Influence of hydrophilic and lipophilic beta-blockers on heart rate, ventricular repolarization and their interrelationship in normal subjects

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Background. **It has been hypothesized that hydrophilic and lipophilic beta-blockers have different antiarrhythmic properties because only the latter seem to reduce the rate of sudden death in post-myocardial infarction patients as well as animal models which seem to be independent of their effect on autonomic nervous system modulation. The aim of this study was to evaluate the different effects of a hydrophilic (nadolol) and lipophilic (metoprolol) beta-blocker on ventricular repolarization in normal subjects.**

Methods. **Seventeen normal subjects entered this randomized, single-blind cross-over study designed to compare the effects of nadolol (80 mg/day) and slow-release metoprolol (200 mg/day) on dynamic ventricular repolarization. The RR intervals, the QT evaluated at the apex (QT apex) and at the end (QT end) of the T wave before and after correction for heart rate, the standard deviation of QT apex and QT end, and the slope of the QT/RR linear relationship (QTa-slope and QTe-slope) were studied using the ELATEC system (ELA Medical, Mountrouge, France), and an evaluation was made of their reproducibility and the effects of each beta-blocker.**

Results. **The most reproducible parameters were QT apex, corrected QT apex and the QTe-slope. Nadolol was associated with a greater adrenergic blockade than metoprolol (lengthening of RR interval +25 ± 7 and +17 ± 8% respectively, $p = 0.0003$) and a lower effect on ventricular repolarization (reduction of corrected QT apex -0.6 ± 3 and -2.5 ± 2.1% respectively, $p < 0.01$; reduction of QTe-slope -5 ± 16 and -15 ± 15% respectively, $p = 0.03$).**

Conclusions. **At the dosages used in the study, metoprolol showed lower adrenergic blockade but greater effect on ventricular repolarization than nadolol.**

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Beta-blockers are the most important drugs in lowering mortality in post-myocardial infarction patients[1]. This favorable effect has been attributed to the fact that they modify autonomic nervous system activity and it has been suggested that this ability could be only related to lipophilic beta-blockers[2]. However, although a number of studies have sought to evaluate whether this benefit was due to differences in the effects of hydrophilic and lipophilic beta-blockers on autonomic nervous system activity[3-7], no difference has been found in either normal subjects[5] or coronary artery disease patients[3,4,6-8].

Beta-blockers are also able to prolong ventricular repolarization time when they are administered chronically but not acutely[9]. This effect could also be beneficial. However, repolarization is under the influence of autonomic nervous system activity and, therefore, changes caused by beta-blockers may be the result of either the heart rate slowing effect and their direct influence on the repolarization phase. As far as our knowledge is concerned, no data have been published so far on the effect of beta-blockers on dynamic changes in ventricular repolarization. In particular, it would be of great interest to evaluate whether two beta-blockers characterized by different degrees of lipophilicity differently influence the dynamic ventricular repolarization in normal subjects.

Methods

Subjects. We studied 22 normal young volunteers (11 males and 11 females with a

mean age of 28 ± 2 years), all of whom were screened by means of a full medical history, physical examination, standard laboratory tests, a 12-lead ECG, 24-hour ECG monitoring, blood pressure measurements, and two-dimensional echocardiography in order to rule out the presence of any cardiac or non-cardiac disease.

Study design. This was a randomized, single-blind, two-period, cross-over trial. After two baseline evaluations separated by a mean period of 15 ± 2 days, the subjects were randomly assigned to nadolol (80 mg/day) or slow-release metoprolol (200 mg/day) treatment for 1 week; the second beta-blocker was administered after a 14-day washout period. The end-of-treatment 24-hour ECG monitoring evaluations were made during the last 2 days of each treatment period.

Instrumentations and data analysis. The measurements were obtained by two-channel 24-hour ECG recordings (Del Mar Avionics Model 445A, Irvine, CA, USA), which were always begun between 8.00 and 9.00 a.m. During the day, the subjects were allowed to undertake all of their usual activities except those requiring intense physical effort; no coffee, tea or alcohol consumption was permitted and the subjects had to go to bed at their usual time. All of the tapes first underwent a 200 Hz A/D conversion using 8 bit and 10 mV amplitude resolution. The digitized signals were then processed by means of the ELATEC software (Ela Medical, Mountrouge, France), which is capable of dividing the recording of templates of 30 s each (2880 templates for each 24-hour recording). For each template, the algorithm automatically measured the QT apex, QT end and RR interval. The T wave apex was determined by fitting a parabola through the peak of the T wave as described by Merri et al.[10], whereas the T wave end was determined by the intersection of the tangent of the downslope of the T wave with the isoelectric baseline (Fig. 1). The software also computed the slopes of the linear regressions of QT end and QT apex values plotted against the corresponding RR interval (QTe/RR and QTa/RR)[11,12].

