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Dependence of QT Interval on the Heart Rate During Alterations of Pulmonary Ventilation in Young Healthy Subjects

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Summary

In 77 young healthy volunteers of both sexes the dependence of the QT interval of ECG on the heart rate was investigated during normal ventilation (control) and after 1, 2, 3, 4 min of voluntary hyperventilation, after 6 min of hypoxic-hypercapnic ventilation (through an enlarged dead space) and during the Valsalva manoeuvre. The absolute coefficients (a) of the regression lines QT = a + b . HR were significantly different in all groups. The slopes of regression lines (b) were significantly different in all groups with the exception of 4 min hyperventilation. Our results indicate that short-term alterations of pulmonary ventilation may change not only the duration of the QT interval but also its dependence on the heart rate. Voluntary hyperventilation lasting 1–2 min and the Valsalva manoeuvre decrease the rate dependence of the QT interval and this change may cause its prolongation at higher heart rates.

Key words

QT interval – Hyperventilation – Hypoxia – Valsalva manoeuvre – Electrocardiography – Vectorcardiography

Introduction

Prolongation of the QT interval of ECG is considered as one of the indicators supporting the origin of heart dysrhythmias (Jervell and Lange-Nielsen 1957, Romano *et al.* 1963, Moss and Schwartz 1979). The view prevailing nowadays points to the fact that even changes and disorders of normal respiration may be a dysrhythmogenic factor (Young *et al.* 1954, Ayres and Grace 1969, McFadden and Ingram 1980) and that the QT interval may also be prolonged (Browne *et al.* 1983, Kujaník *et al.* 1985). This prolongation is realized by a prolongation of its repolarization phase but some alterations in depolarization phase (QRS complex) were found as well (Kujaník *et al.* 1992).

The QT interval is rate-dependent (Bazett 1920, Fredericia 1920, Hegglin and Holzmann 1937, Ashman 1942, Schlamowitz 1946, Simonson *et al.* 1962). It means that its duration may shorten with increasing heart rate. In our previous paper (Kujaník *et al.* 1985) the prolongation of the corrected QT interval during 1 to 3 min hyperventilation and during hypoxic ventilation was found. The prolongation of the measured QT interval above the upper limit of normal values was often found at the higher heart rates during hyperventilation. Therefore the aim of our work was to find out whether the rate dependence of the QT interval may also change in the alterations of the QT interval duration under the influence of pulmonary ventilation.

Material and Methods

The investigation was carried out in 77 young healthy volunteers (38 men, 39 women, aged 20.7±0.7 years) of intermediate height (165–179 cm) in the supine position. The rate dependence of the QT interval was compared in 7 types of pulmonary ventilation: normal ventilation at rest (control),

voluntary hyperventilation lasting 1 min, 2 min, 3 min, 4 min, hypoxic-hypercapnic ventilation lasting 6 min and the Valsalva manoeuvre. Voluntary hyperventilation was attained by submaximal deep breathing with three times higher rate than at rest. The hypoxic-hypercapnic ventilation was performed by breathing through an enlarged dead space formed by a tube 240–300 cm long (according to the body height), 3 cm in diameter, with a volume of 1.6 to 2.1 dm^3 (according to the length of the tube). Volunteers were trained for all types of ventilation to maintain the same depth of breathing.

The Valsalva manoeuvre was accomplished by breathing into the manometer at a pressure of 5.3 kPa (40 mm Hg) during 20 s. The intervals between individual respiratory manoeuvres were chosen so that the pulse rate could return to the original value during normal ventilation. The electrocardiogram was recorded in 3 standard (I, II, III) and 3 Goldberger (aVR, aVL, aVF) leads at rest, immediately after the end of hyperventilation, in the 3rd and 6th min of breathing through the enlarged dead space (for calculations the higher value was taken only) and during all 4 phases of the Valsalva manoeuvre (inflation, strain phase, release, bradycardia) by means of Chiracard 600 T (Chirana) or Mingograf 81 (Siemens) at paper speed of 50 mm/s.

The QT interval was measured from the beginning of the first deflection of the QRS complex to the termination of the T-wave in any of the 6 leads as an average value of at least 5 subsequent heart cycles. Because there were no significant differences between men and women, the results of both sexes were pooled. The heart rate was assessed similarly in the same cardiac cycles. During the Valsalva manoeuvre, when the heart rate as well as the QT interval were oscillating from one cardiac cycle to another, QT was evaluated only from one cycle in which $QTc = QT/\sqrt{RR}$ (RR is the RR interval) according to Bazett (1920) was the largest. This occurred most frequently at the end of the second phase of the Valsalva manoeuvre. The upper limit of the normal values was evaluated according to Doschitsin *et al.* (1981).

