Original Article

The Association of Cardio-Ankle Vascular Index (CAVI) with Biatrial Remodeling in Atrial Fibrillation

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Aim: Arterial stiffness results in elevated left ventricular filling pressure and can promote atrial remodeling due to chronic pressure overload. However, the impact of arterial stiffness on the process of atrial remodeling in association with atrial fibrillation (AF) has not been fully evaluated.

Methods: We enrolled 237 consecutive patients diagnosed with AF who had undergone ablation; data from 213 patients were analyzed. Cardio-ankle vascular index (CAVI) was used as a marker of arterial stiffness. The left atrial (LA) and right atrial (RA) volumes were determined by computed tomography imaging; atrial conduction and voltage amplitude were evaluated using a three-dimensional electromapping system used to guide the ablation procedure.

Result: In univariate analysis, CAVI significantly correlated with atrial structural and electrical remodeling (LA volume index, $r=0.297$, $P=0.001$; RA volume index, $r=0.252$, $P=0.004$; LA conduction velocity, $r=0.254$, $P=0.003$; LA mean voltage, $r=-0.343$, $P=0.001$, RA mean voltage; $r=-0.245$, $P=0.015$). Multivariate regression analysis revealed that CAVI and plasma levels of N-terminal B-type natriuretic peptide were independent determinants of LA and RA remodeling, respectively. On the other hand, age and LA conduction velocity were independent variables with respect to CAVI. Age-adjusted CAVI was highest in long-standing persistent AF when compared with measures of persistent or paroxysmal AF.

Conclusion: CAVI was closely associated with biatrial remodeling in patients diagnosed with AF. These results suggest that arterial stiffness may play a significant role with respect to disease progression.

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Introduction

Atrial fibrillation (AF) is the most common of the cardiac arrhythmias encountered in clinical practice; it is associated with increased risk of potential complications and mortality[1, 2]. Numerous risk factors, including aging, hypertension, obesity, metabolic syndrome, renal disease, and structural heart disease, have been reported to be associated with the development of AF[3-6]. Among these, hypertension and dia-stolic dysfunction are both major risk factors for new-onset AF. Increases in systemic blood pressure can induce chronic diastolic atrial pressure overload, which can result in the structural remodeling within the atria and create conditions conducive to the generation of AF[7]. Notably, atrial remodeling promotes not only the onset but also the maintenance of ongoing AF; increased atrial dilatation is a significant predictor of persistent AF, and it is also an important determinant of multiple-circuit reentry[3, 7].

Arterial stiffness also reflects the severity of atherosclerosis and serves as a predictor of significant cardiovascular events; arterial stiffness is also associated with left ventricular diastolic dysfunction in atherosclerotic patients. Arterial stiffness increases pulse pressure and cardiac afterload; this may result in both left ventricular and atrial structural and electrical changes that serve to promote AF[8].

A recent report has shown that pulse wave velocity (PWV), a marker of arterial stiffness, is associated with lone AF, increased left atrial (LA) remodeling. However, PWV has some important limitations. PWV is profoundly influenced by the distending force exerted by the blood pressure on blood vessels,which either increases or decreases the PWV[9]. In contrast, the cardio-ankle vascular index (CAVI) is widely used as an index of arterial stiffness. CAVI measurements are not dependent on systemic blood pressure; several reports have demonstrated the utility of CAVI for the detection of atherosclerotic disease[10-12]. There are significant correlations between CAVI and the E/A ratio, LA diameter, and plasma levels of N-terminal B-type brain natriuretic peptide (NT-pro BNP), which has been associated with atrial remodeling and fibrosis following a chronic pressure overload[13]. The relationship between arterial stiffness measured by CAVI and paroxysmal AF (Paf) was also reported previously by Miyoshi *et al.*[14] These results suggest a close relationship exists between increased arterial stiffness, as determined by the CAVI, and the progress of atrial remodeling, as detected by both structural and electrical remodeling that promote and maintain AF. To understand the role of arterial stiffness and its role in promoting the development of AF, we explored the relationship between arterial stiffness and atrial remodeling in patients diagnosed with AF.

Methods

Study Participants

We enrolled 237 consecutive patients who underwent catheter ablation for Paf or non-paroxysmal AF (non-Paf), and the measurement of CAVI in our observational cohort study was conducted at Toho Ohashi Medical Center from June 2016 to March 2019. Paf was defined as AF that terminated spontaneously within 7 days of onset; non-Paf was defined as persistent or long-standing persistent AF as per the 2013 guidelines of the Japan Circulation Society (JCS)[16].

The exclusion criteria included severe valvular heart disease, a history of cardiac valve surgery, and cases where a second ablation was performed for AF; we also excluded patients with LA thrombi detected by transthoracic echocardiography (TTE) and/or transesophageal echocardiography due to the high risk of cerebral infarction during the ablation procedure. In addition, we also excluded patients undergoing hemodialysis and/or those with peripheral arterial disease defined as an ankle–brachial index value (ABI) of ＜0.9. A final group of 213 patients with AF was included in the study. The study protocol was approved by the Ethics Committee for Clinical Research of Toho University Ohashi Medical Center (H16032). All the patients provided informed consent.

Atherosclerotic Risk Factors and the CHADS₂ and CHA₂DS₂-VASc Scores

All patients were examined for coronary risk factors, including age, smoking, hypertension, hyperuricemia, diabetes mellitus, obesity, and a history of coronary artery disease. Hypertension was defined as systolic pressure $\geq$ 140 mmHg, diastolic pressure $\geq$ 90 mmHg, and/or currently on medication for hypertension. Dyslipidemia was defined as follows: high total serum cholesterol ($\geq$ 220 mg/dl), high serum low-density lipoprotein-cholesterol ($\geq$ 140 mg/dl), and/or high serum triglycerides ($\geq$ 150 mg/dl). Diabetes mellitus was defined as a routine (non-fasting) plasma glucose level of $\geq$ 200 mg/dl, a fasting plasma glucose level of $\geq$ 126 mg/dl, HbA1c $\geq$ 6.5%, and/or currently on medication for diabetes mellitus. Ischemic heart disease was defined as a positive history of myocardial infarction, current or previous angina pectoris, and/or a confirmed previous coronary intervention. Cerebrovascular disease was identified in patients who experienced a previous ischemic stroke or transient ischemic attacks. Obesity was defined as a body mass index (BMI) of $\geq$ 25, and chronic kidney disease was defined as an estimated glomerular filtration rate of ＜60 mL/min per 1.73 m². Smoking was recorded as positive if the subject was a current or former smoker. The CHADS₂ and CHA₂DS₂-VASc scores were used to provide an overall quantitative assessment of major risk factors associated with cerebral infarction, and the incidence of AF was examined according to the JCS 2013 guidelines[15].

