

Therapy

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PREDICTING THE RISK OF PROLONGATION OF THE MEAN DAILY QT_c INTERVAL IN PATIENTS WITH ARTERIAL HYPERTENSION

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Arterial Hypertension (AH) is one of the leading causes of morbidity and mortality and is an urgent problem for more than 1.4 billion people worldwide. High mortality risks due to hypertension are associated with the risk of developing dangerous arrhythmias. These conditions can be diagnosed by changes in the QT_c interval, which indicates an abnormal repolarization. The aim of the study was to determine the predictors of prolongation of the mean daily QT_c interval in hypertension. We examined 195 patients (166 patients with hypertension and 29 patients without hypertension) who were treated at the (Kharkiv) City Polyclinic No.24. All patients were divided into 2 subgroups depending on the duration of the average daily QT_c interval: 146 patients with normal QT_c and 20 patients with prolonged QT_c interval. Associations were determined using logistic regression with Wald's simultaneous inclusion and backward exclusion methods. The results showed that male gender was significantly associated with QT_c prolongation (Odds Ratio (OR)=4.292 [95.0% confidence intervals (CI) 1.337–13.779], $p=0.014$), as did body mass index (BMI) (OR=1.107 [95.0% CI 0.987–1.243], $p=0.083$) and mean daily Diastolic and Pulse Blood Pressure (DBP and PBP), respectively, OR=1.076 [95.0% CI 1.017–1.139], $p=0.011$ and OR=1.075 [95.0% CI 1.012–1.141], $p=0.018$. The time since the diagnosis of hypertension (OR=1.093 [95.0% CI 0.997–1.197], $p=0.057$) and the office DBP (OR=0.948 [95.0% CI 0.900–0.999], $p=0.046$) were significantly associated with QT_c prolongation. Taking into account the significant associations of male gender, BMI, mean daily DBP and SBP, time from diagnosis of hypertension, and office DBP with the risk of QT_c prolongation, a prognostic model for determining the risk of QT_c prolongation was developed, which has good qualification characteristics (sensitivity was 88.9% and specificity – 70.6%).

Keywords: associations, medical and epidemiological indicators, electrocardiography, Holter monitoring, linear equation.



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Introduction

A significant number of studies indicate that Arterial Hypertension (AH) is one of the leading causes of morbidity and mortality in the world population and is an urgent problem for more than 1.4 billion people worldwide [1].

Epidemiologic studies show that hypertension is widespread among the adult population (more than 30%), and the percentage of people with hypertension increases markedly with age [2; 3]. These data are confirmed by Mancia G. et al. [4], who defined hypertension as the most common CardioVascular Disease (CVD) in the world. According to the WHO, 1.28 billion adults aged 30–79 years worldwide suffer from hypertension, two-thirds of whom live in low- and middle-income countries [4].

In 2019, the global age-standardized average prevalence of AH among adults aged 30–79 years was 34% among men and 32% among women [5]. Other studies confirm that hypertension under the age of 50 is more common among men, and after 65 – among women [6; 7].

The NCD (Non-Communicable Diseases) study indicates that the prevalence of AH is generally similar among European countries, but has some differences between countries with lower values in Western countries and higher values in Eastern European countries. According to the NCD [5], the number of patients with AH aged 30–79 years doubled from 1990 to 2019, from 331 million women and 317 million men to 626 million women and 652 million men. In 2019, the age-standardized prevalence of AH was lowest in Canada and Peru (men and women), Taiwan, South Korea, Japan, and Western Europe (Switzerland, Spain, and the United Kingdom) for women. For men, the lowest rates of AH were in Eritrea, Bangladesh, Ethiopia, and the Solomon Islands. The highest prevalence of AH among women was observed in two countries, and among men – in nine coun-

tries of Central and Eastern Europe, Central Asia, Oceania and Latin America.

