Interatrial dyssynchrony on tissue Doppler imaging predicts progression to chronic atrial fibrillation in patients with non-valvular paroxysmal atrial fibrillation

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ABSTRACT
Objective: To determine prospectively whether interatrial dyssynchrony detected by tissue Doppler imaging (TDI) is useful for predicting the progression to chronic atrial fibrillation (CAF) in patients with non-valvular paroxysmal AF (PAF).

Methods: Thirty-seven patients with non-valvular PAF were prospectively followed after echocardiography. The interval of time from initiation of the P wave on the electrocardiogram (ECG) until the beginning of the late diastolic TDI signal at the lateral border of the mitral annulus (P-A'(M)) and the tricuspid annulus (P-A'(T)) was measured. Interatrial dyssynchrony was defined as the difference between the P-A'(M) and P-A'(T) intervals (A'(M)-A'(T)). The study endpoint was the onset of CAF (>6 months).

Results: During a follow-up period of 28 (SD 23) months, eight patients developed CAF. Compared with those without CAF, the patients who developed CAF had a significantly lower atrial systolic mitral (A'(M)) (7.7 (1.7) vs 10.7 (2.9) cm/s, p<0.01) and tricuspid (A'(T)) (12.9 (3.5) vs 16.6 (5.1) cm/s, p<0.05) annular tissue Doppler velocity, as well as a longer A'(M)-A'(T) interval (47 (13) vs 24 (10) ms, p<0.0001). Kaplan–Meier analysis, using cut-off values determined by analysis of receiver-operating characteristics curves, revealed that progression to CAF was significantly more frequent when the A'(M)-A'(T) interval was >34 ms (p<0.01), the A'(M) velocity was <9 cm/s (p<0.05) and the A'(T) velocity was <16 cm/s (p<0.05).

Conclusions: This prospective study suggests that non-valvular PAF patients with a high risk of developing CAF have “interatrial dyssynchrony” and “atrial systolic dysfunction” on atrial TDI.

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice. It is generally classified as paroxysmal, persistent or permanent AF. Paroxysmal AF (PAF) often precedes the onset of chronic AF (CAF) (ie, persistent or permanent AF). Although various echocardiographic and electrocardiographic parameters (such as the left atrial dimension, pulsed-wave Doppler parameters of transmitral inflow (TMF) and pulmonary venous flow, and P-wave parameters) have been proposed as predictors of atrial function as well as of recurrence and chronicity of AF, some authors have questioned their predictive value and indicated their limitations. Thus, it remains difficult to predict progression from PAF to CAF.

Recently, atrial electromechanical abnormalities have been reported to promote AF. Electromechanical abnormalities have been assessed by determining the time from the onset of the P wave to the beginning of atrial contraction using the electrocardiogram (ECG) and M-mode or Doppler echocardiography. Sequential analysis of atrial electromechanical coupling by tissue Doppler imaging (TDI) allows more precise analysis of atrial electromechanical abnormalities in different regions. In the present study, we evaluated interatrial dyssynchrony (defined by the dispersion of right and left atrial electromechanical coupling) by using TDI, and prospectively investigated whether interatrial dyssynchrony was useful for predicting the development of CAF in patients with non-valvular PAF.

METHODS
Subjects
We screened 336 consecutive patients with PAF who were referred to Zentsuji National Hospital (Kagawa, Japan) between January 2000 and December 2007. A diagnosis of PAF was established if AF terminated spontaneously and had generally lasted for less than 48 h on standard ECG or 24 h Holter ECG recordings. Only patients with non-valvular PAF, who had “pure” lone PAF or PAF associated with mild uncomplicated hypertension, were eligible to be enrolled in this study. Patients with a history of cardiovascular, pulmonary or metabolic diseases were excluded. Other exclusion criteria were the following echocardiographic findings: significant valvular abnormalities, left ventricular hypertrophy (>12 mm) or abnormal wall motion, and left ventricular systolic dysfunction (ejection fraction <50%). Patients were also excluded if their baseline rhythm was not found to be normal sinus rhythm during echocardiographic assessment. As a result, 40 patients with non-valvular PAF (21 men; mean age: 71 (12) years) were enrolled in this study and were followed prospectively after transthoracic echocardiographic assessment by tissue Doppler imaging (TDI). The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all subjects prior to enrolment.

