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Relationships between QT interval and heart rate variability at rest and the covariates in healthy young adults

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ABSTRACT

To clarify the links between ECG QT-related parameters and heart rate variability (HRV) and the covariates possibly distorting them, the averaged RR and QT intervals in a single lead ECG were measured for 64 male and 86 female subjects aged 18–26. The QT index, defined by Rautaharju et al., in the young adults was not significantly related to any HRV parameters nor heart rate, but the Bazett's corrected QT (QTc) interval was associated negatively with the parasympathetic activity and positively with heart rate. No significant differences in the QTc interval, QT index or heart rate were seen between the men and women, but they significantly differed between both sexes after adjustment for possible covariates such as age and body mass index (BMI). Significant sex differences in parasympathetic parameters of the HRV were unchanged before and after the adjustment, but significant differences observed in the unadjusted sympathetic parameters disappeared after adjusting for covariates. Age, BMI and body fat percentage also were significant covariates affecting these ECG parameters. Consequently, QT index, unaffected by heart rate and HRV parameters, appears to be a more useful indicator than the QTc interval. Instead, the QT index and HRV parameters are recommended to be simultaneously measured in epidemiological research because they are probably complementary in assessing autonomic nervous function. Also, these parameters should be analyzed in men and women separately.

1. Introduction

Electrocardiogram (ECG) QT intervals and heart rate variability (HRV) have been more frequently utilized in recent epidemiological studies because of the simplicity (Dekker et al., 1997; de Bruyne et al., 1999; Grandjean et al., 2004; Gruden et al., 2012; Soliman et al., 2012), though autonomic nervous function can be assessed by many diagnostic methods (Bannister and Mathias, 1992). Especially, QT interval prolongation, decreased HRV, and high heart rate at rest have been reported to be associated with increased risks of heart diseases and sudden death (Dekker et al., 1997; de Bruyne et al., 1999; Jouven et al., 2005; Soliman et al., 2012). Thus, these parameters are considered to be promising predictors for health events, and several reports have been published with regard to the covariates affecting such predictors, like age, sex, heart rate, and exercise (Murata et al., 1992; Burke et al., 1997; Kuo et al., 1999; Mayuga et al., 2001; Sloan et al., 2008; Koskinen et al., 2009; Vandeput et al., 2012). Nevertheless, there is little evidence addressing the association between the QT-related and HRV parameters at rest in healthy subjects (Ishii et al., 2005; Murata et al., 2005). For the comprehensive assessment of autonomic nervous function, it is crucial to clarify the relation between QT-related and HRV parameters.

Of the above parameters, QT intervals are readily affected by heart rate in healthy subjects without obvious pathological ECG (Rautaharju et al., 1990; Sagie et al., 1992; Karjalainen et al., 1994); for this reason, there are several formulas to compute the corrected QT (QTc) interval for heart rate (Batchvarov and Malik, 2002; Soliman et al., 2012). Also, the American Heart Association, the American College of Cardiology Foundation, and the Heart Rhythm Society (AHA/ACCF/HRS) have recommended that rate correction of the QT interval should not be attempted when the HRV is large (Rautaharju et al., 2009), inasmuch as most of the QT and RR intervals are automatically obtained with temporal alignment and superimposition from each one cardiac cycle of 12-lead ECGs. That is, whether the QT and RR intervals calculated from one cardiac cycle of 12-lead ECGs reflect the stationary physiology remains questionable. In this study, the links between QT-related and HRV parameters, as well as the covariates distorting them, were investigated using the averaged RR and QT intervals measured in a single lead ECG.

2. Materials and methods

2.1. Subjects

Subjects consisted of 64 male students and 86 female students who resided in Akita, northern Japan, and participated in this study

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voluntarily. General exclusion criteria such as present/past illness affecting cardiovascular, nervous, and metabolic functions were applied, but no one had such illness. The research protocol was approved by the ethical review committee at the Akita University School of Medicine, and the nature of the procedure used in this study was fully explained to all subjects, and the study was carried out with their informed consent.

2.2. Methods

The ECG tests were carried out at the quiet laboratory of our department by one examiner, using the ECG-Amplifier 1271SP (NEC-Sanei Co., Japan) connected to a two-channel analog-to-digital converter (sampling time, 1 ms) and a computer. Body weight, body mass index (BMI), and body fat percentage were measured using a bioelectrical impedance meter (Body Composition Analyzer TBF 110, Tanita Co., Japan). Also, a detailed survey on medical records, smoking and drinking habits, and exercise training, etc. was conducted using a self-reported questionnaire, and the contents were confirmed by the same researcher when the questionnaire was returned: nocturnal sleep duration (min) was computed from the difference between bedtime and wake time for weekdays. Considering the diurnal rhythm in autonomic function, all tests including the questionnaire were conducted between 15:00 and 18:00.

After the subjects rested in the supine position for 5 min, ECG amplitudes per 1 ms were measured in the II lead for 30 s, and were averaged on basis of the R-wave peak. The QT interval was defined as a time from the beginning of the first deflection of the QRS complex to the return to the isoelectric line of the T wave. When the QRS or ST–T patterns were indistinguishable, three ECG electrodes were again attached in other positions and the measurement was redone. The QTc interval was calculated from the averaged RR and QT intervals, according to the Bazett's formula (Bazett, 1920): $\text{QTc} = (\text{QT interval}) / (\text{RR interval})^{1/2}$. Also, the QT interval was corrected for heart rate using the QT index, i.e., $(\text{measured QT interval})/(\text{predicted QT interval}) \times 100$, where the predicted QT $\text{interval} = 656/(1 + 0.01 \times (\text{heart rate}))$ (Rautaharju et al., 1990).

