CLINICAL RESEARCH

Slower heart rate and altered rate dependence of ventricular repolarization in patients with lone atrial fibrillation

Fréquence cardiaque plus lente et altération de la fréquence-dépendance de la repolarisation ventriculaire chez les sujets avec fibrillation atriale idiopathique

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KEYWORDS
Lone atrial fibrillation; Short QT syndrome; QT interval

Summary

Background. — Electrophysiological alterations in atrial fibrillation (AF) may be genetically based and may lead to changes in ventricular repolarization. Short QT syndrome is a rare channelopathy with abbreviated ventricular repolarization and a propensity for AF.

Aims. — To determine if minor unrecognized forms of short QT syndrome can explain some cases of lone AF.

Methods. — We prospectively compared QT intervals in 66 patients with idiopathic lone AF and 132 age- and sex-matched controls. QT intervals were measured during sinus rhythm in each of the 12 surface electrocardiogram leads and corrected using Bazett’s formula (QTc). QT intervals

Abbreviations: AF, atrial fibrillation; bpm, beats per minute; ECG, electrocardiogram; ICC, intraclass correlation coefficient; QTc, corrected QT; SQTS, short QT syndrome.
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were also corrected using other formulae. Uncorrected QT and heart rate regression lines were compared between AF patients and controls.

**Results.** — AF patients presented with a slower resting heart rate (64 ± 10 beats per minute [bpm] vs 69 ± 9 bpm; P = 0.0006). QTc intervals were shorter in AF patients in 11/12 electrocardiogram leads (significant in 7/12, borderline in 2/12; mean QTc 381 ± 21 ms vs 388 ± 22 ms; P = 0.02). QTc intervals were also shorter in AF patients, significantly or not, using other correction formulae. For similar heart rates, uncorrected QT intervals were shorter in patients when heart rates were greater than 70 bpm and longer when heart rates were less than 60 bpm. AF patients displayed steeper QT/heart rate regression line slopes than controls (P = 0.009).

**Conclusion.** — Heart rate is significantly slower and the rate dependence of ventricular repolarization is significantly altered in patients with lone AF compared with controls. Further study is warranted to determine if AF induces subsequent ventricular repolarization changes or if these modifications are caused by an underlying primary electrical disease.

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**Background**

Atrial fibrillation (AF) is the most common cardiac arrhythmia, reaching a prevalence of 1% in the general population [1]. In 2 to 30% of cases, AF occurs without any cardiac alteration or facilitating extracardiac abnormality and is called lone AF [2—5]. Most of the time, AF is a consequence of a multifactorial process involving various acquired structural alterations, while primitive electrical disease can be suspected in lone AF, where no structural heart disease is present. A genetic background is suspected in familial cases, which account for 15% of lone AF cases [6]. Several mutations or variants have been discovered during the past decade [7,8], mainly on genes encoding various membrane ion channels involved in atrial but also ventricular action potentials.

Short QT syndrome (SQTS) is a recently recognized channelopathy associating abbreviated atrial and ventricular repolarizations and a propensity for atrial and ventricular arrhythmias [9—11]. In particular, AF is frequently observed in SQTS patients [10]. To date, discovered mutations in SQTS mainly involve potassium channels, leading to a gain of function [12—15], similar to that observed in some familial cases of AF [7,8], although QT intervals are apparently normal in these patients.

The aim of this study was to compare QT interval durations in patients with lone AF and matched controls, based on the hypothesis that minor unrecognized
forms of SQTS may explain some cases of lone AF.

Methods

We performed a case-control study at two centres, comparing QT interval durations during sinus rhythm in patients with lone AF and matched controls.

