Subject-specific profiles of QT/RR hysteresis

Marek Malik,1,2 Katerina Hnatkova,1,2 Tomas Novotny,3 and Georg Schmidt4

1Saint Paul’s Cardiac Electrophysiology, London, and 2Saint George’s, University of London, London, United Kingdom; 3University Hospital Brno, Masaryk University, Brno, Czech Republic; and 4Medizinische Klinik, Technische Universität München, Munich, Germany

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METHODS

Population. The data of the study originated from clinical investigation CARISEPY 1025 sponsored by Johnson & Johnson Pharmaceutical Research and Development (Titusville, NJ). The study included repeated, long-term, 12-lead ECG recordings obtained during daytime hours. For the purposes of this investigation, the data were available in 40 healthy subjects (18 females; mean age, 30.4 ± 8.1 yr; range, 19 to 48 yr; interquartile range, 24 to 36 yr). Female subjects were marginally older (32.3 ± 19.4 yr) than male subjects (28.9 ± 6.7 yr), but the difference was not statistically significant. All subjects had a normal physical examination and a normal resting ECG at the study onset. During the ECG recordings of this investigation, the subjects were not on any medication, including hormonal contraceptives or hormone replacement therapy, homoeopathic or herbal remedies, and dietary supplements. They also refrained from smoking or digesting caffeine or alcohol. Also, during the actual ECG recordings, the subjects were not permitted to sleep. The study was conducted at the clinical facility of PPD Development (Austin, TX) and was approved by the Ethics Committee of the facility. All subjects gave informed, written consent.

ECG recordings. This investigation used ECG recordings obtained during the baseline of three phases of clinical study CARISEPY 1025 when the subjects were not exposed to any investigational drug. Thus, we could then reliably measure QT/RR hysteresis.

HEART RATE DEPENDENCY of the electrocardiographic QT interval has been the subject of numerous studies. Electrocardiographic data sets of variable sizes, sources, and quality have been used to investigate the relationship of the QT interval to heart rate (3, 12, 14, 26, 28), most frequently with the aim of finding a universally applicable heart rate correction formula. On the contrary, the adaptation of QT interval duration to rapid rate changes, which is the lag with which QT interval duration responds to heart rate changes, has been studied much less frequently. Indeed, in numerous studies that investigated the relationship between QT interval and heart rate in short-term (such as 10 s) electrocardiograms (ECG), the QT adaptation to heart rate changes has been, as a rule, impossible since no heart rate history preceding the measured ECGs was available.

The time scale of the adaptation of QT interval to heart rate changes, most frequently termed the QT/RR hysteresis, has been previously approximated in investigations with constant pacing rates. Such experiments measured both the action potential durations (11) and QT intervals in surface ECGs (17). Studies of QT/RR hysteresis in long-term ECG recordings without pacing provocation appeared only recently, made possible by the electronic capture and analysis of substantial ECG data. Differences in the QT/RR hysteresis profile were reported to stratify the risk in survivors of myocardial infarction (25, 29). It has also been reported that the correction of the QT interval for both heart rate and QT/RR hysteresis leads to more stable corrected QT (QTc) data with possible implications for clinical studies of repolarization changes (20). Proposals have also been made that the graphic display of the QT/RR hysteresis might be helpful in the detection of drug-induced QT interval changes (10).

Still, there is little knowledge on the basic physiology of QT/RR hysteresis, and detailed investigations in healthy subjects are lacking. With this in mind, this study investigated QT/RR hysteresis in a population of healthy subjects for whom repeated high-quality, long-term, 12-lead ECG recordings were available. The study aimed at studying whether QT/RR hysteresis can be consistently measured in long-term 12-lead ECGs, whether the hysteresis profiles differ among healthy subjects, and whether there is any relationship between the static QT/RR relationship and the dynamic QT/RR hysteresis.

Address for reprint requests and other correspondence: M. Malik, St. Paul’s Cardiac Electrophysiology, London, 16 Verulam Ave., Purley, Surrey CR8 3NQ, UK (e-mail: marek.malik@btinternet.com).

