Original Article

Left Atrial Mechanical Function and Aortic Stiffness in Middle-aged Patients with the First Episode of Atrial Fibrillation

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Abstract

Background: In the early stages of atrial remodeling, aortic stiffness might be an indication of an atrial myopathy, in particular, atrial fibrosis. This study aimed to investigate the association between left atrial (LA) mechanical function, assessed by two-dimensional speckle tracking echocardiography, and aortic stiffness in middle-aged patients with the first episode of nonvalvular atrial fibrillation (AF).

Methods: This prospective study included 34 consecutive patients with the first episode of AF, who were admitted to Kartal Koşuyolu Research and Training Hospital between May 2013 and October 2015, and 31 age- and gender-matched healthy controls. During the 1st month (mostly in the first 2 weeks) following their first admission, 34 patients underwent the first pulse wave measurements. Then, 21 patients were recalled for their second pulse wave measurement at 11.8 ± 6.0 months following their initial admission. Echocardiographic and pulse wave findings were compared between these 34 patients and 31 healthy controls. We also compared the pulse wave and echocardiographic findings between the first and second measurements in 21 patients.

Results: Pulse wave analysis showed no significant differences between the AF patients and healthy controls with respect to PWV (10.2 ± 2.5 m/s vs. 9.7 ± 2.1 m/s; $P = 0.370$), augmentation pressure (9.6 ± 7.4 mmHg vs. 9.1 ± 5.7 mmHg; $P = 0.740$), and aortic pulse pressure (AoPP; 40.4 ± 14.0 mmHg vs. 42.1 ± 7.6 mmHg, $P = 0.550$). The first LA positive peak of strain was inversely related to the augmentation pressure ($r = −0.30$; $P = 0.02$) and aortic systolic pressure ($r = −0.26$, $P = 0.04$). Comparison between the two consecutive pulse wave measurements in 21 patients showed similar results, except for AoPP. In 21 patients, the AoPP at the second measurement (45.1 ± 14.1 mmHg) showed a significant increase compared with AoPP at the first measurement (39.0 ± 10.6 mmHg, $P = 0.028$), which was also higher than that of healthy controls (42.1 ± 7.6 mmHg, $P = 0.000$).

Conclusion: The association between aortic stiffness with reduced atrial strain and the key role of AoPP in the development of AF should be considered when treating nonvalvular AF patients with normal LA sizes.

Key words: Aortic Stiffness; Atrial Fibrillation; Atrial Strain

Introduction

The pathogenesis of atrial fibrillation (AF) involves multifactorial processes that lead to left atrial (LA) remodeling following electrical, contractile, and structural remodeling that take place in succession, resulting in an evolution from a paroxysmal to a persistent stage.[1,2] AF is usually initiated by a trigger.[3] Hypertension (HTN) is a significant independent predictor of AF. A community-based study demonstrated that increased pulse pressure (PP), as a surrogate marker of aortic stiffness, was an important risk factor for the incidence of AF.[4,5] Pulse wave analysis allows us to estimate aortic stiffness through a number of indicators, including central systolic pressure, central PP, augmentation pressure (AP), and pulse wave velocity (PWV).[6] A recent study found increased aortic stiffness characterized by increased PP and AP in lone AF patients. It was proposed that despite normal LA dimensions, ventricular thickness, and brachial systolic blood pressure (SBP), aortic stiffness

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signifies "atrial-myopathy".[7] In an attempt to determine the amount of fibrosis in patients with paroxysmal and persistent AF, Kuppahally *et al*.[8] used delayed-enhanced magnetic resonance imaging (DE-MRI) and found an inverse relationship between atrial strain, strain rate (SR), and LA structural remodeling. In this study, we used two-dimensional speckle tracking strain imaging to investigate the association between LA mechanical function and aortic stiffness in middle-aged patients with the first episode of AF, who had no structural heart diseases and had normal LA dimensions.

