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QT interval measurement and correction in patients with atrial flutter: a pilot study ☆

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Abstract

Background and Purpose: Measurement of QT intervals during atrial flutter (AFL) is relevant to monitor the safety of drug delivery. Our aim is to compare QT and QTc intervals in AFL patients before and after catheter ablation in order to validate QT measurement during AFL.

Methods: 25 patients suffering from AFL underwent catheter ablation; 9 were in sinus rhythm and 16 were in AFL at the time of the procedure. Holter ECGs were continuously recorded before, during and after the procedure. In AFL signals, flutter waves were subtracted using a previously-validated deconvolution-based method. Fridericia's QTc was computed before and after ablation after hysteresis reduction.

Results: Comparing QTc values obtained before and after ablation showed that (1) the intervention did not significantly affect QTc, and (2) the QTc during AFL was concordant with the QTc value in sinus rhythm.

Conclusion: QTc can be reliably measured in patients with AFL using flutter wave subtraction and hysteresis reduction.

Keywords: QT intervals; Atrial flutter; Catheter ablation

Introduction

Reliable and consistent QT interval measurement is critical for ensuring the safety of drug administration, which includes, but is not limited to, antiarrhythmic drugs [1]. Patients with atrial flutter (AFL) or atrial fibrillation may receive pharmacological treatment [2–5], thus creating a need for accurate monitoring of the QT interval during these arrhythmias [6,7]. In the ECG of a patient in AFL, T wave morphology is altered by the superimposed continuous electrical activity of the atria (F waves), which hinders accurate detection of fiducial points (onset of the Q wave and offset of the T wave) as well as proper identification of isoelectric points.

Our recently developed F wave subtraction algorithm enables the extraction of T waves during AFL and the subsequent reconstruction of RR and QT time series [8,9]. Validation of these ECG processing tools necessitates comparing QT and RR measurements in patients during AFL and after sinus rhythm is restored, for instance by catheter ablation. This presumes that the intrinsic value of the QT interval, i.e. ventricular depolarization and repolarization, remains unchanged after the ablation procedure. Although no data are available in the case of AFL, some evidences suggest that radiofrequency ablation of the atrioventricular junction might transiently affect QT value and dispersion [10–12]. Studies by Malik et al. have demonstrated that, as a general rule, carefully measured and validated QT intervals combined with an individualized QT correction formula tend to show far less variability than previously speculated [13,14].

In this pilot study, two groups of AFL patients underwent catheter ablation while being continuously monitored using a Holter ECG recording system. Patients in the first group were in sinus rhythm the day of the procedure while those in the second group were in AFL. The objectives of this study are: (1) to investigate whether

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the catheter ablation procedure alone affects the QT interval in the first group; (2) to compare QT intervals before and after ablation in the second group to evaluate the reliability of QT measurement during AFL.

Material and methods

Clinical protocol

Twenty-five patients suffering from AFL and scheduled to undergo catheter ablation were selected. Among them, 9 patients were in sinus rhythm at the beginning of the procedure. Catheter ablation was performed in these patients to prevent AFL re-initiation. These patients form the control group (7 men and 2 women; age 55 ± 15 years). The flutter group is composed of the other 16 patients initially in AFL (15 men and 1 woman; age 68 ± 14 years). Catheter ablation restored sinus rhythm in all of them. All patients in both groups were taking one or several drugs (15/25 class II beta-blockers, 3/25 class III antiarrhythmic drugs, 5/25 calcium channel blockers, 2/25 digitalis). Drug intake was not discontinued before the procedure. Possible drug-induced modulation of the QT interval was assumed to remain the same before and after ablation within a time frame of a few hours.

Three-lead ECGs were continuously recorded before, during and after each intervention (signal duration: 6 to 25 h; at least one hour before and one hour after ablation) using a standard Holter monitoring system (Burdick, Model 6632) and a sampling frequency of 500 Hz. Electrode configuration was designed to generate 3 pseudo-orthogonal leads X, Y and Z (X = V5 vs V6R; Y = S vs LL; Z = E vs V9), as in Jacquemet et al. [9]. Sternal electrodes (E and S) come from the EASI lead system [15]; LL is the left leg electrode; V6R and V9 are extended precordial electrodes. The time segment during the ablation procedure was excluded from the subsequent analyses.

