Left Atrial Volume Combined With Atrial Pump Function Identifies Hypertensive Patients With a History of Paroxysmal Atrial Fibrillation

Norihisa Toh, Hideaki Kanzaki, Satoshi Nakatani, Takahiro Ohara, Jiyoung Kim, Kengo F. Kusano, Kazuhiko Hashimura, Tohru Ohe, Hiroshi Ito, Masafumi Kitakaze

Abstract—Identifying patients at high risk for the occurrence of atrial fibrillation is one means by which subsequent thromboembolic complications may be prevented. Left atrial enlargement is associated with progression of atrial remodeling, which is a substrate for atrial fibrillation, but impaired atrial pump function is also another aspect of the remodeling. Our objective was to differentiate patients with a history of paroxysmal atrial fibrillation using echocardiography. We studied 280 hypertensive patients (age: 66±7 years; left ventricular ejection fraction: 65±8%), including 140 consecutive patients with paroxysmal atrial fibrillation and 140 age- and sex-matched control subjects. Left atrial volume was measured using the modified Simpson method at both left ventricular end systole and preatrial contraction and was indexed to body surface area. Peak late-diastolic mitral annular velocity was measured during atrial contraction using pulsed tissue Doppler imaging as an atrial pump function. Left atrial volume index measured at left ventricular end systole had a 74% diagnostic accuracy and a 71% positive predictive value for identifying patients with paroxysmal atrial fibrillation; these values for the ratio of left atrial volume index at left ventricular end systole to the peak late-diastolic mitral annular velocity were 82% and 81%, respectively, and those for the ratio of left atrial volume index at preatrial contraction to the peak late-diastolic mitral annular velocity were 86% and 90%, respectively. In conclusion, left atrial size combined with atrial pump function enabled a more accurate diagnosis of a history of paroxysmal atrial fibrillation than conventional parameters. (Hypertension. 2010;55:1150-1156.)

Key Words: hypertension • echocardiography • atrial fibrillation • left atrium • remodeling

Atrial fibrillation (AF) is not generally life threatening but is considered to be the most common cause of ischemic stroke, which often yields serious complications because of acute occlusion of intracranial arteries without collateral circulation. The incidence of stroke is increased by 5-fold in the presence of nonvalvular AF.1–5 Moreover, recent studies have demonstrated that stroke risk is no less in patients with paroxysmal atrial fibrillation (PAF) than in those with persistent AF.6 Therefore, it is crucial to identify patients who have PAF in order to prevent subsequent thromboembolic complications, especially in patients with hypertension, which is a major etiologic factor associated with both AF and stroke.7–9

Left atrial (LA) enlargement associated with the progression of atrial structural remodeling plays a key role in the initiation and maintenance of AF.10,11 The most recent recommendations for echocardiographic chamber quantification indicate that LA volume (LAV) provides an accurate measurement of asymmetrical remodeling of the LA chamber.12 LAV is increased in patients with PAF13 and is also an important predictor of cardiovascular outcome, including the occurrence of AF,14 supporting the concept that LAV is a hallmark of atrial remodeling.

In patients with PAF, Doppler transmitral flow velocity and tissue Doppler imaging (TDI)–derived mitral annulus velocity during atrial contraction, which are considered to reflect atrial pump function,15–20 have been reported to be decreased compared with those in control subjects.11,16,21 According to the Frank-Starling law, atrial pump function is also enhanced with an increase in LAV; however, excessive LA enlargement leads to atrial dysfunction.22,23 Accordingly, we hypothesized that adding information on atrial pump function may provide a better marker of atrial remodeling.

In the present study, we aimed to differentiate patients with a history of PAF among those with hypertension more accurately by means of LAV combined with atrial pump function.