Methods

Patients

This prospective study included 34 consecutive patients with the first episode of nonvalvular AF (19 males and 15 females; mean age: 48.5 ± 10.4 years) who were admitted to the emergency service of Kartal Koşuyolu Research and Training Hospital between May 2013 and October 2015, requiring either medical or electrical cardioversion, and 31 age- and gender-matched healthy individuals were also included in the study as healthy controls. Patients who had any of the following conditions were excluded from the study: structural or valvular heart diseases, coronary artery disease, chronic kidney disease, abnormal thyroid and hepatic functions, or chronic obstructive lung diseases. We also excluded those with previously attempted AF ablation, LA diameters >40 mm, or systolic left ventricular (LV) dysfunction. Each patient would perform an exercise stress test to exclude coronary heart disease. The weight, height, and blood pressure measurements were made and recorded appropriately. During the 1st month (mostly in the first 2 weeks) after the first admission, 34 patients underwent the first pulse wave measurements. Twenty-one patients were recalled for the second pulse wave measurements at 11.8 ± 6.0 months following the first admission. Only three patients had symptomatic AF episode during the follow-up period. Echocardiographic examination and pulse wave measurement were also performed on the same day. Echocardiographic and pulse wave findings were compared between these 34 patients and 31 healthy controls. We also compared the pulse wave and echocardiographic findings between the first and second measurements of 21 patients. This study was approved by the Ethics Committee of Kartal Koşuyolu Research and Training Hospital (No. 09.2016.465), and all participants provided written informed consents.

Pulse wave analysis

A central aortic pressure waveform was used to determine central SBP, central PP, and AP. Central arterial waveforms were derived using the SphygmoCor system (AtCor Medical, Sydney, Australia). The radial artery waveform was recorded from the radial artery at the wrist using high-fidelity applanation tonometry (Millar Instruments, Houston, TX, USA). The SphygmoCor system automatically generated the corresponding central (aortic) waveforms from an averaged radial artery waveform. Information on central SBP was derived from the central waveform.

Pulse wave velocity

PWV is a direct measure of the arterial stiffness of large arteries. To determine aortic PWV, waveforms of the common carotid and femoral arteries were obtained using the SphygmoCor system. PWV was calculated as the distance between the suprasternal notch and femoral artery recording site and divided by the time interval between the trough of the pressure waves.

Echocardiographic analysis

Standard echocardiographic evaluations were performed using a 1–5 MHz X5-1 transducer (iE33, Philips Healthcare, Inc., Andover, MA, USA) by the same physician. Patients were examined in the left lateral position. Measurements were averaged over three consecutive heart cycles. All standard two-dimensional transthoracic echocardiographic images (parasternal long-axis, short-axis, and apical 4-, 3-, and 2-chamber views), color Doppler, and tissue Doppler images were triggered to the QRS complex and stored in a cine-loop format. LV diastolic and systolic diameters were measured using the M-mode or two-dimensional echocardiography. The LV ejection fraction was calculated according to Simpson's formula employing a two-dimensional image of LV chamber during systole and diastole in the four- and two-chamber apical views.

Mitral inflow velocities were measured by pulsed-wave Doppler, with the sample volume placed at the tips of the mitral valve in the left ventricle. E and A waves were recorded. Mitral annular velocities were measured by pulsed-wave Doppler tissue imaging, with the sample volume placed at the level of the lateral and septal mitral annulus. Septal and lateral e' and a' waves were recorded; E/e' for the septal and lateral mitral annulus and E/A were calculated.

The pulmonary arterial pressure was estimated from the tricuspid regurgitation jet. Evaluation of the right ventricular function was performed using the tricuspid annular plane systolic excursion in the apical four-chamber view and the tricuspid annulus peak systolic velocity by tissue Doppler imaging.

LV strain (circumferential and longitudinal) was evaluated using two-dimensional speckle tracking imaging. Global circumferential strain was assessed by applying the two-dimensional speckle tracking imaging to the parasternal short-axis views of the left ventricle. Longitudinal peak systolic strain was assessed by applying the two-dimensional speckle tracking imaging to the apical 4-, 3-, and 2-chamber views.