Numerous epidemiological studies have shown that AH is the main cause of a number of cardiac, cerebral, and vascular diseases, with stroke, coronary heart disease, heart failure, atrial fibrillation, peripheral arterial disease, and cognitive dysfunction being the most common [8; 9]. In addition, according to Lu S. et al. [10], AH is associated with risk factors such as dyslipidemia, impaired glucose tolerance, and type 2 diabetes, which further increase the risk of developing CVD. The close association of hypertension with cardiovascular events was also pointed out by Stergiou G.S. et al. [11].

In addition, AH provokes the development of high levels of negative medical and social consequences – mortality, disability, morbidity, and disability. The data of Burnier M. et al. [12] indicated an exponential increase in mortality from coronary heart disease and stroke from BP levels of 115/75 mm Hg, these risks were noted in all age groups starting from 40 years.

Solanki J.D. et al. [13] determined that high risks of mortality provoked by AH are associated with cardiac dysautonomy, which can result in dangerous arrhythmias. These conditions are confirmed by Electro-CardioGraphy (ECG), determining changes in the QTc interval, which indicates an abnormal repolarization. QTc interval testing is recommended for all patients with AH. Since most patients do not diagnose their condition in time and get sick at a young age, this creates a high risk of left ventricular hypertrophy. This situation can provoke repolarization abnormalities and cause life-threatening arrhythmias. Repolarization abnormalities are diagnosed by determining the QTc interval during an ECG. A prolonged QTc interval is a risk factor for CVD and mortality.

The need to check the QTc interval is also determined by NCD specialists [5]. They point out that due to the high preva-

lence of AH and its major role as a cause of death and morbidity, its diagnosis is crucial for global health. The NCDs confirmed that a significant number of patients with AH are unaware of their condition, which negatively affects the increase in the negative health and social consequences of AH. There are suggestions that screening of people with suspected AH by determining the QTc interval on the ECG can significantly increase the detection of the disease [14], however, participation in screening should be lower among young people and men compared to others [15]. In the United States, the U.S. Preventive Services Task Force emphasizes the need for screening for AH by examining the ECG QTc interval in adults over 18 years of age [16]. First of all, they suggest annual screening in adults over 40 years of age and in people at increased risk of developing AH (people with risk factors for AH) [16; 17].

The **aim** of our study was to determine the predictors of prolongation of the mean daily QTc interval in arterial hypertension.

Materials and Methods

195 patients (166 patients with AH and 29 patients without AH) were examined who were treated at the City Polyclinic No.24 of the Kharkiv City Council. The mean age of the subjects was $[58.9 \pm 9.9]$ years and $[59.9 \pm 8.2]$ years, respectively ($p=0.821$).

All patients were divided into 2 subgroups depending on the duration of the average daily QTc interval: 146 patients with normal QTc (mean age – $[59.7 \pm 8.8]$ years) and 20 patients with prolonged QTc interval (mean age – $[56.3 \pm 12.8]$ years). Subjects with different QTc interval duration were completely comparable in terms of age characteristics ($p=0.441$).

The degrees of AH were determined in accordance with the Unified Clinical Protocol for Primary, Emergency and Secondary (Specialized) Medical Care "Arterial Hypertension", approved by the Order of

the Ministry of Health of Ukraine No.384 of May 24, 2012.

The effect of the studied characteristics of patients, their average daily values and Blood Pressure (BP) variability on the QTc duration was determined by outpatient ECG monitoring and daily BP monitoring.

The duration of the QTc interval was calculated using the CardioSense program. The calculations used the corrected QT interval (QTc), taking into account the Heart Rate (HR) according to the Bazett formula. QTc prolongation was recorded at a duration of >430 ms for men and >450 ms for women.

All patients included in the study signed informed consent to participate.

The associations of certain parameters with the risks of QTc prolongation were determined using logistic regression with Wald's simultaneous inclusion and reverse exclusion methods. The critical level of reliability was considered to be $p<0.05$. Calculations were performed using the SPSS 25.0 (IBM, USA).

Results and Discussion

According to the results, it was found that male patients significantly ($p=0.075$) have 2.5 times higher risks of prolongation of mean daily QTc (Odds Ratio (OR)= 2.412 [95.0% Confidence Interval (CI) $0.917-6.345$] compared with women (*Table 1*).

