Acta Cardiol Sin 2020;36:33–43
Original Article
doi: 10.6515/ACS.202001_36(1).20190704B

Cardiomyopathy & Heart Failure

Echocardiographic Evaluation of Left Atrial Function to Discriminate Non-Valvular Atrial Fibrillation Development in Patients with Apical Hypertrophic Cardiomyopathy

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Background: Data is limited on baseline left atrial (LA) myocardial mechanics between apical hypertrophic cardiomyopathy (ApHCM) patients who develop non-valvular atrial fibrillation (NVAF) during follow-up and those who do not.

Methods: This retrospective study investigated the clinical outcomes of consecutive patients newly diagnosed with ApHCM between August 2011 and July 2014 who were followed-up for at least 3 years. The patients underwent 12-lead surface electrocardiography and/or 24-hour Holter electrocardiography at least once a year. The patients were divided into two groups, namely those who did or did not exhibit NVAF during follow-up, respectively. The baseline clinical and echocardiographic data of the two groups were compared.

Results: Twenty patients were studied, five of whom were lost to follow-up. Of the remaining 15 ApHCM patients, seven developed NVAF. No differences were observed in the clinical characteristics of the two groups. However, for the echocardiographic data, the NVAF development group exhibited a larger LA volume and impaired LA reservoir, conduit and booster functions. The NVAF development group also showed lower peak LA strain and stiffer left atrium. The LA volume, function, global strain and stiffness were all statistically associated with NVAF development. Among these parameters, a LA conduit function of $\leq$ 24.9% was found to be the best parameter to discriminate NVAF development.

Conclusions: The baseline LA function was impaired in the ApHCM patients who subsequently developed NVAF during follow-up. A LA conduit function of $\leq$ 24.9% was strongly associated with NVAF development.

Key Words: Apical hypertrophic cardiomyopathy • Atrial fibrillation • Speckle tracking • Strain imaging

INTRODUCTION

Apical hypertrophic cardiomyopathy (ApHCM) is a form of hypertrophic cardiomyopathy in which myocardium thickening is located mainly at the apical wall of the left ventricle. It is characterized by an electrocardiographic pattern of giant inverted T waves and an 'ace-of-spades' shape of the end-diastolic left ventricular cavity on angiographic images.[1] Patients with ApHCM generally have a benign cardiovascular outcome.[2,3] However, ApHCM may be associated with serious co-morbidities such as myocardial infarction and atrial fibrillation (AF).[2-4] Several studies have shown that Asian AF patients exhibit a two-fold higher risk of death and a three- to four-fold higher risk of stroke than those without

Received: November 16, 2018 Accepted: July 4, 2019
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AF.[5,6] Similarly, a cohort study of 5171 nonpermanent AF patients worldwide showed that the annual risk of cardiovascular events was approximately 18%, and included cardiovascular death, nonfatal myocardial infarction, stroke and hospitalization.[7] Therefore, the early identification of AF in ApHCM patients is essential to allow for early management strategies to be implemented.[4]

In addition to traditional echocardiography, the left atrial (LA) function can also be evaluated using 2-dimensional speckle tracking (2DST) strain imaging.[8] 2DST strain is angle-independent, and therefore less susceptible to the Doppler limitation inherent in the echocardiographic assessment of strain. The main role of the left atrium is to modulate left ventricular (LV) filling through its reservoir, conduit and booster functions. Accordingly, alterations in LA strain are often apparent in patients with hypertension, AF and diastolic heart failure.[9-11] However, while some studies have investigated the LV myocardial mechanics in patients with ApHCM,[12,13] the LA function in ApHCM patients who subsequently do and do not develop non-valvular AF (NVAF) is still not fully understood. In this study, we hypothesized that baseline LA myocardial mechanics may be different between ApHCM patients with and without NVAF development during follow-up. To test this hypothesis, we examined whether any of the echocardiographic LA parameters could serve as particularly reliable clinical indicators of the subsequent development of NVAF in ApHCM patients.

METHODS

Study population

This retrospective study investigated the clinical outcomes of consecutive patients newly diagnosed with ApHCM at Chang Gung Memorial Hospital, Keelung, Taiwan between August 2011 and July 2014 and who were followed up for at least 3 years. For each patient, data on demographic characteristics, coronary risk factors, symptoms, physical examination findings, and ApHCM diagnosis were recorded. The enrolled patients were assigned to two groups, namely a study group consisting of patients with ApHCM and paroxysmal, persistent, or permanent NVAF in outpatient clinical follow-up visits, and a control group consisting of patients with ApHCM but no NVAF during clinical follow-up. This study was approved by the Research Ethics Review Board of Chang Gung Memorial Hospital (201700836B0).

