Left Atrial Expansion Index Predicts Atrial Fibrillation in Dyspnea
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Background: The left atrial (LA) expansion index for predicting atrial fibrillation (AF) in a relatively low-risk cohort is not fully understood.

Methods and Results: In this prospective study of 2,200 dyspnea patients, the LA expansion index was calculated as \((\text{Vol}_{\text{max}}-\text{Vol}_{\text{min}}) \times 100/\text{Vol}_{\text{min}}\), where \(\text{Vol}_{\text{max}}\) was defined as maximum LA volume and \(\text{Vol}_{\text{min}}\) as minimum volume. The endpoints were 2-year frequency of AF, including both paroxysmal and persistent. Of the 180 participants (8.2%) who had AF attacks over a median follow-up of 2.7 years, 90 (4.1%) had at least 1 episode of persistent AF. Compared to patients with paroxysmal AF, those with persistent AF had a much lower LA expansion index (100±59% vs. 44±24%). LA expansion index was associated exponentially with the incidence of persistent AF. Independent predictors of AF included age, renal function impairment, pulmonary artery systolic pressure, and LA expansion index. Persistent AF, however, had significant independent associations only with prior heart failure, renal function impairment, diastolic dysfunction, and LA expansion index (odds ratio, 0.970; 95% confidence interval: 0.959–0.981 per 1% increase, \(P<0.0001\)). Compared to other parameters, LA expansion index <61.4% was the best cut-off point to predict persistent AF.

Conclusions: The LA expansion index is associated with the presence of AF, and a reduced LA expansion index has a strong association with persistent AF. (Circ J 2013; 77: 2712–2721)

Key Words: Atrial fibrillation; Left atrial expansion index; Maximum indexed left atrial volume; Tissue Doppler imaging

Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia. It is associated with markedly increased risks of stroke, heart failure, and cardiovascular death, underscoring the importance of AF as a public health problem. AF has been also shown to be associated with increased risk for cardiovascular morbidity and mortality. For example, among participants with new-onset AF in the Framingham Heart Study, the relative risk for mortality was 1.5 (95% confidence interval [CI]: 1.2–1.8) in men and 1.9 (95% CI: 1.5–2.2) in women. Identifying predisposing factors in AF may improve the effectiveness of preventive measures and may facilitate detection of patients most susceptible to AF and its sequelae.

Recent studies show that left atrial (LA) volume provides a sensitive morphophysiological indicator of the severity of left ventricular (LV) dysfunction and may also be a useful index of cardiovascular risk. Although LA volume indicates the chronicity and severity of diastolic dysfunction, no studies have determined the exact relationship between LA volume and LV filling pressure. Recent work by the authors showed that the LA expansion index, which accurately reflects instantaneous LV filling pressure (logarithmic correlation) in many disease entities, is useful for predicting AF after coronary artery bypass graft surgery. Because the LA expansion index mirrors LV filling pressure, we hypothesized that the LA expansion index predicts long-term events not only in patients with heart disease, but also in relatively low-risk subjects such as consecutive patients visiting cardiovascular clinics for dyspnea.

Methods

Subjects
Between August 2009 and April 2010, this prospective study recruited 2,516 patients aged ≥50 years who had undergone echocardiography for dyspnea on their first visit to the cardiovascular outpatient clinic of Kaohsiung Veterans General Hospital in Kaohsiung, Taiwan. Exclusion criteria were the following: (1) potential confounders including acute or recent...
myocardial infarction or cardiac surgery (within 6 months), presence of mitral stenosis, prostatic mitral valve, a history of long QT syndrome, Brugada syndrome, substance abuse, electrolyte imbalance, hyperthyroidism, or hypothyroidism; (2) need for cardioversion or catheter ablation for AF during the follow-up period (cardioversion or catheter ablation will change the course and duration of AF, which would affect the classification of AF); (3) any atrial septum abnormality (eg, atrial septal defect or aneurysm, which would affect the measurements of LA expansion index); (4) rhythm other than sinus rhythm or prior history of AF; (5) inadequate image quality; and (6) lack of informed consent. Of the initial 2,516 subjects, 142 did not meet all enrollment criteria, and another 154 were lost to follow-up, or declined to participate. Another 20 were excluded due to cardioversion/catheter ablation for AF during the follow-up period. Therefore, the final analysis included 2,200 patients. Subjects were considered hypertensive if they had high blood pressure or were currently receiving hypertension drug treatment. Diabetes mellitus was defined according to American Diabetes Association criteria. For each participant, creatinine clearance (CCr) was estimated using the Cockcroft-Gault equation and renal dysfunction was defined as CCr <60 ml · min⁻¹ · 1.73 m⁻² at enrollment. Coronary artery disease was defined as any history of the following: (1) myocardial infarction; (2) at least 70% stenosis in 1 or more coronary vessels on cardiac catheterization; (3) exercise-induced ischemia indicated on treadmill electrocardiogram (ECG) or nuclear perfusion stress imaging; or (4) coronary revascularization. The aim was to evaluate clinical and echocardiographic parameters as predictors of AF events, either paroxysmal or persistent, during the follow-up period. CHADS: scores were calculated as a measure of baseline risk of embolic complication. The protocol was approved by the institutional review board of Kaohsiung Veterans General Hospital. Patients were invited to participate in this study after giving written informed consent.

