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CLINICAL STUDY

24-hour outpatient ECG as a screening method in patients with primary hyperparathyroidism

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ABSTRACT

PURPOSE: Patients with primary hyperparathyroidism are characterized by increased calcium plasma concentrations, which in turn could have a potential to induce ECG changes, especially shortening of the QT interval. Therefore, the aim of this study was to evaluate, whether the routine 24-hours outpatient ECG monitoring could be used for screening the primary hyperparathyroidism.

METHODS: Totally, 31 patients (mean age, 59.2 ± 12.99 years) with primary hyperparathyroidism were compared to 20 healthy controls. All patients underwent mineral metabolism biochemical evaluation, ultrasound or scintigraphy of the neck, and a 24-hour outpatient ECG. The device detected QT, QTc, and RR intervals during a 24-hour period.

RESULTS: Significantly higher calcium concentrations were confirmed in patients when compared to controls (2.38 ± 0.12 vs 2.92 ± 0.29 mmol/l; $p < 0.001$). However, no significant differences were found between controls and patients in QT interval and overall heart rate.

CONCLUSION: Although shortening of the QT interval is a common ECG finding in patients with hyperparathyroidism, it seems that 24-hour outpatient ECG is not suitable for primary hyperparathyroidism screening *(Tab. 2, Fig. 4, Ref. 28)*. Text in PDF *www.elis.sk.*

KEY WORDS: primary hyperparathyroidism, hypercalcemia, 24 hour outpatient electrocardiography, QT interval and QTc interval.

Introduction

Primary hyperparathyroidism (pHPT) is a generalized disorder of calcium and phosphate metabolism due to an excessive secretion of parathyroid hormone (PTH). Over the past 30 years, there has been a shift in clinical presentation from a disorder associated with overt skeletal and renal disease to an asymptomatic form (1, 2). The term "asymptomatic primary hyperparathyroidism" was created to describe patients who lack obvious signs and symptoms associated with either excess calcium or PTH (3, 4).

Resulting hypercalcemia can induce electrocardiogram (ECG) abnormalities, mainly changes in the ST segment, as well as QT interval shortening, prolongation of PR interval and QRS duration (5, 6). Moreover, T waves may flatten or invert, and a variable degree of heart block may develop (7, 8). Shawn et al described the case of a patient with ST segment elevation induced by hypercalcemia (9, 10). Hypercalcemia can also cause an ECG finding mimicking hypothermia, known as an Osborn wave (11). The conclusions of two large studies, NHANNES III (Third National Health and Nutrition Examination Survey) and ARIC (Atherosclerosis Risk in Communities) pointed that QT interval duration was inversely associated with serum total and ionized calcium (12). Shortening of QT interval duration was associated with an increased risk of arrhythmias and sudden cardiac death (13). Data from NHANNES III suggested that shortened and prolonged QT interval durations, even within a reference range, were associated with an increased risk of mortality in the general population (14). Patients with pHPT may have an increased risk of death, mainly as the consequence of cardiovascular complications, although the data regarding patients with asymptomatic pHPT are limited and controversial (15).

The diagnosis of pHPT, especially asymptomatic, most commonly comes from accidental biochemical finding of an increased calcium in blood serum. For pHPT confirmation, another sampling is needed along with parathyroid hormone evaluation (16). Indeed, term asymptomatic is unclear, since the patients may present with non-specific symptoms as is fatigue, weakness, joint pain (17) or anorexia (18). Nonetheless, the calcium measurement in such asymptomatic patients is uncommon, more common is outpatient ECG or a 24-hour outpatient ECG evaluation.

Therefore, the aim of this study was to assess, whether hypercalcemia would affect QT and QTc intervals in our patients with pHPT, and whether these changes could be successfully detected by a 24-hour outpatient ECG, which in turn could be used as a screening test for pHPT.

