Delayed adaptation of ventricular repolarization after sudden changes in heart rate due to conversion of atrial fibrillation. A potential risk factor for proarrhythmia?

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Submitted 10 November 2003

Abstract Aims Onset and termination of atrial fibrillation are often associated with abrupt changes in heart rate. Presence and time-course of delayed adaptation of the QT/QTc interval are unknown, but a temporary “mismatch” between rate and the QT interval may enhance the risk of proarrhythmia.

Methods In a prospective two-part study, time-course of adaptation of ventricular repolarization after abrupt changes in heart rate was assessed during termination of Holter ECG-documented atrial fibrillation episodes (Group 1, 32 patients) and subsequently in 20 patients with sick sinus syndrome and cardiac pacing initiating abrupt bi-directional changes in paced heart rate (Group 2).

Results Conversion of atrial fibrillation showed a 32 ± 21 bpm fall in heart rate (P < 0.05). Restoration of the QTc interval afterwards was delayed by ≤1 min in 27%, by 1–2 min in 21%, by 2–5 min in 11% and by >5 min in 41% of the cases. Atrial pacing simulating a 30 bpm fall/increase in atrial rate demonstrated that a subsequent transient rate–QT mismatch is a physiological phenomenon (fall of 100 to 70 bpm: initially 90% of the proper QTc interval, compared with 94% after conversion of atrial fibrillation). The restoration curve of QTc adaptation showed an initially fast and subsequently slower time component, with interindividual variation. Clinical parameters, baseline heart rate or the direction of rate changes were not predictive.
Conclusion Delayed adaptation of ventricular repolarization following atrial fibrillation onset and termination is common, requiring minutes for restoring the QT/QTc steady state. Clinical parameters fail to predict patients with a long-lasting rate–QT mismatch. It may carry a significant arrhythmogenic risk particularly in patients on QT altering medication.

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Introduction Ventricular repolarization is of crucial importance for the electrophysiological integrity and vulnerability of the myocardium. Instantaneous changes in heart rate are accompanied by prompt adaptation of the QT interval (e.g. shortening in the case of shorter cycle lengths during stress and lengthening in longer cycles) in order to restore the proper steady-state level. This adaptive process seems to be delayed in the case of abrupt changes in rate. Experimental findings using action potential duration in isolated cardiac muscle cells, in Langendorff-perfused guinea pig hearts and in intact dog models, as well as limited clinical evidence have indicated that abrupt changes in rate result in a characteristic QT restoration curve [1–7]. This curve is determined by an initially fast, and subsequently slower, time component for establishing the new steady-state QT interval. Suggested cellular mechanisms include the rate-dependent inward fast Na⁺ and slow Ca²⁺ currents, consequently altering both the Na⁺–K⁺ exchange pump and Na⁺–Ca²⁺ exchange activity. Homeostatic mechanisms within myocardial cells would then take a finite time to readjust to a new steady state [8].

In the clinical situation abrupt changes in rate are common during the onset and conversion of atrial fibrillation, but the presence, time-course, determinants and potential hazards of delayed QT interval restoration in this situation are unknown. However, any transient rate–QT interval “mismatch” early after atrial fibrillation (AF) conversion would have major implications, e.g. on inducing and aggravating torsade-like proarrhythmia resulting from other risk factors in this situation (severe bradycardia, ischaemia, QT prolonging drugs etc., [9–10]).

This prospective study aimed (1) to assess the presence, characteristics and time-course of the QT interval immediately following termination of spontaneous AF and (2) to compare the resulting QT restoration curve with the one obtained after bi-directional abrupt rate changes similar to the ones observed during AF onset and termination induced by a standardized atrial pacing protocol.

Methods

The study was initiated as a prospective two-part investigation at the University Hospital of Freiburg. The study protocol was reviewed by the Ethics Committee of the Hospital and all patients included in the pacing arm gave prior written consent.

The first part of the study included 32 consecutive patients in whom episodes of AF, including onset and conversion to sinus rhythm, were documented by 24-h Holter monitoring. Patients were excluded from the study in the case of poor quality of Holter registration, incomplete documentation of any AF episode, bundle branch block or presence of cardiac pacing. The study group consisted of 15 women and 17 men with a mean age of 68 ± 9 years (range: 50–81 years). Inclusion in the study was not affected by the documented underlying heart disease, left ventricular function etc. To assess the effect of QT prolonging drugs on the repolarization behaviour after AF conversion 10 patients with these drugs (31%) were not excluded from the study.

