Abnormalities of pulmonary venous flow in patients with lone atrial fibrillation

Wojciech Kosmala*, Monika Przewlocka-Kosmala, and Walentyna Mazurek

Cardiology Department, Medical University, Wroclaw, Poland

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Aims

Mechanisms underlying lone atrial fibrillation (LAF) are poorly defined. We sought to investigate indices of left atrial (LA) function in patients with recurrent LAF, in comparison with that in healthy subjects.

Methods and results

Investigations were performed in 42 patients aged 51.8 ± 8.7 at least 30 days after the last episode of LAF and in 38 healthy controls. Each subject underwent echocardiographic evaluation including left ventricular parameters and LA function indices. LA ejection fraction served as a measure of LA systolic performance, and acceleration (SAT) and deceleration time (SDT) of systolic phase of pulmonary venous flow (PVF) corresponded to LA relaxation and compliance, respectively. Patients with LAF showed significantly lower values of SAT (179.1 ± 63.2 vs. 199.2 ± 45.1 ms, P < 0.02) and higher values of SDT (250.8 ± 81.6 vs. 211.7 ± 57.3 ms, P < 0.01) when compared with controls. No significant differences were found with respect to other measured parameters. The combination of SAT < 185 ms and SDT > 239 ms showed a positive predictive value of 92% in the identification of patients prone to LAF.

Conclusion

This study suggests that (i) patients with LAF have abnormalities of the systolic phase of PVF and (ii) Doppler estimation of PVF seems to be very valuable in the evaluation of patients with LAF.

Introduction

Lone atrial fibrillation (LAF), according to the definition proposed in 1954 by Evans and Swann, denotes the occurrence of this arrhythmia in the absence of clinically detectable organic heart disease, hypertension, or thyrotoxicosis. It accounts for 2.7–11.4% of all cases of atrial fibrillation (AF). The underlying pathology of LAF still remains poorly understood. Although LAF is suggested to be a more benign form of AF with lower risk of thrombo-embolic complications, its actual impact on survival has not been precisely estimated.

The echocardiographic evaluation of patients with LAF previously comprised the exclusion of cardiac disorders potentially underlying AF and searching for intra-atrial thrombi. Recently, transoesophageal and intracardiac echocardiography have been employed to predict recovery of left atrial (LA) function and recurrence of AF after ablation including pulmonary vein antrum isolation, which seem to be an important diagnostic application also in patients with LAF.

Prior echo studies of LAF cohorts did not demonstrate any particular abnormalities of cardiac function and morphology. Nonetheless, echocardiographic examination in available reports did not include estimation of LA function, which, assuming that the cause of the arrhythmia lies in the atrial tissue, might be altered in LAF. Although the echocardiographic assessment of LA systolic function is widespread in clinical practice, non-invasive evaluation of LA diastolic performance is very uncommon. As it was shown in previous studies, the systolic phase of pulmonary venous flow (PVF) might indirectly reflect the LA diastolic function.

The objective of the present study was to investigate—besides the left ventricular (LV) parameters—indices of LA function in patients with LAF, in comparison with those in healthy subjects.

Methods

Patients

The studied population consisted of 42 patients: 27 males and 15 females aged 51.8 ± 8.7 years with at least two documented episodes of AF classified as lone, who were prospectively enrolled in the study between April 2001 and January 2004. Among 44 initially
recruited patients, two were excluded because of inadequate quality of echocardiographic imaging. The diagnosis of LAF was made in the absence of any organic heart disease, pulmonary disorders, hypertension, thyroid diseases, diabetes, history of alcohol, drugs and caffeine abuse (defined as more than three cups of coffee a day), and electrolyte disturbances. Among other, exclusion criteria were age ≥ 60 and LA dimension ≥ 40 mm. None of the included patients was a current or former athlete as long-term exercise may be associated with LAF. The exclusion of coronary artery disease was based on a lack of clinical symptoms and negative treadmill exercise test and dobutamine stress echocardiography. During investigations, all the patients were in sinus rhythm and the time interval from the last episode of AF was at least 30 days.

In the studied population, 12 patients received sotalol and 14 propafenone, whereas in the other 16 patients, no long-term antiarrhythmic therapy was prescribed. Both sotalol and propafenone were stopped five half-lives before the study. No patient was on anticoagulant or hypolipidaemic therapy. Trivial mitral regurgitation were in nine patients and tricuspid regurgitation in seven not exceeding 1/4 were found.

The control group encompassed 38 apparently healthy volunteers (24 males and 14 females) aged 50.5 ± 9.3.

**Echocardiography**

All study participants underwent standard echocardiography with Doppler studies, using a GE Vingmed System Five machine with a 2.5 MHz multifrequency transducer. The measurements of LA and LV dimensions and wall thicknesses were performed from two-dimensionally targeted M-mode tracings, according to the recommendations of the American Society of Echocardiography. LV ejection fraction was estimated using a modified Simpson’s biplane method. LV fractional shortening was derived from the standard formula.