Methods

Study Population

Patients referred to our laboratory were classified into the PAF group if they met the following criteria: (1) ≥1 episode of self-terminating
PAF documented by a 12-lead ECG, 24-hour Holter monitoring, or continuous monitoring during hospitalization without taking any antiarrhythmic drugs and having been free from arrhythmic episodes for >1 week before undergoing echocardiography; (2) hypertension (systolic blood pressure $\geq 140$ mm Hg and/or diastolic blood pressure $\geq 90$ mm Hg or treatment for hypertension); (3) less than moderate mitral regurgitation; (4) sinus rhythm during echocardiography; (5) no medical history of other arrhythmias (including persistent AF), valvular heart disease (including mitral annular calcification), heart failure, ischemic heart disease, cardiomyopathy, cardiac surgery, thyroid disease, or pulmonary disease; and (6) age between 40 and 80 years.

Control subjects were recruited from a clinical health examination in Arita, Japan. All of the attendees underwent a formal medical history interview, ECG, and physical and laboratory examinations. Blood pressure was measured at each of $\geq 2$ visits to the office, and the average of $\geq 2$ seated blood pressures was used according to established recommendations. Of the attendees who also underwent echocardiography, age- and sex-matched subjects who met criteria 2 through 6 were classified as the control group. The study was approved by the institutional review board, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All of the subjects provided informed consent.

**Echocardiography**

All of the echocardiographic studies were performed with either a Vivid 7 Dimension (GE Healthcare) or Aplio XV (Toshiba Medical Systems) ultrasound system. Cardiac chamber size, left ventricular (LV) ejection fraction (LVEF), LV mass, and LA dimension were evaluated according to the recommendations of the American Society of Echocardiography. LAV was measured using the biplane modified Simpson’s method at the ventricular end-systolic frame just before the mitral valve opening from apical 4- and 2-chamber views. Strictly speaking, however, LA does not contract from the size of LV at ventricular end systole. Thus, pretrial contraction LA (LAVpreA) was also obtained from the last frame just before mitral valve opening. Active LA emptying fraction (active LAEF) was calculated by the following formula: $\text{LAV}_{\text{preA}} - \text{LAV}_{\text{min}}/\text{LAV}_{\text{preA}} \times 100\%$, where LAV$_{\text{min}}$ is the minimal LAV at atrial end systole. All of the LAVs were indexed to body surface area as LAVi, LAVi$_{\text{preA}}$, and LAVi$_{\text{min}}$, respectively. LV mass was also indexed to body surface area (LV mass index). LV hypertrophy was defined as LVM index $>104$ g/m$^2$ in women and $>116$ g/m$^2$ in men.

The sample volume of pulsed-wave Doppler imaging was placed at the tip level of the mitral leaflets in the apical 4-chamber view. Then the peak mitral inflow early diastolic and atrial filling (E and A) velocities and the E-wave deceleration time were obtained. The sample volume of the pulsed TDI was placed at the septal and lateral margins of the mitral annulus. Peak early and late-diastolic mitral annular velocities were measured, and then the average values of septal and lateral velocities were used as Ea and Aa, respectively. E/Ea was calculated as a surrogate for the LV filling pressure.

**Statistical Analysis**

Data are expressed as mean±SD. An ANOVA was performed to test for statistically significant differences between 2 unpaired mean values, and categorical data and percentage frequencies were analyzed by the $\chi^2$ test. Correlations were determined with Pearson product moment correlation analysis. Receiver operating characteristic (ROC) curves were constructed to determine the optimal sensitivity and specificity. The area under the curve (AUC) was calculated to assess the overall performance of various variables for the detection of PAF. Univariate and multivariate logistic regression analyses were performed to characterize diagnostic factors of a history of PAF. Variables considered included age, sex, body weight, LV hypertrophy, E/Ea, and diabetes mellitus. A scatter diagram was used to illustrate the relationship between LA size and LA pump function in each patient. A straight line was drawn passing through the origin to discriminate the best between the PAF and control groups, and another line was drawn to establish the boundary above which spots belonging to the PAF group existed. The slope indicates the ratio of LA size to LA pump function: the former corresponds to the optimal cutoff value from the ROC analysis and the latter is the minimum of the ratios of the PAF group. Most statistical tests were performed with SPSS version 12.0 (SPSS Inc). The calculation and comparison of AUC values and the logistic regression analyses were performed with Stata SE version 8.2 (Stata Corp). A $P$ value $<0.05$ was considered to be statistically significant. The statistical power of the present study was finally calculated.

