac amyloidosis. (**A**) Severe LGE at the atrial septum (yellow arrow). (**B**) Mild LGE at the interatrial septum.

Table 1. Comparison of Clinical and Laboratory Data Characteristics Between AF and SR in All Patients

Characteristic	All (n=27)	AF (n=7)	SR (n=20)	P value (AF vs. SR)
Age (years)	72.0±7.7	74.6±5.0	71.2±8.3	0.3286
BMI (kg/m^2)	23.2±2.6	23.9±1.8	23.0±2.9	0.4136
NYHA II	18 (66.7)	1 (14.3)	17 (85.0)	0.0006
NYHA III	9 (33.3)	6 (85.7)	3 (15.0)	0.0006
SBP (mmHg)	117.1±20.4	109.6±18.8	119.7±21.3	0.2758
DBP (mmHg)	72.5±11.6	68.3±13.1	74.0±11.4	0.2807
Heart rate (beats/min)	76.1±11.0	67.9±12.6	79.0±9.3	0.0205
ATTR amyloidosis	18 (66.7)	6 (85.7)	12 (60.0)	1.0000
AL amyloidosis	9 (33.3)	1 (14.3)	8 (40.0)	0.2142
Female	5 (18.5)	0 (0)	5 (25.0)	0.1428
HT	19 (70.4)	5 (71.4)	14 (70.0)	0.9432
Diabetes	7 (25.9)	2 (28.6)	5 (25.0)	0.8528
Stroke or TIA	3 (11.1)	2 (28.6)	1 (5.0)	0.0877
Smoking	15 (55.6)	4 (57.1)	11 (55.0)	0.9218
SSS	1 (3.7)	1 (14.3)	0 (0)	0.0850
ACEI/ARB/ARNI	11 (40.7)	3 (42.9)	8 (40.0)	0.8947
SGLT-2	3 (11.1)	0 (0)	3 (15.0)	0.2771
MRA	7 (25.9)	3 (42.9)	4 (20.0)	0.235
Diuretic	18 (66.7)	5 (71.4)	13 (65.0)	0.7542
NT-proBNP (pg/dL)	1,824 [813–3,522]	2,988 [2,125–4,539]	1,119 [641–3,154]	0.1842
Troponin T (ng/dL)	0.047 [0.034–0.084]	0.036 [0.025–0.089]	0.048 [0.035–0.081]	0.3910
Hb (g/dL)	13.3±2.0	14.1±2.2	13.1±2.0	0.2916
eGFR (mL/min/1.73 m^2)	62.7±12.8	60.2±13.0	63.6±13.3	0.5718
AST (U/L)	25.0 [18.0–32.0]	28.0 [18.0–36.0]	24.0 [18.3–32.0]	0.9558
ALT (U/L)	21.6±10.4	24.0±16.4	20.8±8.2	0.4946
WBC (×10^3/μL)	5,259±1,314	5,586±1,350	5,145±1,351	0.4645
HbA1c (%)	6.0±0.5	6.3±0.7	5.9±0.5	0.1851
LDL-C (mg/dL)	108.0 [75.0–142.0]	105.0 [82.0–115.0]	115.5 [65.5–143.8]	0.7191
FT4 (ng/dL)	1.28 [1.16–1.44]	1.16 [1.00–1.40]	1.29 [1.18–1.50]	0.2289
TSH (μIU/mL)	2.60 [1.71–3.68]	2.68 [1.28–3.41]	2.50 [1.84–3.70]	0.5930

Unless indicated otherwise, data are presented as n (%), median [IQR] or mean±SD. ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AL, amyloid light chain; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; AST, aspartate aminotransferase; ATTR, amyloid transthyretin; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FT4, free thyroxin T4; Hb, hemoglobin; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT-2, sodium-glucose cotransporter 2; SR, sinus rhythm; SSS, sick sinus syndrome; TIA, transient ischemic attack; TSH, thyroid stimulating hormone; WBC, white blood cell.