Pulsed-wave Doppler recordings of the LV inflow were performed from the apical four-chamber view with the sample volume placed between the tips of the mitral leaflets. The following variables were measured: peak early (E) and late (A) diastolic flow velocity, E/A ratio, deceleration time of E-wave (DT).

Isovolumic relaxation time (IVRT) defined as an interval between the end of aortic outflow and the onset of mitral inflow was measured in the apical five-chamber view using continuous wave Doppler with a beam placed in the intermediate position for simultaneous visualization of mitral and aortic tracings.

The flow propagation velocity of E-wave (Vp) was calculated using colour Doppler M-mode from the apical four-chamber view by measuring the slope of the first aliasing velocity from the mitral annulus to 4 cm distally into the LV cavity.

PVF was evaluated from the apical or modified apical four-chamber view by pulsed-wave Doppler positioning the sample volume in the right superior pulmonary vein 1 cm proximal to its entry into the LA. The PVF measurements included the following variables: peak and integral velocities of systolic (S, Si), diastolic (D, Di), and atrial contraction phases (AR, ARI) and acceleration (SAT) and deceleration time (SDT) of the systolic flow (Fig. 1). In the case of a biphasic pattern of systolic flow with a second component caused by mitral annular excursion, the maximal velocity from the taller peak was used as S and SAT and SDT were estimated from the first waveform being related to atrial diastole. SDT was then measured from the peak of the first wave to an extrapolation of its slope to the baseline. Systolic forward fraction (SFF) of the PVF was achieved from the formula:

\[ SFF = \frac{S}{S + D} \]

The maximal and minimal LA volumes were measured in two-dimensional apical two-chamber and four-chamber views by single frame advancement from cineloop recordings using the area-length method and averaged from both views afterwards. LA ejection fraction was calculated as:

\[ \frac{(\text{LA maximal volume} - \text{LA minimal volume})}{\text{LA maximal volume}} \times 100\% \]

All acquisitions were performed at heart rate < 90 bpm.

The measurements of each echocardiographic parameter were averaged from three consecutive heart cycles.

All echocardiograms were analysed by one observer (W.K.), and intra-observer variability estimated in 15 consecutive patients was 6.8% for SAT, 7.1% for SDT, 4.1–8.4% for other Doppler parameters, and 6.3% for LA volumes.

**Electrocardiography**

Twelve-lead surface ECG with 50 mm/s paper speed was performed in each patient and control. P-wave duration was assessed by a flatbed scanner interfaced with a personal computer using commercially available software PhotoFinish 3.0 (WordStar Atlanta, Technology Center Inc., Atlanta, GA, USA). The measurements were averaged from three consecutive beats in every lead. The maximal P-wave duration in any ECG lead served as a measure of prolonged atrial conduction time. The difference between the maximal and minimal P-wave duration occurring among any 2 of 12 leads was defined as P-wave dispersion and reflected inhomogeneity of atrial conduction.

All ECGs were analysed by one observer (M.P.-K.), and intra-observer variability for maximal P-wave duration was 7.1% and for P-wave dispersion 7.8%.

**Statistical analysis**

Results are expressed as mean ± SD. Student’s two-tail t-test and χ² and Pearson rank correlation tests were used where appropriate.

Data were analysed using standard statistical software (Statistica for Windows 5.5, StatSoft, Inc., Tulsa, OK, USA). The level of statistical significance was set at P-value less than 0.05.

All subjects were informed regarding the purpose of the study and gave informed consent. Investigations were in accordance with the Declaration of Helsinki and were approved by the local Ethics Committee.

**Results**

The groups of patients and controls were comparable with respect to age, gender, heart rate, SBP and DBP (Table 1).

No significant differences were seen between the patient group and the controls regarding LV and LA morphology parameters (left ventricular end-diastolic dimension,
interventricular septum thickness, posterior wall thickness, LA dimension, and maximal and minimal LA volume) as well as systolic function parameters (left ventricular ejection fraction, left ventricular fractional shortening, and LA ejection fraction) (Table 2).

Likewise, none of the LV diastolic function indices estimated both from the mitral flow (E/A, DT, IVRT, Vp) and from the PVF (S, D, AR, SFF) differed significantly between patients with LAF and healthy subjects (Table 3).

The patient group demonstrated significantly shorter SAT and longer SDT when compared with the controls (Table 3 and Fig. 2). The combination of SAT < 185 ms and SDT > 239 ms had a positive predictive value of 92% and a negative predictive value of 66% in predicting the presence of LAF.