Echocardiography

Conventional Echocardiography and Tissue Doppler Imaging

Pulmonary artery systolic pressure was estimated using Doppler echocardiography by calculating the right ventricular to right atrial pressure gradient during systole. Right atrial pressure, estimated on the basis of echocardiographic characteristics of the inferior vena cava, was then added to the calculated gradient. The LV mass was calculated using the formula described by Devereux and Reichek. The LV mass was indexed to body surface area. Pulsed-wave tissue Doppler imaging (TDI) was performed in the apical views and a pulsed-wave Doppler sample volume was placed at the level of the mitral annulus over the septal and lateral borders. The pulsed-wave TDI tracing recorded over 5 cardiac cycles at a sweep speed of 100 mm/s was used for offline calculations. The average early-diastolic velocity (e') of the septal and lateral mitral annulus was chosen to estimate LV filling pressure by the E/e' method. The severity of mitral regurgitation (MR) was evaluated semiquantitatively from the area of regurgitant jet on color Doppler, and MR was classified as absent or trivial (0), mild (1+), moderate (2+), or severe (3+). Diastolic dysfunction was assessed as described previously. Based on Doppler measurements of mitral inflow and TDI, diastolic function was classified into 4 categories: normal; mild (impaired relaxation without evidence of increased filling pressures); moderate (pseudonormal with moderately elevated filling pressures); and severe (advanced reduction in compliance).

LA Volume Parameter Measurements

All LA volume measurements were calculated from apical 4- and 2-chamber views using the biplane area-length method. The LA volumes were measured at 3 points: (1) immediately before the mitral valve opening (maximum LA volume or Volmax); (2) at the onset of the P-wave on ECG (pre-P wave LA volume or Volp); and (3) at the mitral valve closure (minimum LA volume or Volmin). The LA expansion index was calculated as (Volmax–Volmin)×100%/Volmin. The LA ejection fraction (EF) was calculated as (Volp–Volmin)×100%/Volp. In all patients, LA volume was indexed to body surface area. Tachycardia, particularly heart rate >110 beats/min, with the merging of T and P waves on ECG made the measurements of LAEF impossible, leading to missing data in 84 patients.

Clinical Follow-up

Participants were followed up at the cardiovascular clinic every 3 months for at least 2 years and a resting ECG was obtained every time through the whole follow-up period. Participants were encouraged to visit the outpatient clinic for any feeling of palpitation or irregular heart beat. At every unscheduled visit for this, resting and 24-h Holter ECGs were performed to detect AF. Discharge diagnoses for all hospitalizations were entered into the database. For participants with AF events, another visit would be scheduled the following week to confirm persistence of AF. The prescription of oral anticoagulant, rate-control medications, or anti-arrhythmic drugs was dependent on the discretion of the treating physician. All study ECGs were interpreted by a cardiologist (S.-H.H.) and the diagnosis of AF was verified. Paroxysmal AF was defined as AF that was self-terminating with episode duration <7 days. Persistent AF was defined as AF that was not self-terminating with episode duration >7 days. Because cardioversion was not attempted in the present study, permanent AF was not diagnosed. Participants with AF events were subdivided into 2 groups according to whether or not they had experienced at least 1 persistent AF attack during the follow-up period. Medical assistants checked medical records once every 3 months.

