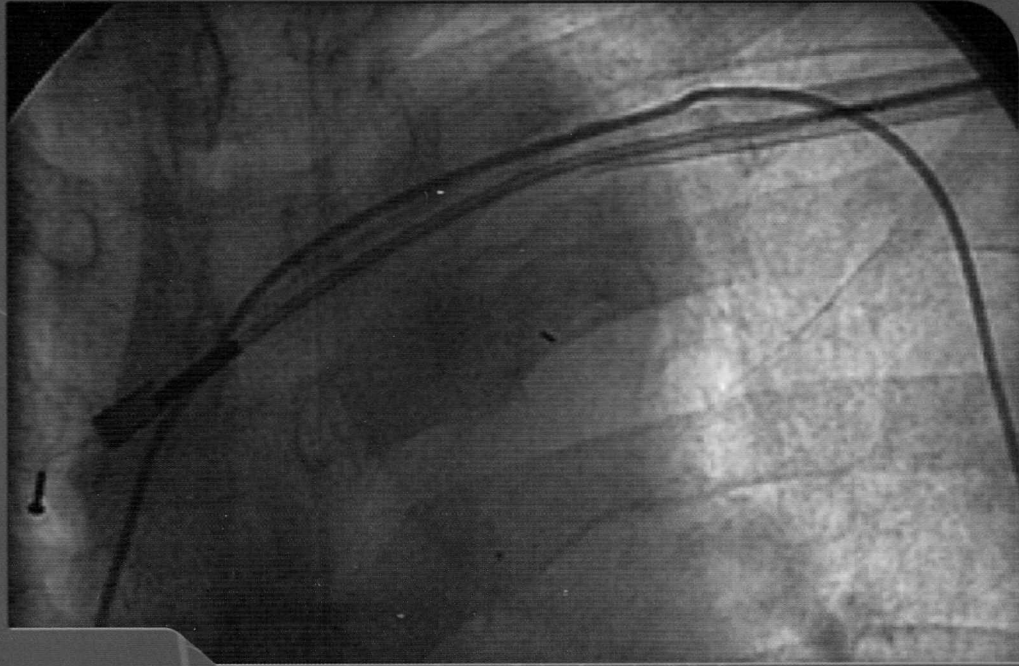


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The QT Interval and “QT Dynamicity” During Holter Monitoring in Children and Adolescents

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ABSTRACT

Long QT interval and short QT interval are among the basic risk factors for life threatening arrhythmias. The cornerstone of QT interval analysis in pediatrics, is precise knowledge of the normal limits of analyzed parameters according to gender and age. Moreover, many patients with long QT syndrome may have normal QT intervals at resting ECG’s. The use of long term ambulatory (Holter) recordings are very helpful in these situations. QT dynamicity, measured by Holter recordings provide more insight into certain genetic arrhythmogenic disorders such as long QT syndromes and Brugada syndrome.

KEYWORDS

Long QT syndrome, Brugada syndrome, QT dynamicity, QT interval

Çocuk ve Adölesanlarda Holter İzlemi Sırasındaki QT İntervalı ve QT Dinamisitesi

ÖZET

Uzun ve kısa QT intervalı, hayatı tehdit edici aritmiler için temel risk faktörleri arasındadır. Pediatrie QT intervalı analizinin köşe taşı yaşa ve cinsiyete göre normal sınırlarının bilinmesidir. Bunun yanında uzun QT sendromlu bir çok hastanın istirahat EKG’sinde normal QT intervalı bulunabilir. Bu durumda uzun dönem ambulatuvar (Holter) kayıtlarının kullanılması çok yardımcıdır. Holter kayıtlarından ölçülen QT dinamisitesi, uzun QT sendromları ve Brugada sendromu gibi genetik aritmogenetik bozuklukların öngörülmesinde yardımcı olmaktadır.