Diagnostic criteria

The inclusion criteria for echocardiographic ApHCM wereas follows: 1) asymmetric left ventricular hypertrophy confined predominantly to the LV apex below the papillary muscle level; 2) apical wall thickness ≥ 15 mm; and 3) ratio of maximal apical to posterior wall thickness ≥ 1.5. The exclusion criteria were: 1) moderate to severe mitral stenosis or prosthetic heart valves; 2) sustained atrial or ventricular arrhythmias; 3) prior percutaneous intervention; 4) prior cardiac surgery; 5) prior myocardial infarction; 6) pericardial disease; 7) immunological disease; 8) active infection; 9) moderate to severe anemia; and 10) hyper- or hypothyroidism.

Clinical data

Current smoking status was defined as having smoked more than 100 cigarettes in their lifetime and having smoked within 1 month before enrollment. Diabetes mellitus was defined as a fasting glucose level ≥ 126 mg/dL, or the use of hypoglycemic medication. Hypercholesterolemia was defined as a low-density lipoprotein level ≥ 160 mg/dL in a fasting blood sample, or the use of statin medication. Hypertension was defined as the use of antihypertensive medication, or a blood pressure reading > 140/90 mmHg. Ischemic heart disease was confirmed by 1) coronary angiography, with ≥ 50% diameter stenosis in one or more coronary vessels after the administration of intracoronary nitroglycerin, or 2) a ^{201}thallium myocardial perfusion scan showing reversible/irreversible perfusion defects. The glomerular filtration rate was estimated using the Modification of Diet in Renal Disease Study 4-variable equation.[14] Chronic kidney disease was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2.

Electrocardiography

For each enrolled patient, 12-lead electrocardiograms were recorded at least once a year at the physicians' discretion. The presence of AF was documented according to electrocardiograms obtained either after the acute onset of symptoms or incidentally during routine medical examinations in asymptomatic patients. AF

was defined as being paroxysmal, persistent or permanent in accordance with the guidelines in Taiwan.[15] NVAF was defined as AF without moderate to severe mitral stenosis or prosthetic heart valves.

Standard echocardiography

Transthoracic echocardiograms were performed every year by two experienced physicians using a commercial system (Vivid E9, General Electric-Vingmed, Milwaukee, Wisconsin). Two-dimensional gray-scale images were acquired in standard and apical (apical 4-chamber, 2-chamber, and long-axis) views, and 3 cardiac cycles were recorded. In the apical 4-chamber view, the mitral inflow was recorded at the end of expiration. Pulsed-tissue Doppler studies were performed using a 2-mm sampling volume from the apical 4-chamber view in the septal and lateral sides of the mitral annulus. The maximal apical wall thickness was calculated as the average value of the measurements in the apical 4-chamber and 2-chamber views at end-diastole. The LV ejection fraction was evaluated using a quantitative 2-dimensional method, as previously described.[16] The LA maximal diameter was obtained at LV end-systole by anteroposterior measurements in the parasternal long-axis view using M-mode echocardiography. Pulsed-wave Doppler velocities of the pulmonary venous flow were obtained in the right-upper pulmonary vein. Tissue Doppler imaging of the septal and lateral mitral annuli was used to measure the mitral and lateral annular velocities in the peak-systole (s′), early-diastole (e′) and late-diastole (a′) stages. The diastolic function was categorized as being normal, impaired relaxation, pseudonormalized filling, or restrictive filling.[17] The time interval from the end to onset of the septal mitral annular velocity pattern during diastole (a_m) and the duration of the S-wave (b_m) were measured and used to calculate the myocardial performance index as $(a_m\text{-}b_m)/b_m$.[18] The isovolumic relaxation time was calculated as the time interval between s′ and e′, while the isovolumic contraction time was calculated as the time interval between a′ and s′.

The LA volume was analyzed using a disk technique with apical 2- and 4-chamber views. The LA volume was divided by the body surface area to obtain the LA volume index. Calculation of the LA phasic function was performed to assess the conduit, reservoir and booster functions.[19] The LA volumes (maximal, minimal and pre-atrial contraction) were identified from a manual review of the LA time-volume curve, with selection of the LA volume at pre-atrial contraction timed to the onset of the p-wave from the surface electrocardiogram. Briefly, the reservoir function (or LA expansion index) was calculated as: [(maximal LA volume - minimal LA volume) / minimal LA volume] × 100. Meanwhile, the conduit function (passive emptying index) was calculated as: [(maximal LA volume – pre-atrial contraction LA volume) / maximal LA volume] × 100. Finally, the booster function (active emptying index) was calculated as [(pre-atrial contraction LA volume – minimal LA volume) / pre-atrial contraction volume] × 100.