CAVI Measurements

CAVI was measured using a VaSera CAVI instrument (Fukuda Denshi Co. Ltd., Tokyo, Japan), as described previously[11]. Briefly, cuffs were applied bilaterally to the upper arms and the ankles of the supine subject, with the head held in the midline position. After a 10-min rest in this position, the examinations were performed. To detect the brachial and ankle pulse waves, a low cuff pressure of 30–50 mmHg was

used to ensure a minimal effect on hemodynamics; blood pressure was then measured. CAVI was calculated using the following formula:

$$CAVI = a\{(2\rho/\Delta P) \times ln(Ps/Pd)PWV^2\} + b$$

Where Ps is the systolic blood pressure, Pd is the diastolic blood pressure, PWV is pulse wave velocity, ΔP is Ps – Pd, ρ is blood density, and a and b are constants. Scale conversion was performed to compare CAVI with PWV (Hasegawa's method). The VaSera instrument is equipped with systems to perform both measurements and calculations; as such, CAVI was calculated automatically.

For CAVI measurements in this study, we changed the time setting of VaSera for analyzing pulse wave data from 5 s to 8 s. The CAVI value calculated from each pulse wave obtained in 8 s was automatically averaged regardless of whether the patient was in sinus rhythm (SR) or AF while the measurement was performed. The validation of the reproducibility of this automated device has been reported previously[10].

Echocardiography

TTE was performed prior to ablation to obtain two-dimensional (2D) echocardiographic images of the atria and ventricles with standard parasternal and apical views. The LA dimension was measured by M-mode, and the left ventricular ejection fraction (LVEF) was calculated by Simpson's method. Early (E) and late (A) diastolic mitral inflow velocity and the E/A ratio were determined by Doppler echocardiography. Tissue Doppler imaging of the septal mitral annulus was recorded to measure early diastolic velocity (e'), and the ratio of early trans-mitral valve flow velocity to mitral annular velocity (E/e') was calculated. TTE was only carried out on those with non-Paf to rule out the existence of intracardiac thrombi.

Computed Tomography (CT) Imaging and Remodeling

All patients underwent a contrast-enhanced electrocardiogram (ECG)-gated CT imaging with an 80-slice multi-detector CT (MDCT) scanner (Aquilion; Canon Medical Systems, Tochigi, Japan; parameters include collimation, 80 sections each of 0.5 mm; gantry rotation speed, 275 ms; tube voltage, 120 kV; effective charge, AUTO mA/rot; and pitch, heart rate dependence) prior to catheter ablation. The actual CT data acquisition was performed using prospective ECG-gating during single-breath holding at the end-expiration phase in the craniocaudal direction via the intravenous injection of nonionic contrast agent (22.5 mg/kg/s; 370 mg/mL, Oypalomin; Fuji Pharma Co., Ltd., Tokyo, Japan). Data sets were reconstructed using a retrospective ECG-gating technique with a slice thickness of 0.5 mm and section width of 0.5 mm; image reconstruction was performed at 75% of the ECG R-to-R interval, corresponding to the atrial end-diastole phase. The LA and right atrial (RA) volumes were calculated during the atrial end-diastolic phase using a semiautomated three-dimensional (3D) reconstruction technique. MDCT parameters were assessed using visualization and analysis software (AZE Virtual Place; AZE, Tokyo, Japan). The MDCT data were also transferred to the NavX system, and the atrial and pulmonary veins (PVs) were reconstructed and segmented using image integration software (EnSite Verismo, St. Jude Medical, St. Paul, MN, USA); the fusion of the MDCT images and electro-anatomical mapping were performed. For measurements of the LA volume, the basal portion of the LA appendage and the PVs at their ostia were manually excluded. For measurements of the RA volume, the inferior and superior vena cava at their ostia were manually excluded. Previous reports have documented a correlation between atrial volume as determined by CT and recurrence of AF after catheter ablation[16, 17].; 2D echocardiography is also frequently used for the estimation of atrial volumes. However, we have found that enhanced MDCT can generate high-quality 3D images of not only the LA but also RA and provides a more accurate measurement of both atrial volumes compared with 2D echocardiography. As such, the RA and LA volumes were determined by 3D-CT in this study and were performed, as previously reported[19]. The LA and RA volumes were divided by the body surface areas in order to index to these values; the measurements were thus expressed as the LA volume index (LAVI) and RA volume index (RAVI).

Electro-Anatomical Mapping

A NavX system (NavX with CFE software; St. Jude Medical, Inc., St. Paul, MN, USA) was used for catheter ablation. A 5-F deflectable catheter was inserted into the coronary sinus via the right supraclavicular vein. The transseptal procedure was performed under the guidance of intracardiac ultrasound (View Flex Xtra ICE catheter; St. Jude Medical, Inc.) using an 8-F SL0 sheath (St. Jude Medical, Inc.) and an 11-F variable sheath (Agilis NxT™ Steerable Introducer, St. Jude Medical, Inc.) to advance into the LA. After the transseptal procedure, a heparin bolus was given intravenously, followed by a continuous and additional bolus infusion of heparin to maintain the activated clotting time between 250 s and 350 s. 3D biatrial geometry was created on the NavX system, and sequential contact mapping was performed by using a 7-F decapolar circular catheter (REFLEXION HD; St. Jude Medical, Inc.). Voltage and conduction

mapping were performed in order to investigate the relationship between structural and electrical remodeling during SR, as previously described[18, 19]. Voltage and activation timing was recorded in a bipolar contact map using the high-density circular mapping catheter. The catheter was positioned tangentially on the endocardial surface and held stable for at least 5 s to acquire the peak-to-peak voltage (maximum peak positive to minimum peak negative deflections) at each bipole pair. The maximum sensitivity for each acquisition was 0.1 mV. A stationary electrode from an octapolar catheter in the coronary sinus was used as a timing reference for the map during SR and abnormally low-voltage electrograms as follows: >0.5 mV, healthy; 0.2–0.5 mV, diseased; <0.1 mV, scarred. LVA were defined as sites of ≥ 3 adjacent low-voltage points of <0.5 mV, and the conduction velocity was calculated in each of the right and left atriums as the time from the start to the end of excitation in the atrium[19].