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for the purposes of this investigation, each subject underwent three long-term, digital 12-lead ECG recordings that were initiated between 7 AM and 8:00 AM and lasted \( \geq 13 \) h. Periods of 2 to 3 wk separated individual recordings in each subject, but the recordings were obtained in the same place and under the same environmental conditions. The recordings were obtained with SEER MC digital portable electrocardiographs (GE Healthcare, Milwaukee, WI) with the electrodes placed in Mason-Likar positions. The electrode placements were marked on the skin of each subject, and the electrode positions were carefully reproduced from recording to recording.

**Selection of ECG data for QT interval measurements.** Short-term, 10-s ECG segments were selected in each long-term ECG recording for an accurate QT interval measurement with the aim of characterizing 1) QT/RR profile in which the QT interval durations have been already adapted to heart rate and 2) QT interval adaptation to heart rate due to QT/RR hysteresis. Specifically, the following three separate steps of short-term ECG extractions were used.

During each recording period, the subjects were placed 26 times into standardized positions, mainly supine but also unsupported sitting and supporting standing. Each of these stable positions defined a 5-min window during which up to five 10-s ECG segments were selected from the long-term recording, all preceded by \( \geq 90 \) s of stable heart rate with fluctuations less than \( \pm 2 \) beats/min with the heart rate calculated in 10-s segments. The selected ECG segments were not adjacent, and all of the ECG segments preceded by stable heart rate had the lowest noise content (1). The noise was characterized by a square root of the product of the SD noise and the root mean square of successive difference noise (1). This procedure defined up to 130 segments in each long-term recording.

In addition, all 10-s ECGs were found in each recording that were preceded by \( > 120 \) s of stable heart rate (variability, less than \( \pm 2 \) beats/min). These were sorted according to the preceding stable heart rate and divided, in each long-term recording, into 100 bins as equidistant as possible in the underlying heart rate. In each bin, the ECG with the lowest noise content (1) was selected.

Furthermore, all 10-s ECG segments were found in each recording preceded by 120 s during which the heart rate varied by greater than \( \pm 2 \) beats/min. Specifically, the variability of heart rate was calculated as the difference between the slowest and fastest heart rate in 10-s segments of the preceding 2 min. Of these ECG segments, 100 were selected that were separated by at least 2 min from each other and of which 50 and 50 were preceded by the largest heart rate deceleration and acceleration, respectively. An additional 30 ECG segments preceded by variable heart rate were obtained from six prespecified 5-min windows during which the subjects were changing their postural positions.

Thus, in total, up to 360 ECG segments, each of 10-s duration, were selected for a detailed QT interval measurement from each long-term recording.

**ECG measurements.** Each selected 10-s ECG segment was filtered, and its baseline wander was removed. [Modified versions of published filtering (4) and baseline wander removal (23) techniques were used.] From the filtered signals, the median representative beats were constructed and the QT intervals (from global QRS onset to global T-wave offset) were measured using a pattern matching algorithm. In each ECG, the Q onset and T offset triggers were visually checked and, where necessary, manually corrected by two independently working cardiologists. These visual checks and measurement corrections were performed on a computer screen in median beats with superimposed images of all 12 leads in a 1-KHz resolution (cubic spline interpolation). Cardiologists were also permitted to declare an ECG as nonmeasurable.

The results of these measurement checks by the two cardiologists were compared, and the ECGs in which the cardiologists differed either in their decision on measurability or in the QT interval duration by \( > 6 \) ms were identified. These ECGs were returned to the same pair of cardiologists for repeated verification. After the second measurement, the results provided by the two cardiologists were again compared and cases of disagreement reconciled by a senior cardiologist. All ECGs of the same individual were processed by the same pair of cardiologists and by the same senior cardiologist.

After obtaining these manually verified and reconciled measurements, all measured ECGs of the same subject were pattern classified with an adjustment algorithm to ensure that similar ECG morphological patterns were measured systematically. Thereafter, the measurement was again visually checked and, where necessary, manually corrected by a senior cardiologist. Subsequently, the Q onset and T offset triggers were projected from the median beats into the individual beats of the measured ECG segment (18).

For each measured 10-s ECG segment, the QRS positions were identified, and a history of \( \geq 250 \) RR intervals preceding the measured segment was obtained [the number of 250 RR intervals was based on previous observations (25) and practicality]. The computer identification of the QRS complexes and of RR interval measurement was verified and, if necessary, corrected by a cardiologist on a computer screen displaying the 12-lead rhythm.