Table 2. Comparison of Echocardiography and CMRI Parameters Between AF and SR in All Patients

	All (n=27)	AF (n=7)	SR (n=20)	P value
Echocardiography data				
LAD (mm)	41.7±7.1	46.3±4.6	40.2±7.4	0.0512
LAV (mL)	80.4±34.8	101.6±22.0	73.0±36.6	0.0646
LAVI (mL/m^2)	45.1±20.0	56.1±13.0	41.2±21.2	0.0948
LVEF (%)	53.0±13.0	50.3±14.4	53.9±13.1	0.5509
GLS (%)	−13.1 [−13.1, −9.15]	−10.1 [−11.5, −8.8]	−11.5 [−15.9, −9.8]	0.2683
IVST (mm)	14.2±3.4	15.3±3.7	13.8±3.1	0.3153
PWT (mm)	13.3±3.0	14.6±3.2	12.9±2.8	0.2102
LVDD (mm)	43.6±5.9	46.0±7.2	42.8±5.2	0.2342
LVSD (mm)	31.7±7.0	33.9±7.7	31.0±6.6	0.3629
LVMI (g/m^2)	136.0±39.4	156.5±33.7	128.8±40.5	0.1188
DT (ms)	206.5±59.9	223.9±108.5	200.5±35.1	0.3932
Average E/e′	15.1 [10.6–20.8]	21.3 [18.1–30.3]	12.6 [10.3–17.0]	0.0062
CMRI data				
Native T1	1,381±90	1,364±83	1,387±96	0.5787
T1–0 value	0.32 [0.29–0.33]	0.33 [0.30–0.33]	0.30 [0.27–0.33]	0.5931
LGE				
Ventricle severe	23 (85.2)	7 (100.0)	16 (80.0)	0.1998
Atrium severe	15 (55.6)	7 (100.0)	8 (40.0)	0.006

Unless indicated otherwise, data are presented as n (%), median [IQR] or mean±SD. AF, atrial fibrillation; CMRI, cardiac magnetic resonance imaging; DT, deceleration time; GLS, global longitudinal strain; IVST, interventricular septal thickness; LAD, left atrial dimension; LAV, left atrial volume; LAVI, left atrial volume index; LGE, late gadolinium enhancement; LVDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular volume mass index; LVSD, left ventricular end-systolic diameter; PWT, posterior wall thickness; SR, sinus rhythm.

Speckle Tracking Left Ventricular (LV) Analysis

Speckle-tracking analysis was performed offline using the software package, EchoPAC (version 204; General Electric) to evaluate LV global longitudinal strain.

Cardiac Magnetic Imaging

We used CMRI because previous studies have used CMRI for evaluating atrial lesions in patients with AF[6,7] and for detecting CA.[8] Late gadolinium enhancement (LGE) was observed in the interatrial septum (IAS),[9] and we evaluated LGE in the IAS.

Magnetic Resonance (MR) Protocol

Patients underwent CMRI using a 3T scanner (MAGNETOM Vida, Siemens Healthineers AG, Erlangen, Germany) with body and spine coils.

For LGE imaging, single-shot 2D phase-sensitive inversion recovery (PSIR) true fast imaging with steady-state precession (trueFISP) images were acquired in short-axis planes 15–20 min after intravenous administration of a contrast agent (gadolinium 0.10 mmol/kg). The details are as follows: time to repetition (TR) 3.18 ms; time to echo (TE) 1.32 ms; flip angle (FA) 55°; slice thickness 6 mm; 10 slices from base to apex; 1 breath hold; field of view (FOV) 360×292 mm^2; matrix 224×166; Grappa 2; and bandwidth 603 Hz/pixel. The magnitude and PSIR reconstructions were then performed. Based on the scout scan, the inversion time was set such that the normal myocardial signal was null in the magnitude of the image.

Retrospective gating of segmented 2D trueFISP cine imaging was performed with compressed sensing (CS) acceleration in the same slices and FOV, as in the LGE scan. Five slices were imaged during breath holding. The details are as follows: TR 3.40 ms; TE 1.49 ms; FA maximum 80°; matrix 256×256; CS factor 8.7; and bandwidth 977 Hz/pixel. The actual temporal resolution was 40.8 ms, and 25 phase images per heartbeat were reconstructed retrospectively.

