Abnormal atrial activation in young patients with lone atrial fibrillation

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Aims

Patients with a history of atrial fibrillation (AF) have previously been shown to have altered atrial conduction, as seen non-invasively using signal-averaged P-wave analysis. However, little is known about the P-wave morphology in patients in the early phases of AF with structurally normal hearts.

Methods and results

Thirty-six patients with lone AF were included before the age of 40 years (34 ± 4 years, 34 men) and compared with age- and gender-matched control subjects. Standard 12-lead electrocardiogram (ECG) was recorded for at least 10 s. P-wave morphology and duration were estimated using signal-averaged P-wave analysis. Echocardiography was performed in association with the ECG recording. Heart rate (67 ± 13 vs. 65 ± 7 b.p.m., P = 0.800) and PQ-interval (163 ± 16 vs. 164 ± 23 ms, P = 0.629) were similar in AF cases and controls, as was P-wave duration (136 ± 13 vs. 129 ± 13 ms, P = 0.107). The distribution of P-wave morphology differed between the AF cases and controls [33/58/0/8 vs. 75/25/0/0% (Type 1/Type 2/Type 3/atypical), P = 0.001], with a larger proportion of patients with AF exhibiting signs of impaired interatrial conduction.

Conclusion

A significant difference in P-wave morphology distribution was seen between patients with early-onset, lone paroxysmal AF and age- and gender-matched healthy control subjects. This finding indicates that alterations in atrial electrophysiology are common in the early stage of the arrhythmia, and since it occurs in young patients without co-morbidity may well be the cause rather than the consequence of AF.

Keywords

P-wave morphology • Atrial fibrillation • Early onset • Signal-averaged ECG

Introduction

Atrial fibrillation (AF) is the most common form of arrhythmia encountered in clinical practice, accounting for approximately one-third of hospital admissions for cardiac rhythm disturbances.1,2 Although it is primarily seen in the elderly (its prevalence doubles with each advancing decade), it is also present in the relatively young on rarer occasions.3,4 The genesis of AF is believed to be multifactorial, including the classical cardiovascular risk factors such as hypertension, as well as increasing age and concomitant heart disease.5,6 The trigger for starting an AF episode is commonly ectopic atrial activity originating from the pulmonary veins,6 and the substrate, which is required for maintaining the arrhythmia, is believed to be due to deteriorated atrial conduction.7–10 Although the ultimate manifestation of AF is the same, it is reasonable to believe that the mechanisms leading to the arrhythmia are different in the elderly and the relatively young patient populations. Hence, it may be of value to study young AF patients with structurally normal hearts, in whom it could be assumed that the cause of AF is likely to be ‘electrical’ to a larger extent, in order to identify the electrophysiological properties associated with AF.
In previous studies, patients with paroxysmal AF have also been shown to have altered atrial conductive properties during sinus rhythm.\textsuperscript{11–14} These studies focused primarily on P-wave duration measured with different methods, and although the differences are statistically different, they are generally quite small. Our group has used signal-averaged P-wave analysis in several studies to examine P-wave morphology to obtain information apart from P-wave duration.\textsuperscript{15–17} The morphology has been found to change with increasing age, advancing cardiac disease, and has been shown, in a limited group, to differ between patients with a history of AF and controls without.\textsuperscript{15,17,18} These morphological changes are seen, despite the lack of major differences in P-wave duration. The various P-wave morphologies have been shown to be due, at least in part, to differences in interatrial conduction\textsuperscript{16} and have also been shown to contain information regarding the future risk of AF and non-sudden cardiovascular death in patients with structural heart disease.\textsuperscript{19} In the present study, signal-averaged P-wave analysis was used to investigate the P-wave morphology in patients with early-onset, lone paroxysmal AF, i.e. a group of patients in whom the ‘electrical’ cause of AF is likely to be dominating.

Methods

Patient population

Consecutive patients <40 years old with lone paroxysmal AF [i.e. absence of clinical or echocardiographic findings of other cardiovascular disease (including hypertension) or related pulmonary disease] were included at four Scandinavian centres (Lund, Sweden; Copenhagen, Denmark; Rud, Norway; and Helsinki, Finland). Exclusion criteria were ongoing treatment with class I or III anti-arrhythmic drugs (Vaughan–Williams classification), previous catheter ablation in the atria, or AF at the time of inclusion. Age- and gender-matched healthy control subjects were recruited from two databases of healthy volunteers in Sweden\textsuperscript{16} and Norway for a 1:1 case–control comparison. The study was approved by the local Ethics Committees and complied with the Declaration of Helsinki. All subjects gave their informed consent to participation.

