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Clinical aspects of QTc interval analysis in adult patients with anorexia nervosa

Analiza odstępu QT u pacjentów z jadłowstrętem psychicznym

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Abstract

Introduction. Patients with anorexia nervosa (AN) are at increased risk of ventricular arrhythmias, which are considered to be associated with QT interval prolongation. The aims of this study was to analyze the QT interval in patients with AN considering the potential impact of pharmacotherapy and to verify various QT correction formulas.

Materials and methods. Fifty-six patients hospitalized with AN (average age: 22.8 ± 5.6 years; female/male: 54/2, mean body mass index = 13.6 ± 2.6 kg/m^2) were enrolled in analysis: group non-D (n = 44; 78.6%) included patients who did not use drugs that prolong the QT interval, group D (n = 12; 21.4%) included patients who were treated with such drugs. QT intervals were measured in a 12-lead electrocardiogram and corrected using the four formulas: Bazett, Fridericia, Framingham and Hodges.

Results. Mean heart rate (HR) was similar in both groups (61 ± 16.3 bpm in group D vs. 63.1 ± 18.7 bpm in non-D, p > 0.05). Pathological bradycardia (HR < 50 bpm) was present in 5 patients (41.7%) in group D and in 13 patients (29.5%) in group non-D. QTc interval corrected with Framingham formula was longer in group-D (459 ± 81 ms) vs. non-D group (413 ± 33 ms), p = 0.04. QT interval corrected with Bazett and Hodges formulas was significantly dependent on HR (R = –0.29, p = 0.03 and R = –0.42, p = 0.001, respectively). Influence of HR on results of Fridericia and Framingham formulas was not significant (R = –0.22, p = 0.1 and R = –0.11, p = 0.4).

Conclusions. Information about pharmacotherapy in AN patients is key for QTc assessment. Choice of correction formula has impact on the QTc. QTc obtained using Framingham and Fridericia formulas were the least dependent on heart rate.

Key words: anorexia nervosa, heart rate, QT correction formulas, QT interval, QTc prolongation

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Introduction

Anorexia nervosa (AN) is a severe, often deadly, eating disorder that leads to cachexia and many somatic complications [1]. Among mental disorders, AN has the highest mortality and, according to current data, about 10 percent of patients die from sudden cardiac death (SCD) [2].

Increased risk of SCD in AN is due to many negative factors occurring in the course of the disease that damage the cardiovascular system [1].

Sinus bradycardia is quite commonly observed in patients with AN [3], while the most common reasons of SCD are serious ventricular arrhythmias (such as ventricular tachycardia or ventricular fibrillation). Probability of ventricular arrhythmia increases with changes in repolarization of the ventricular muscle, what is reflected by the changes in the electrocardiogram (ECG). The most common changes associated with an increased risk of SCD in this group of patients are QT prolongation [4, 5] or QT shortening. Most reports on QT interval in AN are based on measurement of QT interval without correction or with correction using the Bazett formula, which is not recommended for patients with bradycardia [6], and these are often people with AN. An important factor causing the frequent occurrence of QT abnormalities in this group are the drugs used by these patients, which may affect the QT interval and have a proarrhythmic effect [7]. Most papers on this subject do not consider the impact of the drugs used by patients on the obtained results and in this group of patients this is particularly important. An example is that these patients often use e.g. antidepressants, many of which have a documented negative effect on the cardiovascular system, which is reflected by changes in the ECG.

The aims of this study was to analyze the QTc interval in patients with AN considering the potential impact of pharmacotherapy on the QTc interval and to verify various QT correction formulas.

Materials and method

This is a retrospective, single-center study. Data of 64 consecutive adult patients with anorexia nervosa hospitalized in the Department of Internal Medicine and Metabolic Diseases of the Medical University of Silesia between 2002 and 2017 were screened. The exclusion criteria were lack of ECG at admission, family history of long QT syndrome or sudden cardiac death, left or right bundle branch blocks, paced rhythms, repeated hospitalizations (only first hospitalization of each patient was taken into consideration). The final analysis included 56 patients who were divided into two groups: group non-D (n = 44; 78.6%) consisted of patients who did not use drugs that prolong the QT interval, group D (n = 12; 21.4%) included patients who had chronic pharmacotherapy with drugs that may prolong the QT interval. Demographic and clinical data at admission were analyzed.