ANAHTAR KELİMELEER

Uzun QT sendromu, Brugada sendromu, QT dinamisitesi, QT intervalı

İLETİŞİM ADRESİ

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Long QT interval as well as short QT interval is considered as one of the basic risk factors for life threatening arrhythmias and sudden cardiac death. The cornerstone of QT interval analysis in pediatrics, is precise knowledge of the normal limits of analyzed parameters according to gender and age. The first level assessment of QT interval is making the measurement on a resting ECG. To define the normal limits of QT interval in children, we analyzed the 12 lead resting ECG's of 1537 apparently healthy children (1) (0-17 years old) and measured the QT interval manually in lead II. The mean values for the heart rate (bpm), QT and QTc intervals (that was calculated by Bazetts formula) are given in Table 1.

Normal, borderline and maximal limits for the QTc interval on rest ECG in all children aged 1 to 12 years old and for boys between 12 and 17 years old were < 440, 440-460 and > 460 msec accordingly. For girls older than 12 years normal, borderline and maximal limits for the

QTc interval were < 450, 450-470 and > 470 msec accordingly. Minimal limits for the QTc interval on rest ECG did not demonstrate any age or gender dependence and were > 450, 320-434 and < 320 msec for normal, borderline and minimal limits for the QTc interval accordingly.

Our normal limits for QT and QTc intervals were practically identical to the results of the previous studies. Davignon et al (2) in a white Canadian population of children found similar results for median, maximum and minimum of QT interval by automatic analysis. Rijnbeek et al (3) also found practically the same limits for median and longest (98%) QTc interval in white Scandinavian population of children with slightly shorter limits for minimal QTc interval (98%).

One of the problem in the diagnosis of long QT syndrome (LQTS) is that patients with genetic LQTS can have normal QTc intervals on rest ECG. In a study by Tester et al (4) 27% of subjects known to carry a LQTS genetic defect

TABLO I

Heart Rate, QT and QTc intervals by Bazetts formula (median, 2nd-98th %) in healthy children 0-17 years-old (upper row – boys, lower row – girls). n = 1531 (QT was measured manually in II lead)

Years old	0-1	1-2	3-4	5-7	8-11	12-15	16-17
Heart Rate (bpm)	131 (105 -198)	120 (85 -187)	99 (78 -120)	89 (67-123)	78 (54 - 108)	73 (48 -103)	70 (48 -102)
	136 (102 -197)	126 (88 -175)	100 (77 -150)	90 (64-120)	80 (58 -117)	79 (53 -116)	72 (53- 111)
QT (msec)	281 (223-304)	295 (239- 295)	308 (258 -337)	317 (265-389)	337 (289 - 396)	345 (296 - 425)	337 (304-417)
	287 (208 - 295)	278 (236 -317)	319 (256 -367)	305 (268-356)	338 (297 -397)	367 (287-438)	357 (317- 436)
QTc (msec)	400 (333 - 451)	420 (349 -443)	390 (347- 423)	383 (326-442)	378 (345 -436)	390 (337 - 440)	380 (331-436)
	400 (344 - 462)	387 (346 - 443)	400 (351 - 442)	381 (330-431)	395 (338-466)	403 (350 - 471)	396 (349-464)

had a QTc interval less than 440 ms. These cases of so-called "concealed" LQTS syndrome cases can be underdiagnosed if we rely too heavily on the ECG. Also, most physicians, including many cardiologists, cannot accurately calculate the QTc and cannot correctly identify a long QT (5). A significant number of individuals with LQTS have concealed LQTS, with QTc values that cross well into the normal range (6).

The use of 24 hour Holter monitoring (ambulatory ECG monitoring) can be very helpful in the assessment of long or short QT interval. Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommends ambulatory ECG monitoring as a Class I indication when there is a need to clarify the diagnosis by detecting arrhythmias, QT interval changes and T-wave alternans (7). What are the approaches in assessment of QT interval by Holter monitoring (HM) in children? For assessment of the QT interval by HM in children we use manual and automatic methods. In the manual method, measurement of QT interval is made at minimal heart rate during 24 hour (at night as a rule) recording without any heart rate correction. Automatic analysis in our system (Holter system GE, USA device, version 7.5) include evaluation of longest QT interval (QT max), corrected QT (QTc), calculated according the formula $QTP = QT/\sqrt{RR}$, average daily QT interval, average daily QT peak (QTp) interval, measured from the beginning of Q wave to the top of T wave, and corrected QTp (QTpc) interval.