Evaluation of LGE

One cardiologist and 1 radiologist, with >10 years of experience in CMRI, independently analyzed the MR images. We evaluated whether LGE was present or absent in the IAS on axial LGE MR with cine MR for anatomical landmarks in the IAS because the IAS is very thin and difficult to identify on LGE MR alone. When different findings were obtained, final decisions were reached by consensus between the cardiologist and the radiologist.

Severe LGE of the atrium was defined as LGE length of >80% or width of 5 mm in the IAS. Severe LGE of the ventricle was defined as global transmural LGE according to a previous report (**Figure**).[8]

Interobserver Variability

An additional investigator independently interpreted the LGE images using a test set of 20 patients to assess interobserver variability.

Statistical Analysis

Baseline characteristics were summarized as mean±standard deviation, or median and interquartile range for continuous variables with normal distribution or non-normal distribution, respectively, and counts (%) for categorical variables. The characteristics of the 2 groups (SR and AF) were compared using the Wilcoxon rank-sum or Fisher's exact test. We used logistic regression analysis to determine

Table 3. Comparison of Clinical and Laboratory Data Characteristics Between AF and SR in Patients With Severe Atrial LGE

	AF (n=7)	SR (n=8)	P value
Age (years)	74.6±5.0	70.0±9.2	0.2513
BMI (kg/m^2)	23.9±1.8	22.2±3.9	0.3009
NYHA II	1 (14.3)	6 (75.0)	0.0187
NYHA III	6 (85.7)	2 (25.0)	0.0187
SBP (mmHg)	109.6±18.8	116.3±23.8	0.5609
DBP (mmHg)	68.3±13.1	73.6±14.1	0.4639
Heart rate (beats/min)	67.9±12.6	74.8±8.5	0.2298
ATTR amyloidosis	6 (85.7)	4 (50.0)	0.1432
AL amyloidosis	1 (14.3)	4 (50.0)	0.3104
Female	0 (0)	3 (37.5)	0.0701
HT	5 (71.4)	6 (75.0)	0.8760
Diabetes	2 (28.6)	3 (37.5)	0.7144
Stroke or TIA	2 (28.6)	0 (0)	0.1044
Smoking	4 (57.1)	5 (62.5)	0.8327
SSS	1 (14.3)	0 (0)	0.2685
ACEI/ARB/ARNI	3 (42.9)	3 (37.5)	0.8327
SGLT-2	0 (0)	1 (12.5)	0.3329
MRA	3 (42.9)	1 (26.7)	0.1847
Diuretic	5 (71.4)	4 (50.0)	0.3980
NT-proBNP (pg/dL)	2,988.0 [2,125.0–4,539.0]	698.0 [368.8–4,683.8]	0.3253
Hs-TnT (ng/dL)	0.036 [0.025–0.089]	0.041 [0.031–0.081]	0.6852
Hb (g/dL)	14.1±2.2	12.6±1.9	0.2028
eGFR (mL/min/1.73 m^2)	60.2±13.0	67.0±12.2	0.3178
AST (U/L)	28.0 [18.0–36.0]	26.0 [18.3–43.0]	0.9079
ALT (U/L)	24.0±16.4	25.4±9.3	0.8442
WBC (×10^3/μL)	5,586±1,350	4,825±1,540	0.3309
HbA1c (%)	6.3±0.7	6.2±0.6	0.7826
LDL-C (mg/dL)	105.0 [82.0–115.0]	120.0 [57.3–191.0]	0.7285
FT4 (ng/dL)	1.16 [1.00–1.40]	1.28 [1.14–1.46]	0.4314
TSH (μIU/mL)	2.68 [1.28–3.41]	2.36 [1.63–2.98]	1.0000

Unless indicated otherwise, data are presented as n (%), median [IQR] or mean±SD. Hs-TnT, high sensitivity troponin T. Other abbreviations as in Table 1.

the association of significant variables for AF.

All hypothesis tests were 2 sided, and statistical significance was set at P<0.05. All analyses were performed using JMP statistical software (JMP 17Pro, SAS Institute, Cary, NC, USA).

