QT-RR Relation Is Different in Humans and Rats

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Abstract

The QT interval (QT) variability has been recently computed to infer cardiac control of rats. It has been suggested that QT variability markers in rats have the same physiological meaning as in humans. However, some evidences indicate a different dependence of QT on the previous RR interval (RR).

Thus, the aim of this study was to compare the relation of the QT to the preceding RR in humans and in rats.

Electrocardiogram was recorded in supine position (REST) and during tilt test (T90) in 23 healthy subjects and in 9 Wistar (WI) and 14 wild-type Groningen (WT) rats during the dark period. Pearson product moment correlation coefficient r computed between RR and QT was calculated for each subject or animal within each experimental condition.

In humans we found that r was positive and decreased from REST to T90. Conversely, r was negative in rats and did not differ between WI and WT. The r absolute value was significantly higher in humans than in rats. Our results showed that trends toward longer RRs lead to longer QTs in humans but shorter QTs in rats and that the strength of the QT-RR association is lower in rats.

We conclude that attention should be paid when using the rat model in translational studies assessing the QT-RR relation.

1. Introduction

In the last years QT interval (QT) variability markers have been added to those computed over the spontaneous fluctuations of RR interval (RR) [1-6]. The rationale underlying this strategy is that the QT variability analysis seems to provide additional information about the cardiac neural control since QT variability is more useful to assess neural control directed to ventricles, while RR variability is more suitable for the evaluation of neural regulation directed to the sinus node [3]. In humans, part of the QT variability is dependent on RR variations given the strong link of QT with the preceding RR [5,7].

Only recently the QT variability has been successfully exploited in rats for the assessment of the cardiac control. It was suggested that QT variability has the same physiological meaning in humans as in rats [1]. This observation seems to hold despite the difference between humans and rats concerning the response of the QT to the RR shortening induced by a sympathetic stimulus: indeed, rats respond to sympathetic stimulation with a prolongation of the QT interval, while humans with a QT shortening [8,9].

Thus, the aim of this study is to evaluate the relation of QT to the preceding RR in humans and in rats. The hypothesis is that, despite the presence of similar physiological interpretation of both RR and QT variabilities, the relation between RR and QT is different in humans and rats. In humans, the relation between RR and QT is studied in young healthy subjects performing a maneuver inducing a sympathetic activation and vagal withdrawal, namely the head-up tilt test. In rats, the relation between QT and RR is studied in two different rat strains known to exhibit different social traits that are mirrored by diverse autonomic states at rest, namely the Wistar (WI) rats and wild-type Groningen (WT) rats [10].

2. Experimental protocols

TABLE 1. TIME DOMAIN RR AND QT VARIABILITY INDEXES OF THE HUMAN PROTOCOL

Index	REST	T90
μ_{RR} [ms]	937.18±135.11	715.18±96.47*
μ_{QT} [ms]	327.91±33.6	295.09±30.19*
σ^2_{RR} [ms^2]	2755.2±2083.51	1773.36±940.24
σ^2_{QT} [ms^2]	11.43±12.29	23.21±33.49

REST: at rest in supine position; T90: head-up tilt at 90°; RR: RR interval; QT: QT interval; μ_{RR}: RR mean; μ_{QT}: QT mean; σ^2_{RR}: RR variance; σ^2_{QT}: QT variance. The symbol * indicates $p<0.05$ versus REST.

TABLE 2. TIME DOMAIN RR AND QT VARIABILITY INDEXES OF THE ANIMAL PROTOCOL

Index	WI	WT
μ_{RR} [ms]	169.99±7.37	185.6±8.31
μ_{QT} [ms]	59.54±2.21	56.23±2.32#
σ^2_{RR} [ms^2]	23.76±19.62	21.38±15.5
σ^2_{QT} [ms^2]	2.98±3.49	2.95±6.01

WI: Wistar rats; WT: Wild-type Groningen rats; RR: RR interval; QT: QT interval; μ_{RR}: RR mean; μ_{QT}: QT mean; σ^2_{RR}: RR variance; σ^2_{QT}: QT variance. The symbol # indicates $p<0.05$ versus WI.

Two different experimental protocols were utilized in this study, one of young healthy human subjects and one of rats. A full description of the protocols was given elsewhere [1]. Briefly, in the human protocol we enrolled 23 young healthy subjects (11 males, age 26.3±5.6 years). Subjects were asked to avoid alcoholic and caffeinated beverages in the 24 hours preceding the test. Electrocardiogram (ECG) from modified lead II was acquired with a sampling rate of 1000 Hz (Biosignal Conditioning Device, Marazza, Monza, Italy) for 10 minutes at rest in supine position (REST) and for 10 minutes during head-up tilt test with tilt table inclination at 90° (T90). Attention was paid in positioning the electrodes to obtain an adequate T-wave. All the subjects completed the test without any sign of presyncope. The study adhered to the principles of the Declaration of Helsinki and was approved by the L. Sacco Hospital ethics committee. All the subjects signed a written informed consent before the starting of the experimental protocol.

