Cardiac Effects of Chronic Oral Beta-Blockade: *Lack of Agreement Between Heart Rate and QT Interval Changes*

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Background: Although well established on the sinus node, the effects of beta-blockade on ventricular repolarization are still conflicting. The aim of the study was to investigate the effects of a chronic beta-blockade on sinus node and repolarization parameters and their relationship.

Methods: Sixteen healthy volunteers (10 males, mean age: 40 ± 6.7 years) were randomized to placebo or atenolol (100 mg). After 7 days, subjects were crossed over. Heart rate (HR) and HRV indices were calculated from long-term ECG recordings separately during the day and at night, together with ventricular repolarization parameters (QT interval duration and QT rate-dependence).

Results: Mean R-R intervals were significantly and consistently increased after atenolol (Day: 916 ± 103 ms vs. 712 ± 89 ms, and Night: 1149 ± 93 vs. 996 ± 125 ms). HRV changes under atenolol were also consistent, with a significant decrease in sympathovagal ratio. In contrast, atenolol only lowered diurnal QT rate-dependence (0.123 ± 0.032 vs. 0.190 ± 0.065 on placebo, $P < 0.001$), but not the nocturnal pattern. After multivariate analysis QT rate-dependence changes induced by atenolol were correlated with pretreatment QT/RR relation ($r = 0.65$, $P < 0.01$) but not with any HR or HRV parameters.

Conclusions: In healthy subjects, repolarization changes following chronic beta-blockade cannot be predicted by HR or HRV changes, but are dependent on pretreatment rate-dependence.

A.N.E. 2002;7(4):379–388

autonomic nervous system; ECG; beta-blockers; heart rate variability; QT interval

Autonomic imbalance and, in particular, sympathetic hyperactivity increases ventricular electrical instability and so facilitates life-threatening ventricular arrhythmias. Furthermore, beta-blocker administration in patients surviving acute myocardial infarction and in those with dilated cardiomyopathy has proven to be of beneficial effect, mainly for the reduction of cardiovascular mortality and sudden cardiac death.[1-4] Accordingly, the complete understanding of cardiac effects of chronic beta-blockade is of considerable interest.

The effects of beta-blockade on the sinus node are well established with a decreased heart rate (HR) and an increased heart rate variability (HRV) particularly when a high sympathetic tone is present.[5] The association between a reduction in heart rate and the beneficial effects of beta-blockers has been demonstrated,[3,6] but beta-blockers slow heart rate by inhibiting cardiac adrenergic stimulation and their global cardioprotective effects can be mediated by more complex factors. In addition, the cardiac effects of a sympathetic inter-

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vention on the sinus node might differ from those on ventricle cells. Although the HR decrease induced by beta-blockers is considered as a marker of efficacy, its correlation with repolarization changes remains unclear.

Everybody agrees that a rational evaluation of beta-adrenergic blockade impact should also include ventricular electrical markers, but strikingly as of today, the effects of chronic beta-blockade on ventricular repolarization are still debated. Ventricular action potential duration (APD) is mainly influenced by the basic cycle length.[7] In addition, both catecholamines and acetylcholine affect ventricular APD. Acetylcholine prolongs ventricular APD directly and throughout the cycle length prolongation.[8,9] The sympathetic limb of the nervous system also exerts its control on the duration of ventricular repolarization directly : catecholamines affect the ionic currents involved in determining the duration of action potential.[10-12] However, the amount of membrane current available during the action potential is a function of cycle length,[13] thus, the effects of catecholamines on repolarization are likely to vary with heart rate. Furthermore, isoprenaline may either increase APD[14] or shorten APD.[15,16] At low concentrations, isoprenaline increases APD, whereas at higher concentration it shortens it.[17] Regarding antiadrenergic intervention, beta-blockers effect has been associated with as an increased APD at fast pacing rates,[18] but also with a shortened effective refractory period.[19,20]

These experimental controversial findings might result from evaluations at different cycle lengths. It remains very difficult to assess a clinical effect on ventricular repolarization when heart rate changes. To overcome this problem, a recent alternative approach is to evaluate the relation between QT interval duration and heart rate. QT rate-dependence is one of the major properties of ventricular repolarization with demonstrated circadian modulation,[21] and it allows to directly compare QT interval between groups at identical heart rates, thus avoiding the use of a rate correction formula. The circadian pattern of QT rate-dependence is related to the long-term variations of sympathovagal balance and it might bear some meaningful information to interpret an antiadrenergic intervention.