Patients with lone AF were prospectively recruited over the past 2 years at our two institutions (University Hospital Rangueil, Toulouse, France and Hôpital de la Tour, Meyrin, Switzerland). To be included, patients had to be aged less than 75 years and present with a history of documented paroxysmal AF without any detectable underlying heart disease and without diabetes, hypertension or any precipitating condition, such as a history of renal, hormonal or pulmonary disease [3,5]. Transthoracic echocardiography was available in each case and had to be compatible with the diagnosis of lone AF [2] (no ventricular hypertrophy or dilatation, normal ventricular systolic function, no valvular or pericardial abnormality, no increased left ventricular diastolic filling pressure). An isolated left atrial dilatation was not an exclusion criterion [16]. Patients with a recent episode of AF occurring during the previous 48 h – either documented or suspected by suggestive symptoms — were excluded, as well as patients under antiarrhythmic drugs, digoxin, beta-blockers, calcium channel blockers or, more generally, under any cardioactive drug or medication with some electrophysiological action or known to alter cardiac repolarization or to perturb ionic homeostasis. Patients aged <16 years and those with a familial history of AF were excluded, as were professional sportmen or patients practising intensive physical activity (>7 h a week).

Once this population was selected, we prospectively recruited age- and sex-matched controls over the following months. Controls were matched with a 2:1 ratio according to sex and age (patients and controls were grouped in sections of 10 years of age). Control patients were recruited during preoperative consultations before non-cardiac surgery or by means of consultations for non-organic cardiovascular symptoms or from the medical or paramedical staff. These recruits were men or women without any personal or familial cardiovascular history, with unremarkable physical examination and without any cardioactive medication. Exclusion criteria for patients with AF also applied for controls. Patients or controls with a resting sinus node heart rate that was too high (> 85 beats per minute [bpm]) or too low (< 45 bpm) were excluded because of the inaccuracy of most QT correction formulae at these rates [17].

One standard 12-lead surface electrocardiogram (ECG) was used for analysis for each patient or control. The ECG was recorded at rest during the same standard clinical conditions in patients and controls (i.e. common conditions for ECG recording as performed during usual medical consultation, at a paper speed of 25 mm/s with a standard ECG recorder [1 kHz sampling rate, 0.1–250 Hz filters]). For each tracing, sinus node heart rate, PR interval and QRS duration were measured in lead II. The QT interval duration was then measured in each of the 12 ECG leads, from the QRS onset to the end of the T wave, as defined by the intersection of the tangent of the steepest slope of the last part of the T wave and the isoelectric line, according to the technique described by Surawicz [18]. QT was not measured in case of flat T wave (less than 0.1 mV) or when the end of the T wave was difficult to determine. Measurements were averaged over five successive beats in case of sinus node arrhythmia (defined by instantaneous heart rate variations ≥10% of the mean heart rate). ECG analysis was independently performed by two cardiologists blinded to the groups in a subset of 20 cases, for evaluation of interobserver variability.

To allow determination of corrected QT (QTc), QT durations were then corrected according to Bazett’s formula (QTc = QT/√RR) [19]. For each ECG, the mean QTc was determined over the 12 leads. QT durations were additionally corrected according to the formulae by Hodges (QTc = QT + 1.75 [heart rate – 60]) [20], Fridericia (QTc = QT/√3RR) [21], Rautaharju (QTc = QT + [410 – 656/(1 + heart rate/100)]) [22] and Sagie Framingham (QTc = QT + 154 [1 – RR]) [23].

Statistical analysis

Statistical analysis was performed using StatView 5 (version 4.5; Abacus Concepts, Inc., Berkeley, CA, USA; 1992–1996) and Stata (version 11.1; StataCorp LP, College Station, TX, USA). Numerical values are presented as means ± standard deviations (ranges) and categorical data as proportions. Normal distribution was expected, given the significant number of patients in each group, so unpaired t tests were used to compare numerical data between groups. Proportions were compared using the Chi² test. The intraclass correlation coefficient (ICC) was calculated to determine the reliability of QT measurements; interobserver variability was assessed by comparing the results from observers 1 and 2. Furthermore, due to the imperfection of correction formulae, especially in case of different heart rates between groups, uncorrected QT interval durations were compared in subgroups sharing a similar heart rate. In addition, significant interaction between uncorrected QT/heart rate regression lines for patients and controls was determined. A P value < 0.05 was considered significant for each analysis.