Holter recordings

All Holter recordings were performed using a two-channel bipolar recording device (ECG leads C2, C5), data assessment was based on a semi-automatic analysis using the Hellige “Epicardia”-system. Its reliability was evaluated in previous investigations [11]. Atrial fibrillation was diagnosed by a combination of (1) the absence of P-waves in the two ECG leads and (2) an “irregularly irregular” response of QRS-complexes. In the case of repetitive AF episodes, each episode had to be separated by at least 5 min for QT interval assessment. In order to obtain data on the reproducibility of the QTc behaviour after AF conversion comparison to a subsequent episode was made in these patients. Primary analysis was based on 32 AF episodes, secondary analysis on 24 AF episodes. To diminish the influence of atrial fibrillation waves, QT measurement was made in the lead with less overlay of atrial fibrillation waves. In 30/56 (89%) analyzed episodes this was lead C5.
Beat-to-beat determination of the RR- and QT-interval was performed at given time points before, during and after the AF episode (Fig. 1A). In contrast with heart rate changes assessed during AF onset and termination, detailed QT analysis was restricted to the AF conversion phase due to marked beat-to-beat variations of the QT interval resulting from RR irregularities after AF onset. Heart rate and QT were measured separately for the last 10 beats of the episode of atrial fibrillation. The averages for heart rate and QT for these 10 beats were calculated. To compare the QT at different heart rates the QTc interval was calculated ($QTc = \frac{QT}{\sqrt{RR}}$) according to Bazett [12], the most commonly used rate adaption of the QT. In atrial fibrillation QTc calculation was based on the means of heart rate and QT in the last 10 beats before termination of atrial fibrillation. Steady-state QTc interval was defined by using the QTc interval measured before AF onset (differences are given in % or ms, steady-state level was achieved with a variation of $\pm 3$ ms). Clinical parameters and additional Holter data recorded in all patients included: gender, age, underlying cardiac disease, risk factors, medication, duration of Holter registration, duration of sinus rhythm and AF, number of AF episodes, minimum and maximum heart rate, supraventricular and ventricular premature beats, and pauses.

**Pacing protocol**

In the second part of the study, there were 20 patients with a history of sick sinus syndrome (Morgagni—Adams—Stokes: 11 patients, lone sinus bradycardia: 9 patients) and permanent pacemaker implantation (AAI, DDD). Patients were included only when the Wenckebach point was found to be $>$100 bpm despite a highly depressed sinus rate. Exclusion criteria were II-/III-degree AV-block, left bundle branch block and atrial fibrillation. Fourteen women and six men with a mean age of 71 $\pm$ 18 years (range: 17—93 years) were included in the study.

After a diagnostic work-up (e.g. recording of gender, age, assessment of underlying cardiac disease, medication, standard 12-channel surface-ECG, left ventricular function and proper pacemaker function), a standardized stimulation protocol was used in all patients (Fig. 1B) at rest. The pacing protocol was limited to the atrial site and considered abrupt changes in heart rate of a defined extent similar to those observed during onset and conversion of AF. The following ECG parameters were analyzed at rest, 10 beats before and after any change in pacing rate: RR, QRS, QT, QTc. Steady-state QTc interval was assessed after 5 min of pacing at 70 bpm before all pacing induced sudden changes in heart rate.

**Figure 1**  
A: Time-course of analysis performed on the Holter recordings: Mean RR-, QT- and QTc-intervals were calculated for the given time intervals before and after atrial fibrillation. These values were also calculated for 10 beats directly before the onset, 10 beats before and 10 beats directly after termination of atrial fibrillation. Values are given in the text and the following figures. B: Time-course of the stimulation protocol in the second part of the study: AAI pacemaker stimulation was programmed to the given heart rates and time intervals.
Statistical analysis

Data are expressed as mean ± standard deviation (SD), except for Fig. 3 where the standard error of mean (±SEM) is given. Differences in group means were analyzed using the two-tailed unpaired t-test. Further statistical tests were according to Wilcoxon and the Mann Whitney U-test. Results were considered to be significantly different when confidence limits exceeded 95% (P < 0.05).

Results

Patients

The most common underlying heart disease in the patient group with intermittent AF was coronary heart disease (10/32 pts, 31%); this was followed by valvular heart disease (5/32 pts, 16%). Other diseases documented in this patient group were hypertension (18/32 pts, 56%), history of myocardial infarction (6/32 pts, 19%), diabetes (2/32 pts, 6%), history of stroke (4/32 pts, 13%) and history of pulmonary embolism (1/32 pts, 3%). Medication consisted of digitalis (16/32 pts, 50%), class III antiarrhythmics (10/32 pts, 31%), class I antiarrhythmics (3/32 pts, 9%), calcium channel blockers (10/32 pts, 31%), ACE-inhibitors (8/32 pts, 25%), diuretics (6/32 pts, 19%), beta blockers (1/32 pts, 3%) and nitrates (7/32 pts, 22%).