The aim of the present study was to assess the effects of the autonomic nervous system on both atrial and ventricular electrophysiological parameters in normal subjects by using beta-adrenergic blockade as a long-term autonomic manipulation. In a randomized, double-blind, cross-over study, we compare heart rate, heart rate variability, QT interval duration, and QT rate-dependence after administration of placebo or atenolol.

METHODS

Study Population

The study population consisted of 16 normal volunteers (10 males and 6 females, mean age 40.0 ± 6.7 years). All individuals were free of any cardiovascular abnormality detectable by physical examination, 12-lead ECG recording, 24-hour ambulatory recording, and stress test. Subjects with hypertension, diabetes, or any other condition known to influence the autonomic nervous system were excluded, as well as individuals with contraindication for β-blockade. None of the volunteers took any medication before randomization.

Study Protocol

The trial was a randomized double-blind cross-over study. After inclusion, subjects were randomized to placebo or atenolol 50 mg, twice daily for 7 days. After 7 days, subjects were crossed over. Within the last 2 days of each study period, a 24-hour ambulatory ECG was performed. The investigation conforms with the principle outlined in the Declaration of Helsinki. All volunteers provided written informed consent and this study protocol was approved by the ethical committee of the Ghent University hospital.

Ambulatory ECG Recordings Analysis

Two ECG channels (modified bipolar leads V1 and V5) were continuously recorded (DelMar 456A tape recorder, DelMar Medical, Irvine, CA, USA). Analog data were then digitized (200 samples per second) and edited on an ELATEC system (Ela Medical, Le Plessis Robinson, France).

Analysis focused on atrial and ventricular parameters, on two different circadian periods defined according to subject diaries and average hourly heart rate tables. The first period consisted of the 8 consecutive daily hours with fastest heart rate (diurnal period), the second of the 4 consecutive sleeping hours with lowest heart rate (nocturnal period).

Atrial parameters consisted of diurnal and nocturnal mean R-R intervals (RR8 and R-R4, respec-

Table 1. Atrial and Ventricular Effects of Chronic Oral Beta-Blockade

	Placebo		Atenolol	
	Day	Night	Day	Night
RR (ms)	712 ± 89	996 ± 125*	916 ± 103††	1149 ± 93*††
SD (ms)	99 ± 23	94 ± 25	123 ± 37†	111 ± 32†
PNN50 (%)	6.9 ± 5.0	21.2 ± 13.9*	16.9 ± 11.9††	32.2 ± 15.6*†
HFnu	24 ± 13	48 ± 17*	41 ± 16††	56 ± 14*†
LFnu	75 ± 12	52 ± 15*	61 ± 13††	47 ± 12*
LF/HF	6.9 ± 4.4	1.7 ± 1.4*	2.8 ± 2.1††	1.0 ± 0.5*†
QT_{800}	393 ± 23	408 ± 24*	390 ± 23	414 ± 30*
QT_{1000}	431 ± 31	433 ± 25	414 ± 24	434 ± 28*
QT/RR	0.190 ± 0.065	0.126 ± 0.040*	0.123 ± 0.032††	0.104 ± 0.040

* $P < 0.01$ day versus night; † $P < 0.05$; †† $P < 0.01$ placebo versus atenolol.

tively), the standard deviation of the R-R intervals (SDNN), the percentage of R-R intervals that differed by > 50 ms (pNN50).[22] Frequency-domain HRV was computed using an auto-regressive model.[23] Raw and normalized (nu) powers in the LF band (0.04 to 0.15 Hz) and power in the HF band (0.15 to 0.40 Hz) were measured. The ratio of LF over HF power (LF/HF) was calculated from these values.

Ventricular repolarization analysis from Holter recordings combined patient's specific and rate-independent approaches. This method starts with selection and averaging of normal QRS-T complexes preceded by a 1-minute period of stable heart rate (Selective Beat Averaging, SBA). Details of the method have already been published.[21,24-26] QT interval (time interval between QRS onset and the end of T wave) was automatically measured by a dedicated algorithm and measurement outputs were blindly edited by two cardiologists. In case of aberrant positions of the T wave end cursor, the template was rejected. To avoid interlead variability, we only analyzed V5-lead data for each subject because this lead consistently provided bell-shaped T wave patterns. For each individual, for each recording and for each circadian period, a linear regression analysis between QT intervals and corresponding R-R intervals was performed ($QT = \alpha * RR + b$). The linear model was used to assess QT rate-dependence (coefficient α or slope) and to calculate the length of the QT interval corresponding to R-Rs equal to 1000 ms (QT_{1000}) and to 800 ms (QT_{800}). For each individual, the cardiac effects of beta-blockade was evaluated by direct comparison of pre- and posttreatment values of coefficient α, QT_{1000} and QT_{800}.

