Clin. Cardiol. 29, 534–539 (2006)

Control of Rapid Heart Rate Changes for Electrocardiographic Analysis: Implications for Thorough QT Studies

Fabrice Extramiana, M.D., Ph.D., Pierre Maison-Blanche, M.D., Abdeddayem Haggui, M.D., Fabio Badilini, Ph.D.,* Philippe Beaufils, M.D., Antoine Leenhardt, M.D

Lariboisière University Hospital, Paris, France; *AMPS LLC New York, New York, USA

Summary

Background: Following an abrupt change in heart rate (HR), QT adaptation is achieved within a delayed time frame.

Hypothesis: The exclusion of electrocardiograms (ECGs) showing rapid HR changes influences the level of a drug-induced QT prolongation.

Methods: Continuous 12-lead ECG-Holter monitoring was performed in 31 healthy subjects. Using the "bin" method, we evaluated moxifloxacin effects on (1) QT interval duration at different RR intervals and (2) on the rate dependence of QT interval. These endpoints were calculated separately for five types of ECG analysis: classification of cardiac complexes based on (a) the single preceding RR interval (RR-1) and (b) RR filters excluding rapid HR changes according to the formula RR-1 = $RR_{[time-window]} \pm$ threshold, where the time-window could be 30 or 60 s (R30 and R60) and the threshold 15 or 30 ms (th15 or th30).

Results: Moxifloxacin-induced QT prolongation was consistently higher using the stable models when compared with the RR-1 model. Moxifloxacin-induced QT prolongation at RR = 1000 ms was 8.2 ± 11.2 vs. 10.9 ± 10.4 ms using the RR-1 and R60th15 stable models, respectively ($p < 0.05$). Moxifloxacin-induced QT prolongation was more pronounced at slow than at fast HR. This so-called "reverse rate-dependent" effect was more pronounced when assessed using stable HR models (0.023 IC95% [0.019;0.027] vs. 0.015 IC95% [0.012;0.017] using the RR-1 model).

Conclusion: The exclusion of ECGs with rapid HR changes influences the magnitude of drug-induced QT changes. The hysteresis phenomenon should not be neglected when dedicated QT studies are performed.

Key words: electrocardiogram, Holter, QT interval, hysteresis, moxifloxacin

Clin. Cardiol. 2006; 29: 534–539.

Introduction

The association between drug-induced QT prolongation and the risk of life-threatening ventricular arrhythmias is well documented.[1,2] However, the evaluation of drug effects on QT interval might be difficult because of the complexity of repolarization properties.[3] The main electrophysiologic property of ventricular repolarization is inversely related to heart rate (HR).[4,5] To compare QT intervals within and between subjects, numerous solutions have been proposed to take this phenomenon into account. The so-called "universal-correction" formulae have been shown to over- or undercorrect the QT interval potentially when HR changes.[6,7] New techniques have been proposed, such as population-specific formula,[8] subject-specific correction formula,[9] as well as the "bin" method avoiding the need for any QT-correction formulae.[10–13]

Less attention has been paid so far to the hysteresis phenomenon. Following an abrupt change in HR, the QT adaptation is not immediate but is achieved within a 3-min time frame, although most QT adaptations occur over the first minute.[4,14,15] From a theoretical point of view, QT interval measurement performed just after a

Address for reprints:

Fabrice Extramiana, M.D., Ph.D.
Cardiology Department
Lariboisière University Hospital
2 rue Ambroise Paré—75475 Paris Cedex 10, France
e-mail: fabrice.extramiana@lrb.ap-hop-paris.fr

Received: May 29, 2006
Accepted with revision: September 12, 2006

Published online in Wiley InterScience
(www.interscience.wiley.com).
DOI:10.1002/clc.020

sudden HR change would lead to a potential error in the estimation of QT duration. Thus, the rate correction of QT interval duration based on the single preceding RR interval may introduce a potential confounding factor whatever the strategy used to correct QT interval.

Our group published several studies using specific HR filters aimed to take the hysteresis phenomenon into account.[16,17] Our approach is based on the identification and exclusion of individual QRST complexes when preceded by rapid HR changes.[10,12]

The aim of the present study was to determine whether the level of drug-induced QT changes would be influenced by the use of HR stability filters in the electrocardiographic (ECG) analysis process.

Methods

The data reported in the present paper are part of a single center, randomized, double-dummy, placebo-controlled, thorough QT study using a parallel design.