Transthoracic echocardiography and definition of interatrial dyssynchrony
Echocardiographic measurements were carried out prospectively by investigators blinded to clinical data after sinus rhythm had been maintained for at
least 1 month. Standard transthoracic echocardiography was performed in the left lateral position with an Acuson Sequoia 512 system and a 3.5 MHz transducer. The left atrial (LA) and left ventricular (LV) diameters were measured from two-dimensional guided M-mode tracings, according to the recommendations of the American Society of Echocardiography. The LV ejection fraction was calculated by the Simpson method on apical two-dimensional images. The LA volume was calculated by the Simpson method from apical four-chamber views obtained just before mitral valve opening. Pulsed-wave Doppler recordings of TMF were obtained in the apical four-chamber view with the sample volume placed at the orifice of the mitral valve. Then, the peak early (E) and late (A) diastolic flow velocity were measured, and the E/A ratio of TMF was calculated.

Pulsed-wave tissue Doppler recordings were obtained in the apical four-chamber view with the sample volume placed at the lateral aspect of the mitral annulus and the tricuspid annulus to measure the peak early and late diastolic mitral (E(M), A(M)) and tricuspid (E(T), A(T)) annular velocities. We also measured the time from initiation of the P wave on the ECG until the beginning of the late diastolic TDI signal at the lateral border of the mitral annulus (P-A(M)) and the tricuspid annulus (P-A(T)). Interatrial dyssynchrony was defined as prolongation of the difference between the P-A′(M) and P-A′(T) intervals (A′(M)-A′(T)) (fig 1). All Doppler measurements were calculated as the average over three beats.

Follow-up and study endpoint

All patients were followed as outpatients at our institution every 1 to 2 months. The study endpoint was defined prospectively as the onset of CAF (persistent or permanent AF) on a standard ECG or 24 h Holter ECG during the follow-up period. A diagnosis of CAF was established if AF did not terminate spontaneously and had generally lasted for more than 6 months. Patients in whom drug therapy was changed during the follow-up period were excluded from this study.

Statistical analysis

Continuous variables are expressed as the mean (SD) and were assessed by analysis of variance (ANOVA) followed by posthoc multiple comparison. Comparisons between clinical variables were done by the χ² test. The time until the onset of CAF was estimated by the Kaplan–Meier method, and comparisons between two indices were done by the logrank test. For these analyses, p<0.05 was considered to indicate statistical significance.

RESULTS

Patient characteristics

Three patients were excluded from follow-up because of changes in their antiarrhythmic drugs due to side effects (one patient) or for other reasons (two patients). Table 1 summarises the clinical characteristics of the remaining 37 patients for whom follow-up data were available. During an average follow-up period of 28 (23) months (range: 2 to 94 months), eight of these 37 patients (21.6%) developed CAF. There were no significant differences between the patients with or without progression to CAF with respect to age, gender or use of antiarrhythmic agents and other drugs.

Transthoracic echocardiographic parameters and interatrial dyssynchrony

The transthoracic echocardiographic data obtained at baseline are summarised in table 2. There were no significant differences between patients with or without progression to CAF with respect to LA and LV morphological parameters (LA diameter, LA volume, LV end-diastolic diameter and LV end-diastolic volume) or LV systolic function (LV ejection fraction).

Figure 1  P-A′(M) and P-A′(T) intervals, measured as the time from initiation of the P wave on the ECG until the beginning of the late diastolic tissue Doppler imaging (TDI) signal at the lateral border of the mitral (P-A′(M)) and tricuspid (P-A′(T)) annuli. Interatrial dyssynchrony was defined as prolongation of the difference between the P-A′(M) and P-A′(T) intervals (A′(M)-A′(T)).
Regarding pulsed-wave Doppler parameters of TMF, the peak E wave velocity did not differ between the two groups. However, in our relatively elderly patients with a mean age of 71 (11) years, those who developed CAF had a significantly lower peak A wave velocity (57 (19) vs 75 (19) cm/s, p < 0.05) and a higher peak E/A ratio (1.41 (0.49) vs 0.92 (0.26), p < 0.001) than those without CAF.