Drug classification

To assess drug's potential to prolong QT interval and induce torsades de pointes (TdP), classification system from CredibleMeds was used [8]. Group D consisted of patients, who were taking drugs with:

- known risk of TdP — cisapride (n = 1);
- possible risk of TdP — mianserin (n = 2), mirtazapine (n = 1);
- conditional risk of TdP (under certain condition like electrolyte imbalance, drugs interaction) — fluoxetine (n = 1), sertraline (n = 2), olanzapine (n = 1), diuretics with omeprazole (n = 3), hydroxyzine (n = 1).

Electrocardiography

The standard 12-lead ECGs at rest were recorded (paper speed 25 mm/s, 10 mm/mV) at admission. Analyses of ECG recordings were performed by single, experienced cardiologist. We measured QT intervals looking for the longest and shortest ones to calculate QT dispersion (QTd). Results were corrected using the four commonly used formulas:

- Bazett: $QTc = QT / \sqrt{RR}$ [9]
- Fridericia: $QTc = QT / \sqrt[3]{RR}$ [10]
- Framingham: $QTc = QT + 0.154 \times (1 - RR)$ [11]
- Hodges: $QTc = QT + 1.75 \times (HR - 60)$ [12]

QT and QTc interval prolongation was defined as QT or QTc duration in women > 460 ms and in men > 450 ms [13].

Statistical analysis

All statistical analyses were performed using Statistica version 13 (TIBCO Software Inc., Palo Alto, California, United States). The continuous variables were expressed as the mean ± standard deviation or median and 1–3 quartile boundaries and the categorical variables as the number and percentage of subjects. The normality of distribution was verified with the Shapiro-Wilk test. Differences between any unpaired normally distributed samples were calculated using the Student's *t*-test, while the non-normal data were compared using the Mann-Whitney U test. The Wilcoxon signed-rank test was used for paired data (within group). Differences in categorical variables were assessed using the Fisher's exact test. The Spearman's rank correlation coefficient was used for testing the strength of the correlation between two variables. A p value of < 0.05 was considered to be significant.

Results

Demographic and clinical data

A total of 56 patients were incorporated into study. Detailed demographic and clinical characteristic of study population was presented in Table 1 as well as comparison of two

Table 1. Demographic and clinical characteristic of study population stratified by drugs that prolong QT*

Variable	Whole population (n = 56)	Group non-D (n = 44)	Group D (n = 12)	p value
Age (years)	21.5 (19–25)	20 (19–24.5)	23 (18.5–30)	NS
Male sex	2 (3.57%)	1 (2.23%)	1 (8.3%)	NS
Weight [kg]	35.6 (31.7–40.1)	35.7 (31.6–40.2)	35.8 (32–38.9)	NS
BMI [kg/m^2]	12.75 (11.5–15.6)	12.9 (11.5–15.7)	12.6 (11.7–14.9)	NS
HR [bpm]	57 (47–75)	58 (49–75)	68 (47–75)	NS
HR < 50 [bpm]	18 (32.1%)	13 (29.5%)	5 (41.7%)	NS
SBP < 90 [mm Hg]	24 (43.6%)	20 (45.5%)	4 (50%)	NS
WBC [×10^3/μL]	4.4 (3.6–5.7)	4.2 (3.5–5.4)	4.9 (3.7–7.3)	NS
Hemoglobin [g/dL]	12.3 (11.3–13.3)	12.3 (11.4–13.2)	12.2 (10.1–14.6)	NS
Sodium [mmol/L]	140 (138–142)	141 (139–144)	138.5 (134.8–140)	**0.02**
Potassium [mmol/L]	4 (3.7–4.3)	4 (3.7–4.6)	3.9 (3.5–4.0)	NS
Hypokalemia	11 (19.6%)	8 (18.2%)	3 (25%)	NS
Phosphate [mg/dL]	3.15 ± 1.04	3.24 ± 1.07	3.05 ± 1.12	NS
Total calcium [mg/dL]	9.24 ± 0.87	9.28 ± 0.86	8.95 ± 1.38	NS
Ionized calcium [mg/dL]	1.24 ± 0.04	1.24 ± 0.05	1.23 ± 0.03	NS
TSH [mIU/L]	1.95 (1.39–2.76)	1.86 (1.17–2.76)	1.99 (1.56–2.8)	NS
Total protein [g/dL]	6.48 ± 0.9	6.4 ± 0.86	6.74 ± 1.01	NS
Glucose [mg/dL]	75 (69–83)	75 (68–81)	80 (71.5–91.5)	**0.03**
Total cholesterol [mg/dL]	168 (131–194)	169 (131–192)	156 (109–261)	NS
HDL [mg/dL]	67.2 ± 21.1	66.4 ± 20.4	69.8 ± 24	NS
LDL [mg/dL]	85 (58–124)	84 (62–113)	102 (32–145)	NS
Triglyceride [mg/dL]	76.5 (55–125)	78 (58–138)	74 (54–82)	NS