The LA diameter was measured at end systole in the parasternal long-axis view. The LA volume (LAV) was calculated from the apical 4- and 2-chamber views of LA using the biplane area length method. The LAV index (LAVI) was calculated by dividing the LAV by the body surface area. The LA strain and SR values were obtained from the apical 2- and 4-chamber views by the speckle tracking method. The first positive peak of strain (LAS), plateau (COND),

and return to the zero line (ATRIAL) were considered to represent LA reservoir, conduit, and contractile phases, respectively. Accordingly, the following three SR parameters were obtained: peak-positive SR (SRs, corresponding to atrial reservoir function), peak early-negative SR (SRe, corresponding to atrial conduit function), and peak late-negative SR (SRa, corresponding to atrial contraction).

Statistical analysis

Data were analyzed using IBM SPSS Statistics 17.0 software (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation (SD) or median (range) for quantitative variables and as percentages for categorical variables. Categorical variables were compared using Chi-square or Fisher's exact test as appropriate. The variables between AF patients and healthy controls were compared using Student's *t*-test. The variables between first and second measurements in 21 patients were compared using the paired *t*-test with the null hypothesis. Correlation analyses included both intra- and inter-group variables. Correlations between the aortic strain and pulse wave parameters were analyzed using Pearson's or Spearman's correlation tests as appropriate. A $P < 0.05$ was considered statistically significant.

Results

Baseline clinical and echocardiographic findings are summarized in Tables 1–3. The AF patients and healthy controls were similar in terms of age and gender. There were no significant differences in the body mass index ($P = 0.450$), heart rate (HR; 69.2 ± 10.1 beats/min vs. 71.9 ± 11.4 beats/min, $P = 0.330$), SBP (125.5 ± 19.4 mmHg vs. 130.3 ± 11.6 mmHg, $P = 0.250$), and diastolic blood pressure (DBP; 72.7 ± 10.5 mmHg vs. 74.0 ± 10.1 mmHg, $P = 0.630$) between the AF patients and healthy controls. The rate of smoking was higher in the AF patients compared with healthy controls (14.7% vs. 9.6%, $P = 0.020$).

Pulse wave analysis showed no significant differences between the AF patients and healthy controls with respect to PWV (10.2 ± 2.5 m/s vs. 9.7 ± 2.1 m/s; $P = 0.370$), AP (9.6 ± 7.4 mmHg vs. 9.1 ± 5.7 mmHg; $P = 0.740$), and aortic PP (AoPP; 40.4 ± 14.0 mmHg vs. 42.1 ± 7.6 mmHg, $P = 0.550$).

The first LA positive peak of strain was inversely correlated with AP ($r = -0.30$, $P = 0.020$) and aortic systolic pressure ($r = -0.26$, $P = 0.040$). There was a positive correlation between the first LA positive peak strain and the mitral E wave ($r = 0.37$, $P = 0.020$), E/A ratio ($r = 0.44$, $P = 0.000$), lateral annular e' ($r = 0.42$, $P = 0.000$), and septal annular e' ($r = 0.27$, $P = 0.020$). The first LA positive peak strain was also inversely correlated with the DBP ($r = -0.28$, $P = 0.030$). The 4- and 2-chamber conduit phases showed significant positive correlations with PWV ($r = 0.30$, $P = 0.020$ and $r = 0.34$, $P = 0.010$, respectively).

AP had a positive correlation with SBP ($r = 0.43$, $P = 0.001$) and a negative correlation with HR ($r = -0.58$, $P = 0.000$). AoPP and aortic SBP were positively correlated with SBP ($r = 0.76$, $P = 0.000$ and $r = 0.93$, $P = 0.000$, respectively).

Table 1: Clinical characteristics and pulse wave measurements of the study population

Items	AF patients ($n = 34$)	Healthy controls ($n = 31$)	*P*
Age (years)	48.5 ± 10.4	46.5 ± 8.7	0.390
Gender (male/female), *n*	19/15	19/12	0.660
Risk factors			
DM	2 (5.8)	1 (3.2)	0.610
HTN	10 (39.4)	4 (12.9)	0.100
Smoking	5 (14.7)	3 (9.6)	0.020
HL	4 (11.7)	7 (22.5)	0.250
BMI (kg/m²)	29.0 (26.3–31.7)	25.5 (24.1–29.4)	0.450
HR (beats/min)	69.2 ± 10.1	71.9 ± 11.4	0.330
SBP (mmHg)	125.5 ± 19.4	130.3 ± 11.6	0.250
DBP (mmHg)	72.7 ± 10.5	74 ± 10.1	0.630
CRP (mU/ml)	0.34 (0.26–0.42)	0.52 (0.30–1.90)	0.190
TSH (mg/L)	19.0 ± 13.4	17.0 ± 9.8	0.660
AoSP (mmHg)	113.9 ± 19.6	115.7 ± 10.9	0.650
AoPP (mmHg)	40.4 ± 14.0	42.1 ± 7.6	0.550
AP (mmHg)	9.6 ± 7.4	9.1 ± 5.7	0.740
ED (ms)	320.0 ± 18.0	312.7 ± 21.8	0.037
SEVR (%)	145.8 ± 22.5	144.9 ± 21.5	0.880
PWV (m/s)	10.2 ± 2.5	9.7 ± 2.1	0.370