The QT variability indices were the standard deviation of the QT intervals over the 24-hour period and the slope of the regression line between QT and RR during the 24-hour period (QT slope). The QT slope indicates the correlation between the two parameters (i.e. the QT interval and RR cycle length), and so the steeper the slope, the greater the QT changes relating to small changes in the RR intervals. The calculation was made using only one lead (CM5) and templates with an amplitude of Ž 0.15 mV. Corrected QT was calculated using Bazett's formula.

Data reproducibility was checked, and then the effects of the two beta-blockers were compared with each other, and finally with baseline data.

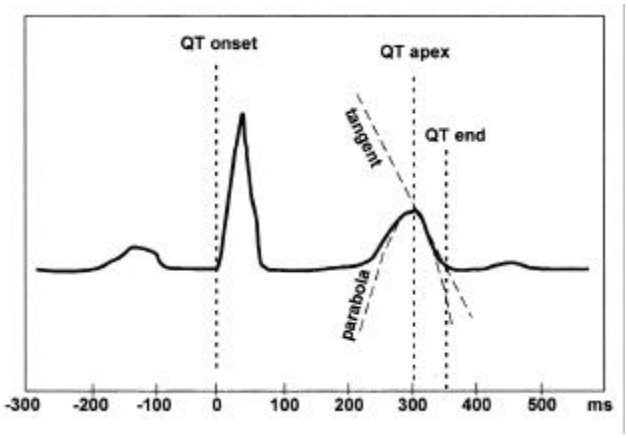

Figure 1. QT end and QT apex as calculated using the module of averaged QT. In the case of QT end, the end of QT corresponds to the intercept between the maximum negative slope and the isoelectric line; in the case of QT apex, the end of QT corresponds to the maximum of the parabola that best fits the top of the T wave.

Statistical analysis. Data are expressed as mean values ± SD. Intrasubject data reproducibility was evaluated by means of the intraclass correlation coefficient, which measures the strength of the association between the two baseline recordings[13]. Data were considered reproducible if the intraclass correlation coefficient was > 0.60; in particular, reproducibility was considered good if the intraclass correlation coefficient was between 0.61 and 0.80, and almost perfect if it was between 0.81 and 1.00[14].

The normal data distribution was verified using the W-Shapiro-Wilk test. Mean values of each parameter were compared using Student's t test for dependent sample. Statistical analyses were performed by using Statistica 5.0 for Windows '95 (StatSoft Inc., Tulsa, OK, USA). A p value of < 0.05 was considered statistically significant.

Results

Two subjects were excluded from the study because of the occurrence of dizziness (one during nadolol and one during metoprolol administration), and a further 3 were excluded because it was not possible to make an automatic baseline recording suitable for analyzing QT variability. Therefore, final analysis was performed on 17 subjects. The incidence of supraventricular beats was < 0.5%, and the 2 subjects with premature ventricular beats experienced < 10 in the 24-hour period.

The intraclass correlation coefficient values of the studied parameters are shown in figure 2. The highest values of reproducibility were found for RR intervals, QT apex, corrected QT apex and QTe-slope.

Table I shows the effects of the beta-blockers on the studied parameters. Both beta-blockers significantly lengthened RR intervals in comparison with both baseline recordings although metoprolol had a significantly lower heart rate slowing effect than nadolol (Table I, Fig. 3).

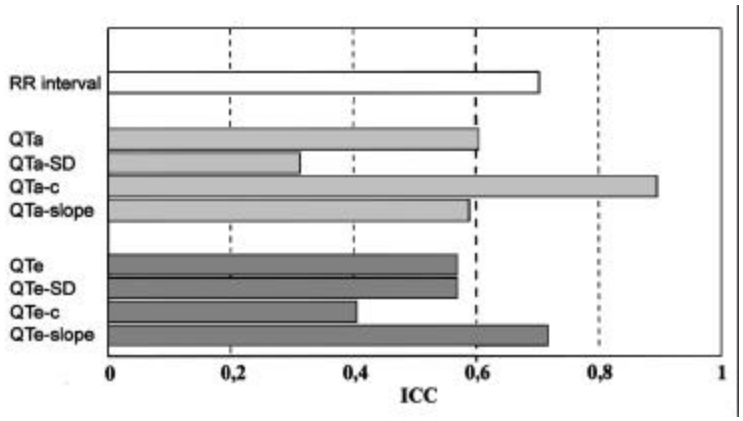

Figure 2. Reproducibility of the studied parameters evaluated by means of the intraclass correlation coefficient (ICC) between the two baseline recordings. The dotted line indicates the cut-off point for good reproducibility.