We found that the QT intervals measured automatically were nonsignificantly longer than the QT intervals measured manually (measurement by minimal heart rate) in 60 healthy children and adolescents 7-17 years old ($432,4 \pm 21,9$ vs $419,4 \pm 25,4$ msec respectively, $p > 0,05$). In both methods, maximal QT interval in healthy

adolescents aged 17 years or less did not exceed 480 msec. Average 24 hour QT interval was 363 ± 20 (327 – 401) msec, average QTc 427 ± 13 (401 – 444) msec, and QTpeak was 285 ± 18 (255-314) msec.

Similar to the situation for resting ECG, about 1/4 of patients with long QT syndrome have normal QT levels during the ambulatory monitoring period maximal normal range (8). One of the relatively new methods for assessment of QT interval changes is the "QT dynamicity" or "QT dynamics", which evaluates the influence of heart rate and autonomic nervous system on the QT interval. This method is based on calculation of the QT/RR linear regression. It has been used for evaluation of QT interval in researches for a long time, but it was only recently installed into a commercial Holter monitoring system as an option. Advances in Holter technology in recent years allowed for continuous tracking of RR intervals and corresponding QT intervals.

The most widely used method estimates "QT dynamicity" by QT/RR slope is which measured by the slope of the linear regression between QT and RR intervals. Measurement is performed separately for 24 hours, day and night periods (Figure 1). A "Steep slope" indicates marked shortening of QT in high HR and lengthening in low HR but "Flat slope" indicates modest changes of QT/RR. At the present time, there are many studies performed in this field in the adult population (9-11). Unfortunately, the researchers obtain controversial results on QT dynamics, because the interpretation of mathematical parameters from the physiological and clinical points of view is difficult and there is a need for normal limits for interpretation. We have evaluated the "normal values" of QT/RR dynamicity in children (20 healthy newborns 14 boys/16 girls, aged 1-4 days (2.6 ± 1.3) of life and 60 healthy child-