Regarding the pulsed-wave tissue Doppler parameters recorded at the mitral and tricuspid annulus, the peak E(M) and E(T) velocity and E/E(M) ratio did not differ between the two groups. However, the patients with CAF showed a significantly lower peak atrial systolic mitral and tricuspid annular tissue Doppler velocity compared with those without CAF (A(M); 7.7 (1.7) vs 10.7 (2.9) cm/s, p<0.01, A(T); 12.9 (3.5) vs 16.6 (5.1) cm/s, p<0.05). With respect to interatrial dyssynchrony, the patients with CAF had a significantly longer A(M)-A(T) interval than those without CAF (47 (13) vs 24 (10) ms, p<0.0001).

Kaplan–Meier event-free curves for progression to CAF based on atrial pulsed-wave tissue Doppler parameters are shown in fig 2. Kaplan–Meier analysis with the logrank test, using cut-off values determined by analysis of receiver-operating characteristics curves, revealed that progression to CAF was more frequent when the A(M)-A(T) interval was >34 ms (p<0.01), the A(M) velocity was <9 cm/s (p<0.05), and the A(T) velocity was <16 cm/s (p<0.05).

Even if an analysis was restricted to 27 patients for whom the follow-up period was >12 months, the patients who developed CAF also had a significantly lower A(M) (7.7 (1.9) vs 10.6 (2.6) cm/s, p<0.01) and A(T) (12.3 (5.3) vs 16.6 (5.8) cm/s, p<0.05) velocity, as well as a longer A(M)-A(T) interval (48 (15) vs 25 (10) ms, p<0.0001). Kaplan–Meier analysis also revealed that progression to CAF was significantly more frequent when the A(M)-A(T) interval was >35 ms (p<0.05), the A(M) velocity was <9 cm/s (p<0.05) and the A(T) velocity was <17 cm/s (p<0.05).

Table 1 Clinical characteristics of the subjects

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Transition to CAF</th>
<th>Not CAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>37</td>
<td>8</td>
<td>29</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 (11)</td>
<td>70 (9)</td>
<td>71 (12)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (49%)</td>
<td>2 (25%)</td>
<td>16 (55%)</td>
</tr>
<tr>
<td>Male</td>
<td>19 (51%)</td>
<td>6 (75%)</td>
<td>13 (45%)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.6 (0.2)</td>
<td>1.6 (0.2)</td>
<td>1.6 (0.2)</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>12 (32%)</td>
<td>3 (37%)</td>
<td>9 (31%)</td>
</tr>
<tr>
<td>Cibenzoline</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pirmenol</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pilsicainide</td>
<td>7</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>None</td>
<td>25</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Values are mean (SD) or n (%). There were no significant differences between the patients with and without the transition to chronic atrial fibrillation (CAF).

