Electrocardiographic evidence of ventricular repolarization remodelling during atrial fibrillation

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Aims Some atrial fibrillation (AF) patients develop excessive QTc prolongation and torsade de pointes when they take QTc-prolonging antiarrhythmic drugs (class IA/III) immediately after termination of AF. We hypothesized that this is caused by changes in ventricular repolarization during AF. We aimed to establish whether such ‘ventricular repolarization remodelling’ occurs.

Methods and results We studied all patients who visited our cardiac emergency room with AF and converted to sinus rhythm (SR) in a 30 months’ period. We defined four groups: (i) no antiarrhythmic drugs, electrical cardioversion (n = 30), (ii) no antiarrhythmic drugs, spontaneous AF termination (n = 19), (iii) antiarrhythmic drugs, electrical cardioversion (n = 29), and (iv) antiarrhythmic drugs, spontaneous AF termination (n = 9). We studied QTc duration at SR before AF (SRbaseline), immediately after termination of AF (SRpostAF), and at follow-up (SRfollowup: /C21 7 days after SRpostAF). Moreover, we studied determinants of QTc prolongation at SRpostAF. We found that, in all groups, QTc at SRpostAF was significantly and transiently prolonged compared with SRbaseline. Although of limited magnitude on average (<5%), the increase was substantial (<15%) in some individuals. The only independent predictor of the magnitude of QTc prolongation was QTc duration at SRbaseline; this relation had a negative correlation.

Conclusion AF causes ventricular repolarization remodelling, resulting in QTc prolongation. QTc prolongation is substantial in some patients and may render these patients vulnerable to pro-arrhythmia from class IA/III antiarrhythmic drugs immediately after termination of AF.

KEYWORDS
Atrial fibrillation; QT interval; Long QT syndrome; Remodelling

Introduction
Cardiac repolarization-prolonging antiarrhythmic drugs (Vaughan–Williams class IA and III) effectively prevent atrial fibrillation (AF). Yet, their clinical applicability is limited because they provoke life-threatening arrhythmias in some patients, notably torsades de pointes ventricular tachycardia, secondary to excessive prolongation of ventricular repolarization (acquired long QT syndrome).1 For instance, for quinidine, this risk is estimated at ≥1.5% per year.1 This risk is particularly high in the period shortly following conversion from AF to sinus rhythm (SR), because of increased propensity to excessive QT prolongation during this period.2–5 We hypothesized that such fortuitous QT prolongation is based on ventricular repolarization remodelling during AF, i.e. AF-induced changes in ventricular repolarization. Ventricular repolarization remodelling reduces ‘repolarization reserve’, i.e. the capacity of the ventricle to complete repolarization in the presence of QT-prolonging factors such as drugs.6 Although normal ventricular repolarization is restored after termination of AF (reverse remodelling), this process requires time to complete. Repolarization-prolonging drugs, used during the period when reverse remodelling is not yet complete and repolarization reserve is still reduced, may evoke excessive QT prolongation. Clear clinical evidence of ventricular repolarization remodelling during AF is, however, lacking. With the aim of providing such evidence, we studied changes in electrocardiographic (ECG) QTc interval duration shortly after the termination of AF. We found that QTc duration increases significantly during this period. This increase is substantial in some individuals. The magnitude of QTc...
prolongation is determined by QTc duration at baseline. These findings support the concept that ventricular repolarization remodelling occurs during AF, and that this process depends on a patient's baseline repolarization properties.