Therefore, the potential drawbacks related to the use of a QT rate-correction formula (HR changes induced by beta-blockers are large) were eliminated.

Statistical Analysis

Results are given as mean ± standard deviation. Means were compared between groups or between circadian periods using a paired Student's *t*-test. Relations between ventricular electrical variables (QT_{1000}, coefficient α) and HR and HRV data were assessed using single and multiple linear regression analyses. In order to investigate whether the magnitude of QT rate-dependence change after oral beta-blockade is affected by the pretreatment QT rate-dependence (α_1), we used the Oldham's transformation and the approach proposed by MacGregor et al.[27,28] Briefly, the QT rate-dependence change (pretreatment slope α_1 minus post-treatment slope α_2) is mathematically related to α_1. To avoid such an artificial association, we correlated ($\alpha_1 - \alpha_2$) with the mean of the pre- and posttreatment values, $(\alpha_1 + \alpha_2)/2$.

Statistical analysis was performed with BMDP software (BMDP Statistical Software Inc, California, USA). In all tests, a P value less than 0.05 was considered statistically significant.

RESULTS

Heart Rate and Heart Rate Variability

As shown in Table 1, in both treatment groups, the nocturnal R-R was longer than the diurnal one. As shown in Figure 1, mean R-R intervals were

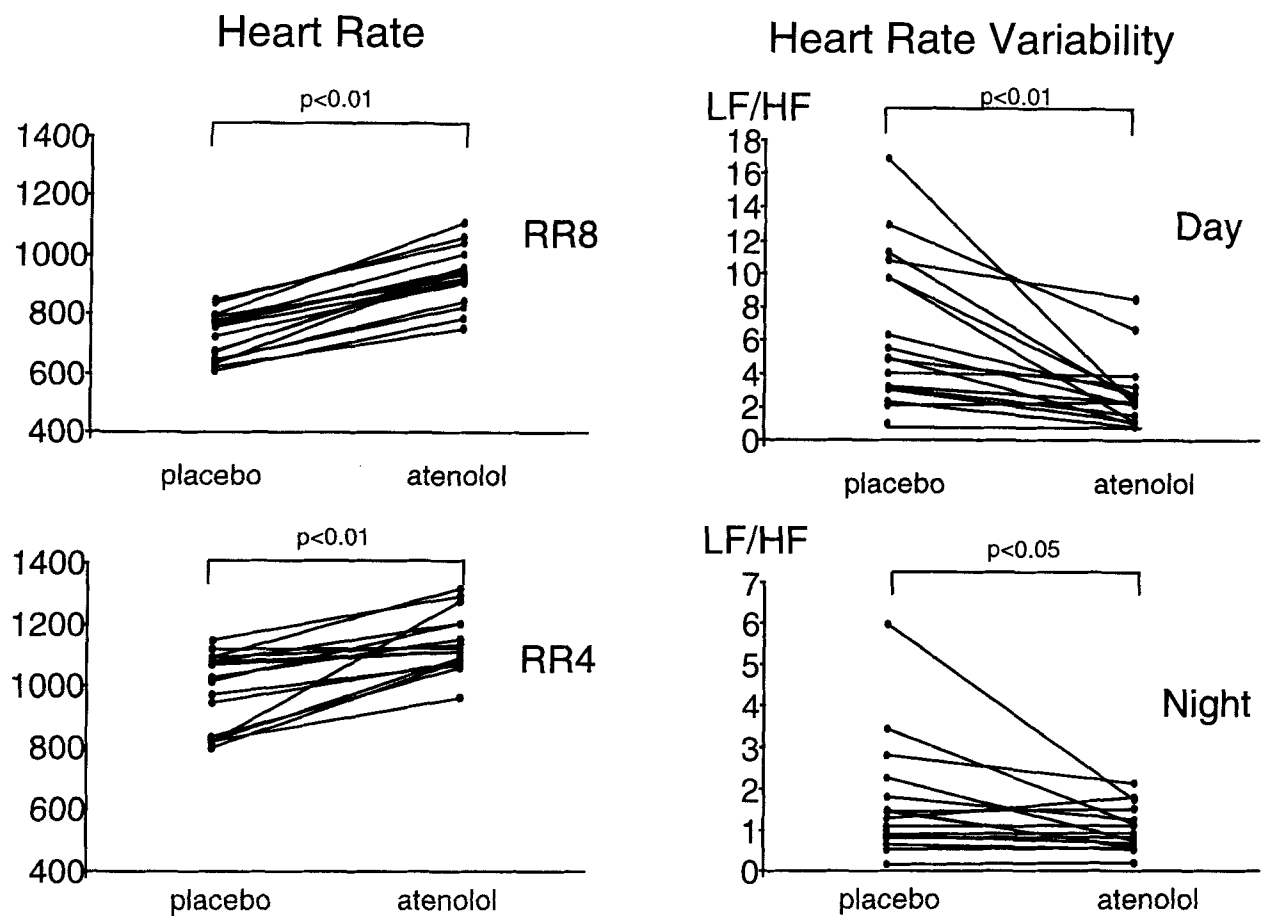