Forty subjects were randomly selected from each group and analyzed blindly by 2 authors (N.T. and H.K.) to assess reproducibility. The interobserver and intraobserver variabilities were, respectively, 4.0% and 4.2% for LAV, 4.2% and 4.2% for LAVpreA, 12.3% and 9.9% for LAVmin, 4.4% and 4.1% for peak A velocity, 3.6% and 3.5% for septal Aa, and 4.0% and 3.7% for lateral Aa.

**Results**

**Clinical and Echocardiographic Characteristics**

A total of 280 subjects with hypertension (mean age: 66±7 years; range: 40 to 80 years; 148 men; LVEF: 65±8%) were enrolled in the present study. There were no significant differences in clinical parameters or the use of antihypertensive drugs between the 140 control and 140 PAF subjects (Table 1). The median time interval between the first PAF episode and this examination was 2.0 years (25th to 75th percentile: 0.2 to 7.0 years), and 62% of the patients with PAF were asymptomatic. Echocardiographic characteristics are depicted in Table 2. No significant group differences were found for the following parameters: LV end-diastolic diameter, LV end-systolic diameter, and LVEF. LV mass index, LA dimension, and indices related to the LAV were significantly increased in the PAF group compared with those in the control group, whereas active LAEF was decreased in the PAF group. The prevalences of LV hypertrophy were 45% in the PAF group (37 women and 25 men) and 28% in the control group (18 women and 21 men). The E-wave decel-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group (n=140)</th>
<th>PAF Group (n=140)</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66±7</td>
<td>66±8</td>
</tr>
<tr>
<td>Women, %</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>Height, cm</td>
<td>158±9</td>
<td>160±10</td>
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<tr>
<td>Weight, kg</td>
<td>58±10</td>
<td>60±10</td>
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<tr>
<td>Body surface area, m²</td>
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<td>1.60±0.26</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.2±3.3</td>
<td>23.6±3.0</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>140±18</td>
<td>137±16</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>82±10</td>
<td>80±11</td>
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<tr>
<td>Diabetes mellitus, %</td>
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<td>21</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>31</td>
<td>23</td>
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<tr>
<td>Concomitant cardiovascular therapies</td>
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<td></td>
</tr>
<tr>
<td>ACE inhibitors, %</td>
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<td>5</td>
</tr>
<tr>
<td>ARBs, %</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>$\beta$-Blockers, %</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Calcium channel blockers, %</td>
<td>32</td>
<td>37</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD unless otherwise specified. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blockers. No significant differences were found between groups.
Although the statistical power calculated was 76% because of LAVipreA/Aa correlation was still observed in patients with severely enlarged LV mass index, g/m² 100 LV ejection fraction, % 65 LV end-systolic dimension, mm 28 LV end-diastolic dimension, mm 47 LV atrial volume, mL 21.6 ± 10.01 LV atrial volume/Aa ratio, mL/m² 14 ± 4 Active LAEF, % 34 ± 6 Peak E velocity, cm/s 64 ± 15 Peak A velocity, cm/s 80 ± 18 E/A ratio 0.85 ± 0.24 E wave deceleration time, ms 233 ± 44 Ea, cm/s 7.5 ± 1.9 Aa, cm/s 11.1 ± 2.3 E/Ea ratio 9.0 ± 2.5 LA volume, mL/m² 0.39 ± 0.11 LA/Aa ratio 2.9 ± 1.01 LA volume/active LAEF 0.64 ± 0.28 LA volume/Aa ratio 0.27 ± 0.08 LA/Aa ratio 1.9 ± 0.4

Values are expressed as mean±SD.

Parameters. The ROC curves for the LAVi/preA/Aa, LAVi/Aa, and LA dimension are shown in Figure 1.