Radiofrequency (RF) Catheter Ablation

Pulmonary vein isolation (PVI) was performed using one 7-F decapolar circular catheter (Optima; St. Jude Medical, Inc.) positioned at the ostia of ipsilateral PVs; 3D-CT reconstruction was integrated into an electro-anatomical mapping system (EnSite NavX system, St. Jude Medical, Inc.). We created bilateral circular lesions with wide-area circumferential ablation encircling the ipsilateral PV; each application of RF energy was delivered for 30–60 by using a 3.5-mm irrigated tip RF catheter (FlexAbility; St. Jude Medical, Inc.), with the temperature limited to 42℃, power output at 25–35 W, and a flow rate of 13 mL/min. Biphasic direct current cardioversion restored the SR if AF did not terminate spontaneously after successful PVI. The endpoint of PVI was the creation of a bidirectional conduction block between LA and PVs[20]. At the end of the procedure, all PVs were successfully isolated.

Statistical Analysis

All group data are presented as mean ± standard deviation or counts (%). Categorical variables were summarized as frequencies and percentages and were compared between the groups using Pearson chi-square or Fisher's exact test as appropriate. Continuous variables were compared between groups using 2-tailed, unpaired t tests, or Mann–Whitney test, as appropriate. Stratified analyses of three types of AF, such as Paf, persistent AF, and long-standing AF, were performed with the mean CAVI value using one-way ANOVA and ANCOVA, adjusted for the covariates of age. Bonferroni's post hoc test was then used to iden-

tify the group with the greatest effect on the responsible variable. The relationships between CAVI and various clinical parameters were analyzed using simple regression analysis. NT-pro BNP was not normally distributed; as such, log-transformed NT-pro BNP was used as a variable for regression analysis. Multivariate analysis included all variables analyzed by simple regression analysis and was performed using stepwise regression analysis with backward elimination to identify independent risk factors associated with CAVI and atrial remodeling. To validate the measurement of CAVI in patients with AF, CAVI was measured two times before and two days after electrical cardioversion in 20 non-Paf patients. Bland–Altman plot and intraclass correlation coefficient (ICC) were analyzed to assess the reproducibility and reliability of CAVI.

P-values <0.05 were considered to be statistically significant. All the analyses were performed with SPSS version 21 for Microsoft Windows (SPSS, Inc., Chicago, IL, USA).

Results

Characteristics of the Study Population

We initially evaluated 237 consecutive patients with symptomatic and drug-refractory AF. We excluded all patients who were undergoing anything beyond a first ablation for AF ($n=16$), those who could not undergo enhanced CT ($n=2$), who had undergone previous cardiac valve surgery ($n=4$), who had an atrial septal defect ($n=2$), who had a peripheral arterial disease with an ABI of <0.9 ($n=2$), or who were currently on hemodialysis ($n=8$). We enrolled 213 patients (mean age, 64.7 ± 10.5 years; male, 72.6%) in whom CAVI was determined prior to catheter ablation for AF. The demographic characteristics of the study population are summarized in **Table 1**. We categorized the patients into two groups, including the Paf group ($n=142$) and the non-Paf group ($n=71$), according to the type of AF diagnosed. We found that heart rate, CAVI, LA diameter (LAD), and plasma NT-pro BNP levels were significantly higher among those in the non-Paf group than in the Paf group. No other significant differences were identified.

Comparison of the Clinical Characteristics and Atrial Remodeling Parameters in CAVI

The mean CAVI value was 8.87 ± 1.55. CAVI values were also categorized into two groups, as described previously[21]. In our study, 118 participants (55.4%) had abnormal CAVI values (≥ 9). The patients with abnormal CAVI values were older and had higher $CHADS_2$ scores, CHA_2DS_2VASc scores,

Table 1. Baseline Characteristics of the Study Population by AF Classification

Clinical Parameter	Total (*n*=213)	Paf (*n*=142)	non Paf (*n*=71)	*p* value
Age (yr, mean ± SD)	64.7 ± 10.5	64.9 ± 10.9	64.3 ± 9.5	P=0.192
Male (%)	167 (72.6)	107 (75.3)	60 (85)	P=0.077
BMI (kg/m²)	24.6 ± 4.5	24.1 ± 4.6	25.4 ± 4.3	P=0.083
Body Surface Area (m²)	1.76 ± 0.19	1.73 ± 0.19	1.81 ± 0.19	P=0.062
SBP (mmHg)	134.2 ± 18.9	135.3 ± 19.4	132.2 ± 17.9	P=0.189
DBP (mmHg)	84.2 ± 12.8	83.1 ± 12.3	86.4 ± 13.8	P=0.094
HR (beats/min)	73.8 ± 20.4	68.7 ± 16.3	84.2 ± 23.9	P=0.001
CAVI	8.87 ± 1.55	8.68 ± 1.31	9.28 ± 1.95	P=0.006
Hypertension (%)	104 (49)	66 (46)	38 (53)	P=0.501
Diabetes mellitus (%)	38 (18)	28 (20)	10 (14)	P=0.165
Dyslipidemia (%)	60 (28)	47 (33)	13 (18)	P=0.105
Heart failure (%)	33 (15)	18 (13)	15 (21)	P=0.23
Stroke/TIA (%)	17 (8)	12 (8)	5 (7)	P=0.157
Ischemic heart disease (%)	8 (4)	7 (5)	1 (2)	P=0.207
CHADS$_2$ score	1.16 ± 1.01	1.13 ± 1.04	1.21 ± 0.97	P=0.216
CHA$_2$DS$_2$ VASc score	1.85 ± 1.37	1.85 ± 1.42	1.84 ± 1.28	P=0.262
Medications				
β-blocker (%)	116 (54)	67 (47)	49 (69)	P=0.121
Amiodarone (%)	11 (5)	7 (5)	4 (6)	P=0.663
Bepridil (%)	38 (16)	28 (20)	10 (14)	P=0.107
Class 1 antiarrhythmic drugs (%)	64 (30)	54 (38)	10 (14)	P=0.055
LAD (mm)	40.6 ± 5.6	39.4 ± 5.8	42.9 ± 4.6	P=0.001
LVEF (%)	61.1 ± 14.1	61.8 ± 12.4	59.7 ± 16.9	P=0.064
Serum creatinine (mg/dl)	0.9 ± 0.20	0.9 ± 0.21	0.9 ± 0.18	P=0.639
eGFR (ml/min/1.73 m²)	66.1 ± 15.09	66.7 ± 16.1	64.9 ± 13.1	P=0.932
NT-pro BNP level (pg/ml)	555 ± 751	403 ± 677	852 ± 809	P=0.001

Data are presented as mean ± SD or number (%) of subjects. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; CAVI = Cardio-Ankle Vascular Index; TIA = transient ischemic attack; LAD = left atrial diameter; LVEF = left ventricular ejection fraction; eGFR = estimated glomerular filtration rate; BNP = brain natriuretic peptide.

and serum NT-pro BNP level compared with those with normal CAVI values **(Table 2)**. CT Imaging and 3D electro-anatomical mapping data are shown in **Table 3**. Patients with abnormal CAVI values also had higher LAVI and RAVI, longer LA conduction velocity, and lower LA average voltage.