Results

Sixty-six successful patients with paroxysmal lone AF were prospectively included and compared with 132 matched controls. Two controls — but no patients — were excluded before enrolment because of intensive sporting activity. There were no differences in sex (72% men) or age (mean, 49 ± 13 years) between groups due to the matching. All patients or controls were Caucasian. ECGs were always recorded during the daytime (12:00 ± 3 h without difference between groups). Mean heart rate was 67.1 ± 10 bpm (45–85 bpm). Mean PR interval was 156 ± 26 ms (100–220 ms) and mean QRS duration was 82 ± 4 ms (80–100 ms).

Heart rate was significantly slower in patients with lone AF than in controls (64 ± 10 bpm vs 69 ± 9 bpm; P = 0.0006). Prevalence of sinus node arrhythmia was similar between groups (17% in both groups; P = 0.8). The PR interval was longer in patients with lone AF (160 ± 29 ms) than in controls (154 ± 24 ms), although the difference was not significant (P = 0.15). No complete bundle branch block
Slower heart rate and shorter corrected QT in lone atrial fibrillation

Table 1 Corrected QT durations in each electrocardiogram lead and mean corrected QT duration for the 12 leads for patients with lone atrial fibrillation and matched controls.

<table>
<thead>
<tr>
<th>ECG lead</th>
<th>QTc duration (ms)</th>
<th>P</th>
<th>Controls</th>
<th>AF patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>381 ± 24</td>
<td>0.03</td>
<td>389 ± 23</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>386 ± 25</td>
<td>0.09</td>
<td>391 ± 21</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>377 ± 27</td>
<td>0.01</td>
<td>387 ± 25</td>
<td></td>
</tr>
<tr>
<td>AVR</td>
<td>381 ± 23</td>
<td>0.06</td>
<td>388 ± 22</td>
<td></td>
</tr>
<tr>
<td>AVL</td>
<td>370 ± 23</td>
<td>0.002</td>
<td>382 ± 26</td>
<td></td>
</tr>
<tr>
<td>AVF</td>
<td>386 ± 25</td>
<td>0.3</td>
<td>390 ± 25</td>
<td></td>
</tr>
<tr>
<td>V1</td>
<td>368 ± 30</td>
<td>0.01</td>
<td>378 ± 26</td>
<td></td>
</tr>
<tr>
<td>V2</td>
<td>383 ± 23</td>
<td>0.8</td>
<td>383 ± 25</td>
<td></td>
</tr>
<tr>
<td>V3</td>
<td>388 ± 23</td>
<td>0.18</td>
<td>393 ± 22</td>
<td></td>
</tr>
<tr>
<td>V4</td>
<td>386 ± 22</td>
<td>0.04</td>
<td>393 ± 24</td>
<td></td>
</tr>
<tr>
<td>V5</td>
<td>384 ± 22</td>
<td>0.01</td>
<td>393 ± 24</td>
<td></td>
</tr>
<tr>
<td>V6</td>
<td>382 ± 23</td>
<td>0.005</td>
<td>392 ± 23</td>
<td></td>
</tr>
<tr>
<td>Mean for the 12 leads</td>
<td>381 ± 21</td>
<td>0.02</td>
<td>388 ± 22</td>
<td></td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; ECG: electrocardiogram; QTc: corrected QT. QTc durations were significantly shorter in the AF group in leads I, III, V1, V4, V5 and V6 (P < 0.05) and were shorter with borderline significance in leads II and VR (P < 0.1). Mean QTc duration was also significantly shorter in the AF group.

or pre-excitation was observed in any ECG. There was no difference in QRS width between groups (82 ± 4 ms for both groups).