The study population consisted of 31 healthy subjects who were randomly allocated to moxifloxacin (repeated once-daily doses of placebo for 27 days followed by a single dose of moxifloxacin 400 mg on Day 28).

The study was approved by the institutional review board, and subjects signed an informed consent form.

Continuous ECG-Holter monitoring over 24 h was performed on baseline conditions (run-in placebo) and on drug (moxifloxacin or placebo), using a 12-lead Holter recorder (H12 plus®, Mortara Instrument Inc, Milwaukee, Wisc., USA). Electrodes were positioned according to the so-called Mason-Likkar configuration at the same place for each recording.

Moxifloxacin's plasma concentration time course displays a sharp peak after a single dose. Therefore, the ECG analysis was performed from 1 through 5 h after moxifloxacin administration (T1–T5).[13]

Electrocardiographic analysis was performed using a subject-specific protocol of time-matched ECGs. The on-treatment data were compared with the baseline data during the T1–T5 time window. A single reader (PMB) performed all HR-controlled QT measurements in a blinded manner using the Holter bin method through the use of a validated software (WinAtrec®, Version 4.02).[10,12,13] (Analyzing Medical Parameters for Solutions, N.Y., N.Y.) The analysis was performed for a single preferred lead in each subject.

For each Holter recording, individual cardiac complexes of sinus origin were classified by RR interval according to the value of the single preceding RR interval (RR-1).

In addition, cardiac complexes were also classified according to the value of the preceding RR interval only if it was considered as stable over the preceding 30 or 60 s (stable RR). The control of HR stability was defined by the following formula:

$$\text{RR-1} = \text{RR}_{[\text{time}-\text{window}]} \pm \text{threshold} \quad (1)$$

where $\text{RR}_{[\text{time}-\text{window}]}$ is the mean RR interval of the period considered and the threshold is set by the user and equal to 15 (th15) or 30 ms (th30). The time-window consisted of the preceding 30 s (R30) or the preceding 60 s (R60). Therefore, four models of stability were used: R30th30, R30th15, R60th30, and R60th15.[10,12]

All cardiac complexes belonging to the same RR interval were averaged within the T1h–T5h period of each assessment day, separately for each strategy (RR-1 and the four stable RR models). QT intervals were measured on each of these averaged complexes.

The product of the blinded data processing was the average QT interval for each RR bin (4 stable RR models and RR-1) and each treatment period by subject.

QT interval changes induced by moxifloxacin versus baseline were calculated at different RR intervals (ΔQTxxx, where xxx = RR interval in ms). In addition, the rate dependence of QT interval change was assessed by the slope of the linear ΔQT/ΔRR relationship.

These endpoints were calculated separately for the five types of analysis, that is, classification of cardiac complexes based on (1) RR-1 interval, and (2) the four stable RR models.

A sample size of 26 subject per treatment group would provide at least 90% power to detect true mean differences of 5 ms between active treatment and placebo, assuming a total standard deviation equal to 5.5 ms.[13] Method effects and rate effects were assessed using paired analysis of variance (ANOVA).

Results

Study Population

Two subjects withdrew from the study: one for adverse event and one for personal reasons. Therefore, the moxifloxacin groups included 29 subjects (24 men) with a mean age of 30.2 ± 9.5 years (range 18–46).

Moxifloxacin-Induced QT-Interval Changes

The actual pharmacokinetic profile of moxifloxacin 400 mg is shown in Figure 1. The time window selected for ECG analysis (T1–T5) is superimposed on the plasma concentrations curve of moxifloxacin.

QT-interval changes versus baseline for different RR intervals are shown Table I. Moxifloxacin-induced QT prolongation was observed with statistical significance at RR = 800, 900, and 1000 ms. This QT prolongation was consistently higher when controlling for HR compared with the RR-1 model. These differences reached statistical significance between RR-1 model and "stable" models for RR = 900 and 1000 ms (Table I). Conversely, no significant differences among the four "stable" models were evident.