Comparison of CAVI Values in AF Types

As shown in **Fig. 1**, the age-adjusted CAVI was significantly higher among those in the non-Paf group than those in the Paf group (non-Paf: 9.21 ± 1.9 vs. Paf: 8.67 ± 1.3, *P*=0.023; **Fig. 1A**). After dividing this cohort into three groups, Paf (*n*=141), persistent AF (*n*=55), and long-standing AF (*n*=16), according to the AF classifications defined by the JCS 2013 guidelines, the age-adjusted CAVI was highest in the long-standing persistent AF group and was significantly higher than in those observed in the Paf group (long-standing AF: 9.58 ± 2.0 vs. Paf: 8.67 ± 1.3, *P*=0.006).

Likewise, CAVI was higher among those in the persistent AF group than in those in the Paf group (Persistent AF: 9.19 ± 1.9 vs. Paf: 8.67 ± 1.3, *P*=0.013). No significant differences were identified in the comparisons between those in the persistent AF group vs. the Paf group **(Fig. 1B)**.

Association of CAVI with Clinical Variables and Atrial Remodeling Parameters

To clarify the correlation between CAVI and various clinical parameters, simple regression analyses were performed, with CAVI as a dependent variable **(Table 4)**. CAVI correlated with age (*r*=0.621, *P*=0.001), BMI (*r*=–0.204, *p*=0.005), body surface area (*r*=–0.272, *P*=0.001), CHADS$_2$ score (*r*=0.352, *P*=0.001), CHA$_2$DS$_2$-VASc score (*r*=0.487, *P*= 0.001), serum creatinine levels (*r*=0.204, *P*=0.012), serum NT-pro BNP levels (*r*=0.204, *P*=0.012), LAVI (*r*=0.297, *P*=0.001), RAVI (*r*=0.252, *P*=0.004), LA

Table 2. Comparison of clinical characteristics according to CAVI value

Clinical Parameter	Normal CAVI (n=95)	Abnormal CAVI (n=118)	p value
Paf (%)	36 (38)	68 (58)	
Age (yr, mean ± SD)	59.6 ± 10.4	68.8 ± 9.05	P=0.0001
Male (%)	76 (80)	91 (77.1)	P=0.251
BMI (kg/m^2)	25.0 ± 4.1	24.2 ± 5.1	P=0.108
Body Surface Area (m^2)	1.79 ± 0.20	1.72 ± 0.19	P=0.092
SBP (mmHg)	132.5 ± 19.6	135.8 ± 18.9	P=0.134
DBP (mmHg)	84.5 ± 11.1	83.9 ± 14.6	P=0.279
HR (beats/min)	72.1 ± 20.8	75.3 ± 21.0	P=0.243
CAVI	7.75 ± 0.80	10.02 ± 1.36	P=0.001
Hypertension (%)	36 (38)	68 (58)	P=0.058
Diabetes mellitus (%)	16 (17)	22 (19)	P=0.509
Dyslipidemia (%)	22 (23)	38 (32)	P=0.113
Heart failure (%)	14 (15)	19 (16)	P=0.624
Stroke/TIA (%)	5 (5)	12 (10)	P=0.163
Ischemic heart disease (%)	3 (3)	5 (4)	P=0.671
CHADS$_2$ score	0.85 ± 0.94	1.52 ± 1.04	P=0.001
CHA$_2$DS$_2$ Vasc score	1.32 ± 1.31	2.54 ± 1.30	P=0.001
Medication			
β-blocker (%)	47 (49)	69 (58)	P=0.209
Amiodarone (%)	7 (7)	4 (3)	P=0.104
Bepridil (%)	17 (19)	21 (18)	P=0.774
Class 1 antiarrhythmic drugs (%)	31 (33)	33 (28)	P=0.748
LAD (mm)	40.3 ± 5.6	40.8 ± 5.7	P=0.853
LVEF (%)	61.2 ± 12.4	61.0 ± 16.5	P=0.534
Serum creatinine (mg/dl)	0.89 ± 0.17	0.94 ± 0.21	P=0.106
eGFR (ml/min per 1.73 m^2)	69.8 ± 13.8	63.1 ± 14.8	P=0.002
NT-pro BNP level (pg/ml)	362 ± 458	708 ± 963	P=0.002

Data are presented as mean ± SD or number (%) of subjects. Paf=paroxysmal atrial fibrillation; BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; CAVI=Cardio-Ankle Vascular Index; TIA=transient ischemic attack; LAD=left atrial diameter; LVEF=left ventricular ejection fraction; eGFR=estimated glomerular filtration rate; BNP=brain natriuretic peptide.

Table 3. Comparison of atrial remodeling parameters by 3D-CT and mapping system according to CAVI value

Atrial remodeling Parameter	Normal CAVI (n=95)	Abnormal CAVI (n=118)	p value
LAVI (ml/m^2)	52.3 ± 16.8	61.9 ± 20.8	P=0.001
RAVI (ml/m^2)	58.7 ± 21.1	67.2 ± 28.0	P=0.017
LA conduction velocity (m/s)	73.2 ± 10.7	79.9 ± 16.1	P=0.005
RA conduction velocity (m/s)	87.8 ± 12.7	90.6 ± 14.9	P=0.253
LA average voltage (mV)	2.18 ± 0.74	1.71 ± 0.69	P=0.001
RA average voltage (mV)	2.37 ± 0.84	2.10 ± 0.67	P=0.071

Data are presented as mean ± SD. LAVI=left atrial volume index; RAVI=right atrial volume index; LA=left atrial; RA=right atrial.