Data are presented as mean ± standard deviation (SD), median (1 to 3 boundaries) or number (percentage). All measurements are taken at admission; n — number; NS — not significant; BMI — body mass index; HR— heart rate; SBP — systolic blood pressure; WBC — white blood count; TSH — thyroid-stimulating hormone; HDL — high-density lipoprotein; LDL — low-density lipoprotein

groups. The mean age was 22.8 ± 5.6 years. High female predominance was observed [female/male (F/M): 54/2]. Sodium level was lower and glucose level was higher in group D than in group non-D. No other differences were observed in laboratory findings.

ECG analysis

Sinus rhythm was present in all ECG. Mean heart rate (HR) was similar in both groups (61 ± 16.3 bpm in group D vs. 63.1 ± 18.7 bpm in non-D, p > 0.05). Pathological bradycardia (HR < 50 bpm) was observed in 5 patients (41.7%) in group D and in 13 patients (29.5%) in group non-D, p > 0.05. The mean QTd did not differ between group D and non-D (40 ms vs. 36.8 ms, respectively, p > 0.05).

QTc interval prolongation was found in 2 to 4 patients (16.7–33.3%) in D-group and in 3 to 5 patients (6.8–11.4%) in non-D group depending on correction formula. The percentage was significantly greater in group D than in group non-D when Fridericia formula was used. QTc interval tended to be longer in Group-D: 459 ± 81 ms vs. 413 ± 33 ms, p = 0.04, correction with Framingham formula, and borderline p values (0.05–0.07) was found for others (Table 2).

QTc interval prolongation over 500ms was present in 5 patients (all female) — 3 in group D and 2 in group non-D (25% vs. 4.5%, p = 0.06).

The variability of QTc values depending on used correction formula was assessed in whole population and within each group (Table 3). QTc interval obtained with Hodges formula was the longest. Significant differences were found between values of QTc interval obtained with Hodges, Framingham and Fridericia formulas in analysis for all patients and group non-D, but not in group D.

Relationship of the QTc internal with the selected clinical parameters

No significant correlations were found between QTc interval and potassium, sodium, calcium levels as well as weight and body mass index (BMI). QT interval corrected with Bazett and Hodges formulas was significantly dependent on heart rate: R = –0.29, p = 0.03 and R = –0.42, p = 0.001,

Table 2. QT interval in group non-D and group D corrected with four formulas

	Group non-D (n = 44)			Group D (n = 12)			p*	p**
	Mean ± SD [ms]	Range [ms]	> 460 ms# N [%]	Mean ± SD [ms]	Range [ms]	> 460 ms# N [%]		
Bazett correction	417 ± 35	350–500	5 (11.4%)	464 ± 92	383–698	2 (16.7%)	0.05	NS
Fridericia correction	416 ± 34	325–505	3 (6.8%)	465 ± 85	394–678	4 (33.3%)	0.06	0.03
Framingham correction	413 ± 33	335–505	3 (6.8%)	459 ± 81	391–665	3 (25%)	0.04	NS
Hodges correction	423 ± 36	339–532	4 (9.1%)	472 ± 82	393–660	4 (33.3%)	0.07	0.06