In the 20 pts with pacemakers in the second part of the study the following diagnoses were found: hypertension (8/20 pts, 40%), coronary artery disease (5/20 pts, 25%), diabetes (3/20 pts, 15%), history of myocardial infarction (2/20 pts, 10%), valvular heart disease (1/20 pts, 5%) and pulmonary hypertension (1/20 pts, 5%). Medication of these patients included diuretics (6/20 pts, 30%), ACE-inhibitors (4/20 pts, 20%), calcium channel blockers (2/20 pts, 10%), beta blockers (2/20 pts, 10%), digitalis (2/10 pts, 10%), class III antiarrhythmics (1/20 pts, 5%) and nitrates (5/20 pts, 25%).

Rate and QT interval during onset and termination of atrial fibrillation

In the 32 patients with intermittent AF, 1–50 episodes were documented during 24-h Holter recording, each episode lasting from 9 s to 11 h (duration: 84 ± 160 min). In case of >1 documented AF episodes (13 patients) a shorter mean duration of the AF episodes was observed (43 ± 114 min vs. 166 ± 205 min, P < 0.01), but no difference in the abrupt change in heart rate associated with conversion from AF to sinus rhythm (36 ± 31 bpm vs. 31 ± 13 bpm, not significant).

By predefined criteria, 56 entirely documented AF episodes were selected for primary and secondary analysis. A typical example is given in Fig. 2. Compared with sinus rhythm, mean rate in AF (calculated for the last 10 beats of the episode) was significantly higher (102 ± 26 bpm vs. 77 ± 17 bpm, P < 0.01). The shortest RR interval within one AF episode was 377 ± 78 ms, with the longest being 1285 ± 424 ms.

Heart rate behaviour before, during and after AF is given in Figs. 3A and 4. During AF onset, an abrupt rate increase (+26 ± 24 bpm, P < 0.01) was present in 45 cases (80%); in 11 cases (20%) no change in mean heart rate could be documented. During conversion to sinus rhythm, heart rate decreased in all but 1 case (mean rate difference: −33 ± 21 bpm, P < 0.01) (Fig. 4). Abrupt changes in heart rate ≥50 bpm at this time were present in 9 cases (16%, AF onset) and 10 cases (18%, AF conversion, Fig. 4), respectively.

After conversion to sinus rhythm, early QTc interval was 27 ms shorter compared with the steady-state level (5.9%, Fig. 3B,C). Steady-state QTc interval was restored <10 sinus beats after 12/56 (21%) analyzed AF episodes. Restoration required <1 min after 15/56 (27%), 1–2 min after 12/56 (21%), and 2–5 min after 6/56 (11%) AF episodes. More than 5 min to re-establish the steady-state QTc interval were required after 23/56 AF episodes (41%). The time-course of the QT and QTc interval after AF conversion is given for all patients in Fig. 3.

Rapid or delayed restoration of the steady-state QTc interval was independent of clinical variables, e.g. age, gender, underlying heart disease or the use of class III antiarrhythmic agents (10/32 patients, 31%). Similarly, neither the number, the duration, nor the heart rate of the preceding AF episode demonstrated any correlation with the presence of a marked delay in QT restoration. The QT restoration curve was not different for AF episodes included in the primary or secondary analysis in 13 patients with multiple episodes. In 4/13 patients in all episodes shortening of the QT compared with the steady-state level was found and in 2/13 patients in all episodes there was prolongation. In the majority of patients (7/13) with more than one episode of AF both shortenings and prolongations were documented.

Comparison of patients with and without QT prolonging drugs

Ten patients on QT prolonging drugs were compared with the other patients in our study. Mean
duration of atrial fibrillation in this subgroup was longer compared with the other patients (163 ± 238 min vs. 73 ± 142 min, P < 0.05). Heart rate during atrial fibrillation and after conversion was slightly lower than in other patients (atrial fibrillation: 95 ± 19 bpm vs. 102 ± 26 bpm, not significant; sinus rhythm: 56 ± 18 bpm vs. 71 ± 22 bpm, not significant). The fall in heart rate after conversion of atrial fibrillation seems greater, but is statistically not significant (39 ± 18 bpm vs. 31 ± 20 bpm). The QT before and after atrial fibrillation in patients on QT prolonging drugs did not differ (1 ± 17 ms), but there was a significant change in the QTc (−36 ± 72 ms). This constellation could be caused by the pronounced fall in heart rate after cardioversion in this group. In comparison with other patients the change in the QT and QTc intervals was not statistically different (QT: 1 ± 17 ms vs. 14 ± 32 ms; QTc: −36 ± 72 ms vs. −24 ± 34 ms).