**Measurement of QT/RR hysteresis.** In each recording, the QT/RR hysteresis was assessed using an optimized version of a previously published methodology (25). The assessment used the data obtained from the ECG segments preceded by variable heart rates.

Presently, it is not known whether the influence of the RR interval history on the QT interval duration diminishes with every cardiac cycle or whether it decreases with time. To distinguish this, two different modes of hysteresis were investigated. The first expressed the history of the QT measurement in terms of the number of RR intervals; the other, in terms of the time elapsed. In the following text, these modes are called the “interval-based” and the “time-based” hysteresis.

As previously published, the profile of the QT/RR hysteresis was modeled by a numerical parameter of exponential decay (25), i.e., the two modes of hysteresis were characterized by numerical parameters \( \lambda_1 \) and \( \lambda_2 \) with the hysteresis contribution of the preceding \( n \) RR intervals to the QT interval duration weighted as follows:

\[
1 - e^{-\lambda_1 n R R}
\]

for the interval-based QT/RR hysteresis, and

\[
1 - e^{-\lambda_2 \sum_{i=1}^{n} R R}
\]

for the time-based QT/RR hysteresis, where \( L \) is the number of all RR intervals in the history (RR)\(_{\text{RR}}\) \(_{\text{RR}}\) of the QT interval measurement.

In addition to the QT/RR hysteresis assessment in each separate recording, the data of the 10-s ECG segments preceded by the most variable heart rate were also pooled from all three repeated recordings in each subject and the same algorithms provided pooled hysteresis profile and coefficients \( \lambda_1 \) and \( \lambda_2 \). Hence, for each hysteresis mode, four different values of the \( \lambda \) coefficients were found for each subject: three corresponding to the three separate recordings and one corresponding to the pooled data of all three recordings.

**Correction for QT/RR hysteresis.** Each QT interval measurement was related to four different RR-interval values. These were 1) the averaged RR interval in the 10-s ECG segment in which the QT interval measurement was made, 2) the average of RR intervals in 120-s history of the QT interval measurement, 3) the RR interval value obtained from the interval-based hysteresis profile applied to the RR history of the measured segment (the profiles were calculated for each cardiac beat within the measured segment and subsequently averaged), and 4) the same as in 3 above using the time-based hysteresis.
For each of these possibilities, the pairs of QT and RR interval data were processed with a previously described spectrum of linear and nonlinear regression models (2, 19, 25) from which the model leading to the lowest regression residual was selected.

These regression residuals (i.e., the SD of QTc values when the optimum regression model is converted into an individualized correction formula) were calculated for 1) all the QT data measured in the same recording and 2) all the QT data measured in the same subject (i.e., pooling the 3 separate recordings together).

Correction for heart rate. From the spectrum of linear and nonlinear regression models (2, 19, 25), the model that led to the lowest sum of regression residuals over all study subjects was identified and the slope parameter $\alpha$ of this model (i.e., the parameter used for heart rate correction with this population optimum model) was optimized for each subject using all the measured data. The same individual optimization of the slope parameter $\alpha$ was also performed for the linear model $\text{QT} = \alpha \times \text{RR} + \beta$, as well as for the parabolic log/log model $\text{QT} = \beta \times \text{RR}^T$. These individually optimal $\alpha$ parameters were correlated with the individual $\lambda_I$ and $\lambda_T$ coefficients (obtained from pooled data of the same subject) to study the relationship between QT/RR hysteresis and the static QT/RR relationship.

Statistics and data evaluation. The RR interval measurements and the records of RR history for the purposes of hysteresis calculation were expressed in seconds. The QT intervals and QT/RR regression residuals were expressed in milliseconds.

In each subject, each of the three recordings provided separate values of $\lambda_I$ and $\lambda_T$. From these three values, the intrasubject average and intrasubject SD of the $\lambda_I$ and $\lambda_T$ values were calculated. The intrasubject SDs were compared (1-sample, 2-tailed $t$-test) with the intersubject SD of the $\lambda_I$ and $\lambda_T$ values obtained from the pooled three recordings. A statistically significant difference with lower intrasubject SD was interpreted as $J$ proof of consistency in the measurement of the $\lambda_I$ and $\lambda_T$ values and 2) subject-specific individuality of the QT/RR hysteresis. To test whether the comparison between intrasubject and intersubject SDs distinguishes between individual-specific values and measurement characteristics that are substantially influenced by random errors, the same comparison was also applied to the maximum noise contents found in the analyzed ECG segments of separate long-term recordings.