ECG preprocessing and automatic QT measurement

ECG data were transferred to a computer for analysis. Signals were band-pass filtered (0.01 to 100 Hz). In ECG segments with AFL, atrial waves were subtracted using a dedicated spectral deconvolution-based method described and validated previously [9]. This algorithm processes the signals by segments of one minute during which we assumed stable flutter waveforms with slowly varying atrial dominant frequency. The method exploits the frequency (spectral) content of flutter waves extracted within TQ intervals (presumably containing only atrial activity) to interpolate flutter waves in nearby QT intervals. The process of computing the spectrum a signal with "holes" (the flutter wave is *a priori* not known within the QT intervals) is a deconvolution problem.

R waves, the onset of Q waves and the offset of T waves were identified using a previously-validated fiducial point detector [16] based on the vector magnitude signal (root mean square of the 3 leads) after flutter wave suppression (unless stated otherwise). As described in Jacquemet et al. [8], the marker R was defined as the location of the center of gravity of the QRS complex, the marker Q as the position at 2% of the maximum of the R wave and the marker T as the intersection between the baseline and the tangent at the steepest negative slope of the low pass-filtered T wave [17]. RR and QT time series were extracted and semi-automatically validated using a combination of ECG analysis software VCGMI [16] and Burdick Vision Premier Holter (Cardiac Science, Bothell, WA).

Analysis of matched segments of RR intervals

In order to compare QT intervals before and after ablation in the absence of heart rate dependence effects, pairs of segments (one sequence of beats before and one after ablation) with stable and matching RR intervals were identified. Criteria for RR-matched segment selection were: duration of segment > 1 min; range of RR fluctuations (min to max) within a segment < 100 ms; difference in the median of the RR < 10 ms between the two segments. Memory and hysteresis effects for the QT interval typically lasted for about 2–3 min [18]. Obtained segment durations were a trade-off between QT stability and the existence of long segments with stable RR intervals. During sinus rhythm, RR fluctuations corresponding to roughly ±5% of the median RR interval were common, so this constraint was relatively restrictive. During AFL, segments with very stable RR intervals were easily found. Multiple pairs of RR-matched segments were identified in some patients. The limit of 10 ms difference in median RR between the two segments corresponded to about 1% difference in RR, which, when using the Fridericia's formula, would correct the QT interval by about 0.3% (<2 ms for a QT of 400 ms).

QT intervals of the last 5 beats of each segment (presumably after steady-state is reached) were measured both manually by a cardiologist on raw ECG signals and using the automatic fiducial point detector after flutter wave suppression. The average value of the QT interval over these last 5 beats was used for statistical analysis.

Heart rate correction of the QT interval

The difficulty to find pairs of RR-matched segments in the flutter group suggested relieving the constraint of matching RR intervals and applying heart rate correction techniques to the QT and RR time series in order to compute and compare the heart rate-corrected QT interval (QTc) before and after ablation.

Simple QT correction formulae assuming a unique static QT–RR relationship for all subjects have been proposed [19–22]. These formulae are usually applied to short ECG recordings (10 s). In this study, Fridericia's [20] formula was used in combination with a universal hysteresis correction model. In this framework, the QT correction formula was not applied to the RR interval but instead to an effective RR interval (RR_{eff}) computed using the following recursive equation (autoregressive filter):

$$RR_{eff}(n) = c\,RR(n) + (1-c)RR_{eff}(n-1),$$

where n is the beat number, c = 0.02526 and $RR_{eff}(1) = RR(1)$. Hysteresis reduction is particularly critical during

AFL because of abrupt variations in RR intervals resulting from a change in atrioventricular block ratio [8].

The QT–RR relationship has been shown to be nonlinear, subject-specific [23] and not instantaneous [18,24–26]. Based on previous models [23,24,27], we have developed and validated a subject-specific, nonlinear, transfer function-based correction method to compute the QTc from Holter ECG recordings [8]. This model includes 5 parameters: 3 describing the static QT–RR relationship and 2 representing the memory/hysteresis effects that intervene in the calculation of effective RR values. A parameters identification procedure was designed to minimize QTc fluctuations and enforce zero correlation between QTc and effective RR. This individualized QTc time series (QTcI) was used in the second part of the analysis.

