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 Board of Peking University Third Hospital.

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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 left ventricular end systolic diameter (LVESD), septum wall thickness (IVS) and posterior wall thickness (PW) were measured using M-mode tracings. Peak early diastolic transmural velocity (E) and late diastolic transmural 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 cm², \(P = 0.006\)) and larger LAAI (11.1 ± 1.7 vs. 10.6 ± 1.7 cm²/m², \(P = 0.007\)) 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/m²                        | 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             | 68.9 ± 10.4                 | 0.392     |
| BMI, kg/m²                        | 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 |                        |                             |           |
| 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     |
| FG, mmol/L                        | 5.95 ± 2.06             | 5.78 ± 1.97                 | 0.489     |
| NT-proBNP, pg/dL                  | 128 (71, 260)           | 105 (53, 213)               | 0.161     |
| HbA1C                             | 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/m²                       | 20.7 ± 2.6              | 20.7 ± 2.4                  | 0.940     |
| LAA, cm²                          | 19.6 ± 3.1              | 18.6 ± 3.2                  | 0.006     |
| LAAL, cm²/m²                      | 11.1 ± 1.7              | 10.6 ± 1.7                  | 0.007     |
| LVEDD, mm                         | 47.3 ± 5.7              | 47.1 ± 5.2                  | 0.744     |
| LVMI, g/m²                        | 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; FG: fasting blood-glucose; HbA1C: glycated hemoglobin; HDL-C: high density lipoprotein cholesterol; HsCRP: high sensitivity C-reactive protein; HR: heart rate; LAA: left atrial area; LAAI: left atrial area index; LAD: left atrial diameter; LADD: left atrial diameter index; LDL-C: low density lipoprotein cholesterol; LVEDD: left 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      | 1.269| 1.009–1.598 | 0.042   |
| coronary artery           |      |             |         |
| SBP                       | 1.008| 0.996–1.020 | 0.183   |
| DBP                       | 0.974| 0.950–0.999 | 0.013   |
| PP                        | 1.023| 1.009–1.037 | 0.001   |
| TC                        | 0.961| 0.973–1.164 | 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   |
| LAAI                      | 1.001| 0.923–1.086 | 0.974   |
| LVMI                      | 1.162| 1.040–1.298 | 0.008   |
| E/Em ratio                | 0.996| 0.986–1.005 | 0.370   |

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: left 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 cm²/m². Kaplan-Meier survival curves for patients with LAAI < 10.6 cm²/m² and those with LAAI ≥ 10.6 cm²/m² were shown in Figure 1. The curriculum events-free rate was significantly higher in patients with LAAI < 10.6 cm²/m² than those with LAAI ≥ 10.6 cm²/m² (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: 1.001–1.034, P = 0.004) were identified as independent predictors of adverse CV events (Table 4).

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 AML,[14,15,16] with CHF,[3,17] and those with hypertrophic, idiopathic and ischemic dilated cardiomyopathy.[18] A study reported that LAVI had similar predictability as LVEF for poor prognosis in ambulatory CHD adults.[15] 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/m²) and in those without events (84.21 ± 21.74 g/m²), 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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