Figure 1. Left panels show R-R intervals on placebo and atenolol during the diurnal period (upper left panel) and the nocturnal period (lower left panel). During the both circadian periods, R-R interval is significantly and consistently increased by atenolol. Right panels display the LF/HF ratio on placebo and atenolol during the diurnal period (upper right panel) and the nocturnal period (lower right panel). Once again, the LF/HF ratio is significantly and consistently increased by atenolol whatever the circadian period considered.

significantly and consistently greater in the atenolol group, both during the diurnal (916 ± 103 ms vs. 712 ± 89 ms) and the nocturnal periods (1149 ± 93 vs. 996 ± 125 ms). However, the nocturnal R-R prolongation (RR8/RR4 ratio) was less pronounced under atenolol when compared to placebo group (0.82 ± 0.08 vs. 0.74 ± 0.06, $P < 0.01$).

Diurnal and nocturnal time-domain HRV parameters were significantly increased under atenolol. Regarding frequency-domain HRV parameters, in the atenolol group, HFnu and LFnu powers were respectively larger and smaller than those in placebo group. Consequently, the LF/HF ratio decreased significantly during the day and at night (Table 1). Figure 1 shows the consistency of LF/HF variations between treatment groups.

Ventricular Repolarization Parameters

Circadian Modulation

As shown in Table 1 and in Figure 2, QT rate-dependence was steeper during the day than at night under placebo (0.190 ± 0.065 vs. 0.126 ± 0.040, $P < 0.01$), whereas under beta-blockade the circadian QT rate-dependence pattern was no longer significant (0.123 ± 0.032 during the day vs. 0.104 ± 0.040 at night).

Pharmacologic Modulation

QT_{1000} and QT_{800} interval duration were not significantly different between placebo and atenolol