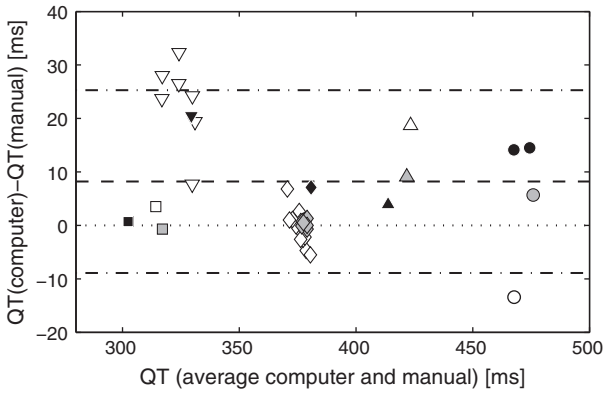

Fig. 2. Bland–Altman plot of manual versus automatic QT interval measurement in raw ECG signals during atrial flutter (white symbols), in ECG signals after flutter wave suppression (gray symbols) and in ECG signals during sinus rhythm (black symbols). Each symbol shape corresponds to a different patient. The mean bias and mean ± 2 SD (in the absence of flutter wave cancellation) are displayed as dashed lines.

Results

QT measurements in RR-matched segments

Pairs of RR-matched segments were identified in 6 patients (38%) in the flutter group and in 8 patients (89%) in the control group. Between 1 and 13 pairs (2-3 on average) were found in each of these patients, typically several segments before ablation corresponding to the same segment after ablation. In this case, for the subsequent statistical analysis, QT values were averaged over the pairs with the same RR interval separately in each patient.

In the other patients, the distributions of RR intervals before and after ablation did not sufficiently overlap, or a large number of premature ventricular contractions prevented the selection of a one-minute segment with stable RR intervals. An example of RR-matched segments is displayed in Fig. 1. As ascertained visually, the QT intervals were also comparable during AFL (trace A/B) and during sinus rhythm (trace C). This figure also illustrates the usefulness of flutter wave suppression for accurately measuring the QT intervals.

Comparison between manual and automatic QT measurements during the last five beats of segments with stable RR intervals is shown in Fig. 2. The correlation coefficient between manual and automatic QT measurements in raw signals was 0.98 and the discrepancy (Bland–Altman statistics, computer − manual) was 9.8 ± 9.0 ms. This difference was sometimes due to interference between the T waves and the flutter waves. When manual and automatic measurements were performed on processed ECG signals after flutter wave suppression, this difference was reduced to −1.9 ± 3.1 ms (gray symbols on Fig. 2). These discrepancies are similar to those reported by previous studies during sinus rhythm [28–30] and confirm that flutter wave suppression improves QT measurement consistency and does not introduce a bias, as demonstrated previously [9]. Subsequent analyses in this paper will only consider automatic QT measurements after flutter wave cancellation.

In the pairs of RR-matched segments, QT intervals before and after ablation were compared (each pair is shown in Fig. 3A). The difference QT(after) − QT(before) was −2.2 ± 8.3 ms ($p = 0.54$) with a correlation coefficient of 0.99 in the flutter group and 3.3 ± 5.3 ms ($p = 0.13$) in the control group, also with a correlation coefficient of 0.99. These differences are of the order of the sampling interval of the ECG (2 ms); they are not statistically significant from