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Subjects and methods

We studied totally 31 patients (mean age 59.2 ± 12.99 years) with pHPT in the Cardiology Department of Nitra Faculty Hospital between January 2009 and December 2012. We defined pHPT as the presence of hypercalcemia and an inappropriately high level of intact parathyroid hormone. Over the same period in the same department, 20 healthy control subjects (mean age 58 ± 13.2 years) without cardiovascular risk factors were enrolled in the study. The patients had neither renal nor hepatic disease, nor did they exhibit other disturbances in sodium, potassium, chloride, or calcium levels. Patients or healthy subjects with medication that could impact the QT interval were not included in the study. Biochemical analyses were performed in the laboratory of Nitra Faculty Hospital (serum calcium levels were analyzed on a Beckmann Coulter Olympus 640A system, intact PTH and serum concentrations of 25-hydroxy-vitamin D were measured on an Elecsys 2010 system, Roche). Renal function was estimated by calculating the glomerular filtration rate (GFR) according to Cockcroft-Gault formula: GFR=(140 age in year) × (weight in kg/creatinine) × (1.23 in men or 1.04 in women) (19). QT intervals were measured via 24 hour outpatient ECG recordings. The study was approved by the institutional Ethical committee, and the informed consent was obtained from each participant prior to study enrolment.

All participants underwent 24-hour outpatient ECG. The device was specifically set to detect QT interval, corrected QT interval (QTc), and RR intervals during a 24-hour period. The ECG device (Medilog Holter, Oxford Instruments Medical Ltd.) analyzed the following data over the 24 hour period in one hour intervals: QT min (most shortened QT interval), QT max (most prolonged QT interval), QT average (average QT interval), QTc min (most shortened QTc interval), QTc max (most prolonged QTc interval), QTc average (average QTc interval), RR min (minimal RR interval), RR max (maximal RR interval), RR average (average RR interval). The 24-hour outpatient ECGs were set and further evaluated by one (the same) cardiologist.

Tab. 1. Clinical data for controls and patients with primary hyperparathyroidism.

	Controls (n = 20)	pHPT patients (n = 31)
Age [years]	58±13.2	59.2±12.99
Weight [kg]	70.64±10.30	72.9±12.48
Height [cm]	163.14±6.76	164.55±6.03
BMI [kg/m2]	26.79±4.58	26.975±4.45
GF [ml/s]	1.37±0.26	1.39±0.29
Calcium [mmol/l]	2.38±0.12	2.92±0.29***
iPTH [ng/ml]	56.07±6.62	145.05±90.64***
Phosphorus [mmol/l]	1.16±0.15	0.85±0.17***
25-OH-vitamin D [ng/ml]	12.3±5.6	10.8±6.03

No significant differences were observed between basic clinical data as is age, weight, height, BMI, GF and vitamin D levels. BMI – Body mass index, GF – glomerular filtration according to Cockcroft-Gault formula, iPTH – intact parathormone, pHPT – primary hyperparathyroidism; 25-OH-vitamin D – 25-hydroxyvitamin D. *** denotes $p < 0.001$ vs. controls. Data presented as mean ± standard deviation.

Statistical analysis

Graphpad Prism 6.01 was used for statistical evaluations. Unpaired t-test was used to analyze the results. Pearson correlation test and regression analysis were used to evaluate correlation between serum calcium concentrations and QT interval length. Data are presented as scatter plots with mean ± SD.

Results

Firstly, all basic clinical and biochemical data for patients with pHPT and for the control group are shown in Table 1. No significant differences were found in age, BMI, height, weight, vitamin D concentrations, and glomerular filtration. However, in patients with pHPT, significantly higher serum calcium, lower serum phosphorus and higher serum iPTH were observed when compared to control patients (Tab. 1) ($t = 7.92$, $t = 6.65$, $t = 4.367$ respectively; $p < 0.001$ for all parameters).