The sensitivity, specificity, diagnostic accuracy, and positive predictive value for the detection of PAF were determined with an optimal cutoff value according to the ROC analysis, as shown in Table 4. Diagnostic accuracy and positive predictive value of the LAVi/preA/Aa ratio at the cutoff value of >2.7 mL·m⁻²·cm⁻¹·s⁻¹ were clearly superior to those of the LAVi of >32.0 mL/m².

From the results of univariate analysis for age, sex, body weight, LV hypertrophy, E/Ea, and diabetes mellitus, LV hypertrophy (odds ratio: 2.059 [95% CI: 1.251 to 3.386]; P<0.001) and E/Ea (odds ratio: 1.205 [95% CI: 1.108 to 1.309]; P<0.001) were considered as significant covariates. However, multivariate analysis demonstrated that the LAVi/preA/Aa ratio was the single significant factor of a history of PAF (odds ratio: 11.786 [95% CI: 6.178 to 22.483]; P<0.001).

LA Size Against Atrial Pump Function
The relationship between LA size and atrial pump function in our population is illustrated in Figure 2. LA size and Aa showed an inverse correlation (LAVi: r = -0.503, P<0.001; LAVi/preA/Aa: r = -0.440, P<0.001; LAVi/Aa: r = -0.459, P<0.001; LAVi/preA: r = -0.517, P<0.001).

Echocardiographic Detection of PAF Among Hypertensive Patients
Various parameters, listed in Table 3, were examined using ROC analysis. LAVi/preA/Aa was best for detecting patients with a history of PAF considering the AUC. The AUC of LAVi/preA/Aa was statistically greater than those of the LAVi/preA/Aa, LAVi/preA/active LAEF, LAVi/Aa, and LA volume (P = 0.024, P = 0.003, P < 0.001, and P < 0.001, respectively). Although the statistical power calculated was 76% because of the limited number of subjects, statistically significant differences were found between the LAVi/preA/Aa ratio and other parameters. The ROC curves for the LAVi/preA/Aa, LAVi/Aa, and LA dimension are shown in Figure 1.

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increase in LV wall stress, leading to increased wall thickness, myocyte hypertrophy, and myocardial fibrosis. Impaired myocardial relaxation and increased LV diastolic stiffness can cause elevated LV diastolic filling pressure, consistent with the increase in E/Ea. Moreover, long-standing hypertension results in interstitial fibrosis and arrhythmic substrate even in the LA. In a large cohort study, increased LV mass and LA diameter were independently associated with the occurrence of AF in patients with hypertension. Similarly, we found that LV mass index, E/Ea, and LAVi values were significantly increased in our hypertensive patients with PAF compared with those in hypertensive patients without PAF. In addition, LAVi showed a significant correlation with both LV mass index and E/Ea. These findings do not contradict the concept that the occurrence of PAF in hypertension is associated with LA remodeling as a consequence of LA overload because of elevated LV filling pressure.

The LAVi/Aa and LAVi/A ratios showed a very modest but yet significant correlation with the time interval between the first PAF episode and this examination. LA remodeling is thought to progress according to not only the LA overload but also the duration of AF. Thus, the indices that we proposed may be markers representing the degrees of progressive LA remodeling.

**Frank-Starling Mechanism of LA Function**

According to the Frank-Starling mechanism, contractile force of the ventricular myocardium is proportional to its initial length; this mechanism also applies to the LA myocardium. LA pump function is enhanced in response to elevated LV filling pressure as long as the Frank-Starling mechanism holds. Within the range of compensation, therefore, the points in Figure 2 should range toward the upper right direction; in contrast, the points belonging to the PAF group are located in the upper left area. This disproportional distribution is also thought to demonstrate a shift of or a deviation from the Frank-Starling curves because of further progression of atrial remodeling in the PAF group. In addition, Figure 2 shows that patients with an LAVi/Aa ratio $\geq 2.3$ mL·m⁻²·cm⁻¹·s⁻¹

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### Discussion

The LA of hypertensive patients with PAF was characterized by further enlargement and impaired pump function as compared with that of hypertensive patients in whom PAF had never been documented. Thus, the ratio of LAVi to Aa was most powerful, and the ratio of LAVi to Aa was the next most powerful for differentiating hypertensive patients with a history of PAF.