To test the stability of the QT/RR hysteresis assessment from long-term ECG recordings, the averages of the $\lambda_I$ and $\lambda_T$ values obtained from the three separate recordings in the same subject were also compared with the $\lambda_I$ and $\lambda_T$ values derived from the pooled QT and RR interval data of the three recordings. The correspondence between the averages and the values obtained from the pooled data was interpreted as a further confirmation of measurement stability. For the same purpose, the individual $\lambda_I$ and $\lambda_T$ values were mutually correlated.

To test the relationship between the QT/RR hysteresis and the static QT/RR relationship, the $\lambda_I$ and $\lambda_T$ values were correlated with the individual correction parameters.

The QT/RR regression residuals (i.e., the SDs of the QTc values) were compared (1-sample, 2-tailed $t$-test) for the four different possibilities of expressing the RR interval.

The $\lambda$ values, their intraindividual SDs, and the QT/RR regression residuals were compared between both sexes (2-sample, 2-tailed $t$-test, assuming different variances).

Continuous data are presented as means $\pm$ SD. Statistical significance was assumed if $P < 0.05$.

RESULTS

After the exclusion of nonmeasurable segments, the study used QT interval and RR history measurements of 43,046 individual 10-s ECG segments. The averaged slowest and fastest heart rates in individual long-term recordings were 51.6 $\pm$ 6.1 and 113.7 $\pm$ 12.4 beats/min, respectively. The differences between the fastest and slowest heart rates in the individual long-term recordings were 60.0 $\pm$ 11.5 (range, 39.7–96.0) beats/min. The averaged heart rates of the analyzed ECG segments were 73.4 $\pm$ 6.7 (range per individual long term recordings, 59.0–89.1) beats/min.

Characteristics of QT/RR hysteresis. In the total population, the mean values of $\lambda_I$ and of $\lambda_T$ obtained from the pooled data in the same subjects were 4.68 $\pm$ 0.63 and 5.04 $\pm$ 0.70, respectively. There was a trend toward higher $\lambda$ values (i.e., faster QT adaptation to heart rate changes) in males than in females ($\lambda_I$ of 4.85 $\pm$ 0.59 vs. 4.48 $\pm$ 0.64; $\lambda_T$ of 5.21 $\pm$ 0.66 vs. 4.82 $\pm$ 0.71), but it did not reach statistical significance ($P = 0.07$ and 0.08, respectively). Since the averaged heart rates were above 60 beats/min, $\lambda_T$ values were larger than $\lambda_I$ values ($P < 0.0001$), but the $\lambda_I$ and $\lambda_T$ values in the same subjects were highly correlated ($r = 0.899$).

Intrasubject and intersubject spread of $\lambda$ values is shown in Fig. 1. The $\lambda$ values were found highly individual with the intrasubject SDs (0.354 $\pm$ 0.221 for $\lambda_I$, and 0.390 $\pm$ 0.197 for $\lambda_T$) substantially smaller than the intersubject SDs of individual means of $\lambda$ (0.641 for $\lambda_I$, $P < 0.0001$; and 0.711 for $\lambda_T$, $P < 0.0001$), as well as the intersubject SDs of $\lambda$ values obtained from pooled recordings in the same subjects (0.631 for $\lambda_I$, $P < 0.0001$; and 0.702 for $\lambda_T$, $P < 0.0001$). High statistical significances confirming the individuality of $\lambda$ values were also found when repeating these tests separately in women and in men. The intrasubject SDs of $\lambda_I$ and $\lambda_T$ were not different between women and men.

Figure 1 also shows the comparison of the maximum noise levels analyzed in the same way. The intersubject SDs of maximum noise (15.6 $\pm$ 16.1 technical units) were not statistically different from the intersubject SD (19.1, $P = 0.19$).