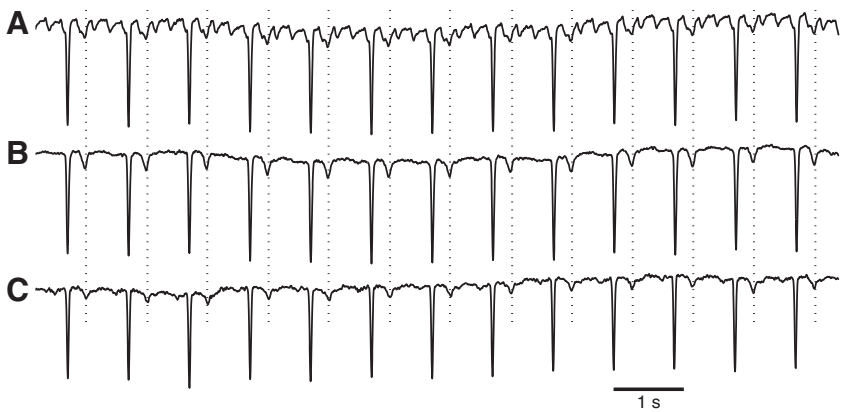

Fig. 1. Example of RR-matched segments. (A) ECG segment (lead Y) during atrial flutter; (B) the same segment after flutter wave suppression; (C) RR-matched segments during sinus rhythm after catheter ablation. Vertical dotted lines show how T waves are aligned in traces A, B and C.

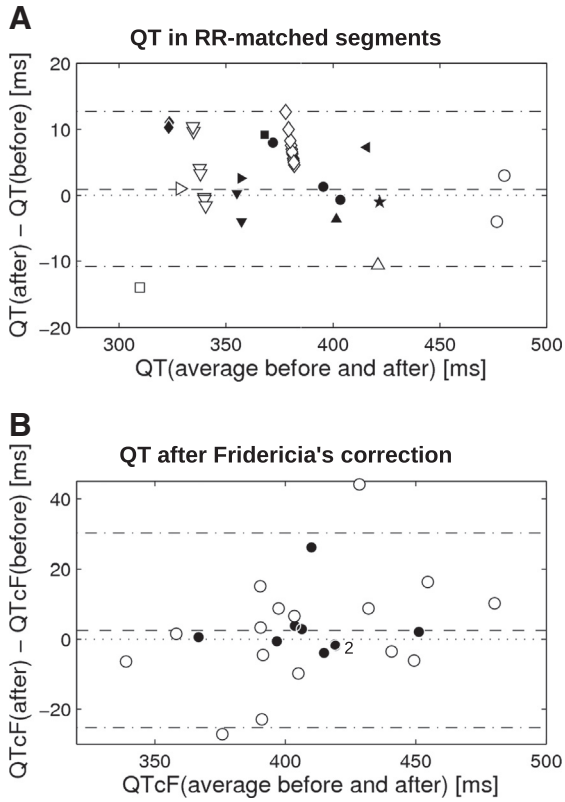

Fig. 3. (A) QT intervals before versus after ablation for each pair of RR-matched segments in the flutter group (white symbols) and in the control group (black symbols). Each symbol shape corresponds to a different patient. Multiple identical symbols represent different pairs of RR-matched segments. (B) QTc interval by Fridericia's formula (QTcF) before and after ablation for the flutter group (white circles) and for the control group (black circles). The annotation "2" means that the data point nearby masks a second superimposed data point.

zero in part due to small group sizes (n = 6 and n = 8 patients).

QT–RR relation before and after ablation

The QT–RR relation was modeled separately in the period before ablation and in the period after ablation. A patient-specific linear QT–RR model was used in combination with universal hysteresis reduction. The resulting slopes of the QT–RR relation before and after ablation were studied. Patients with standard deviation of RR intervals smaller than 25 ms (2 in the control group, 3 in the flutter group) were excluded from the slope analysis.

Table 1 shows the population statistics of mean QT and RR intervals for the two groups of patients. The QTc was computed from the effective RR intervals using Fridericia's formula. The median of the resulting QTc time series was documented. P-values (before vs after ablation) were determined using a paired T-test. In the sinus rhythm group, heart rates were slightly faster, but not significantly, after ablation, and the QT interval shortened accordingly. Fridericia's QTc values (QTcF) before and after ablation were very close: no systematic intra-patient difference was found. The suitability of Fridericia's correction was *a posteriori* justified by the relatively limited intra-patient difference in heart rate between AFL and sinus rhythm and by observed heart rates in the range 60 to 90 bpm. The slopes of the patient specific QT–RR relation were also similar. In the flutter group, heart rates tended to be slower after ablation (it was however faster in 6/16 patients). The differences were not large since almost all patients took rate control drugs. Along with increasing mean RR interval, a statistically significant decrease in QT–RR slope was observed in this small group of patients, in agreement with the known saturation of QT duration at long RR. The relative uncertainty on the slope [8] was 0.034 ± 0.037. These narrow confidence intervals reflect the large number of beats, not necessarily the goodness of the linear fit. The population averaged QTcF was essentially the same before and after ablation. Fig. 3B shows the QTcF changes observed in each patient following ablation. The correlation coefficient between the QTcF before and after ablation was 0.92; 19 patients out of 25 had a change in median QTcF smaller than 10 ms. The Bland–Altman statistics (QTcF after − before) was 3.1 ± 9.0 in the control group and 2.2 ± 16.6 in the flutter group.