Repolarization was found to be unremarkable on every ECG (positive T wave in each lead except V1, V2, VR and sometimes III). There was good agreement between observers for the determination of QT intervals (ICC 0.83). Differences in QTc intervals are shown in Table 1. In each ECG lead (except V2), Bazett-corrected QT intervals were found to be shorter in patients with lone AF than in controls. Differences were significant for 7/12 ECG leads and borderline in two other leads (Fig. 1): in V5, for example, QTc was 384 ± 22 ms vs 393 ± 24 ms in controls (P = 0.01). Mean QTc was 381 ± 21 ms in AF patients and 388 ± 22 ms in controls (P = 0.02) (a difference of 7 ms).

These results were also globally observed when QT corrections were made according to the Hodges formula (significantly shorter QTc in the lone AF group in every lead except V1 and V2), or the Sagie-Framingham and Rautaharju formulae (shorter QTc in most leads in AF patients with significant differences in VL, V1 and V6 and borderline in lead III). QTc intervals were also shorter in patients with lone AF but without any significant difference when the Friedericia formula was used.

A short QT (defined by mean QTc < 340 ms and/or mean QT < 320 ms) was found in two AF patients and none of the controls. No QTc cutoff value could be found due to the overlap between groups.

Significant differences in QTc between AF patients and controls were also found in the subgroup of men but the differences were no more significant in the subgroup of women. Men with lone AF had a significantly lower heart rate than controls (63 ± 11 bpm vs 69 ± 10 bpm; P = 0.0005) while the difference was not significant for women (66 ± 9 bpm vs 68 ± 8 bpm). Similar differences in QTc and heart rate were also present in each age subgroup, but were often borderline or not significant due to the low number of patients and controls in each subgroup.

Due to the imperfection of correction formulae, especially in case of different heart rates between groups, as documented here, we performed additional analyses using uncorrected QT interval durations in subgroups of patients sharing similar heart rates (see statistical analysis section). In the subgroup of patients/controls with a resting heart rate greater than 75 bpm, the QT intervals in most leads as well as mean QT were significantly shorter in AF patients than in controls. Similar but non-significant differences were observed in most ECG leads for patients and controls with heart rates between 70 and 75 bpm. QT intervals were often quite similar in patients and controls in most leads between 60 and 70 bpm, while the reverse situation was observed in most leads between 50 and 60 bpm (longer QT intervals in AF patients), although the difference was not significant.

Uncorrected QT/heart rate regression lines for patients and controls displayed significant interaction (P = 0.01).

**Figure 1.** Graphic representation of the differences in corrected QT (QTc) in each electrocardiogram lead and in mean QTc between atrial fibrillation patients (grey) and controls (white). * indicates a significant difference (P < 0.05); b indicates a borderline difference (P < 0.1).
Discussion

In this study, we compared resting heart rate and QT interval duration in patients with lone AF without any condition or therapy leading to alteration in ventricular repolarization and matched controls. We found that the resting heart rate was significantly slower and QTc intervals were significantly shorter in patients with paroxysmal lone AF compared with the control group. QTc interval durations were shorter in most leads in patients with lone AF, the differences being significant (Bazett, Hodges, Rautaharju and Framingham) or not (Fridericia) according to the formula used, with a difference of 7 ms between the mean QTc intervals in each group using Bazett’s formula. Both findings were also observed in the subgroups of men or women and in each age-related subgroup, even if the differences were sometimes not significant because of the low number of cases in some subgroups. No cutoff value could be found due to the overlap in QTc durations between both groups and a short QT interval was diagnosed in two patients with lone AF but in none of the controls.

As heart rates were different between AF patients and controls, and because of the imperfection of most correction formulae, we performed additional analyses of uncorrected QT intervals in subgroups of patients and controls sharing similar heart rates: QT intervals were shorter in AF patients compared with controls when the heart rate was greater than 70 bpm and longer when the heart rate was less than 60 bpm. We also demonstrated that QT/heart rate regression lines had different slopes; patients with lone AF displayed steeper slopes than controls. Both these results mean that QT intervals were longer in AF patients than in controls when the heart rate was low and that the reverse was true for faster heart rates. Even if no firm conclusions about differences in corrected QT intervals could be drawn here because of the non-similar heart rates, it appears, however, that the rate dependence of ventricular repolarization is significantly different in patients with lone AF.