Methods
Patient inclusion
In this retrospective single-centre study, we studied all patients with available 12-lead ECGs who presented to the cardiac emergency room from January 2005 to June 2007 with AF and converted to SR. We studied four groups. Group 1: patients who used no QT-prolonging antiarrhythmic drugs (class IA or III) at any time point of ECG analysis (see the following subsection), who converted to SR after electrical cardioversion. Group 2: patients who used no class IA or III antiarrhythmic drugs at any time point, who converted spontaneously to SR (no electrical cardioversion). Group 3: patients who used class IA (disopyramide, \( n = 2 \)) or III (sotalol, \( n = 13 \); amiodarone, \( n = 14 \)) antiarrhythmic drugs (type and dose unchanged at all time points), who converted to SR after electrical cardioversion. Group 4: patients who used class I (disopyramide, \( n = 2 \)) or II (amiodarone, \( n = 5 \); amiodarone, \( n = 4 \)) antiarrhythmic drugs (type and dose unchanged at all time points), who converted spontaneously to SR (no patient who used class IA drugs converted spontaneously). Patients who used class IC antiarrhythmic drugs at any time point were excluded because the effects of these drugs on ventricular repolarization are equivocal. Patients who used non-cardiac drugs generally accepted to modify QT duration (www.torsades.org and\(^3\)) at any time point were excluded.

Electrocardiographic analysis
Twelve-lead ECGs were analysed at various time points: (i) last ECG of SR within 3 months before presentation, but at least 3 months after any preceding AF episode (SR\(_{\text{baseline}}\)); (ii) AF episode at presentation (AF); (iii) SR within 15 min after termination of AF (SR\(_{\text{postAF}}\)); (iv) first ECG of SR between 1 week and 3 months after termination of AF (SR\(_{\text{followup}}\)); (v) last ECG of SR between 3 and 12 months after termination of AF (SR\(_{\text{followup2}}\)). To study the primary endpoint in this study (QT prolongation at SR\(_{\text{followup}}\)), ECGs at time points 1–4 were required in all patients. Electrocardiographic analysis results at time point 1 were available because they had been previously recorded for related or unrelated cardiac or non-cardiac disease. QT durations were measured by hand in leads II or V5\(^7\) (paper speed 25 mm/s) by investigators who were blinded to the study group, and were required to reach consensus. Electrocardiographic results were enlarged (Adobe Portable Document Format\(^{16}\)) to what ever magnification was needed for accurate measurements. QT durations were rate-corrected using Bazett’s formula (QTc = QT/\(\sqrt{RR}\)). Between leads II and V5, we used the lead in which QT could be most reliably measured. Although these leads differed between patients, they did not differ between time points within a patient, i.e. the same lead was always used in a particular patient.

Clinical determinants of QT duration
To establish possible determinants of AF-associated changes in QTc duration (QTc duration at SR\(_{\text{postAF}}\)), we studied known modifiers of QT duration, including serum potassium levels (at presentation),\(^8\) and indices of heart failure,\(^9\) including NT-proBNP levels (within 1 month before or after presentation),\(^10\) and left ventricular ejection fraction (LVEF) calculated using gated scintigraphy or cardiac magnetic resonance imaging (within 1 year before or after presentation). We also studied categorical clinical determinants of QTc duration, including hypertension, left ventricular hypertrophy (proved by imaging modalities, such as echocardiography), valvular heart disease, coronary artery disease (proved by enzymatically documented prior myocardial infarction, coronary angiography, or myocardial perfusion scintigraphy), and diabetes.

Statistical analysis
Data were tested for normal distribution using the residuals from (repeated) ANOVA models. Except for AF duration and NT-proBNP, all variables were normally distributed (Shapiro-Wilk W > 0.9) and are presented as means ± SEM. Atrial fibrillation duration and NT-proBNP are presented as median and interquartile range. QTc durations at baseline, post-AF, follow-up, and follow-up 2 within groups were compared with paired Student’s t-test. Effects of medication, electrical cardioversion, time point, and their interactions on QTc duration were tested using a repeated measures ANOVA. Comparisons within groups were made using a repeated measures ANOVA with time point as only effect. In all models, age, gender, QRS, and HR were included as covariates. The effects of known determinants of QTc duration on the change in QTc duration from SR\(_{\text{baseline}}\) to SR\(_{\text{postAF}}\) were analysed using (multiple) linear regression. In addition, patients were separated into those who did not use antiarrhythmic drugs (Groups 1 and 2) and those who did (Groups 3 and 4). Differences between groups in the prevalences of clinical determinants of QTc duration were analysed using Fisher’s exact test. All analyses were carried out using SPSS 14.0, and \(P\)-values < 0.05 were considered statistically significant.