The addition of additional factors (time of AH diagnosis, Body Mass Index (BMI), and abdominal obesity) did not significantly change the associations, but the effect of gender on mean daily QTc prolongation increased: men, compared with women, were significantly ($p=0.032$) 3 times more likely to develop prolongation (OR= 3.094 [95.0% CI $1.102-8.685$]) (*Table 2*).

It was also found that the presence of grade 2 AH significantly ($p=0.035$) increased the chances of prolongation of the mean daily QTc by 5.7 times compared with patients with normal BP: OR= 5.786 [95.0% CI $1.128-29.673$] (*Table 3*).

Table 1. Association of medical and epidemiological parameters with changes in mean daily QTc

Factors	p	OR	95.0% CI for OR
Male gender	0.075	2.412	0.917–6.345
Age, years	0.368	0.979	0.935–1.025

Notes: CI – confidence interval;
OR – Odds Ratio.

Table 2. Association of medical and epidemiological parameters with changes in mean daily QTc

Factors	p	OR	95.0% CI for OR
Male gender	0.032	3.094	1.102–8.685
Age, years	0.189	0.965	0.916–1.018
Time since diagnosis of AH, years	0.236	1.052	0.967–1.145
BMI, kg/m ²	0.151	1.078	0.973–1.195
Abdominal obesity	0.411	2.564	0.272–24.211

Notes: AH – arterial hypertension;
BMI – body mass index;
CI – confidence interval;
OR – Odds Ratio.

Table 3. Association of hypertension grades with changes in mean daily QTc

Factors	p	OR	95.0% CI for OR
Normal BP	0.010		<i>Reference group</i>
Controlled BP	0.795	1.246	0.236–6.567
AH of the 1 st degree	0.287	0.265	0.023–3.053
AH of the 2 nd degree	0.035	5.786	1.128–29.673
AH of the 3 ^d degree	0.398	2.455	0.306–19.678

Notes: BP – blood pressure;
AH – arterial hypertension;
CI – confidence interval;
OR – Odds Ratio.

The addition of the indicator of the presence of bad habits to the analysis showed that, as previously, the presence of grade 2 AH, compared with normal BP, significantly increased the odds of prolongation of the mean daily QTc by 6.8 times (OR=6.857 [95.0% CI 1.203–39.076]; p=0.030).

Male gender also had a significant effect compared with female gender (2.4-fold increase in odds; OR=2.448 [95.0% CI 0.861–6.961]; p=0.093). A history of alcohol consumption significantly increased the odds of mean daily QTc prolongation by almost 10 times (OR=9.311 [95.0% CI 1.018–

85.151]; $p=0.048$) compared with no alcohol use (Table 4).

Determination of the association of independent ECG predictors with changes in QTc identified a probable 11.1% increase in the chance of developing ECG QTc prolongation with an increase in HR by 1 bpm: OR=1.117 [95.0% CI 1.035–1.206]; $p=0.005$ (Table 5).

Subsequently, to determine reliable predictors of QTc prolongation, we analyzed the clinical and anamnestic characteristics of patients (age, gender, presence of comorbidities and bad habits, abdominal obesity, BMI), indicators of the CVS functional state of the (office systolic and diastolic BP and pulse BP (SBP, DBP, PBP), HR), indicators of heart rate variability (type of

variability of SBP and DBP, average daily values of SBP and DBP and PBP), the presence of heart rhythm disorders (total number of arrhythmias, bradycardias, tachycardias, pauses).

The linear equation for determining the risk of QTc prolongation is as follows:

$$\begin{aligned} \text{QTc prolongation} = & -13.875 + [1.457 \text{ if male}] + [0.102 \times \text{BMI, kg/m}^2] + \\ & + [0.074 \times \text{Mean daily DBP, mm Hg}] + \\ & + [0.072 \times \text{Mean daily PBP, mm Hg}] + \\ & + [0.089 \times \text{Time since diagnosis of hypertension, years}] - [0.053 \times \text{Office PBP, mm Hg}]. \end{aligned}$$

The threshold value of the model was 2.4566, at which sensitivity – 88.9% and specificity – 70.6% (Fig.).