conduction time (r=0.254, P=0.003), LA mean voltage (r=−0.343, P=0.001), and RA mean voltage (r=−0.245, P=0.015). Regression analysis was performed after dividing the cohort into two groups based on the type of AF; interestingly, the correlation between CAVI and LAVI, RAVI, LA conduction velocity, and RA conduction velocity was identified only among those in the non-Paf group (Table 4). The correlations between CAVI, LAVIs, and RAVIs are depicted in **Figs. 2A and 2B**. Multiple regression analysis revealed that older age (unstandardized coefficient β=0.108, P=0.0001) and longer LA conduc-
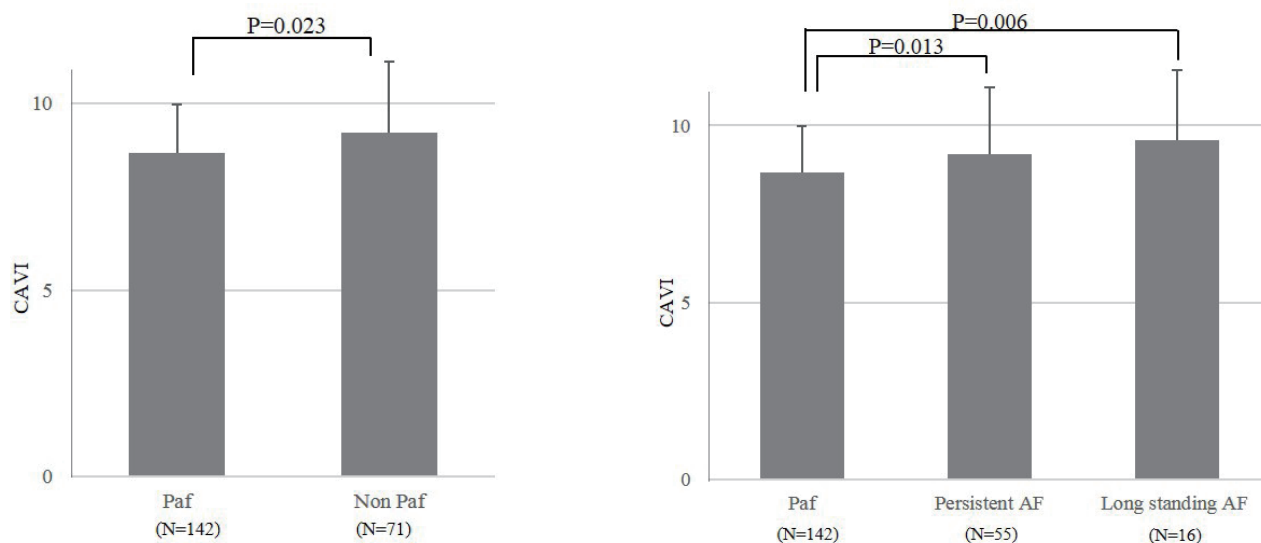
Fig. 1.

A. Comparison of CAVI values in AF types. CAVI was significant among those in the non-Paf group compared with the Paf group; *P*=0.023. Data are presented as mean ± standard deviation.

B. Comparison of CAVI values among the three groups classified according to type of AF.

Age-adjusted CAVI was highest in the long-standing persistent AF group and significantly higher than those values observed in the Paf group (*P*=0.006). CAVI was also higher in the persistent AF group than in the Paf group (*P*=0.013). No other significant differences were identified in a comparison between the persistent AF group and the long-standing AF group. Data are presented as mean ± standard deviation.

CAVI, Cardio-ankle vascular index; AF, atrial fibrillation; Paf, paroxysmal atrial fibrillation.

Table 4. Simple linear regression analysis documenting correlations between CAVI and clinical parameters

	All subject (*n*=213)		Paroxysmal AF(*n*=142)		non-Paroxysmal AF (*n*=71)	
	r	*p* value	*r*	*p* value	*r*	*p* value
vs Age	0.621	0.001	0.663	0.001	0.634	0.001
vs BMI	-0.204	0.005	-0.131	0.139	-0.387	0.002
vs Body Surface Area	-0.272	0.001	-0.261	0.003	-0.413	0.001
vs SBP	0.134	0.067	0.258	0.003	0.001	0.993
vs DBP	0.074	0.312	0.188	0.034	-0.089	0.504
vs HR	0.149	0.041	0.118	0.184	0.072	0.586
vs AF duration	0.061	0.429	0.092	0.337	-0.032	0.817
vs CHAD$_2$	0.352	0.001	0.366	0.001	0.342	0.009
vs CHA$_2$D$_2$-VASc	0.478	0.001	0.498	0.001	0.487	0.001
vs LAD (mm)	0.047	0.537	-0.008	0.931	0.014	0.921
vs LVEF (%)	0.006	0.94	-0.046	0.624	0.067	0.622
vs E/e'	0.163	0.042	0.141	0.15	0.318	0.024
vs serum creatinine	0.204	0.012	0.189	0.032	0.115	0.386
vs eGFR	-0.186	0.022	-0.311	0.001	-0.197	0.136
vs NT pro-BNP	0.307	0.001	0.269	0.002	0.271	0.038
vs LA volume index	0.297	0.001	0.158	0.75	0.366	0.004
vs RA volume index	0.252	0.004	-0.004	0.964	0.381	0.008
vs LA conduction velocity	0.254	0.003	0.115	0.272	0.374	0.004
vs RA conduction velocity	0.021	0.839	-0.086	0.498	0.056	0.753
vs LA mean voltage	-0.343	0.001	-0.299	0.003	-0.345	0.004
vs RA mean voltage	-0.245	0.015	-0.153	0.223	-0.382	0.008

BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; AF=atrial fibrillation; LAD=left atrial diameter; LVEF=left ventricular ejection fraction; eGFR=estimated glomerular filtration rate; BNP=brain natriuretic peptide; LA=left atrial; RA=right atrial.
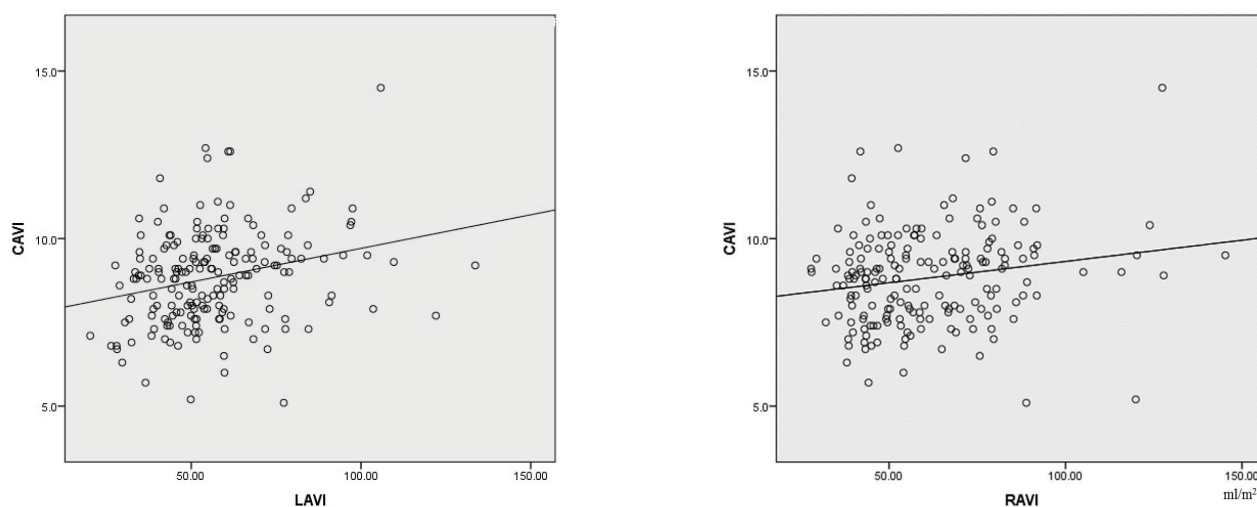
Fig. 2.
A. Relationship between CAVI and LAVI on univariate regression analysis CAVI was significantly correlated with LAVI ($r=0.297$, $P=0.001$). The solid line represents the regression line.
B. Relationship between CAVI and RAVI on univariate regression analysis CAVI was also significantly correlated with RAVI ($r=0.252$, $P=0.004$).
The solid line represents the regression line.
CAVI, Cardio-ankle vascular index; LAVI, Left atrial volume index. RAVI, Right atrial volume index.