Data acquisition and analysis

Standard 12-lead electrocardiogram (ECG) data, of at least 10 s duration, were recorded using clinical equipment (a minimal sampling frequency of 500 Hz and a sampling resolution of 5 μV were required). To enable the analysis of orthogonal P-wave morphology, orthogonal-lead ECG data were derived from the 12-lead ECG using the inverse Dower transform. Unfiltered, signal-averaged P-waves were analysed to determine P-wave morphology. Following high-pass (0.5 Hz) and bandstop (50 Hz) filtering, the QRS complexes were automatically identified and grouped according to similarity (cross-correlation coefficient, \(\rho > 0.9\)). P-waves were extracted using signal windows 250 ms wide preceding each QRS complex. The signal windows were then shifted in time to estimate the maximal correlation in each lead. P-waves with a cross-correlation coefficient of \(\rho > 0.9\) (analysed separately in all three leads) were grouped together and averaged. The averaged P-wave duration was defined by the manual setting of the onset and end. The morphology was subsequently classified into one of three predefined classes [Type 1: positive Leads X and Y and negative Lead Z; Type 2: positive Leads X and Y and biphasic Lead Z (±); and Type 3: positive Lead X and biphasic signals in Leads Y (±) and Z (±), as schematically illustrated in Figure 1]. The method used is described in detail elsewhere.\textsuperscript{20} A standard transthoracic echocardiographic examination was performed in association with the inclusion of the subjects (both AF and healthy control groups). The dimensions of the cardiac chambers and the global systolic function [left ventricular ejection fraction (LVEF)] were measured according to the standard criteria.\textsuperscript{21}

Statistics

Data are expressed as mean ± standard deviation. The Mann–Whitney U-test or the \(\chi^2\) test was used, as appropriate, for statistical testing. All tests were two-sided, and \(P < 0.05\) was considered statistically significant. All statistical analyses were performed using PASWStatistics for Mac, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 36 patients (mean age 34 ± 4 years, 34 men), with AF debut before the age of 40, without any concomitant diseases, were included. The control subjects (\(n = 36, 34\) men; mean age 34 ± 6) were healthy, normotensive volunteers without a history of cardiac disease. All individuals were found to have normal LVEF, and no case with more than mild atrial enlargement was seen (mean 38 ± 7 vs. 39 ± 3 mm, \(P = 0.698\)). The AF subjects had higher body mass (90 ± 15 vs. 80 ± 9 kg, \(P = 0.004\)) and body mass index (BMI) than the control subjects (27 ± 4 vs. 25 ± 2 kg/m\(^2\), \(P = 0.045\)), but were not significantly taller (Table 1). The systolic and diastolic blood pressures were similar and within the normal range in cases and in controls (128 ± 9 vs. 125 ± 15 mmHg, \(P = 0.209\) and 79 ± 6 vs. 77 ± 8 mmHg, \(P = 0.093\)). The mean age at AF debut of the AF subjects was 28 ± 7 years, and the number of previous cardioversion attempts was 1.1 ± 1.8 (range, 0–6). The only kind of cardioactive drug used among the AF subjects was \(\beta\)-blockers (22%). None of the control subjects were on medication. The clinical characteristics are summarized in Table 1.

Heart rate (67 ± 13 vs. 65 ± 7 b.p.m., \(P = 0.800\)) and PQ-time (163 ± 16 vs. 164 ± 23 ms, \(P = 0.629\)) were similar in the patients and healthy controls. The P-wave duration was not significantly different in the patients compared with the controls (136 ± 13 vs. 129 ± 13 ms, \(P = 0.107\)), but the distribution of P-wave morphologies differed \([33/58/0/8 vs. 75/25/0/0\% (Type1/Type2/ Type3/Atypical), \(P = 0.001\)]\) (Table 2).

<table>
<thead>
<tr>
<th>Type</th>
<th>AF Subjects (%)</th>
<th>Controls (%)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>25/58/0/8</td>
<td>75/25/0/0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type 2</td>
<td>13/32/0/8</td>
<td>15/27/0/0</td>
<td>0.386</td>
</tr>
<tr>
<td>Type 3</td>
<td>0/3/0/8</td>
<td>0/5/0/0</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Six AF subjects, but none of the controls, were obese (BMI > 30 kg/m\(^2\)). The distributions of P-wave morphology in obese and non-obese AF subjects were not significantly different (17/83/0 vs. 37/52/11, \(P = 0.346\)). The BMI in the non-obese AF subjects and the controls was similar (25.2 ± 2 ± 24.7 ± 2.0 kg/m\(^2\), \(P = 0.386\)), but the observed difference in distribution of P-wave morphology between the groups was in close resemblance with the difference seen when comparing the complete study population (37/52/11 vs. 75/25/0/0, \(P = 0.007\)).