Table 4. Association of hypertension severity, gender, and smoking with changes in mean daily QTc

Factors		p	OR	95.0% CI for OR
Normal BP		0.009	<i>Reference group</i>	
Controlled BP		0.617	1.568	0.270–9.107
AH of the 1 st degree		0.204	0.191	0.015–2.454
AH of the 2 nd degree		0.030	6.857	1.203–39.076
AH of the 3 ^d degree		0.554	1.990	0.204–19.387
Male gender		0.093	2.448	0.861–6.961
Bad habits	Absent	0.109	<i>Reference group</i>	
	Smoking	0.299	2.016	0.537–7.575
	Alcohol	0.048	9.311	1.018–85.151

Notes: BP – blood pressure;
AH – arterial hypertension;
CI – confidence interval;
OR – Odds Ratio.

Table 5. Association of independent predictors of ECG with QTc changes

Factors	p	OR	95.0% CI for OR
HR, beats per minute	0.005	1.117	1.035–1.206

Notes: HR – Heart Rate;
CI – confidence interval;
OR – Odds Ratio.

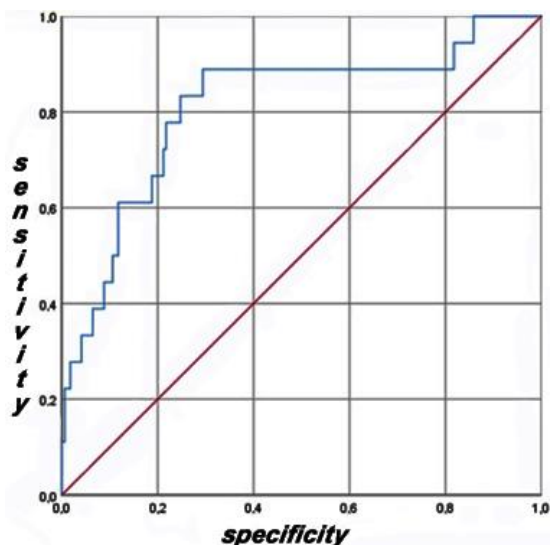


Fig. ROC curve of the developed model (AUC=0.811 [95.0% CI 0.693-0.929], $p<0.001$).

Notes: ROC – Receiver Operating Characteristic;

AUC – Area Under the Curve.

Based on the results of our mathematical analysis of reliable predictors of QTc prolongation, we tested the calculated model and conducted its practical testing. For this purpose, several patients were randomly selected and the relevant parameters were evaluated to predict the risk of developing a prolonged QTc interval. Additionally, the presence of cardiovascular events was prospectively assessed according to medical records.

Thus, the risks of developing a prolonged QTc interval in a male patient V., aged 65 years, were assessed. The duration of AH since diagnosis was 16 years. BMI – 32.80 kg/m². BP parameters: office PBP – 30 mm Hg, mean daily DBP – 82 mm Hg, mean daily PBP – 45 mm Hg. When applying the developed mathematical model, it was determined that the probability of having a prolonged QTc interval is 51.74%. During the daily Holter monitoring, this indicator was 437 ms, which is higher than the established reference standards. It was

prospectively determined that this patient was hospitalized with a diagnosis of coronary heart disease.

Assessing the risks of developing a prolonged QTc interval in a female patient A., aged 61 years, it was stated: the duration of AH since the diagnosis was 5 years. BMI – 29.30 kg/m². BP indicators: office PBP – 20 mm Hg, mean daily DBP – 72 mm Hg, mean daily PBP – 42 mm Hg. When applying the developed mathematical model, it was determined that the probability of having a prolonged QTc interval was 4.11%. During the daily Holter monitoring, this indicator was 371 ms, which is within the established reference norm. It was prospectively determined that she was diagnosed with cerebrovascular disease.