Table 5. Multiple regression analysis of documenting the association between CAVI and clinical variables

Independent Variable	Standardized coefficient	Regression coefficient	Standard error	t value	P value
Age	0.578	0.108	0.016	6.771	0.0001
LA conduction velocity	0.241	0.032	0.011	2.814	0.006

Variables that were not independent included, male sex [0:(–), 1:(+)], BMI, SBP, HR, DM [0:(–), 1:(+)], hyperlipidemia [0:(–), 1:(+)], stroke [0:(–), 1:(+)], heart failure [0:(–), 1:(+)], non-Paf [0:(–), 1:(+)], CHAD$_2$ score, LVEF, NT-proBNP, E/e', and eGFR. Abbreviations as in the legends to Tables 1 and 2.

Table 6. Multiple regression analyses documenting the association of LAVI with clinical variables

Multiple regression analysis documenting the association of LA remodeling with clinical variables

Independent Variable	Standardized coefficient	Regression coefficient	Standard error	t value	P value
NT-proBNP	0.241	0.007	0.003	2.415	0.016
non-Paf	0.229	9.963	3.712	2.684	0.008
CAVI	0.225	2.755	1.322	2.049	0.039

Variables that were not independent included age, male sex [0:(–), 1:(+)], BMI, SBP, HR, DM [0:(–), 1:(+)], hyperlipidemia [0:(–), 1:(+)], stroke [0:(–), 1:(+)], heart failure [0:(–), 1:(+)], [0:(–), 1:(+)], CHAD$_2$ score, LVEF, E/e', and eGFR. Abbreviations as in the legends to Tables 1 and 2.

tion velocity (unstandardized coefficient $\beta=0.032$, $P=0.006$) were independent variables contributing to CAVI **(Table 5)**.

Association of LAVI and RAVI with Additional Variables

Multiple regression analyses were performed for parameters associated with LA and RA remodeling to identify independent variables. In the multiple regres-

sion analyses of LAVI, serum NT-pro BNP (unstandardized coefficient $\beta=0.007$, $p=0.016$), non-Paf (unstandardized coefficient $\beta=9.963$, $p=0.009$), and CAVI (unstandardized coefficient $\beta=1.322$, $p=0.039$) were all identified as independent variables **(Table 6)**. In contrast, in the multiple regression analyses of RAVI, LVEF (unstandardized coefficient $\beta=-0.595$, $p=0.014$), non-Paf (unstandardized coefficient $\beta=11.728$, $p=0.03$), and CAVI (unstandardized

Table 7. Multiple regression analyses documenting the association of RAVI with clinical variables

Multiple regression documenting the association of RA remodeling with clinical variables

Independent Variable	Standardised coefficient	Regression coefficient	Standard error	t value	*P* value
LVEF	-0.233	-0.595	0.792	-2.491	0.014
non-Paf	0.196	11.728	5.332	2.201	0.03
CAVI	0.244	4.131	1.898	2.176	0.032

Variables that were not independent included age, male sex [0:(–), 1:(+)], BMI, SBP, HR, DM [0:(–), 1:(+)], hyperlipidemia [0:(–), 1:(+)], stroke [0:(–), 1:(+)], heart failure [0:(–), 1:(+)], [0:(–), 1:(+)], CHAD$_2$ score, serum NT-proBNP, E/e', and eGFR. Abbreviations as in the legends to Tables 1 and 2.
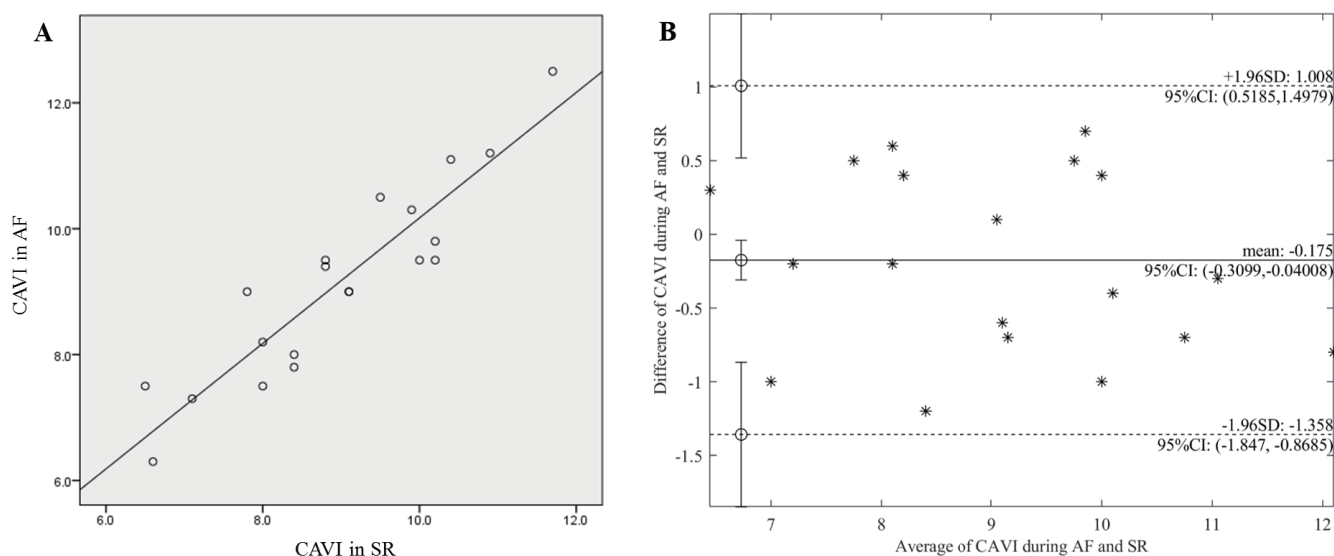
Fig. 3. Regression plot (A) and Bland–Altman Plots (B) comparing CAVI in sinus rhythm with CAVI in AF in 20 AF patients

CAVI value in sinus rhythm correlated significantly with CAVI value in AF ($r=0.919$, $P=0.0001$) (A). Bland–Altman analysis revealed a small bias of –0.175, and 95% limit of agreement ranged from 1.008 to –1.358, indicating lower variability of CAVI measurement at sinus rhythm and AF (B).