Discussion

In the present study, a significant difference in P-wave morphology distribution was seen between patients with early-onset, lone AF, and structurally normal hearts, and age- and gender-matched
Furthermore, the difference was observed in spite of the similar values of P-wave duration, which underlines the necessity of detailed P-wave analysis in this context.

Signal-averaged P-wave analysis, without subsequent band-pass filtering, allows detailed analysis not only of P-wave duration, but also of P-wave morphology. It has been shown to produce robust and reproducible results when using lead transformation and recording resolution and length, as in the present study.

### Table 1 Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>AF (n = 36)</th>
<th>Controls (n = 36)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>34.3 ± 4.2</td>
<td>34.1 ± 5.8</td>
<td>0.689</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>94</td>
<td>94</td>
<td>1.000</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>183 ± 7.6</td>
<td>180 ± 7.4</td>
<td>0.079</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>90 ± 15</td>
<td>80 ± 8.9</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 3.7</td>
<td>25 ± 2.0</td>
<td>0.045</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>128 ± 9.4</td>
<td>125 ± 15</td>
<td>0.209</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79 ± 6.0</td>
<td>77 ± 7.5</td>
<td>0.093</td>
</tr>
<tr>
<td>LA dimensions (mm)</td>
<td>38 ± 6.5</td>
<td>39 ± 3.3</td>
<td>0.698</td>
</tr>
<tr>
<td>Normal LVEF (%)</td>
<td>100%</td>
<td>100%</td>
<td>1.000</td>
</tr>
<tr>
<td>Age at AF debut (y)</td>
<td>28.4 ± 6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cardioversions (n)</td>
<td>1.1 ± 1.8</td>
<td></td>
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</tbody>
</table>

### Table 2 Measured parameters

<table>
<thead>
<tr>
<th></th>
<th>AF (n = 36)</th>
<th>Controls (n = 36)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>67 ± 13</td>
<td>65 ± 7</td>
<td>0.800</td>
</tr>
<tr>
<td>PQ-interval (ms)</td>
<td>163 ± 16</td>
<td>164 ± 23</td>
<td>0.629</td>
</tr>
<tr>
<td>P-wave duration (ms)</td>
<td>136 ± 13</td>
<td>129 ± 13</td>
<td>0.107</td>
</tr>
<tr>
<td>Classification</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Type 1 (%)</td>
<td>33</td>
<td>75</td>
<td>0.001</td>
</tr>
<tr>
<td>Type 2 (%)</td>
<td>58</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Type 3 (%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Atypical (%)</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

All statistical analyses were performed using the Mann–Whitney U-test or the χ² test. P-values <0.05 are given in bold.

Figure 1 Schematic illustration of the three P-wave morphology classes. Type 1 is characterized by a right-to-left (positive Lead X), superior-to-inferior (positive Lead Y), and posterior-to-anterior activation pattern (negative Lead Z). Type 2 is also characterized by positive signals in Leads X and Y, but the biphasic signal in Lead Z indicates a more complex activation pattern (posterior-to-anterior-to-posterior). Type 3 P-wave morphology also exhibits a positive signal in Lead X, and a biphasic signal in Lead Z, as does Type 2, but the signal in Lead Y reflects the retrograde activation of the left atrium (superior-to-inferior-to-superior).
The automatic morphology classification algorithm used makes the methodology operator-independent, increasing its applicability.

The age- and gender-matched healthy control group was comparable with the AF subjects in all aspects with only two exceptions. The AF subjects were heavier and had a higher BMI than the controls. The difference in height did not reach statistical significance. A high BMI in youth as well as an increase in weight from youth to mid-life are recognized risk factors for the development of AF. In previous studies, this has, at least in part, been explained by a simultaneous increase in atrial size (i.e. modulation of the substrate sustaining the arrhythmia). This could, however, not be verified in the present study, where the dimensions of the left atria were virtually identical in the AF subjects and the healthy controls. The finding that the difference in P-wave morphology distribution was seen irrespective of whether the obese AF subjects were excluded or not indicates that the major finding of this study is not driven by differences in body size. In all other aspects, the AF population and the healthy control population were well matched and no other bias, likely to influence the results significantly, was inferred.