TABLE 1 Moxifloxacin effects on QT interval for each method and at different RR intervals

	RR-1	R30th15	R30th30	R60th15	R60th30
ΔQT700	4.3 ± 3.9 [−1.9; 10.5]	7.0 ± 4.7 [−0.5; 14.5]	5.0 ± 7.7 [−7.3; 17.3]	6.8 ± 3.9 [0.6; 13]	4.3 ± 5.1 [−3.4; 12.4]
ΔQT800	2.7 ± 3.9 [−0.3; 5.7]	4.4 ± 3.2 [1.9; 6.9]	4.0 ± 3.0 [1.7; 6.3]	5.1 ± 4.0 [2.0; 8.2]	3.7 ± 3.2 [1.2; 6.2]
ΔQT900	4.2 ± 7.2 [1.1; 7.3]	7.3 ± 6.7[a] [4.4; 10.2]	7.4 ± 7.3[a] [4.2; 10.6]	7.8 ± 6.6[a] [4.9; 10.7]	7.5 ± 6.4[a] [4.7; 10.3]
ΔQT1000	8.2 ± 11.2 [2.6; 13.8]	10.7 ± 9.4[a] [6.0; 15.4]	9.3 ± 10.3 [4.2; 14.4]	10.9 ± 10.4[a] [5.7; 16.1]	11.1 ± 10.6[a] [5.8; 16.4]
ΔQT1100	10.5 ± 13.0 [−0.4; 21.4]	12.6 ± 13.0 [1.7; 23.5]	11.9 ± 11.2 [2.5; 21.3]	14.1 ± 10.7 [5.1; 23.0]	13.8 ± 9.5 [5.9; 21.7]
ΔQT1200	15.0 ± 21.2 [−175; 205]	15.0 ± 11.3 [−87; 117]	15.0 ± 14.1 [−112; 142]	13.5 ± 9.2 [−69; 96]	13.0 ± 14.1 [−114; 140]

Numbers in brackets indicate the lower and upper bounds of the 95% confidence interval.
[a] Analysis of variance for repeated measures post test $p < 0.05$ versus RR-1.

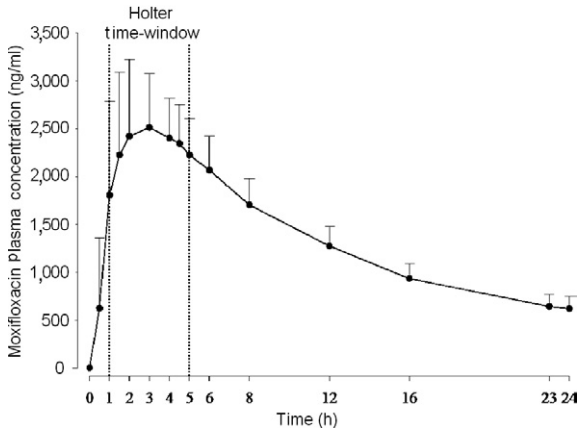

FIG. 1 Moxifloxacin plasma concentrations profiles. Moxifloxacin was administered at T0, and ECG collection was performed from h1 through h5 (T1-T5). Mean ± standard deviation. ECG = electrocardiogram.

TABLE 2 Rate dependence of moxifloxacin-induced QT prolongation

	RR-1	R30th30	R60th15
Alpha	0.015 [0.012; 0.017]	0.021 [0.018; 0.024]	0.023 [0.019; 0.027]
P value for alpha	$<10^{-4}$	$<10^{-4}$	$<10^{-4}$
Beta	−7.7	−11.4	−12.5
r	0.92	0.96	0.93
R^2	0.85	0.92	0.86

Alpha and beta coefficients, r, and R^2 describe the linear relationship of QT-prolongation rate dependence.

Rate Dependence of Drug-Induced QT-Interval Changes

Figure 2 shows that the level of HR influences the magnitude of moxifloxacin-induced QT prolongation. Regardless of the ECG analysis process, QT prolongation was higher at slow than at fast HR (ANOVA, $p < 0.05$).

This "reverse rate dependence" was significantly more pronounced when QT changes were assessed using stable HR models. Table II shows that a 100 ms RR interval increment led to a 2.3 ms QT prolongation with the R60th15 model, whereas this prolongation is 1.5 ms using the RR-1 model ($p < 0.05$).

The Electrocardiographic Data Set

Table III shows the number of sinus beats available for each of the methods used. When no HR stability filter was used, only nonsinus beats were excluded, thus leading to a very high percentage of used beats in normal subjects. A large number of beats was still available after the use of any of our four stability filters.

The duration of the time window chosen for the assessment of the RR stability had only little effect on the percentage of used beats (R30 vs. R60). The former was mainly influenced by the value chosen for the threshold. For instance, using a time window of 30 s, a threshold of 30 ms led to 5393 ± 1763 available beats, whereas using a threshold of 15 ms was associated with 2881 ± 1015 available beats.