QT–RR relations before and after ablation were plotted to determine whether and how these curves overlapped. Fig. 4 shows examples of such curves for the control group. QT–RR relations were typically superimposed (Figs. 4A–C), although regression lines differed when extrapolated far from the observed range of RR intervals. In cases where heart rate decreased (Fig. 4D) or increased (Fig. 4E) after ablation, the two curves prolonged each other over a broader range of RR intervals. Exceptionally, the QT–RR curve seemed shifted after ablation (Fig. 4F), suggesting a slight variation in the QTc interval.

During atrial flutter, both the mean and the range of effective RR intervals varied considerably between patients. Fig. 5 displays examples of QT–RR curves in atrial flutter and in sinus rhythm. In Figs. 5A–B, the two curves prolonged each other and overlapped. When the atrio-ventricular block ratio remained stable during atrial flutter (4-to-1 in Fig. 5C), the range of RR interval variations became narrower. Sometimes the available range of RR intervals was hardly sufficient to accurately determine a patient-specific QT–RR slope (Fig. 5D–E). In a few cases, the overlap was sufficient to identify a small change in QTc

Table 1
Population statistics of mean RR interval, mean QT interval, median QTc interval by Fridericia's formula (QTcF), and the slope of the QT/RR relation (patients with standard deviation of RR intervals < 25 ms were excluded). SR = sinus rhythm; AFL = atrial flutter.

	Before ablation	After ablation	p-value
SR–ablation–SR	(control group)		n = 9
RR	916 ± 252 ms	851 ± 204 ms	0.15
QT	393 ± 29 ms	385 ± 39 ms	0.19
QTcF	408 ± 23 ms	411 ± 23 ms	0.34
QT/RR slope	0.16 ± 0.05	0.12 ± 0.06	0.15
AFL–ablation–SR	(flutter group)		n = 16
RR	830 ± 204 ms	933 ± 153 ms	0.08
QT	384 ± 57 ms	400 ± 52 ms	0.14
QTcF	407 ± 35 ms	409 ± 41 ms	0.61
QT/RR slope	0.15 ± 0.12	0.11 ± 0.06	0.03

