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Left atrial area index predicts adverse cardiovascular events in patients with unstable angina pectoris

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Abstract

Background The left atrial size has been considered as a useful marker of adverse cardiovascular outcomes. However, it is not well known whether left atrial area index (LAAI) has predictive value for prognosis in patients with unstable angina pectoris (UAP). This study was aimed to assess the association between LAAI and outcomes in UAP patients. **Methods** We enrolled a total of 391 in-hospital patients diagnosed as UAP. Clinical and echocardiographic data at baseline were collected. The patients were followed for the development of adverse cardiovascular (CV) events, including hospital readmission for angina pectoris, acute myocardial infarction (AMI), congestive heart failure (CHF), stroke and all-cause mortality. **Results** During a mean follow-up time of 26.3 ± 8.6 months, 98 adverse CV events occurred (84 hospital readmission for angina pectoris, four AMI, four CHF, one stroke and five all-cause mortality). In a multivariate Cox model, LAAI [OR: 1.140, 95% CI: 1.016–1.279, $P = 0.026$], diastolic blood pressure (OR: 0.976, 95% CI: 0.956–0.996, $P = 0.020$) and pulse pressure (OR: 1.020, 95% CI: 1.007–1.034, $P = 0.004$) were independent predictors for adverse CV events in UAP patients. **Conclusions** LAAI is a predictor of adverse CV events independent of clinical and other echocardiographic parameters in UAP patients.

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Keywords: Adverse cardiovascular events; Left atrial area index; Prognostic factor; Unstable angina pectoris

1 Introduction

During ventricular diastole, the pressure falls below atrial pressure to allow the opening of atrioventricular valves. Blood then begins to flow passively from the atria into the ventricles to about 80% of their final volume. The atria then contract to propel the remaining 20% blood into the ventricles. As a result, factors increasing left ventricular (LV) filling pressure will lead to left atrial (LA) pressure overload and LA dilation.[1] It has been documented that LA dilation was a sensitive marker reflecting both the severity and duration of LV diastolic dysfunction,[1,2] and LA size was recognized as a powerful predictor of adverse cardiovascular outcomes in several diseases, including heart failure, myocardial infarction, ambulatory adults with coronary artery disease (CHD).[3–6] However, the prognostic value of LA dilation in unstable angina pectoris (UAP) patients was not well known.

The American Society of Echocardiography recommends LA volume (LAV) as a golden standard to measure LA size.[7] However, LA area (LAA) was easier to perform in our clinical routine work, and LAA has been suggested a superior index of LA size to left atrial dimension (LAD),[8] The purpose of this study was to assess the predictive value of LA area index (LAAI) for adverse CV events in patients with UAP.

2 Methods

2.1 Study population

The study population included 471 consecutive patients with UAP who were admitted to Peking University Third Hospital from Jan 1 to Dec 31, 2011. Patients were excluded if they had acute myocardial infarction (AMI), congestive heart failure (CHF), left ventricular ejection fraction (LVEF) < 50%, valvular heart disease, congenital heart disease, cardiomyopathy, arrhythmia treatment with pacemaker implantation, renal function impairment, liver function impairment, or infectious disease. Patients who didn't undergo invasive coronary angiography or computed tomography angiography were also excluded from the study.

This study was approved by the Institutional Review

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Board of Peking University Third Hospital, and was carried out according to the Declaration of Helsinki.

2.2 Clinical data

The clinic data, including age, gender, height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), heart rate (HR), body mass index (BMI), body surface area (BSA), history of old myocardial infarction (OMI), cardiovascular risk factors, medication, laboratory findings, and results of invasive coronary angiography or computed tomography angiography were recorded at enrollment.

2.3 Echocardiographic data

Standard transthoracic echocardiography was performed according to the recommendations of American Society of Echocardiography guideline, using a commercially available ultrasound diagnostic systems (Vivid E9, GE Medical Systems, USA) equipped with a 1.7/3.3 MHz probe. LAD was measured using M-mode tracings and indexed to BSA (LADI). LAA was evaluated from the apical 4-chamber view at the end-ventricular systole, planimetered with the inferior LA border defined as the plane of the mitral annulus, excluding the confluence of the pulmonary veins and the LA appendage, then indexed to BSA (LAAI). Left ventricular end-diastolic diameter (LVEDD) and 1eft ventricular end systolic diameter (LVESD), septum wall thickness (IVS) and posterior wall thickness (PW) were measured using M-mode tracings. Peak early diastolic transmitral velocity (E) and late diastolic transmitral velocity (A) were determined by pulse wave Doppler. Peak early diastolic mitral annular velocity (Em) was determined by tissue Doppler imaging. The E/A ratio and E/Em ratio was calculated. LVEF was calculated by the Teicholz formula. Left ventricular mass (LVM) was calculated by the Devereux formula: $LVM = 0.8 \times 1.04 \times [(IVS + PW + LVEDD)^3 – LVEDD^3] + 0.6$, then indexed to BSA (LVMI).