The data are shown as mean ± SD, *n* (%) or median (range). DM: Diabetes mellitus; HTN: Hypertension; HL: Hyperlipidemia; BMI: Body mass index; HR: Heart rate; SBP: Systolic blood pressure; CRP: C–reactive protein; DBP: Diastolic blood pressure; TSH: Thyroid–stimulating hormone; AoSP: Aortic systolic pressure; AoPP: Aortic pulse pressure; AP: Augmentation pressure; SEVR: Subendocardial viability ratio; ED: Ejection duration; PWV: Pulse wave velocity; SD: Standard deviation.

Table 2: Standard echocardiographic features of the study population

Items	AF patients ($n = 34$)	Healthy controls ($n = 31$)	*t*	*P*
LVEDD (cm)	4.80 ± 0.49	4.70 ± 0.47	0.82	0.410
LVESD (cm)	3.00 ± 0.43	2.8 0 ± 0.44	1.37	0.170
LVEF (%)	62.60 ± 4.50	65.70 ± 0.97	−3.70	0.000
LA (cm)	3.40 ± 0.45	3.20 ± 0.47	1.80	0.770
LAV (ml)	52.1 ± 14.5	47.9 ± 12.2	1.21	0.230
LAVI (ml/m²)	1.80 ± 0.50	1.70 ± 0.58	−0.05	0.630
E (cm/s)	70.6 ± 14.6	74.6 ± 19.1	−0.97	0.330
A (cm/s)	64.1 ± 14.2	66.2 ± 18.0	−0.53	0.590
E/A ratio	1.14 ± 0.29	1.19 ± 0.39	−0.57	0.570
DECT (m/s)	227.6 ± 62.1	198.8 ± 49.7	2.02	0.048
LAT E/e'	7.36 ± 2.4	6.19 ± 1.6	2.20	0.030
SEPT E/e'	8.99 ± 3.2	7.89 ± 2.3	1.50	0.130
TAPSE (mm)	25.3 ± 4.6	24.5 ± 3.9	0.79	0.420
ST (cm/s)	14.5 ± 2.5	15.0 ± 2.3	−0.84	0.400

The data are shown as mean ± SD. LVESD: Left ventricular end–systolic diameter; LVEDD: Left ventricular end–diastolic diameter; LVEF: Left ventricular ejection fraction; LA: Left atrium; LAV: Left atrial volume; LAVI: Left atrial volume index; E: Mitral inflow E wave; A: Mitral inflow A wave; DECT: Deceleration time; LAT E/e': Lateral annular E/e'; SEPT E/e': Septal annular E/e'; TAPSE: Tricuspid annular plane systolic excursion; ST: Tricuspid annular peak systolic velocity; SD: Standard deviation.

Table 3: Two-dimensional speckle tracking echocardiographic values of the study population