In the animal protocol, we monitored 9 male WI rats (age: 5.5±0.5 months; weight: 436±34 g) and 14 male WT rats (age: 4.4±0.5 months; weight: 395±40 g). Rats were individually housed with controlled temperature and light (lights on from 7:00 P.M. to 7 A.M.) and implanted with a radio-telemetric transmitter (TA11CTA-F40, Data Sciences International, St. Paul, MN, United States) while anesthetized. After 14 days from surgery, ECG was recorded for 1 hour during the dark period by the platform receiver (RPC-1 and ART-Gold 4.2 data acquisition system, Data Sciences International, St. Paul, MN, United States) placed under the animal's cage. ECG was sampled at 1000 Hz. The animal experimental protocol was approved by the Veterinarian Animal Care and Use Committee of the University of Parma, Parma, Italy, and the animals were cared in accordance with the European Community Council Directives (2010/63/UE).

3. Methods

3.1. RR and QT beat-to-beat series extraction

In both human and animal protocols, the RR and QT beat-to-beat series were obtained from the recorded ECG. The time distance between two consecutive R-wave peaks was considered as the RR interval. The R-wave apexes were fixed by parabolic interpolation. The QT interval was approximated as the temporal distance between the R-wave peak and the end of the T-wave [11]. The offset of the T-wave was set where the absolute value of the first derivative of the descending part of the T-wave became lower than the 30% of its maximum value calculated over the T-wave downslope [11]. The *i*th QT [i.e. QT(*i*)] started from the second R-wave delimiting the offset of the *i*th RR [i.e. RR(*i*)], where *i* is the progressive measure counter.

The detections of the fiduciary points (i.e. R-wave peak and T-wave end) were visually checked to avoid errors. Ectopic beats or artifacts were corrected by means of linear interpolation between measurements unaffected by ectopics or artifacts. Attention was paid to never correct more than 5% of the total considered measures.

As to the human protocol, stationary segments of 300 consecutive beats were selected for further analysis for each experimental condition (i.e. REST and T90). As to the animal protocol, stationary segments of 2000 beats were selected. The segments were as much as possible long according to [12] within each experimental condition. The lengths of the series in human and animal protocols were similar when expressed in absolute time given that mean RR was about five times shorter in rat than in man. In rats we carried out also an additional analysis that considered sequences of 300 beats extracted at random from the overall segment. Over the selected RR and QT series we calculated mean and variance. We indicated them as μ_{RR}, μ_{QT}, σ^2_{RR} and σ^2_{QT}. Means were expressed in ms, while variances in ms^2.

3.2. Evaluation of QT-RR relation

We estimated the linear relation of QT(*i*) to RR(*i*) according to [12]. The strength of this relation was assessed via the Pearson product moment correlation coefficient *r*. We checked the significance of the association between RR(*i*) and QT(*i*) by computing the probability *p* of type I error associated with *r*. A $p<0.05$ was considered to be significant. The same analysis was

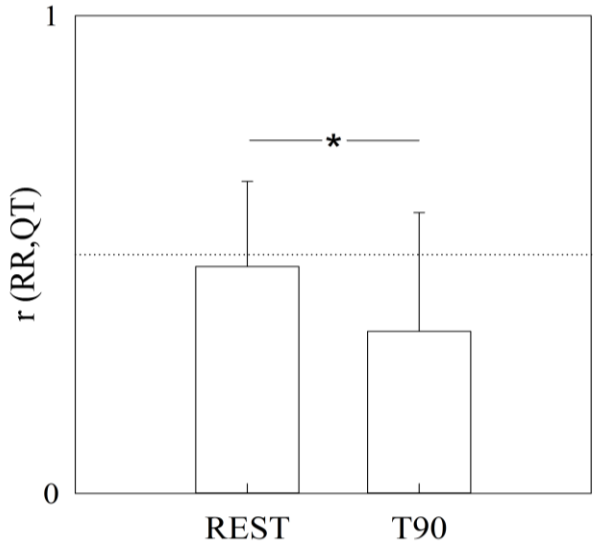

Figure 1. Comparison of *r* computed in the plane [RR(*i*),QT(*i*)] in healthy subjects at REST and during T90. The results are presented as mean±standard deviation. The dotted line denotes r=0.5. The symbol * indicates p<0.05 REST vs T90.

repeated by computing the Spearman rank correlation coefficient ρ to check for eventual discrepancies due to non-normal distributions of RR and QT series.

3.3. Statistical analysis

The effect of T90 in humans was tested by paired t test, or Wilcoxon signed rank test, when appropriate. The difference between strains in the animal protocol was tested by unpaired t test, or Mann-Whitney rank sum test, when appropriate. Results were always presented as mean±standard deviation. Statistical analysis was carried out using a commercial statistical program (Sigmaplot, Systat Software, Inc., Chicago, IL, United States, version 11.0). A p< 0.05 was considered as significant.