Results
Changes in QTc duration immediately after termination of atrial fibrillation
Table 1 summarizes demographic and clinical variables (including clinical determinants of QT duration), and ECG parameters at various time points. In Group 1, QTc duration at SR\(_{\text{postAF}}\) was significantly longer than at SR\(_{\text{baseline}}\) and returned to SR\(_{\text{baseline}}\) levels at SR\(_{\text{followup2}}\) (Figure 1). To study whether the increase in QTc duration at SR\(_{\text{postAF}}\) was due to electrical cardioversion, we studied QTc duration in patients who underwent no electrical cardioversion (Group 2). We found that QTc duration at SR\(_{\text{postAF}}\) was prolonged to a similar extent as in Group 1 and was significantly longer than at SR\(_{\text{baseline}}\) (Figure 1). Similar changes occurred in patients who used QT-prolonging antiarrhythmic drugs and underwent electrical cardioversion (Group 3, Figure 1) or converted to SR without electrical cardioversion (Group 4, Figure 1). The increases in QTc duration were not due to increases in QRS duration, as QRS duration did not differ significantly between SR\(_{\text{baseline}}\), SR\(_{\text{postAF}}\), and SR\(_{\text{followup2}}\) in any group. Of note, multivariate analysis revealed that the use of antiarrhythmic drugs impacted on the rate at which QTc returned to baseline values after termination of AF. Accordingly, QTc durations in Groups 3 and 4 took longer to normalize, reaching baseline values only at SR\(_{\text{followup2}}\).

Determinants of atrial fibrillation-associated changes in QTc duration
To establish the determinants of the AF-associated increase in QTc duration (QTc prolongation at SR\(_{\text{postAF}}\)), we studied which variables impacted on the change in QTc duration at SR\(_{\text{postAF}}\) in patients who did not use antiarrhythmic drugs (Groups 1 and 2) and those who did (Groups 3 and 4). We found that QTc duration at SR\(_{\text{baseline}}\) was the only independent determinant, and that it correlated inversely with the increase in QTc duration at SR\(_{\text{postAF}}\) (Table 2). This correlation was stronger in Groups 1 and 2 (Figure 2A) than in
Groups 3 and 4 (Figure 2B, Table 2). Although LV-EF correlated with increase in QTc duration at SR_{postAF} in univariate analysis, multiple linear regression analysis revealed that LV-EF was not an independent determinant. We found no correlation between increase in QTc duration at SR_{postAF} and external factors which modify cardiac repolarization, including serum potassium levels, and markers of congestive heart failure, such as serum NT-proBNP levels (Table 2). To explore whether the extent of repolarization remodelling depends on AF variables (duration of AF, ventricular rate during AF), we studied how these variables impacted on QTc duration at SR_{postAF}. We found no correlation between increase in QTc duration at SR_{postAF} and duration of AF, ventricular rate during AF, or reduction in ventricular rate from AF to SR_{postAF} (Table 2). Finally, we investigated the role of demographic and clinical variables. Neither age nor sex was a predictor of changes in QTc duration. Although the prevalences of hypertension and left ventricular hypertrophy were significantly different between the four groups, neither hypertension (P = 0.78) nor left ventricular hypertrophy (P = 0.76) had a significant correlation with the increase in QTc duration at SR_{postAF}. Although coronary artery disease was equally distributed between the four groups, there seemed to be an association between the presence of coronary artery disease and an attenuation in the increase in QTc duration at SR_{postAF}. This association reached marginal statistical significance.