Discussion

Our study demonstrates that the control of rapid HR changes from continuously recorded ECG data influences the magnitude of drug-induced QT changes in healthy subjects. We also confirm that moxifloxacin-induced QT prolongation is dependent on the level of HR at which the effect is observed. This reverse rate-dependent pattern of moxifloxacin effect on QT interval is also influenced by using HR stability algorithms.

The delay in the adaptation of QT interval duration after abrupt HR changes has been long recognized.[4,15]

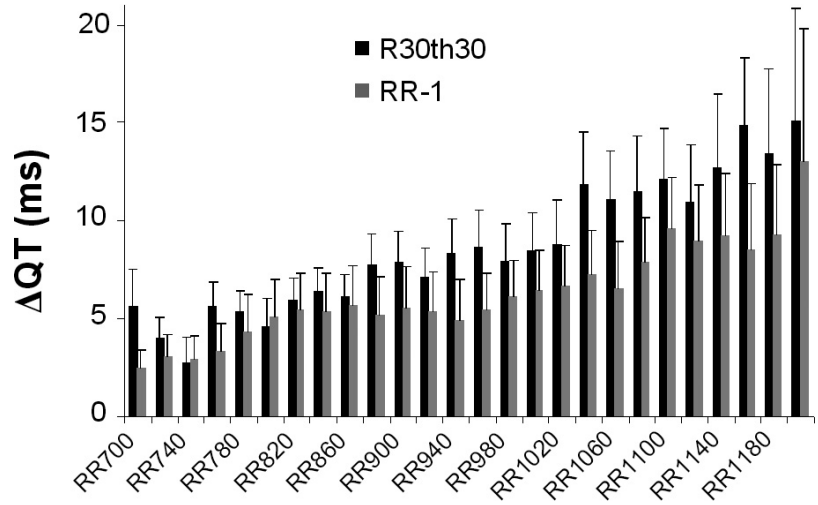

FIG. 2 QT interval changes with moxifloxacin at various heart rates. Mean + standard error of the mean.

TABLE 3 Number of lost beats

	ECG 10s/5 min	Holter RR-1	Holter R30th15	Holter R30th30	Holter R60th15	Holter R60th30
Number of beats	$15,117 \pm 1,184$	$15,117 \pm 1,184$	$15,117 \pm 1,184$	$15,117 \pm 1,184$	$15,117 \pm 1,184$	$15,117 \pm 1,184$
Available beats	499[a]	$14,944 \pm 2,031$	$2,881 \pm 1,015$	$5,393 \pm 1,763$	$2,622 \pm 926$	$4,952 \pm 1,654$
% Available beats	3.3%[a]	$98.7 \pm 2.2\%$ [86%;100%]	$18.8 \pm 5.3\%$ [10%;31%]	$35.2 \pm 8.8\%$ [20%;54%]	$17.1 \pm 4.8\%$ [9%;28%]	$32.3 \pm 8.3\%$ [18%;50%]

Numbers in brackets indicate minimum and maximum percentage observed within the 29 subjects.
[a] Theoretical calculation.
Abbreviation: ECG = electrocardiogram.

The so-called "hysteresis" phenomenon presents a two-phase pattern. The initial adaptation (around 50%) of QT change occurs the order of a 50 to 60 s time frame, the terminal adaptation lasting above 2 min.[4,15,18] Less is known about QT hysteresis during physiologic HR fluctuation not associated with atrial pacing or acute exercise. In a recent study, Pueyo *et al*. showed that the hysteresis phenomenon was different among subjects and was also influenced by amiodarone.[18]

In this study, we excluded QRST complexes preceded by rapid HR changes from the ECG selection process.[10,12] This approach is intended to consider only "stable" QRST complexes for the purpose of QT measurement. At any HR considered, the impact of ECG selection was a 2 to 3 ms difference in moxifloxacin-induced QT prolongation, the rate control leading to a larger QT prolongation. This effect could not be related to a placebo effect since it showed no rate dependence (data not shown).

The relatively small difference observed after excluding rapid HR changes should be considered, taking into account the ability of detecting a 5 ms drug-induced QT-interval prolongation required by regulatory agencies according to the International Conference on Harmonisation (ICH)14 guidance.[19] Controlling for the hysteresis phenomenon may shift a given drug above a cut-off value (an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms) for a positive QT trial. Although the guidance clearly states that "care should be taken to exclude ECG recordings collected during times of HR instability," the current recommended cut-off for a positive trial is based on any selection process. Further studies are needed to determine whether a change in the method of QRST complexes selection would be associated with changes in cut-off values suggested by the ICH14 guidance.