The solid line represents the mean CAVI value, and dotted lines mean ± 1.96 standard deviation.

SR, Sinus rhythm; AF, Atrial fibrillation

coefficient $\beta = 4.131$, $p=0.032$) were identified as independent variables (Table 7).

Association between CAVI in SR and CAVI in AF

To validate the measurement of CAVI in patients with AF, we evaluated CAVI two times before and two days after electrical cardioversion in 20 (28%) of persistent AF patients. CAVI values obtained when patients were in SR were significantly correlated with CAVI values in these patients when in AF ($r=0.919$, $P=0.0001$, **Fig. 3**). Bland–Altman analysis revealed a small bias, indicating a lower variability of CAVI measurement in SR and AF. The reliability analysis showed excellent agreement for CAVI measurement in SR and AF [ICC=0.955; 95% confidence interval (CI): 0.887–0.982] (data not shown). Finally, high reproducibility was observed between scores obtained from patients in SR vs. AF.

Discussion

Main Findings

In this study, CAVI was strongly associated with LAVI and RAVI, both indicators of atrial structural remodeling, and was particularly notable in patients diagnosed with persistent AF (Table 4). Multiple regression analysis revealed that LA remodeling reflects serum NT-pro BNP levels (Table 6), non-Paf, and CAVI, and that RA remodeling is associated with LVEF, non-Paf, and CAVI (Table 7). We speculate that increased arterial stiffness, as determined by CAVI, was independently associated with biatrial remodeling in AF.

In our study, the patients diagnosed with AF had a mean CAVI value of 8.87 ± 1.55, which is higher than previously reported CAVI values that are in the normal range[10, 11]. The age-adjusted CAVI was higher

in patients with long-standing persistent AF (9.58 ± 2.0) than in those diagnosed with Paf (8.67 ± 1.3) or persistent AF (9.19 ± 1.9). These results indicate that CAVI may increase along with the progression of AF; as such, a high risk of AF progression might be identified via the use of CAVI values. Taken together, our results led to major insights into the effects of arterial stiffness on atrial remodeling.

Arterial stiffness plays a key role in the pathophysiology of cardiovascular disease and is an independent predictor of cardiovascular morbidity and mortality[12]. Recently, particular attention has been given to the association between increased arterial stiffness and the incidence of AF[22, 23]. As such, we conducted this study in order to understand the clinical significance of CAVI, an established parameter and indicator of arterial stiffness, and its relationship to atrial remodeling in AF. We hypothesized that CAVI will be a strong marker for atrial remodeling. We performed an evaluation in an effort to obtain insights into specific mechanisms. A previous report identified increased PWV as an independent predictor of new-onset AF[24]. Although atrial remodeling is a complex process that remains poorly understood, it has been defined as a persistent change in atrial size or function[25]. In a broad clinical context, atrial remodeling is largely due to the development of rapid atrial tachyarrhythmias and/or may be consequent to alterations in the atrial structure secondary to pressure or volume overload[26]. Increased arterial stiffness induces elevations in the left ventricular filling pressure, which can result in atrial remodeling and fibrosis due to chronic pressure overload[27]. Lee *et al.*[28] evaluated the effects of AF on arterial stiffness in patients with hypertension and reported that AF significantly correlated with increased arterial stiffness, independent of age or blood pressure. Chen SC *et al.*[29] also reported that AF was significantly associated with increased brachial–ankle PWV. These reports suggest that the alterations in arterial physiology observed among AF patients may be associated with an increase in arterial stiffness. Arterial stiffness may also result in the structural and electrical remodeling of the myocardium, leading to the development of AF[30].

In contrast, Masugata *et al.*[31] reported that increases in CAVI are associated with both elevated plasma BNP and dilated left atria in hypertensive patients. They also concluded that CAVI, a known parameter reflecting arterial stiffness, also reflects LV afterload, resulting in increased atrial pressure. Moreover, Miyoshi *et al.*[14] first reported the relationship between CAVI and Paf, suggesting that increased CAVI may be involved in AF maintenance. Interestingly, we found that CAVI strongly correlated not only with LA remodeling but also with RA remodeling, a condition known as biatrial remodeling. While the relationship of CAVI with LA remodeling has been reported previously[32], to the best of our knowledge, this is the first report that documents the relationship between CAVI and RA remodeling and increasing CAVI according to AF progression.

We also found that CAVI strongly reflects not only atrial structural remodeling but also atrial electrical remodeling; the latter was measured as atrial voltage or conduction velocity using an electromapping system. This was particularly apparent among Paf patients compared with non-Paf patients **(Table 4)**, and was a clear and important result from the multiple regression analysis performed focusing on CAVI. As shown in **Table 5**, CAVI was an independent variable associated with both age and LA conduction velocity. Our current understanding of this process includes the fact that atrial electrical remodeling precedes atrial structural remodeling. As such, these findings suggest that CAVI may be a marker of the initial stages of atrial remodeling. This is a finding of profound clinical significance.

Next, we determined whether stiffness might be evaluated during AF and during SR. Irregular RR intervals are somewhat difficult to evaluate in the absence of a stable pulse wave; beat-to-beat variation, as would be anticipated in AF, may lead to technical difficulties in obtaining accurate measurements. In an attempt to address this issue, Caluwé *et al.*[33] examined carotid–femoral PWV in 34 patients diagnosed with AF both before and after elective electrical cardioversion. The authors concluded that PWV measurements are reliable in patients with AF, as no effect of arrhythmia was revealed by ICC evaluation and the coefficient of variation; low variability was also observed in completed Bland–Altman plots. This study revealed a strong agreement between PWV measurements obtained before and after electrical cardioversion, thus demonstrating the reliability of PWV measurements in patients diagnosed with AF.