Figure 2 shows the comparison between $\lambda$ values obtained when averaging the results of the separate recordings in each subject and when pooling these recordings together. There were only negligible differences (correlation coefficient: $r = 0.988$ for $\lambda_I$ and $r = 0.989$ for $\lambda_T$; differences pooled minus the average of $-0.003 \pm 0.098$ for $\lambda_I$ and $0.005 \pm 0.104$ for $\lambda_T$).

The population range of $\lambda_I$ values was between 3.51 and 6.07, corresponding to the 50% QT adaptation to RR interval change after 48 and 28 cardiac cycles (90% adaptation after 148 and 95 cycles, respectively). Correspondingly, the population range of $\lambda_T$ values was between 3.82 and 6.42, corresponding to the 50% QT adaptation to RR interval change after 44 and 27 s (90% adaptation after 140 and 90 s, respectively). The averaged $\lambda_I$ and $\lambda_T$ values corresponded to 50% QT/RR adaptation completed after 37 cardiac cycles and 34 s (90% adaptation after 120 cycles and 112 s).

Relationship between QT/RR hysteresis and QT/RR patterns. With both hysteresis modes, the smallest QT/RR regression residuals were on average found with the arcus hyperbolic sine regression model (2, 25) $\text{QT} = \alpha \times \text{arcus hyperbolic sine}(\text{RR}) + \beta$.

Figure 3 shows that individually optimized $\alpha$ parameters of this model, as well as of the linear and parabolic log/log models, were not influenced by the hysteresis mode; i.e., once the QT/RR hysteresis was considered, the same QT/RR pattern was found in each individual irrespective of whether correcting for interval-based or time-based hysteresis.
As previously reported (19), we found different parameters in women and men, confirming that women have steeper QT/RR patterns. These differences between the parameters in men and women were 0.165 ± 0.022 vs. 0.188 ± 0.014, *P* < 0.0004; 0.365 ± 0.042 vs. 0.395 ± 0.028, *P* = 0.0112; and 0.219 ± 0.026 vs. 0.246 ± 0.018, *P* = 0.0004; for the linear, parabolic log/log, and arcus hyperbolic sine regression model, respectively.

Figure 4 shows that the λ values were unrelated to the α parameters of QT/RR regression models. With all the previously published regression models (25), the correlation coefficients between α parameters and λ_I values ranged between −0.298 and 0.136, whereas between α parameters and λ_T values, the correlation range was between −0.206 and 0.207. Even without corrections for multiplicity of comparisons, none of these correlation coefficients was statistically significant.

**QT/RR regression residuals.** On average, the QT/RR regression residuals were slightly but statistically significantly lower when combining the optimized QT/RR regression model with individually optimized time-based hysteresis correction rather than with the individually optimized interval-based hysteresis correction.

As previously reported (19), we found different α parameters in women and men, confirming that women have steeper QT/RR patterns. These differences between the α parameters in men and women were 0.165 ± 0.022 vs. 0.188 ± 0.014, *P* = 0.0004; 0.365 ± 0.042 vs. 0.395 ± 0.028, *P* = 0.0112; and 0.219 ± 0.026 vs. 0.246 ± 0.018, *P* = 0.0004; for the linear, parabolic log/log, and arcus hyperbolic sine regression model, respectively.
When calculating the QT/RR regression residuals in the pooled data of all three recordings in the same subject (Fig. 5), the mean residuals for 10-s RR average, 120-s average, interval-based hysteresis, and time-based hysteresis were 11.8 ± 2.16, 6.96 ± 1.41, 5.53 ± 1.13, and 5.46 ± 1.07 ms, respectively. All the differences were statistically significant ($P < 0.0023$ for the difference between the hysteresis modes, and $P < 0.0001$ for all other comparisons).

Similar differences were found when calculating the QT/RR regression residuals in each recording separately and averaging them in each subject (Fig. 6). The mean residuals for 10-s RR average, 120-s average, interval-based hysteresis, and time-based hysteresis were 11.8 ± 2.16, 6.96 ± 1.41, 5.53 ± 1.13, and 5.46 ± 1.07 ms, respectively. All the differences were statistically significant ($P < 0.0023$ for the difference between the hysteresis modes, and $P < 0.0001$ for all other comparisons).
hysteresis were 11.36 ± 2.00, 6.33 ± 1.31, 4.75 ± 0.93, and 4.66 ± 0.85 ms, respectively. All the differences were again statistically significant (P = 0.0016 for the difference between the hysteresis modes, and P < 0.0001 for all other comparisons).