Just after determining the above QT parameters, 300 RR intervals and/or 5-min RR intervals were measured in real time and stored on a hard disc, using the same device. Consecutive 100 RR intervals with the minimal standard deviation (SD) were automatically extracted from the obtained data to minimize non-stationarities (Murata et al., 1992; Grandjean et al., 2004; Murata et al., 2005), and the CV_{RR} (%) was defined as the ratio of the SD of the RR intervals to the average value (RR_{mean}, ms). The power spectrum of RR intervals was computed by autoregressive spectral analysis according to the Akaike information criteria (Murata et al., 1992; Ishii et al., 2005). The spectrum of each of two components of the high frequency (HF) component at the center frequency of 0.15–0.4 Hz and low frequency (LF) component at 0.01–0.15 Hz, was separated by component analysis. Each component coefficient of variation (i.e., CCV_{HF} and CCV_{LF}) was defined as the ratio of the square root of each component power spectral density (PSD_k, ms^2) to the RR_{mean}: $CCV_k\ (\%) = 100 \times (PSD_k)^{1/2} / RR_{mean}$, where $k = HF$ or LF. Since parasympathetic blockade abolishes the HF component but β-sympathetic blockade has no effect, the PSD_{HF} and CCV_{HF} reflect the vagal activity (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Murata et al., 2005). Also, the LF component is considered to be derived from the fluctuation in the vasomotor activity through the baroreflex mechanism and to show a β-adrenergically mediated increase in the standing posture, suggesting that the PSD_{LF} and CCV_{LF} reflect the sympathetic activities, and the %HF (i.e., $PSD_{HF} / (PSD_{HF} + PSD_{LF}) \times 100$) and LF/HF ratio (i.e., PSD_{LF}/PSD_{HF}) represent a sympathovagal balance.

The bioelectrical impedance meter used a tetrapolar footpad-style electrode arrangement. In accordance with the manufacturer's manual, the subjects stood on the metal contacts in bare feet, and body fat percentage was determined. The validity of this device has been reported in another paper (Pateyjohns et al., 2006).

2.3. Statistical analysis

The comparison between men and women was made by the Mann–Whitney *U* test or Fisher exact probability for ECG parameters and possible covariates (i.e., age, BMI, body fat percentage, drinking and smoking habits, sleep duration, and exercise training), and by analysis of covariance for the former to adjust for the latter. The drinking and smoking habits, and exercise training were scored as "absence" = 0 and "presence" = 1; likewise, sex was scored as "man" = 0 and "woman" = 1. The relations of possible covariates to ECG parameters were analyzed by the Pearson product–moment correlation coefficient and by multiple regression analysis. Also, the strength of links between the QT-related parameters (i.e., QTc interval and QT index) and HRV parameters (i.e., CV_{RR}, CCV_{HF}, CCV_{LF}, PSD_{HF}, PSD_{LF}, %HF, LF/HF ratio, and heart rate) was examined by the simple and partial correlation coefficients. The PSD_{HF}, PSD_{LF}, and LF/HF ratio were transformed into common logarithmic values in the following analyses because they were highly skewed to the left. All analyses, with two-sided *P* values, were performed using the Statistical Package for the Biosciences (Murata and Yano, 2002).

3. Results

Not only young men but also young women participated in our study without hesitation. Our method recorded the averaged RR and QT intervals, in addition to individual cardiac waves, and the Q and T points (i.e., two vertical lines in Fig. 1) were identified based on these waves. After then, 300 RR intervals were measured in the same resting posture. Totally, it took around 10 min to conduct these ECG tests. ECG parameters and possible covariates in the students are illustrated in Table 1. BMI was significantly larger in the men than in the women; by contrast, body fat percentage was significantly larger in the women. The proportion of exercise training, which meant to belong to a sport club and to be an active member, was significantly higher in the men than in the women. The median values of 100% ethanol ingestion in drinkers were 53 (range, 18–285) ml/week for 31 men and 27 (9–295) ml/week for 55 women, and the ethanol ingestion was significantly more in the former than in the latter (Mann–Whitney *U* test, $P = 0.001$). Still, since the smoker was only a male student, the variable "smoking habit" was excluded in the following analyses.

Our subjects had no pathological ECGs including flattened or inverted T wave, but two men showed tachycardia (116 and 101 beat/min, respectively). There was no significant difference in the QTc interval, QT index or heart rate between the men and women (Table 1), but they differed significantly between both sexes after adjustment for possible covariates (Fig. 2). The CCV_{HF}, LF/HF ratio, PSD_{HF}, and %HF showed consistently significant differences between the two groups. However, the significant sex difference seen in the unadjusted CV_{RR}, CCV_{LF}, and PSD_{LF} disappeared after adjusting for possible covariates.

As shown in Table 2, age, sex, BMI, body fat percentage, and exercise training were significant covariates affecting ECG parameters. The QTc interval was related negatively to the PSD_{HF} and positively to heart rate (Table 3), implying that the latter does not remove the influence of heart rate from QT intervals. Still, the QT index was not significantly connected with any HRV parameters or heart rate.

4. Discussion

As shown in Table 3, we observed a negative association between the QTc interval and PSD_{HF}. This is consistent with two previous findings, reporting that the QTc interval was significantly correlated with the CCV_{HF} and PSD_{HF} in 87 male day workers (Murata et al., 2005) and in 36 female non-shift nurses (Ishii et al., 2005). Namely, the QTc interval