Maximal P-wave duration in ECG was significantly longer in patients with LAF than in the control subjects, whereas P-wave dispersion was not statistically different between the two groups (Table 4).

There were no statistical differences in all evaluated echocardiographic and ECG parameters between patients with and without previous antiarrhythmic therapy.

Significant correlations were found between maximal P-wave duration and SAT ($r = -0.35$, $P < 0.04$) and between maximal P-wave duration and SDT ($r = 0.30$, $P < 0.05$).

### Discussion

The main findings of the present study are that (1) patients with LAF show abnormalities of the systolic phase of PVF, having parameters of LV systolic and diastolic and LA systolic function unaltered, and (2) Doppler estimation of PVF should be included in the evaluation of patients with LAF.

LAF is defined not to have underlying overt structural heart disease. However, it has been shown in studies using histopathological assessment that the atrial myocardium in patients with LAF may exhibit vacuolar degeneration, lymphomononuclear infiltrates with necrosis and fibrosis suggesting myocarditis, non-inflammatory cardiomyopathy, or degenerative process confined to the atrial tissue. Moreover, a number of patients with LAF foci localized mainly in the pulmonary veins and functioning as triggers of AF were identified. All these findings may represent substrates involved in the development of LAF.

In the present study, we demonstrated disorders of the systolic phase of PVF as expressed by shortening of SAT and prolongation of SDT. The combination of values of SAT < 185 ms and SDT > 239 ms showed, in particular, very high positive predictive value in the identification of patients with LAF. All parameters of cardiac morphology in LAF patients including LA size and LA volumes did not differ from those in healthy population. Likewise, indices of LV systolic and diastolic function and LA ejection fraction reflecting systolic activity of left atrium were also within the normal limits determined in the controls.

PVF profile is known to be influenced by changes in LA pressure, which are partially dependent on LA diastolic properties. As validated by haemodynamic measures, the upslope of the systolic phase of PVF expressed by SAT

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### Table 1 Clinical characteristics of patients with lone atrial fibrillation and of controls

<table>
<thead>
<tr>
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<th>Patients (n = 42)</th>
<th>Controls (n = 38)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.8 ± 8.7</td>
<td>50.5 ± 9.3</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (%male)</td>
<td>64</td>
<td>63</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72.1 ± 9.2</td>
<td>73.7 ± 9.5</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>125 ± 12</td>
<td>124 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76 ± 6</td>
<td>76 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Number of documented AF episodes</td>
<td>4.3 ± 3.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Duration of AF history (years)</td>
<td>3.6 ± 3.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotalol (%)</td>
<td>12 (29%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Propafenone (%)</td>
<td>14 (33%)</td>
<td>—</td>
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</table>

### Table 2 LV and LA morphology parameters and systolic function parameters in patients with lone atrial fibrillation and in controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 42)</th>
<th>Controls (n = 38)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>48 ± 3</td>
<td>49 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>LVIVST (mm)</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>LVPWT (mm)</td>
<td>8 ± 1</td>
<td>9 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>67 ± 7</td>
<td>67 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>LVFS (%)</td>
<td>32 ± 4</td>
<td>33 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>38 ± 3</td>
<td>37 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>LAV max (cm³)</td>
<td>44 ± 9</td>
<td>43 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>LAV min (cm³)</td>
<td>21 ± 7</td>
<td>21 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>LAEF (%)</td>
<td>54 ± 11</td>
<td>56 ± 10</td>
<td>NS</td>
</tr>
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</table>

LVEDD, left ventricular end-diastolic dimension; LVIVST, interventricular septum thickness; LVPWT, left ventricular posterior wall thickness; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LAV max, left atrial maximal volume; LAV min, left atrial minimal volume; LAEF, left atrial ejection fraction.

### Table 3 LV and LA diastolic function parameters in patients with lone atrial fibrillation and in controls

<table>
<thead>
<tr>
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<th>Patients (n = 42)</th>
<th>Controls (n = 38)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/A</td>
<td>0.98 ± 0.14</td>
<td>0.99 ± 0.21</td>
<td>NS</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>178.7 ± 34.2</td>
<td>183.1 ± 41.7</td>
<td>NS</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>96.1 ± 15.5</td>
<td>94.2 ± 16.8</td>
<td>NS</td>
</tr>
<tr>
<td>Vp (cm/s)</td>
<td>55.1 ± 14.6</td>
<td>55.6 ± 15.4</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary venous flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S (cm/s)</td>
<td>58.3 ± 10.4</td>
<td>60.2 ± 13.1</td>
<td>NS</td>
</tr>
<tr>
<td>D (cm/s)</td>
<td>60.1 ± 10.8</td>
<td>61.9 ± 11.3</td>
<td>NS</td>
</tr>
<tr>
<td>AR (cm/s)</td>
<td>31.1 ± 4.3</td>
<td>30.7 ± 4.9</td>
<td>NS</td>
</tr>
<tr>
<td>SFF</td>
<td>0.58 ± 0.07</td>
<td>0.57 ± 0.08</td>
<td>NS</td>
</tr>
<tr>
<td>SAT (ms)</td>
<td>179.1 ± 63.2</td>
<td>199.2 ± 45.1</td>
<td>0.02</td>
</tr>
<tr>
<td>SDT (ms)</td>
<td>250.8 ± 81.6</td>
<td>211.7 ± 57.3</td>
<td>0.01</td>
</tr>
</tbody>
</table>