As other IKr current blockers, moxifloxacin has been shown to increase the steepness of the QT/RR relationship.[20] Because the QT/RR relationships under placebo and moxifloxacin crossed at relatively fast HR, these changes in the relationship between QT-interval duration and RR interval led to the well known "reverse rate-dependent" effect described with class III antiarrhythmic agents,[21,22] that is, the effect of moxifloxacin on QT interval increased when HR decreased. Although this phenomenon is well documented at the cellular level as well as in clinical settings,[11,22–24] it is generally omitted in clinical trials assessing a drug's effects on QT interval duration.

We show in this study that not only the magnitude of QT prolongation but also the reverse rate-dependent effect of moxifloxacin were influenced by stability. The

reason for such a method-dependent change is not clear. The use of stability filters has been shown to induce an increase in the slope of the QT rate-dependence.[25] This phenomenon may be explained by an underestimation of the QT duration by measuring the QT interval before it is fully adapted following an HR slowing from a resting HR together with an overestimation after HR acceleration. This phenomenon may account for the steeper "reverse rate-dependent effect" observed in our study, but not for the difference in the magnitude of QT prolongation. Indeed, from a theoretical point of view, if "unstable" times of acquisition were evenly divided between accelerating and decelerating cycle lengths, and these had equivalent deviations from a stable cycle length in the middle, the mean QT values for the "stable" and "unstable" ECGs would be equal. This was not the case in the present study.

One might hypothesize that the shorter moxifloxacin-induced QT prolongation, when using the "unstable" model, might be the consequence of the occurrence of more deceleration than acceleration episodes on moxifloxacin. In such conditions, the "stable" models would exclude more complexes underestimating QT-interval duration. This hypothesis could, however, not be tested with our data and remains to be assessed.

We chose a simple time-domain filter that excluded QRST complexes when the difference in RR intervals fluctuated above prespecified values. We have shown that the use of any of our four stability filters made a large number of sinus beats still available. In particular, with our method the number of used beats was strikingly higher than the proportion of beats recorded using repeated 10-s ECG recordings as it is usually done in thorough QT studies.[19] In addition, it is difficult to control HR stability when recording 10-s ECGs only intermittently. One solution would be to record the 12-lead ECG signals continuously and then to accept the rejection of the ECGs that do not achieve the prespecified stability criteria.

Pueyo *et al*. proposed a new method that considers weighted averages of RR intervals preceding each cardiac beat to express RR-interval history accounting for the influence on repolarization duration.[18] Although this method may more accurately correct for the hysteresis phenomenon, the method used in the present study has the advantage of avoiding the need for the determination of the hysteresis model for each subject and for each tested drug.

Conclusions

The exclusion of rapid HR changes slightly influences the results of the magnitude of drug-induced QT changes in healthy subjects. Therefore, the hysteresis phenomenon should not be neglected when thorough QT studies are performed. However, the best strategy for taking the hysteresis (exclusion or correction) into account remains to be determined.