*Comparison between QTc intervals (ms) in both group; **comparison between number of prolonged QTc intervals in both group; #for men > 450 ms; n — number; NS — not significant; SD — standard deviation

Table 3. Comparison between QTc intervals depending on correction method

	p value for whole population (n = 56)	p value for group non-D (n = 44)	p value for group D (n = 12)
QTc Bazett vs. QTc Fridericia	NS	NS	NS
QTc Bazett vs. QTc Framingham	NS	NS	NS
QTc Bazett vs. QTc Hodges	NS	NS	NS
QTc Fridericia vs. QTc Framingham	**0.001**	**0.008**	0.07
QTc Fridericia vs. QTc Hodges	**< 0.001**	**< 0.001**	NS
QTc Framingham vs. QTc Hodges	**0.001**	**< 0.001**	NS

NS — not significant

respectively. Influence of heart rate on results of Fridericia and Framingham formulas was not significantly important (R = –0.22, p = 0.1 and R = –0.11, p = 0.4). *See* Table 4.

Discussion

The present study focused on analysis of QTc interval in patients suffered from AN depending on pharmacological treatment. We used and compared four QT correction formulas: Bazett, Fridericia, Framingham and Hodges to find the most appropriate one for patients with AN. The QTc interval tended to be longer in patients, who were administrated drugs with potential to prolong the myocardial repolarization (p value: 0.04–0.07, depending on used correction formula). The percentage of patients with prolong QTc (> 460 ms for women and > 450 ms for men) was depended on used formula and was greater in drug-group, when using Fridericia method.

There are several studies focused on the QT interval in patients with AN and the results are inconsistent. QTc interval prolongation was observed in considerable amount of small studies [4, 14–20]. Majority of those study used only Bazett formula, which is highly dependent on heart rate [21]. Another limitations were small samples and various upper limit of normal for QT interval. Most of novel studies are not in line with previous results and usually failed to prove higher prevalence of QTc interval prolongation in AN patients [22–27]. Bomba et al. [28] found reduced QTc interval in drug-free AN patients compared to controls. What is worth to mention, majority of those studies assessed patients on drug and those without treatment together, so influence of medication was not taken into account. Janzen at al. analyzed changes on the electrocardiogram in AN and considered impact of pharmacotherapy [29]. There were no differences in the QT interval and QTc with Hodges as well as T-wave abnormality between drug-free and drug-on patients. Drug-free patients were compared to controls and results were dependent on used formula — QTc interval in AN patients was shorter (Bazett, Fridericia), longer (Framingham) or similar (Hodges) than controls. Comparison between drug-on and drug-free patients was also conducted in study by Padfield et al. [26] — there was also no difference in QTc interval between these groups.

The choice of correction method is still not clear. Walter et al. suggested Hodges formula, because of lack of correlation with heart rate in their study [27]. It is not consistent with our results, Bazett and Hodges formulas correlated

Table 4. Correlation between QTc intervals and selected variables for whole population

	Variable	R Spearman	p value
QTc Bazett	**HR**	**0.29**	**0.03**
	Weight	0.17	NS
	BMI	0.15	NS
	Phosphate	–0.07	NS
	Sodium	–0.06	NS
	Potassium	0.2	NS
	Total calcium	–0.05	NS
	Ionized calcium	–0.14	NS
	TSH	–0.04	NS
QTc Fridericia	HR	–0.22	NS
	Weight	0.02	NS
	BMI	–0.06	NS
	Phosphate	–0.12	NS
	Sodium	–0.11	NS
	Potassium	0.17	NS
	Total calcium	–0.12	NS
	Ionized calcium	–0.33	NS
	TSH	0.1	NS
QTc Framingham	**HR**	**–0.11**	**NS**
	Weight	0.06	NS
	BMI	–0,01	NS
	Phosphate	–0.15	NS
	Sodium	–0.09	NS
	Potassium	0.15	NS
	Total calcium	–0.12	NS
	Ionized calcium	–0.3	NS
	TSH	0.1	NS
QTc Hodges	HR	–0.42	0.001
	Weight	–0.01	NS
	BMI	–0.11	NS
	Phosphate	–0.23	NS
	Sodium	–0.18	NS
	Potassium	0.16	NS
	Total calcium	–0.17	NS
	Ionized calcium	–0.29	NS
	TSH	0.12	NS