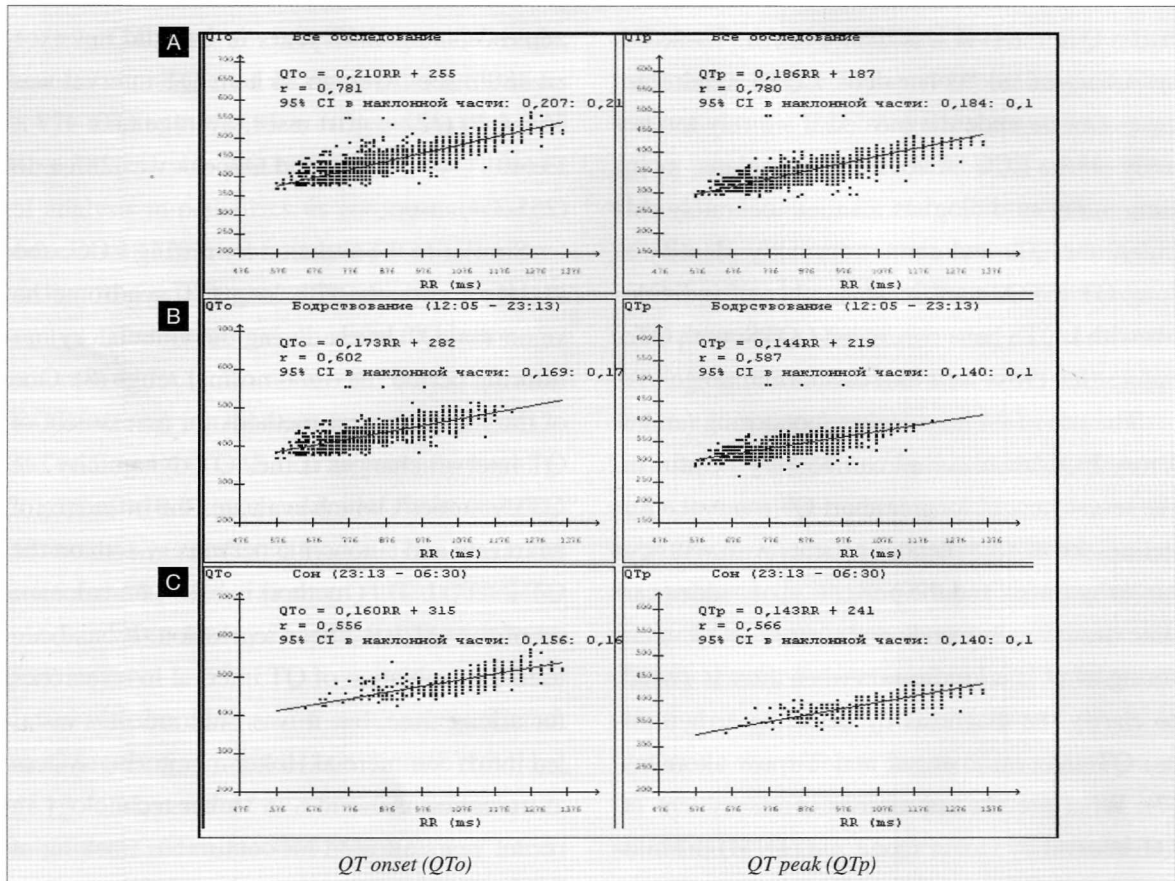


FIGURE 1

Option for QT dynamicity in modern Holter system.
a) – 24 hour; b)- Day; c) Night period

ren (32 boys and 28 girls) 7-17 years old ($10,3 \pm 4,1$). In all children, parameters of “QT dynamics” were measured, with calculation of QT/RR slope, QT/RR intercept and correlation coefficient between QT and RR intervals (r QT/RR) (12). In the healthy newborns the slope QT/RR was 0,37 (0,304 – 0,505); intercept QT/RR was 126 (92,0 – 151,0), and QT/RR correlation (r) was + 0,65 (0,56 -0,84). The QT/RR slope in the first day was statistically lower than the QT/RR slope in the fourth day. In healthy children 7-17 years old this parameters were significantly lower: Slope QT/RR- 0,19 (0,13-0,24); Intercept QT/RR – 230 (190-280); r QT/RR – 0,79 (0,69-0,89).

This age-dynamics reflects influences of the autonomic nervous system on QT/RR relation. Beta-adrenergic stimulation induces increases in the QT/RR slopes in healthy persons. In our studies we observed a decrease in the slope of QT/RR with increase in heart rate variability. Correlation of the 24 hour slope QT/RR with SDNNi and LF were – 0,59 and -0,58 accordingly ($p < 0,05$). In a study by Genovesi et al. (13) it was observed that trained athletes had significantly flatter QT/RR slopes and correlation coefficients QT/RR (r) than nonathletes. Regular physical training is known to increase the parasympathetic activity and its influence on the cardiovascular system (14). We found a

circadian change in the slope and correlation of QT/RR intervals with a decrease at night time. On the contrary, dynamic intercept showed increases during the awake period with strong negative correlation between slope and intercept QT/RR (0.88, $p < 0.05$).

The QT dynamicity is one of the informative parameters for risk stratification in adult patients at high risk of sudden cardiac death. In a study by Tavernier et al, it was observed that the QT/RR slopes were significantly flatter in adult patients with idiopathic ventricular fibrillation than controls (211 ± 59 vs 156 ± 29 , $p < 0,05$) (15). A few case reports showed abrupt changes in the QT/RR values before onset of malignant ventricular arrhythmias (16). This may indicate that an abrupt increase in QT/RR slope steepness may be a trigger for the terminal rhythm disturbance.