2DST echocardiography

Two-dimensional strain analyses were performed offline using Echopac software (version 110.1.2, General Electric-Vingmed) by two independent observers who were unaware of the patients' condition. All of the strain images were obtained at a rate of 60-90 frames/s.

For each of the three short-axis views, sampling points were placed manually along the endocardium at the LV base, middle and apex during end-systole, respectively. Meanwhile, for each of the 2-, 3- and 4-chamber views, three sampling points were placed manually at the septal mitral annulus, lateral corner and apical endocardium. The software covered the myocardial thickness along the entire LV wall, and then generated a region of interest. The region of interest was adjusted manually to ensure that the inner margin conformed to the whole LV endocardial border, and the entire thickness of the LV myocardium was included. The software subsequently identified the tissue speckles and tracked their movement frame-by-frame through the cardiac cycle. The LV wall was divided into six segments arranged circumferentially at the basal, middle and apical levels. The software then calculated the longitudinal, circumferential and radial strains for each segment in a graphical form, with automated measurements recorded in a tabular form. The peak systolic longitudinal, circumferential and radial strain values were recorded for each segment. The strain values for all of the myocardial segments in each patient were then averaged to obtain global values. End-systole was defined as the time of aortic valve closure, while end-diastole was defined as the time of mitral valve closure (as identified by Doppler

ultrasonography based on the apical 4-chamber view in both cases).

For LA 2DST analysis, a line was drawn manually along the LA endocardium at the point when the left atrium reached its minimal volume after contraction. The LA myocardium was divided into 12 equidistant regions, including six in the apical 4-chamber view and six in the 2-chamber view.[20] The peak atrial longitudinal strain (PALS) was measured at the end of the reservoir phase (PALSr) using the QRS-wave onset as the reference point. The peak atrial longitudinal strain of LA contraction (PALSc) was also obtained. The strain during LV early diastole (PALSe) was measured as PALSr minus PALSc. In patients for whom some segments were excluded due to suboptimal visualization and tracking, PALSr, PALSe and PALSc (Figure 1) were calculated as the average of the values measured in the remaining segments.

LA stiffness estimation

The LA stiffness was estimated as the ratio of the invasively measured pulmonary capillary wedge pressure to the LA systolic strain.[21] The average value of PALSr was used in the calculation. E/e' (average e', mean of mitral and lateral e') was also used in conjunction with PALSr to derive a noninvasive dimensionless parameter, since the ultimate clinical application was obtained noninvasively.[22]

Reproducibility

Inter-observer variability was assessed by two experienced physicians evaluating the raw data (PALSr) of the 15 patients with ApHCM independently from one another. Intra-observer variability was assessed by one of the experienced physicians evaluating the 15 patients in a blinded manner at baseline and 1 week later.

Statistical analysis

There was insufficient power to test the normality of the continuous variables due to the small sample size in the present study (n = 15). Therefore, all of the statistical tests were performed using nonparametric statistics. The continuous variables were presented as medians (25^{th}, 75^{th} percentiles). The data of the patients with and without NVAF development were compared using Mann-Whitney U tests for the continuous variables and Fisher's exact tests for the categorical variables. The associations between the echocardiographic parameters and the risk of NVAF development were examined using univariate Cox proportional hazard models. To prevent