Results

Of the 27 patients (wild-type transthyretin CA [ATTRwt-CA], 18 patients; light chain CA [AL-CA], 9 patients), 7 had AF, and 20 had SR. No significant difference was found in clinical characteristics between patients with SR and those with AF except for New York Heart Association (NYHA) classification (III; AF, 6/7 patients; SR, 3/20 patients; P=0.0006), and heart rate (AF, 67.9±12.6; SR, 79.0±9.3; P=0.03557; **Table 1**). The 2 groups had no significant differences in laboratory data (**Table 1**).

Echocardiography examination showed that the average E/e′ was higher in the AF group than in the SR group (average E/e′: AF, 21.3 [18.1–30.3]; SR, 12.6 [10.3–17.0]; P=0.0062; **Table 2**).

The CMRI showed that severe atrial LGE was more common in the AF group than in the SR group (AF, 7/7 [100%] patients; SR, 8/20 [40%] patients; P=0.0060), whereas severe ventricular LGE was not (**Table 2**).

We also evaluated the echocardiography data of patients with severe atrial LGE between the SR and AF groups. Although there were no significant differences in baseline clinical and laboratory data except for NYHA severity (III: AF, 6/7 patients; SR, 2/8 patients; P=0.0187; **Table 3**), the left atrial volume index (LAVI) and average E/e′, and LV mass index (LVMI) were significantly higher in AF group than in the SR group, respectively (LAVI: AF, 56.1±13.0; SR, 31.6±10.3; P=0.0013; average E/e′: AF, 21.3 [14.5–30.3]; SR, 10.5 [9.8–14.8]; P=0.0032; LVMI: AF, 156.5±33.7; SR, 107.9±37.7; P=0.0214; **Table 4**). Interobserver agreement for the presence and pattern (mild or severe) of LGE (κ 0.89; 95% confidence interval [CI] 0.68–1.0) was excellent.

Moreover, we evaluated these parameters in 18 patients with ATTRwt-CA. No significant difference was found in clinical characteristics between patients with SR and those with AF, except for the NYHA classification (III: AF, 5/6 patients; SR, 1/12 patients; P=0.0062; **Table 5**). The 2 groups had no significant differences in laboratory data (**Table 5**).

Echocardiography examination showed that the average

Table 4. Comparison of Echocardiography and CMRI Parameters Between AF and SR in Patients With Severe Atrial LGE

	AF (n=7)	SR (n=8)	P value
Echocardiography data			
LAD (mm)	46.3±4.6	38.3±8.5	0.0438
LAV (mL)	101.6±22.0	52.9±24.0	0.0013
LAVI (mL/m^2)	56.1±13.0	31.6±10.3	0.0013
LVEF (%)	50.3±14.4	54.3±4.6	0.3915
GLS (%)	−10.1 [−11.5, −8.8]	−12.5 [−16.4, −10.5]	0.0745
IVS (mm)	15.3±3.7	12.8±3.8	0.2325
PWT (mm)	14.6±3.2	11.5±2.7	0.0745
LVDD (mm)	46.0±7.2	41.8±6.6	9.2718
LVSD (mm)	33.9±7.7	29.4±7.7	0.2983
DT (ms)	223.9±108.5	211.8±28.6	0.765
Average E/e′	21.3 [18.1–30.3]	10.5 [9.8–14.8]	0.0032
LVMI (g/m^2)	156.5±33.7	107.9±37.7	0.0214
CMRI data			
Native T1	1,364±83	1,374±87	0.8357
T1–0 value	0.33 [0.30–0.33]	0.30 [0.26–0.37]	0.4269
LGE			
Ventricle severe	7 (100)	8 (100)	1.0000

Unless indicated otherwise, data are presented as n (%), median [IQR] or mean±SD. Abbreviations as in Table 2.