E/A, peak early to peak late diastolic velocity ratio; DT, deceleration time of E-wave; Vp, flow propagation velocity of E-wave; S, peak velocity of systolic phase; D, peak velocity of diastolic phase; AR, peak velocity of atrial contraction phase; SFF, systolic forward fraction; SAT, acceleration time of systolic phase; SDT, deceleration time of systolic phase.
Abnormalities of PVF in patients with LAF

Table 4 Maximal P-wave duration and P-wave dispersion in patients with lone atrial fibrillation and in controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 42)</th>
<th>Controls (n = 38)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal P-wave duration (ms)</td>
<td>$128 \pm 18$</td>
<td>$106 \pm 14$</td>
<td>0.01</td>
</tr>
<tr>
<td>P-wave dispersion (ms)</td>
<td>$37 \pm 21$</td>
<td>$32 \pm 16$</td>
<td>NS</td>
</tr>
</tbody>
</table>

Figure 2 Distribution of SAT and SDT values in patients and controls. SAT, acceleration time of systolic phase; SDT, deceleration time of systolic phase.

corresponds to the x-wave of LA pressure curve and reflects LA relaxation, whereas the downslope measured by SDT coincides with the v-wave of intra-atrial pressure tracing and represents LA filling dependent on LA atrial compliance. However, it is not completely clear to what extent both Doppler indices, i.e. SAT and SDT, can characterize true abnormalities of LA diastolic function.

We speculate that the disturbances of the systolic component of PVF demonstrated in our population may be attributable to altered properties of the LA myocardium related to some of the aforementioned histopathological findings in specimens from atrial tissue in patients with LAF. However, as none of the patients included in our study was subjected to atrial biopsy, it is only a hypothetical explanation. Interestingly, similar changes of SAT and SDT have been already described in hypertrophic cardiomyopathy, indicating an LA myopathic process.

We confirmed in our LAF cohort, shown already in previous reports, prolongation of maximal P-wave duration reflecting delay in atrial conduction. Notwithstanding, P-wave dispersion in our patients being a consequence of non-uniformity of atrial conduction was not significantly increased, which is in contrast to the observations of Dilaveris et al. The correlations found between maximal P-wave duration and SAT and between maximal P-wave duration and SDT, although weak, might suggest the same underlying pathological process leading to the disorders of both the Doppler systolic waveform of PVF and atrial conduction.

Limitations of the study

1. We cannot exclude that patients have missed some self-terminating episodes of AF within the period directly preceding the echo evaluation, which could potentially lead to transient impairment of atrial function.
2. The size of the studied group was limited, but the rigorous criteria for inclusion hampered the recruitment of patients.
3. We did not evaluate the influence of the motion of mitral annulus on SAT and especially on SDT. However, both studied and control groups did not differ with respect to LV systolic function and, consequently, to mitral annular excursion, and therefore, we presume that this effect was comparable between the two groups.
4. In spite of the fact that pharmacological therapy was discontinued before the examination, we cannot definitely rule out the influence of the drugs on the results of the study.
5. We did not perform cardiac catheterization with LA pressure measurements which could resolve some of the remaining questions but because of lack of apparent clinical indications, it would be unjustifiable on ethical grounds.

Conclusion

The present study revealed in highly selected population with LAF abnormalities of the systolic phase of PVF possibly related to altered LA diastolic performance which might represent a condition predisposing to the occurrence of AF. Nonetheless, whether demonstrated alterations are actually a cause or only a consequence of recurrent AF cannot be currently disclosed and remains to be explored in the future. Our results suggest that the estimation of PVF, especially SAT and SDT, should be an integral part of routine echocardiographic examination in patients with a suspicion of LAF. The established values of SAT < 185 ms and SDT > 239 ms may be helpful in the diagnosis of LAF. The possible prognostic significance of SAT and SDT in predicting the development of AF as well as their compliance with modification by treatment needs to be evaluated in further studies. Likewise, comparative studies with other forms of AF, i.e. with recognized disease background, seem to be necessary. Our findings can be applicable only to the age group that has been investigated. As Doppler parameters of PVF are partially preload dependent, the accuracy of proposed cut-off values may change in different loading conditions.

References