Our data are confirmed by other studies in this area. Thus, the study by Solanki J.D. et al. [13] proved that patients with AH for 5 years or more have a significantly higher QTc value compared with those with normal blood pressure both among men (0.42 vs. 0.40, $p<0.001$) and women (0.44 vs. 0.41, $p<0.001$) and in general (0.43 vs. 0.40 vs., $p<0.001$). Among patients with AH, the OR was 1.63 in men ($p=0.15$), 23.71 in women ($p=0.003$) and 3.83 in general ($p<0.001$) for the development of prolonged QTc.

Another study [18] showed a prolongation of the QTc interval in patients with AH compared with the control group ([454.8±29] ms compared with [429.8±18] ms, $p<0.001$). The QTc interval was directly correlated with an increase in right ventricular end-diastolic volume ($r=0.67$, $p<0.001$) and its mass ($r=0.51$, $p<0.05$) and inversely with right ventricular ejection fraction ($r=-0.49$, $p<0.05$).

Conclusions

Thus, the study found that male gender, BMI, mean daily DBP and PBP, and time since diagnosis of AH, as well as office DBP, were significantly associated with significant risks of QTc prolongation.

Taking these associations into account, a predictive model was developed to determine the risk of QTc prolongation, which

has good qualification characteristics (sensitivity was 88.9%, and specificity – 70.6%).

Conflict of interest is absent.

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Целік Н.Є.

Прогнозування ризиків подовження середньодобового інтервалу QTc у хворих із артеріальною гіпертензією

Артеріальна Гіпертензія (АГ) є однією з основних причин захворюваності та смертності населення і є актуальною проблемою для більш ніж 1,4 мільярда людей у всьому світі. Високі ризики смертності через АГ пов'язані з ризиками розвитку небезпечних аритмій. Дані стани можна діагностувати за допомогою змін інтервалу QTc, який вказує на аномалію реполяризації. Метою роботи було визначення предикторів подовження середньодобового інтервалу QTc при АГ. Було обстежено 195 осіб (166 пацієнтів із АГ і 29 – без АГ), які проходили лікування на базі КНП «Міська поліклініка № 24» (м. Харків). Всі пацієнти були розподілені на 2 підгрупи залежно від тривалості середньодобового інтервалу QTc: 146 осіб із нормальним QTc; і 20 – із подовженим інтервалом QTc. Визначення асоціацій проводили за допомогою логістичної регресії з методами одночасного включення та зворотного виключення Вальда. За отриманими результатами визначено, що чоловіча стать достовірно асоційована з подовженням інтервалу QTc (Відношення Шансів (ВШ)=4,292 [95,0 % Довірчі Інтервали (ДІ) 1,337–13,779], $p=0,014$), як й Індекс Маса Тіла (ІМТ) (ВШ=1,107 [95,0 % ДІ 0,987–1,243], $p=0,083$) і середній Добовий Діастолічний та Пульсовий Артеріальний Тиск (ДАТ та ПАТ) – відповідно ВШ=1,076 [95,0 % ДІ 1,017–1,139], $p=0,011$ та ВШ=1,075 [95,0 % ДІ 1,012–1,141], $p=0,018$. З подовженням інтервалу QTc вірогідно були асоційовані час зі встановлення АГ (ВШ=1,093 [95,0 % ДІ 0,997–1,197], $p=0,057$) й значення офісного ДАТ (ВШ=0,948 [95,0 % ДІ 0,900–0,999], $p=0,046$). Враховуючи отримані вірогідні асоціації чоловічої статі, ІМТ, середнього добового ДАТ та ПАТ, часу зі встановлення діагнозу АГ, значення офісного ДАТ з ризиками подовження інтервалу QTc розроблено прогностичну модель визначення ризиків

подовження QTс, яка має гарні кваліфікаційні характеристики (чутливість склала 88,9 %, специфічність – 70,6 %).

Ключові слова: асоціації, медико-епідеміологічні показники, електрокардіографія, Холтерівське моніторування, лінійне рівняння.

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