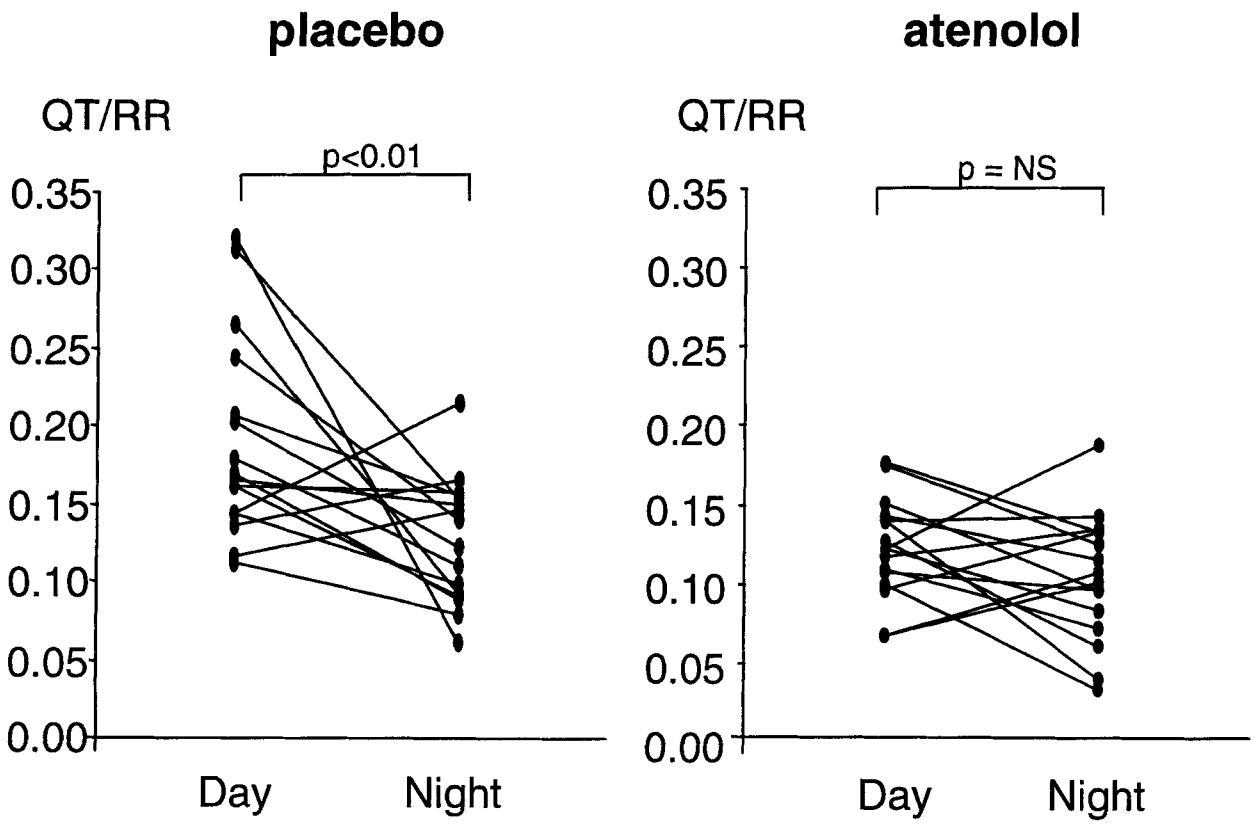

Figure 2. Left panel shows the individual QT rate-dependence during the day and at night on placebo. The diurnal QT rate-dependence is significantly steeper than the nocturnal one, but some subjects have a steeper nocturnal QT rate-dependence when compared to the diurnal one. Right panel displays the individual QT rate-dependence during the day and at night on atenolol. QT rate-dependence is not significantly different within the two circadian periods. Six out of 16 subjects have a steeper nocturnal QT rate-dependence when compared to the diurnal one.

groups regardless the circadian period considered (Table 1).

Effects of atenolol on QT/RR relations were dependent on the circadian period considered (Table 1 and Fig. 3). At night, QT rate-dependence was not significantly different between treatment groups (0.126 ± 0.040 vs. 0.104 ± 0.040) whereas, during daytime, QT rate-dependence significantly decreased after atenolol administration (0.123 ± 0.032 vs. 0.190 ± 0.065, $P < 0.001$).

In contrast with HR and HRV data, the sympathetic intervention on ventricular repolarization parameters did not yield homogeneous changes. Although the average effect of the sympathetic blockade was a decrease of the rate-dependence, its magnitude ranged from −62 to +30%. Then, in some individuals atenolol could even increase QT rate-dependence (in one subject during the day and in 4 cases at nighttime, Fig. 3).

Determinants of Drug-Induced Ventricular Repolarization Changes

Within treatment groups, QT_{1000} at multivariate analysis was correlated with HRV parameters (LFnu partial $r = -0.80$, $P < 0.01$ and PNN50 partial $r = -0.59$, $P < 0.05$). Regarding QT rate-dependence, it was only correlated with the mean R-R interval using a multiple regression analysis. The correlation with HRV parameters found at univariate analysis (PNN50 r = -0.41, $P < 0.001$, LF/HF r = 0.30, $P < 0.05$ and HFnu $r = -0.28$, $P < 0.05$) was no more evidenced at multivariate analysis.

The correlation between ventricular and atrial parameters found within treatment groups was no more evidenced when ventricular repolarization changes after autonomic modulation were examined. Neither QT_{1000} changes nor QT rate-depen-