Interobserver Variability

In the first 100 enrolled cases, Volmax and Volmin were measured by 2 independent observers. Interobserver variability was calculated as the difference between the values obtained by the 2 observers divided by the mean. Interobserver variability and variability were 3.2±5.4 ml/m² and 5.4±8.7% for Volmax, 2.7±3.6 ml/m² and 5.1±7.2% for Volp, and 2.9±1.1 ml/m² and 6.1±8.9% for Volmin, respectively. Therefore, interobserver variability in LAEF and in LA expansion index measurements were 5.3±6.8% and 5.8±7.6%, respectively.

Statistical Analysis

SPSS was used for all statistical analysis. Baseline characteristics and echocardiographic parameters were analyzed according to AF event. All continuous variables are presented as mean±SD. P<0.05 was considered statistically significant. Clinical characteristics were compared using chi-squared test for categorical variables. Group differences were analyzed using analysis of variance and post-hoc test for unpaired data. AF event-free survival was calculated using the Kaplan-Meier method and compared with log-rank test. Cox proportional hazards regression was used for examining the association between potential covariates and AF on univariate analysis and while controlling for baseline characteristics. The independent prognostic value of the LA expansion index was determined using multivariate models adjusted for covariates showing significant associations (P<0.05) with events in univariate models. Regarding the
(ROC) curve (AUC) was used to evaluate the sensitivity and specificity of predictors of paroxysmal/persistent AF. The C-statistic was calculated to compare the conventional maximum indexed LA volume, E/e’, LAEF, and LA expansion index in terms of accuracy in predicting AF events.

Results

Clinical Characteristics

Of the 2,200 participants analyzed in this study, 1 case of restric-
Incidence of AF

Of the 2,200 participants analyzed, 180 (8.2%) had experienced at least 1 episode of AF. Ninety had at least 1 episode of persistent AF during 2-year follow-up. The mean annual frequency of AF was 0.8 in the paroxysmal AF group and 1.2 in the persistent AF group (either paroxysmal or persistent). In the persistent AF group, 16 participants had more than 1 persistent AF event. Of the 90 participants with a history of persistent AF, AF did not recover to sinus rhythm in 8. Fifty-six (15.9%) of a total 352 AF events were asymptomatic. For symptomatic AF, patients commonly experienced palpitation (86%), chest pain (24%), light-headedness (23%), dyspnea (18%), and fatigue (11%).

Table 2. Medications During First AF Attack

|                | Paroxysmal AF (n=90) | Persistent AF (n=90) | P-value |
|----------------|-----------------------|----------------------|---------|
| Oral anticoagulant | 34 (37.8)             | 42 (46.7)            | 0.046   |
| Aspirin         | 25 (27.8)             | 27 (30.0)            | 0.562   |
| β-blocker       | 34 (37.8)             | 37 (41.1)            | 0.443   |
| Diltiazem       | 8 (8.9)               | 10 (11.1)            | 0.476   |
| Verapamil       | 5 (5.5)               | 8 (8.9)              | 0.284   |
| Digitalis       | 10 (11.1)             | 9 (10)               | 0.896   |
| ACEI            | 33 (36.7)             | 34 (37.8)            | 0.912   |
| AII             | 21 (23.3)             | 20 (22.2)            | 0.892   |
| Diuretic        | 8 (8.9)               | 9 (10)               | 0.667   |
| Any anti-arrhythmic drug | 38 (42.2)     | 34 (37.8)            | 0.723   |
| Propafenone     | 12 (13.3)             | 10 (11.1)            | 0.445   |
| Sotalol         | 25 (27.8)             | 28 (31.1)            | 0.562   |

Data given as n (%). Abbreviations as in Table 1.

Figure 1. Paroxysmal and persistent atrial fibrillation: 2-year incidence vs. decile of left atrial expansion index.
The LA size predicts the risk of AF, cerebrovascular events, acute coronary syndrome, heart failure and all-cause mortality. Some reports show that LA volume is a powerful mortality predictor, although the relationship is not linear and the highest LA expansion index is associated with persistent AF. Persistent AF was associated significantly with LA expansion index, which shows exponential increase from fifth decile of LA expansion index. Beyond the fifth decile, only paroxysmal AF occurred.