Table 5. Comparison of Clinical and Laboratory Data Characteristics Between AF and SR in Patients With ATTR Cardiac Amyloidosis

Characteristic	All (n=18)	AF (n=6)	SR (n=12)	P value (AF vs. SR)
Age (years)	74.4±4.7	74.2±5.4	74.6±4.5	0.8642
BMI (kg/m^2)	23.9±2.1	24.4±1.4	23.6±2.4	0.4418
NYHA II	11 (61.1)	1 (16.7)	10 (83.3)	0.0062
NYHA III	7 (38.9)	5 (83.3)	1 (9.1)	0.0062
SBP (mmHg)	123.7±20.4	113.8±16.5	128.6±21.0	0.1532
DBP (mmHg)	75.2±12.2	71.3±11.3	77.2±23.6	0.3596
Heart rate (beats/min)	73.8±10.7	68.7±13.6	76.3±8.4	0.1565
Female	0 (0)	0 (0)	0 (0)	NA
HT	16 (88.9)	5 (83.3)	11 (91.7)	0.6431
Diabetes	7 (38.9)	2 (33.3)	5 (41.7)	0.7324
Stroke or TIA	3 (16.7)	2 (33.3)	1 (8.3)	0.1797
Smoking	12 (66.7)	3 (50.0)	9 (75.0)	0.1688
SSS	1 (5.6)	1 (16.7)	0 (0)	0.1456
ACE/ARB/ARNI	8 (44.4)	3 (50.0)	5 (41.7)	0.7373
SGLT-2	3 (16.7)	0 (0)	3 (25.0)	0.1797
MRA	4 (22.2)	2 (33.3)	2 (16.7)	0.4227
Diuretic	12 (66.7)	4 (66.7)	8 (66.7)	1.0000
NT-proBNP (pg/dL)	1,574 [730–3,101]	2,904 [1,653–4,591]	914 [563–2,220]	0.1466
Troponin T (ng/dL)	0.044 [0.032–0.088]	0.033 [0.023–0.066]	0.046 [0.035–0.068]	0.2606
Hb (g/dL)	13.8±2.2	14.2±2.4	13.6±2.2	0.3726
eGFR (mL/min/1.73 m^2)	63.5±13.7	61.0±14.0	64.8±13.9	0.5988
AST (U/L)	23.0 [18.8–31.3]	24.0 [17.3–33.0]	23.0 [19.8–33.0]	0.9625
ALT (U/L)	19.8±10.3	20.9±15.4	19.3±7.5	0.7777
WBC (×10^3/μL)	5,250±1,303	5,733±1,292	5,008±1,233	0.2786
HbA1c (%)	6.1±0.6	6.4±0.7	6.0±0.5	0.1517
LDL-C (mg/dL)	88.5 [68.5–132.3]	108.5 [80.3–119.5]	82.5 [59.5–140.3]	0.4824
FT4 (ng/dL)	1.23 [1.14–1.42]	1.14 [0.95–1.80]	1.25 [1.17–1.44]	0.2275
TSH (μIU/mL)	2.40 [1.65–3.55]	2.44 [1.80–3.68]	2.40 [1.80–3.68]	0.7250

Unless indicated otherwise, data are presented as n (%), median [IQR] or mean±SD. Abbreviations as in Tables 1,3.

Table 6. Comparison of Echocardiography and CMRI Parameters Between AF and SR in Patients With ATTR Cardiac Amyloidosis

	All (n=18)	AF (n=6)	SR (n=12)	P value
Echocardiography data				
LAD (mm)	43.7±6.4	47.0±4.6	42.1±6.7	0.1281
LAV (mL)	83.8±24.1	100.8±24.0	75.3±20.0	0.0288
LAVI (mL/m^2)	45.2±17.0	55.3±14.1	40.2±16.5	0.0724
LVEF (%)	48.1±11.4	50.3±15.7	47.0±9.2	0.5754
GLS (%)	−10.6 [−11.9, −9.18]	−10.1 [−11.5, −8.8]	−10.7 [−13.0, −9.8]	0.5241
IVST (mm)	15.0±3.1	14.7±4.0	15.1±2.7	0.7567
PWT (mm)	13.8±2.9	13.8±3.1	13.8±3.0	1.0000
LVDD (mm)	45.5±6.2	47.0±8.0	44.8±5.3	0.4823
LVDS (mm)	34.3±6.8	34.5±8.9	34.2±5.9	0.9251
LVMI (g/m^2)	148.6±31.7	149.8±31.4	148.0±33.2	0.9155
DT (ms)	196.5±57.9	197.5±91.0	195.9±37.5	0.9585
Average E/e′	17.4 [13.3–20.9]	19.8 [17.2–27.2]	15.0 [10.3–18.7]	0.0549
CMRI data				
Native T1	1,365±82.5	1,350±80	1,372±80	0.5933
T1–0 value	0.33 [0.29–0.33]	0.33 [0.30–0.33]	0.31 [0.27–0.33]	0.5392
LGE				
Ventricle severe	17 (94.4)	6 (100.0)	11 (91.7)	0.4669
Atrium severe	11 (61.1)	6 (100.0)	5 (41.7)	0.0167