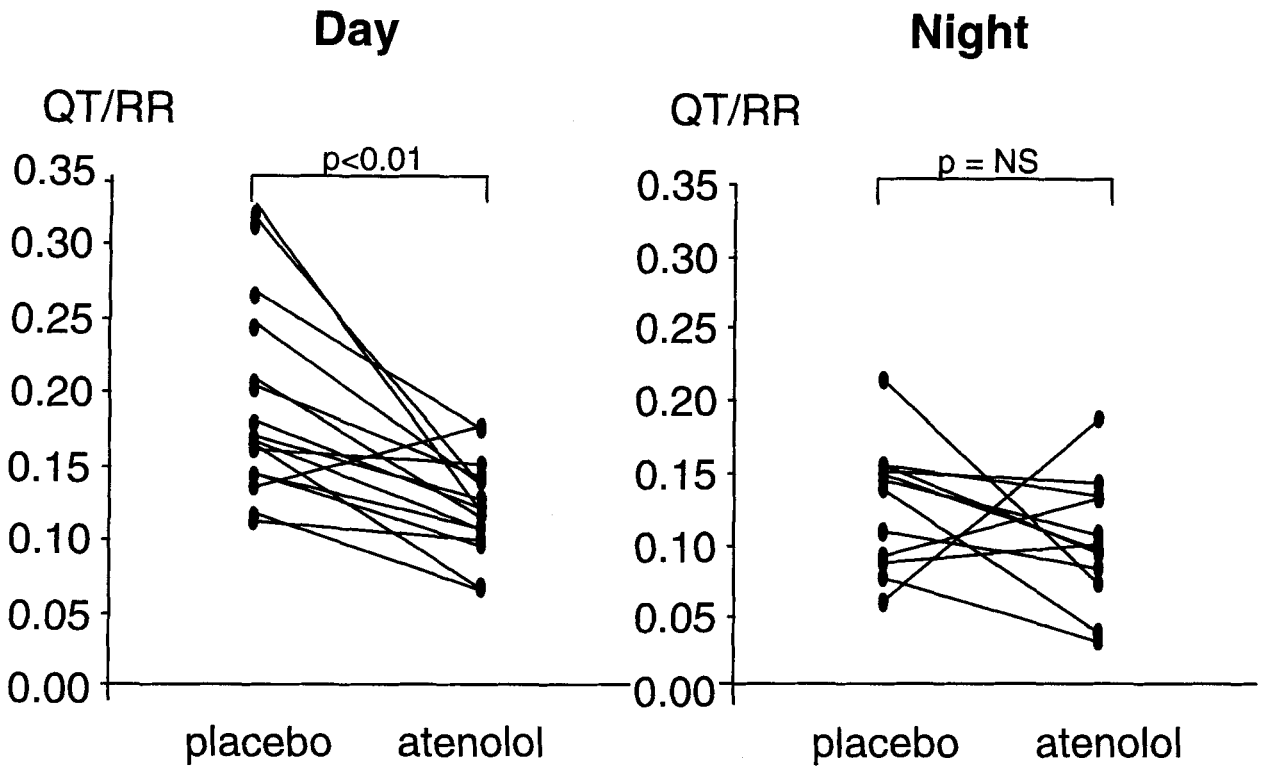

Figure 3. Left panel shows the individual QT rate-dependence on placebo and on placebo during the diurnal period. QT rate-dependence on atenolol is significantly lower than on placebo, but one subject has a steeper QT rate-dependence on atenolol than on placebo. Right panel displays the individual QT rate-dependence on placebo and on placebo during the nocturnal period. QT rate-dependence is not significantly different within the two groups. Some subjects have a steeper QT rate-dependence on atenolol than on placebo.

dence changes did correlate with heart rate or HRV variations. Using Oldham's transformation and the logarithmic transformation of MacGregor, we further investigated the determinants of QT rate-dependence changes. As said above, this approach allows us to include in the statistical model not only HR and HRV parameters, but also pretreatment QT rate-dependence data. A lack of correlation between QT rate-dependence changes induced by atenolol and atrial parameters was once more evidenced. Figure 4 shows that the decrease in QT rate-dependence induced by beta-blockade during the day was significantly dependent on the pretreatment QT/RR relation ($r = 0.65$, $P < 0.01$). The logarithmic transformation provided the following equation: ln [QT/RR (atenolol)] = 0.415* ln [QT/RR (placebo)] −1.42 ($r = 0.48$, $R^2 = 0.23$, $P = 0.06$). Using the same approach, no correlation was found at night.

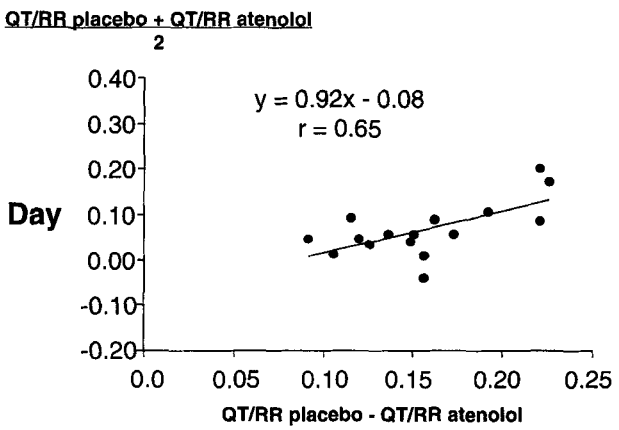

Figure 4. Oldham's transformation: Diurnal QT rate-dependence changes induced by atenolol are plotted on the horizontal axis, and the mean of pre and posttreatment QT rate-dependence on the vertical axis. The linear regression analysis shows a significant correlation. The baseline QT rate-dependence explains about 42% (R^2) of the variability in the data.