**QT interval during abrupt changes in rate simulated by atrial pacing**

Based on the documented changes in heart rate during the onset and termination of AF (mean: +26 and −32 bpm), abrupt bi-directional changes in
atrial pacing rate of 30 bpm were introduced within a physiological range of 40—100 bpm. A printout of a stimulated episode is given in Fig. 5. When the atrial rate was abruptly increased (40 to 70 bpm and 70 to 100 bpm), shortening of the QT- and QTc-interval started within the first 10 beats during 37/40 pacing episodes (93%), resulting in a delayed change in the QTc interval of 30 ± 21 ms within the first 5 min. Similarly, an abrupt decrease in rate (70 to 40 bpm, 100 to 70 bpm) initiated an early lengthening of the QT and QTc interval in 36/40 cases (90%) with further lengthening of + 30 ± 28 ms within the first 5 min. The presence of delayed QT interval adaptation after abrupt rate changes in the majority of patients, the high reproducibility of this finding and its independence from the direction of change and the preceding heart rate is shown in Fig. 6. Overall, the extent of the transient rate—QTc mismatch ranged from 10.4 to 12.9% in the case of a preceding 30 bpm rate decrease and from 6.4 to 9.1% in the case of a preceding 30 bpm rate increase (Fig. 7).

Comparison of the delay in QT interval adaptation after AF conversion vs. during atrial pacing rate decrease

Delayed adaptation of the QTc interval after abrupt changes in heart rate is similar whether it results from AF conversion or a regular atrial rhythm. An initially fast and subsequently slow restoration time component was found in both cases. Directly after conversion of atrial fibrillation the QTc differed 6% from its steady-state level followed by a QTc adaptation of 4% in the first 2 min and a further adaptation of 0.5% until the 5th minute. After a comparable abrupt decrease in atrial pacing rate (100 to 70 bpm), the initial difference of the QTc to the steady-state QTc interval was higher when compared with the early post-AF phase (difference from steady-state level: 10%), 5 min after the abrupt rate change QTc interval abnormality was similar in the two groups. In case of an abrupt 30 bpm increase in paced heart rate (40 to 70 bpm) initial QTc was calculated to be 105.2% of the steady-state QTc duration. After 5 min a small overshoot in normalization of the QTc was found with a QTc shortening of 1% compared with steady-state level.

Discussion

This study was intended to improve our insight into the physiological response of ventricular...
Repolarization following abrupt changes in heart rate due to spontaneous onset and termination of atrial fibrillation.

Based on experimental studies, one would expect that an abrupt increase or decrease in heart rate within the physiological range will result in delayed restoration of the corresponding steady-state QT interval characterized by an initial fast and subsequently a slow time component [1–5,13]. The present study firstly investigated the presence, time-course and reproducibility of delayed adaptation of the QT interval after abrupt changes in rate associated with the onset and, more importantly, the termination of atrial fibrillation.

Conversion from atrial fibrillation to sinus rhythm is commonly associated with a drop in heart rate (30 bpm in this study). Immediately after conversion, the QTc interval is set to 94% of the steady-state QTc interval, indicating a transient rate–QT mismatch which, for restoration, requires >10 sinus beats during 79%, and even >2 min during 52% of the analyzed episodes. There is evidence in almost all patients for a similar, initially fast and subsequently slower restoration component. Recently, a similar time curve could be found for the QT and QTc dispersion after cardioversion [20]. Interindividual variations in the duration required for QTc restoration seem to be marked, but are poorly predicted by parameters describing the AF episode, such as duration, mean heart rate, time of onset etc., or clinical variables such as age, gender, underlying cardiac disease, left ventricular function, history of myocardial infarction or medication. In contrast, intraindividual variations were of minor importance.

![Figure 5](https://academic.oup.com/europace/article-abstract/7/2/113/557191/211357191)

**Figure 5** Printout of the ECG during the stimulation protocol. Five minutes of stimulation at 70 bpm are followed by 2 min at 100 bpm and then again at 70 bpm. QT is marked in the ECG, QTc is given in the bottom line.