Unless indicated otherwise, data are presented as n (%), median [IQR] or mean±SD. Abbreviations as in Table 1,2.

Table 7. Logistic Regression Analysis for a Predictor of AF in Patients

	OR	95% CI	P value
All cardiac amyloidosis patients			
Age	1.08	0.92–1.24	0.2753
HT	1.07	0.16–7.12	0.9432
Obesity	1.60	0.22–11.4	0.6404
Diabetes	1.20	0.17–8.24	0.8529
Smoking	1.13	0.19–6.19	0.9218
Average E/e′	1.20	1.02–1.42	0.0282
Severe atrial LGE	–	–	–
ATTRwt-CA patients			
Age	0.98	0.79–1.21	0.8540
HT	0.45	0.02–8.82	0.6024
Obesity	1.50	0.17–12.7	0.7106
Diabetes	0.70	0.09–5.43	0.7330
Smoking	0.30	0.04–2.63	0.2973
Average E/e′	1.19	0.98–1.44	0.0864
Severe atrial LGE	–	–	–

ATTRwt-CA, wild-type transthyretin cardiac amyloidosis; CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1,2.

E/e′ was higher in the AF group than in the SR group without significance, but with the significance trend defined as P<0.1 (average E/e′: AF, 19.8 [17.2–27.2]; SR, 15.0 [10.3–18.7]; P=0.0549; **Table 6**).

The CMRI showed that severe atrial LGE was more common in the AF group than in the SR group (AF, 6/6 [100%] patients; SR, 5/12 [42%] patients; P=0.0167), whereas severe ventricular LGE was not (**Table 6**).

Univariate logistic regression analysis showed that average E/e′ demonstrated significant association with AF in all patients (odds ratio [OR] 1.24; 90% CI 1.03–1.51; P=0.0251; **Table 7**). We found no significance but significant trend of average E/e′ in association with AF in patients with ATTRwt-CA (OR 1.19; 90% CI 0.98–1.44; P=0.0864; **Table 7**). However, univariate logistic regression analysis of severe atrial LGE could not show the result because of an insufficient number of patients in all patients and in patients with ATTRwt-CA (**Table 7**). Therefore, we could not perform multivariate analysis of these parameters.

Discussion

The present study demonstrated that: (1) severe atrial LGE was more in patients with amyloidosis and AF than those with amyloidosis and SR; (2) average E/e′ was significantly higher in patients with CA and AF than those with CA

and SR; (3) in patients with CA and severe atrial LGE, average E/e′, LAVI, and LVMI was significantly higher in the AF group than in the SR group; and (4) average E/e′ demonstrated a significant association with AF in all CA patients.

Amyloid accumulates in all cardiac structures, including the left and right atria. Amyloid deposition in the atrial myocardium impairs atrial conduction, which promotes AF.[3] Isolated atrial amyloidosis (IAA) due to local overproduction of atrial natriuretic peptide in the absence of systemic disease and ventricular involvement affects atrial conduction and increases AF risk.[3,10] A previous autopsy study reported that significantly more hearts with high-grade IAA were associated with atrial tachyarrhythmias compared with those with low-grade IAA.[11] Moreover, AF is also a prevalent arrhythmia in patients with amyloid transthyretin (ATTR) and amyloid light chain (AL) CA.[10,12] However, Bandera et al.[13] demonstrated that ATTR-CA is related to significant infiltration of the atrial wall while remaining in SR.