**Univariate and Multivariate Predictors of AF**

Table 3 lists the results of univariate and multivariate analyses of the clinical features and echocardiographic parameters as predictors of AF events (either paroxysmal or persistent). Patients with AF tended to be older and male, and tended to have a higher prevalence of prior heart failure, LV systolic or diastolic dysfunction, renal insufficiency, pulmonary hypertension, LV and LA dilation, low LAEF, and reduced LA expansion index. When a probability threshold of P=0.05 was chosen, only age, renal dysfunction, pulmonary hypertension and LA expansion index were independently associated with the presence of AF in the multivariate model. According to the model, renal dysfunction increases the odds of AF by a factor of 1.734. Additionally, the odds of AF are increased by a factor of 1.041 for each 1-mmHg increase in pulmonary artery systolic pressure, by a factor of 1.005 for each year increase in age, and by a factor of 0.995 for each % increase in LA expansion index. Table 4 lists the results of univariate and multivariate analyses of predictors of persistent AF. In the multivariate model, only prior heart failure, diastolic dysfunction, renal dysfunction and LA expansion index were significantly associated with persistent AF.

**Power for Predicting AF: Comparison of E/e’, Maximum Indexed LA Volume, LAEF and LA Expansion Index**

The C-statistic of the ROC curve was used to compare E/e’, maximum indexed LA volume, LAEF, and LA expansion index in terms of power in predicting AF (either paroxysmal or persistent). The comparison showed that an LA expansion index ≤79% had a 73% sensitivity and a 73% specificity for predicting AF and was superior to both E/e’ and LAEF (Figure 2A). ROC curve analysis was also done to compare the performance of the 4 parameters for predicting paroxysmal and persistent AF (Figure 2B, C). According to C-statistics, the performance of those parameters was better for predicting persistent AF than for predicting paroxysmal AF. Although maximum indexed LA volume >32.4 ml/m², LAEF <22%, and E/e’ >12.5 were predictors of persistent AF, LA expansion index <61.4% had the best predictive power with 81% sensitivity and 84% specificity. For comparison of AF event rates, participants were divided into 2 groups with LA expansion index less than or greater than 79% based on ROC curve analysis for predicting paroxysmal/persistent AF. The basic characteristics and echocardiographic parameters are listed in Table 5. Figure 3 shows the Kaplan-Meier curve for AF event-free survival for LA expansion index >79%.

**Discussion**

The LA size predicts the risk of AF, cerebrovascular events, acute coronary syndrome, heart failure and all-cause mortality. Some reports show that LA volume is a powerful mortality predictor, although the relationship is not linear and the highest LA expansion index is associated with persistent AF. Persistent AF was associated significantly with LA expansion index, which shows exponential increase from fifth decile of LA expansion index. Beyond the fifth decile, only paroxysmal AF occurred.

### Table 3. Predictors of AF (Paroxysmal or Persistent)

| Variables                     | Univariate analysis | Multivariate analysis |
|-------------------------------|---------------------|-----------------------|
|                              | HR (95% CI) P-value | HR (95% CI) P-values  |
| Age (years)                  | 1.007 (1.005–1.010) | <0.0001               |
| Gender (male)                | 0.700 (0.509–0.961) | 0.024                 |
| Diabetes                     | 2.957 (2.192–3.898) | <0.0001               |
| Hypertension                 | 2.193 (1.614–2.980) | <0.0001               |
| Current smoker               | 1.638 (1.214–2.209) | 0.001                 |
| BMI (kg/m²)                  | 0.994 (0.452–2.187) | 0.989                 |
| Prior heart failure          | 1.998 (1.736–2.341) | <0.0001               |
| Renal dysfunction            | 4.179 (3.112–5.613) | <0.0001               |
| LVIDd (mm)                   | 1.106 (1.081–1.132) | <0.0001               |
| E-deceleration time (ms)     | 0.995 (0.992–0.998) | <0.0001               |
| Diastolic dysfunction        | 2.700 (2.330–3.130) | <0.0001               |
| LVEF (%)                     | 0.930 (0.919–0.940) | <0.0001               |
| PASP (mmHg)                  | 1.071 (1.060–1.081) | <0.0001               |
| Maximum indexed LAV (ml/m²)  | 1.009 (1.007–1.012) | <0.0001               |
| LAEF (%)                     | 0.937 (0.926–0.949) | <0.0001               |
| LA expansion index (%)       | 0.981 (0.977–0.985) | <0.0001               |
| E/e’                         | 1.079 (1.062–1.096) | <0.0001               |
| LV mass index (g/m²)         | 1.012 (1.010–1.014) | <0.0001               |

CI, confidence interval; HR, hazard ratio; LV, left ventricular. Other abbreviations as in Table 1.
predictor after myocardial infarction regardless of systolic function. Because LA enlargement is directly proportional to the severity of LV filling abnormality, it accurately indicates the severity of underlying clinical or subclinical cardiovascular disease.