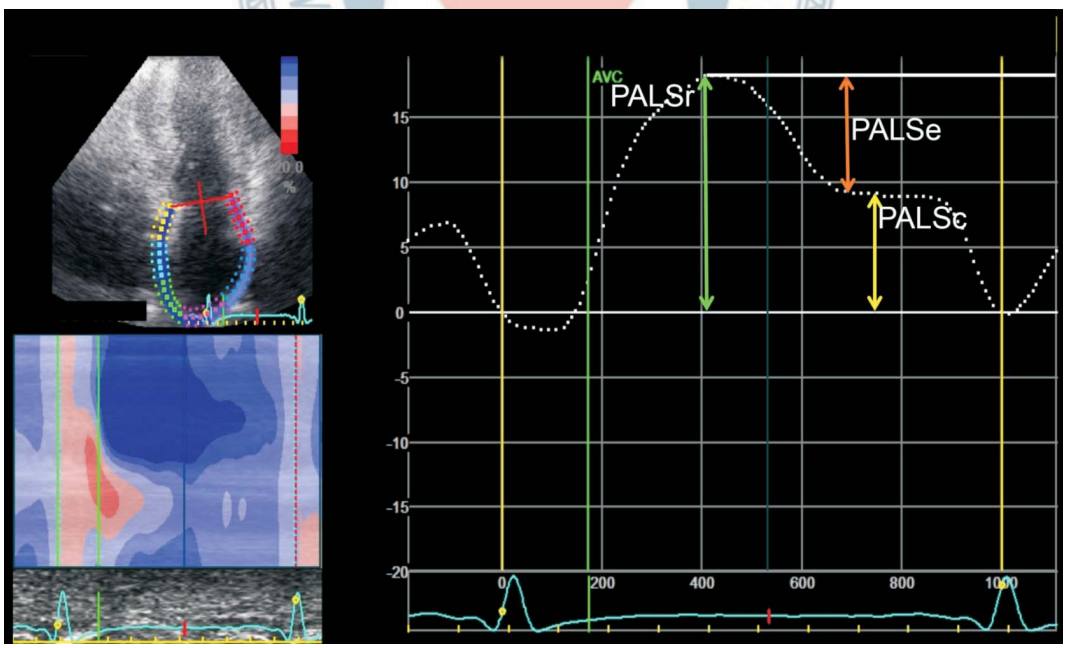

Figure 1. *Example of LA strain referenced to QRS-wave onset of electrocardiogram. The peak atrial longitudinal strain was measured at the end of the reservoir phase (PALSr), whereas the strains during LV early-diastole (PALSe) and atrial-contraction (PALSc) correspond to the left atrial (LA) conduit and pump phases, respectively.*

bias of the empirical estimates (i.e., Wald test) due to the small sample size, the results of the Cox proportional hazard models were presented using a bias-corrected and accelerated method based on 1,000 bootstrap samples. The discriminative ability of the individual parameters in diagnosing NVAF was determined based on the area under the receiver operating characteristic curve, where the optimal cutoff points were determined according to the Youden Index. The parameters were then dichotomized and Kaplan-Meier survival curves of NVAF development between groups were generated with log-rank tests. The reproducibility (both inter-observer and intra-observer variability) of the measured echocardiographic parameters was assessed using interclass correlation coefficients under a two-way random model. All of the statistical tests were 2-tailed; with a p value of less than 0.05 considered to be statistically significant. No adjustment of multiple testing (multiplicity) was made. All of the data were analyzed using SPSS 22 for Windows (IBM Corp., Armonk, NY).

RESULTS

Baseline clinical characteristics

Twenty patients with ApHCM were enrolled. However, five patients were subsequently lost to follow-up and were hence excluded. The remaining 15 ApHCM patients were followed for a median of 3.9 years (25^{th} to 75^{th} percentiles: 1.9-5.9 years). Among these patients, seven developed NVAF during follow-up. The median age of the 15 patients at the time of ApHCM diagnosis was 63 years (25^{th} to 75^{th} percentiles: 58-71 years). The median duration from the diagnosis of ApHCM to the development of NVAF was 2 years (25^{th} to 75^{th} percentiles: 0.6-3.9 years) with an incidence of 12.7 events per 100 person-years. No significant differences were found in the clinical characteristics of the two groups (Table 1).

Table 1. Comparison of baseline clinical characteristics between ApHCM patients with and without development of NVAF

Variable	Total patients (n = 15)	ApHCM with NVAF (n = 7)	ApHCM without NVAF (n = 8)	p-value
Age (years)	63 (58, 71)	67 (58, 71)	60 (52, 68)	0.417
Female (%)	33	57	13	0.119
BMI (kg/m^2)	30 (26, 33)	30 (22, 33)	29 (27, 33)	0.728
Heart rate (beats/min)	69 (60, 76)	69 (54, 76)	68 (61, 76)	0.683
Symptoms at presentation (%)				0.190
Chest pain	27	0	50	
Palpitation	20	29	13	
Syncope	0	0	0	
Dyspnea on exertion	40	57	25	
Asymptomatic	13	14	13	
NYHA class at presentation (%)				0.569
I	27	14	38	
II	73	86	63	
III and IV		0	0	
Smoking (%)	60	43	75	0.315
Hypertension (%)	93	86	100	0.467
Diabetes (%)	53	57	50	1.000
Ischemic heart disease (%)	47	57	38	0.619
Dyslipidemia (%)	80	86	75	1.000
Estimated GFR (ml/min/m^2)	57 (47, 81)	81 (51, 97)	55 (44, 61)	0.064
Chronic kidney disease (%)	53	29	75	0.132
Medications (%)				
β-blockers	53	57	50	1.000
ACEI/ARB	53	57	50	1.000
Calcium antagonists	80	71	88	0.569
Diuretics	40	43	38	1.000
Nitrates	13	29	0	0.200
Aspirin	25	29	13	0.569
Statins	33	14	50	0.282

Continuous data are presented as medians (25^{th}, 75^{th} percentiles).
ACEI, angiotensin-converting enzyme inhibitor; ApHCM, apical hypertrophic cardiomyopathy; ARB, angiotensin II receptor blocker; BMI, body mass index; GFR, glomerular filtration rate; NVAF,non-valvular atrial fibrillation.