Items	AF patients (n = 34)	Healthy controls (n = 31)	Statistical values	P
GCS (%)	22.5 ± 5.2	22.8 ± 4.6	−0.26*	0.790
GLS (%)	18.5 ± 3.6	21.0 ± 2.3	−3.19*	0.002
LASTR4 (%)	40.0 ± 20.2	50.5 ± 19.4	−2.13*	0.030
COND4 (%)	15.4 ± 9	19.6 ± 10.4	−1.62*	0.109
ATRIAL4 (%)	19.8 ± 9.2	25.1 ± 11.0	−2.00*	0.049
SRs4 (s^{-1})	1.0 (0.8/1.5)	1.0 (0.4/1.0)	2.04†	0.049
SRe4 (s^{-1})	−2.0 (−1.0/−2.4)	−2.0 (−1.0/−3.0)	1.70†	0.090
SRa4 (s^{-1})	−2.0 (−1.3/−3.0)	−3.0 (−2.0/−4.0)	2.14†	0.030
LASTR2 (%)	36.9 ± 17.1	41.7 ± 16.7	−1.12*	0.260
COND2 (%)	13.0 ± 10.1	15.73 ± 10.1	−1.00*	0.310
ATRIAL2 (%)	17.8 ± 9.5	23.5 ± 12.2	−1.95*	0.050
SRs2 (s^{-1})	0.8 (0.6–1.0)	0.8 (0.4–1.2)	0.34†	0.730
SRe2 (s^{-1})	−1.6 (−1.0/−2.1)	−1.6 (−0.9/−3.0)	0.68†	0.500
SRa2 (s^{-1})	−2.0 (−1.3/−3.0)	−3.0 (−2.0/−4.0)	2.37†	0.020

Values were derived from four- to two-chamber views.*t values; †Chi-square values. AF: atrial fibrillation; GCS: Global circumferential left ventricular strain; GLS: Global longitudinal left ventricular strain; LASTR4−2: Left atrial first positive peak of strain; COND4−2: Plateau and return to the zero line; ATRIAL4−2: The contractile phase; SRs4−2: Peak–positive strain rate (SRs corresponds to the atrial reservoir function); SRe4−2: Peak early–negative strain rate (SRe corresponds to the atrial conduit function); SRa4−2: Peak late–negative strain rate (SRa corresponds to the atrial contraction).

Table 4: Comparison of two pulse wave measurements of 21 patients (paired t-test)

Parameters	t	df	P
Pair 1 – AoSP−AoSP2	−1.75	20	0.095
Pair 2 – AoPP−AoPP2	−2.37	20	0.028
Pair 3 – AP−AP2	−1.48	20	0.155
Pair 4 – SEVR−SEVR2	1.88	20	0.075
Pair 5 – ED−ED2	0.31	20	0.758
Pair 6 – PWV−PWV2	1.27	19	0.219

AoSP: Aortic systolic pressure; AoPP: Aortic pulse pressure; AP: Augmentation pressure; SEVR: Subendocardial viability ratio; ED: Ejection duration; PWV: Pulse wave velocity.

Aortic SBP and PP showed a positive correlation with the LA diameter (r = 0.38, P = 0.003 and r = 0.33, P = 0.010, respectively), LV end-diastolic diameter (r = 0.40, P = 0.002 and r = 0.33, P = 0.009, respectively), and LV end-systolic diameter (r = 0.40, P = 0.002 and r = 0.27, P = 0.003, respectively). There was also a positive correlation between aortic SBP and LAV (r = 0.32, P = 0.010), whereas AoPP was negatively correlated with the HR (r = −0.49, P = 0.000).

Among the 21 patients who underwent a repeat pulse wave measurement at 11.8 ± 6.0 months, the body mass index, HR, and SBP and DBP remained similar, compared with the first measurements [P = 0.197, P = 0.800, P = 0.660, and P = 0.970, respectively]. AoPP was significantly higher in the second measurement (P = 0.028), whereas PWV, aortic SBP, and the augmentation pressure showed no significant changes (P = 0.219, P = 0.095, and P = 0.155, respectively; Table 4). Of note, AoPP increased significantly from 39.0 ± 10.6 mmHg (the first measurement) to 45.1 ± 14.1 mmHg (the second measurement) in the 21 AF patients (P = 0.028), moreover the result of the second measurement was significantly different from that of the healthy controls (P = 0.000).

Discussion

Our study demonstrated a significant inverse association between aortic stiffness and reduced LA strain in middle-aged patients with the first episode of nonvalvular AF. The patients in this study exhibited reduced atrial strain during the reservoir phase of the cardiac cycle. Even though PWV, AP, aortic SBP, and PP in the AF patients did not differ from those in healthy controls, the first LA positive peak of strain indicated that the reservoir phase was inversely correlated with AP and aortic SBP in the AF patients. This association was not observed in healthy controls.