### LA Remodeling in Hypertension

LA size has been reported to serve as a surrogate measure of chronic LV diastolic dysfunction. Hypertension induces an increase in LV wall stress, leading to increased wall thickness, myocyte hypertrophy, and myocardial fibrosis. Impaired myocardial relaxation and increased LV diastolic stiffness can cause elevated LV diastolic filling pressure, consistent with the increase in E/Ea. Moreover, long-standing hypertension results in interstitial fibrosis and arrhythmic substrate even in the LA. In a large cohort study, increased LV mass and LA diameter were independently associated with the occurrence of AF in patients with hypertension. Similarly, we found that LV mass index, E/Ea, and LAVi values were significantly increased in our hypertensive patients with PAF compared with those in hypertensive patients without PAF. In addition, LAVi showed a significant correlation with both LV mass index and E/Ea. These findings do not contradict the concept that the occurrence of PAF in hypertension is associated with LA remodeling as a consequence of LA overload because of elevated LV filling pressure.

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### Table 4. Evaluation of Echocardiographic Parameters According to Sensitivity, Specificity, and Diagnostic Accuracy for Detection of PAF in Hypertensive Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Diagnostic Accuracy, %</th>
<th>PPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA dimension &gt;41 mm</td>
<td>72</td>
<td>67</td>
<td>71</td>
<td>69</td>
</tr>
<tr>
<td>LAVi &gt;32.0 mL/m²</td>
<td>82</td>
<td>66</td>
<td>74</td>
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<tr>
<td>LAVi/A &gt;0.50 mL·m⁻²·cm⁻¹·s⁻¹</td>
<td>75</td>
<td>87</td>
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<td>LAVi/Aa &gt;3.6 mL·m⁻²·cm⁻¹·s⁻¹</td>
<td>78</td>
<td>84</td>
<td>82</td>
<td>81</td>
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<tr>
<td>LAVi/A &gt;0.36 mL·m⁻²·cm⁻¹·s⁻¹</td>
<td>80</td>
<td>85</td>
<td>83</td>
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</tr>
<tr>
<td>LAVi/Aa &gt;2.7 mL·m⁻²·cm⁻¹·s⁻¹</td>
<td>82</td>
<td>91</td>
<td>86</td>
<td>90</td>
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Values are expressed as percentage. PPV indicates positive predictive value.

Figure 2. Relationship between LA size and pump function in patients with and without PAF. Scatter diagrams showing the distribution of plots of the LAVi against Aa values (left) and LAVi/Aa against Aa values (right). Red points indicate hypertensive patients with PAF, and blue points indicate hypertensive patients in whom PAF has never been documented. Patients with LAVi/Aa ratios $>2.3$ mL·m⁻²·cm⁻¹·s⁻¹ or LAVi/Aa ratios $>1.9$ mL·m⁻²·cm⁻¹·s⁻¹ may have PAF.
or LAVi/preA/Aa ratio ≥1.9 mL·m⁻²/cm·s⁻¹ may potentially have a history of PAF.

Preload is originally reflected as the initial stretching of cardiac myocytes before contraction. Thus, when adding atrial function to LA size for assessing atrial remodeling, LAVi/preA is thought to be physiologically more preferable to LA size than is LAVi. Therefore, it was a reasonable result that the LAVi/preA/Aa ratio showed better diagnostic ability than the LAVi/Aa ratio.

Measurement of Atrial Pump Function

Several past studies have demonstrated that Aa velocity correlates well with atrial contractile function and can be used as a rapid and accurate marker of atrial function.¹⁶–₂⁰ Similar to results of these studies, Aa showed a significant correlation with active LAEF in our study, and the correlation of Aa with active LAEF also remained in patients with excessive LA enlargement.

The changes in flow velocity profile with different positions of the pulsed-wave Doppler sample volume may affect the diagnostic accuracy of the LAVi/preA/Aa ratio. Even slight changes in sample volume position can easily cause a decrease in peak A velocity.³⁴ In contrast, TDI-derived mitral annulus velocities are relatively independent of these problems.³⁵ Our results also show that Aa is a marker reflecting atrial pump function.