Secondly, in our sample of patients with pHTP, hypercalcemia was negatively correlated with the average QT interval (Fig. 1A) ($r = –0.416$, $p < 0.05$) and average QTc (Fig. 1B) ($r = –0.328$; p

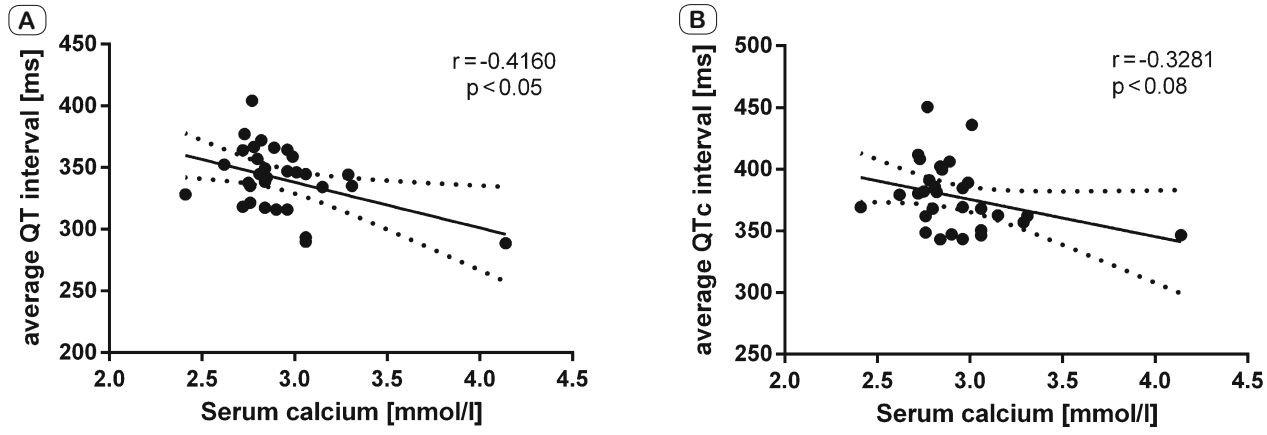

Fig. 1. Average QT (A) and average QTc (B) correlations to serum calcium levels. Average QT significantly correlated with serum calcium levels. Average QTc marginally correlated with serum calcium levels. Dotted line – 95% confidence interval, r – correlation coefficients.

Tab. 2. Correlation coefficients of a 24-hour outpatient ECG with observed variables in pHPT patients.

	Serum calcium	
	r coefficient	p value
QT minimal	–0.092	0.63
QT maximal	–0.093	0.62
QTc minimal	–0.072	0.70
QTc maximal	–0.236	0.12
RR minimal	–0.271	0.15
RR maximal	–0.053	0.79
RR average	–0.148	0.43
HR average	–0.028	0.89

r – correlation coefficient, HR – heart rate, QTc – corrected QT interval.

< 0.08). However, no significant correlations were found when analyzing minimum or maximum QT and QTc with serum calcium concentrations. Also, higher serum calcium did not correlate with the average heart rate or average, minimal and maximal RR intervals (Tab. 2).

Lastly, no significant differences were observed between control and pHPT group in average QT and QTc interval length (Figs 2C and 3C, respectively) on 24-hour outpatient ECG. Similarly, no such differences were found in minimal QT and minimal QTc interval length (Figs 2A and 3A, respectively). Also, maximal QT and maximal QTc interval length did not differ between the control and pHPT group (Figs 2B and 3B, respectively). Additionally, primary hyperparathyroidism did not influence minimal, maximal, average RR interval as well as average heart rate per hour (Figs 4A–D, respectively).