Differences were also found between LQT1 and LQT2 patients. In patients with LQT1 Neyroud et al. (17) found that the circadian rhythm of the Slope QT/RR was reversed with increased values at night Slope QT/RR. Vitasalo et al. (8) defined flat slope as an important parameter for differences between LQT1 and LQT2 patients. Lande et al. (18) also showed the reversal of the circadian characteristic of the slope QT/RR with increasing of the night Slope in LQT1 pts 2-69 years old (0.204 ± 0.037 for day and 0.149 ± 0.028 for night) and control group (0.169 ± 0.03 for day and 0.133 ± 0.029 for night) accordingly. For LQT3 patients steep 24 hour slope QT/RR reflected marked shortening of QT in tachycardia and prolongation of QT at night time during bradycardia. Examples of QT dynamicity in children with LQT1 and LQT3 are given at Figures 2 and 3.

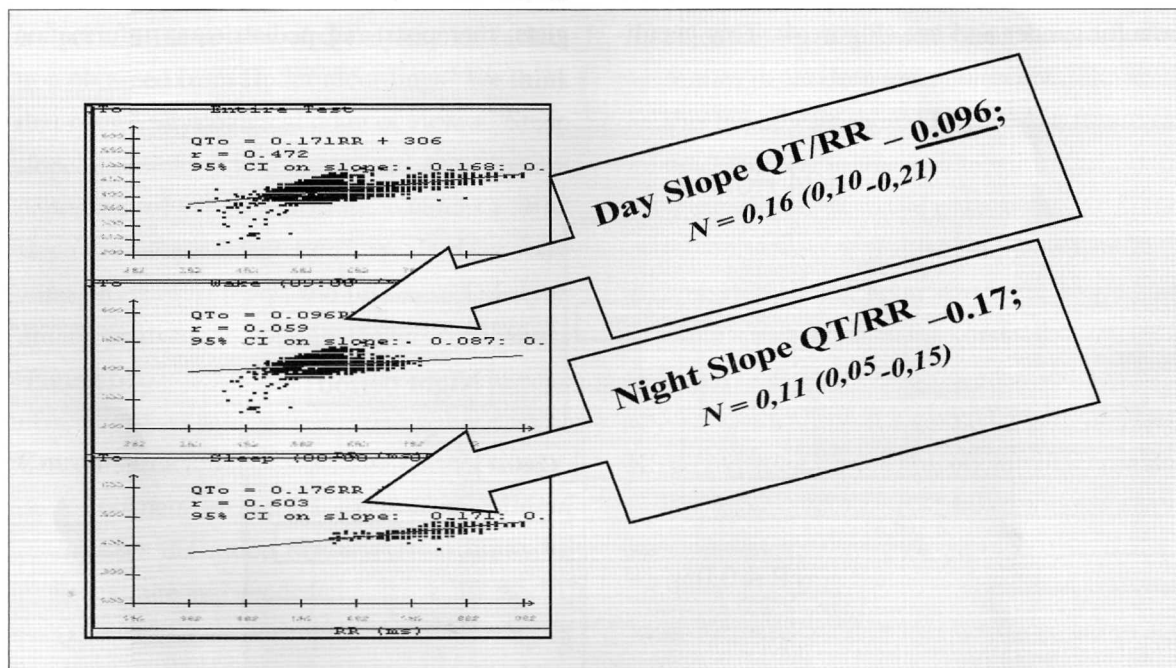


FIGURE 2

Circadian inversion of the Slope QT/RR in a 14 years old girl with LQT1 and exercise induced syncope: Flat Slope QT/RR during the day period and Steep QT/RR at night.

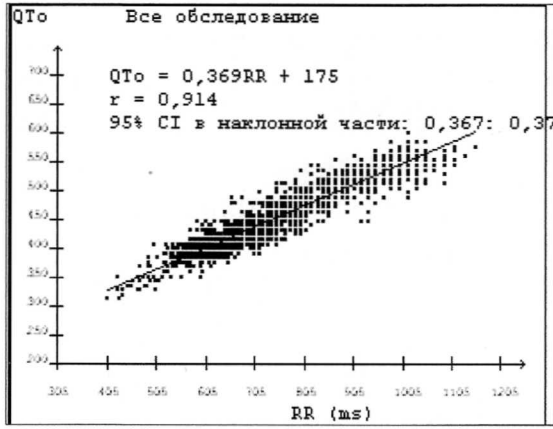


FIGURE 3

Steep Slope QT/RR in 14 years old boy with LQT3: 24 hour Slope QT/RR 0,37 with normal limit 0.19 (0.13-0.24)