Aortic stiffness is an independent predictor of vascular morbidity and mortality in patients with HTN, diabetes mellitus, or end-stage renal disease as well as in patients older than 70 years.[9] Pulse wave analysis is a clinically validated, noninvasive, and reproducible method to measure arterial stiffness.[7,10] The SphygmoCor system has been proven to be the gold standard for the measurement of arterial stiffness. It allows surrogate measures of aortic stiffness, including central SBP, central PP, AP, augmentation index, and PWV of the aorta.[6,11,12] In the Framingham community-based observational cohort, arterial stiffness, as evidenced by elevated PP, was a potentially modifiable risk factor for AF and was an important predictor of incident AF; this was true even after other risk factors associated with AF had been ruled out.[5] However, increased PP and AP were demonstrated to be prominent in lone AF patients, who had larger LA dimensions than the controls.[7] Age-related aortic stiffness was independently associated with the atrial size in patients with persistent AF.[13] In our study, even though the patients had normal LA dimensions, there was a remarkable association between aortic stiffness and atrial remodeling. Lone AF patients may have several atrial abnormalities that can predispose them to the development of persistent AF, such as increased inflammation, diastolic dysfunction,

increased fibrosis, and microvascular dysfunction.[7] Using DE-MRI, Mahnkopf *et al*.[14] demonstrated structural remodeling in lone AF patients, and Kuppahally *et al*.[8] showed that LA strain and SR were negatively associated with LA wall fibrosis, contributing to AF burden. AF of short duration was associated with less structural remodeling.[14] In our study, LA strain was significantly reduced in the AF patients and showed an inverse correlation with aortic stiffness parameters. Our patient group consisted of younger participants than most prior studies. Although our patients had normal LA dimensions and brachial arterial blood pressures, LA strain was evident as an early sign of atrial remodeling. Our data on the association between LA strain and aortic stiffness further supported the findings of other studies, which showed a significant association between aortic stiffness and the development of AF.[1,5] Kuppahally *et al*.[8] noted that the amount and severity of fibrosis increased with the persistence and recurrence of AF. They also noted that the association between atrial strain and fibrosis, as shown by DE-MRI, was more prominent in patients with persistent AF than those with paroxysmal AF. Our study suggested that, even in the early stages of atrial remodeling, aortic stiffness might be an indication of an atrial myopathy, in particular, atrial fibrosis.

In our study, pulse wave measurements of 21 patients were repeated at 11.8 ± 6.0 months after the first measurements and the results of two measurements were compared. The only remarkable change was observed in AoPP, which showed a significant increase, not only compared with the first measurement of these patients but also with that of the healthy controls [Table 4]. In the Strong Heart Study, it was found that central AoPP predicted a cardiovascular outcome more strongly than brachial pressures; it also had a greater importance over systolic pressure.[15] In a large, multi-ethnic, community-based cohort, increased SBP and PP, but not mean arterial or DBPs, were related to an increased risk for AF. This conclusion was made after adjustment for other risk factors, with a higher PP being an independent risk factor for AF.[16] In another study, PP showed a significant correlation with atrial size and arterial stiffness, thereby contributing to LA enlargement and increasing the risk for AF.[17] Mitchell *et al*.[5] reported that intermittent increases in SBP and PP in individuals with increased aortic stiffness might contribute to the development of AF. This was independent of pressure-induced effects on LA dimensions and LV mass. LV structural change and myocardial fibrosis can be an alternative mechanism to explain the association between PP and AF.[16] Central PP expresses the pulsatile component of the left ventricle afterload and has a strong association with LV filling pressures.[18] Increased PP increases the cardiac load and increases AF risk.[5] Moreover, higher PP was found related to smoking; as in our study smoking rate was higher in AF patients.[18] As suggested by our findings, PP might play the key role in the development of AF in middle-aged patients.

In conclusion, given our findings from middle-aged nonvalvular AF patients with normal LA dimensions, in those with first episode AF, aortic stiffness was associated with reduced atrial strain. AoPP played a key role in the development of AF, even in early stages of atrial remodeling.

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Conflicts of interest

There are no conflicts of interest.

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