**Discussion**

We found ECG evidence that AF slows ventricular repolarization. Although the increase in QTc duration at SR_{postAF} was of limited magnitude on average, it was substantial in some
individuals. On the basis of the following observations, we regarded this QTc prolongation as evidence that ventricular repolarization was slowed by the preceding AF episode (repolarization remodelling): (i) the increase was transient and QTc duration returned to its baseline level at follow-up; (ii) the magnitude of increase depended on baseline QTc duration; this indicates that it was determined by a patient’s baseline repolarization properties. Both observations provide evidence for a biological basis of the increase in QTc duration. The increase was of similar magnitude in patients who underwent electrical cardioversion and those who did not, indicating that it was not due to electrical cardioversion and/or general anaesthesia. Accordingly, previous studies showed that propofol (used by us for electrical cardioversion) does not affect QT interval \(^{11}\) or QTc duration. The increase was of similar magnitude in patients who did not, indicating that it was not due to electrical cardioversion and/or general anaesthesia. Accordingly, previous studies showed that propofol (used by us for electrical cardioversion) does not affect QT interval \(^{11}\) or QTc duration.

The ventricular remodelling process may involve downregulation of repolarization-controlling ion channels, similar to atrial electrophysiological remodelling during AF \(^{13}\) (it must be noted that, in the atrium, other ion currents are also downregulated, e.g. the L-type calcium channel \(^{14}\) ). The pathophysiological basis of ventricular repolarization remodelling is unresolved. The fast ventricular rates during the preceding AF episode and/or the abrupt slowing of heart rate after termination of AF may play a role. For instance, abrupt slowing of heart rates may cause excessive QTc prolongation and torsade de pointes in inherited long QT syndrome \(^{15}\) and following His bundle ablation for AF with intractably fast ventricular rates \(^{16,17}\). Yet, QTc prolongation at \(SR_{postAF}\) did not correlate with ventricular rates during AF at presentation or with reduction in ventricular rate after termination of AF.

Our evidence of ventricular repolarization remodelling during AF and the resulting QT prolongation may underlie previous observations that administration of QT-prolonging antiarrhythmic drugs confers particularly high risk of excessive QT prolongation and syncpe in the period immediately following termination of AF \(^{1–5}\) It is conceivable that, during this period, reverse remodelling is not yet complete, and QT-prolonging drugs, which act by blocking repolarizing currents (particularly \(I_{Kr}\)), may produce excessive QT prolongation. In accordance with this concept, the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with AF state that ‘after cardioversion to sinus rhythm, patients receiving drugs that prolong the QT interval should be monitored in the hospital for 24–48 h to evaluate the effects of heart rate slowing and allow for prompt intervention in the event torsades de pointes develops’ \(^{18}\). We hypothesize that this period of enhanced susceptibility to torsades de pointes ends when reverse remodelling is complete. Yet, there is no evidence from human studies to indicate how long this process takes. Accordingly, the duration of the waiting time after termination of AF which must be observed before QT-prolonging drugs can be given safely without the risk of provoking torsades de pointes is unknown. To complicate matters, we found that the rate of reverse remodelling is variable, being slower in patients who used class IA or III antiarrhythmic drugs than in those who did not. It is conceivable that even more factors may impact on the rate of reverse remodelling.

QTc prolongation at \(SR_{postAF}\) was highly variable among patients. Importantly, it was particularly large in some patients, e.g. QTc duration increased from 410 ms at \(SR_{baseline}\) to 475 ms at \(SR_{postAF}\) (~15%) in a patient of Group 1. It may be these patients who develop excessive

### Table 2 Effects (95% confidence intervals) and explained variance (\(R^2\)) of known determinants of QTc duration at \(SR_{postAF}\) on the basis of univariate and multiple linear regression