We investigated the peculiarities of the “QT dynamics” parameters in young patients 4- 18 years old ($12,3 \pm 6$) with Brugada syndrome (BrS) ECG pattern. We found significantly lower values of the 24 hr slope QT/RR ($p < 0.005$), night slope QT/RR ($p < 0.02$), and night r QT/RR ($p < 0.0005$) in patients with BrS vs controls for gender and age (Figure 4). This peculi-

arities of the QT/RR dynamicity reflected poor adaptation of QT to RR intervals, especially in sleep period that could be one of the predisposing factors for ventricular arrhythmia in BrS.

A study by Mizumagi et al (19) showed that inhibited prolongation of the QT interval during bradycardia was characteristic of symptomatic patients with BrS. On the contrary, the slope QT/RR was typically flat during the daytime in children with catecholaminergic ventricular tachycardia with normalization of the QT dynamicity during the night period. It is known that day time it is the period of highest sympathetic activity and triggering of polymorphic bidirectional tachycardia usually occurs in daytime in these patients (Figure 5).

RR During The Day Period

The fact that obtaining steep or flat slope QT/RR values from ambulatory recordings does not give direct information to the cardiologists, therapists and pediatricians information

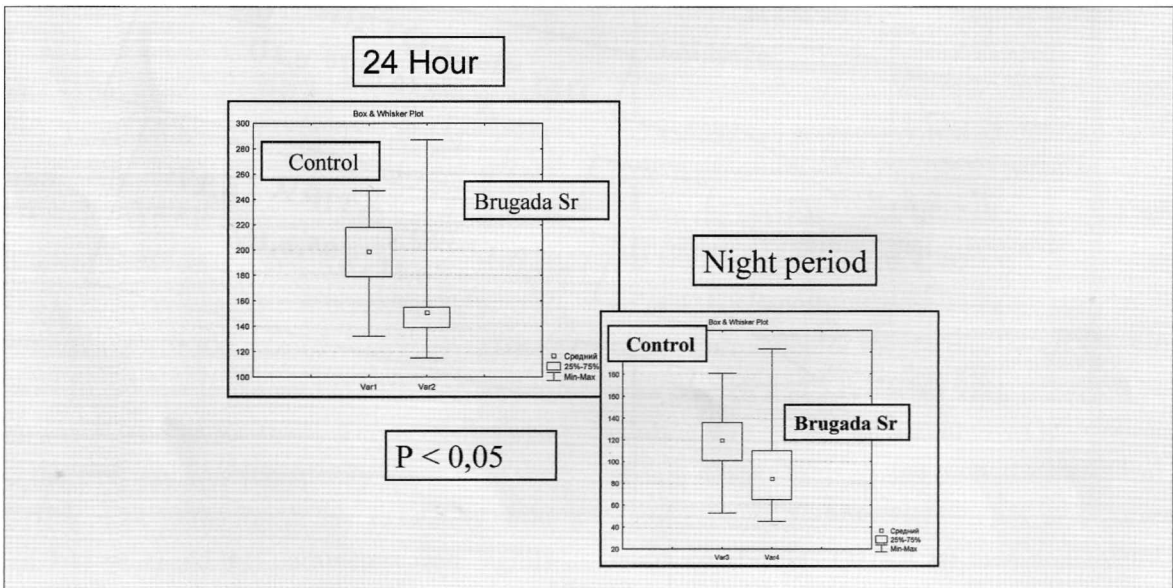


FIGURE 4

Flat slope QT/RR in children with Brugada syndrome (n = 5) vs Control (n = 22): Flat Slope QT/RR during 24 hour and night period.