Is CAVI or PWV a good marker reflecting atrial remodeling in AF patients? We need to understand the limitation of PWV and the merit of CAVI for assessing AF patients. CAVI is not influenced by blood pressure, and PWV is strongly affected by blood pressure. PWV in patients with hypertension could be overestimated. In particular, AF progression itself elevates the sympathetic nervous system or the renin–angiotensin system, which likely affects the PWV in AF patients. In contrast, CAVI is emerging as an important tool for noninvasive assessments of arterial stiffness. CAVI is calculated by converting the pulse wave into a parameter of stiffness known as β. The

influence of the pulse wave and blood pressure is quite small[34]. As such, in measuring CAVI, there is a possibility that the influence of the fluctuation of RR is smaller than that of PWV. Furthermore, we changed the measurement time from 5 s to 8 s to reduce the error associated with pulse wave variation during AF. We anticipated that CAVI would provide better reproducibility than PWV, although no earlier reports had provided the validation of CAVI measurements in AF. To verify the reproducibility of this modality in our study, we evaluated CAVI in 20 consecutive patients diagnosed with persistent AF before and two days after cardioversion; we found that the correlation coefficient was 0.919 ($p = 0.0001$), and Bland–Altman and the reliability analysis showed excellent agreement for the CAVI measurement in SR and AF. As such, a strong correlation was observed between CAVI values in AF and those in SR (Fig. 3). From this result, we speculate that the reproducibility of CAVI during AF may be quite high and that CAVI may be useful for evaluating arterial stiffness in patients diagnosed with AF.

Our results revealed an independent association between CAVI and biatrial electrical and structural remodeling as well as AF progression; this finding is in agreement with previous studies. Although various hypotheses have been proposed to explain the link between increases in CAVI and progression in AF, which reflects arterial stiffness, was independently associated with biatrial remodeling via as yet poorly understood physiological mechanisms. Several studies have evaluated this specific association; several possible explanations are based on the observation that increased arterial stiffness and AF share common risk factors, including age, hypertension, obesity, metabolic syndrome, sleep disorder, and renal disease. Our study also revealed a strong association between CAVI and CHA$_2$DS$_2$-VASc scores, which are known to be major predictors of a cardiovascular event. These links may explain why CAVI closely reflects atrial remodeling. Further prospective studies will be needed to evaluate the association between increased arterial stiffness and AF.

Study Limitations

The results of this study may be subject to certain limitations. First, our findings were based on a single-center trial with relatively small sample size. Second, since histological examination and atrial function were not examined with speckle-tracking echocardiography; as such, the etiology of atrial remodeling observed in this study cannot be fully confirmed. Additionally, our patients were relatively elderly and predominantly male; as such, our findings may not be generalizable for conditions associated with younger or female patients. Third, because this study is cross-sectional in design, we cannot draw full conclusions regarding the cause or effect of the relationship between CAVI and biatrial remodeling, and we are unable to provide full clarity with respect to the mechanism. Although we evaluated findings from 20 patients in order to verify the reproducibility of CAVI, the use of this modality for patients with AF will need to be determined by clinical consensus. Further research will be needed to resolve this issue.

Conclusions

Our findings indicate that CAVI, a value used as a measure of arterial stiffness, is closely associated with both structural and electrical biatrial remodeling in AF. This relationship was most prominent in the early phases of atrial remodeling. A marked increase in arterial stiffness was noted in association with persistent AF, which suggested that this may play a role in the development of this conduction disorder. To confirm these findings, further large-scale prospective studies will be required.

Acknowledgements

Financial Disclosure

Conflict of Interest

None to declare.

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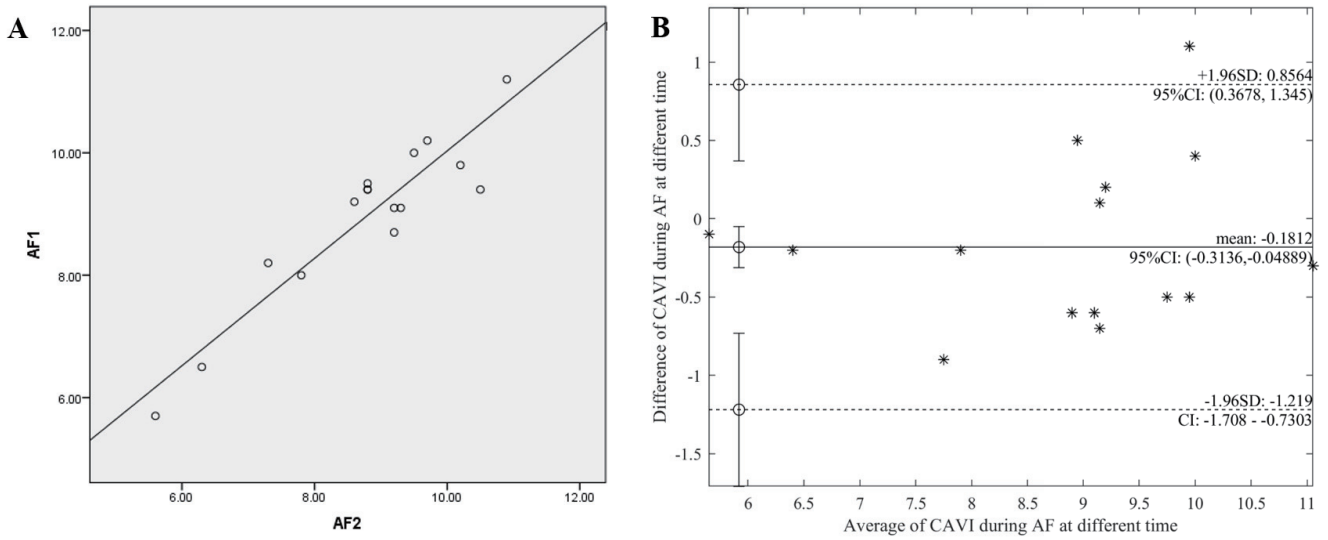
Supplemental Fig. 1. Regression plot (A) and Bland–Altman Plots (B) for the measurement of the different time during AF in 16 AF patients

CAVI values correlated significantly at the different two times during AF (r=0.930, P=0.0001) (A). Bland–Altman analysis revealed a small bias of –0.181, and 95% limit of agreement ranged from 0.856 to –1.219, indicating lower variability of CAVI measurement at different times (B). The solid line represents the mean CAVI value, and dotted lines mean ± 1.96 standard deviation. AF, Atrial fibrillation