The rate dependence of QT was tested by means of the coefficients of regression lines $QT = a + b \cdot HR$, where HR is the heart rate, a - absolute coefficient, b - regression coefficient (the slope of the regression line). The coefficients of regression lines were estimated by the method of least squares, as modified by Kubáček (1983). The linear dependence was selected because of the dispersion of values in the regression field for all the measured values. The quadratic polynomial regression led to statistically insignificant values of quadratic terms and was therefore not applied in our investigation.

The statistical significance of differences of the absolute and regression coefficients at the significance level of 0.05 was tested against normal ventilation (control) by Student's t-test according to the method proposed by Rao (1973). However, before such testing the dispersion homogeneity of the investigated groups was evaluated during normal ventilation. The dispersion differences were insignificant in all cases. The numerical data are always expressed as the mean value ± standard deviation (mean ± S.D.). The differences for $p < 0.05$ were considered as statistically significant.

Results

In all the studied subjects, only the sinus rhythm with more or less evident respiratory arrhythmia was observed during normal ventilation at rest and during all respiratory manoeuvres. Other arrhythmias were not found. The Valsalva manoeuvre and one minute-hyperventilation prolonged the QT interval above the upper limit of normal values in most subjects (Fig. 1).

The values of the QT interval and of the heart rate as well as the coefficients of regression lines for individual groups are given in Tables 1 and 2. It can be seen that the absolute coefficients (QT interval duration) are significantly different in all groups, i.e. all ventilation manoeuvres used in our study significantly changed the QT interval duration. With the exception of 4 min hyperventilation the regression coefficients are also significantly different i.e. the ventilation manoeuvres changed the rate dependence of the QT interval as well. This means that, when compared with normal ventilation, the regression lines do not run in parallel.

The rate dependence of the QT interval is mostly decreased in our conditions. It is characterized by a decrease of the regression coefficient (b) of the regression line during the Valsalva manoeuvre, 1 and 2 min hyperventilation and hypoxic-hypercapnic ventilation. Thus, QT is shortened with increasing heart rate less than at normal ventilation at rest.

The relationship of the regression lines to the upper limit of normal QT values (after Doschitsin *et al.* 1981) is illustrated in Fig. 1. It can be seen that when the rate dependence decreases, some QT values surpass the upper limit of normal values, particularly at the highest heart rates. At the lowest heart rates the QT interval values are normal. During the Valsalva manoeuvre the average heart rate is raised (mostly at the end of the second phase), but it does not significantly influence the noncorrected QT interval (see Table 1). Although the heart rate is increased in 74.6 % and not changed in 5.5 % , the QT interval is longer in 38.2 % of subjects and not changed in 5.5 % compared to normal ventilation. This means that the QT interval prolongation occurs in 38 % of subjects, but the heart rate shortening in 20 % only.