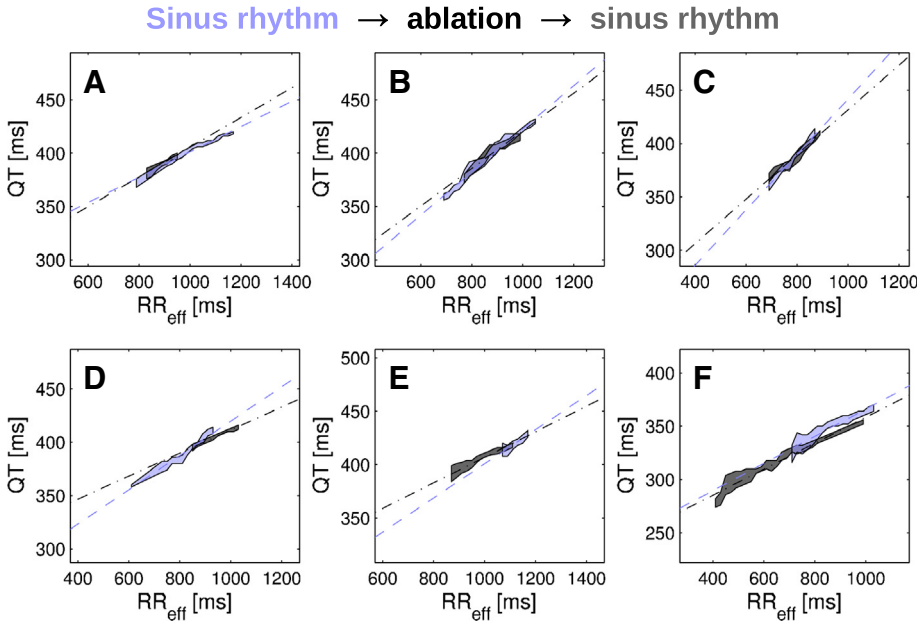

Fig. 4. QT–RR relation in 6 patients (A to F respectively) in sinus rhythm both before and after ablation (control group). Colored regions (blue: before ablation; grey: after ablation) correspond to the interval between the first and the third quartile of the QT distribution (computed with bins of 20 ms). Regression lines are shown as dashed lines (before ablation) and dash-dotted lines (after ablation). Duration of analyzed signal ranged from 1 to 4.2 h (3190 to 18,356 beats) before ablation and 1.2 to 3.8 h (4470 to 17,631 beats) after ablation. Color illustration online.

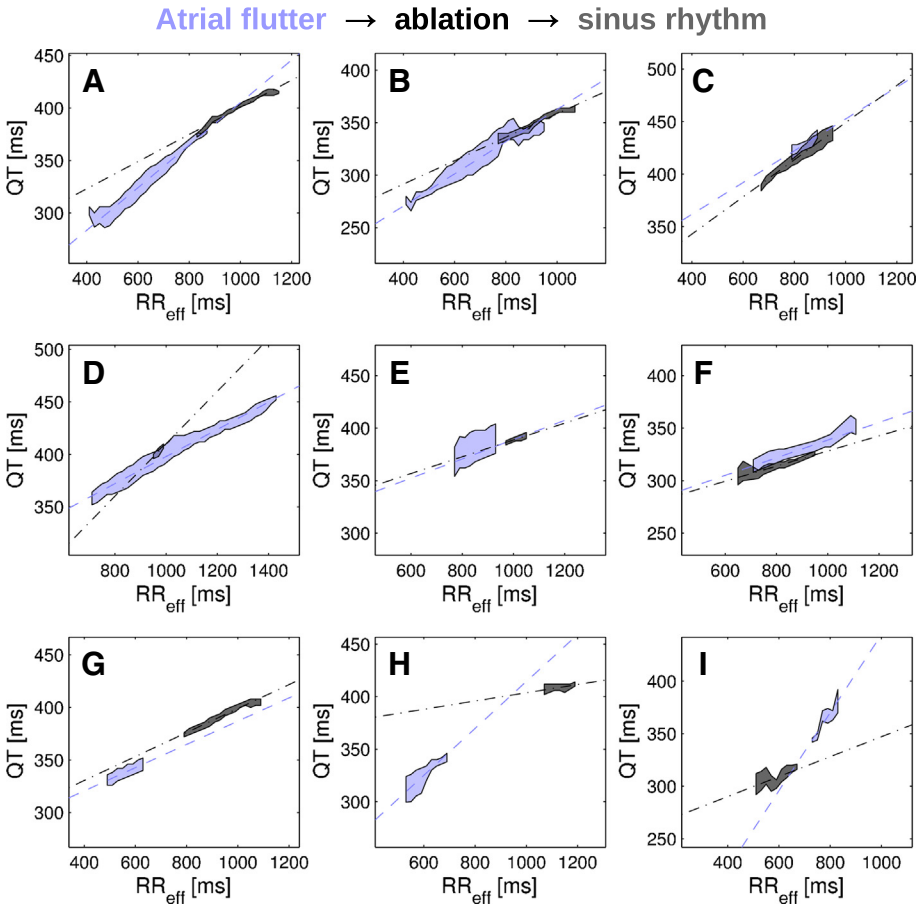

Fig. 5. QT–RR relation in 9 patients in before ablation (during atrial flutter) and after ablation (in sinus rhythm). Colored regions (blue: before ablation; grey: after ablation) correspond to the interval between the first and the third quartile of the QT distribution (computed with bins of 20 ms). Regression lines are shown as dashed lines (before ablation) and dash-dotted lines (after ablation). Duration of analyzed signal ranged from 1.2 to 21.2 h (5044 to 103,944 beats) before ablation and 1.2 to 17.8 h (4373 to 107,228 beats) after ablation. Color illustration online.