![Figure 6](https://academic.oup.com/europace/article-abstract/7/2/113/557191/211357192)

**Figure 6** QTc intervals after abrupt changes in heart rate according to the stimulation protocol for individual patients. The stimulation protocol is as displayed in Fig. 1B. Directions of adaption of the QTc interval are marked with arrows.

![Figure 7](https://academic.oup.com/europace/article-abstract/7/2/113/557191/211357193)

**Figure 7** Early and steady-state QT/QTc interval (±SD) after abrupt rate change in the entire patient group (differences are given as percentage; the stimulation protocol was as shown in Fig. 1B).
How does the observed delay in restoring a proper QTc interval after AF conversion compare with the non-AF state? Moreover, does this phenomenon depend on the regularity of the preceding rhythm and/or the direction of rate change? These questions were addressed in the second part of the study. Abrupt changes in atrial pacing rate also resulted in a QTc interval which was initially 6–13% different from the steady-state QTc interval and showed a delayed restoration curve with an initially fast and subsequently slow time component. Restoration of the proper QTc interval starts immediately after setting of the new rate in almost all cases (93% after an abrupt decrease in rate, 90% after an abrupt increase in rate). A transient mismatch between heart rate and the corresponding QTc interval appears to be a physiological phenomenon and common after abrupt changes in heart rate. As a consequence, an abrupt rate increase (e.g. during the onset of ventricular tachycardia), will be temporarily associated with a ”too-long” QT interval for the newly established heart rate; in case of an abrupt rate decrease (e.g. conversion of AF) the expected QT interval will temporarily be too short. The consequences of this ’physiological’ phenomenon are unknown, but certain interest will result from its potential impact in increasing myocardial vulnerability and thus inducing and/or aggravating ventricular tachyarrhythmias. This is emphasized by the recently described new clinical entity, the short-QT syndrome, associated with a high risk of sudden cardiac death [22,23]. An inappropriately long QT interval during ventricular tachycardia onset may enhance electrophysiological inhomogeneities and facilitate early degeneration into ventricular fibrillation [14]. The importance of preservation of a physiological QT interval became apparent especially in the situation of cardioversion, when dofetilide, a QT prolonging antiarrhythmic drug, was tested and dosage had to be QT adjusted to minimize the proarrhythmic risk [21]. In the case of an inappropriately short QT interval after AF conversion, the potential protective effect of a longer QT interval at lower heart rates is transiently abolished. It seems possible that re-entrant and polymorphic tachyarrhythmias could be facilitated in this situation, an effect which may become of crucial importance when the additional influence of sotalol is considered [9].

Limitations of the study

The study included 13 patients with > 1 AF episode in order to assess a broad variety of shorter and longer AF episodes and to assess data on the reproducibility of the phenomenon of delayed QTc adaptation. Furthermore, a subgroup of 10 patients with QT prolonging drugs (class III antiarrhythmic drugs) was included to assess the influence of this medication. Data on the rate—QT mismatch in the two subgroups were not found to differ from the remaining patients and therefore did not affect the physiological phenomenon of delayed QT restoration. Data were not analyzed for patient activity at the time of the occurrence and the conversion of atrial fibrillation.

Conclusions

Delayed adaptation of ventricular repolarization after conversion of AF is a physiological phenomenon with an initially fast and subsequently slow time component. The phenomenon is similar to that which can be observed during abrupt changes in paced atrial rate, is widely independent of the direction of change and poorly predicted by clinical information or parameters derived from the preceding AF episode.

The amount of the QTc shortening directly after a pacing induced sudden decrease in heart rate seems higher compared with conversion of atrial fibrillation (10% vs. 6%). This could be caused by the regularity of pacing in contrast with the arrhythmic ventricular rhythm during atrial fibrillation.

The potential arrhythmogenic impact of a transient mismatch between rate and the corresponding QT interval induced by abrupt changes in heart rate remains uncertain. However, abrupt changes in rate are very common, e.g. during the onset and termination of atrial or ventricular tachyarrhythmias, in case of ”short-long-sequences” [13,15,16], the ”R-on-T-phenomenon” [16,17], or post-pause atrial and/or ventricular pacing [18,19], situations which are known to be associated with a significantly increased risk of initiating life-threatening ventricular tachyarrhythmias, particularly in patients with severely diseased hearts. The transient mismatch between heart rate and the corresponding QT interval, therefore, may provide a link with the mechanisms underlying proarrhythmic events in these situations.

References

Changes in heart rate due to conversion of AF