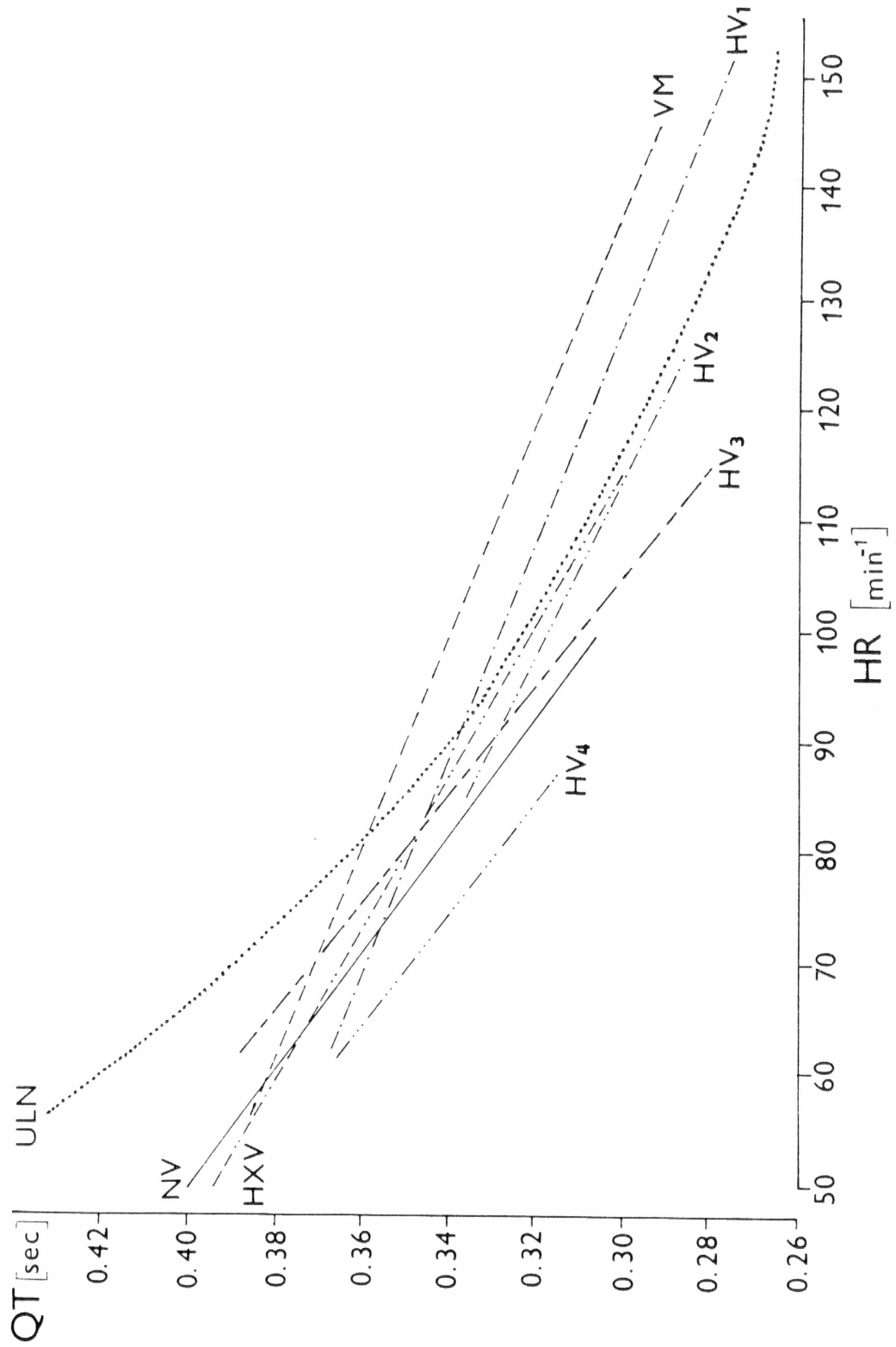

Fig. 1
Regression lines for individual types of pulmonary ventilation. ULN – upper limit of normal values, NV – normal ventilation, HV_1 – 1 min of hyperventilation, HV_2 – 2 min of hyperventilation, HV_3 – 3 min of hyperventilation, HV_4 – 4 min of hyperventilation, HXV – hypoxic-hypercapnic ventilation (through the enlarged dead space), VM – Valsalva manoeuvre.

Table 1
Heart rate and noncorrected QT interval during some respiration manoeuvres (mean ± S.D.). NV = normal ventilation at rest, HV 1, 2, 3, 4 = 1, 2, 3, 4 min hyperventilation, HXV = hypoxic-hypercapnic ventilation, VM = Valsalva manoeuvre. The statistical significance compared with NV

Type of Ventilation	n	Heart rate [min^{-1}] Average	Minimal Maximal	Noncorrected QT interval [ms]
NV = control	77	71.53 ± 11.10	49 99	359.80 ± 28.35
HV 1	59	99.32 ± 19.53 P < 0.001	62 152	330.33 ± 28.12 P < 0.001
HV 2	20	107.90 ± 10.13 P < 0.001	85 125	308.97 ± 18.60 P < 0.001
HV 3	23	84.48 ± 16.10 P < 0.001	61 115	342.36 ± 37.66 P < 0.05
HV 4	21	72.33 ± 9.01	61 87	345.30 ± 21.68 P < 0.05
HXV	77	84.34 ± 14.90 P < 0.001	50 114	346.06 ± 29.03 P < 0.005
VM	55	86.27 ± 23.32 P < 0.001	56 146	363.06 ± 35.08

Table 2
Regression lines QT = a + b. HR. CI = confidence interval, NV = normal ventilation at rest, HV 1, 2, 3, 4 = 1, 2, 3, 4 min hyperventilation, HXV = hypoxic-hypercapnic ventilation, VM = Valsalva manoeuvre. The statistical significance compared with NV

Ventilation	Absolute coefficient a	P < 0.05	95 % CI	Regression coefficient (slope) b	P < 0.05	95 % CI
NV	489.74		460.26 519.21	−1.82		−2.22 −1.41
HV 1	428.64	+	400.59 456.69	−0.99	+	−1.27 −0.71
HV 2	438.27	+	363.65 512.88	−1.20	+	−1.89 −0.51
HV 3	508.94	+	459.88 558.01	−1.97	+	−2.54 −1.40
HV4	481.73	+	429.53 533.93	−1.89	−	−2.60 −1.17
HXV	466.37	+	440.21 492.53	−1.43	+	−1.73 −1.12
VM	453.57	+	416.40 490.73	−1.04	+	−1.47 −0.62

Discussion

The dependence of the QT interval on the heart rate is expressed by means of various linear (Adams 1936, Schlamowitz 1946, Simonson *et al.* 1962) or nonlinear equations (Bazett 1920, Fredericia 1920, Mayeda 1934, Ashman 1942, Sandera 1960, Simonson 1962). All these investigations were carried out at rest and correspond to our control group during normal ventilation. The course of the regression line at normal ventilation is practically identical with the line reported by Simonson *et al.* (1962) and is approximately parallel with the line published by Adams (1936), which is shifted to higher QT values.