2.4 Follow-up study

We followed up all patients via medical record review, office visits or telephone contact regarding the development of adverse CV events in January and February 2014. Adverse CV events were defined as: hospital readmission for angina pectoris, AMI, CHF, stroke and all-cause mortality. For patients with recurrent events, the time to the first event was recorded.

2.5 Statistical analysis

Continuous variables were presented as mean ± SD. Categorical variables were displayed as percentages. Comparisons between groups were performed by *t* tests (continuous variables) or Chi square analyses (categorical variables), as appropriate. Survival curves were generated from Kaplan–Meier estimates and compared by using log-rank tests. Cox proportional hazards modeling was used to determine the association between all the covariates with adverse CV events. A two-tailed *P* value of less than 0.05 was considered to be statistically significant. All analyses were performed with SPSS 17.0.

3 Results

3.1 Baseline characteristics

A total of 429 patients were included in the study. During a mean follow-up time of 26.3 ± 8.6 months, 38 patients were lost and the lost rate was 8.86%. We obtained complete information of 391 patients (mean age 64.4 ± 10.3 years, 69.1% males). Among these patients, 60 (15.3%) had a history of old MI. A total of 289 (73.9%) had hypertension, 156 (39.9%) had diabetes mellitus, 195 (49.9%) had dyslipidemia, and 194 (49.6%) were smokers, 12 patients (3.1%) had no significant coronary artery lesion, 117 (29.9%) had single-vessel stenosis, 117 (29.9%) had double-vessel stenosis, and 145 (37.1%) had triple-vessel stenosis. Characteristics of the study population are outlined in Table 1.

3.2 Adverse events

During follow-up, 98 adverse CV events (25.1%) occurred, including 84 hospital readmission for angina pectoris (21.5%), four AMI (1.0%), four CHF (1.0%), one stroke (0.3%) and five all-cause mortality (1.3%). Among patients readmitted to hospital for angina pectoris, 32 patients (38.1%) underwent coronary revascularization (Table 1).

3.3 Comparison of clinical characteristics between events group and events-free group

As compared with the events-free patients, the patients with adverse events had lower DBP (72.6 ± 9.6 *vs.* 75.4 ± 9.7 mmHg, $P = 0.013$] and larger PP (58.4 ± 15.7 mmHg *vs.* 53.4 ± 13.5 mmHg, $P = 0.002$] at baseline. There were no significant differences between two groups in terms of demographic data, medical history, quantity of involved coronary artery, medication and laboratory parameters (Table 2).

Patients with adverse events had larger LAA (19.6 ± 3.1 *vs.* 18.6 ± 3.2 cm^2, $P = 0.006$) and larger LAAI (11.1 ± 1.7 *vs.* 10.6 ± 1.7 cm^2/m^2, $P = 0.007$) than those without events. There were no significant differences between two groups in other echocardiographic parameters (Table 2).

Table 1. Baseline clinical characteristics of the study population.

Variable	Data
Demographic data	
Male	270 (69.1%)
Age, yrs	64.4 ± 10.3
SBP, mmHg	129.4 ± 16.2
DBP, mmHg	74.7 ± 9.7
PP, mmHg	54.7 ± 14.2
HR, beats/min	69.5 ± 10.3
BMI, kg/m^2	25.8 ± 3.2
Medical history	
Hypertension	289 (73.9%)
Diabetes	156 (39.9%)
Dyslipidemia	195 (49.9%)
Smoking	194 (49.6%)
OMI	60 (15.3%)
Lesions and treatments	
CAG	375 (95.9%)
CTA	16 (4.1%)
2-vessel stenosis	117 (29.9%)
3-vessel stenosis	145 (37.7%)
Coronary vascularization	263 (67.3%)
Medication	
Antiplatelet drugs	388 (99.2%)
Nitrates	206 (52.7%)
CCB	167 (42.7%)
β-blocks	257 (65.7%)
ACEI/ARB	199 (50.9%)
Statin	383 (97.9%)
Adverse outcome	
CV adverse events	98 (25.1%)
Hospital readmission for AP	84 (21.5%)
Coronary revascularization	32 (8.2%)
AMI	4 (1.0%)
CHF	4 (1.0%)
Stroke	1 (0.3%)
All-cause mortality	5 (1.3%)