Lateral Aa is a favorable discrimination parameter because its amplitude is greater than that of septal Aa. However, the left lung often attenuates tissue Doppler signals from the lateral annulus margin. The mitral septal annulus motion is always parallel to the Doppler beam, and its measurements are certain. Septal Aa could, however, be influenced by right atrial pump function. In the present study, therefore, we used the average of the septal and lateral Aas.

Study Limitations

First, this was a cross-sectional study. To clarify whether the present index can predict future AF development or complications, further research must provide longitudinal assessments. Second, it is difficult to distinguish whether the impaired atrial pump function was attributed to LA remodeling or showed a recovery process after spontaneous conversion of AF. This issue does not concern the diagnosis of PAF, but it may slightly affect the cutoff value for detecting PAF. Third, atrial reservoir function was not examined in the present study. Some reports indicate that evaluating LA reservoir function using strain or strain rate is useful for the prediction of AF relapse after treatments.³⁶,³⁷ Nevertheless, we chose to use pulsed TDI parameters for the following reasons: (1) measurement of strain or strain rate with high reproducibility or using the speckle tracking method requires a high-end ultrasound machine and special dedicated software, but pulsed TDI is available on almost all machines; (2) peak late-diastolic atrial strain rate during atrial contraction has been reported to be correlated well with Aa;³⁸,³⁹ (3) speckle tracking software, which is used when measuring atrial strain or strain rate, is designed primarily for the LV and not the LA; and (4) atrial strain or strain rate reflects only regional function of the LA, and the position of regions of interest for assessing LA global pump function is still controversial, whereas Aa is a marker of atrial global function and has been validated by cardiac catheters.¹⁷ We preferred this general technology because our goal was to make our method accessible. Fourth, we did not measure pulmonary venous flow for assessing LV diastolic function because obtaining an adequate signal for analysis has been reported to be difficult in all subjects.⁴⁰,⁴¹ Furthermore, a recent consensus statement recommends tissue Doppler velocities as a first-line echocardiographic diagnostic approach to LV diastolic dysfunction.⁴² Fifth, obtaining an accurate time interval between the first PAF episode and the current examination was practically difficult because PAF is, by nature, an elusive disease, and the majority of PAF episodes are known to be asymptomatic.⁴³ Similarly, the first PAF episode in asymptomatic patients was noticed incidentally as an irregularly irregular rhythm during auscultation or palpitating arterial pulse and was confirmed using ECG at a monthly or biweekly consultation day; thus, the interval may be not accurate. Little information on the number and duration of PAF episodes was available in the present study. Finally, we cannot clearly state that self-terminating spontaneous AF was never present in hypertensive patients with PAF within 1 week of examination or in patients with hypertension alone; nonetheless, we addressed this concern by performing repeated 12-lead ECGs, 24-hour Holter monitoring, and strict medical interviews for the subjects of the study.

Perspectives

Our observations that the LA of hypertensive patients with PAF is characterized by dilatation and impaired pump function and that the ratio of LA size to pump function is useful for identifying patients with PAF have important public health and clinical implications. If the presence of PAF is suspected at the time of echocardiography, further examinations and careful monitoring (including repeated 24-hour or event-ECG Holter recording) may be considered. This is especially true for patients with multiple risk factors for stroke (eg, congestive heart failure, hypertension, age >75 years, diabetes mellitus, and previous stroke or transient ischemic attack). In other words, the present indices may be useful for recommending preventive therapy in high-risk patients, because clinicians can prevent the greater part of ischemic stroke from AF with anticoagulation therapy.⁴⁴ A recent report from the Framingham Heart Study proposed a risk score for the future development of AF; but echocardiographic parameters provided only slight improvement in the risk assessment score.⁴⁵ The measurements derived from the conventional M-mode method may have attenuated the benefits of echocardiography in the aforementioned study. We expect that the new marker presented here (LA size divided by atrial pump function) will improve risk classification in future prospective studies.

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