However, the female patients were more prone to develop NVAF than the male patients (p = 0.119). Four of the patients (all with NVAF) died during follow-up as a result of heart failure, sepsis, acute myocardial infarction, and hepatocellular carcinoma, respectively.

Standard and 2DST echocardiography

The NVAF development group exhibited a larger LA volume and impaired LA reservoir, conduit and booster functions (Table 2). However, the LA maximal diameter was not associated with the development of NVAF. The NVAF development group also showed lower LV longitudinal, PALSr and PALSc strains but greater LA stiffness (Table 3).

Association of LA echocardiographic markers with NVAF development

The LA volumes, functions, global strains (PALSr and

Table 2. Comparison of standard echocardiographic parameters between ApHCM patients with and without development of NVAF

Parameter	ApHCM with NVAF (n = 7)	ApHCM without NVAF (n = 8)	p-value
LV volume and function			
End-diastolic volume index (mL/m^2)	29 (21, 45)	30 (27, 38)	0.817
End-systolic volume index (mL/m^2)	9.2 (6.7, 11.8)	9.5 (6.8, 11.7)	1.000
Ejection fraction (%)	68 (59, 73)	70 (61, 73)	0.728
Mitral E/A ratio	1.19 (0.70, 1.48)	0.78 (0.65, 0.88)	0.165
Myocardial performance index	0.60 (0.50, 0.98)	0.77 (0.61, 0.84)	0.563
IVRT (ms)	138 (102, 152)	109 (105, 136)	0.452
IVCT (ms)	82 (70, 121)	65 (60, 80)	0.203
Average E/e'	16 (15, 21)	12 (10, 17)	0.165
Intra-LV pressure gradient (mmHg)	10.0 (8.8, 22.6)	20.6 (11.4, 22.1)	0.536
Diastolic function, grade (%)			0.119
Normal	0	0	
Impaired relaxation, I	43	88	
Pseudonormalized filling, II	57	13	
Restrictive filling, III	0	0	
LA maximal diameter (mm)	51.5 (47.2, 54.5)	46.0 (42.6, 48.3)	0.121
LA volume and function			
Maximum volume index (mL/m^2)	46 (44, 61)	34 (24, 41)	0.021
Minimum volume index (mL/m^2)	26 (22, 40)	12 (9, 17)	0.008
Pre-A volume index (mL/m^2)	40 (34, 50)	23 (17, 25)	0.008
Reservoir, expansion index (%)	66 (51, 108)	155 (134, 190)	0.008
Conduit, passive emptying fraction (%)	20 (10, 24)	32 (28, 39)	0.001
Booster, active emptying fraction (%)	30 (20, 37)	41 (32, 53)	0.049

Continuous data are presented as medians (25th, 75th percentiles).
A, atrial contraction; E, rapid filling; e', annular early diastolic velocity; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LA, left atrial; LV, left ventricular. Other abbreviations as in Table 1.

Table 3. Comparison of 2DST echocardiographic parameters of left ventricle and left atrium between ApHCM patients with and without development of NVAF

Parameter	ApHCM with NVAF (n = 7)	ApHCM without NVAF (n = 8)	p-value
LV global strains			
Longitudinal strain (%)	-12 (-14, -10)	-17 (-20, -15)	0.032
Circumferential strain (%)	-14 (-20, -11)	-16 (-17, -15)	0.563
Radial strain (%)	36 (17, 37)	25 (21, 31)	0.418
Twist (%)	15 (9, 31)	23 (15, 28)	0.728
LA global strains			
PALSr (%)	11 (10, 13)	17 (13, 20)	0.049
PALSc (%)	5 (5, 8)	10 (6, 12)	0.028
PALSe (%)	5.2 (4.5, 6.7)	5.0 (4.1, 10.6)	1.000
LA stiffness	1.25 (1.16, 2.07)	0.77 (0.66, 1.14)	0.015

Data are presented as medians (25th, 75th percentiles).
PALSc, peak atrial longitudinal strain was measured at LA contraction; PALSe, atrial strain during LV diastole; PALSr, peak atrial longitudinal strain measured at the end of the reservoir phase; 2DST, 2-dimensional speckle tracking. Other abbreviations as in Tables 1 and 2.