Table I. Effects of beta-blockers on RR intervals and QT parameters.

	First baseline	Second baseline	Metoprolol	Nadolol
RR (ms)	829.1 ± 64.8	850.7 ± 83.7	969.7 ± 97.2*§	1034.2 ± 98.6*
QT apex (ms)	279.0 ± 15.0	282.2 ± 18.9	293.7 ± 14.9*§	308.9 ± 12.9*
QT end (ms)	355.2 ± 14.1	358.5 ± 21.1	364.7 ± 16.9*§	380.4 ± 13.5*
QT apex-c (ms)	306.8 ± 17.5	306.6 ± 19.1	299.1 ± 16.1§	304.7 ± 16.6
QT end-c (ms)	386.0 ± 24.5	389.3 ± 18.3	370.1 ± 20.1*	375.0 ± 17.4*
QT apex-SD (ms)	27.1 ± 6.1	26.2 ± 8.3	19.0 ± 4.4*	19.7 ± 5.2*
QT end-SD (ms)	24.2 ± 6.7	24.4 ± 7.9	19.0 ± 4.7*	21.0 ± 5.6*
QTa-slope	0.189 ± 0.03	0.177 ± 0.05	0.141 ± 0.04*	0.139 ± 0.03*
QTe-slope	0.157 ± 0.037	157 ± 0.040	0.132 ± 0.035§	0.147 ± 0.031

Data are expressed as mean ± SD. QT apex-c = QT apex corrected; QT end-c = QT end corrected; QT apex-SD = standard deviation of QT apex; QT end-SD = standard deviation of QT end; QTa-slope = slope of the regression line between QT apex and RR interval; QTe-slope = slope of the regression line between QT end and RR interval. * $p < 0.05$ vs baseline; § $p < 0.05$ vs nadolol.

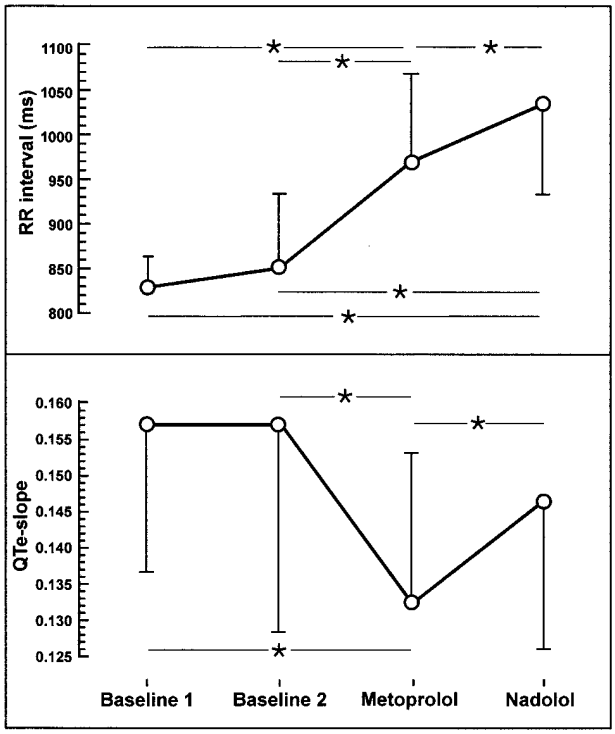

Figure 3. The effects of the two beta-blockers on the reproducible parameters. Top panel: mean RR intervals; bottom panel: QTe-slope. * $p < 0.05$.

This difference was also evident when the percentage change from baseline was calculated (metoprolol +17 ± 8% vs nadolol +25 ± 7%, $p = 0.0003$).

Both beta-blockers reduced the QTe-slope in comparison with the two baseline values, but only the effect of metoprolol was significant (Table I, Fig. 3); the percentage change from baseline was -15 ± 15% for metoprolol and -5 ± 16% for nadolol ($p = 0.03$).

Discussion

The main results of the present study are that QT apex, corrected QT apex and QTe-slope are the most reproducible QT variability parameters, that lipophilic beta-blockers have greater effects on ventricular repolarization dinamicity than hydrophilic ones and, finally, that this influence is independent of their heart rate slowing effect.