HR — heart rate; NS — not significant; BMI — body mass index; TSH — thyroid-stimulating hormone

significantly with heart rate in the present study. Hodges formula tended to overestimate QT duration. According to our results, Fridericia and Framingham were the least dependent on heat rate, so they may be useful with patients with bradycardia. On the other hand, duration of QT interval corrected with Hodges, Fridericia and Framingham differed significantly, but when compared to Bazett method, the results were similar. The larger research is needed to establish if QT interval duration corrected with specific method have prognostic value in long-term follow-up.

Another finding was that in our study there was no relationship between QTc interval and electrolytes or weight and BMI. Several studies reached similar conclusion [15, 26, 30]. In contrary, Swenne et al. showed significant relationship between QT value and BMI, weight and sodium concentration [18].

Study limitations

This is a retrospective, single center study. Main limitation is small number of patients, especially in group treated with drugs, which may prolong QT interval. We analyzed medication at the moment of the hospital admission, which reflected chronic treatment. There was variability of administrated drugs, which might affect myocardial repolarization, so group D was not homogenous. ECG was not reassessed after refeeding.

Conclusions

Information about pharmacotherapy in AN patient is key for QTc assessment. Choice of correction formula may have impact on results. Framingham and Fridericia formulas were the least dependent on heart rate in contrary to Bazett and Hodges formulas.

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Streszczenie

Wstęp. Pacjenci z jadłowstrętem psychicznym (AN) są narażeni na zwiększone ryzyko komorowych zaburzeń rytmu, które wiąże się z wydłużeniem odstępu QT. Celem pracy była analiza odstępu QT u pacjentów z AN z uwzględnieniem potencjalnego wpływu farmakoterapii oraz weryfikacja różnych formuł korekcji QT.

Materiał i metody. Do analizy włączono 56 pacjentów hospitalizowanych z powodu AN (średni wiek: 22,8 ± 5,6 roku; kobiety/mężczyźni: 54/2, średni wskaźnik masy ciała = 13,6 ± 2,6 kg/m^2): grupę nie-D (n = 44; 78,6%) stanowili chorzy niestosujący leków wydłużających odstęp QT, a grupę D (n = 12; 21,4%) chorzy leczeni takimi lekami. Odstępy QT mierzono w 12-odprowadzeniowym zapisie elektrokardiograficznym i korygowano przy użyciu czterech wzorów: Bazetta, Fridericia, Framinghama i Hodgesa.

Wyniki. Średnia częstość rytmuserca (HR) była podobna w obu grupach (61 ± 16,3 bpm w grupie D *vs.* 63,1 ± 18,7 bpm w grupie nie-D; p > 0,05). Bradykardia (HR < 50 bpm) była obecna u 5 chorych (41,7%) w grupie D i 13 chorych (29,5%) w grupie nie-D. Odstęp QTc skorygowany z użyciem wzoru Framinghama był dłuższy w grupie D (459 ± 81 ms) niż w grupie nie-D (413 ± 33 ms); p = 0,04. Odstęp QT skorygowany z użyciem wzorów Bazetta i Hodgesa był istotnie zależny od HR (odpowiednio R = –0,29, p = 0,03 i R = –0,42, p = 0,001). Wpływ HR na wyniki z wzorów Fridericia i Framinghama nie był istotny (R = –0,22, p = 0,1 i R = –0,11, p = 0,4).

Wnioski. Informacje na temat farmakoterapii u chorych na AN mają kluczowe znaczenie dla oceny QTc. Wybór wzoru korekcji wpływa na QTc. Odstępy QT uzyskane przy użyciu formuł Framinghama i Fridericia były najmniej zależne od tętna.

Słowa kluczowe: jadłowstręt psychiczny, częstość rytmu, wzory korekcji QT, odstęp QT, wydłużenie QT

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