DISCUSSION

This is the first study to evaluate the effects of pharmacological sympathetic blockade on QT interval duration and QT rate-dependence in stable heart rate conditions and at steady-state oral beta-blockade, in healthy subjects, using patient's specific and ECG recording's specific approaches. We found that, although QT rate-dependence was correlated with the mean R-R interval, the cardiac effects of beta-blockade on QT rate-dependence cannot be predicted by R-R or HRV changes. In addition, drug-induced QT rate-dependence changes were dependent on the patient specific rate-dependence on placebo.

Autonomic Modulation of Ventricular ECG Parameters: Previous Studies

The clinical evaluation of autonomic influences on QT interval provided controversial results. Ahnve, et al. reported an increased QT interval after atropine administration but no change in QT duration after beta-blockade.[29] Other studies found either a decreased[30,31] or an increased QT interval after beta-blockade.[32,33] Since these authors compared QT interval durations at identical heart rate, the conflicting results cannot be related to the limitations of Bazett's formula.[32,34,35] Our results show that the data provided by the previous studies are not contradictory but can be easily reconciled.

Beta-blockade changes the relation between QT interval duration and heart rate QT rate-dependence slopes. Pre and posttreatment slopes have a crossing point which in our experience is located around a R-R interval value of 900 ms (800 to 1000 ms). Thus, the effect of beta-blockade on QT interval duration will be different according to heart rate considered. Studies reporting an increased QT interval after beta-blockade were performed with short basic pacing length (i.e., 500 ms in reference,[33] < 500 ms in reference[32]), whereas those showing a shortened QT interval used a longer R-R threshold (900 ms).[30] This underlines the need to escape from the concept of QT rate-correction to move to the relation between QT interval duration and heart rate (i.e., QT rate-dependence).

Comparisons with previous studies must be undertaken with extreme caution. Rate influences on QT interval have been evaluated using either invasive pacing protocols or spontaneous heart rate variations, but these two environments are far from being equivalent.

Pacing protocols allow to obtain perfectly stable heart rate conditions, but paced cycle lengths are shorter than spontaneous sinus cycle lengths and most importantly atrial pacing abolishes the autonomic modulation of ECG intervals. Using an invasive pacing protocol, Cappato et al. reported that complete autonomic blockade (coadministration of atropine and propranolol) flattens QT rate-dependence, whereas under propranolol alone QT rate-dependence remained unchanged.[36] However high pacing rates are not associated with a sympathetic stimulation and consequently the cardiac effects of adrenergic blockade might be partly blurred.

A large range of spontaneous heart rates can be obtained by exercise testing or with ambulatory Holter ECG recordings. Algra, et al. and Sarma, et al. used exercise protocols to assess the effect of beta-blockers on QT rate-dependence. In contrast in our findings, both studies reported an increased QT rate-dependence under beta-blocker.[37,38] Firstly, the autonomic and neurohumoral responses triggered by an exercise test are probably not comparable to ambulatory conditions, generally more gentle.

Then, regardless of the noninvasive method used, it is critical to measure QT duration in stable heart rate conditions to implement a linear QT/RR model. Indeed, in the absence of stable heart rate, QT rate-dependence fits a more complex curvilinear relationship.[39] To the best of our knowledge, the study of Viitasalo, et al. is the only other one measuring QT intervals at stable heart rate from long-term ECG segments and they also found a decrease of QT rate-dependence following beta-blocker administration.[40]

Accordingly, ambulatory long-term ECG recordings and selection of stable heart rate environment might represent the best compromise between invasive protocols and noninvasive studies to investigate drug effects on ventricular repolarization. Using this innovative model, we found that effects of atenolol on QT rate-dependence were different according to the circadian period considered. It is now well established that QT interval is prolonged during sleep state,[21,40,41] and QT rate-dependence also shows a circadian modulation. The steeper QT rate-dependence in awake state (in the placebo group) reported in this study is concordant with previous studies.[21,40,42] Therefore, the effect of a pharmacological sympathetic intervention on ECG

parameters should be evaluated at different circadian periods. In other words, rate-independent influences on ventricular repolarization are often ignored. During the day, ventricular repolarization rate-dependence was lower under atenolol when compared to subjects under placebo whereas, at night, QT rate-dependence revealed no difference between treatments. One can hypothesize that the decrease of sympathetic activity and/or of secretion of circulating catecholamines during sleep provides an explanation for the weaker cardiac effects of atenolol at night.