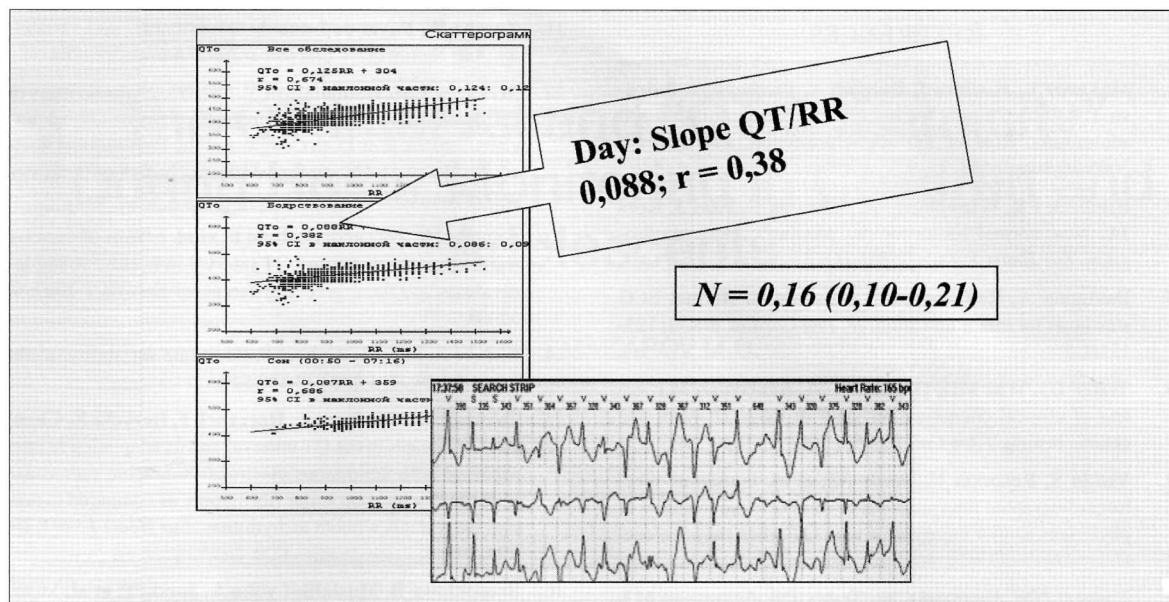


FIGURE 5

QT dynamicity in a 17 years old girl with catecholaminergic ventricular tachycardia and exercise induced syncope: Flat Slope QT/RR during the day period.

about changes in the pathophysiology and their clinical importance. This data also does not have any clinical implications. Then how should we present the results of QT dynamics estimation obtained from Holter recordings? We think that from a physiological point of view, a “Steep slope” possible should be defined as a “hyperadaptation” of QT to heart rate, whereas a “Flat slope” as a “hypoadaptation”. We used the following protocol to report the results of QT dynamicity analysis in routine Holter conclusions (Figure 6).

Conclusions

- Assessment of the QT interval in children includes definition of the normal limits based on age and gender.
- QT dynamicity during Holter monitoring in children and adolescents is modulated by age, heart rate, gender, autonomic influences, circadian trends, mutations of genes encoding cardiac channel and drugs

In clinical practice, evaluation of the QT dynamicity by Holter monitoring can be helpful in diagnosing diseases and risk stratification for life threatening cardiac arrhythmias in children and adolescents. However, this hypothesis should be tested in future clinical studies.

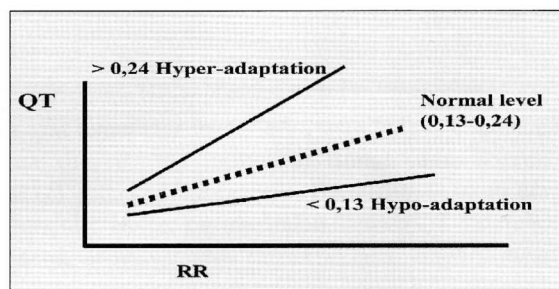


FIGURE 6

The Conclusion on QT dynamicity in routine Holter monitoring assesing adaptation of QT interval to Heart Rate (Protocol of Center for Syncope and Cardiac Arrhythmias in Children and Adolescents of Federal Medico-Biology Agency of Russia).

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