A previous study had already found shorter QTc intervals in patients with AF compared with matched controls [24] but the patients and controls were older, most presented with hypertension and some presented with diabetes; their results could not, therefore, be compared with ours, as hypertension, age and diabetes are known to modify repolarization, which means that such patients cannot be considered as having lone AF. Moreover, heart rate was faster in this study than in our population and did not differ between patients and controls.

The population in our study was quite representative of lone AF patients, with a male predominance, which is known to be present in lone AF [25,26]. Due to the low number of female patients, some results were non-significant in this subgroup, although a trend for lower heart rate and shorter QTc was also present in women.

The relationships between AF and ventricular repolarization are poorly known. AF may induce subsequent ventricular repolarization changes but primary electrical disease may also facilitate the development of AF. The interpretation of these results remains difficult and beyond the scope of this study, although some hypotheses may be postulated.

The main hypothesis relates to the existence of underlying genetic mutations or variants leading to electrophysiological alterations in both atrial and ventricular myocardial cells. To date, discovered mutations in patients with lone AF involve different genes [7,8] but frequently lead to gains of function of potassium channels. Some of these mutations are associated with a reduction in duration of atrial action potentials [27,28]. Mutations with gain of function of potassium channels have also been described in patients with SQTS [12–15] and the prevalence of AF in patients with SQTS is high (around 25%), occurring at every age, even during childhood [10]. In view of our results, it is tempting to postulate that patients with lone AF may be considered as presenting with minor subclinical forms of SQTS, at least in some cases. The different behaviour of ventricular repolarization according to the heart rate present in patients with lone AF in this study is, however, the reverse to what is observed in SQTS patients, where QT adaptation to heart rate is poor [29].

A decrease in the QT interval because of previous fast AF terminated in the last minutes before the ECG recording and due to restitution or QT hysteresis is less likely. The QT interval is known, rather, to increase immediately after spontaneous or electrical restoration of sinus rhythm, remaining 5–10 ms longer than baseline over the following weeks to months [30], which rather reinforces our findings of shorter QT intervals in patients with paroxysmal AF.

The QT interval is modulated by parasympathetic agents [31]. A more marked basal vagal tone in patients with lone AF would therefore explain the lower heart rate, the higher risk of AF (i.e. vagally mediated AF), together with shorter QT intervals. However, PR intervals were not significantly longer in patients with AF, ECG recordings were always performed under the same conditions, there was no apparent difference in sporting activity between the populations due to age and sex matching and competitive or high-intensity sportsmen or women had been excluded.
Slower formed expected common deserves repolarization concerning being able. Artificially longer QTc intervals in controls, as the heart rate was faster in this group. However, even if they were different, the mean heart rates were close to 60 bpm in both groups, a rate at which correction formulae are more reliable. Furthermore, this difference was found again using most other correction formulae. For these reasons, we performed additional analyses on uncorrected QT intervals and demonstrated a significantly different rate dependence behaviour between patients and controls (see results section), validating the significant difference in the ventricular repolarization process in AF patients found in this study, even if no firm conclusions about QTc should be made.

Echocardiography was performed for the control group. It is, however, highly probable that left atrial size was larger in patients than in controls [16]. It is unclear if changes in left atrial size only, without underlying heart disease, would have an action on ventricular repolarization, but this deserves further study.

Genetic analysis was not performed. These results would be confirmed, therefore, if correlated to mutations in candidate genes.

Conclusion

Heart rate and rate dependence of ventricular repolarization are significantly altered in patients with lone AF. Underlying variants or mutations in various genes encoding for cardiac ionic currents leading to altered ventricular repolarization and slower sinus node heart rate may be suspected as an explanation for these results, although other alternative mechanisms cannot be ruled out. Further studies are mandatory for validating these findings and subsequent mechanistic hypotheses. If confirmed, the existence of a common genetic background may help in targeting adapted antiarrhythmic therapies in patients with lone AF.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