Data are presented as mean ± SD or *n* (%). ACEI: angiotensin converting enzyme inhibitor; AMI: acute myocardial infarction; AP: angina pectoris; ARB: angiotensin receptor blocker; BMI: body mass index; CAG: coronary angiography; CCB: calcium channel blockers; CHF: congestive heart failure; CTA: computed tomography angiography; CV: cardiovascular; DBP: diastolic blood pressure; HR: heart rate; OMI: old myocardial infarction; PP: pulse pressure; SBP: systolic blood pressure.

3.4 Univariate predictors of adverse CV events

Using univariate Cox model, univariate variables significantly associated with CV adverse events included quantity of involved coronary artery (P = 0.042), DBP (P = 0.013), PP (P = 0.001) and LAAI (P = 0.008) (Table 3).

Table 2. Clinic characteristics of events group and events-free group.

Variable	Events group, n = 98	Event-free group, n = 293	P-value
Demographic data			
Male	70 (71.4%)	200 (68.3%)	0.615
Age, yrs	64.8 ± 10.4	64.2 ± 10.3	0.630
SBP, mmHg	131.1 ± 17.4	128.8 ± 15.8	0.224
DBP, mmHg	72.6 ± 9.6	75.4 ± 9.7	0.013
PP, mmHg	58.4 ± 15.7	53.4 ± 13.5	0.002
HR, beats/min	68.7 ± 10.0	69.8 ± 10.4	0.392
BMI, kg/m^2	26.1 ± 3.2	25.7 ± 3.2	0.403
Medical history			
Hypertension	75 (76.5%)	214 (73.0%)	0.595
Diabetes	42 (42.9%)	114 (38.9%)	0.551
Dyslipidemia	52 (53.1%)	143 (48.8%)	0.486
Smoking	51 (52.0%)	143 (48.8%)	0.641
OMI	19 (19.4%)	41 (14.0%)	0.199
Quantity of involved coronary artery			0.142
No apparent lesion	0	12 (4.1%)	
1-vessel stenosis	27 (27.6%)	90 (30.7%)	
2-vessel stenosis	29 (29.6%)	88 (30.0%)	
3-vessel stenosis	42 (42.9%)	103 (35.2%)	
Medication			
Antiplatelet drugs	97 (99.0%)	291 (99.1%)	1.000
Nitrates	50 (51.0%)	156 (53.2%)	0.727
CCB	37 (37.8%)	130 (44.4%)	0.289
β-blocks	67 (68.4%)	190 (64.8%)	0.542
ACEI/ARB	46 (46.9%)	153 (52.2%)	0.414
Statin	98 (100%)	285 (97.3%)	0.210
Laboratory parameters			
TC, mmol/L	4.16 ± 1.02	4.20 ± 1.08	0.772
TG, mmol/L	2.06 ± 1.47	1.84 ± 1.28	0.167
HDL-C, mmol/L	0.93 ± 0.22	0.95 ± 0.22	0.492
LDL-C, mmol/L	2.43 ± 0.76	2.43 ± 0.89	0.988
UA, μmol/L	336.0 ± 83.4	327.9 ± 79.5	0.413
Cr, μmol/L	80.9 ± 17.2	80.5 ± 14.8	0.855
FBG, mmol/L	5.95 ± 2.06	5.78 ± 1.97	0.489
NT-proBNP, pg/dL	128 (71, 260)	105 (53, 213)	0.161
HbA_1C	6.8% ± 1.3%	7.0% ± 4.9%	0.670
HsCRP, mg/dL	2.0 (0.9, 4.1)	1.4 (0.9, 3.4)	0.714
Echocardiographic parameters			
LAD, mm	36.4 ± 4.6	36.2 ± 3.8	0.700
LADI, mm/m^2	20.7 ± 2.6	20.7 ± 2.4	0.940
LAA, cm^2	19.6 ± 3.1	18.6 ± 3.2	0.006
LAAI, cm^2/m^2	11.1 ± 1.7	10.6 ± 1.7	0.007
LVEDD, mm	47.3 ± 5.7	47.1 ± 5.2	0.744
LVMI, g/m^2	82.7 ± 21.3	84.2 ± 21.7	0.545