Discussion

Asymptomatic hyperparathyroidism is a common manifestation of primary hyperparathyroidism. On the other hand, pHPT is associated with an increased mortality, mainly due to the cardiovascular complications, such as hypertension, ventricular hypertrophy, arrhythmia or valvular/vascular calcification (20, 21). Increased cardiovascular morbidity and mortality observed in severe pHPT has not been definitively confirmed in milder forms of the disease, but there is evidence for subtle cardiovascular abnormalities, such as increased vascular stiffness (22). Nevertheless, some of these complications can be reversed by surgical treatment (23) suggesting early diagnosis to be important in asymptomatic pHPT

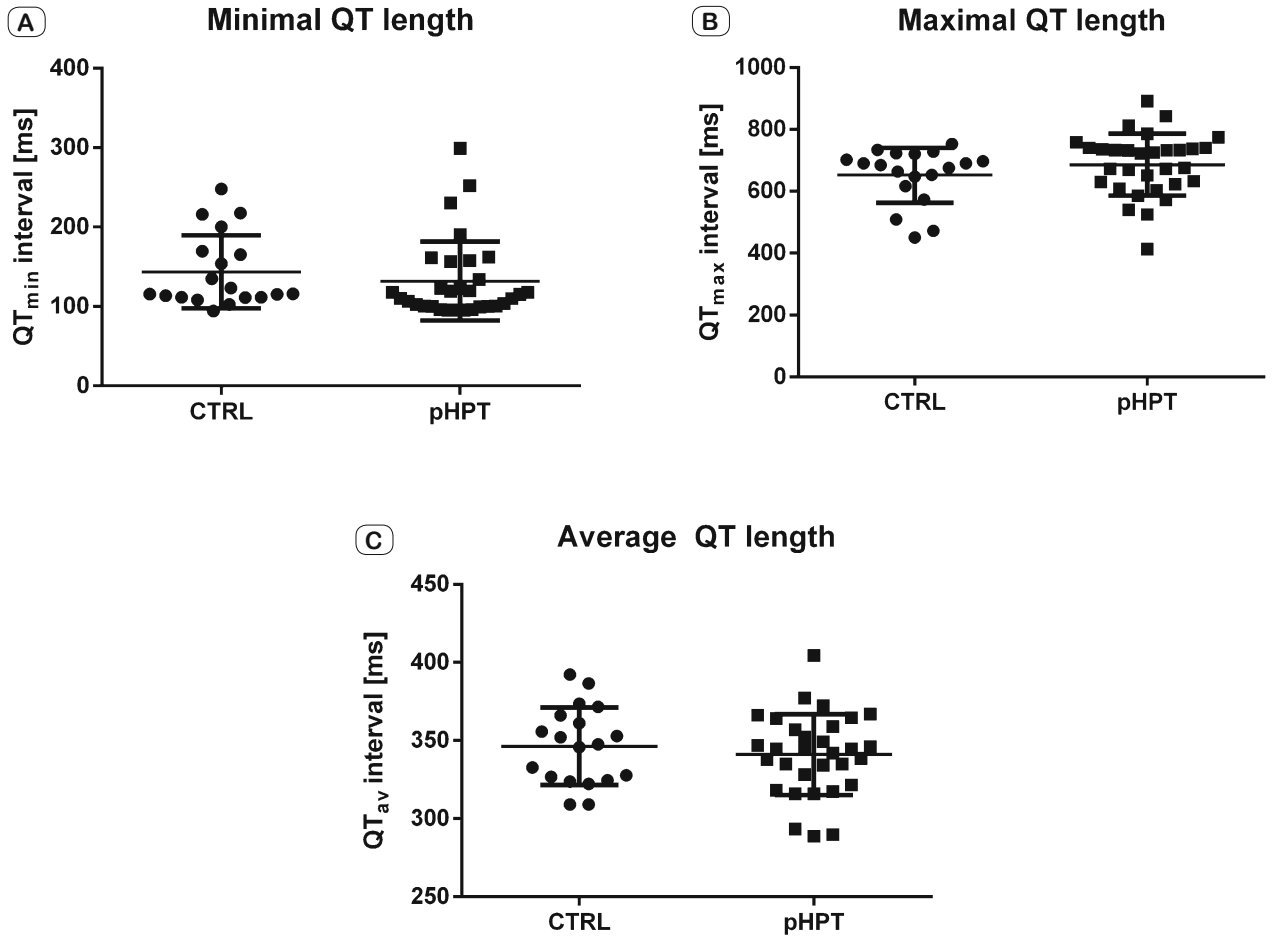

Fig. 2. Minimal (A), Maximal (B) and Average (C) QT interval length on a 24-hour outpatient ECG in CTRL and pHPT. No significant differences were observed. CTRL – control, pHPT – patients with primary hyperparathyroidism.