**DISCUSSION**

Three principal conclusions can be made from this study. First, the QT/RR hysteresis can be reliably and consistently assessed from the long-term ECG recordings.

Second, similar to the static QT/RR relationship, the dynamic patterns of QT/RR hysteresis show substantial intrasubject stability with a high intersubject variability. Although we have not obtained identical values in repeated recordings of the same individual, the intrasubject spread was remarkably smaller than the spread in the population. Not only were the differences highly statistically significant, but intersubject SDs were practically twice as large as intrasubject SDs.

Third, it appears that the static QT/RR relationship, which is by how much the QT interval shortens or prolongs when cardiac cycles reach stable faster or slower rate, and the QT/RR hysteresis, which is how quickly the QT interval adapts to heart rate acceleration or deceleration, are two different and unrelated physiological processes. Both these processes are individually specific to separate subjects. Their population assessment suggests that there are no combinations that would be more normal or physiological than others (see the spread of values in Fig. 4).

In addition to these conclusions, we also observed statistical differences between the two hysteresis modes. When using the QT/RR residual as an arbitration, the time-based QT/RR hysteresis led to lower QTc variability than interval-based hysteresis. It thus seems that the influence of the heart rate history on the QT interval duration diminishes more likely with the time elapsed rather than with the number of cardiac cycles.

As far as we are aware, this is the first study investigating the individuality of QT/RR hysteresis in healthy subjects. Consequently, there is little published data with which we can compare our principal results. Nevertheless, the averaged λ values agree well with the previously reported adaptation of both monophasic action potentials and surface QT intervals in response to abrupt changes in pacing rate (11, 17). With both these experiments, 90% adaptation was reported after ~2 min (11, 17), whereas the mean value of λ found in our study corresponds to 90% of adaptation after 112 s.

The individuality of the hysteresis profiles also agrees well with the observed individuality of other dynamic ECG parameters that were reported not only for QT/RR profiles (2, 19) but also for heart rate dependencies of other ECG intervals (22). Indeed, in consideration of the intrasubject stability of the hysteresis profiles, the spread of values in Fig. 4 resembles fingerprint-like differences. The identification of the mechanisms responsible for such stable intersubject differences is well beyond the scope of this investigation. We can only speculate that the observed differences between subjects are a manifestation of highly individual distributions of ionic chan-

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**Fig. 5.** Individually optimized QT/RR regression residuals [i.e., SDs of individually calculated corrected QT (QTc) values] calculated after correcting the QT/RR data for time-based hysteresis plotted against the QT/RR residuals with RR values taken from 10-s RR averages (left), QT/RR residuals with RR values taken from the 120-s RR interval averages (middle), and QT/RR residuals with RR values taken from the correction for interval-based hysteresis (right). All the regression residuals were calculated in pools of the 3 recordings made in the same subject. Dashed lines show the identity.

**Fig. 6.** Graphical representation of the statistical comparisons (see main text for exact values and statistical tests) of individually optimized QT/RR residuals (i.e., SDs of individually calculated QTc values). The individual bars correspond to QT/RR residuals with RR values taken from 10-s RR averages, RR values taken from the RR interval averages of the preceding rhythm, RR values taken from the correction for interval-based hysteresis, and RR values taken from the correction for time-based hysteresis. Gray bars, pools of the 3 recordings made in the same subject; white bars, averaged values of the QT/RR residuals obtained in each of the 3 recordings separately. Population mean values and SDs are shown.
nels and of their interactions in different cardiac tissues. It is likely that the individual ECG phenotype is related to the intersubject genotype differences. However, it is equally plausible that the details of ionic channel distributions and interactions are caused by congenital embryonic chance rather than genetically determined. Future studies are needed to address these possibilities, e.g., by comparing high-precision electrocardiography in monozygotic and dizygotic twins.

The values of the QT/RR regression residuals (i.e., SDs of the individually heart rate- and hysteresis QTc intervals) also confirmed the minimum spread and little variability of QTc values in healthy subjects that our group has recently reported in an independent population (20). Although there is a circadian pattern of QTc intervals during the daytime hours (e.g., due to postprandial changes), the variability of QTc values when accurately measured and corrected is much smaller than previously reported (13, 24, 27).