Habibi et al.[6] reported that patients with AF had increased LGE compared with healthy volunteers. Recent studies have demonstrated the diagnostic value of LGE and T1 mapping as techniques to improve CA detection.[14] Kwong et al.[7] reported that the extent of LA LGE was highly predictive for diagnosing CA.

Our study showed that all AF patients with CA had severe atrial LGE, and that may be associated with AF in patients with CA. No reports have been made on the association between atrial LGE and AF in patients with CA. However, in our study, some patients with CA and SR had severe atrial LGE. This suggests that severe atrial LGE may not be the only factor associated with AF. Diastolic dysfunction is also associated with AF.[4] A previous report showed that tissue Doppler septal e′ was low and median E/e′ was high in patients with CA (AL or ATTR).[15] Mints et al.[16] demonstrated that the mean diastolic dysfunction grade was higher in AF than in SR despite no differences in LV ejection fraction or LA volume in CA with AF and SR.

In our study, the average E/e′ was significantly higher in the AF group than in the SR group. We also demonstrated that average E/e′ was significantly higher in AF with severe atrial LGE than in SR with severe atrial LGE.

Taken together, these results suggest that both diastolic dysfunction and atrial damage related to CA may be associated with AF in patients with CA. However, the relationship between amyloid deposition and diastolic dysfunction in patients with CA is complex.

CA at the ventricular level also plays a role in the pathophysiology of AF by increasing the atrial and ventricular filling pressures that induce non-specific fibrosis.[1] The left and right atria involvement may be due to the hemodynamic effects of ventricular diastolic dysfunction in CA.[10]

Other factors may be associated with AF in patients with CA. Cardiac autonomic dysfunction is associated with a higher risk of AF.[17] CA is also associated with autonomic dysfunction.[18] Thus, autonomic dysfunction may be associated with AF in patients with CA. However, autonomic dysfunction was not examined in this study.

Histological correlates of atrial structural remodeling in patients with AF include fibrosis, increased intercellular space, myofibrillar loss, and decreased nuclear density.[19] However, the histopathological features in patients with CA and AF remain unknown although tissue abnormalities of atria including amyloid deposition and fibrosis may contribute to AF occurrence in CA.[20]

Previous studies in patients with CA have demonstrated that AF was seen more in patients with ATTRwt-CA than those with AL-CA.[20,21] Sinigiani et al.[20] showed that age, interatrial block, and left atrial ejection fraction were independent predictors of incident AF. These suggested that types of amyloidosis may be related to AF in patients with CA. Therefore, we also evaluated patients with ATTRwt-CA. However, average E/e′ was not significantly associated with AF in patients with ATTRwt-CA. That may be due to an insufficient number of patients, or other factors such as autonomic dysfunction, and atrial tissue abnormalities (atrial transthyretin amyloid deposition and/or fibrosis) might be associated with AF in ATTRwt-CA. Further studies are needed to evaluate factors associated with AF in patients with ATTRwt-CA.

Recently, atrial LGE on CMRI has been reported for the diagnosis of atrial involvement from CA and for establishment of appropriate treatment.[22] However, its precise evaluation is difficult, and the association between atrial LGE and atrial amyloid deposition is unknown. That may be one of the reasons why we could not easily find a significant association between atrial amyloid deposition and AF instead of an insufficient number of patients with CA using CMRI.

Catheter ablation for AF should be considered a treatment option in patients with CA.[23] However, it was associated with a significant risk of complication in advanced-stage CA.[24] Therefore, identification of atrial legions using CMRI may be clinically important in especially decision of catheter ablation.

Study Limitations

This study has several limitations. This was a single-center retrospective study with a small sample size, which may not have been sufficient to detect statistical significance. Further studies are required to evaluate the factors associated with AF in patients with CA. However, patients were selected to ensure SR and AF were as closely related to CA as possible. Thus, our results were affected mainly by CA itself.

Conclusions

AF may be associated with atrial lesions and diastolic dysfunction in patients with CA.

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None.

Disclosures

The authors declare no conflicts of interest. K.M. is a member of *Circulation Reports*' Editorial Team.

IRB Information

Ethics committees at Nagasaki University Hospital (Registration no. 23022010).

Data Availability

None.

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