4. Results

The results of the time domain analysis in humans are shown in Tab.1. μ_{RR} and μ_{QT} both decreased during T90. No statistically significant variation was observed in σ^2_{RR} and $\sigma^2_{QT.}$ The results of time domain analysis in rats are shown in Tab.2. μ_{RR} was similar in WI and WT rats, but μ_{QT} was lower in WT rats compared to WI. WI and WT exhibited alike σ^2_{RR} and σ^2_{QT}.

Pearson correlation coefficient *r* computed in the young healthy subjects is shown in Fig.1 as a function of the experimental condition (i.e. REST and T90). *r* was positive in both the experimental conditions and significantly decreased during T90 compared to REST. The degree of QT-RR association was significant in 96% of the subjects at REST and in 92% during T90.

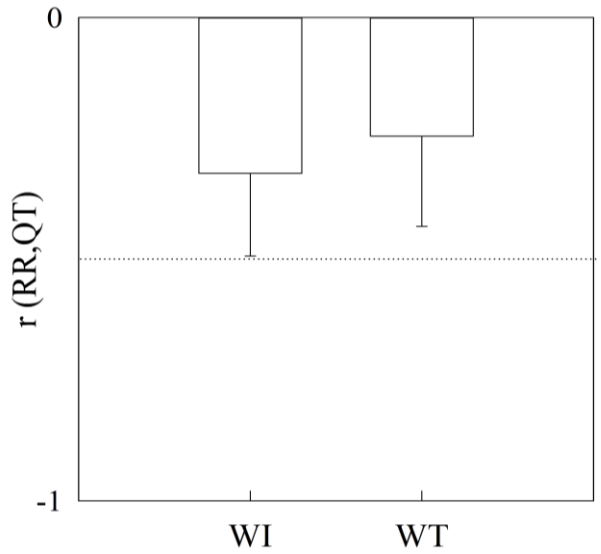

Figure 2. Comparison of *r* computed in the plane [RR(*i*),QT(*i*)] computed over WI and WT rats. The results are presented as mean±standard deviation. The dotted line denotes r=−0.5.

Pearson correlation coefficient *r* computed in the rat strains is shown in Fig.2. It was assessed over the overall RR and QT series. *r* was negative in both the strains and did not differ between WI and WT. The QT-RR correlation was statistically significant in 100% of the WI rats and in 93% of the WT rats. Similar results were obtained when we considered sequences of 300 consecutive measures but in this case QT and RR were not significantly associated in about 30% of animals.

The absolute value of *r* was significantly higher in humans than in rats (0.41±0.22 vs 0.27±0.18), when data were pooled together regardless of the experimental condition or rat strain. This conclusion held even when *r* was computed over sequences of 300 consecutive measures in the rat protocol (0.41±0.22 vs 0.19±0.16).

The results of the QT-RR analysis carried out via Spearman correlation coefficient ρ was not shown given that results were similar to those derived from Pearson correlation coefficient *r*.

5. Discussion

The main novelty of this study lies in the evaluation of the QT-RR relation in rats by means of an automatic assessment of QT and RR variability and in the comparison of the QT-RR correlation in humans and rats. The main findings of this study can be summarized as follow: i) the correlation coefficient of the QT-RR relation is positive in humans, but negative in rats; ii) the degree of correlation is weaker in rats than in humans; iii) the degree of the QT-RR association decreased during the sympathetic activation induced by head up tilt test; iv) the degree of the QT-RR association did not differ between WI and WT rats.

Our study first demonstrates using beat-to-beat variability series extracted automatically from ECG recordings that the QT-RR relation differs profoundly between humans and rats. Indeed, the sign of the correlation between QT and the previous RR is opposite in the two species. The strength of the QT-RR correlation is influenced by the sympathetic challenge, as demonstrated by its decrease during head-up tilt test in humans. A decrease of the QT-RR strength during orthostatic challenge was reported in the frequency and information domain as well [5,13]. The lack of difference between WI and WT could be attributable to the known sympathetic dominance in rats [14], that could also explain the weaker correlation between RR and QT in rats compared to humans. Our results are corroborated by studies carried out on manual RR and QT measurements in rats [15-17] showing that in rats the sign of the QT-RR correlation could be affected by drugs [15] and that the QT has negligible variations in presence of important RR changes induced by pharmacological challenges [17].

The main limitation of the present study lies in the lack of a sympathetic challenge in the animal protocol. In addition, the choice of a simple linear model for the evaluation of the QT-RR relation could be considered an additional restraint. Indeed, the QT-RR relation has been demonstrated to exhibit nonlinear terms [18]. Future studies are needed to confirm the results of the present study with more adequate dynamical models of the QT-RR relation accounting for the dynamical dependences of QT on several RRs [3,13].

6. Conclusions

In this study we evaluated the QT-RR correlation in healthy young subjects performing head-up tilt test and in different rat strains. Results showed that the correlation coefficient of the relation of QT to the preceding RR is of opposite sign in humans and rats. We conclude that attention should be paid in the use of the rat model in translational studies assessing the QT-RR relation.

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