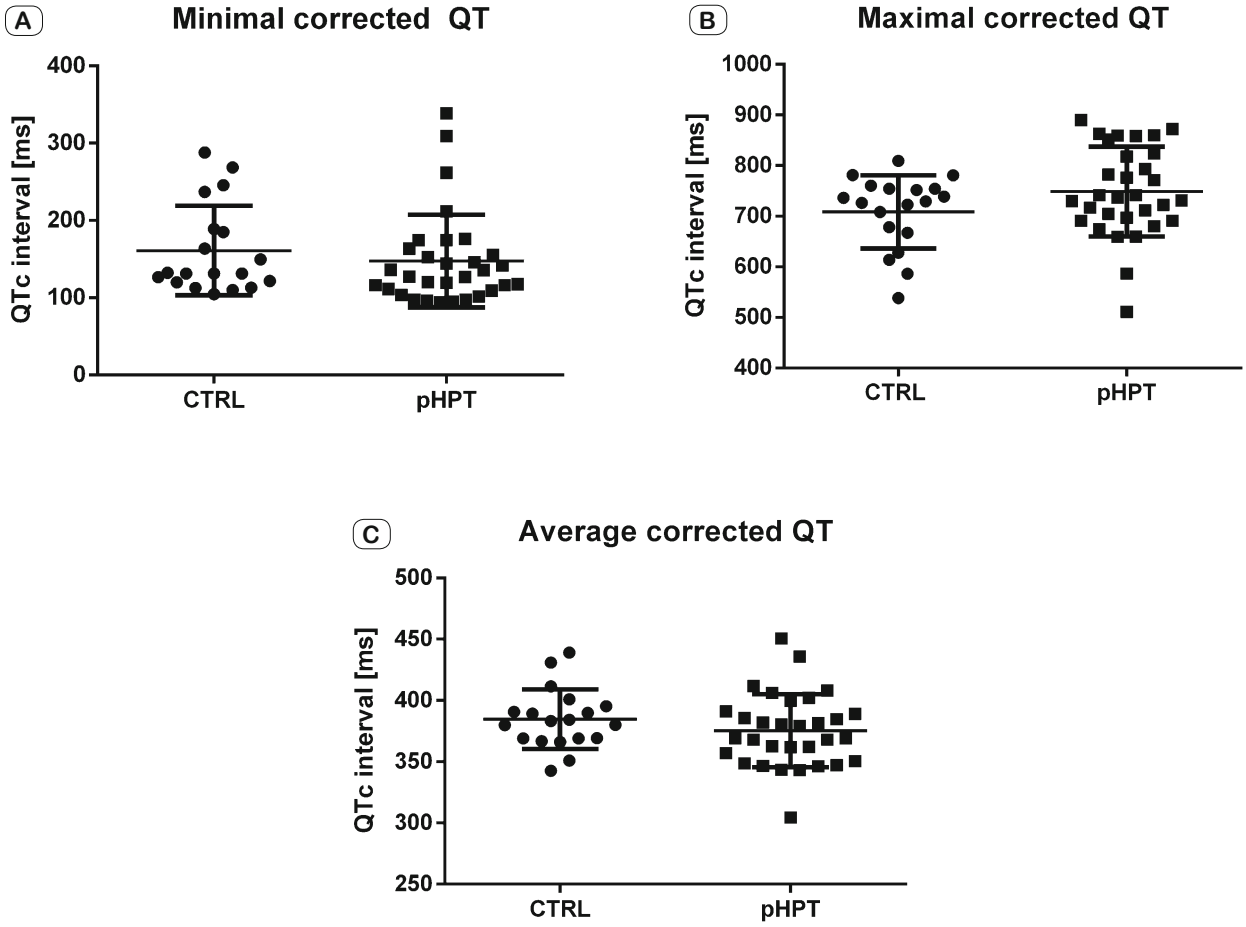

Fig. 3. Minimal (A), Maximal (B) and Average (C) corrected QT interval length on a 24-hour outpatient ECG in CTRL and pHPT. No significant differences were observed. CTRL – control, pHPT – patients with primary hyperparathyroidism.

management. Although diagnosis of primary hyperparathyroidism seems to be quite straightforward, the clinical suspicion itself for pHPT is low and it is usually diagnosed because of accidental calcium evaluation rather than due to the focused assessment (24).

In our study, the patients with pHPT were characterized by mineral disorder in terms of increased serum calcium and decreased serum phosphate concentrations when compared to controls. Additionally, the patients did not report additional symptoms. This calcium disorder may further be responsible for at least some of the complications of pHPT, which can be seen in early stages with direct relation to increased serum calcium. Arrhythmia (25) and shortening of QT interval (26) are the most common ECG findings associated with hypercalcemia. Generally, the QT interval represents the phase of electrical depolarization and repolarization of the ventricles. The 12-lead ECG is the most frequently used technique for obtaining ECG signals for the evaluation of ventricular repolarization. The main difficulty in technical analysis is in the correct identification of the point at which the descending limb of the T wave intersects the isoelectric line and usually requires the concentrated ECG description by cardiologist. 24-hour outpatient ECG can be more suitable way to overcome this problem. Moreover, 24-hour ECG allows analysis of wide range of other heart variables. More specifically minimal, maximal and average QT and corrected QT intervals were chosen to be analyzed in our study. In contrast to published data (27), a higher occurrence of supraventricular or ventricular arrhythmias, or any degree of heart block in hyperparathyroidism patients was not observed when compared to the control group. In line with other studies, the calcium concentrations negatively correlated with the average QT interval in our patients (6, 28). This could potentially advocate the use of 24-hour outpatient ECG for the screening of the pHTP. However, in our study, there were no significant differences in average QT and QTc interval measurements between pHPT and control patients. Additionally, RR intervals and average heart rate did not differ along with the measured QT parameters. Lastly, the shift towards more extreme low or high values as well as frequency of these extreme values expressed as minimal and maximal QT and QTc was not described. One of the reasons, why our results did not fit into our hypothesis is a fact, that 24-hour ECG recordings were not further analyzed and “cleaned” by cardiologist for artefacts in electronic recordings, placing thus a lot of variability into the results. Nevertheless doing so, would be time consum-