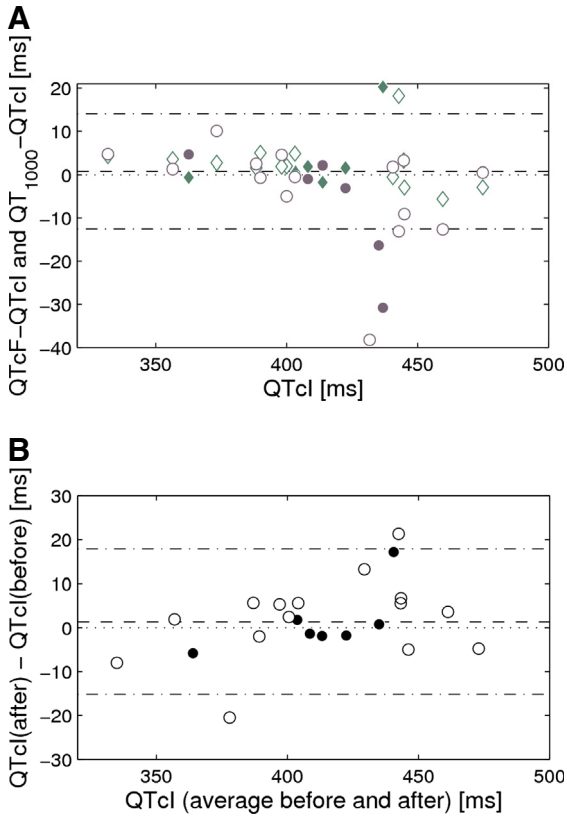

Fig. 6. (A) Relation between the individualized QTc based on a fitted nonlinear QT–RR relationship (QTcI; horizontal axis), the Fridericia QTc (QTcF; circles) and the median QT occurring when the RR interval is around 1000 ms (QT_{1000}; diamonds). The flutter group is shown as open symbols and the control group as filled symbols. (B) QTc before and after ablation computed using the same individualized correction formula (QTcI). The flutter group is shown as open symbols and the control group as filled symbols.

(Fig. 5F). Often, there was no overlap (Fig. 5G–I). It was however possible to construct a single QT–RR curve connecting the two clouds of points. In the patient of Fig. 5I, conversion to sinus rhythm revealed a large number of premature atrial contractions that actually increased the average heart rate.

Comparison of QTc values

The overlap between the QT–RR relation curves before and after ablation provides a rationale to fit a single QT–RR curve to the pooled datasets. In order to balance the relative weights given to the data points before and after ablation, weighted nonlinear regression was used, the weights being assigned in relation to the RR histogram [8]. A patient-specific QT correction model was derived from the resulting QT–RR relation. This defined the individualized QTc time series (QTcI), from which the median and quartiles were computed. Whenever possible, QT intervals following RR intervals in the range from 990 ms to 1010 ms were extracted. The median of these QT intervals was denoted by QT_{1000}. Finally, the QTcF was also considered for comparison.

Fig. 6A illustrates the correlation between the different corrected QT intervals over the whole signal. The QTcF was well correlated with the QTcI ($r = 0.95$; Bland–Altman QTcF − QTcI = −4.3 ± 11 ms). Large differences (> 10 ms) were however observed when the range covered by the RR intervals was systematically far from RR = 1000 ms. This observation also held for sinus rhythm patients (black symbols on Fig. 6B). When available, the QT_{1000} was consistent with the QTcI ($r = 0.95$; Bland–Altman: QT_{1000} − QTcI = −2.9 ± 6.2 ms).

Because the QTcI was computed for every beat, its values before and after ablation could be compared, and were found to be similar ($r = 0.97$; Bland–Altman: QTcI(after) − QTcI(before) = 1.8 ± 8.8 ms), as shown in Fig. 6B. Differences in QTcI occurred when the two QT–RR data set (before and after ablation) did not overlap perfectly, as in Figs. 4F and 5F. Fig. 6 should therefore be interpreted as a measure of consistency of the QT–RR relation over time.