Data are presented as mean ± SD, *n* (%) or median (range). ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; AMI: acute myocardial infarction; BMI: body mass index; CCB: calcium channel blockers; CHF: congestive heart failure; Cr: creatinine; DBP: diastolic blood pressure; FBG: fasting blood-glucose; HbA_1C: glycated hemoglobin; HDL-C: high density lipoprotein cholesterol; Hs-CRP: hypersensitivity C-reactive protein; HR: heart rate; LAA: left atrial area; LAAI: left atrial area index; LAD: 1eft atrial diameter; LADI: 1eft atrial diameter index; LDL-C: low density lipoprotein cholesterol; LVEDD: 1eft ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; NT-proBNP: N terminal pro-B type natriuretic peptide; OMI: old myocardial infarction; SBP: systolic blood pressure; PP: pulse pressure; TC: total cholesterol; TG: triglyceride; UA: uric acid.

Table 3. Univariate predictors of adverse CV events.

Variable	OR	95%CI	*P* value
Male	0.912	0.588–1.416	0.682
Age	1.005	0.985–1.024	0.647
BMI	1.032	0.970-1.098	0.319
Hypertension	1.263	0.785–2.032	0.335
Dyslipidemia	1.221	0.819–1.821	0.327
Diabetes	1.146	0.767–1.713	0.507
Smoking	1.080	0.725–1.608	0.707
OMI	1.363	0.825–2.250	0.227
Quantity of involved coronary artery	1.269	1.009–1.598	0.042
SBP	1.008	0.996–1.020	0.183
DBP	0.974	0.955-0.994	0.013
PP	1.023	1.009–1.037	0.001
TC	0.961	0.793–1.164	0.682
TG	1.083	0.960–1.223	0.194
LDL-C	0.989	0.785–1.246	0.926
HDL-C	0.684	0.259–1.805	0.443
Hs-CRP	0.997	0.965–1.029	0.833
HbA1C	0.985	0.918–1.058	0.684
UA	1.001	0.999–1.004	0.391
LVEF	0.978	0.949–1.008	0.151
LADI	1.001	0.923–1.086	0.974
LAAI	1.162	1.040-1.298	0.008
LVMI	0.996	0.986–1.005	0.370
E/Em ratio	1.034	0.968–1.105	0.315

BMI: body mass index; CV: cardiovascular; DBP: diastolic blood pressure; E/Em: the ratio of peak early diastolic transmitral velocity to mitral annular velocity; HbA1C: glycated hemoglobin; HDL-C: high density lipoprotein cholesterol; Hs-CRP: hypersensitivity C-reactive protein; LAAI: left atrial area index; LADI: 1eft atrial diameter index; LDL-C: low density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; OMI: old myocardial infarction; SBP: systolic blood pressure; PP: pulse pressure; TC: total cholesterol; TG: triglyceride; UA : uric acid.

The medium LAAI of 391 patients was 10.6 cm^2/m^2. Kaplan-Meier survival curves for patients with LAAI < 10.6 cm^2/m^2 and those with LAAI ≥ 10.6 cm^2/m^2 were shown in Figure 1. The curriculum events-free rate was significantly higher in patients with LAAI < 10.6 cm^2/m^2 than those with LAAI ≥ 10.6cm^2/m^2 ($P < 0.001$).

3.5 Independent predictors of adverse CV events

All significant univariate variables and other known risk predictors were entered into the multivariate Cox regression model. After adjusted for age, gender, BMI, hypertension, dyslipidemia, diabetes, smoking, OMI, LVEF, LVMI and E/Em ratio, LAAI (OR = 1.140, 95%CI: 1.016–1.279, P = 0.026), DBP (OR: 0.976, 95%CI: 0.956–0.996, P = 0.02), and PP (OR: 1.020, 95%CI: 1.007–1.034, P = 0.004) were identified as independent predictors of adverse CV events (Table 4).

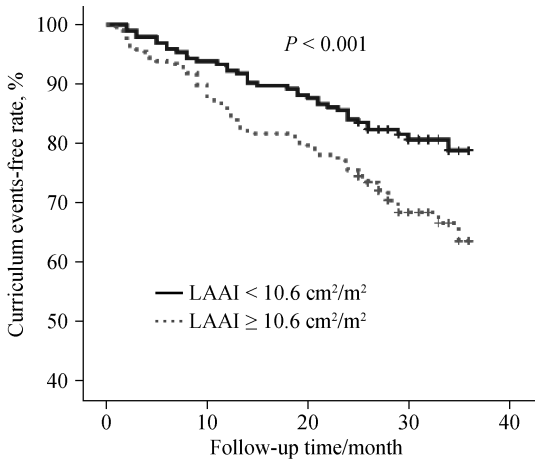

Figure 1. Kaplan-Meier analysis showed LAAI < 10.6 cm^2/m^2 was associated with the higher curriculum events-free rate. LAAI: left atrial area index.