Table 2 Comparisons of echocardiographic parameters and interatrial dyssynchrony between the groups with and without progression to chronic atrial fibrillation (CAF)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Transition to CAF</th>
<th>Not CAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>37</td>
<td>8</td>
<td>29</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>44 (7)</td>
<td>46 (6)</td>
<td>43 (7)</td>
</tr>
<tr>
<td>Left atrial volume (ml)</td>
<td>111 (29)</td>
<td>120 (27)</td>
<td>108 (29)</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter (mm)</td>
<td>48 (5)</td>
<td>49 (5)</td>
<td>48 (5)</td>
</tr>
<tr>
<td>Left ventricular end-diastolic volume (ml)</td>
<td>78 (21)</td>
<td>75 (15)</td>
<td>79 (23)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>65 (8)</td>
<td>64 (5)</td>
<td>65 (8)</td>
</tr>
<tr>
<td>Transmitral inflow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E velocity (cm/s)</td>
<td>68 (15)</td>
<td>74 (7)</td>
<td>67 (16)</td>
</tr>
<tr>
<td>A velocity (cm/s)</td>
<td>72 (20)</td>
<td>57 (19)*</td>
<td>75 (19)</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.03 (0.38)</td>
<td>1.41 (0.49)***</td>
<td>0.92 (0.27)</td>
</tr>
<tr>
<td>Tissue Doppler imaging</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>E(M) velocity (cm/s)</td>
<td>9.0 (2.4)</td>
<td>10.8 (1.9)</td>
<td>8.6 (2.3)</td>
</tr>
<tr>
<td>A(M) velocity (cm/s)</td>
<td>10.1 (2.9)</td>
<td>7.7 (1.7)**</td>
<td>10.7 (2.9)</td>
</tr>
<tr>
<td>E(T) velocity (cm/s)</td>
<td>11.2 (3.0)</td>
<td>11.0 (2.8)</td>
<td>11.3 (3.0)</td>
</tr>
<tr>
<td>A(T) velocity (cm/s)</td>
<td>15.8 (5.0)</td>
<td>12.9 (3.5)*</td>
<td>16.6 (5.1)</td>
</tr>
<tr>
<td>E/E(M) ratio</td>
<td>8.3 (4.0)</td>
<td>7.1 (1.5)</td>
<td>8.7 (4.5)</td>
</tr>
<tr>
<td>P-A(T) interval (ms)</td>
<td>138 (25)</td>
<td>134 (37)</td>
<td>138 (21)</td>
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<tr>
<td>P-A(M) interval (ms)</td>
<td>167 (27)</td>
<td>180 (39)</td>
<td>163 (22)</td>
</tr>
<tr>
<td>A(M)-A(T) interval (ms)</td>
<td>30 (14)</td>
<td>47 (13)****</td>
<td>24 (10)</td>
</tr>
</tbody>
</table>

Values are mean (SD).
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.
DISCUSSION

AF is the most common sustained arrhythmia. It is well known that PAF often precedes the development of chronic (persistent or permanent) AF. In this study, during an average follow-up period of 28 (23) months, eight patients (21.6%) with non-valvular PAF developed CAF. The probability of progression to CAF (permanent AF) has been reported to be about 8.6% after 1 year, 21% after 2 years and 24.7% after 5 years in PAF patients, which is consistent with our results made on a standard ECG or 24 h Holter ECG, though such a 7-day Holter ECG would have been a more robust method, if possible in our patients. Several echocardiographic and electrocardiographic parameters were investigated as predictors of AF, but it still remains difficult to predict progression from PAF to CAF.

In this study, the patients with CAF showed a significantly lower peak A wave velocity and higher peak E/A ratio than those without CAF. The peak A wave velocity and E/A ratio of TMF have been used as surrogate markers of LA contractile function. It has been reported that a “pseudorestrictive pattern” of the E/A ratio occurs as a result of functional impairment of the LA after AF develops. These Doppler parameters of TMF, which reflect LA contractile function, were useful for predicting progression from PAF to CAF.

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Atrial conduction delay is one of the important features of AF. Recently, atrial electromechanical abnormalities caused by atrial conduction abnormalities have been reported as a risk factor for AF. In this study, we used TDI to evaluate interatrial dyssynchrony, which was defined by the dispersion of right and left atrial electromechanical coupling. Our patients with CAF had prolonged interatrial dyssynchrony compared with those without CAF. Thus, we demonstrated for the first time that interatrial dyssynchrony is useful for predicting progression from PAF to CAF. Dispersion of interatrial electromechanical coupling has been reported in patients with PAF, mitral stenosis, and heart failure. Cui et al reported that the interatrial electromechanical delay was about 25 ms in PAF patients, which is consistent with our results in the PAF patients without CAF, while our patients with CAF showed more prolonged interatrial electromechanical delay. Progression of interatrial conduction abnormalities may be associated with non-homogeneity of atrial conduction and perpetuation of AF. Van Beeumen et al evaluated intraatrial and interatrial dyssynchrony in patients with heart failure by colour tissue Doppler imaging. Their method might evaluate interatrial dyssynchrony more precisely than our TDI method. Multimodality imaging to assess atrial function has also been reported. However, our method is simple, fast and sufficiently reliable for clinical use.