The marked decrease in the rate dependence occurs regularly at a time, when greater tachycardia is observed, i.e. during increased adrenergic influences on the heart. This may indicate that the increased adrenergic activation not only prolongs the QT interval, but also decreases its rate dependence. The higher rate dependence probably occurs less frequently. Its moderate increase occurred after hyperventilation for 3 min, but this difference was not significant after 4 min hyperventilation.

The cause of the difference between these types of hyperventilation is not yet known. The short-lasting hyperventilation probably induces different changes in the heart than the long-lasting one. Hyperventilation is associated with hyperoxaemia and respiratory alkalosis, but hyperoxia probably does not last in the heart for an appreciable period of time. Hyperventilation is a stress factor which can reduce the oxygen supply rapidly and produce transmural ischaemia of the myocardium (Lisker and Leff 1983).

The QT interval duration may probably be altered in two ways – with a change of the rate dependence or without. The alteration of QT duration without the change of its rate dependence means that the QT value compared with the normal ventilation (control) is clearly less different, but the QT interval changes proportionally with the heart rate, i.e. the difference compared with the normal ventilation is the same at any heart rate. The QT interval in these types of ventilation runs in parallel with the regression line for normal ventilation. The QT interval after 4 min hyperventilation was most similar to these changes.

The alteration of the QT interval duration with the change of its rate dependence means that the regression lines are not parallel. Then, in the area of those heart rates where the regression lines cross each other, the QT values differ slightly, but in the heart rates where they do not cross, the QT values markedly differ. The most typical example for these changes of QT is the Valsalva manoeuvre, hyperventilation lasting 1 and 2 min and less hypoxic-hypercapnic ventilation. All these four types of ventilation decreased the rate dependence. Therefore, the QT prolongation over the upper limit of normal values occurs at higher heart rates only. Analogously, the increase in the QT rate dependence would also be possible when the QT is prolonged at lower heart rates and is shorter at higher heart rates. However, such a relationship was not found in our investigation.

The higher is the rate dependence of the QT interval, the more is the QT interval prolonged at lower heart rates and *vice versa*. Similar changes of QT duration with or without an alteration of the rate dependence probably occur under various pathological conditions, in which the QT interval prolongation and tachycardia were described (White and Mudd 1929, Doschitsin *et al.* 1981, Surawicz and Knoebel 1984).

The Valsalva manoeuvre probably represents an exception to the rule that the noncorrected QT interval decreases during increasing heart rate. Although the significant increase in heart rate occurs during this manoeuvre, the QT interval duration does not change substantially. It is widely accepted that the QT interval and heart rate are controlled relatively independently (Manion *et al.* 1980, Anderson 1981, Davidowski and Wolf 1984). The Valsalva manoeuvre may serve as an example for this type of control. The cause of partially independent control of the QT interval and heart rate is probably due to the asymmetric nervous control of the heart. It is supposed (Rothberger 1926) that the chronotropic parasympathetic influence is exerted mainly through the right vagus nerve acting predominantly on the sinus node. The left vagus nerve acts predominantly on the AV-node (Martin 1977) and thereby on the conduction velocity in the ventricles. There exist some experimental (Randall and Ardell 1985) and clinical data (Strasberg *et al.* 1982) concerning the independence of sympathetic and parasympathetic or sinoatrial and atrioventricular cardiac influences.

In accordance with other authors (Ashman and Hull 1945, Simonson *et al.* 1962, Ahnve and Vallin 1981, Davidowski and Wolf 1984) we suggest that the QT interval should always be expressed in an noncorrected form and together with its heart rate. Different groups of patients should be characterized most suitably by some kind of a regression curve. The expression of QT interval in the corrected form only does not take into account the changes of its rate dependence, reduces the statistical significance of differences (Kujaník *et al.* 1990) and may provide misleading values at higher heart rates (Simonson *et al.* 1962, Davidowski and Wolf 1984).

However, the question arises what means the prolongation of QT interval since there exist some data (Mirvis 1985, Morganroth *et al.* 1991) that the normal values of the QTc interval can be even longer than 440 ms. It would therefore be probably useful to define the limits of physiological values for each type of altered conditions separately.

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