References

1. Crouch MA, Limon L, Cassano AT: Clinical relevance and management of drug-related QT interval prolongation. *Pharmacotherapy* 2003;23:881–908
2. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, *et al*: Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 2004;351:1089–1096
3. Moss AJ, Zareba W, Benhorin J, Couderc JP, Kennedy H, *et al*: ISHNE guidelines for electrocardiographic evaluation of drug-related QT prolongation and other alterations in ventricular repolarization. *Ann Noninvas Electrocardiol* 2001;6:333–341
4. Franz MR, Swerdlow CD, Liem LB, Schaefer J: Cycle length dependence of human action potential duration in vivo: Effects of single extrastimuli, sudden sustained rate acceleration and deceleration, and different steady state frequency. *J Clin Invest* 1988;82:972–979
5. Viitasalo M, Karjalainen J: QT Intervals at heart rates from 50 to 120 beats per minute during 24-hour electrocardiographic recordings in 100 healthy men. *Circulation* 1992;86:1439–1442
6. Funck-Brentano C, Jaillon P: Rate-corrected QT interval: Techniques and limitations. *Am J Cardiol* 1993;72:17B–22B
7. Malik M: The imprecision in heart rate correction may lead to artificial observations of drug-induced QT interval changes. *PACE* 2002;25:209–216
8. Hnatkova K, Malik M: "Optimum" formulae for heart rate correction of the QT interval. *PACE* 1999;22:1683–1687
9. Malik M, Farbom P, Batchvarov V, Hnatkova K, Camm AJ: Relation between QT and RR intervals is highly individual among healthy subjects: Implications for heart rate correction of the QT interval. *Heart* 2002;87:220–228
10. Badilini F, Maison-Blanche P, Childers R, Coumel P: QT interval analysis on ambulatory electrocardiogram recordings: A selective beat averaging approach. *Med Biol Eng Comput* 1998;36:1–10
11. Lande G, Maison-Blanche P, Fayn J, Ghadanfar M, Coumel P, *et al*: Dynamic analysis of dofetilide-induced changes in ventricular repolarization. *Clin Pharmacol Ther* 1998;64:312–321
12. Badilini F, Maison-Blanche P: Holter monitoring for QT: The RR bin method in depth. In *Cardiac Safety of Noncardiac Drugs* (Eds. Morganroth J, Gussak I). Totowa, New Jersey: Humana Press, 2004
13. Extramiana F, Maison-Blanche P, Cabanis MJ, Ortemann-Renon C, Beaufils P, *et al*: Clinical assessment of drug-induced QT prolongation when associated with heart rate changes. *Clin Pharmacol Ther* 2005;77:247–258
14. Seed WA, Noble MI, Oldershaw P, Wanless RB, Drake-Holland AJ, *et al*: Relation of human cardiac action potential duration to the interval between beats: Implications for the validity of rate corrected QT interval (QTc). *Br Heart J* 1987;57:32–37
15. Lau CP, Freedman AR, Fleming S, Malik M, Camm AJ, *et al*: Hysteresis of ventricular paced QT interval in response to abrupt changes in pacing rate. *Cardiovasc Res* 1988;22:67–72
16. Extramiana F, Maison-Blanche P, Tavernier R, Jordaens L, Leenhardt A, *et al*: Cardiac effects of chronic oral beta-blockade: Lack of agreement between heart rate and QT interval changes. *Ann Noninvas Electrocardiol* 2002;7:379–388
17. Extramiana F, Denjoy I, Badilini F, Chabani I, Neyroud N, *et al*: Heart rate influences on repolarization duration and morphology in symptomatic and asymptomatic KCNQ1 mutation carriers. *Am J Cardiol* 2005;95:406–409
18. Pueyo E, Smetana P, Caminal P, de Luna AB, Malik M, *et al*: Characterization of QT interval adaptation to RR interval changes and its use as a risk-stratifier of arrhythmic mortality in amiodarone-treated survivors of acute myocardial infarction. *IEEE Trans Biomed Eng* 2004;51:1511–1520
19. International Conference on Harmonisation (ICH): The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs ICH E14, Step 4, May 12, 2005.; http://www.emea.eu.int/pdfs/humanich/000204en.pdf

20. Extramiana F, Maison-Blanche P, Badilini F, Beaufils P, Leenhardt A: Individual QT-R-R relationship: Average stability over time does not rule out an individual residual variability: Implication for the assessment of drug effect on the QT interval. *Ann Noninvas Electrocardiol* 2005;10:169–178
21. Hondeghem LM, Snyders DJ: Class III antiarrhythmic agents have a lot of potential but a long way to go. Reduced effectiveness and dangers of reverse use dependence. *Circulation* 1990;81:686–690
22. Gintant GA, Limberis JT, McDermott JS, Wegner CD, Cox BF: The canine Purkinje fiber: An in vitro model system for acquired long QT syndrome and drug-induced arrhythmogenesis. *J Cardiovasc Pharmacol* 2001;37:607–618
23. Varro A, Nakaya Y, Elharrar V, Surawicz B: Effect of antiarrhythmic drugs on the cycle length-dependent action potential duration in dog Purkinje and ventricular muscle fibers. *J Cardiovasc Pharmacol* 1986;8:178–185
24. Funck-Brentano C, Kibleur Y, Le Coz F, Poirier JM, Mallet A, *et al*: Rate dependence of sotalol-induced prolongation of ventricular repolarization during exercise in humans. *Circulation* 1991;83:536–545
25. Lande G, Funck-Brentano C, Ghadanfar M, Escande D: Steady-state versus non-steady-state QT-RR relationships in 24-hour Holter recordings. *Pacing Clin Electrophysiol* 2000;23:293–302