There was no statistically significant difference in P-wave duration between the AF subjects and the age- and gender-matched healthy controls. This is in keeping with findings reported in the literature, where differences in P-wave duration between AF subjects and control populations are sometimes reported, but are generally quite small. In spite of this lack of significant difference in P-wave duration, a major difference was seen in P-wave morphology distributions. The distribution of P-wave morphologies seen in the AF subjects, showing a predominance of Type 2, with only a minority of the patients exhibiting Type 1 P-wave morphology, is well in keeping with previous findings in AF populations. A similar shift in distribution has previously been seen in patients with hypertrophic cardiomyopathy and in patients with impaired left ventricular function due to ischaemic heart disease prior to the development of AF. The major difference compared with the present study is that these two patient subsets both represent patients with grossly abnormal hearts, which is in stark contrast to the structurally normal hearts of the patients in this study. Another study performed by our group included healthy controls between the ages of 20 and 80 years. In that study, the distribution between Type 1 and 2 P-waves seen in patients above the age of 50–60 years was similar to that seen in the young AF subjects in the present study. Furthermore, over a 3-year follow-up period, patients with Type 1 tended to move towards Type 2 more often than vice versa. Hence, a shift in P-wave morphology from Type 1 to 2 is associated with a worse state of disease in patients with various forms of congestive heart failure (i.e. structurally abnormal hearts), but also over time within individuals and with increasing age in presumably healthy individuals (i.e. most likely structurally normal hearts). Changes in interatrial conduction, more specifically various degrees of interatrial block, have been shown to be associated with increased risk of atrial arrhythmia. Findings in an earlier, invasive study by our group in which P-wave morphology was compared with left atrial activation maps indicated that the atrial impulse in AF patients with Type 1 P-wave morphology is more likely to be conducted from right to left via fibres in the vicinity of the foramen ovale, whereas individuals with Type 2 P-wave morphology were more likely to depend on Bachmann’s bundle conduction. In the present study, this shift (from Type 1 to 2) is seen in young individuals with structurally normal hearts, whose only burden is lone paroxysmal AF. This implies that the observed morphological changes are likely to be the result of changes in atrial conductive properties, rather than differences in structure and anatomy. It is well known that the connexins are altered in AF with heterogeneous localization and expression, which could give rise to altered activation direction of the atria, but other factors, such as fibrosis, are also likely to play a role. The exact reason for the observed changes in interatrial conductive properties in the present study is unknown.

Intriguingly, all three AF patients with ‘atypical’ P-wave morphology (i.e. non-Type 1 through 3) exhibited the same pattern of positive signals in all leads. This P-wave morphology pattern has been described previously in a study on patients with congestive heart failure following myocardial infarction, but its electrophysiological significance remains to be elucidated.

Since the AF subjects were all included after AF debut, the question of which comes first, the change in P-wave morphology or the AF, cannot be answered by the present study. However, findings in previous studies suggest that the changes seen in P-wave morphology may well precede the onset of arrhythmia. Given the relatively large overlap of P-wave morphology in healthy controls and AF subjects, the clinical value of P-wave morphology analysis alone in young individuals to identify subjects at risk of developing AF is likely to be limited.

**Study limitations**

The echocardiographic data were recorded as part of a clinical routine, and no alternative atrial measures were available. The LVEF was estimated to rule out ventricular systolic dysfunction, but was not quantified above ‘normal’. Therefore, differences within the normal range between the AF subjects and controls cannot be ruled out. The number of women was very low in the present study, with only two women in each group (6%). However, this might be due to the known overrepresentation of male subjects among patients with AF, which is particularly notable at younger age. The patients were consecutively included, and the study may therefore be regarded as a representative of this patient subset, but the validity of these findings with regard to women with early-onset AF remains an open question.

Although unlikely, a significant impact of the observed differences between study subjects and controls (BMI and weight) on the study findings cannot be excluded.

**Conclusions**

In the present study, a significant difference in P-wave morphology distribution was seen between patients with early-onset, lone paroxysmal AF and an age- and gender-matched healthy control group. The changes are seen without significant differences in P-wave duration, which underlines the necessity of detailed P-wave analysis in this context. The present findings show that alterations in atrial electrophysiology are common in the early...
stages of AF, which may indicate that these changes are fundamental in AF development.

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Conflict of interest: none declared.

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