Underlying Mechanism of LA Expansion Index

While the limits of distension are dictated by the fully unfolded and inextensible collagen fibers, the LA reaches its maximum volume and further elongation is halted. Progressively increasing pressure is needed for further LA dilation. With the sustained increase in LA pressure and LV filling pressure, the atrium dilates so that remodeling of the LA after increasing maximum LA volume results in further reduction of cyclic LA volume change. Therefore, the LA expansion index accurately reflects LV filling properties. Compared to LA volume, LA function has a stronger independent correlation with LV diastolic dysfunction and arterial stiffness in many categories of patients; these data support the hypothesis that, for predicting heart events, LA dysfunction is more sensitive than morphologic parameters. For these reasons, LA expansion index is superior to LA volume for assessing AF events. Although LAEF is also a good predictor of AF, it cannot be measured in patients with tachycardia and it also offers less power than LA expansion index for predicting paroxysmal and persistent AF (Figure 2). The TDI parameters, particularly E/e’, have been reportedly associated with elevated LV filling pressure and are useful for predicting late outcome of many cardiovascular diseases. Nevertheless, TDI offers regional measures of the systolic and diastolic function. When E/e’ is used to assess some disease entities with only regional myocardial impairment, such as coronary artery disease, it infers that regional parameters obtained on TDI may not reflect global LV function precisely.

Prior Reports of LA Expansion Index

The AF rate correlated negatively with LA expansion index (Figure 1). Even after adjusting other covariates, LA expansion index was independently associated with AF events, which confirms its potential use for stratifying the risk of AF events in relatively low-risk patients. These results are consistent with prior reports that LA expansion index is applicable for predicting events in high-risk cohorts. Therefore, the broad clinical applications of the LA expansion index make it valuable for assessing prognosis in a variety of patients. The calculation for LA expansion index is more time-consuming compared to that for maximum LA volume, but if the equation for calculating LA expansion index is programmed into the echocardiography machine in advance, the index can be calculated in <2 min.

LA Expansion Index and Initiation of AF

The negative association between LA expansion index and frequency of AF events has several possible explanations. First, poor LA expansion index might represent greater dilation of the atria. Additionally, dilated atria also induce endo-epicardial dissociation, which increases the number of simultaneously wavefronts in the atrial wall. Second, poor LA expansion index indicates poor LV compliance with increased atrial pressure according to prior studies. Increased atrial pressure causes

| Variables                        | Univariate analysis | Multivariate analysis |
|---------------------------------|---------------------|-----------------------|
|                                | HR (95% CI)         | P-value               | HR (95% CI)         | P-value               |
| Age (years)                     | 1.007 (1.004–1.010) | 0.002                 | 1.005 (0.995–1.015) | 0.298                 |
| Gender (female)                 | 0.747 (0.480–1.163) | 0.19                  |                       |                       |
| Diabetes                        | 2.477 (1.611–3.808) | <0.0001               |                       |                       |
| Hypertension                    | 1.827 (1.197–2.790) | 0.005                 |                       |                       |
| Current smoker                  | 1.902 (1.253–2.888) | 0.003                 |                       |                       |
| BMI (kg/m²)                     | 0.480 (0.155–1.490) | 0.204                 |                       |                       |
| Prior heart failure             | 2.243 (1.932–2.776) | <0.0001               | 3.468 (2.094–5.743)  | <0.0001               |
| MR                              | 2.500 (2.092–2.988) | <0.0001               | 1.143 (0.900–1.452)  | 0.774                 |
| Renal dysfunction               | 5.280 (3.488–7.994) | <0.0001               | 1.822 (1.162–2.858)  | 0.009                 |
| LVIDd (mm)                      | 1.132 (1.100–1.166) | <0.0001               |                       |                       |
| E-deceleration time (ms)        | 0.987 (0.983–0.992) | <0.0001               |                       |                       |
| Diastolic dysfunction           | 4.247 (3.419–5.277) | <0.0001               | 1.724 (1.220–2.435)  | 0.002                 |
| LVEF (%)                        | 0.911 (0.896–0.925) | <0.0001               | 1.010 (0.988–1.034)  | 0.378                 |
| PASP (mmHg)                     | 1.081 (1.068–1.095) | <0.0001               |                       |                       |
| Maximum indexed LAV (ml/m²)     | 1.011 (1.008–1.013) | <0.0001               | 1.004 (0.993–1.016)  | 0.441                 |
| LAEF (%)                        | 0.980 (0.962–0.999) | <0.0001               |                       |                       |
| LA expansion index (%)          | 0.952 (0.944–0.960) | <0.0001               | 0.969 (0.959–0.978)  | <0.0001               |
| E/e’                            | 1.102 (1.083–1.122) | <0.0001               | 0.970 (0.939–1.002)  | 0.065                 |
| LV mass index (g/m²)            | 1.013 (1.011–1.016) | <0.0001               |                       |                       |