The study has several important practical implications. Scrambling the effects of the dynamic QT/RR hysteresis with the effects of the stable QT/RR relationship (10, 16, 30) into one descriptor of repolarization dynamics seems counterproductive. Rather, both physiological processes should be measured and characterized separately and only subsequently combined in studies of QTc interval dynamics. The very substantial reduction of SD of QTc values achieved with the combination of individual hysteresis and individual heart rate correction suggests that both these corrections should be used in accurate studies investigating QTc changes. This concerns not only physiological influences of the QTc interval by various provocations but also the studies of drug-induced QTc changes (6). The power of such investigations will be substantially increased (and thus the necessary study size decreased) if the combined individual-specific corrections for both heart rate and hysteresis are used. Correcting QT interval individually for both rate and hysteresis appears clearly preferable to preselecting ECG data in which the effect of QT/RR hysteresis is observed and characterized separately and only subsequently combined in studies of QTc interval dynamics. The very substantial reduction of SD of QTc values achieved with the combination of individual hysteresis and individual heart rate correction suggests that both these corrections should be used in accurate studies investigating QTc changes. This concerns not only physiological influences of the QTc interval by various provocations but also the studies of drug-induced QTc changes (6).

Further detailed facets should be researched to characterize the physiology of QT/RR hysteresis more fully. Among others, we have not investigated whether the hysteresis profiles are different when QT interval durations respond to heart rate acceleration and deceleration. Similarly, the influence of heart rate levels is not known, i.e., whether the hysteresis profile is the same for, say, heart rate acceleration between 50 and 60 and between 80 and 90 beats/min.

A number of limitations of this investigation should also be considered. Our data were restricted to daytime hours in only 40 subjects. It is well known that the QT/RR relationship is different during the day and night (7, 15), and the same might apply to QT/RR hysteresis. The restriction of our data prevents us from commenting on such a possibility. Furthermore, we have confirmed the individuality of the QT/RR hysteresis by studying parameters of the exponential decay model. Although this model was previously reported in a study of cardiac patients (25) and corresponds well to the patterns previously observed in experimental studies with fixed rate pacing (11), it is not guaranteed that it is the truly optimum model for the description of QT/RR hysteresis in healthy subjects. It is possible that with different models, the intraindividual stability would be further increased. In other words, the individuality of the hysteresis can only be stronger compared with what we found in this investigation. Despite the validation of the statistical evaluation of intraindividual variability and intersubjects SDs with the maximum noise levels, standard statistical analysis of variance would have been preferable. The data restriction to three repeated recordings in each subject prevented us from employing these standard tests. A different model might also influence our conclusion on the difference between interval- and time-based hysteresis. Also, the range of ages of the subjects of this study was rather narrow, and, therefore, we were unable to relate the hysteresis profiles to age. Similar to other regulatory mechanisms (5, 9), the influence of age might be expected. In addition, the population of the study was not massive, which to some extent restricted the statistical power. It is possible that with a larger number of subjects, statistically significant sex differences in the hysteresis profiles would be found. In any case, however, these would not be as marked as the differences in QT/RR profiles (19) and in the heart rate correction parameters that we easily detected in this investigation. Since we have neither distinguished QT/RR hysteresis linked to heart rate acceleration and deceleration nor studied hysteresis changes during the day, we are unable to comment on the possibility of such differences. Finally, several of the numerical parameters used during ECG processing (e.g., the 6-ms alignment limit for separate readings between the two cardiologists) were derived from previous experience (21), as well as reflecting an ECG measurement practicality. We are unable to comment on the influence of these particular settings on the overall ECG measurement process.

Despite these limitations, the investigation shows very convincingly that the profile of QT/RR hysteresis, i.e., the speed with which the QT interval adapts to heart rate changes, can be reliably assessed in long-term ECG recordings. The profile of the hysteresis is highly individual with intraindividual stability and intersubject variability. The characteristic of QT/RR hysteresis is independent of the static QT/RR relationship and should thus be treated as a separate physiological process. The combination of the individual-specific heart-rate correction with the individual-specific hysteresis correction of the QT interval is likely to lead to substantial improvements in the precision of studies of cardiac repolarization.

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