We believe that the QTe-slope represents the most reliable parameter for evaluating the effect of beta-blockers on ventricular repolarization variability. This is due to its high degree of reproducibility and, perhaps more importantly, because simple QT measures are over-in-

fluenced by the heart rate slowing effect of beta-blockers. Moreover, a number of studies have shown that the effect of beta-blockers on ventricular repolarization cannot be predicted by means of corrected QT measures[15]. Furthermore, in comparison with that of QT apex, the dynamic behavior of QT end better reflects the entire repolarization phenomenon.

The interest in drugs capable of modifying QT intervals is due to the fact that experimental and clinical studies have shown that an increased QT interval at surface ECG is associated with cardiac electrical instability and could lead to the development of ventricular arrhythmias not only in patients with congenital long QT syndrome but also in those with other cardiac diseases[16-20]. The lengthening of the QT interval may reflect an increase in the dispersion of repolarization, and this may contribute to the genesis of malignant ventricular arrhythmias by enhancing triggered activity[21] or reentrant mechanisms[22].

Effects of beta-blockers on the QT interval. Although it is known that beta-blockers may influence QT intervals, the exact mechanism of action as well as whether this is a class or specific effect of some beta-blockers are far from being completely understood. There are several ways by which beta-blockers could modify ventricular repolarization. First, this class of drugs is known to slow down heart rate and blunt adrenergic activity. Second, it may be that at least some beta-blockers could directly modify repolarization by a direct cellular mechanism. Third, they could show an indirect effect (i.e., a reduction in oxygen requirement and/or an improvement in myocardial perfusion). Beta-blockers are a heterogeneous class of drugs with different degrees of heart rate slowing effect, antiadrenergic properties and lipophilicity. On the basis of our results, it seems that they also have different effects on ventricular repolarization which are independent of their effects on heart rate and adrenergic system activity.

The published studies reported so far have shown that the effects of beta-blockers on QT intervals differ depending on whether they are administered acutely or chronically. In general, it seems that the intravenous administration of beta-blockers does not modify ventricular repolarization, whereas an increase in corrected QT intervals has been reported when they are given chronically[9]. These studies limit the role of heart rate change and support the hypothesis that beta-blockers have a direct effect on ventricular repolarization. We have previously demonstrated that the administration of nadolol lengthens QT intervals, but the restoration of heart rate by means of atrial pacing showed that this hydrophilic beta-blocker did not modify the relationship between cardiac cycle lengths and QT intervals: i.e., the shorter the cycle length, the shorter the QT interval[22]. Ahnve and Vallin[15] have studied the modifications in QT and corrected QT intervals occurring during sinus and pacemaker-induced rhythm before and after the administration of propranolol or propranolol plus atropine. The increase in heart rate was associated with a significant reduction in QT intervals that remained evident after both treatments. The fact that the trend of the changes in QT intervals at different heart rates was not influenced by drug administration suggested that ventricular repolarization is intrinsically capable of adapting to heart rate.

The results of the present study suggest that, although both beta-blockers are capable of modifying ventricular repolarization, the effect of the lipophilic beta-blocker, metoprolol, is more pronounced. This finding is particularly interesting if one considers that the antiadrenergic properties of metoprolol were found to be less that those of nadolol. Therefore, this paper hypothesize for the first time that the influence of beta-blockers on ventricular repolarization dynamicity is independent of the heart rate slowing effect and, of even greater importance, it is not a class characteristic but is specific for some of them. We do not know whether the greater influence on ventricular repolarization found for metoprolol may or may not depend on its ability to pass the blood-brain barrier or to other cellular or peripheral effects.

These data refer to the method used; we cannot exclude that other methods of evaluation of QT variability could attain different results.

From the clinical point of view, the QTe-slope has demonstrated to be a good marker for evaluating the influence of beta-blockers. Although QTe-slope is not a universally accepted measurement of ventricular repolarization, these results are even more interesting considering the recent demonstration that this parameter has a negative prognostic significance in patients surviving a myocardial infarction[23].

Since these results were obtained in normal, young subjects, further studies need to be designed in order to evaluate the prognostic significance of the QTe-slope in different cardiovascular diseases and to test whether the greater efficacy of metoprolol in modifying heart rate-dependent repolarization changes may explain its beneficial role in reducing mortality.

In conclusion, the effect of the metoprolol on ventricular repolarization dinamicity in normal subjects is greater than that of nadolol, is independent of the heart rate slowing effect and seems to be a specific characteristic of some beta-blockers.

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