Abbreviations as in Table 1,3.
a decrease in atrial effective refractory period and action potential duration and an increase in AF inducibility. 

Third, although LA dilation might be caused by chronic stretch of LA, LA expansion index reflects the physiology in more detail. It mirrors the instantaneous stretchability. Atrial stretch-activated ion channels are responsible for the decrease in atrial effective refractory period and increase in AF vulnerability. 

**LA Expansion Index and Persistence of AF**

Regarding the prognostic effect of LA expansion index described in prior studies and the close correlation between LA expansion index and AF progression (Figure 1), it may be conjectured that structural rather than electrical remodeling of the atria is involved in AF progression. Underlying disease might cause chronic stretch and atrial dilation, which seem to be important stimuli for chronic atrial structural remodeling. The bur-

![Figure 2](image-url)
LA Expansion Index Predicts AF

**Table 5. Patient Characteristics vs. LA Expansion Index**

| Variables                        | LA expansion index >79% (n=1504) | LA expansion index ≤79% (n=696) | P-value |
|----------------------------------|----------------------------------|----------------------------------|---------|
| Age (years)                      | 57±21                            | 66±14                            | <0.0001 |
| Gender (M/F)                     | 885/619                          | 465/231                          | <0.0001 |
| BMI (kg/m²)                      | 24.6±3.6                         | 24.5±3.8                         | 0.419   |
| Hypertension                     | 610 (40.6)                       | 386 (55.5)                       | <0.0001 |
| Diabetes                         | 222 (14.8)                       | 221 (31.8)                       | <0.0001 |
| History of heart failure         | 28 (1.9)                         | 52 (7.5)                         | <0.0001 |
| CAD                              | 121 (8)                          | 339 (48.7)                       | <0.0001 |
| MR >mild severity                | 102 (6.8)                        | 204 (29.3)                       | <0.0001 |
| Renal dysfunction                | 195 (13)                         | 206 (29.6)                       | <0.0001 |
| Diastolic function               | (Normal) 731 (48.6)              | 130 (18.7)                       |         |
| (Impaired relaxation)            | 706 (46.9)                       | 288 (41.4)                       |         |
| (Pseudonormal)                   | 56 (3.7)                         | 178 (25.6)                       |         |
| (Restrictive)                    | 11 (0.7)                         | 100 (14.4)                       |         |
| LV mass index (g/m²)             | 122±33                           | 149±38                           | <0.0001 |
| PASP (mmHg)                      | 28±8                             | 37±12                            | <0.0001 |
| LVEF (%)                         | 59±8                             | 48±12                            | <0.0001 |
| Max indexed LAV (ml/m²)          | 25±16                            | 37±17                            | <0.0001 |
| Pre-P indexed LAV (ml/m²)        | 17±9                             | 31±15                            | <0.0001 |
| Min indexed LAV (ml/m²)          | 11±6                             | 25±13                            | <0.0001 |
| E/e'                             | 9.9±3.9                          | 14.3±7.0                         | <0.0001 |
| LAEF (%)                         | 38±12                            | 21±9                             | <0.0001 |
| LA expansion index (%)           | 154±75                           | 54±18                            | <0.0001 |
| AF                               | (Paroxysmal) 52 (3.5)            | 38 (5.5)                         | <0.0001 |
| (Persistent)                     | 8 (0.5)                          | 82 (11.8)                        |         |

Abbreviations as in Table 1,3.