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Effect (95% confidence interval)</th>
<th>(P)-value</th>
<th>(R^2) (%)</th>
<th>Multiple Determinant</th>
<th>Effect (95% confidence interval)</th>
<th>(P)-value</th>
<th>(R^2) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication, yes</td>
<td>-7.8 (-15.1 to -0.6)</td>
<td>0.034</td>
<td>5.2</td>
<td></td>
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<tr>
<td>QTc(_{baseline}), ms</td>
<td>-0.25 (-0.37 to -0.13)</td>
<td>&lt;0.001</td>
<td>17.0</td>
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<tr>
<td>K, mmol/L</td>
<td>-1.7 (-11.2 to 7.8)</td>
<td>0.718</td>
<td>0.2</td>
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<tr>
<td>LVEF, %</td>
<td>-0.8 (-1.5 to -0.05)</td>
<td>0.038</td>
<td>21.8</td>
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<tr>
<td>NT-proBNP, ng/L</td>
<td>-0.004 (-0.011 to 0.003)</td>
<td>0.279</td>
<td>3.2</td>
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<tr>
<td>AF duration, h</td>
<td>-0.02 (-0.11 to 0.07)</td>
<td>0.636</td>
<td>0.3</td>
<td></td>
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<tr>
<td>HRaf, bpm</td>
<td>0.04 (-0.08 to 0.17)</td>
<td>0.502</td>
<td>0.5</td>
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<tr>
<td>Change HRaf(_{postAF}), bpm</td>
<td>0.00 (-0.14 to 0.14)</td>
<td>0.955</td>
<td>&lt;0.1</td>
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<tr>
<td>Male, yes</td>
<td>3.5 (-3.9 to 10.9)</td>
<td>0.353</td>
<td>1.0</td>
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<tr>
<td>Age, year</td>
<td>-0.16 (-0.39 to 0.07)</td>
<td>0.164</td>
<td>2.3</td>
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<tr>
<td>Hypertension, yes</td>
<td>1.1 (-6.7 to 8.9)</td>
<td>0.778</td>
<td>0.1</td>
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<tr>
<td>Left ventricular hypertrophy, yes</td>
<td>-1.2 (-8.9 to 6.5)</td>
<td>0.762</td>
<td>0.1</td>
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<tr>
<td>Valvular heart disease, yes</td>
<td>-0.8 (-15.7 to 0.0)</td>
<td>0.051</td>
<td>4.4</td>
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<tr>
<td>Coronary artery disease, yes</td>
<td>-8.6 (-16.4 to -0.7)</td>
<td>0.033</td>
<td>5.3</td>
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<tr>
<td>Diabetes, yes</td>
<td>2.1 (-10.0 to 14.2)</td>
<td>0.729</td>
<td>0.1</td>
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<tr>
<td>Determinant</td>
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<tr>
<td>No medication (Groups 1 and 2)</td>
<td>-0.31 (-0.52 to -0.10)</td>
<td>0.005</td>
<td>16.0</td>
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<td></td>
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<tr>
<td>QTc(_{baseline}), ms</td>
<td></td>
<td></td>
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<tr>
<td>Medication (Groups 3 and 4)</td>
<td>-0.15 (-0.30 to -0.01)</td>
<td>0.046</td>
<td>10.6</td>
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</tbody>
</table>

\(\text{Change HRAF–postAF}\) change in heart rate from AF to \(SR_{postAF}\); other abbreviations as in Table 1.
who are extremely sensitive to QT-prolonging drugs, included in Group 3 or 4. It is possible that such patients, previously taken off these drugs and were therefore not upon the use of class IA/III drugs had been pre-

patients who had experienced excessive QT prolongation and were within the normal range. It is conceivable that with the longest QTc at SRbaseline, although we expected that immediately following termination of AF.

QT syndrome is particularly likely to occur in the period providing further support for our hypothesis that acquired long QT prolongation is substantial in some individ-

uals. Prospective studies are required to establish the time course of repolarization remodelling and reverse remodel-

ling, because this determines the minimal waiting time after termination of AF which must be observed before repolarization-prolonging drugs can be given without the risk of inducing excessive QT prolongation and torsades de pointes. At the same time, patients who develop excessive repolarization remodelling must be identified.

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References


