"Normal" Response of the QT Interval and QT Dispersion Following Intravenous Injection of the Sodium Channel Blocker Disopyramide: Methodological Aspects

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Summary. Measurement of the QT dispersion (the maximal interlead difference) on the surface electrocardiogram has been suggested for assessing the risk for ventricular arrhythmias and for examining drug effects and their proarrhythmic potential. The acute response of QT dispersion was assessed in 10 healthy subjects receiving disopyramide, which is known to delay repolarization and to prolong global measures thereof. The QRS, JT, and QT intervals and their dispersion were assessed at spontaneous rhythm and at atrial pacing at baseline and after an intravenous injection of disopyramide 2 mg/kg over 5 minutes. The short-term (within 30 minutes) and long-term (≥2 weeks) variabilities of the QT interval and the QT dispersion, expressed as the coefficient of variation, were also analyzed. At spontaneous rhythm the group average QT interval was between 369 and 375 msec, and the QT dispersion was between 33 and 37 msec; both were relatively stable over time. All subjects responded homogeneously to disopyramide with a significant QT prolongation (p < 0.001), but no consistent response of the QT dispersion was observed. This discrepancy reflects the significant difference in time-dependent variability with a coefficient of variation of spontaneous, paced, and heart rate–corrected QT dispersion between 25% and 42%, 8–42 times greater than the corresponding values of 1–4% for the QT intervals. The individual response of the QT dispersion to drug challenge should therefore be interpreted with caution. Furthermore and as a consequence, QT dispersion is less sensitive for assessing drug effects on ventricular depolarization and repolarization than the QT interval.

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Heterogeneity of the recovery of ventricular excitability might be a substrate for ventricular arrhythmias. Thus, vulnerability to ventricular fibrillation increased in parallel with the increase in regional differences (dispersion) of the ventricular refractory period [1]. Furthermore, an increased dispersion of left ventricular recovery of excitability, due either to regional differences in activation time or to differences in refractoriness, was observed in patients with ventricular tachycardia compared with controls [2]. Other studies on the recovery of ventricular excitability in humans have shown a strong correlation over a range of different heart rates between, on the one hand, the invasively assessed effective refractory period of the ventricular myocardium and the monophasic action potential duration and, on the other hand, the noninvasively recorded QT interval [3,4]. In addition, there is strong evidence that QT dispersion, or the maximal interlead difference in the QT interval in the surface electrocardiogram (ECG), reflects dispersion of ventricular recovery of excitability and conveys similar information [5–8]. Measurement of QT dispersion has therefore been suggested for the purpose of assessing risk for ventricular arrhythmias [9], and for examining drug effects [6–10] and their proarrhythmic potential [11]. This raises the issue of what can be considered a normal response, especially on the individual level. The purpose of the present study was to address this issue.

Materials and Methods

The ECG recordings were made in connection with a comparative study on the acute effects of disopyramide and its main metabolite (randomly given at investigations I and II, respectively), the details of which have been presented elsewhere [12]. The protocol, which was approved by the locally appointed ethics committee of the Karolinska Institute, included ECG recording at a fixed heart rate, with rate being a crucial determinant for the QT interval and its dispersion [3,4].

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Subjects
Ten healthy persons (six males), the majority being health professionals, volunteered for two invasive electrophysiologic studies. Their mean age was 28 years (range 22–34), and their average body weight was 69 kg (range 55–83 kg). They were considered healthy on the basis of clinical history, physical examination, routine blood tests, and standard 12 lead ECG. They were not taking any medicine.