PALSc) and stiffness were all associated with the risk of NVAF development (Table 4). The LA conduit function showed an outstanding ability to discriminate NVAF development, with a cut-off value of ≤ 24.9%, a sensitivity of 100% and a specificity of 87.5% (Table 5, Figure 2A). The LA global strains and stiffness also demonstrated satisfactory discrimination performance (Table 5, Figure 2B). According to the Kaplan-Meier curves of NVAF development stratified by the optimal cut-off point of the associated parameters, an LA conduit function of ≤ 24.9% was significantly associated with NVAF development (Figure 3).

Reproducibility

The inter- and intra-observer interclass correlation coefficients for PALSr were 0.97 [95% confidence interval (CI): 0.92 to 0.99] and 0.96 (95% CI: 0.88 to 0.99), respectively.

DISCUSSION

Compared with the ApHCM patients who did not develop NVAF, those with NVAF exhibited a more dilated left atrium, impaired LA function, lower LA global strain, and greater LA stiffness. The LA volumes, function, global strains, and stiffness were all associated with NVAF development. An LA conduit function of ≤ 24.9% was a particularly good discriminator of NVAF development.

LA function and ApHCM

LA enlargement is not only a consequence of im-

Table 4. Associations between echocardiographic parameters and development of NVAF[#]

Explanatory variable	Hazard ratio (95% CI[†])
LV volume and function	
End-diastolic volume index (mL/m^2)	1.01 (0.91-1.09)
End-systolic volume index (mL/m^2)	1.02 (0.82-1.16)
Ejection fraction (%)	1.01 (0.88-1.12)
Mitral E/A ratio	1.08 (0.97-1.21)
Myocardial performance index	2.06 (0.001-34.67)
IVRT (ms)	1.02 (0.97-1.09)
IVCT (ms)	1.02 (0.99-1.19)
Average E/e'	1.08 (0.93-2.58)
LA maximal diameter (mm)	1.19 (0.97-1.45)
LA volume and function	
Maximum volume index (mL/m^2)	1.17 (1.01-1.90)*
Minimum volume index (mL/m^2)	1.31 (1.12-1.96)*
Pre-A volume index (mL/m^2)	1.24 (1.09-2.51)*
Reservoir, expansion index (%)	0.95 (0.79-0.98)*
Conduit, passive emptying fraction (%)	0.85 (0.19-0.89)*
Booster, active emptying fraction (%)	0.86 (0.66-0.97)*
LV global strains	
Longitudinal strain (%)	1.40 (0.97-33.89)
Circumferential strain (%)	1.13 (0.57-2.69)
Radial strain (%)	1.03 (0.91-1.49)
Twist (%)	0.97 (0.83-1.10)
LA global strains	
PALSr (%)	0.83 (0.52-0.94)*
PALSc (%)	0.75 (0.53-0.85)*
PALSe (%)	0.88 (0.62-1.23)
Stiffness	27.4 (2.9-257)*

HR, hazard ratio; CI, confidence interval. Other abbreviations as in Tables 2 and 3.
* Significant association; [#] Age and sex were adjusted; [†] The 95% confidence intervals were calculated based on 1000 bootstrap samples using bias-corrected and accelerated method.

Table 5. Detailed properties of receiver operating characteristic curve analysis

Predictor	AUC (95% CI)	Cut-off*	Sensitivity (95% CI)	Specificity (95% CI)
LA maximal diameter	0.75 (0.47-0.93)	NA#	NA[#]	NA[#]
LA volume and function				
Maximum volume index	0.86 (0.58-0.98)	> 42.6	85.7 (42.1-99.6)	87.5 (47.3-99.7)
Minimum volume index	0.91 (0.65-1.00)	> 20.7	85.7 (42.1-99.6)	100.0 (63.1-100.0)
Pre-A volume index	0.91 (0.65-1.00)	> 29.2	85.7 (42.1-99.6)	100.0 (63.1-100.0)
Reservoir, expansion index	0.91 (0.65-1.00)	≤ 108.2	85.7 (42.1-99.6)	87.5 (47.3-99.7)
Conduit, passive emptying fraction	1.00 (0.78-1.00)	≤ 24.9	100.0 (59.0-100.0)	87.5 (47.3-99.7)
Booster, active emptying fraction	0.80 (0.52-0.96)	≤ 44.9	100.0 (59.0-100.0)	50.0 (15.7-84.3)
LA global strains				
PALSr	0.80 (0.52-0.96)	≤ 12.5	85.7 (42.1-99.6)	75.0 (34.9-96.8)
PALSc	0.84 (0.56-0.97)	≤ 8.8	100.0 (59.0-100.0)	62.5 (24.5-91.5)
Stiffness	0.88 (0.61-0.99)	> 0.77	100.0 (59.0-100.0)	62.5 (24.5-91.5)

AUC, area under the curve; NA, not applicable. Other abbreviations as in Table 2 and Table 3.
* According to Youden index. [#] The value of AUC was not statistically significant (p = 0.065).

paired LV diastolic function, but also a biological marker that can be used to predict AF development in the general population.[23] Tani et al.[24] further found that LA enlargement was a reliable discriminator of AF development in patients with hypertrophic cardiomyopathy.