The LA dimension tended to be enlarged in patients with CAF, and it showed a positive correlation with interatrial electromechanical delay (∆A′(M)-A′(T)), but this association was not statistically significant. This suggests that interatrial dyssynchrony is explained not only by LA enlargement but also by the time dispersion from electrical activation in the atrium to atrial myocardial contraction. Some authors have reported that it is not LA size but rather LA structural remodelling (ie, altered atrial tissue architecture or interstitial...
fibrosis) that is important for predicting the restoration of sinus rhythm.3 24 Progressive histopathological changes, such as atrial fibrosis and loss of atrial muscle mass, may lead to non-homogeneity of atrial conduction and perpetuation of AF.4 20 However, we could not find any significant differences in the P-A'(M) and P-A'(T) intervals between our patients with or without CAF. Our patients were relatively elderly, and both the P-A'(M) and P-A'(T) intervals were longer in the patients without CAF than were previously reported for patients with PAF.18–22 32 This might have led to the lack of a difference in intra-atrial dysynchrony.21 In this study, a decrease in the A'(M) and A'(T) velocities was also useful for predicting progression from PAF to CAF. Some studies have shown that the late diastolic mitral annular tissue Doppler velocity (A'(M) ≤ 9 cm/s) is independently related to the incidence of post-operative AF.20 27 Left atrial contractility using strain rate imaging has been reduced in CAF after cardioversion.30 Both the right and left atrial systolic dysfunction patterns of atrial TDI may be useful for predicting CAF, but this is the first study suggesting it to our knowledge. Histopathological changes in AF might account for atrial contractile dysfunction.4 23 27 32

AF was classified as paroxysmal or chronic AF in our study, because of the time when it was performed. Recently, AF has been classified as paroxysmal, persistent and permanent, so different classification of AF is a limitation.9 In addition, the exclusion criteria for the study limited our sample size and the number of patients who developed CAF. The A'(M)-A'(T) interval tended to be an independent predictor of CAF on multivariate Cox proportional hazard analysis, but this might not have been statistically significant because of our small CAF group. Also, we did not investigate the relation between QRS prolongation and A'(M)-A'(T) interval.39 Further prospective studies involving more patients are needed to address this subject. Another limitation was that we could not characterise the episodes of PAF (duration, frequency, and symptoms) before and after enrolment, factors which could also influence the development of CAF, and this could have been helpful to establish the influence of clinical parameters on echocardiographic findings.

In conclusion, this prospective study suggested that patients with non-valvular PAF at high risk for progression to CAF have “interratial dyssynchrony” and an “atrial systolic dysfunction” pattern on atrial TDI. Transthoracic echocardiography with TDI may be useful for identifying patients with a high risk for progression from non-valvular PAF to CAF and has the advantages of being an inexpensive and accessible method. Our study provides a basis for further prospective trials involving larger numbers of patients.

Competing interests: None.

Ethics approval: Ethics approval was provided by the institutional ethics committee (National Hospital Organization, Zentsuji National Hospital).

Patient consent: Obtained.

Portions of the results were presented at the American Heart Association Scientific Sessions 2007, Orlando, Florida, USA, 4–7 November 2007.

REFERENCES

Calcified left ventricular aneurysm with a giant mural thrombus

A 74-year-old male patient was admitted to our department with exertional angina. He had a history of anterior wall myocardial infarction that occurred 14 years ago. Echocardiography showed Q wave and ST-segment elevation in anterior leads; the ST-segment elevation was unchanged from an electrocardiogram obtained 2 years previously. Coronary angiography demonstrated total occlusion of the proximal left anterior descending coronary artery with collateral flow from the right coronary artery. Left ventriculography showed a calcified left ventricular aneurysm (panel A). A contrast computed tomographic scan showed the calcified left ventricular aneurysm and a giant mural thrombus in the anterior-apical wall of the left ventricle (panel B). Left ventricular aneurysms occur as a complication of acute myocardial infarction. Calcified ventricular aneurysms are seen infrequently. This report demonstrates a calcified cardiac aneurysm containing a giant mural thrombus.

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Images in cardiology
Interatrial dyssynchrony on tissue Doppler imaging predicts progression to chronic atrial fibrillation in patients with non-valvular paroxysmal atrial fibrillation

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