Lack of Agreement Between Heart Rate Changes and Repolarization Changes

As previously described, the level of QT rate-dependence was correlated with the mean R-R interval, a crude index of the sympathovagal balance.[21,43,44] Because the sinus node and the ventricle are on the influences of the same autonomic nervous system, it is not surprising to observe such correlation. QT rate-dependence changes induced by atenolol were correlated with the baseline mean R-R interval, but this correlation was no more observed after multiple linear regression analysis. Thus, heart rate reduction and HRV increase induced by atenolol cannot account for ventricular repolarization changes. Our results suggest that ECG variations induced by atenolol on the ventricle are more dependent on the baseline QT rate-dependence than on the baseline mean R-R interval. Since our population only included 16 patients, a lack of statistical power cannot be ruled out.

Nevertheless, such a differential effect is not surprising. $I_{ks,}$ a major component of ventricular repolarization, is activated by fast heart rates but also directly by catecholamines[45] and in these conditions shortens ventricular repolarization duration. I_{Ks} polymorphism and/or different spatial organization or densities might be the substratum of different behavior despite a similar heart rate change. Furthermore, adrenergic actions are not uniform throughout the heart. Less propranolol is required to block sympathetically induced shortening of ventricular refractoriness than is needed to prevent shortening of sinus cycle length.[46] Thus, since the magnitude of ventricular repolarization shortening during heart rate increase not only depend on heart rate change, the two component have not to be correlated.

The relation between heart rate reduction induced by beta-blockers and mortality in patients after myocardial infarction (MI) has been extensively reported by Kjekshus.[3] We cannot extrapolate our findings from healthy subjects to patients with an impaired cardiac substrate. Actually, the alteration of the substrate is associated with a trend in larger QT/RR relations.[47,48] In addition, we reported that postMI patients with documented ventricular arrhythmias have a steeper QT/RR relation than patients without tachyarrhythmias.[47] Provided that similar ventricular electrical patterns following chronic oral beta-blockade could be obtained in postMI patients (i.e., large interindividual variations), the clinical impact of an association between a consistent heart rate lowering and different QT rate-dependence changes (from −62% to +30%) is not clear. It seems conceivable that patients with both a drug-induced HR and a QT/RR relation decrease may have a different outcome from those with an HR decrease and a QT/RR relation increase. The latter subgroup may benefit from a combination with other medication such as amiodarone, as shown in the retrospective analysis of the EMIAT and CAMIAT trials.[49] So far, there is no prospective study to support this hypothesis.

QT Rate-Dependence: An Individual Feature?

We are the first to demonstrate that pharmacological sympathetic modulation was not consistent in healthy subjects but related to the baseline QT rate-dependence. The individual QT rate-dependence changes following pharmacological beta-blockade follow different patterns, as shown in Figure 3. Baseline steep QT/RR slopes are strongly depressed by beta-blockers, whereas initial low QT/RR slopes are only slightly modulated by atenolol administration and even in one case the QT/RR relation increased. Using the Oldham's transformation we showed that these patterns are statistically valid: the baseline QT rate-dependence explains about 42% of the variability in the data. After logarithmic transformation, the correlation between diurnal QT rate-dependencies on placebo and on atenolol reached 0.42 (i.e., < 1). It is therefore reasonable to conclude that the proportional change induced by chronic beta-blockade was increasing with increasing baseline QT rate-dependence. Since QT rate-dependence has been shown

to be stable over time,[50] our results cannot be due to a variability in the measure of this parameter.

Clinical Implications

Firstly, the large interindividual variability of the QT/RR patterns led to the concept of a patient's specific approach as an alternative to evaluate the potential effect of a drug on the QT interval. The use of a universal or of a population specific correction formula (based on the concept of rate influence alone and ignoring rate-independent influences) in a group of individuals has been shown to be incorrect.

Data from the present study also allow to hypothesize that the sudden cardiac death reduction by ß-adrenergic blocking agents after myocardial infarction might be related in part to a decrease of QT rate-dependence, leading to longer ventricular refractory periods at fast heart rates. Our data suggest that the protective beta-blockade effect might not be observed in all patients. Further studies are needed to investigate whether or not individual QT rate-dependence changes can predict beta-blockers efficiency in reducing mortality.

Evaluation of QT interval rate-dependence from long-term ECG recordings may provide a better understanding of the complex interactions between ventricular repolarization, heart rate and autonomic nervous system influences. We found a decreased magnitude of QT rate-dependence on atenolol when compared to placebo. Another new finding from the present study is that the beta-blockade cardiac effects are not predicted by heart rate or heart rate variability changes, but significantly related to individual ventricular repolarization properties.

Acknowledgments: *We are thankful to Fabio Badilini for his technical contribution to the achievement of this work and to Nathalie Neyroud for her assistance in preparing the Holter database.*

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