**Figure 3.** Kaplan-Meier curves of atrial fibrillation event-free survival according to left atrial (LA) expansion index.
den of cellular hypertrophy, fibroblast proliferation, and tissue fibrosis enables maintenance of AF. Regarding the independent predictors for paroxysmal and persistent AF, the severity and duration of ventricular filling dysfunction is the key point in chronic atrial stretch and fibrosis, which facilitates the persistence of AF. Therefore, prior heart failure, renal insufficiency, and diastolic dysfunction correlate significantly with persistent AF. Certainly, LA expansion index predicts persistent AF better than paroxysmal AF because it reflects the LA stiffness due to fibrosis, which is a common substrate for persistent AF. In other words, the LA expansion index seems to be a good index to quantify the AF substrate. Accordingly, this survey showed that, for predicting persistent AF, the LA expansion index is better than maximum indexed LA volume and LAEF.

Potential Application of LA Expansion Index

This longitudinal prospective study investigated whether LA expansion index corresponds with the onset and progression of AF. In the previous studies, almost all investigators observed AF progression from paroxysmal AF. There are few studies focused on the series change from absence of AF to paroxysmal AF to persistent AF and the evaluation of the predictive value of a single echocardiographic parameter. Given that the occurrence of AF, particularly in those with AF progression, increases the risk of death and cardiovascular events, LA expansion index may also influence outcome. For example, a potential application of this parameter in clinical practice is in the identification of high-risk patients with AF progression who require intensive medical treatment or catheter ablation. Further studies, however, are needed to confirm the prognostic power of this parameter and the feasibility of such a strategy.

Study Limitations

This study had several limitations. First, this study analyzed cardiovascular outpatients with dyspnea at only a single institution. Because the present cohort was not a true low-risk group free of cardiovascular disease, further large-scale studies are needed to confirm the applicability of the results to the general population of extremely low-risk individuals. Second, the present patients received regular ECG/Holter follow-up and were asked to return to the outpatient clinic if they experienced palpitation. Patients who had normal ECG and Holter results, however, might have experienced silent AF events or returned to sinus rhythm after the events, which would have caused an underestimated incidence of AF. Nevertheless, an underestimated incidence of AF would not diminish the predictive capacity of the LA expansion index. Additionally, none of the present subjects had been diagnosed with permanent AF, because none had received cardioversion or catheter ablation. This study used an arbitrary definition of AF progression. In clinical practice, it is extremely difficult to robustly determine the progression from persistent to permanent AF because a firm endpoint is lacking. We believe, however, that transformation from paroxysmal to persistent AF reflects a change in severity. Third, only a single measure of resting LA expansion index was evaluated. Other echocardiographic measures of LA function, including segmental atrial function assessment, strain, strain rate, and atrial response to exercise, were not examined. Fourth, the 5–6% interobserver variability obtained in the present study was much lower than the 10% reported in a previous study. This analysis, however, was limited to a Taiwanese patient group. Compared to Western subjects, the present subjects had a relatively smaller body size and a thinner chest wall, which enabled better quality of echocardiographic imaging and a low interobserver difference.

Conclusions

The LA expansion index reflects both LA stretchability and LV filling status. LA expansion index has a significant negative association with AF progression. A poor LA expansion index indicates a high possibility of persistent AF, and the predictive power of the index exceeds that of other well-established echocardiographic parameters such as E/e', maximum indexed LA volume and LAEF. Because AF is sustained by structural remodeling of the atria after chronic stretching, the LA expansion index predicts AF events, and the rate of persistent AF is exponentially proportional to the LA expansion index.

Disclosures

Conflict of interest: None declared. Relationship with industry: None.

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Supplementary Files

Supplementary File 1
Figure S1. Prediction of atrial fibrillation (AF) after excluding severe mitral regurgitation.

Figure S2. Prediction of persistent atrial fibrillation (AF) after excluding severe mitral regurgitation.

Table S1. Pearson correlations between LA expansion index and other diastolic parameters.

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