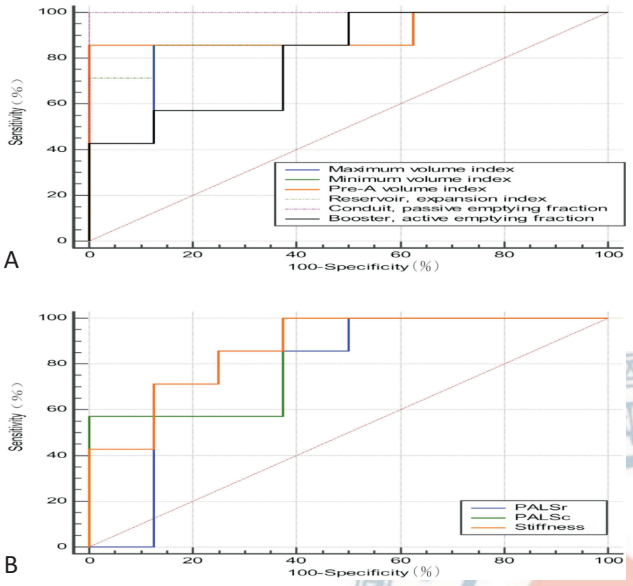

Figure 2. *Receiver operating characteristic curve analysis of left atrial (LA) volume and function (A) and LA global strains (B) in discriminating development of not develop non-valvular AF (NVAF).*

However, even though evaluating the LA size and mechanical function in hypertrophic cardiomyopathy patients has prognostic importance, its implications in ApHCM patients are unclear.[2-4] The LA remodeling and dilation in ApHCM may be due to LV diastolic dysfunction, LV intracavitary obstruction, and elevated LV filling pressure, or to other background factors such as hypertension and aging. Therefore, patients with ApHCM and a dilated left atrium are prone to develop AF. Accordingly, for patients with ApHCM, risk stratification is essential when estimating the likelihood of AF development during follow-up. Lee et al.[4] found that AF was a significant risk factor for stroke and mortality in patients with ApHCM. In addition, the authors noted that AF could be independently predicted by an older age and enlarged left atrium (> 45 mm); however, we did not find this association. The reason may be that Lee et al. did not provide the LA functional parameters in their study.[4] In addition, using M-mode measurements of LA anteroposterior dimension assumes that all LA dimensions enlarge similarly when the left atrium dilates, which is often not the case during LA remodeling.[25,26] Therefore, the LA maximal volume is recommended when assessing LA size and remodeling.[16] To date, however, the role of baseline LA function in ApHCM patients in dis-