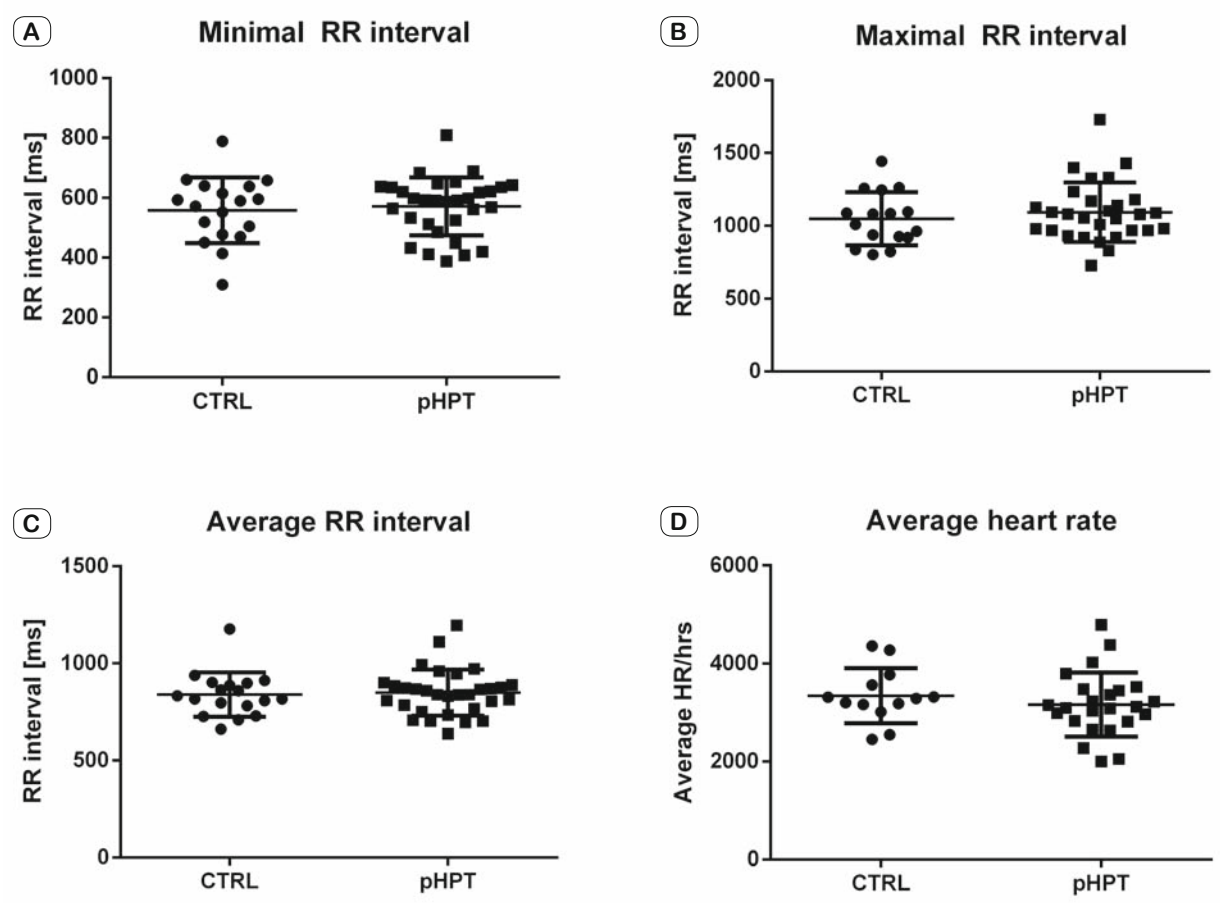

Fig. 4. Minimal (A), Maximal (B) and Average (C) RR interval length and Average heart rate (D) on a 24-hour outpatient ECG in CTRL and pHPT. No significant differences were observed. CTRL – control group, HR/hrs – average heart rate per hour, pHPT – patients with primary hyperparathyroidism.

ing and therefore unsuitable for the clinical practice. The main answer of our study was to verify, whether native 24-hour ECG recoding would be sensitive enough to detect any changes in the QT interval, suggesting thus diagnosis of asymptomatic primary hyperparathyroidism.

Indeed, the study had its limitations. One major limitation was a relatively small number of patients with pHPT making the statistical analysis less sensitive to detection of potential differences. Additionally, the low number of patients mainly in the mild group did not allow to perform a subgroup analysis. It is therefore possible that 24-hour ECG would be suitable only for the more severe pHPT, but not its mild form.

In conclusion, more increased serum calcium seemed to be related to larger shortening of QT interval in patients with pHPT. Nonetheless, in our study, the use of 24-hour outpatient ECG did not prove to be a useful method for screening the patients with primary hyperparathyroidism. Further studies including more severe cases should be performed in the future to confirm suitability or inconvenience of a 24-hour ECG in patients with primary hyperparathyroidism.

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