Methods
Two electrophysiologic studies were performed ≥2 weeks apart with the subjects in the nonsedated post-absorptive state. Under local anesthesia, two 6 French quadripolar electrode catheters were introduced percutaneously via the right femoral vein and positioned in the right atrium in the vicinity of the sinus node and over the tricuspid valve. The atrial catheter was used for pacing with a stimulus duration of 2 msec at an amplitude two to four times the diastolic threshold. An eight channel mingograph (Siemens-Elema) was used for the simultaneous recording of high and low right atrial potentials and the His bundle potential, respectively, together with five surface ECG leads (I, II, V1, V2, and V6). These were chosen to allow definition of the frontal plane electrical axis, to allow diagnosis of right- and left-sided intracardiac conduction abnormalities, and included leads that usually give values close to the maximal and minimal QT interval, leads V2 and II, respectively [13]. The QRS and QT intervals were measured in all surface leads, and the JT interval was calculated as the QT interval minus the QRS interval. Dispersion was expressed in absolute terms (in milliseconds) by the differences between the maximal and minimal QRS, JT, and QT intervals, respectively. QT dispersion was also expressed in relative terms (in percent), as recently proposed, by dividing the standard deviation of the QT intervals from all leads by their mean value multiplied by 100 [7]. The QRS, JT, and QT intervals, and their dispersion, were assessed at spontaneous rhythm, at the end of a 1-minute recording at a paper speed of 100 mm/sec. The same variables were measured at the end of an eight-beat train of atrial pacing (ap) at 100 beats/min or at the closest rate with 1:1 conduction (for assessment of the effective refractory period of the atrioventricular node) at a paper speed of 50 mm/sec. Heart rate–corrected values of JT and QT were computed from intervals at spontaneous rhythm according to the method by Bazett, such that JTc = JT/√RR in seconds and QTc = QT/√RR.

In each study (I and II) the conduction intervals at spontaneous rhythm were assessed twice at baseline within 30 minutes apart (A and B). In total, all intervals were therefore assessed four times at the spontaneous rate and twice after atrial pacing.

Disopyramide was then given intravenously at 2 mg/kg over 5 minutes. After injection drug effects and plasma levels were assessed every fifth to seventh minute for 1 hour [12]. For analysis of the drug-induced effects in this study, we selected the time point for the maximal QT effect in each individual as measured in lead II in the previous study [12].

For the purpose of this study and in order to avoid interobserver variation and to minimize bias, the intervals were then measured de novo by a technician, who was unaware of the condition under which the recording had been made. The QT interval was measured from the onset of the QRS complex to the end of the T wave. The T end was defined as the point at which the downsloping limb of the T wave returned to the T-P baseline, represented by a line drawn through the isoelectric parts of consecutive PQ intervals. In the rare instances of U waves, the QT interval was measured to the nadir of the curve between the T and the U wave. All intervals were measured manually, and the mean of three intervals was calculated for spontaneous rhythm. After pacing only one interval was measured, that is, when the extrastimulus was no longer conducted and the end of the T wave was unaffected by the pacing artifact and the evoked P wave.

Statistics
Student's t test for paired data was used for comparison of ECG variables before and after drug. For analysis of their time-dependent variations, we calculated the coefficient of variation (CV) as previously described [14]. The within-subject, that is, intraindividual, standard deviation (s) was first calculated as

$$s = \sqrt{\frac{d_1^2/2 + \ldots + d_n^2/2}{n}},$$

where $d$ is the difference between the two compared measurements for each individual. From this the CV was computed as

$$CV = \left(\frac{s}{\bar{x}}\right) \times 100(\%),$$

where $\bar{x}$ is the total mean of the two sets of observations under comparison, that is, the mean of 20 observations.

The correlation coefficient and regression analysis was used to evaluate any relation between the size of the paired observations made at different time points in any individual ($|x_1 - x_2|/2$) and the size of their difference ($|x_1 - x_2|$); that is, if the variation showed any tendency to change with the magnitude of the measurements.

Results
At each investigation the interval between the two baseline recordings (A and B) was 20–30 minutes, and the mean interval between investigation I and II was 25 days (range 14–63). The variation range and the maximal change in sinus cycle length, which reflect the autonomic tone and sinus node function, were within the age-related reference limits on both occasions [15].

Baseline
The group mean values were relatively stable over time, as shown in Figure 1. At the four assessments