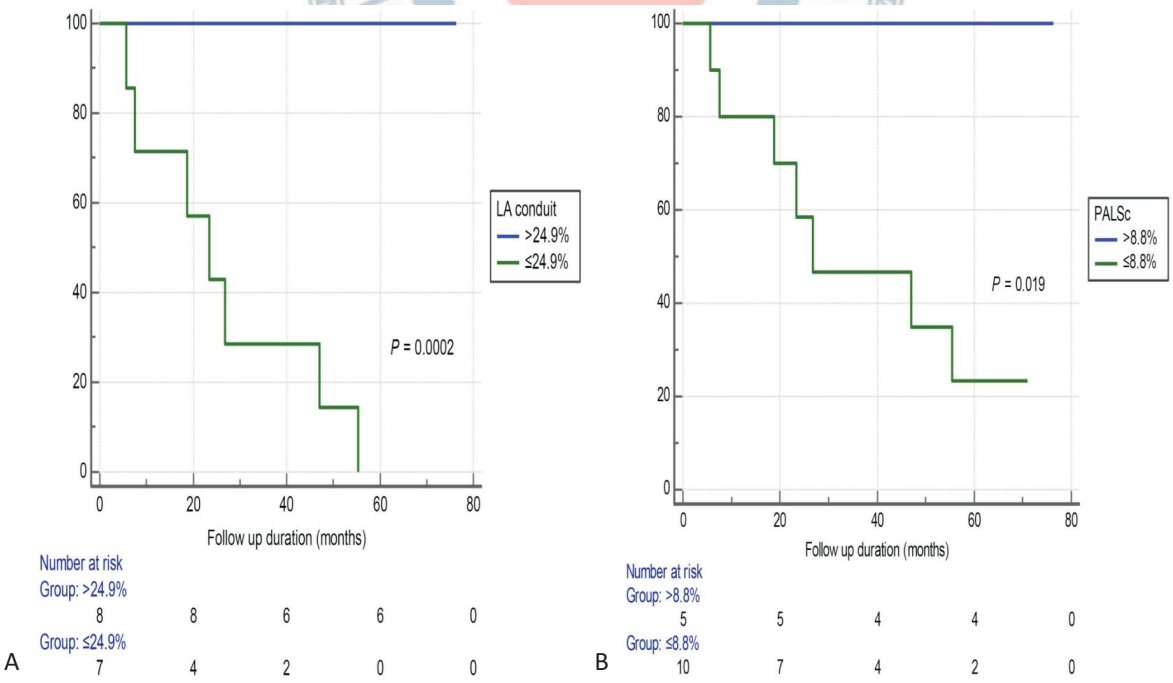

Figure 3. *Kaplan-Meier survival curves of development of not develop non-valvular AF (NVAF) stratified by optimal cut-off point of left atrial (LA) conduit function (A) and peak atrial longitudinal strain of LA contraction [peak atrial longitudinal strain of LA contraction (PALSc), B].*

criminating the subsequent development of nonvalvular AF is still unclear. The present results showed that the entire baseline LA function was significantly more impaired in the ApHCM patients with subsequent NVAF development than in those who did not develop NVAF. Of the LA echocardiographic parameters measured in the present study, the LA conduit function exhibited particularly severe impairment in the patients with subsequent AF development. The LA conduit function is responsible for the active relaxation of the left atrium, and hence the present results indicate that an increased LA afterload occurs in ApHCM patients with subsequent NVAF development. This finding is consistent with those of a previous study which showed that LA afterload could be determined by the elastic properties and downstream pressure of the left atrium, and that it increased with a poorer LV diastolic function and an elevated LV filling pressure.[27] To the best of our knowledge, the present study is the first to demonstrate the prognostic implications of LA function in patients with ApHCM.

LA strains, stiffness and AF in ApHCM

The electrocardiographic remodeling of atrium predicts the future risk of AF.[28] In addition, the functional and structure remodeling of both atria are associated with the development of stroke in patients with paroxysmal and persistent AF.[29] The present study analyzed differences in echocardiographic LA stiffness and 2DST results for LA function (PALSr and PALSc) in ApHCM patients with and without subsequent NVAF development, respectively. The results showed that the ApHCM patients with subsequent NVAF development were prone to a higher LA stiffness and lower global PALSr and PALSc. Previous studies have also reported that PALSr is significantly reduced in patients with paroxysmal AF, and that it is strongly associated with AF progression to a persistent or permanent status.[30,31] In addition, a lower PALSr has also been associated with the recurrence of AF after catheter ablation.[32] As in prior LA deformation studies, the present results revealed that baseline global LA contractility was reduced in ApHCM patients. Furthermore, both PALSr and PALSc were decreased in the ApHCM patients with the subsequent development of NVAF, indicating a lower global LA contractility in NVAF development.

The LA stiffness was further analyzed noninvasively and was found to be markedly increased in the patients with subsequent AF development. Impaired PALSr and LA reservoir function in patients with systolic and diastolic heart failure has been reported previously.[11,33] However, to the best of our knowledge, the present study is the first to assess the significance of baseline LA stiffness in the evaluation of the prognosis of ApHCM patients. In general, stiffness is defined as the force required to displace a passive spring by a unit length. In this context, it describes the mechanical characteristics of the left atrium and the extent to which the left atrium is affected by fibrosis, which is known to be a marker of AF occurrence during follow-up.[34,35] Stiff LA syndrome has previously been reported in patients undergoing catheter ablation for AF.[36] In addition, it has been shown that noninvasively estimated LA stiffness is associated with the short-term recurrence of AF after electrical cardioversion.[37] Moreover, a previous study showed that severe LA scarring, as assessed by voltage mapping, played a more important role than atrial dilation in predicting the development of stiff LA syndrome.[38] The present study also revealed that LA structural and functional remodeling were statistically associated with subsequent NVAF development in ApHCM patients.

Limitations

Several limitations of this study should be acknowledged. First, the small sample size (n = 15) prevented the use of multivariate analysis to identify the parameters independently associated with NVAF development. Second, the median follow-up period was only 3.9 years, and a longer follow-up period may be useful in providing further information regarding long-term NVAF development.

CONCLUSIONS

Baseline LA function was impaired in ApHCM patients with subsequent NVAF development. The development of NVAF could reliably be discriminated by a LA conduit function of $\leq$ 24.9%.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

FUNDING

This study was supported partly by Grant CLRPG2G 0101 from Chang Gung Memorial Hospital-Keelung, Taiwan.

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