Discussion

In this study, the validity of measuring QT intervals during AFL was evaluated by comparing QT measurements during AFL and after sinus rhythm restoration. Since it was *a priori* not clear whether the ablation procedure itself could lead to changes in QT interval duration, the same measurements were performed in a control group already in sinus rhythm before ablation. The results of the control group (Table 1) corroborated the hypothesis that QT intervals are not significantly affected by catheter ablation. QT intervals during sinus rhythm after ablation were therefore used as reference to validate QT measurement in the AFL group.

Comparison of RR-matched segments before and after ablation showed that the QT intervals measured during AFL were consistent with the reference QT intervals obtained during sinus rhythm (Fig. 3A). This suggests that the flutter wave suppression algorithm suitably extracted the T waves (Fig. 1).

These results were confirmed by comparison of Fridericia's QTc before and after ablation (Fig. 3B and Table 1). Bazett's correction was not used because of its well documented overcorrection for faster heart rates [31]. Better correspondence could be achieved using individualized QT correction [23], but its application to AFL patients is limited. The range of RR intervals (after hysteresis reduction) observed in AFL patients is often too narrow (Fig. 5) and sometimes too far from 60 bpm to allow reliable extrapolation of the QT–RR relation. The recording conditions (supine position in an electrophysiology lab) and the use of beta-blocker in most patients affected heart rate variability. It was nevertheless possible to combine QT–RR data in the entire recording to create a single individualized QT–RR relationship for each patient. The two point clouds of QT–RR values before and after ablation were consistent with each other whenever they overlapped, as illustrated in Fig. 5 and as reflected in the comparison of individualized QTc (Fig. 6B). Pooling the two point clouds for QT–RR curve fitting was motivated by the fact that QT was not found to be affected by the ablation procedure. The QTcI values were

very close to QTcF values (Fig. 6A), suggesting that Fridericia's formula may be used for computing the QTc during AFL. Note that in our small group of AFL patients, heart rate in AFL ranged from 50 to 110 bpm (at rest) and became only slight faster (not statistically significant) after sinus rhythm restoration. If they were all the time in 2:1 atrioventricular block, Fridericia's correction would be influenced by the faster heart rate and the comparison before vs after ablation might be hindered by the larger difference in heart rate between AFL and sinus rhythm. Also, the accuracy of Fridericia's correction would be limited when testing the effect of a drug that significantly alters ventricular rate.

In all AFL cases, hysteresis reduction (i.e., the use of effective RR intervals) was a critical step before undertaking QT–RR analysis because of frequent high-amplitude fluctuations in RR intervals (for instance, between 4:1 and 2:1 atrioventricular block), as demonstrated previously [8]. If a patient was continuously in stable rhythm (e.g. always 2:1 block), hysteresis reduction would be less essential. Although the use of patient-specific hysteresis reduction improves QT–RR modeling [24], universal hysteresis reduction with fixed parameters (e.g. autoregressive filter) provides a reasonable alternative, as illustrated in Figs. 4 and 5, when optimization of patient-specific parameters is difficult.

Circadian variation is a possible confounding factor in QTc measurement [14]. In this study, all ablations were performed in the morning and patients did not eat before the recording, which minimized inter-patient variability as well as differences before-vs-after ablation. Drugs may have affected ventricular repolarization, and consequently the QT interval. Ventricular remodeling following a long-lasting episode of AFL or abnormal serum electrolyte levels may also have this effect. Note however that the same drug effect was present before and after ablation since we obtained an immediate comparison between two clinical states and we did not compare these values to population-based normal values. As a result, these effects are not confounding factors and we expect that our ECG signal processing technique for T wave extraction and QT measurement during AFL would be as effective in the absence of drug intake. It has been reported that QT–RR dynamics are different in males and females [32]. In this study with a small group of patients, most were male, and females were not outliers in the point clouds representing the QT interval before vs after ablation, so that male and female data were pooled for statistical analyses.

In summary, this study proposes that QT intervals can be accurately measured in patients with AFL using flutter wave subtraction and hysteresis reduction, provided that sufficiently long recordings (at least 5 min.) are available.

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