Table 4. Independent predictors of adverse CV events.

Variable	OR	95%CI	*P* value
Age	0.990	0.965–1.011	0.353
Male	0.740	0.468–1.170	0.198
BMI	1.056	0.993–1.123	0.084
Hypertension	1.181	0.718–1.945	0.512
Dyslipidemia	1.126	0.744–1.703	0.574
Diabetes	1.051	0.692–1.596	0.816
Smoking	1.140	0.689–1.887	0.610
OMI	1.119	0.620–2.020	0.708
Quantity of involved coronary artery	1.255	0.989–1.593	0.061
DBP	0.976	0.956–0.996	0.020
PP	1.020	1.007–1.034	0.004
LAAI	1.140	1.016–1.279	0.026
LVEF	0.976	0.947–1.007	0.126
LVMI	0.991	0.982–1.001	0.092
E/Em ratio	0.995	0.921–1.074	0.898

BMI: body mass index; CV: cardiovascular; DBP: diastolic blood pressure; E/Em: the ratio of peak early diastolic transmitral velocity to mitral annular velocity; LAAI: left atrial area index; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; OMI: old myocardial infarction; PP: pulse pressure.

4 Discussion

The major findings of this study were to confirm LAAI as an independent predictor of adverse cardiovascular events for UAP patients. To the best of our knowledge, this is the

first study to report that LAAI provides prognostic information in UAP subjects, independent of clinical characteristics and other echocardiographic predictors of outcome, including parameters reflecting diastolic function such as E/Em ratio and LVMI.

LA enlargement has been considered to reflect the elevated left ventricular filling pressure, and was to be a sensitive expression of the severity and duration of diastolic dysfunction.[1] Furthermore, LA enlargement could be caused by various pathologic processes, including systemic hypertension, diabetes mellitus and endothelial dysfunction.[9–11] Therefore, LA dilation presented not only diastolic dysfunction, but also increased cardiovascular risk burden. LA dilatation has been proved to be a strong predictor of CHF,[12] stroke,[13] cardiovascular mortality and all-cause mortality.[3,14] The prognostic significance of LA dilatation was evaluated in different patient groups, including those with AMI,[4,15,16] with CHF,[3,17] and those with hypertrophic, idiopathic and ischemic dilated cardiomyopathy.[14,18,19] A study reported that LAVI had similar predictability as LVEF for poor prognosis in ambulatory CHD adults.[5] Gunasekaran, *et al*.,[20] had shown that an increased LAVI leads to a significantly higher occurrence of cardiovascular complications as early as with six months of acute coronary syndrome. Our study extended the conclusions to a population of UAP subjects without concomitant cardiac pathological conditions, and showed that LAAI was an independent predictor of adverse cardiovascular events in UAP.

In the present study, neither E/Em ratio nor LVMI reached significant difference in either univariate or multivariate Cox model, although previous studies have shown their powerful predictive value of adverse outcomes.[21,22] Our study showed that, compared with these conventional parameters, LAAI appeared to be a better indicator of poor prognosis. Tsang, *et al*.,[1] demonstrated that LAVI was a superior measurement over E/Em ratio for the detection of abnormal diastolic function, suggesting that E/Em ratio is suited for monitoring hemodynamic status in a short term, while LA size is more suitable for monitoring chronic hemodynamic changes.[23] Otherwise, in our study, the average values of LVMI were within normal range both in patients with adverse events (82.68 ± 21.31 g/m^2) and in those without events (84.21 ± 21.74 g/m^2), which might not be a subtle predictor of poor prognosis.

In the present study, we also demonstrated that decreased DBP and increasing PP predict poor prognosis for UAP patients, which were in agreement with the results of previous studies.[24,25]

Some limitations of the present study should be noted. First, this is a retrospective cohort study, and subject to biases inherent to the design. Second, because of the limited number of events due to the relatively small sample size and short-term follow-up period, we didn't develop a unique prediction model for each outcome event. Third, subjects with OMI were not excluded in the study, which could bring possible interference to the results. Fourth, the study population was strictly selected, so that the results should be extrapolated to the general UAP population with caution.

In conclusion, the present study demonstrated that LAAI, a simple, easily acquired parameter in daily clinic practice, was an independent predictor of adverse CV events, and appeared to be a useful tool for risk stratification in UAP patients. Future studies to include larger number of UAP patients and longer follow-up time will be warranted.

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